UNIVERSITY OF LJUBLJANA
BIOTECHNICAL FACULTY

Tatjana ROBIČ

TRACEABILITY OF PHYSICAL DEVELOPMENT OF FULL-TERM AND PREMATURE CHILDREN

DOCTORAL DISSERTATION

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PREPOZNAVANJE RAZLIK V FIZIČNEM RAZVOJU MED DONOŠENIMI IN NEDONOŠENIMI OTROCI OD ROJSTVA DO POZNE ADOLESCENCE

DOKTORSKA DISERTACIJA

Ljubljana, 2015

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AB Preterm (PT) birth and physical characteristics (PC) of mothers may impair growth and development of the child, increase morbidity and mortality, and affect PC later in life. We therefore evaluated the anthropometric equations for assessing body fat percentage (BFP) in pregnant women, effects of their PC on infant's growth during the first year of life, and consequences of prematurity later in life in PT and full-term (FT) individuals. In pregnant women the evaluated BFP varied between 26 % and 38 %, depending on the method used and. Infants of mothers with higher pre-pregnancy mass, body mass index (BMI), and pregnancy mass gain had smaller relative increases in PC. At twenty six years of age illnesses were rare; however, in childhood more very PT (VPT) than FT children experienced the majority of health problems, while infections occurred more often in FT children. VPT males had lower body height than FT males up to the age of seventeen, while in females this difference persisted into adulthood. Body mass and BMI were lower in VPT individuals up to the age of thirteen, later on, in VPT females, body mass remained low; but BMI was higher than in their peers. FT individuals performed aerobic and the majority of anaerobic tests better than PT individuals. Before puberty, however, the agility and fine motor tests were performed better by PT females. VPT females experienced peak height velocity and menarche earlier than their peers. Triceps skinfold thickness and BFP were higher in FT than in PT males before and in PT females after puberty. Lean body mass was lower in VPT individuals than in their peers after the age of eight years. Our results thus clearly confirmed that PC of mothers and PT birth affect individual's growth from childhood into early adulthood.

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AI Nedonošenost (PT) in fizične lastnosti (PC) mater potencialno lahko poslabšajo rast in razvoj otroka, povečujejo obolevnost in smrtnost, in vplivajo na otrokove PC kasneje v življenju. Zato smo ovrednotili antropometrične enačbe za ocenjevanje odstotka telesne maščobe (BFP) pri nosečnicah, učinke njihovih PC na otrokovo rast v prvem letu življenja, in posledice prezgodnjega poroda na PC kasneje v življenju pri PT in donošenih (FT) posameznikih. Pri nosečnicah so bile ocenjene vrednosti BFP med 26 % in 38 %, odvisno od uporabljene metode. Dojenčki mater z višjo pred-nosečniško maso, indeksom telesne mase (ITM) in pridobljeno maso v nosečnosti so imeli manjša relativna povečanja PC. Pri šestindvajsetih letih so bile bolezni redke, v otroštvu pa je več zelo nedonošenih (VPT) kot FT otrok doživelo večino zdravstvenih težav, le okužbe so bile pogostejše pri FT otrocih. VPT moški so imeli nižjo telesno višino kot FT moški do sedemnajstega leta starosti, medtem ko je bila pri ženskah ta razlika opazna tudi v odraslosti. Telesna masa in ITM sta bila najnižja pri VPT posameznikih do trinajstega leta starosti, kasneje je pri VPT ženskah masa ostala nizka, ITM pa je bil višji kot pri vrstnicah. Aerobni in večino anaerobnih testov so FT opravili bolje kot PT posamezniki, vendar pa so bile pred puberteto PT ženske uspešnejše pri spretnostnih in fino-motoričnih testih. VPT ženske so vrh rastnega sunka in menarho doživele prej kot njihove vrstnice. Debelina tricepse kožne gube in BFP sta bila višja pri FT kot pri PT moških pred in pri PT ženskah po puberteti. Pusta telesna masa je bila pri VPT posameznikih nižja kot pri vrstnikih po starosti osmih let. Naši rezultati torej jasno dokazujejo, da PC mater in PT rojstvo vplivajo na rast posameznika od otroštva do zgodnje odraslosti.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GLOSSARY

ACTH	Adrenocorticotrophic hormone; regulates growth and function of adrenal cortex
AGA	Appropriate for gestational age; birth mass between -2 and +2 SD or between the 10^{th} (or 5^{th}) and 90^{th} (or 95^{th}) percentile
ANOVA	Analysis of variance
APMD	Assessment of the psychomotor development, uncorrected and corrected developmental quotient
ARRS	Slovenian Research Agency
BD	Body density
BFP	Body fat percentage
BMI	Body mass index; = body mass [kg] / (body height [m])^2; [kg/m^2]
C	Circumference
CPAP	Continuous positive airway pressure, artificial ventilation, a particular type of ventilation (breathing) therapy
CV	Cardiovascular
D	Difference between two measurements
DDST	Denver's developmental screening test
DEXA	Dual-energy x-ray absorptiometry; synonym: DXA
DNA	Deoxyribonucleic acid
E_2	Prostaglandin; dinoprostone
EDB	Expected date of birth
EFSA	European Food Safety Authority
e.g.	"exempli gratia", a Latin phrase meaning "for example"
ELBW	Extremely low birth weight; birth mass under 1,000 g
FAS	Fetal alcohol syndrome
Fig.	Figure or Figures
F_IO_2	Fraction of inspired oxygen
FM	Fat mass
FT	Full-term: born between the 37^{th} and 42^{nd} week of gestation
GA	Gestational age [weeks], synonym: menstrual age, it is a measure of pregnancy duration starting with the woman's last normal menstrual period
GH	Growth hormone or somatotrophin
GP	General physician
$H_0$1-6	Null hypotheses 1 to 6
HIV	Humani imunodeficientni virus
H_W1-6	Working hypotheses 1 to 6
i.e.	"id est", a Latin phrase meaning "that is"

Ig	Immunoglobulin
IGF	Insulin-like growth factor
IL	Interleukins; a group of cytokines (secreted proteins and signaling molecules) expressed by white blood cells (leukocytes)
IOM	Institute of Medicine
IPAQ	International physical activity questionnaire
IUGR	Intrauterine growth restriction; synonym: FGR (fetal growth restriction); birth mass below a given cut-off point (usually 10^{th} or 5^{th} percentile) for gestational age
kDa	Kilo Dalton, s standard unit used for indicating atomic or molecular mass
LBW	Low birth weight; birth mass under 2,500 g
LGA	Large for gestational age; birth mass over +2 SD or over the 90^{th} (or 95^{th}) percentile
M'ABC	Movement ABC, Movement Assessment Battery for Children
MBH	Maternal body height
MET-minutes	Metabolic minutes; equivalent for measuring physical activity
MLBW	Moderately low birth weight; birth mass between 1,500 and 2,500 g
MPT	Moderately preterm; born between the 32^{nd} and 37^{th} week of gestation
N	Number of subjects
NBW	Normal birth weight; birth mass between 2,500 and 4,000 g
NIOH	National Institutes of Health
p	"p-value" in statistics, a function that is used for testing a statistical hypothesis, it is equal to or smaller than the significance level
p.	Page
PHV	Peak height velocity, pubertal spurt
PMG	Pregnancy mass gain, gestational mass gain, body mass gained from the beginning till the end of pregnancy
POPS	Project On Preterm and SGA in Netherlands in 1983
PpBM	Maternal pre-pregnancy body mass
PpBMI	Maternal pre-pregnancy body mass index
ppm	Parts per million
PPROM	Preterm premature rupture of membrane
PT	Preterm or gestationaly premature; born before the completed 37^{th} week of gestation
R	Coefficient of reliability
RV	recommended values for maternal mass gain during pregnancy
RV/PpBMI	Appropriateness of pregnancy mass gain determined relative to the recommended values according to maternal pre-pregnancy body mass index
s^2	Between-subject variance

SD	Standard deviation; a measure that is used to quantify the amount of variation or dispersion of a set of data values
SFT	Skinfold thickness
SGA	Small for gestational age; synonym: SFD (small for dates), due to IUGR; birth mass under -2 SD or under the 10^{th} (or 5^{th}) percentile
SLOfit	SLOfit system; sports-educational records; s systematical annual monitoring of physical and motor development of children in primary and secondary schools in Slovenia
T3, T4	Triiodothyronine and thyroxin, thyroid hormones
Tab.	Table or Tables
TEM	Technical error of measurement
$TNF_{-\alpha}$	Tumor necrosis factor
TSH	Thyroid stimulating hormone; thyrotrophin
VLBW	Very low birth weight; birth mass between 1,000 and 1,500 g
VO_2 max	Maximum rate of oxygen consumption, which reflects the aerobic physical fitness of an individual [$ml*kg^{-1}*min^{-1}$]
VPT	Very preterm; born before the completed 32^{nd} week of gestation
UK	United Kingdom
USA	United States of America
WDI	World Development Indicators
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio

Antenatal	Occurring before birth; synonym: prenatal
Apgar score	A method invented by Virginia Apgar in 1952 for summarizing the health of newborn children on five simple criteria on a scale from zero to two
Enteral nutrition	A way to provide food through a tube placed in the nose, the stomach, or the small intestine
Extrauterine pregnancy	A complication of pregnancy in which the embryo is implanted outside the uterus; synonym: ectopic pregnancy
Gestation	Carrying of an embryo or fetus inside female
Gestational age	Duration of pregnancy, the amount of time the fetus spent in the uterus, usually expressed in weeks
Iatrogenic birth	Labor induced by the physician
Idiopathic preterm birth	Spontaneous preterm labor after own contractions of the uterus
Multiple pregnancy	Pregnancy with more than one fetuses – twins, triplets…
Parenteral nutrition	Feeding a person intravenously
Parity	The number of times a female has given birth

Perinatal	Period between the 22 completed weeks (154 days) of gestation and the 7^{th} day after birth
Postterm	Born between the 42 and 44 completed weeks of gestation
Premature	Not mature at birth, due to preterm birth or intrauterine growth restriction
Prenatal	Occurring before birth; synonym: antenatal

1 INTRODUCTION

1.1 RESEARCH PROBLEM

A premature status of an individual, also called prematurity, results from birth before the 37th week of pregnancy (with full pregnancy lasting for 40 weeks after the first day of the last menstrual period) (Euser et al., 2008). Experts distinguish within preterm (PT) infants moderately preterm (MPT) infants, who include individuals born between the 32nd and 36th weeks of pregnancy, very preterm (VPT) infants, who include individuals born before the 32nd week of pregnancy, and extremely premature infants born before the 28th week of pregnancy (Euser et al., 2008). Other definitions classify different groups of infants by the birth mass, distinguishing between premature infants with low birth mass (under 2,500 g; LBW), who include individuals with extremely low birth mass (under 1,000 g; ELBW), very low birth mass (between 1,000 and 1,500; VLBW), and moderately low birth mass (between 1,500 and 2,500 g; MLBW), and those that are heavier than 2,500 g (normal birth mass; NBW) (Wehkalampi et al., 2010). On average, preterm births occur in approximately 7 % of all births in Slovenia (Babnik J., 1988). According to data from the Statistical Office of Slovenia, approximately 20,000 children are born yearly in Slovenia, which means approximately 1,400 PT infants every year.

The earlier the pregnancy ends, the lower is the birth mass of a newborn, thus the more life threatening condition he or she experiences. Low birth mass increases the risk of prenatal morbidity (Brundtland, 2002), increases mortality in childhood (Jarvis et al., 2003), seems to impair growth and development, as well as increase the risk of diseases in adulthood (Barker D.J. et al., 1993). Technological advances in medicine over the past 25 years have successfully reduced the mortality and health problems of (very) premature infants, and the first generation of (very) premature infants has entered into early adulthood today (Euser et al., 2008).

The prematurity most likely has long-term consequences for the physical development of an individual. Growth and development of full-term (FT), who include individuals born after the completed 37th week of pregnancy, and PT infants can, in principle, be traced from birth, through childhood, and into adulthood, however, research on tracking of these two groups of infants into early adulthood are extremely rare. Namely, such studies require longitudinal following of the same people from birth for up to the completion of their physical growth, which is logistically difficult, because it requires the willingness of researchers to work consistently over a very long period of time, but also the willingness of individuals to participate in such a long study uninterruptedly. With such long-term longitudinal studies, the sample of subjects inevitably decreases over the years, which ultimately affects the quality of research conclusions.

Due to dedicated work of the individuals working in the field of neonatology and due to systematic monitoring of health, physical and motor development of children and adolescents, there most probably exists a unique opportunity in Slovenia to extend the existing systematic work into a combination of prospective and retrospective research. Namely, medical examinations of all children are performed on a regular basis and standardized assessment of motor development takes place annually on all Slovenian primary and secondary schools.

1.2 AIM OF THE RESEARCH

To investigate long-term effects of prematurity we initiated a project that included both, prospective and retrospective approach, which was possible only due to the specific Slovenian situation shortly presented above. This research approach enabled us to follow both, PT and FT individuals from their birth up to their late adolescence or even into early adulthood by combining four pre-existing data sources and by obtaining entirely new information. We believe this study is therefore unique worldwide, as it effectively overcame some of the drawbacks of long-term longitudinal studies, in particular an extensive drop out of subjects that is always experienced in long-term research.

The aims of the present study were thus:

- to evaluate the existing anthropometrical methods, which are used by researchers to assess body composition of pregnant women (prospective research approach);
- to analyze neonatal, gestational, and birth factors that may result in a poor outcome during a child's development (retrospective research approach);
- to examine differences in growth between FT and PT infants (retrospective and prospective research approach);
- to assess differences in physical and motor development of the two groups in the period from birth up to late adolescence or early adulthood (retrospective research approach); and finally
- to compare the incidences of cardiovascular, respiratory, and musculoskeletal disorders in both groups (retrospective and prospective research approach).

Our goal was to study approximately 200 FT and 200 PT individuals. We aimed to obtain their data on prematurity, physical, motor development, and health from birth up to late adolescence or early adulthood in order to evaluate potential long-term effects of prematurity.

1.2.1 The expected results and the contribution to science

The results of the present doctoral thesis aimed to clarify, whether the growth pattern of FT and PT children during the first year of life is influenced by the physical characteristics of their mothers, and evaluate how effective the currently available methodology to assess anthropometric characteristics of pregnant women is. Furthermore, the research work aimed to identify differences in growth and development of FT and PT children from childhood into adolescence and, if possible, into early adulthood. The thesis also evaluated the incidence of diseases associated with prematurity, and clarified, whether some effects of prematurity can be also observed in childhood and adolescence.

The evaluation of early indicators of adult physical properties is undoubtedly important, as we may be in this way able to identify key indicators of growth and development. Thus, by regular monitoring of these parameters, we may be able to work preventively against the negative consequences of prematurity and thus, potentially, against abdominal obesity, cardiovascular, and musculoskeletal disorders in adulthood. Furthermore, the evaluation of existing anthropometric methods seems to be crucial for a reliable assessment of any associations between the morphological characteristics of parents and their children and for their further interpretation. Namely, the existing methodology for determining body composition in pregnant women often neglects specificity of tissue composition in pregnancy, so there exists a substantial possibility that different methodological approaches can lead to quite different research conclusions.

We believe that the presented study provided a meaningful, fresh, and broad insight into the processes of growth and physical development of FT and especially of PT infants, from birth into early adulthood. According to our knowledge, the present study is the most extensive longitudinal study in the research field of growth and development of prematurely born infants. The results of the present doctoral thesis will therefore be undoubtedly useful for further research in auxology and neonatology.

1.3 WORKING HYPOTHESES

On the basis of current knowledge on this topic, we set six null and working hypotheses. Our hypotheses were:

$H_0 1$ – The existing anthropometric methods are adequate for assessing body composition in pregnant women.
$H_W 1$ – The existing anthropometric methods are inadequate for assessing body composition in pregnant women.

$H_0$2 – The pattern of growth of full-term and premature children during the first year of life is independent of maternal anthropometric characteristics.
H_W2 – The pattern of growth of full-term and premature children during the first year of life depends on anthropometric characteristics of mothers.

$H_0$3 – The susceptibility to illnesses after the period of accelerated growth will be the same in full-term and premature children.
H_W3 – The susceptibility to illnesses after the period of accelerated growth will be different between full-term and premature children.

$H_0$4 – Frequency of illnesses associated with prematurity experienced after a period of accelerated growth will be the same in all preterm children.
H_W4 – Frequency of illnesses associated with prematurity experienced after a period of accelerated growth will differ between premature and very premature children.

$H_0$5 – The consequences of prematurity, such as lower height, lower mass, and smaller physical exercise capacity, will not be detected in late childhood and adolescence.
H_W5 – The consequences of prematurity, such as lower height, lower mass, and smaller physical capacity, will be detected in late childhood and adolescence.

$H_0$6 – Distribution of body fat will be similar in full-term and premature children.
H_W6 – Distribution of body fat will be different in full-term and premature children.

2 LITERATURE REWIEV

Growth and development are interesting, complex, and multifactorial physiological processes. Previous research in this field has contributed significantly to the understanding of growth and developmental processes of FT and premature infants, yet, many questions still remain unanswered. Especially for premature children, data on growth and developmental processes that occur from birth until early adulthood are only rarely and very scarcely available, or they do not exist at all.

Premature infants, especially those with VLBW (in the literature and in conversations body mass is often referred to inaccurately as body weight) represent only a small fraction of all births, but for their survival a lot of resources and knowledge is required. Some studies have so far observed psychomotor development of PT infants, but less is known about their somatic development (Babnik J., 1990).

In the past, the majority of VLBW or VPT infants died in the first months or years after birth. As technological advances in medicine reduced the mortality and health problems of premature infants, the first generation of (very) premature infants has entered into early adulthood (Euser et al., 2008). For the first time we therefore have the opportunity to evaluate potential long-term consequences of prematurity on growth, development, and susceptibility to diseases.

To understand the difference between the development of FT and premature infants, we first have to clarify what prematurity actually is, how it differs from the usual human development, how often it occurs, and what are the causes and consequences of prematurity.

2.1 PREMATURITY AND PRETERM BIRTH

2.1.1 Definitions and classifications

A full-term human pregnancy lasts for 40 weeks (approximately 280 days from the last menstrual period or 266 days from the conception). When an infant is born, his/hers gestational age (GA) is equal to the number of completed weeks he/she developed first as an embryo and then as a fetus. Newborns born with GA between 37 and 41 weeks are called FT infants. Birth that occurs before 37 completed weeks of pregnancy or before 259 days from the first day of mothers last menstrual period (thus three weeks too soon) is considered to be preterm birth, regardless of the newborns actual birth mass (World Health Organization; WHO). However, the majority of long-term consequences and deaths are experienced by infants delivered before 34 weeks of pregnancy (Marlow N. et al., 2005).

It is therefore convenient to classify preterm birth into the following subgroups (PerkinElmer, 2009):

- late preterm birth occurring between 34 to 36 completed weeks of pregnancy;
- moderately preterm birth occurring between 32 and 33 weeks of pregnancy;
- very preterm birth occurring before 32 completed weeks of pregnancy; and
- extremely preterm birth occurring before 28 weeks of pregnancy.

In addition, when speaking about prematurity, it is not only the infants' GA, but also their birth mass that provides important information. Namely, the cut-off level of 2,500 g (PerkinElmer, 2009) is considered beneficial maturity, regardless of the GA. Although there exists an obvious association between low birth mass and preterm birth (Figure 1), low birth mass (the expression low birth weight (LBW) is most often used in literature) infants are not necessarily born PT. In developed countries, most LBW infants are also PT infants. In under-developed countries, however, the proportion of FT, yet LBW infants, is higher due to the greater prevalence of malnutrition (PerkinElmer, 2009).

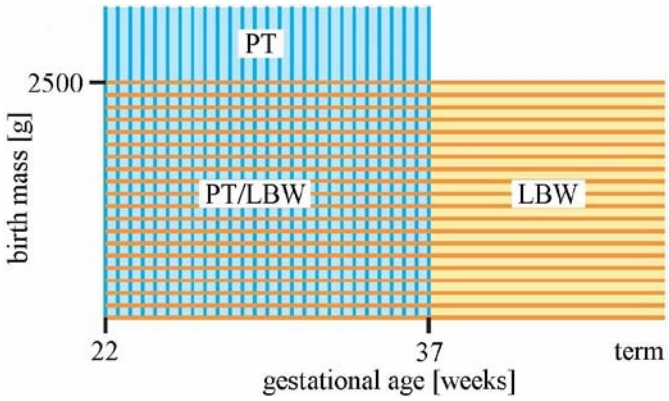


Figure 1: Classifications of infants according to gestational age and birth mass are partly overlapping, as preterm born (PT) infants are not necessarily born with low birth mass (LBW), and similarly, LBW infants are not necessarily born PT (PerkinElmer, 2009: 4)

Slika 1: Razvrstitvi novorojenčkov glede na gestacijsko starost in porodno maso se le delno prekrivata, saj prezgodaj rojeni (PT) novorojenčki niso nujno rojeni tudi z nizko porodno maso (LBW) in prelahki novorojenčki niso nujno tudi rojeni prezgodaj (PerkinElmer, 2009: 4)

LBW infants include both, those born PT and those whose growth has been impaired in uterus (Park, 2005; Paul et al., 2011) during the last trimester, as a result of impaired placental function, which means the lack of an optimal environment normally provided by the uterus (Paz et al., 1993; Euser et al., 2008; Rotteveel et al., 2008). The latter are often noted also as intrauterine-growth-restriction (IUGR) infants. An infant whose mass is significantly lower than the population norm is termed small for GA (SGA infant). The cut-off level is usually an infant's birth mass below the 10^{th} percentile for GA (Park, 2005; Paul et al., 2011). Alternative cut-off levels such as the 5^{th} (PerkinElmer, 2009) or 3^{rd} (PerkinElmer, 2009) percentile for GA have also been

proposed. IUGR and SGA are related terms, but are not synonymous (PerkinElmer, 2009), as the cause of SGA can be either pathological (thus IUGR) or non-pathological. IUGR is thus a failure of normal fetal growth and is caused by multiple adverse effects on the fetus that prevent normal growth potential from being realized.

Nowadays, GA of 23 weeks is considered minimal for infants to survive. In February 2007, a newborn girl Amillia Sonja Taylor in Miami, United States of America (USA), who is by now believed to be the most premature infant to survive, was dismissed from hospital after 4 months of neonatal intensive care. She was born at 23 weeks and 6 days, weighing just 283 g. However, many infants born at 22 to 25 weeks of pregnancy do not survive, and of those who do, many experience some sort of major impairment (Sigelman and Rider, 2012). Although diverse medical and technical progress has indeed increased the number of surviving PT infants, the earlier an infant is born, the higher is the risk of physical, sensory, and cognitive disability, as well as attention disturbance (Frühgeburt, 2012).

Due to large overlapping of both before mentioned classifications (thus, according to birth mass or GA), this thesis will focus primarily on the classification of infants according to their GA, thus on preterm birth.

2.1.2 Labor and birth

Labor and birth are very dramatic changes in the life of an individual. For a newborn infant, the birth is a transition from a regulatory system, which is largely dependent on characteristics of maternal organism, into a system, which is based on infant's genetic and homeostatic mechanisms (Babnik A., 2003). Labor normally starts at 38 weeks after conception or 40 weeks after the last menstrual period (Pajntar, 1998).

The labor is an anatomical, biochemical, endocrinological, and clinical event (Romero et al., 1994). What triggers delivery in humans, is not yet fully discovered. In animals (in mice, rats, dogs, cattle, sheep, goats) the beginning of labor coincides with a reduction of progesterone level and an increase of estrogen level in the blood of the pregnant female (Myers et al., 1992). In sheep, the trigger for labor is a secretion of corticotropin releasing hormone in the brain of the fetus, which causes the release of hormone adrenocorticotropin from the pituitary gland, which in turn stimulates the fetal adrenal glands for cortisol excretion. In humans, such a sequence of hormonal changes has not been confirmed, although in newborns' blood obtained immediately after birth, very high levels of cortisol were observed. It is possible, that in humans other chemical substances, such as oxytocin, prostaglandins, endothelin I, and histamine play a more important role in the induction of labor (Casey M.L. and Mac Donald, 1998).

In general, the common labor can be considered to have three main components: uterine contractility (although the myometrial activity occurs throughout pregnancy), cervical ripening (dilatation and effacement; not yet completely defined processes), and activation of decidua and membranes (Romero et al., 1994). These events are described below in detail.

2.1.2.1 Contractions of the uterus

Labor is characterized by a change in the pattern of uterine contractility (Romero et al., 1994). In contrast to "contractures", which are myometrial activities present through pregnancy lasting several minutes and are associated with modest increase in intrauterine pressure, "contractions" during the labor are epochs of myometrial activity of short duration and associated with dramatic increases in intrauterine pressure (Nathanielsz and Honnebier, 1992). The swift from "contracture" to "contraction" pattern occurs physiologically during normal labor, usually at night, or can be induced by pathological events such as starvation, infection, and maternal intra-abdominal surgery (Romero et al., 1994). However, this switch is a reversible phenomenon. A role of oxytocin in the control of this switch was observed, as increased oxytocin concentrations in maternal plasma followed a circadian pattern similar to that of uterine contractility (Honnebier et al., 1991).

The cellular and molecular events such as the appearance of gap junctions and an increased expression of gap junction protein connexin 43, have also been implicated in the physiological shift from contractions to contractures. The majority of gap junctions seem to develop in myometrium just prior to labor and disappear shortly after delivery (Garfield and Hayashi, 1981). Balducci et al. (1993) indicated that these events occur similarly in term and preterm labor. An increase in human myometrial contractility is thus a common feature of both, term and preterm labor (Romero et al., 1994).

2.1.2.2 Ripening of the cervix

The majority of uterine cervix is a connective tissue organ, as less than 8 % of the distal part of the cervix are represented by smooth muscle cells (Schwalm and Dubrauszky, 1966). The ability of the cervix to hold the fetus during pregnancy may not be depending upon a traditional muscular sphincteric mechanism, but upon the regulation of fibrous connective tissue. This tissue is formed by abundant extracellular matrix, which consists of collagen, proteoaminoglycans, elastin, and various glycoproteins, such as fibronectins (Romero et al., 1994).

Collagen determines the tensile strength of fibrous connective tissue and changes in its content and metabolism have been attributed to changes in cervical characteristics

during pregnancy. Collagen content may have an important role in cervical dilatation (Uldbjerg et al., 1983), as a strong correlation between the collagen content of cervical biopsies obtained after delivery and the time required for the cervix to dilate from 2 to 10 cm was observed. Proteoaminoglycans have also been implicated in cervical physiology, as some of them may have high affinity for collagen, which stabilizes and promotes the formation of thicker collagen fiber bundles (Romero et al., 1994).

The biochemical events, which may be involved in cervical ripening are: a decrease in total collagen content, increase in collagen solubility (probably due to degradation or new synthesis of weaker collagen), and increase in collagenolytic activity. Extracellular matrix turnover in the cervix is very high, and thus, mechanical properties of the cervix can change very quickly (Romero et al., 1994).

During cervical ripening there is an influx of inflammatory cells (macrophages, neutrophils, mast cells, eosinophils...) into the cervical stroma. It has been proposed that these cells produce cytokines and prostaglandins, which have an effect on extracellular matrix metabolism. Namely, prostaglandins have been widely used to induce cervical ripening prior to induction of labor or abortion (Romero et al., 1994).

Sex steroid hormones may play a role in this process, as estradiol induces cervical ripening, estrogen stimulates collagen degradation, progesterone blocks the estrogen-induced collagenolysis, and the administration of progesterone receptor antagonist induces cervical ripening in the first trimester of pregnancy (Chwalisz et al., 1987).

Cervical ripening occurs also in the context of preterm labor. Wood et al. (1965) were the first to report that a short cervix was a risk factor for preterm labor and delivery. After several following confirmations of this fact (Catalano at al., 1989), Papiernik et al. (1986) conducted serial digital examinations in 8,303 women. Once dilatation of the internal part of the cervix occurred, the interval to delivery was similar in women with either spontaneous term or preterm labor. This indicates that also cervical ripening is a general feature of preterm or term labor (Romero et al., 1994).

2.1.2.3 Decidua and membrane activation

During pregnancy the chorioamniotic membranes fuse with the decidua. In preparation for delivery, a complex set of anatomical and biochemical events leads to separation of the lower pole of the fetal membranes from the decidua of the lower uterine segment and to the occurrence of spontaneous rupture of membranes. Fibronectins are a family of important binders of extracellular matrix. The available evidence indicates that

fibronectin dissolves and can be found in the vagina again during both, term and preterm labor, and is therefore a common feature of labor (Lockwood et al., 1991).

2.1.3 Causes of preterm birth

Although term and preterm labor share a common terminal pathway, it was proposed that term labor is the result of physiologic activation, while preterm labor is the consequence of pathologic activation. Preterm labor may be considered as the response to a variety of risk factors (such as infection, ischemia… (Romero et al., 1994); more in Chapters 2.2 and 2.3), which can trigger labor and birth.

In general, two medical causes can lead to preterm birth: one of them is induced (iatrogenic) and the other spontaneous preterm birth (the latter occurs either as preterm labor (idiopathic birth) or as preterm premature rupture of membrane (PPROM)) (Moutquin, 2003).

Approximately 20 % of all preterm deliveries are iatrogenic, i.e. induced as the result of a physician's decision to initiate preterm birth (Goldenberg et al., 2008; Beta et al., 2010), most commonly due to serious maternal or fetal complications, such as severe pre-eclampsia (high blood pressure and significant amounts of protein in the urine; Annex A), IUGR, congenital abnormalities, and trauma (Haas, 2006). In these cases, labor is medically induced or a cesarean section is performed (Goldenberg et al., 2008; PerkinElmer, 2009).

Approximately 80 % of preterm births are either idiopathic spontaneous preterm labors (50 %), which begin with their own contractions of the uterus and cervical ripening, or births after PPROM (30 %) (Romero et al., 1994; Gardosi and Francis, 2000; Di Renzo et al., 2006; Beta et al., 2010). However, only 20 % to 30 % of women with preterm labor deliver preterm (Berghella et al., 2011). Spontaneous preterm labor and birth can occur in any pregnancy, but some women are more prone to it than others (PerkinElmer, 2009). Preterm labor has heterogeneous origins and is the consequence of pathologic activation of uterine contractions (Romero et al., 1994; Gardosi and Francis, 2000).

Increased risk of spontaneous preterm birth has been associated with several genetic and socio-environmental (i.e. demographic) risk factors, such as fetal complications (these include: polymorphisms in the promoter of insulin gene (imprinting of paternal and maternal gene for insulin-like growth factor (IGF) II) that has been associated with infant's size at birth, congenital anomalies, and IUGR), placental complications (that include differences in growth in the third trimester, abruption placenta), and/or maternal complications (which include maternal age, body height (MBH), and parity, as well as

cervical and uterine abnormalities) (Romero et al., 1994; Williams C.E.C.S. et al., 2000; Euser et al., 2008, PerkinElmer, 2009). Furthermore, risk factors for preterm birth also include past reproductive history (previous history of preterm birth or delivery of a LBW infant), low socioeconomic status, African-American origin, the second adolescent pregnancy, substance misuse, urinary tract and uterus infection, hypertension during pregnancy (Slattery and Morrison, 2002; PerkinElmer, 2009), as well as series of disorders that implicate maternal and fetal diseases (Romero et al., 1994; Slattery and Morrison, 2002). Some of the most important risk factors for preterm birth will be described later in more detail.

Iatrogenic and spontaneous preterm births have different overall profiles of association with pregnancy risk factors (Meis et al., 1995). In both situations, however, causes for preterm birth are difficult to study, as they are confounded by multiple shared risk factors.

2.1.4 Incidence of preterm birth

Preterm birth is a rather common pregnancy complication (Bonamy et al., 2008). Stated very generally, premature birth occurs in every 10^{th} to 20^{th} pregnancy (Tideman et al., 2002); however, every 50^{th} singleton pregnancy ends before 34 weeks. There are more than 13,000,000 PT infants born annually worldwide (9.8 %) (Ananth and Vintzileos, 2006). In 2005, around 11,000,000 (85 %) of them were born in Africa and Asia, 500,000 (4 %) in Europe and North-America, and 900,000 (7 %) in Latin-America and the Caribbean (Beck et al., 2010). Obviously, the rate of preterm birth is not uniform all over the world and is not distributed evenly among fertile women (Ananth and Vintzileos, 2006). In 2010, as estimated 14,900,000 infants were born preterm, this is 11.1 % of all live births worldwide (Blencowe et al., 2012).

From 1983 to 2008, for reasons that are not yet fully understood, the worldwide rate of preterm birth has increased (Petrou et al., 2001; Goldenberg et al., 2008) by approximately 14 % (Goldenberg et al., 2008). This increase may, in part, be explained by a failure to identify high-risk group(s) during routine prenatal care (Goldenberg et al., 2008), increase of iatrogenic preterm births (both, preterm inductions and preterm cesarean deliveries without labor (Kramer et al., 1998)), higher maternal age, higher rates of assisted reproductive technologies, and multiple gestations related to these technologies (Ananth and Vintzileos, 2006). It indeed seems that fertility treatment, both assisted conception and ovulation induction (Lumley, 2003), is the predominant risk factor that increased the incidence of preterm birth in developed countries by causing multiple (twins, triplets…) pregnancies, which are more common to end preterm. The observed increase in the incidence of preterm birth has also been attributed

to the increasing use of early ultrasound dating and changes in socio-demographic and behavioral factors (Kramer et al., 1998).

2.1.4.1 Incidence of preterm birth in Slovenia

On average, preterm births occur in approximately 7 % of all births in Slovenia, last reported rate from 2008 was 7.4 % (Zeitlin et al., 2013; Table 1). According to data from the Statistical Office of Slovenia, approximately 20,000 children are born yearly in Slovenia, thus every year approximately 1,400 infants are born preterm and with birth mass of less than 2,500 g, and of those almost 200 infants are born preterm with birth mass of less than 1,500 grams (Babnik J., 1988; Babnik A., 2003).

2.1.4.2 Incidence of preterm birth in other countries

Across 184 countries the rate of preterm birth ranges from 5 % in European countries, up to 18 % in some African countries (Blencowe et al., 2012). High rates of preterm birth have been reported for the whole Africa (11.9 %) (Beck et al., 2010). More than 60 % of PT infants were born in south Asia and sub-Saharan Africa, where 52 % of the global live births occur (Blencowe et al., 2012). In Europe and other developed countries, reported rates are generally 5 % to 9 % (Slattery and Morrison, 2002; Beck et al., 2010). Preterm birth is more common in the USA than in many other industrialized countries (Martin J.A., 2002; Table 1). In the USA, on average, one PT infant is born every minute (Ananth and Vintzileos, 2006), which means preterm birth rate is 12 % to 13 %.

The preterm birth and LBW rate has risen during the last 30 years in most industrialized countries (Casey P.H., 1990, 2008; Goldenberg and Rouse, 1998). With the exception of France (Bréart et al., 1995), Finland (Olsën et al., 1995), Croatia, Ecuador, and Estonia (Blencowe et al., 2012), from 1990 to 2010 none of the 65 countries with estimated time trends, has reported a reduction in incidence of preterm birth. Despite advancing knowledge on risk factors and mechanisms related to preterm birth, as well as the introduction of many public health and medical interventions designed to reduce preterm birth (Goldenberg and Rouse, 1998), the rate of preterm birth in the USA increased from 9.5 % in 1981 to 12.7 % in 2005 (Hamilton, 2006). Hospital's increase in preterm birth since 1978 was reported from USA and Canada (Kramer et al., 1998).

Table 1: The incidence of preterm birth rates in various countries

Preglednica 1: Pogostost prezgodnjega poroda v različnih državah

Country	Year	Preterm birth rate [%]	Reference
Denmark	2008	5.0	Auger et al., 2013
Finland	2008	5.5	Zeitlin et al., 2013
Ireland and Lithuania	2008	5.9	Zeitlin et al., 2013
Estonia	2008	6.2	Zeitlin et al., 2013
Sweden	2012	6.2	Morken et al., 2006; Zimmer, 2012
France	2010	6.6	Zeitlin et al., 2013
Poland	2008	6.6	Zeitlin et al., 2013
Norway	2008	6.7	Zeitlin et al., 2013
Malta	2009	6.7	Zeitlin et al., 2013
Slovakia	2008	6.8	Zeitlin et al., 2013
China	2010	7.1	Blencowe et al., 2012
The Netherlands	2008	7.4	Zeitlin et al., 2013
Slovenia	2008	**7.4**	Zeitlin et al., 2013
Canada	2002	7.6	Joseph et al., 2007
United Kingdom	2006	7.6	Richardson and Mmata, 2007
Belgium: Flanders	2008	8.0	Zeitlin et al., 2013
Spain	2008	8.2	Zeitlin et al., 2013
Australia	2010	8.3	Li Z. et al., 2012
Czech Republic	2008	8.3	Zeitlin et al., 2013
Portugal	2008	9.0	Zeitlin et al., 2013
Brazil	2010	9.2	Blencowe et al., 2012
Germany	2012	9.2	Zimmer, 2012; Zeitlin et al., 2013
Austria	2008	11.1	Zeitlin et al., 2013
Caribbean	2010	11.2	Blencowe et al., 2012
Democ. Repub. of Congo	2010	11.9	Blencowe et al., 2012
USA	2010	12.0	Martin J.A., 2007; Blencowe et al., 2012
Nigeria	2010	12.2	Blencowe et al., 2012
India	2010	13.0	Blencowe et al., 2012
Bangladesh	2010	14.0	Blencowe et al., 2012
Philippines	2010	14.9	Blencowe et al., 2012
Indonesia	2010	15.5	Blencowe et al., 2012
Pakistan	2010	15.8	Blencowe et al., 2012
Gabon	2013	16.3	Blencowe et al., 2013a; WHO, 2014
Mozambique	2014	16.4	Osman et al., 2000; Blencowe et al., 2013a
Equatorial Guinea	2013	16.5	Blencowe et al., 2013a; WHO, 2014
Zimbabwe	2013	16.6	Blencowe et al., 2013a; WHO, 2014
Congo	2013	16.7	Blencowe et al., 2013a; WHO, 2014
Malawi	2013	18.1	Blencowe et al., 2013a; WHO, 2014

In the USA, the prevalence of preterm birth is twice as high in African-American women, as compared with Caucasian or Hispanic women (Goldenberg et al., 2008). Asian (especially eastern) populations experience the lowest preterm birth rates in the USA (Paneth, 1995; Goldenberg et al., 2008). In 1997, approximately 10 % of white and 18 % of black newborns in the USA were born preterm (Martin J.A., 2002). In white women, preterm birth is most commonly caused by preterm labor, while PPROM is the more frequent cause of preterm birth in black women (Ananth and Vintzileos, 2006). These differences between whites and non-whites, in, both, prematurity and stillbirths have persisted over the entire 20th century (Costa, 2004).

2.1.5 Factors that may affect the reported data on incidence of preterm birth

It is worthwhile noting that the data on incidence of PT infants can vary or be inaccurate due to different criterions used and due to culture differences in the world. The definition of WHO for preterm birth (which states that a preterm birth occurs before 37 completed weeks of gestation, or before than 259 completed days since the first day of woman's last menstrual period), for example, has one problematic component: the boundary between a spontaneous abortion and birth (the point in pregnancy when the delivery of a fetus is counted as birth rather than as some other pregnancy outcome) (Lumley, 2003). Additionally, different GA cut-off points for defining preterm birth can be used worldwide, which might explain part of the difference in preterm birth rates (Goldenberg et al., 2008).

Factors, which have been recognized to affect the proportion of reported preterm births in a defined population include national or regional time-associated criteria for the registration of fetal deaths (as these can range from 16 weeks in Norway, 20 weeks in the USA and Australia, to 28 weeks in England, Sweden, New Zealand, and many other countries) (Lumley, 1993), under-registration of stillbirths and live births close to the registration boundary (i.e. close to a time limit that requires registration as a preterm live birth), under-registration of live births, when a stillbirth at the same GA would not require registration, the perception that some extremely small (or extremely PT) live born infants are nonviable, and the exclusion of legal terminations of pregnancy from birth registration, even when the duration of pregnancy would require registration (Lumley, 2003). In Australia, for example, all births with a gestation of 20 weeks, and/or births of infants weighing at least 400 g, if the gestation is not known, require registration (Lumley, 2003), but these criterions differ from those in other countries, as stated before.

Factors that could have affected the reported preterm birth rate are also the shift from "rounding-off" GA to calculate the number of complete weeks, as proposed in the WHO

definition, and the shift from using the date of last menstrual period to measure GA to using early ultrasound assessment of fetal size. Namely, it has been stated that menstrual dates systematically underestimate the prevalence of preterm birth (Mongelli and Gardosi, 1997). In addition, GA estimated from menstrual dates can be very inaccurate, due to great variability in the timing of ovulation in relation to the menstrual cycle. Delayed ovulation, for example, appears to explain the higher post-term birth rate based on menstrual dates (Yang H. et al., 2002). In contrast, an estimation of GA by ultrasound scan is associated with lower average estimate of GA and increases the reported preterm birth rate by reducing GA. Interestingly, it has been suggested that a positive discrepancy of more than 7 days between menstrual dates and ultrasound scan dates (that indicates a prolonged interval between last menstruation and conception) should act as a warning that the pregnancy is at increased risk of premature birth (Gardosi and Francis, 2000).

Cultural and social factors, which influence the completeness of PT infant registration, include the provision of maternity benefits to a mother after birth but not after spontaneous abortion, which may increase the likelihood of preterm birth registration, the requirement for burial or funeral costs after birth, which may have the opposite effect, and different hospital charges following “abortion” and “birth”, which may be a disincentive for complete registration of extremely preterm births (Lumley, 2003).

2.2 TIME BEFORE PREGNANCY

Infants care does not begin on the day the infant is born; it is a process that takes place already before conception. Pre-pregnancy care, which includes nutrition, physical activity, and healthy lifestyle, is crucial for enabling the women to achieve optimal health in their reproductive years (Thomas A. and Duarte-Gardea, 2013). Namely, it has been suggested that already before pregnancy various factors can affect the likelihood that a woman will deliver preterm (PerkinElmer, 2009). Furthermore, reports suggest that health and nutritional status of the mother before and during pregnancy are the major determinants for a good pregnancy outcome (Thomas A. and Duarte-Gardea, 2013).

2.2.1 Parental genetic factors

It has long been proposed that there is a maternal genetic predisposition toward preterm birth (Goldenberg et al., 2008; PerkinElmer, 2009), as genetic differences between individuals i.e. gene polymorphisms, can result in variations in production and activity of proteins. Discovery of a specific gene that predisposes women to preterm birth could likely suggest new therapeutic and preventive targets (PerkinElmer, 2009); therefore the effects of candidate gene polymorphisms on preterm birth have been investigated. Up to

now, the focus has primarily been laid on polymorphisms related to inflammatory and immune response.

It seems that maternal genetic factors affect the risk for preterm birth, whereas paternal and probably fetal genetic factors do not, or exert only a minor impact (Little, 2009). One significant candidate for a maternal gene associated with preterm birth is the gene coding for tumor necrosis factor alpha ($TNF_{-\alpha}$). This is a proinflammatory cytokine that is present in amniotic fluid of women with intrauterine infection, who deliver preterm (Adams K.M. and Eschenbach, 2004). It has also been documented that black women, who were carriers of the interleukin 6 (IL-6) allele and had bacterial vaginosis (an infection of the vagina caused by bacteria), had a twofold greater risk of preterm birth than infected white women (Engel et al., 2005).

Not only genetic factors, but also maternal GA has been suggested to be a risk factor for preterm birth. Women, who were born preterm themselves, are approximately 1.5 times (Klebanoff et al., 1997; Wilcox et al., 2007) more likely to spontaneously deliver a PT infant (Porter et al., 1997), but this association is weaker for fathers (relative risk of approximately 1.12) (Wilcox et al., 2007). In infants born before 35 weeks of gestation, the association is even stronger with maternal GA and weaker with paternal GA (1.85 and 1.06, respectively) (Wilcox et al., 2007). However, other studies have found no increased risk for preterm birth among mothers themselves born preterm (Magnus et al., 1993; Selling et al., 2006).

Furthermore, low correlation coefficient was observed for GA between family generations, since variation in GA does not appear to be influenced by genetic factors to any large degree (Magnus et al., 1993). Mothers with an older sister, who has given birth to a PT infant, had an 80 % higher risk to deliver a PT infant than mothers, whose sister delivered at term (Winkvist et al., 1998; Goldenberg et al., 2008).

Apart from genetic factors and maternal GA, racial predisposition has also been suggested as risk factor for preterm birth, as it has long been recognized with African-American and Afro-Caribbean mothers, who are more prone than Hispanic mothers, who are, in turn, more prone than Caucasian mothers (Aveyard et al., 2002; Goldenberg et al., 2008; PerkinElmer, 2009).

Preterm births seem to cluster in families through generations (transgenerational factors; Coutinho et al., 1997), as there are significant ethnic/racial differences in the incidence of prematurity that cannot be solely explained by traditional risk factors. In for the first time pregnant black women preterm birth increased from 1975 to 1990 and began to decline thereafter, so this cannot be explained by variation in socioeconomic status

(Ward et al., 2005), but with biological variation (Porter et al., 1997; Gardosi and Francis, 2000; Williams C.E.C.S. et al., 2000; Slattery and Morrison, 2002; Little, 2009), complex social factors, earlier maturity of the feto-placental unit, and vaginal flora, which is associated with either genetic differences or with different cultural patterns in relation to genital hygiene (Paz et al., 1993; Aveyard et al., 2002).

Last but not least, heritability component to preterm birth is smaller than heritability of fetal growth (Klebanoff et al., 1997; Ward et al., 2005). Clausson et al. (2000) suggested that genetics affects birth mass and gestational length, primarily through fetal growth (Klebanoff et al., 1989; Emanuel et al., 1992), which can partly be due to maternal anthropometric measures, lifestyle and medical complications during pregnancy. Again, African Americans (black ethnicity) have approximately 1.6 (Meis et al., 1998) to 2.3 (Coutinho et al., 1997) times greater incidence of LBW and greater first-year mortality rate than women of non-black ethnicity.

2.2.2 Preterm birth, stillbirth or abortion in previous pregnancy and parity

A previous history of preterm birth or delivery of a LBW infant is the strongest risk factor (Bakketeig et al., 1979; Lang et al., 1996; Porter et al., 1997; Winkvist et al., 1998; Gardosi and Francis, 2000; Williams C.E.C.S. et al., 2000; Slattery and Morrison, 2002; Wilcox et al., 2007; Little, 2009) for recurrence in the next gestation. This is especially true for early spontaneous preterm birth (Mercer et al., 1999) that contributes a notable portion of all preterm deliveries (Adams M.M. et al., 2000).

There is a tendency for repeated preterm birth to occur at the same GA as in previous pregnancies (Ananth and Vintzileos, 2006).

Preterm birth has also been associated with second trimester stillbirths, history of two or more induced abortions (thus terminations of pregnancy), spontaneous abortions, previous extrauterine pregnancies (the fertilized ovum settles and grows in any location other than the inner lining of the uterus; Voigt et al., 2010), nulliparity (no previous births) (Lang et al., 1996; Selling et al., 2006; Swingle et al., 2009), multiparity (many previous births) (Meis et al., 1995; Lang et al., 1996; Porter et al., 1997; Williams C.E.C.S. et al., 2000; Slattery and Morrison, 2002), and multiple pregnancies (i.e. more than one fetus present in a single pregnancy; presented in detail in Chapter 2.3.1) (Slattery and Morrison, 2002).

After delivery, the uterus takes time to return to its normal state, and depletion of maternal stores of essential vitamins, minerals, and amino acids due to pregnancy occurs. Interpregnancy interval of less than 6 months thus increases the risk of preterm

birth, which is far more likely in women with first preterm birth, than in women who had the first birth at term (Conde-Agudelo et al., 2006; Goldenberg et al., 2008).

2.2.3 Parental anthropometric characteristics before pregnancy

IUGR or LBW of the mother (Klebanoff et al., 1998) and father are a risk factor for IUGR and mortality at birth (Klebanoff and Yip, 1987) of their children, but the association is weaker in fathers than in mothers. Maternal and paternal birth masses may be important risk factors for preterm birth; however, in some studies no association between maternal (Kramer et al., 1992; Goldenberg et al., 2008) and paternal (Klebanoff et al., 1998) birth mass and preterm birth was observed. A risk factor for preterm birth is also when the parents are a large father and a LBW mother, as rapid fetal growth can trigger preterm labor (Bourdon and Brinks, 1982; Klebanoff et al., 1998). According to the so called conflict theory (Moore T. and Haig, 1991), fathers try to ensure maximal growth of their child, while by limiting fetal growth mothers maximize their chances of survival (Griffiths et al., 2007) during delivery.

Parental adult height may have effects on idiopathic preterm labor (Williams C.E.C.S. et al., 2000), as it affects fetal growth. Mother's MBH, in particular, is of known etiologic importance in the growth of the human fetus and is partly determined by her nutritional status during childhood. The latter may be reflected by her uterine size, placental blood flow, and the delivery of placental nutrients (Kramer et al., 1992; Williams C.E.C.S. et al., 2000). Mother's adult MBH has a stronger effect on preterm birth than paternal height (Hyppönen et al., 2004); however, there are also studies, which did not find any relation between the parental height and gestational duration (Kramer et al., 1992).

Maternal pre-pregnancy mass (PpBM) is associated with mode of delivery, preterm birth, birth mass, and maternal postpartum mass retention (Thomas A. and Duarte-Gardea, 2013). Body mass index (BMI; [kg/m^2], defined in Chapter 3.4.1.4) is the most commonly available measure of PpBM and it serves as a baseline for mass gain recommendations (Thomas A. and Duarte-Gardea, 2013). In obese women, underlying medical and obstetric (i.e. related with pregnancy, childbirth, or postpartum) issues may be the dominant cause for preterm delivery (Lammi-Keefe et al., 2008). Maternal pre-pregnancy BMI (PpBMI) on both ends of the mass spectrum (BMI >40 kg/m^2 and BMI <18.5 kg/m^2) have been observed to increase risk of preterm birth in comparison to normal BMI (18.5 to 24.5 kg/m^2) (Williams C.E.C.S. et al., 2000; Lammi-Keefe et al., 2008). Severely obese (BMI >40) women have a 1.5 times greater risk of preterm birth, in comparison with a normal mass control group (Weiss et al., 2004). Reasons for the greater risk of preterm birth in underweight and obese women may differ and have not

yet been clearly defined (Lammi-Keefe et al., 2008). Also, low BMI (related to poor nutrition) can cause preterm labor, for example in women with PpBMI <19.5 kg/m^2 and a rate of gestational mass gain (i.e. mass gained by the pregnant women during pregnancy; PMG) of <0.37 kg/week (Spinillo et al., 1997). Thus, thin women are at elevated risk of preterm birth (Kramer et al., 1992; Lang et al., 1996; Dietz et al., 2006), especially when maternal PpBM is <48 kg, and especially, if mothers are smokers (Meis et al., 1995; Spinillo et al., 1997; Selling et al., 2006). In this case the risk for preterm birth is 6.7 times greater (Weiss et al., 2004) than in non-smokers. It is worth noting, however, that other studies exist, which did not find any relations between the maternal PpBMI and gestational duration (Kramer et al., 1992; Moutquin, 2003).

Similar to the associations between parental adult height and BMI with preterm birth, associations between parental adult height and BMI with infant's birth mass can also be seen, but they are usually weaker (Hyppönen et al., 2004). Also father's adult height and BMI at age 7 may have lower (or even no) effect on infant's birth mass, in comparison to mother's height and BMI (Hyppönen et al., 2004). It has been reported that the highest incidence of FT LBW infants was observed at the critical cut-off points for maternal MBH and PpBM of <148 cm and <45 kg (Rey et al., 1995), <162 cm and <48 kg (Spinillo et al., 1997), or <155 cm and <52 kg (Gardosi and Francis, 2000; Bird, 2014). Severe maternal obesity (BMI >40) was related to 3.3 times more often pre-eclampsia than in women with normal BMI and to 2.1 times more often fetal macrosomia (Lammi-Keefe et al., 2008), which is defined as a birth mass higher than 4,000 g (Jensen et al., 2003), higher than 4,500 g (Spellacy et al., 1985), or above the 90th percentile (Jensen et al., 2003), and is sometimes referred to also as neonatal hypertrophy.

Between 1970s and 1990s mean birth mass has increased, for example, in Denmark (Ørskou et al., 2003) and Sweden (Meeuwisse and Olausson, 1998), and the number of macrosomic newborns increased from 17 % to 20 % with respect to all births. The birth of a very large or macrosomic fetus can result in adverse outcome of birth and damage to mother and infant (Spellacy et al., 1985), such as birth trauma, shoulder dystocia, childhood morbidity and mortality, and lower Apgar scores. The risk for macrosomia increases with higher maternal age, high maternal PpBM and MBH, maternal obesity, pregnancy diabetes, parity greater than 2, GA greater than 42 weeks, male infant gender, non-smokers, low caffeine intake, and 10 or more years of education (Spellacy et al., 1985; Ørskou et al., 2003).

Barker D.J. (1995) promoted the idea that prenatal conditions may have a long-lasting health consequences by articulating the so called "fetal origin hypothesis" or "Barker hypothesis" and providing some early epidemiological evidence of an inverse

relationship between birth mass and the risk of chronic disease later in life (Barker D.J., 1995). Barker was the first to link neonatal macrosomia and degenerative diseases during adolescence. It is now clear, however, that fetal macrosomia is at least as significant in causing later diseases (Briese et al., 2009). The critics of the fetal origins hypothesis claimed, that Barkers argument was too broad and unclear. In addition, the lack of experimental results and the inherent weaknesses of the observational study design used in the studies made it difficult to make causal conclusion (Song, 2013). As a response, researchers have afterwads proposed a famine-based natural experimental approach to test the fetal origins hypothesis and to isolate the causal effect of prenatal exposure of acute malnutrition on adult disease risk (Song, 2013).

2.2.4 Maternal diseases and impairments before pregnancy

As mentioned before, obesity is a risk factor for cardiovascular (CV) disease, diabetes, and other health problems, and can also affect the outcome of pregnancy. Maternal obesity increases the prevalence of gestational diabetes, impaired glucose tolerance, hypertension, thromboembolism (the combination of thrombosis and embolism), pre-eclampsia, sleep apnea, cesarean section, preterm birth, labor induction, maternal postpartum hemorrhage (Doherty et al., 2006; Thomas A. and Duarte-Gardea, 2013), maternal postpartum mass retention, (Zhong et al., 2009), fetal macrosomia, neonatal hypoglycemia, congenital anomalies, shoulder dystocia, and childhood obesity (Walters and Taylor, 2009; Zhong et al., 2009). It has therefore been proposed that, ideally, women should delay conception until they have achieved a normal mass to improve their pregnancy outcome (Thomas A. and Duarte-Gardea, 2013).

Pre-pregnancy diabetes increases the risk for poor perinatal outcomes such as retinopathy and CV disease. Congenital anomalies and increased risk of stillbirth and miscarriage are among the complications associated with hyperglycemia during pregnancy. It has therefore been suggested that conception should be delayed until optimal glycemic levels are achieved (Thomas A. and Duarte-Gardea, 2013).

Hypertension before and during pregnancy is also associated with an increased risk of preterm birth and IUGR, as it is related to obesity. It has been observed that the incidence of hypertension in pregnant teenagers is increasing, which is related to higher rates of obesity among adolescents (Thomas A. and Duarte-Gardea, 2013).

Polycystic ovary syndrome is associated with various metabolic dysfunctions, including menstrual irregularities, infertility, hyperandrogenism (i.e. a medical condition characterized by excessive levels of androgens in the body), hypertension, insulin resistance, and hyperinsulinemia. This increases the risk for developing CV disease and

the metabolic syndrome. Although most women experiencing polycystic ovary syndrome tend to be overweight (and therefore at higher risk to deliver preterm), the same condition is also seen in normal mass women with excessive abdominal fat distribution (Thomas A. and Duarte-Gardea, 2013).

Maternal phenylketonuria is an inborn metabolic disorder involving impaired metabolism of phenylalanine. It is characterized by neonatal mental retardation, microcephaly, LBW, congenital heart defects, and increased risk of delivering infants with congenital anomalies (Matalon et al., 2003), which may lead to preterm birth. The most critical period of pregnancy is in the first 10 weeks after conception, therefore phenylalanine-restricted diet is recommended for those women during the reproductive years (Thomas A. and Duarte-Gardea, 2013).

Obviously, pre-pregnancy time is rather important when studying preterm birth. Hereinafter we will focus on pregnancy and factors that affect it.

2.3 WOMEN DURING PREGNANCY

Woman's pregnancy and infants early childhood are critical periods for child's further growth and development, since the long-term regulation of energy metabolism is still being established in that period (Reilly et al., 2005). Pregnancy starts with conception (presented in detail in Chapter 2.4), after which an embryo (up to 8th week of pregnancy) and then a fetus (from the 8th week of pregnancy till birth) is being formed in woman’s uterus. Pregnancy is therefore a time of increased energy and nutrient needs for a woman to support fetal growth and development, as well as her own metabolic needs (Thomas A. and Duarte-Gardea, 2013). Many factors influence the pregnancy, of which some can be controlled and some are uncontrollable.

2.3.1 Multiple pregnancies

Multiple pregnancies result in 15 % to 20 % of all preterm births. The incidence of multiple pregnancies increased over the past 30 years, largely as a result of increased use of reproductive medicine, such as assisted conception technologies. This increase of multiple pregnancies has contributed much to the overall rise in preterm birth rates, and increased intervention to deliver twins early in the third trimester with iatrogenic induction of labor or caesarean section (Slattery and Morrison, 2002). In addition, women with a multiple pregnancy are more likely to develop pre-eclampsia, gestational diabetes, and experience preterm birth, vacuum, or forceps delivery (Thomas A. and Duarte-Gardea, 2013).

Half of all twin pregnancies, which reach 20 weeks gestation, end preterm, with 10 % being born before 28 weeks gestation, and another 10 % being born between 28 and 31 weeks. About 40 % of twins will have spontaneous labor before 37th week of gestation (Goldenberg et al., 2008) with prenatal complications including maternal hemorrhage and anemia (Thomas A. and Duarte-Gardea, 2013), probably because uterine overdistension, resulting in contractions and PPROM. Another 60 % will have an indicated preterm delivery because of pre-eclampsia, or other maternal or fetal disorders (Romero et al., 2006).

Practically all triplet pregnancies end preterm (Lumley, 2003). Triplet and quadruplet pregnancies often have higher risks for most maternal and neonatal complications than twin pregnancies (Thomas A. and Duarte-Gardea, 2013).

Interestingly, the practice of elective single embryo transfer, which is a transfer of a single fresh and one or more thawed embryos into a women, has an increased risk for preterm birth and LBW, as compared with transfer of two fresh embryos (Grady et al., 2012).

2.3.2 Parental socioeconomic status, socio-cultural factors, and physical effort

Lifestyle affects maternal and fetal health during pregnancy indirectly through unhealthy behaviors, stress or social burden, directly, through hormonal changes, and additively through psychological-immunological factors. By definition, healthy lifestyle includes no smoking, no alcohol consumption (presented in detail in Chapter 2.3.6), sports in leisure time, and vaccinations. Modern ways of life including late pregnancies, collapse of nuclear family, omission of family supports, living in large cities, social discrimination or violence experiences may therefore also cause preterm birth (Goeckenjan, 2012). And among stressed women maladaptive health behaviors such as smoking, substance abuse, and poor mass gain during pregnancy are more prevalent (Copper et al., 1996).

Age of pregnant women can influence the duration of pregnancy. Incidence of preterm birth in white women is the lowest between 20-24 years of age, but increased number of adolescent (less than 18 years of age) and late (greater than 30 years of age) pregnancies have both increased rates of LBW (Delbaere et al., 2007; Shrim et al., 2011) and preterm birth (Meis et al., 1995; Lang et al., 1996; Porter et al., 1997; Gardosi and Francis, 2000; Williams C.E.C.S. et al., 2000; Slattery and Morrison, 2002; Selling et al., 2006; PerkinElmer, 2009; Bird, 2014). Second adolescent births (much more than the first) are also associated with a highly increased risk for preterm birth (Adams M.M.

et al., 2000; Slattery and Morrison, 2002). As expected, paternal age was not reported to be a risk factor for a preterm birth (Marakoglu et al., 2008).

It has been demonstrated that the most important epidemiological risk factor for preterm birth and IUGR is parental socioeconomic status (Slattery and Morrison, 2002; Selling et al., 2006). Lower social class is usually associated with lower education (Voigt et al., 2004; Selling et al., 2006), low income, or unemployment (Rodrigues and Barros, 2008), is reflected in worse nutritional status, worse hygiene, single marital status (Zeitlin et al., 2001; Selling et al., 2006), higher levels of adverse psychological factors (stress, anxiety, mental diseases, and depression) (Porter et al., 1997; Williams C.E.C.S. et al., 2000; Slattery and Morrison, 2002; Little, 2009), help from professional agencies, little contact with neighbors, and increased frequency of cigarette smoking and recreational drug (such as cocaine) use (Paneth, 1995; Peacock et al., 1995); all these factors were also associated with increased risk of preterm birth.

However, in contrast to the above, some studies demonstrated that low education (Joseph et al., 2007), low family income (Kramer et al., 2000), and low social support from the professional agencies (Dole et al., 2003) do not or do only slightly increase the risk for preterm birth (Goeckenjan, 2012). Also, marital status does not directly influence the preterm birth, as non-married couples are very common nowadays (Zeitlin et al., 2001), but a low increase of risk for preterm birth has been reported for single mothers (Zeitlin et al., 2001).

In studies dating to the 1960s, psychosocial measures have been examined as possible risk factors contributing to adverse birth outcomes. Although the quality of studies has improved, evidence for such associations still remains equivocal. Psychosocial factors and critical life events such as stress, (pregnancy-related) anxiety, mental diseases, depression, death in the family, health problems of other children, partnership problems, divorce (Goeckenjan, 2012), unplanned pregnancy (Messer et al., 2005), housing instability, severe material hardship, and self-esteem have been associated with increased rates of prematurity (Copper et al., 1996; Hedegaard et al., 1996; Nordentoft et al., 1996; Goldenberg et al., 2008;), suggesting a role of corticotrophin releasing hormone and increased serum concentrations of inflammatory markers (Goldenberg et al., 2008). Psychological or social stress is more common in women who are black, poor, undernourished, and undereducated. Depression was associated with increase in smoking, drug and alcohol use, and with reduction in natural killer cell activity, higher plasma concentrations of proinflammatory cytokines and their receptors (Goldenberg et al., 2008). Different levels of depression or social support, especially that provided by the father, are important parameters for psychological wellbeing (Dole et al., 2003).

However, in some studies depression or social support were not associated with preterm birth (Dole et al., 2003).

Higher risk for preterm birth is present in the society with discrimination (Dole et al., 2003; Goeckenjan, 2012). Women's perception of discrimination or stress from the neighborhood, unfavorable ratings of neighborhood, and an overall constellation of poor psychosocial attributes increased the risk of preterm birth (Dole et al., 2003). For women with migration history, there was no significant risk for preterm birth observed in Netherlands (Goedhart et al., 2008) and Germany (David et al., 2006), but a research from Italy (Cacciani et al., 2011) reported increased risk for preterm birth for different migrants, with high levels observed especially for Africans. For many USA immigrant groups it has been clearly demonstrated, that the longer the time spent living in the USA for an individual, the higher the preterm birth rate (Goldenberg et al., 2008).

One of the factors that increase the risk for prematurity is also abuse. Abuse directed at pregnant women is recognized as a significant societal and public health issue. Canadian studies suggest that 5.5 % to 6.6 % of women are abused during pregnancy (Stewart and Cecutti, 1993; Muhajarine and D'Arcy, 1999). Namely, women who reported physical (Amaro et al., 1990; Berenson et al., 1994; Curry et al., 1998; Campbell et al., 1999), sexual, or emotional abuse during pregnancy were more likely to give birth to LBW (Murphy et al., 2001) or PT infants (Rodrigues et al., 2008) than non-abused women. Abuse may be part of a complex interaction of factors that contribute to prematurity (Murphy et al., 2001), as violence during pregnancy increases the risk for low maternal mass gain and infections (Wijma et al., 2007; Goeckenjan, 2012). However, some studies have found no influence of abuse on preterm birth on its own (Wijma et al., 2007; Goeckenjan, 2012).

As the existence of association between strenuous physical activity and preterm labor is still questionable, until the impact is fully studied women at risk for preterm labor are advised to reduce their activity in the second and third trimester (Hale and Milne, 1996). For most pregnant women who do not have medical or obstetric risks at least 30 minutes of moderate-intensity physical activity is recommended on most, if not all, days of the week (Thomas A. and Duarte-Gardea, 2013). Physical activity is contraindicated in conditions such as restrictive lung disease, incompetent cervix, multiple gestation, rupture of membranes, placenta previa (an obstetric complication in which the placenta is inserted partially or wholly in the lower uterine segment), and premature labor (Thomas A. and Duarte-Gardea, 2013), as it may increase uterine activity (contractions). However, in some studies no effect of exercise during the last 8 weeks of pregnancy on increased uterine activity was observed (Veille et al., 1985) and the level of physical activity has not been observed to be consistently related with preterm birth

(Goldenberg et al., 2008). Or even more, physical activity during pregnancy, and especially in the 7th month, has been inversely related to the risk of preterm birth (Savitz et al., 1997).

When strenuous physical activity is associated with dietary restrictions, IUGR can develop (Hale and Milne, 1996). It is therefore not surprising that moderate physical activity during pregnancy may reduce the risk of having a large-for-gestational age (LGA) infant (Ørskou et al., 2003). Meanwhile, other studies on vigorous exercise observed either no effect (Sternfeld et al., 1995) or even an increase in infant birth mass (Hatch et al., 1993; Lammi-Keefe et al., 2008).

Physically demanding work during pregnancy was reported to be associated with increased risk of SGA (Naeye and Peters, 1982; McDonald et al., 1988; Launer et al., 1990) and preterm birth (Goldenberg et al., 2008; Rodrigues and Barros, 2008). In contrast, some studies demonstrated that physically demanding work during pregnancy (Goffinet, 2005; Both et al., 2010) does not or does only slightly increase the risk for preterm birth (Goeckenjan, 2012).

2.3.3 Prenatal care and nutrition

One of the contributing factors to the poor pregnancy outcome is the date when a woman enters prenatal care, which includes nutritional counseling for normal pregnancy. If prenatal care does not begin until late in the first trimester or in the second or third trimester, the delay may result in serious health consequences for the mother and her infant (Thomas A. and Duarte-Gardea, 2013).

The quality of maternal nutrition prior and during gestation is very important for the growth of human fetus (Kramer et al., 1992; Thomas A. and Duarte-Gardea, 2013). Maternal malnutrition, especially during the first trimester, a critical period of fetal development, may predispose the infant to chronic diseases in adulthood (Thomas A. and Duarte-Gardea, 2013). Chronic diseases, such as coronary heart disease, hypertension, and type II diabetes, may originate in impaired intrauterine growth and development (Godfrey and Barker, 2000, 2001). Unbalanced nutrition with too little or too much calories, and too rare meals are the cause for preterm contractions (Goeckenjan, 2012). The energy allowance for pregnancy can be estimated by dividing the gross energy cost (80,000 kcal) by the approximate duration (266 days), yielding an average value of additional 300 kcal per day (Thomas A. and Duarte-Gardea, 2013).

Considerable work has been focused on the relationship between anemia, iron deficiency, and birth outcomes, such as prematurity and IUGR. Based on several

observational studies, there is an increased risk of delivering a PT and/or LBW infant for women, who are anemic, as compared to those who are not. Severe maternal anemia has been associated with an increased risk of stillbirth and infant mortality (Brabin et al. 2001; Lone et al., 2004). Interestingly, a U-shaped relationship has been observed between hemoglobin levels and birth mass; obviously, the risk of delivering a LBW infant is increased at, both, the lower and the upper end of hemoglobin distribution. It is important to have in mind, however, that the mechanisms may differ (Lammi-Keefe et al., 2008). Specifically, the increased risk for IUGR and preterm birth at the upper end of hemoglobin levels may not be due to excess iron, but it may rather represent an inadequate plasma volume expansion (Yip, 2000).

Apart from optimal iron intake, all women of reproductive age, regardless of whether they are already pregnant or not, are advised to take 400 μg of folic acid daily through fortified foods and/or supplements (Thomas A. and Duarte-Gardea, 2013). Folate is a water-soluble vitamin required for cell division and normal growth – it is required for the formation of red blood cells and expansion in the number of red blood cells for maternal and fetal circulation (Cunningham F.G. et al., 1993). Restricted folate intake during pregnancy has been associated with poor pregnancy outcomes including preterm birth, LBW, IUGR (Scholl and Johnson, 2000), and neural tube defects, which include incomplete closing of the embryonic neural tube and not fully formed vertebrae overlying the spinal cord, causing a portion of the spinal cord protruding through the opening in the bones (spina bifida) or non-closure of a portion of the neural tube that should become the cerebrum (anencephaly). Biochemical indicators of depleted maternal folate status have been linked to increased spontaneous abortion and pregnancy complications (abruption placenta or placental infarction with IUGR and pre-eclampsia), which increase the risk of LBW and preterm birth (van der Molen et al., 2000; Vollset et al., 2000; Lammi-Keefe et al., 2008).

Eating disorders are psychiatric diseases characterized by disordered eating habits and excessive focus on body mass. Relatively common in women are anorexia and bulimia nervosa (Hovi et al., 2007) and they present high-risk situation during pregnancy. These conditions have been associated with poor energy, poor nutrient intakes, and electrolyte imbalances. Inadequate or excessive mass gain, spontaneous abortion, stillbirth, IUGR, preterm birth (Sollid et al., 2004), delayed fetal growth and LBW, among other adverse outcomes, have been reported in pregnant women with anorexia nervosa and bulimia nervosa and their offspring (Lammi-Keefe et al., 2008; Thomas A. and Duarte-Gardea, 2013).

Nutritional status during pregnancy, as throughout life, results in body size and BMI. Maternal thinness is associated with decreased blood volume (Neggers and Goldenberg,

2003) and reduced uterine blood flow (Neggers and Goldenberg, 2003). Thin women usually consume fewer vitamins and minerals, which decreases blood flow and can increase maternal infections. Obesity can be protective in this respect, but can result with congenital anomalies of infants (neural tube defects), and can increase pre-eclampsia and diabetes, which can lead to preterm birth (Goldenberg et al., 2008).

2.3.4 Maternal physical characteristics during pregnancy

It has been reported that physical properties of pregnant women and their partners (birth mass, body height, body mass, and body composition) predict some of the physical characteristics of their infants (body height, body mass, and body composition) at birth and later in life (Alberman et al., 1992; Kramer et al., 1992; Magnus et al., 1993; Hyppönen et al., 2004; Griffiths et al., 2007; Euser et al., 2008; Klebanoff, 2008). Other studies suggest that fetal growth has a familial, probably genetic, component that is independent of the mother's adult size (Klebanoff et al., 1997). Maternal MBH, her pregnancy BMI, and inappropriate PMG can strongly increase the risk of inappropriate physical height of the infant, and can also increase the risk of subsequent disease (Oken and Gillman, 2003). Infants that are heavy and long at birth, usually become the heaviest adults. Some of them are infants of mothers with diabetes or excessive mass gain during pregnancy (Eide et al., 2005).

Studies have demonstrated that increased maternal BMI, both, before and during pregnancy, and PMG have independent impacts on fetal growth and increase the risk for too high birth mass of the infant (Kramer et al., 1992; Lang et al., 1996; Brown et al., 2002). In contrast, low PMG in combination with low PpBMI is a well-established risk factors for delivering before term (Dietz et al., 2006; Little, 2009). Namely, as mentioned in Chapter 2.2.3, PpBMI <19.5 and a rate of PMG <0.37 kg/week can cause increased risk of spontaneous preterm birth (Spinillo et al., 1997). Mewitz et al. (2012) also reported that small PMG may be associated with higher rates of preterm birth. Studies have suggested that BMI of pregnant women determines fetal growth from mid-pregnancy onwards (Ay et al., 2009).

PMG represents two entities, the products of conception (fetus, placenta, amniotic fluid) and maternal tissues (expansion of blood and extracellular fluid, uterus, mammary glands, and adipose tissue) (Picciano, 2003; Figure 2). Evidence for an effect of excessive pregnancy mass gain on preterm birth has been rather equivocal. Although PMG goals were suggested to be based on the women's PpBMI (IOM, 1990), women with very high mass gain had approximately twice the odds of very preterm birth, regardless of their PpBMI (Dietz et al., 2006). Classifications of PMG differ substantially, depending on whether percentiles calculated from the total study

population or group-specific percentiles are used (Voigt et al., 2013). It is still recommended, however, that a woman with a normal PpBMI of 19.8-26 kg/m^2 gains approximately 11-16 kg (1.6 kg in the first trimester and approximately 0.5 kg per week later on in pregnancy) (Hillhouse and Neiger, 2001). Women with PpBMI lower than 19.8 are suggested to gain approximately 13-18 kg (2-2.5 kg in the first trimester and a little more than 0.5 kg per week later on in pregnancy) (Hillhouse and Neiger, 2001). Women with PpBMI between 26 and 29 should gain approximately 7-11 kg (1 kg in the first trimester and slightly less than 0.5 kg per week later on in pregnancy) (Hillhouse and Neiger, 2001). Obese women (PpBMI>29) are recommended to gain at least 7 kg during pregnancy (Hillhouse and Neiger, 2001; Lammi-Keefe et al., 2008).

2.3.4.1 Body composition of pregnant women

Body composition assessment is often used when nutrition status or metabolism are being determined, or when effects of an intervention that is expected to alter body composition is being studied. Assessment of an individual's body composition allows us to more precisely classify obesity status (Zdesar Kotnik and Golja, 2012) and can point out diet-associated problems (Huston Presley et al., 2000). This is important particularly in overweight subjects or during special periods of life, for example during pregnancy.

Pregnancy is a time of physiological stress and maternal body adapts to be able to handle it (Jansen et al., 1984). It is generally accepted that during pregnancy body mass of an average healthy woman changes, because of fetal and gestational tissue growth (Rasmussen K.M. and Yaktine, 2009), as well as due to additional maternal body fat (Rasmussen K.M. and Yaktine, 2009) which accumulates especially around mid-pregnancy (Figure 2) (Taggart et al., 1967). As pregnancy progresses, protein, fat, water, and minerals are deposited in the fetus, placenta, amniotic fluid, uterus, mammary gland, blood, and adipose tissue (Figure 2). The products of conception (placenta, fetus, amniotic fluid) contribute to approximately 35 percent of the total gestational mass gain (Pitkin, 1976). The extent to which these changes in body composition are critical for normal fetal development or are incidental to pregnancy is not completely understood (Rasmussen K.M. and Yaktine, 2009).

Body fat accumulation alters body composition and, if excessive, may lead to pregnancy diabetes, high blood pressure, or other complications (Jensen et al., 2005; Ay et al., 2009). These changes can affect fetus's maturation (Reilly et al., 2005), therefore information on changes in body fat content is of importance in studies of interrelations between mother's and child's health (Forsum et al., 1989).

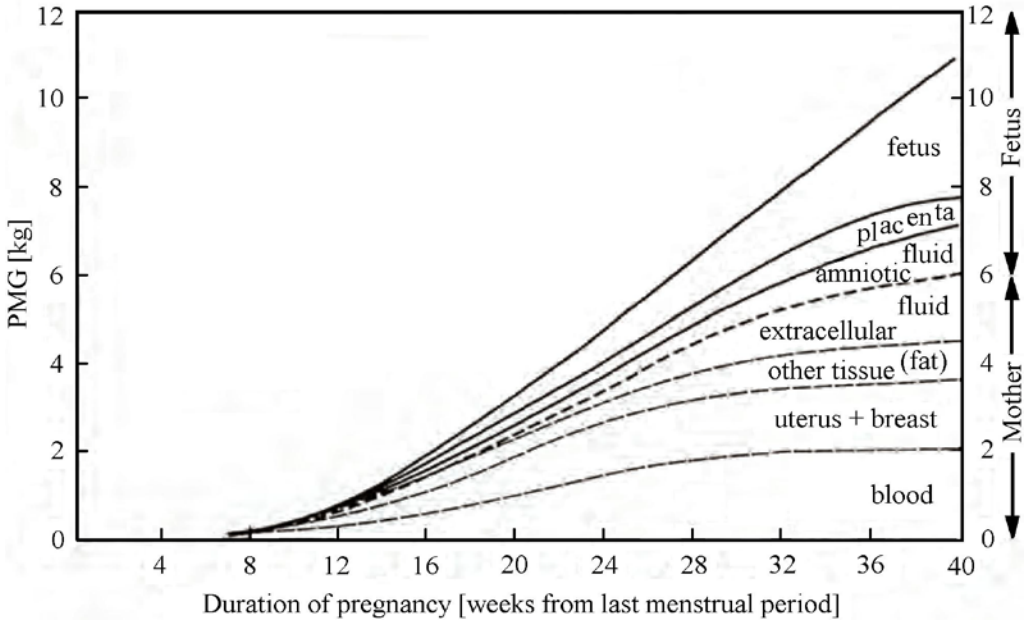


Figure 2: Pattern and components of maternal pregnancy mass gain (PMG) (Pitkin, 1976)

Slika 2: Vzorec in komponente pridobivanja mase matere v nosečnosti (PMG) (Pitkin, 1976)

Although numerous studies (van Raaij et al., 1988; Catalano et al., 1995; Paxton et al., 1998; Huston Presley et al., 2000) have already dealt with changes in body fat content during pregnancy and their physiological consequences, precise determination of body fat content in pregnant women remains challenging for several reasons discussed below.

Several techniques for body composition assessment, such as dual-energy X-ray absorptiometry (DEXA) or computer tomography, are only rarely applied during pregnancy (Cunningham J.L. et al., 1996), because they can be dangerous to the fetus (To W.W.K. et al., 2003). Methods such as near infrared and magnetic resonance imaging also use sophisticated equipment (Paxton et al., 1998) that is often not available for routine use.

Some reference methods for body composition assessment (underwater weighing) assume a constant amount of muscle tissue in longitudinal measurements, which is not necessarily true during pregnancy (Paxton et al., 1998). Namely, because woman's physical activity can change considerably throughout pregnancy, errors in longitudinal body composition assessments can follow.

Not much reliable information is available on women's body composition during pregnancy, as only limited number of epidemiological studies exist (van Raaij et al., 1988; Catalano et al., 1995; Paxton et al., 1998; Huston Presley et al., 2000). The majority of these studies were performed on rather small or selected samples (Ay et al.,

2009), or on the basis of questionnaires (Jensen et al., 2005; Frederick et al., 2008), so those data may be inaccurate or untrue (Ay et al., 2009).

Anthropometry, which seem to be the method of choice during pregnancy, usually rely on skinfold thickness measurements. During pregnancy, changes in body shape affect skin tension and make measurements of skinfolds challenging, especially in the abdomen region. Consequently, only few anthropometric methods can realistically be applied during pregnancy.

The existing anthropometrical methods for body composition assessment were often developed for use in non-pregnant women (Durnin and Womersly, 1974; Jackson et al., 1980; Slaughter et al., 1988; Deurenberg et al., 1991; Rush et al., 1997; Peterson et al., 2003), and only rarely specifically for pregnant women (van Raaij et al., 1988; Catalano et al., 1995; Paxton et al., 1998). This lack resulted in frequent use of pregnancy non-specific methods (Butte et al., 1981; Atalah et al., 1997; Thame et al., 2007; Hronek et al., 2010), which can reduce the validity of results.

The precision of anthropometric measurement technique can be assessed by calculating the technical error of measurement (TEM), which indicates the degree to which the measurement departs from the true value (it is expressed in the same units as that of the anthropometric measurement). To overcome the difficulty of TEM being dependent on the size of original measurement (Gibson, 2005), the percentage TEM (% TEM) and coefficient of reliability (R) can be used. % TEM of the measurement is analogous to the coefficient of variation; it has no units and can be used to make direct comparison of all types of (anthropometric) measurements (Gibson, 2005). R indicates the proportion of between-subject variance in a measured population, which is free from measurement error (Gibson, 2005). Thus, a measurement with $R>0.95$ indicates that more than 95 % of the variance is due to factors other than measurement error (Gibson, 2005).

Although methodological details differ between different existing anthropometric methods, the basic approaches remain similar, as the measurement data are used in equations that more or less correctly associate these measurements with an estimate of body fat content (Paxton et al., 1998). Most anthropometric methods in general rely on the fact that water contributes around 72 % of lean body mass, whereas fat mass is considered as water-free tissue (Huston Presley et al., 2000). Fat content of the human body cannot be measured directly in vivo, therefore the relevant estimates of density of lean body mass 1.1 g/m^2 and fat mass 0.9 g/m^2 ("standard body") are the basis for the assessment of body composition in vivo in humans (Huston Presley et al., 2000).

Some of the existing methods use anthropometrical measurements to first calculate body density and second determine body fat amount from the latter (indirect methods (Siri, 1961; Brožek et al., 1963; van Raaij et al., 1988; Catalano et al., 1995)). Other methods use anthropometric measurements for direct calculation of body fat percentage (direct methods (Slaughter et al., 1988; Deurenberg et al., 1991; Rush et al., 1997; Paxton et al., 1998; Peterson et al., 2003; Steinkamp et al., 1965)). As different equations use different anthropometrical measurements, they by default give somewhat different result.

Although some pregnancy specific anthropometric methods have been developed up to date (van Raaij et al., 1988; Catalano et al., 1995; Paxton et al., 1998), they have not yet been systematically compared to other widely used anthropometric methods. Consequently, no information is available at the moment on how big the differences in estimates of body fat content obtained by different methods really are. Should pregnancy non-specific methods give considerably different estimates of body fat content than pregnancy specific methods, their application on pregnant women should be questioned (Robič et al., 2013).

2.3.5 Maternal diseases and impairments during pregnancy

Maternal medical risk factors for preterm birth are müllerian duct (i.e. the origin tube for development of female reproductive organs) abnormality, proteinuria (i.e. the presence of excess serum proteins in urine) prior to 24 week of gestation, history of chronic hypertension, of previous induced or spontaneous preterm births, and of lung disease (Meis et al., 1998). Other factors include loop electrosurgical excision of the cervix for cervical intraepithelial neoplasia, which is a potentially premalignant transformation and is characterized by the abnormal growth of squamous cells on the surface of the cervix (Noehr et al., 2009).

Maternal infections arising at a preterm period can trigger onset of labor (Meis et al., 1995; Slattery and Morrison, 2002). Important factors resulting in maternal infections are maternal diseases, such as localized infections of the genital and urinary system, poor oral hygiene, viral respiratory infections, diarrhea, and malaria (Andrews et al., 1995; Williams C.E.C.S. et al., 2000; Little, 2009).

Causes for preterm birth can also be infections of amniotic fluid (Frühgeburt, 2012), where microorganisms can reach the amniotic sac (the sac of amnion and chorion in which the fetus develops) by different ways (Mylonas and Friese, 2012). Bacteria may invade the uterus by migration from the abdominal cavity through the fallopian tubes, inadvertent needle contamination at the time of amniocentesis or chorionic-villus

sampling, hematogenous spread through the placenta, or passage through the cervix from the vagina (Goldenberg et al., 2000). Bacterial infections within the uterus can occur between the maternal tissue and the fetal membranes, within the fetal membranes, within the placenta, within the amniotic fluid, or within the umbilical cord or the fetus. Preterm birth may occur in association with leukocytosis (i.e. the leukocyte amount above the normal range in the blood, which is frequently a sign of inflammatory response) of the amniotic fluid (Goldenberg et al., 2000). It has been suggested that bacterial infection that spreads to the uterus and amniotic fluid may trigger inflammation that results in the release of inflammatory cytokines and prostaglandins (Mylonas and Friese, 2012) and consequently in PPROM and cervix maturing. Chronic intrauterine infections even between pregnancies can cause repeated spontaneous preterm deliveries. The most common organism of bacterial vaginosis and intrauterine infections are *Mycoplasma hominis, Ureaplasma urealyticum, Gardnarella vaginalis*, and *Bacteroides* species (Goldenberg et al., 2000; Slattery and Morrison, 2002).

Goldenberg et al. (2000) reported that up to 80 % of women, who deliver before 30 weeks of gestation, have evidence of bacterial infection of the amniotic fluid and/or membranes, which is a far higher rate, as compared to only 30 % of those, who deliver after 37 weeks of gestation. In Germany, approximately 40 % of all preterm births are initialized by infections (Mylonas and Friese, 2012). More black women have bacterial vaginosis, histologically or clinically diagnosed chorioamnionitis (inflammation of the fetal membranes), and postpartum endometritis (inflammation of the endometrium), which may, in part, explain higher rates of preterm deliveries in blacks, as compared to women from other racial groups in the USA (Goldenberg et al., 1996).

There is growing evidence showing that a number of complex human diseases are caused or are at least influenced by periodontal diseases (periodontitis) (Marakoglu et al., 2008). Such diseases include CV and respiratory diseases, diabetes mellitus and osteoporosis (Marakoglu et al., 2008). Inflammatory mediators of periodontal disease (together with bacterial vaginosis) play an important part in the initiation of labor (Williams C.E.C.S. et al., 2000; Vergnes and Sixou, 2007; Marakoglu et al., 2008). Periodontitis represents a previously unrecognized and clinically significant risk factor resulting in either preterm labor or PPROM (Offenbacher et al., 1996). It is a source of Gram-negative anaerobic organisms and bacterial components that can occur in women of childbearing age (18 to 34 years) (Offenbacher et al., 1996) and can release immune modulators such as prostaglandin E_2 and $TNF_{-\alpha}$ (Marakoglu et al., 2008).

Sexually transmitted diseases (*Trichomonas, Chlamydia, Neisseria,* and syphilis) and other genital pathogens (bacterial vaginosis, asymptomatic bacteriuria, *Trichomonas*

infections, and some systemic maternal infections) have been associated with intrauterine infections and premature birth (Mylonas and Friese, 2012).

Vulnerable group are also HIV-infected pregnant women, as they tend to gain less mass during pregnancy, which puts them at high risk for complications (WHO, 2005). Additionally, HIV infection is often associated with wasting and a progressive loss of body mass (Wanke et al., 2003) and, as discussed previously, mass loss or suboptimal mass gain during pregnancy is related to increased risk of IUGR (Picciano, 2003), fetal death, preterm birth, and LBW infants (Brocklehurst and French, 1998; Villamor et al., 2004; Lammi-Keefe et al., 2008).

Pregnant women experiencing diabetes, hypertension, and pre-eclampsia require individualized dietary modification. Gestational diabetes is defined as glucose intolerance occurring during pregnancy and is associated with fetal macrosomia (as already mentioned in Chapters 2.2.3 and 2.2.4), obese infants (Singhal and Lucas, 2004; Ong, 2006), LGA infants, and increased risk of a difficult labor and birth. Gestational hypertension is defined as a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg. Many women with gestational hypertension diagnosed before 30 weeks gestation develop pre-eclampsia. Risk factors for the development of pre-eclampsia include pre-eclampsia in a previous pregnancy, maternal age of less than 20 years or higher than 40 years, obesity, insulin resistance, diabetes, and genetic factors (Kaiser et al., 2002). The cause for pre-eclampsia may be an inadequate placental blood supply, probably due to maternal hypertension, which causes placental oxidative stress and the release of placental factors into maternal circulation that trigger an inflammatory response. The incidence of pre-eclampsia is greater in twins than in single births (Kametas et al., 2003) and is associated with preterm birth, LBW infants, neonatal death, maternal morbidity and mortality, and an increased risk of developing CV diseases later in life (Thomas A. and Duarte-Gardea, 2013). Hypertensive disorders during pregnancy are a leading cause of maternal mortality and are also associated with an increased risk of preterm birth and IUGR (Roberts et al., 2003).

Nutrients and oxygen from the mother and thus maternal diet in pregnancy may program the infant (Williams C.E.C.S. et al., 2000), as the fetus can adapt to undernutrition by modifying metabolism, which can in turn change the rates of hormone production and diminish the growth rate (Barker D.J. et al., 1993). Suboptimal nutritional management in PT infants during a critical or plastic early period of rapid brain growth could impair functional compensation (Lucas et al., 1998).

Cervical shortening and insufficiency is a risk factor for preterm birth (Goldenberg et al., 2008). Screening for spontaneous preterm birth therefore relies on a combination of maternal factors and measurement of cervical length at 20 to 24 weeks (Iams et al., 1996; Heath et al., 1998; To M.S. et al., 2006; Celik et al., 2008) although the endocervical length was already reduced at 11-13 weeks in pregnancies delivering preterm (Greco et al., 2011).

Biological fluids (amniotic fluid, urine, cervical mucus, vaginal secretions, serum or plasma, saliva) have been used to assess the value of biomarkers for the prediction of preterm birth. These include cytokines, chemokines, estriol, fetal fibronectin, and some other substances related to inflammation (Goldenberg et al., 2008). Cytokines are small proteins (~5–20 kDa) that are important in cell signaling and are produced by immune cells, endothelial cells, fibroblasts, and various stromal cells. Chemokines are small cytokines that induce directed chemotaxis in nearby responsive cells (they are therefore also reffered to as chemotactic cytokines). Beside estrone and estradiol, estriol is the main estrogen produced by the human body. Fetal fibronectin present in cervicovaginal fluid is a marker of preterm birth and disruption of choriodecidual interface (Goldenberg et al., 2008), which is the space between the chorionic plate and the endometrium (maternal part of the placenta).

Fetal fibronectin measurements and transvaginal cervical length measurements (Iams et al., 1996) are expensive tools, require training, and can be used only under certain clinical circumstances. Namely, fetal fibronectin determination cannot be performed when the cervix is dilated 3 cm or more, when membranes have ruptured, or after a digital cervical examination (Bastek et al., 2012). Similarly, cervical length measurement is not predictive of preterm birth risk when the cervix is dilated 2 cm or more, is inaccurate, if not performed very precisely, and is generally most useful for predicting future rather than imminent preterm birth (Iams et al., 1996; Bastek et al., 2012).

2.3.6 Toxic exposure

Lifestyle factors, dietary habits, and teratogens (such as cigarette smoking, narcotic use, high alcohol intake, and caffeine consumption) are highly prevalent in the society, and, according to some studies, may be responsible for SGA (Kramer et al., 1992; Fortier et al., 1993; Williams C.E.C.S. et al., 2000) and very preterm birth (Peacock et al., 1995; Goldenberg et al., 2008; Little, 2009). Not all studies are equivocal, however, as some did not reveal any effects of these factors on preterm birth (Peacock et al., 1995; Slattery and Morrison, 2002).

Teratogens are agents that can harm a developing fetus by causing deformities, blindness, brain damage, or even death. Most likely they produce major structural abnormalities between the 3rd and 8th gestational week; however, many organs and body parts remain sensitive to teratogenic agents throughout the whole pregnancy. The main critical periods of prenatal development for defects are presented in Figure 3.

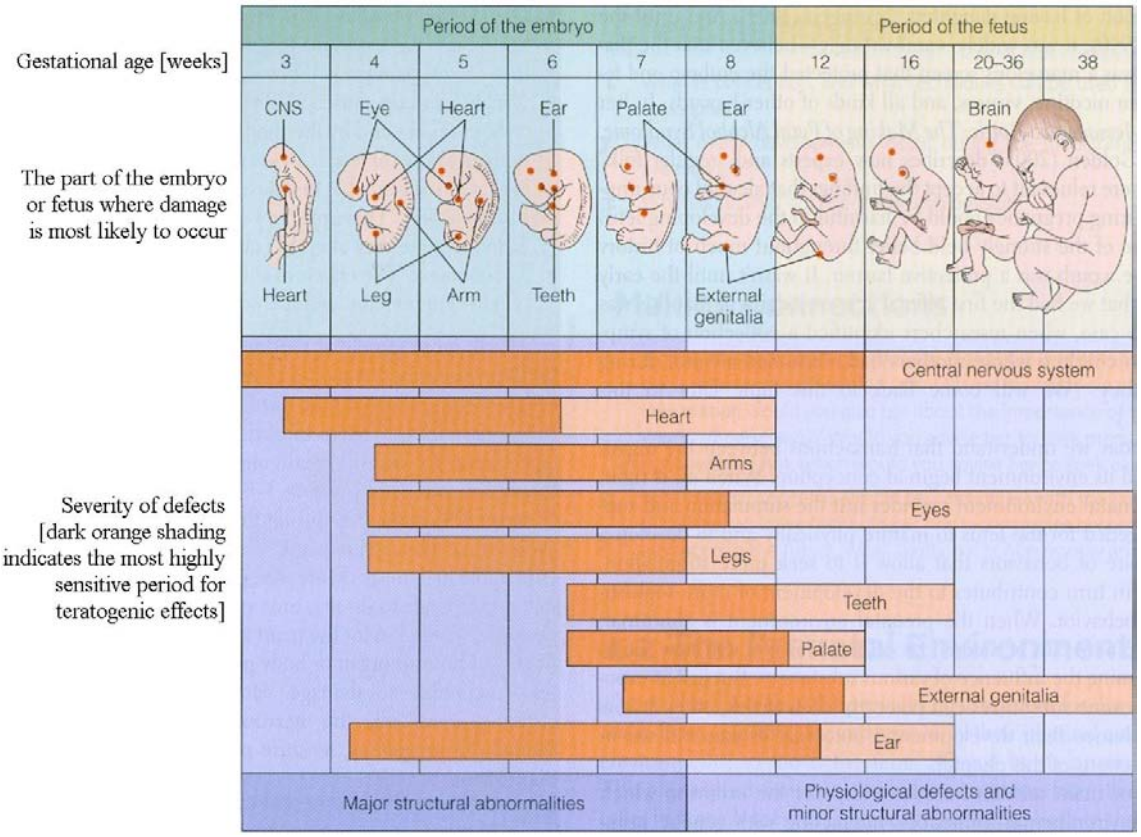


Figure 3: The critical periods for teratogene influences in prenatal development (CNS – central nervous system) (Moore K.L. et al., 2013)

Slika 3: Kritična obdobja za vplive teratogenov v prenatalnem razvoju (CNS – centralni živčni sistem) (Moore K.L. in sod., 2013)

2.3.6.1 Smoking and substance abuse during pregnancy

Maternal cigarette smoking is one of the greatest risks of preterm birth, and also one of the most controllable (Bird, 2014). It was early pointed out as s risk factor for preterm birth (Bird, 2014). Nevertheless, prenatal **s**moking remains a common habit and accounts for a significant proportion of fetal morbidity and mortality through a direct (fetal) and indirect (placental) effect (Salihu and Wilson, 2007; Bergmann et al., 2008). Effects of smoking on the fetus include IUGR, LBW, and sudden infant death syndrome (Thomas A. and Duarte-Gardea, 2013).

Smoking in pregnancy induces early morphological changes of the placenta (abruption placentae, placenta previa and PPROM (Salihu and Wilson, 2007)), a reduced volume of maternal intervillous space, and volume and surface area of fetal capillaries, leading to reduced oxygen diffusion, and chronic fetal hypoxic stress (Bergmann et al., 2008), spontaneous abortion, and gestational bleeding (not in Salihu and Wilson, 2007). Tobacco use increases preterm birth due to vasoconstrictory function of nicotine and carbon monoxide, which are associated with placental damage and decreased utero-placental blood flow, as well as with systematic inflammatory response (Goldenberg et al., 2008). Intrauterine growth is influenced by fetal hypoxia (due to increased carboxy-haemoglobin levels) and maternal catecholamine levels are increased by nicotine and cyanide compounds in tobacco that interfere with fetal oxidative metabolism (Lessa Horta et al., 1997). These conditions are long-term risk factors for the reduction of head circumference, abdominal circumference, and femur length, as well as for obesity, behavioral disorders, asthma, and immunological diseases (Bergmann et al., 2008).

Direct dose-response association between the number of cigarettes smoked per day and the risk of IUGR (Lessa Horta et al., 1997) and preterm birth, especially spontaneous preterm birth (Gao et al., 2006), was found. There also exists an inverse relationship between the birth mass and number of cigarettes smoked during pregnancy (Bergmann et al., 2008), as birth mass was 10-12 g lower for every cigarette smoked per day during pregnancy in infants of smoking mothers, as compared to infants of non-smoking mothers (Papoz et al., 1982). A similar relationship was also reported by Voigt et al. (2006) and Krentz et al. (2011). In some other studies, however, smoking was not confirmed as a risk factor for preterm birth, unless there was a concomitant IUGR (Lessa Horta et al., 1997; Gao et al., 2006; Marakoglu et al., 2008; Goeckenjan, 2012).

One of the strongest confirmations for the effect of smoking on preterm birth was the fact that rates of preterm birth and LBW infants were reduced among women who stopped smoking in the first trimester (Meis et al., 1995; Lessa Horta et al., 1997; Kyrklund-Blomberg and Cnattingius, 1998; Gardosi and Francis, 2000; Selling et al., 2006; Salihu and Wilson, 2007; Bergmann et al., 2008). It has been suggested that detoxification of nicotine, cotinine, and other smoke-related toxic substances may be less effective in female fetuses (Voigt et al., 2006); therefore, termination of smoking before pregnancy is recommended (Thomas A. and Duarte-Gardea, 2013).

IUGR and preterm birth can be caused by other substance abuse (such as drugs, amphetamine, cocaine, marijuana), too (Gouin et al., 2011; Ladhani et al., 2011; Goeckenjan, 2012; Hayatbakhsh et al., 2012). Research on substance misuse revealed that women, who use multiple drugs, often experience preterm labor. This was particularly true for cocaine (Paneth, 1995), although it was not observed in all studies

(Goeckenjan, 2012). Misuse of marijuana during pregnancy was associated with small decrements in fetal birth mass, but was not apparently associated with preterm birth (Slattery and Morrison, 2002).

2.3.6.2 Alcohol consumption during pregnancy

Alcohol and tobacco consumption are often closely correlated (Voigt et al., 2006). Alcohol crosses the placental barrier and can cause fetal growth or mass restriction, distinctive facial stigmata or other physical damage, and can damage neurons and brain structures, which can result in intellectual disability and other psychological or behavioral problems (Ulleland, 1972). Alcohol abuse, even in small amounts, has been associated with increased risk of abortion or stillbirth, but not for preterm birth (Patra et al., 2011). Prenatal exposure to alcohol is the leading cause of otherwise preventable birth defects and developmental disabilities. Risks to the fetus due to maternal alcohol consumption include spontaneous abortion, IUGR, central nervous system and facial malformations, and mental retardation. The term fetal alcohol spectrum disorder describes a range of effects that can occur in the fetus due to alcohol exposure in uterus. Fetal alcohol syndrome (FAS) is the most commonly known of them and describes the condition in which permanent central nervous system is damaged and other before mentioned consequences of alcohol consumption occur. There seems to be no safe level of alcohol consumption during pregnancy, thus women who are pregnant or who may become pregnant should abstain from alcohol use (Thomas A. and Duarte-Gardea, 2013), however, no firm agreement within the scientific community has yet been reached on the topic of “safe” alcohol use during pregnancy (Humphriss et al., 2013).

2.3.6.3 Toxic environmental factors

Fetuses are sensitive to damage by a variety of environmental toxicants (Perera et al., 1999) and the public health implications of exposure can be serious. Therefore, some environmental factors that contribute to reduced birth mass are of great concern, especially because air pollution exposure, being on of the recognized factors for LBW, is universal in the general population (Ha et al., 2001; Weck et al., 2008; Chalupka S. and Chalupka A.N., 2010).

LBW for infants whose mothers lived in areas of high air pollution in the USA was reported (Williams L. et al., 1977; Ritz and Yu, 1999) after exposure to high levels of ambient carbon monoxide (>5.5 ppm) during the last trimester. A China (Wang X. et al., 1997) and Czech Republic (Bobak, 2000) studies reported an inverse exposure-response relation between maternal exposures to sulfur dioxide and total suspended particles during the third trimester of pregnancy and infant birth mass. However, in a Swedish study, air pollution did not affect the odds ratios for LBW (Landgren, 1996).

Exposure to carbon monoxide, nitrogen dioxide, sulfur dioxide, and/or total suspended particle concentrations in the first trimester of pregnancy are risk factors for LBW. The latter might result from decreased in uterus oxygen supply, caused by a reduction of oxygen-carrying capacity or blood viscosity changes induced by air pollution. Namely, carbon monoxide readily crosses the placenta and reaches the fetus in uterus (Longo, 1977), which leads to a rapid accumulation of carboxyhemoglobin and reduces the oxygen carrying capacity of the blood. Another possibility for the effect of pollutant exposure on LBW is that the production of free radicals induced by air pollution might cause an inflammatory response that contributes to enhanced blood viscosity (Peters et al., 1997; Bouthillier et al., 1998).

2.4 DEVELOPMENT OF INFANTS AND CONSEQUENCES OF PRETERM BIRTH

To understand the severity of preterm birth, we first need to understand the normal human development for any further assessments of the consequences of preterm birth.

Prenatal and postnatal growth is an important indicator for premature infant health (Adair, 2007). The process of growth and development starts with fertilization of the ovum, it continues with changes in cell mass and participating components, and progresses in size changes, called growth. Growth of organs can be chronologically classified into three stages (Winick and Noble, 1965): first stage is hyperplasia (also called hypergenesis), which due to cell proliferation includes proportional increases in mass, amount of proteins, and deoxyribonucleic acid (DNA); in the second stage, increases in mass and amount of proteins are faster than increases in DNA amount, increase in cell number and size are in the same extant; the third stage is hypertrophy, during which only increases in mass and amount of proteins are detected, but increases in DNA do not occur, as DNA replication stopped. Growth in the largest part of pregnancy is based on hyperplasia; hypertrophy dominates only towards the end of pregnancy. In addition, growth of different fetal organs is not concomitant (Tanner, 1978), but takes place at specific time intervals during pregnancy.

The process of growth could be described as searching of a pre-defined goal, which can be reached by different ways. This goal is determined by the genetic structure of an individual. Consequently, two children can have different growth curves leading to the same goal, which makes them, after growth is completed, almost identical in their physical constitution.

Important characteristics of living beings are the self-repairing ability and the search for “growth goal”. Namely, every living being has the ability to return from the period of restricted growth to the original set-out growth path, after growth had been attenuated

due to a certain factor. This is possible through the whole process of growth and can be detected, for example, as a response to shorter periods of starving or illness. During starving and illness, growth slows down, but when the conditions improve, growth increases again to reach the set-out growth. Such increased growth after every growing restriction is called "catch-up" growth. It has been reported that children have a high ability to catch-up even after a long period of starving (Tanner, 1978).

Growth is the fastest in the prenatal period and in the first years of postnatal development, thus in newborns and in early childhood. During those periods, infants are very sensitive to the quality of their environment (Johnston, 1978; Babnik A., 2003). Optimal nutritional and medical conditions during pregnancy do not only benefit on a mother's health, but also ensure a good starting point for the next generation (Hyppönen et al., 2004).

2.4.1 Fertilization

A new human being is biologically formed after the merging of two gametes, a male sperm cell and a female ovum (oocyte). This process is termed fertilization (also conception) and has been known for more than 300 years (Bratanič, 2009). Normal fertilization occurs in the outer third of the oviduct (fallopian tube), where a large number of sperm cells meet one ovum. Of the millions of sperm cells arising from the male ejaculation into the uterus, only a small number successfully break through the inner layer of the cluster of follicle cells that surround the ovum (corona radiata). Through the next ovum capsule (outer protective layer of the ovum, i.e. zona pellucida), a sperm penetrates by enzymes that are released from the front part of the sperm body, i.e. the acrosom. Only one sperm penetrates the zona pellucida. Contact of the sperm with this membrane causes an immediate reaction, which changes properties of the ovum capsule and completely closes the entry of other sperm cells (Wassarman, 1987). If two sperm cells penetrate the ovum, a triploid embryo results, which dies in early development due to abnormal number of chromosomes (Carr, 1971).

2.4.2 Prenatal and perinatal development

Period of prenatal (synonym: antenatal) development, thus development in the first nine months from conception to birth, is the most dramatic and very complicated period in the development of human beings (Bratanič, 2009). The prenatal period from conception up to 14 days is called the germinal period, the period from 2 to 8 weeks after fertilization is the embryonic period, and the period from 8 to 40 weeks of GA the fetal period. These three periods will be presented in detail below.

The so called perinatal period starts at 22 completed weeks (154 days) of gestation and ends seven completed days after birth.

2.4.2.1 The germinal period

The germinal period lasts for approximately 2 weeks from fertilization (Sigelman and Rider, 2012). During this time the zygote divides many times through mitosis, forming the blastocyst, a hollow ball of about 150 cells that is the size of the head of a pin (Sigelman and Rider, 2012). When the blastocyst reaches the uterus, which usually happens around day 6 after fertilization, it implants tendrils from its outer layer into the blood vessels of the uterine wall (Sigelman and Rider, 2012). The implantation is quite an accomplishment, as only about half of all fertilized ova are successfully implanted in the uterus (Babnik A., 2003). After embedding, the external layer of the blastocyst forms the placenta and a small part of the internal layer develops into an embryo (Babnik A., 2003).

2.4.2.2 The embryonic period

An embryo is a multicellular organism in its earliest stage of development, generally considered to be between the 3rd and the 8th week after fertilization. The development of embryo is called embryogenesis.

During that time, every major organ takes shape, in at least a primitive form, in a process called organogenesis. The layers of the blastocyst differentiate, forming structures that sustain development. The outer layer becomes, both, the amnion, a watertight membrane that fills with fluid that cushions and protects the embryo, and the chorion, a membrane that surrounds the amnion and attaches root-like extensions called villi to the uterine lining to gather nourishment for the embryo. The chorion eventually becomes the lining of the placenta, a tissue fed by blood vessels from the mother and connected to the embryo by the umbilical cord. Through the placenta and umbilical cord, the embryo receives oxygen and nutrients from the mother and eliminates carbon dioxide and metabolic wastes into the mother's bloodstream. A membrane called the placental barrier allows these small molecules to pass through, but it prevents the large blood cells of embryo and mother from mingling. It also protects the developing embryo from many harmful substances (Sigelman and Rider, 2012).

Meanwhile, the cells in the interior of the blastocyst develop into the ectoderm, mesoderm, and endoderm. These will evolve into specific tissues and organ systems: from the ectoderm including the central nervous system (brain and spinal cord), from the mesoderm muscle tissue, cartilage, bone, heart, arteries, kidneys, and gonads, and from the endoderm gastrointestinal tract, lungs, and bladder (Sadler, 2010).

After 3 to 4 weeks, when the neural plate folds up to form the neural tube, the brain begins to develop. The bottom of the tube becomes the spinal cord. Bulges emerge at the top of the tube and form the forebrain, midbrain, and hindbrain. The so-called primitive or lower portions of the brain develop earliest. These are the parts of the brain that make life possible. They regulate biological functions such as digestion, respiration, and elimination; they also control sleep-wake states and simple motor reactions (Sigelman and Rider, 2012).

Four weeks after conception, the heart not only has formed, but also has begun to beat. The eyes, ears, nose, and mouth rapidly take shape in the second month, and buds appear that will become arms and legs. During the second month, a primitive nervous system also makes newly formed muscles contract. Only 8 weeks after conception, towards the end of the embryonic period, the organism is approximately 2,5 cm long, weights 1 g, and has a distinctly human appearance (Sigelman and Rider, 2012).

The important process of sexual differentiation begins during the 7^{th} and 8^{th} prenatal week. First undifferentiated tissue becomes either male testes or female ovaries. The testes of a male embryo secrete testosterone, the primary male sex hormone that stimulates the development of a male internal reproductive system, and another hormone that inhibits the development of a female internal reproductive system. In the absence of these hormones, the embryo develops the internal reproductive system of a female (Sigelman and Rider, 2012).

Not all implanted embryos survive the early phases of prenatal development. Between 15 % and 20 % of recognized pregnancies are short-lived, ending in miscarriage before survival outside the womb is possible, and as many as 50 % of unrecognized pregnancies are believed to terminate with miscarriage (Friebe and Arck, 2008; Sadler, 2010). Many of these early losses are due to genetic defects (Sigelman and Rider, 2012).

2.4.2.3 The fetal period

A fetus is the term used to refer to an individual between its embryonic state and its birth, also characterized by the presence of all the major body organs, although not yet fully developed, functional, and some not yet situated in their final anatomical location.

In the 9^{th} week, the fetus is already formed like a human. At that time fetus is approximately 3 cm long. Organ systems that were formed during the embryonic period continue to grow and begin to function. Harmful agents will no longer cause major malformations because organs have already formed, but they can stunt the growth of the

fetus and interfere with the wiring of its rapidly developing nervous system (Sigelman and Rider, 2012). Fast growth of the fetus is largely the result of cell division (Tanner, 1978).

In the fetal period neurons continue to proliferate at a staggering rate - the number increases by 100,000 every minute, with most intensive period between 10 and 20 weeks after conception (Nelson C.A. et al., 2006). As a result of this rapid proliferation, a young infant has around 100,000,000,000 neurons. Once formed, neurons migrate along the surface of glial cells from their place of origin to particular locations within the brain, where they will become part of specialized functioning units. Much of this occurs between 8 and 15 weeks after conception. Early in development, stem cells for neurons start with the potential to become any specific type of neuron; what they become - how they differentiate – is dependent on where these stem cells migrate. Such stem cells are also present in adult tissue, but they are much more limited in number and ability to specialize (Sigelman and Rider, 2012).

In the 3rd month of pregnancy, distinguishable external sex organs appear and consequently the gender of the fetus can be determined by ultrasound. The bones and muscles develop, and the fetus becomes frisky: by the end of the third month, it moves its arms, kicks its legs, makes fists, and even turns somersaults. The mother probably does not yet feel all this activity because the fetus is still only approximately 7.5 cm long and weights 14 g. Nonetheless, it can swallow, digest food, and urinate. All this "behaving" contributes to the proper development of the nervous system, digestive system, and other systems of the body, and it is consistent with the behaviors that we observe after birth (Kurjak et al., 2004).

During the 2nd trimester more refined activities appear, and by the end of this period the sensory organs are functioning (Allen and Capute, 1986; Sadler, 2010). The fastest growth occurs in the 4th month, when the fetus can grow up to 1.5 mm per day (in the 16th week the fetus is approximately 17 cm long and weights 100 g) (Tanner, 1978).

At about 23 weeks after conception, midway through the fifth month, the fetus reaches the age of viability, when survival out-side the uterus is possible, if the brain and respiratory system are sufficiently developed. As presented before, the age of viability is earlier today than at any time in the past, because medical techniques for keeping fragile infants alive have improved considerably over the past few decades (Sigelman and Rider, 2012). At the end of the 2nd trimester the fetus grows to approximately 1,000 grams and the length of 25 cm (Tanner, 1978).

During the 3rd trimester, the fetus gains mass rapidly. This time is also critical in the development of the brain, as during the second half of pregnancy neurons increase in size and develop an insulating cover, myelin, which improves their ability to transmit signals rapidly. Guided by both a genetic blueprint and early sensory experiences, neurons connect with one another and organize into working groups that control vision, memory, motor behavior, and other functions. As the brain develops, the behavior of the fetus becomes more like the organized and adaptive behavior seen in the newborn (Sigelman and Rider, 2012).

By 36 weeks of gestation, heart rate activity and movement become increasingly organized into coherent patterns of waking and sleeping known as infant states. Fetuses with slower and more variable heart rates had higher levels of mental and language development in early childhood, as compared with those who had faster and less variable heart rates (DiPietro et al., 2006, 2007).

From the beginning to the end of the 3rd trimester fetus doubles its length. At 30th week it is approximately 40 cm long and weights approximately 1,600 g. With age, the percentage of dividing cells in the tissues decreases and after the 30th week only few nervous and muscle cells still divide. At that time, growth velocity of body lengths slows down (Tanner, 1978) and mass gain happens primarily because of the growth of subcutaneous tissues; especially fat and muscle mass increase (Vaughan and Litt, 1992). However, the fastest mass gain is detected later in approximately 34th week of pregnancy. Between 34th and 36th week the growth of the fetus decreases, probably because the uterus becomes too small for the fetus (Tanner, 1978).

By the middle of the 9th month, the fetus is so large that its most comfortable position in uterus is head down with limbs curled, thus in the so called "fetal position". The mother's uterus contracts at irregular intervals during the last month of pregnancy. When these contractions are strong, frequent, and regular, the mother is in the first stage of labor and the prenatal period is drawing to a close. Under normal circumstances, birth will occur within hours (Sigelman and Rider, 2012).

According to the above, it is not surprising that preterm birth may have long term implications, as it interrupts the period of highest fetal growth velocity and it is also followed by a postnatal period of growth and development retardation and prematurity-associated illness (More in Chapter 2.4.6) (Hovi et al., 2007).

2.4.3 Postnatal growth of body mass and height

For most of the tissues, postnatal growth means the period of development and increase of already existing cells (Tanner, 1978). Postnatal growth consists of at least three phases: infancy, childhood, and puberty (Karlberg, 1987).

First years of child's life are the time of adaptation to the outside, very variable, and, in comparison with the mother's uterus, more hostile environment. First contact of the newborn with the world marks a major change in the physical environment, psychosocial processes, food sources, and changes in sensory stimulations (Tanner, 1978).

At birth, mean body mass of FT infants is approximately 3.4 kg, with 95 % of the population being between 2.5 kg and 4.6 kg, and males are usually heavier than females. It has been reported that birth mass is the most important determinant of childhood survival (Lessa Horta et al., 1997) and is most frequently used as a proxy for fetal nutritional sufficiency in humans (Adair, 2007). Nevertheless, neonatal length increments are also of superior value when choosing a single criterion of growth (Kaempf et al., 1998). Mean birth length is approximately 50 cm, with 95 % being between 45 cm and 55 cm. Mean head circumference, which can be used as a criterion of growth of the brain, is approximately 35 cm, with 95 % being between 32.6 cm and 37.2 cm (Vaughan and Litt, 1992).

Immediately after birth, body mass nevertheless decreases for approximately 5 % of birth mass because of the lower intake of fluids into the body of a newborn. This loss is being compensated in 10 days, when body mass of newborns reaches the birth mass again. Body mass of FT infants doubles till the 5^{th} month of life, and triples till the 1^{st} year. Subcutaneous fat deposition begins in the fetus at about 34 weeks postmenstrual age and reaches the maximum in approximately the 9^{th} month (between 6^{th} and 12^{th} month) after birth (Tanner, 1978; Rolland-Cachera et al., 1984; Hughes, 1998). Body length increases during the 1^{st} year of life for approximately 25 to 30 cm. Head circumference at 6^{th} month is approximately 44 cm, and at the 1^{st} year approximately 47 cm, thus reaching 2/3 of the full brain size (Vaughan and Litt, 1992).

During the second year of life growth slows down, child gains approximately 2.5 kg and becomes approximately 12 cm taller. Between the 10^{th} month and the 2^{nd} year infants have reduced appetite, which is reflected in the loose of subcutaneous fat tissue in the second year of life (Rolland-Cachera et al., 1984; Hughes, 1998). Bellied infants therefore become slim children. Growth of brain decreases too, therefore head

circumference increases for approximately 2 cm only during the second year and at 2 years of age it thus reaches 4/5 of the full adult brain size (Vaughan and Litt, 1992).

During the 3rd, 4th, and 5th year of life growth stabilizes on 2 kg and 6-8 cm per year. At the end of the 3rd year, males weigh approximately 14.7 kg, are 96.5 cm tall, and have a head circumference of 50.5 cm; females weigh approximately 13.9 kg, are 95.6 cm tall, and have a head circumference of 49.3 cm (Vaughan and Litt, 1992).

Growth status and growth velocity are obviously important markers of health and well being (Casey P.H. et al., 1990). To evaluate growth, fetal-infant growth graphs (charts) are commonly used. These exist, both, for FT and for PT infants. For PT infants, charts of Babson and Benda (1976) were in use until 2003, than Fenton (2003) made a new, extended chart, which can be applied to individuals from 22 weeks of GA onwards. Analysis of data of 3,187,920 singleton neonates from the German perinatal survey in the years 2007–2011 also resulted in new growth charts (Voigt et al., 2014).

Studies have demonstrated that FT and PT infants, especially those with birth mass below 1,500 g, have different patterns of growth, which are reflected in differences in their mass, height and fat accumulation during childhood, even with plotting for corrected GA (Casey P.H. et al., 1990, 1991).

In premature infants and SGA individuals, the early post-birth period is almost always characterized by a slow growth (Paz et al., 1993; Saluja et al., 2010) and is strongly influenced by BMI at birth, with rapid early infant mass gain associated with thinness (Adair, 2007). In premature infants mean body mass can remain below the 10th percentile up to 14 weeks (Gill et al., 1986).

In addition, more immature infants have higher postnatal mass loss (PT infants approximately 10 % (Brace, 1998), ELBW infants 10-21 % (Smith et al., 1994; Berry et al., 1997; Pauls et al., 1998)) and longer time to regain birth mass despite a higher milk volume intake in the first week (Gill et al., 1986). ELBW infants thus develop a growth deficit during the first few weeks of life that persists and worsens during hospitalization and is difficult to reverse - immediate postnatal period is therefore a critical time for the growth of ELBW infants (Thureen, 1999; Steward and Pridham, 2002; Parry et al., 2003; Paul et al., 2011), namely, poor growth during the period of maximum growth velocity may prevent the achievement of expected catch-up growth, despite the adequate nutrition for stimulating this growth (Thureen and Hay, 2000).

Findings also suggest that a long-term relationship between IUGR and growth into adolescence exists (Paul et al., 2011).

Interestingly enough, growth pattern of infants, who were associated with increased risk of chronic disease, is characterized by more rapid growth in the first 4 postnatal months (Adair, 2007). Early mass gain thus seems an important prognostic factor in predicting childhood growth (Knops et al., 2005).

2.4.3.1 Catch-up growth

After a period of IUGR, thus, postnatal growth can take two forms, growth at a normal postnatal rate (no catch-up) or accelerated growth (catch-up) (Tanner, 1981), during which premature infants can catch-up with their peers (Brandt et al., 2005). Catch-up growth is a specific term relating to an increase to length rather than mass (Tanner, 1981), but during the first year of life, mass and length increments parallel each other, so catch-up is often used synonymously with increased mass gain. The mechanisms that explains this catch-up phenomenon are not understood (Tanner, 1981), but it is unlikely, as mentioned above (Chapter 2.4.5.2), to be mediated through the growth hormone axis.

The definition of catch-up is not uniform (Brandt et al., 2005). Mostly it was defined as body height reaching the cut-off point of -2 standard deviations (SD; defined in Methods) (Hack et al., 2003), 3rd percentile (Hokken-Koelega et al., 1995), or a z-score of -1.28 (10th percentile) (Seminara et al., 2000). The period of catch-up growth begins in early childhood and usually stops at the age of two to three years (Barker M. et al., 1997; Euser et al., 2008); however, in some cases it continues into adolescence (Euser et al., 2008). According to literature reports, period for height catch-up varies from the age of 20 months to 20 years (Hokken-Koelega et al., 1995; Seminara et al., 2000; Saigal et al., 2001; Hack et al., 2003), thus, theoretically, for as long as growth velocity is sufficiently high. In general, catch-up growth should be considered positive and desirable, although negative effects of catch-up growth were also reported in the literature (such as leading to obesity at adult age) (Brandt et al., 2005).

Catch-up growth in premature infants is often incomplete and therefore premature infants can remain shorter and lighter than their peers in childhood (Commey and Fitzhardinge, 1979; Vohr and Oh, 1983; Casey P.H. et al., 1990; Khalil et al., 1995; Niklasson et al., 2003; Pilviniene et al., 2003; Cooke et al., 2004), adolescence (Paz et al., 1993; Knops et al., 2005), and even in early adulthood (Hack et al., 2003; Euser et al., 2005).

As expected, in some studies, growth pattern of body length of LBW infants was lower than the published standards for FT infants of the same age and gender (Casey P.H. et al., 1991; Fewtrell et al., 2001), as no significant compensatory growth within the first year has been observed (Casey P.H. et al., 1990) and just a little catch-up was noted by

the 3 year examination (Casey P.H. et al., 1991). Between the ages of 5 and 8 years, NBW children grew faster than VLBW and MLBW children combined; VLBW needed a longer time for catch-up growth and had smaller height increments than MLBW children (Kitchen et al., 1992). By the age of 8 years, VLBW had subnormal height (Kitchen et al., 1992). Also, many SGA infants showed persistent height growth stunting even at 10 years of age (Knops et al., 2005). In contrary, a study of Albertsson-Wikland and Karlberg (1994) demonstrated that most (87 %) SGA individuals experienced a full height catch-up growth within 2 years, and only a few (13 %) were short also in later life (short stature is the most visible sign of IUGR). Catch-up growth of height was observed especially in SGA children with a fast initial mass gain (Knops et al., 2005). In one study, mean adult height z-score was lower than that for birth length, however, 46 % of VLBW SGA had complete height catch-up by adult age, and most became even taller than target height (Brandt et al., 2005). It seems that especially female premature infants can experience catch-up growth much later, as in the study of Hack et al. (2003) catch-up growth in height occurred between 8 and 20 years among VLBW females, but not among VLBW males, who remained significantly smaller than their controls at 20 years of age.

Increase in length velocity of VPT infants was observed from 2 to 12 months of corrected age, later catch-up growth period was reported at 4-5 years and at 7 years of age, with almost all reaching the normal height range of the population (Niklasson et al., 2003). In another study, VPT infants experienced no growth stunting for body height at 10 years of age (Knops et al., 2005). Also, studies exist that observed no differences in body height between PT and FT individuals even at the age of 19 years (Tideman, 2000).

Height catch-up growth therefore seems to be unpredictable, it may not be influenced by energy intake and counseling, and may not lead to obesity at adult age (Brandt et al., 2005).

Similar to the growth pattern of body height, growth pattern of body mass of LBW infants was often reported to be lower than the published standards for FT NBW infants (Casey P.H. et al., 1991; Fewtrell et al., 2001), with significant compensatory growth within the first year (Casey P.H. et al., 1990) and just a little catch-up by the 3 year examination (Casey P.H. et al., 1991). In another study VLBW and MLBW children had similar body mass at the age of 8 years, but combined, they had lower body mass than NBW individuals (Kitchen et al., 1992). In contrast, in the study of Hack et al. (2003), VLBW females caught-up in mass between 8 and 20 years (but VLBW males) and reached their controls at 20 years of age.

The majority of VPT infants in the study of Niklasson et al. (2003) had an initial decrease in mass during the first month, which was followed by an increase with a maximum mass gain occurring between 34 and 38 gestational weeks. After another period of decreased mass gain velocity, a second increase in mass gain velocity was demonstrated from 6 months to 2 years of corrected age (Niklasson et al., 2003). PT children reached normal mass before puberty (Niklasson et al., 2003). Similarly, in another study, no differences in body mass between PT and FT individuals at the age of 19 years were observed (Tideman, 2000).

Brandt et al. (2005) reported that mean BMI of PT individuals was lower than in FT controls in early adulthood (Brandt et al., 2005), however, in another study, similar was only true in VLBW males, as BMI was similar between VLBW and NBW females at 20 years of age (Hack et al., 2003).

2.4.3.2 Sexual maturation

Near the end of juvenile stage (i.e. a stage when an individual has not yet reached the sexual maturity and adult form) sexual maturation begins. One of its measurable effects is the adolescent growth spurt. Thus, apart from the first postnatal catch-up growth interval, this is another period in which children grow up more quickly, and is particularly interesting research-wise. This second growth spurt at adolescence provides another opportunity for PT children to close the gap with their peers (Paz et al., 1993). The period from the beginning to the end of adolescent growth spurt is called the adolescent stage (Hermanussen et al., 2012).

The chronology of a child's pubertal growth spurt is evaluated by the velocity and pubertal acceleration of growth, as well as by the age, when an individual reaches the adult height (Wehkalampi et al., 2011). In females it appears at the age of 10.5 to 11 years, in males at 12.5 to 13 years of age and lasts for 2 to 2.5 years. In that time, males grow for approximately 20 cm, especially because of the trunk prolongation, with the maximum velocity of growth, or the so called peak height velocity (PHV), at the age of 14 years on average. Females grow for approximately 16 cm with PHV at the age of 12 years on average. Because the adolescence growth spurt appears earlier in females, there is a period of two years when females are taller than males (Vaughan and Litt, 1992).

During the adolescence, body mass increases too; males gain approximately 20 kg and females approximately 16 kg on average. Enhanced body mass gain normally appears 3 months after the PHV in body height (Sinclair, 1973).

Adolescence ends with the eruption of the third molar (if present) and the termination of growth of the skeleton (Hermanussen et al., 2012). After the adolescence, growth decreases. Females reach 98 % of their final body height between the 16th and 17th year of age, males between the 17th and 18th year of life. On average, growth stops at the age of 18 years in females and at 20 years in males (Vaughan and Litt, 1992). An individual's attained height is thus the result of growth over nearly two decades, especially in infancy and around puberty, and it includes influences from the prenatal phase, as well as the effects of periods of catch-up growth (Hyppönen et al., 2004).

Adulthood and reproductive maturity follow. Body height remains stable up to the age of approximately 30 years and then declines for about 1 cm per decade. Body mass may increase for several decades, especially as fat accumulates, but may decline in old age (Hermanussen et al., 2012) primarily due to muscle tissue loss.

Another noticeable sign of sexual maturation in females is the occurrence of menarche (i.e. the first menstruation). Menarche shows the transition from childhood to maturity of a female. This first bleeding usually occurs between 11 and 14 years, but can also occur already at the age of 8 years or even at the age of 16. In the beginning, the bleeding is anovular (i.e. menstruation occurs without ovulation), the release of ovum is irregular, and the level of sex hormones is still fluctuating. However, the situation stabilizes by 16, 17 years of age (Perilleux et al., 1999; Clayton and Monga, 2006).

According to previous findings, which suggest that the onset of menarche depends more on body mass than on the chronological age of a female, Frisch and Revelle (1971) hypothesized that the menarche occurs, when the girl weighs approximately 48 kg, however, wide variation in the critical body mass for the menarche onset is present (Knott and Apicella, 2007). A critical body composition was therefore proposed to be the trigger for menarche. In 1973, the onset of menarche was associated with the required 17 % of body fat (Frisch, 1987). However, there is no evidence that after reaching the critical amount of body fat, the probability for menarche onset would increase (Knott and Apicella, 2007). In the nineties of the 20th century, the hypothesis about the size of pelvis stated that the onset of menarche can be predicted from biiliacal hip width. The results demonstrated that, regardless of the culture from which the female derived from, the average hip width at the onset of menarche is 24 cm (Worthman, 2002). The release of growth hormones triggers the pubertal growth spurt and the growth of pelvis. It was proposed that during the evolution, the menstruation was postponed until the time that the pelvis has been properly developed and ready for delivery (Bogin, 1999). Obviously, the natural selection has ensured that the female body is large enough for delivery prior the conception and that enough body fat for provision of energy is stored for both, pregnancy and childbirth.

Some epidemiological studies suggested that in FT individuals accumulation of fat tissue induces earlier maturation. Namely, sex hormones are being produced within fat metabolism pathways. Preterm birth was associated with increased accumulation of fat tissue after birth. Therefore, the question of early maturation of PT individuals arises, but data on growth and sexual maturation of PT individuals are lacking (de Ridder et al., 1992; Wehkalampi et al., 2010). Some of the studies have suggested that also LBW subjects sexually develop at an earlier than average age in puberty (Cooper C. et al., 1996; Persson et al., 1999; Adair, 2001; Ong et al., 2009), and very early puberty was linked to short adult stature (Biro et al., 2001).

2.4.4 Body composition

PT infants need special nutritional support during infancy and adulthood and neonatologists need to know their body composition status to evaluate the treatment progress (Quang Dung et al., 2007). Measurements of body composition thus have important implications for nutritional support, both, during infancy and adulthood (Rawlings et al., 1999). When body composition is assessed, the fraction of fat, i.e. adipose, and non-fat, i.e. lean or fat-free tissue is determined (Uthaya et al., 2005).

Fetuses during the last trimester of gestation and infants during the first month of life undergo major changes in body composition. These include: fat deposition, muscle mass gain, and bone mineralization (Rigo et al., 1998). Fat deposition is lower, when growth retardation during pregnancy occurs (Lapillonne et al., 1997). Therefore, it is not surprising that GA seems to positively affect total body fat mass content in PT children at birth (Uthaya et al., 2005; Gianni et al., 2008).

Infants under 4 months of age have a very constant fraction of their adipose tissue located non-subcutaneously as the pericardial fat, abdominal visceral fat, and liver fat, and containing variable concentrations of fat (Olhager et al., 2003). Studies report that the proportion of dietary energy derived from proteins, influences body fat retention in premature children (King and Harrison, 2002; Olhager and Forsum, 2006). Namely, growth for achieving ideal body composition is recognized as a major problem early in life, as most of these infants are fed more than sufficient energy for their growth. Such excessive energy intake starts very soon after birth with relatively high rates of intravenous glucose and lipids. As a result, body fat content of PT infants commonly is higher than that of normal in uterus developed FT infants (Uthaya et al., 2005). At the same time lean body mass is less well developed in these infants. Considerably more amino acids and protein are required for growth of such tissues than these infants commonly have been fed and excessive energy intakes only produce more body fat, but not more muscle and bone (Ziegler et al., 2002; Hay and Thureen, 2010).

During the first week of life, fat deposition in PT infants is high, resulting in a mass gain, but not necessarily in a length gain (Kaempf, 1998). There are conditions in PT infant growth, however, that seem to affect mass gain but not longitudinal growth and vice versa. For example, measurements of mass can easily be influenced by fluid shifts while measurements of length are not (Kaempf, 1998). Body mass therefore may be an insufficient criterion for assessing nutritional outcome in PT infants (Johnson et al., 2011). According to Euser et al. (2005), in VPT infants, mass gain before 32nd week of gestation was positively associated with adult body height, but not with body composition at age 19 years.

Body mass was proposed as the best predictor of bone mineral content, bone area, lean body mass, and fat mass (Rigo et al., 1998; Ong, 2006). Body mass is also the most important determinant of the chances of a infant to survive, grow and develop healthy, but, it is an unrefined measure of fetal growth as infants may have the same mass, but differ in length and proportion of fat (Williams C.E.C.S. et al., 2000).

In vivo body composition studies in infants have often been indirect and therefore unable to quantify specific adipose tissue depots (Uthaya et al., 2005), as only a few methods are adapted to the measurement of body composition and skeletal mineralization in the fetus and the newborn infant; one of them is dual energy X-ray absorptiometry or DEXA (Quang Dung et al., 2007). However, controversy still exists about the use of whole body DEXA for assessing bone mass (Rawlings et al., 1998), since DEXA seems to provide reliable and accurate values for bone mineralization, but overestimates fat content in small infants (Rigo et al., 1998). Potential of skinfold measuring methods for a simple assessment of body composition in premature infants has therefore been pointed out by Rigo et al. (2001), in some other studies, however, it was suggested to produces inaccurate and biased estimates of total body fat in infants (Olhager and Forsum, 2006).

According to several studies, body composition of PT infants seems to differ from their FT peers. Measured with DEXA, total body fat, lean mass, and the bone mineral content of SGA individuals was decreased in comparison with AGA individuals (Lapillonne et al., 1997). PT infants were reported to have similar (Uthaya et al., 2005) levels of total body fat at birth; however, in VPT infants decreased subcutaneous adipose tissue and increased visceral adipose tissue in comparison to FT peers was observed (Uthaya et al., 2005). By the time term age is reached, PT infants often continue to show low levels of subcutaneous body fat (Uthaya et al., 2005) and reduced tendency may be preserved into mid-childhood (Fewtrell et al., 2004).

It is possible that interruption of the normal pattern of in uterus fat deposition in PT infants has a long-term effect on subsequent fat gain, as it could potentially be mediated by alterations in leptin physiology (Singhal et al., 2002). Low fat mass during a critical period early in postnatal life could affect hypothalamic leptin receptors and an increased sensitivity to leptin later in life (Singhal et al., 2002; Fewtrell et al., 2004).

PT infants when reaching term age are lighter and shorter than FT infants but, in addition, body composition may be different, as PT infants may have a significant relative deficit in lean tissue (Peralta-Carcelen et al., 2000; Johnson et al., 2012), but greater proportion of body fat relative to total body mass, as compared to FT infants (Johnson et al., 2011; Daly-Wolfe, 2012); however, in another study, PT children were reported to exhibit lower total body fat mass and total body fat mass index, as compared to FT peers (Gianni et al., 2008).

It is likely that this pattern of body composition is in part a consequence of the nutrition that these infants receive while in hospital (Johnson et al., 2012).

Furthermore, lower birth mass is associated with higher ratio of fat mass to lean mass accumulation in childhood and later life (Ong, 2006). Disproportionate changes in height and mass after birth observed in PT children, in which mass gain is often more pronounced than height gain, are expected to result in a modified body composition in adulthood (Malina et al., 1996), which seems to be especially significant for females (Slattery and Morrison, 2002; Euser et al., 2008). Body composition in PT males and females differs, as for example at the age of 1 year lean mass and bone area were greater in boys than in girls (Rawlings et al., 1998). SGA infants with symmetric IUGR, which means evenly reduced mass, length, and head circumference below -2 SD on the Usher and McLean (1969) curves, have during the first 48 hours of life a body composition that is very different from that of AGA infants at same GA (Lapillonne et al., 1997).

2.4.4.1 Distribution of body fat

When assessing body composition, however, not only the amount, but also the location of fat tissue is an important prognostic factor. Namely, it has been reported that subcutaneous adiposity is primarily related to circulating leptin and generalized obesity, whereas visceral adiposity is associated with insulin resistance (Uthaya et al., 2005). The distribution of adipose tissue, is a marker of morbidity risk, as it is known that the abdominal fat tissue accumulation increases the risk of subsequent metabolic and CV diseases (insulin resistance) (Uthaya et al., 2005).

It has been reported that birth mass contributes 2 % to 8 % of variance in the relative distribution of subcutaneous fat in the primary school children (Malina et al., 1996) and may lead to overweightness and obesity in adolescence. Fat distribution appears to be a more important CV risk factor in young subjects than their overall adiposity (Daniels et al., 1999).

An android fat accumulation pattern with excess fat in the upper (central, abdomen) body region has been associated with increased risk for CV diseases, as compared with the gynoid (hips and buttocks) fat accumulation pattern (Donahue et al., 1987; Hartz et al., 1990; Daniels et al., 1999). In females the android and gynoid type of body shape were significantly associated with the pyknomorphic (lower and robust body) and leptomorphic (higher and narrow body) type, respectively (Scheffler and Obermüller, 2011). This pattern is established by the age of 8 years, when the earliest maturing children start to enter puberty (Scheffler and Obermüller, 2011). The more android, thus, the more central fat distribution, was suggested as an important predictor of plasma triglycerides, HDL cholesterol, systolic blood pressure, and left ventricular mass in children and adolescents (Daniels et al., 1999).

2.4.5 Factors influencing growth and development

Physical growth and development differ between individuals and populations. Because differences in growth and development are influenced by a lot of factors, we have to take them into account, when interpreting growth and development of any individual (Tanner, 1978). These factors are connected to each other and compose a whole microenvironment, in which the child lives.

Factor influencing growth and development are, both, genetic and environmental. The genotype defines the kind of reaction to given environmental conditions, and the environment defines the range of possibilities for genotype realization (Sinclair, 1973).

Infant growth is a continuation of in uterus growth; it is largely growth hormone independent, and influenced by nutrition (Hindmarsh et al., 2008). However, growth during childhood is largely growth hormone dependent, although it follows the same final pathway as uterine growth, namely IGF-1 pathway (Hindmarsh et al., 2008).

2.4.5.1 Genetic factors

Genetic factors cause the differences between individuals and populations (Johnston, 1978). In general, genetic factors determine the limits of the biological potential, are strongly intertwined, and are dependent on the environment, which effects growth (Vaughan and Litt, 1992). Not all the genes are active at birth; some are activated later

and some can be expressed only in particular physiological conditions in the later life (Tanner, 1978).

The genes influence the birth mass, and at the same time play a role in growth, metabolism, and CV diseases (Merlot, 2012). Factors influencing growth velocity are different from factors influencing body height and body composition (Tanner, 1978). Genetic control of growth velocity is independent of genetic control for final body height of a person or its constitution (Tanner, 1978). So, some environmental changes can influence growth velocity, but not the final height or constitution (Tanner, 1978). Genetic factors and hormones are probably a cause for different patterns of growth and development between males and females, the beginning of the adolescence growth spurt, and also the duration and intensity of the adolescence growth spurt (Sinclair, 1973).

In infants with the same genotype, thus in monozygotic twins, different genes are expressed or depressed since the separation of blastocyst, as substances of placenta and umbilical cord influence each fetus in different way. This expression or depression of genes is caused by molecules, which attach to the DNA and cover specific sequences. Already in the uterus, these changes in genotype expression will be influenced by environmental factors and epigenetics, which links environmental and genetic influences on the traits and characteristics of an individual (Rothstein et al., 2009), and consequently, one of the twins will be influenced by different factors than the other. Research on cells from umbilical cord tissue, blood, and placenta demonstrated differences in epigenetics. The epigenetics obviously influences physical development and ageing process and is itself influenced by nutrition and hormones, to which the fetus is exposed in the uterus.

Due to differences in basic health status between study populations, genetic effects on growth are more important in a well-fed and well-nourished population (Clausson et al., 2000).

Furthermore, evidence for genetic regulation comes from intergenerational studies that have shown parental birth mass, growth in childhood, and adult anthropometry to be associated with offspring birth mass (Martin R.M. et al., 2004; Griffiths et al., 2007). There is some evidence to suggest that paternal height is a more important determinant of offspring birth length (i.e. neonatal skeletal size) than maternal MBH, while maternal mass or BMI has the greater influence on offspring birth mass (Griffiths et al., 2007). Maternal and paternal stature may affect mostly the size of the infant at 6 (Hindmarsh et al., 2008) and 9 (Griffiths et al., 2007) months of age. For mass and head circumference,

maternal MBH was reported to be more influential than paternal height, whereas for length, the two coefficients were similar.

And last but not least, parental BMI and obesity are two of the several factors previously associated with infant and early childhood mass, length and adiposity. Parental obesity represents a surrogate marker of the complex interplay among genetic, epigenetic, and shared environmental factors, and is potentially modifiable (Linabery et al., 2012). Strong genetic effects on infant growth were up to now demonstrated by a few authors (van Dommelen et al., 2004; Dubois and Girard, 2006; Linabery et al., 2012).

One of the first assessments of genetic factors that have a profound impact on growth and development is prenatal screening aimed to diagnose birth defects. The latter are defined as abnormalities in structure, function, or body metabolism, which are present at birth and affect how the body looks and works, or both. Genetic factors that will result in a birth defect are, for example, chromosomal abnormalities that include structural chromosomal abnormalities or rearrangements, Down syndrome (trisomy 21), sex chromosome aneuploidy, Turner syndrome (monosomy X), tetraploidy, other chromosome aneuploidy, Patau syndrome (trisomy 13), or Edwards syndrome (trisomy 18) (Dolan et al., 2007). Structural abnormalities associated with birth defects are, for example cardiac, morphological (that include orofacial cleft, club foot, polydactyly, hypospadias, spina bifida), musculoskeletal, and abnormalities in central nervous system (Dolan et al., 2007). It has been demonstrated that an infant with a birth defect is 2.7 times more likely to be delivered before 37 weeks of gestation, 7.0 times more likely to be delivered before 34 weeks, and 11.5 times more likely to be delivered before 32nd week. An infant with a birth defect is also 3.6 times more likely to be MLBW and 11.3 times more likely to be VLBW (Dolan et al., 2007). Similarly, Rasmussen S.A. et al. (2001) reported that in premature infants the risk for birth defects is increased and Mili et al. (1991) demonstrated that a VLBW infant is more likely to have a serious birth defect.

2.4.5.2 Hormonal control

Probably all endocrine glands, controlled by the hypothalamus, affect the growth (Tanner, 1978) and the most important growth-affecting hormonal influences are described below.

Growth hormone (GH) or somatotrophin, which is necessary for normal development, stimulates the metabolism of proteins and inhibits the metabolism of carbohydrates and fats. It indirectly influences the growth of bones through the liver, as it stimulates the

production of another hormone somatomedin, which influences the growth of cartilage cells in the epiphyseal growth plates (Tanner, 1978).

Thyrotrophin (thyroid stimulating hormone; TSH) influences growth indirectly by stimulating thyroid hormones thyroxin (T4) and triiodothyronine (T3), which regulate cell metabolism, growth, skeletal and dental maturity, and brain development. Lack of these hormones in early phase of fetal development can lead to physical and mental retardation. Lack of these hormones in childhood can lead to retardation in skeletal growth, which can be nowadays fixed by adding artificial hormones (Sinclair, 1973).

Adrenocorticotrophic hormone (ACTH) regulates growth and function of adrenal cortex, which constantly releases mineralocorticoids and glucocorticoids, and after puberty, releases androgens, too (Sinclair, 1973). Androgens have a similar effect than male sex hormone testosterone, as they influence muscle mass growth and are involved in the skeletal growth and development especially in transversal dimensions (Tanner, 1978).

Sex hormone secretion, thus the secretion of testosterone in males and estrogen in females, is regulated with gonadotropic hormones (Tanner, 1978). Adolescence growth spurt is the result of androgen and growth hormone collaboration (Tanner, 1978).

2.4.5.3 Intrauterine environment

Intrauterine environment has a large role in infant's growth (Strauss, 2000). The uterus enables a normal neurological development of a fetus and provides it with physical, sensory and tactile stimuli. The largest influence on the fetus is exerted by the placenta, which provides all the necessary nutrients, oxygen, hormones, and enzymes, and is responsible for the selective passage of nutrients and metabolites between the mother and the fetus (Vaughan and Litt, 1992). It also provides appropriate IGF that are crucial for growth (Hughes, 1998).

During pregnancy, the growth of the fetus can be influenced by numerous unfavorable factors. The severity of growth retardation is affected by the time at the beginning and the duration of the influence of those factors (Babnik A., 2003).

2.4.5.4 Nutrition

Whenever we interpret growth patterns, we have to keep in mind that nutrition and nutritional status at birth affect infant's growth (Arifeen et al., 2000) and growth variability between children (Babnik A., 2003). Optimal nutrition must contain all nutrients, and has to have enough calories. Quantity and quality of nutrients and their

ratio in the diet is intertwined with some other factors, for example physical activity and general health (Babnik A., 2003).

The stage of infancy lasts from birth to age 30–36 months and is characterized by breastfeeding, with complimentary foods added from the age of 6 to 9 months. The transition to childhood at about the age of 3 years is characterized by the termination of maternal lactation, eating of soft and nutrient dense foods, and the completion of deciduous tooth eruption (Hermanussen et al., 2012). Very important for growth is the period in which the child was poorly fed and for how long this period lasted and the most sensitive period for growth abnormalities is the period from birth up to 5 years of age (Tanner, 1978).

Inadequate postnatal nutrition is an important factor contributing to growth failure (Dusick et al., 2003) and the appearance of chronic diseases in adult, including pulmonary function deficits (Lima et al., 2005). We have to distinguish the effects of nutrition on growth velocity, on final body height, on shape, and on body composition. Poor nutrition or malnutrition first influences growth velocity, which slows down. When conditions improve and the child is properly fed, growth velocity increases again and growth catches-up (Babnik A., 2003). As the correct combination of nutrients smaller individuals may catch-up in growth with their peers, special attention is required in the nutrition of premature infants.

Providing mother's milk to PT infants has been associated with better neuro-developmental outcomes, but is not considered adequate to meet all of the PT infant's nutrients requirements in early neonatal life (Wauben et al., 1998), as poor mass gain has been noted in VPT infants during the first month (Davies, 1977), as a consequence of major protein and energy deficits (Dusick et al., 2003). It therefore seems that breast milk is inadequate for the growth of PT infants during early postnatal life (Davies, 1977).

2.4.5.5 Socioeconomic status and psychosocial stress

In considering the impact of the socioeconomic status on the growth and development of the infant we must distinguish the conditions that exist in each family, thus income per family member, the number of members in the family, emotional situations and relationships in the family, eating habits, care for hygiene and health, as well as the conditions that exist in the society, thus social welfare, municipal infrastructure, and level of education. Children from higher socioeconomic class are usually taller and heavier than children belonging to lower class. The same conclusion applies to children

from smaller families, as compared with those of more numerous families (Sinclair, 1973).

Great emotional shocks and living in families with inadequate relations, thus living under constant stress, can slow down growth in early childhood, which can be related to inhibition of growth hormone secretion. When the stressful situation ends, the secretion of growth hormone increases again and children will probably catch-up with their peers (Tanner, 1978).

Low socioeconomic status and LBW are often concomitant findings (Tideman et al., 2001). Social class has been demonstrated to be a robust factor in prediction of cognitive competence (Cohen S.E., 1995), and also plays a significant role in influencing developmental outcome in LBW infants (Vohr and Oh, 1983). It has been reported that significantly more PT than FT individuals may have psychological stress during childhood, adolescence, and at 19 years (Tideman et al., 2001).

2.4.6 Illnesses associated with specific organ systems in preterm infants

Medical and research workers are not interested only in the survival of newborns, but also in the quality of live, that will enable their optimal mental and somatic development. We therefore need information on whether there are differences between PT and FT infants in the development and morbidity for infective and other chronic diseases. It would be plausible to identify perinatal and peristaltic factors, which mostly contribute to poor development, and eliminate them with rational actions (Babnik J, 1988).

Mortality in the perinatal period is an important indicator of health (Babnik J., 1989). In developed countries, preterm labor is one of the most intractable problems that contribute to the reasons for the majority of perinatal mortality and morbidity (Babnik J., 1988; Tideman et al., 2002; Goldenberg et al., 2008) and has been so far a widely neglected public health problem (Friese et al., 2003).

Preterm birth is responsible for 60 % to 70 % of all perinatal and neonatal mortality (Babnik J., 1988; Ananth and Vintzileos, 2006), even for 85 %, if deaths associated with congenital malformations are excluded (Porter et al., 1997), and for more than 50 % of long-term morbidity (McCormick, 1985). PT infants have 120 times higher risk of death than FT infants (Romero et al., 1994) and more PT than FT infants need hospital care during the first four years of life (Forslund and Bjerre, 1990).

Morbidity is related primarily to birth mass, which is a reflection of GA (Porter et al., 1997), as abnormal growth is often an early sign of disease (Manser, 1984). PT or/and LBW infants are therefore a prototypical risk group, that may be prone to subsequent somatic health (Tideman, 2000) and developmental problems (Cohen S.E., 1995; Eide et al., 2005).

PT newborns experience an interruption of the intrauterine development, which can be reflected in immaturity of CV, central nervous, respiratory, digestive, immune, and other systems, as well as impaired thermoregulation. Impact of chronic diseases, like heart, kidney, lung, and autoimmune diseases, on infant's growth and development can therefore be much larger (Babnik A., 2003; Babnik J., 2013 - personal communication).

2.4.6.1 Cardiovascular system

The so called fetal origins hypothesis proposes that the intrauterine period is critical for the development of several risk factors for chronic diseases (Barker M. et al., 1997), as many papers have reported that LBW at birth is associated with an increased risk for CV diseases later in life (Barker M. et al., 1997; te Velde et al., 2003), raised blood pressure (Law and Shiell, 1996; Barker M. et al., 1997; Evensen et al., 2008), and osteoporosis (Barker M. et al., 1997).

Preterm birth, size at birth, mass at 1 year, early nutrition (greater nutrient intake in infancy), and accelerated mass and height gain during childhood have all been proposed to cause CV diseases later in life (Barker D.J. et al., 2005; Eriksson et al., 2006), especially in those individuals, who became obese or showed childhood catch-up growth in early postnatal period or later on (Eriksson et al., 1999; Niklasson et al., 2003; Singhal and Lucas, 2004; Barker D.J.P et al., 2005; Eide et al., 2005; Eriksson et al., 2006; Ong, 2006; Dalziel et al., 2007; Ekelund et al., 2007; Evensen et al., 2008; Rotteveel et al., 2008). GA in completed weeks is inversely associated with systolic blood pressure in young adult FT males (Yang S. et al., 2010).

IUGR is thought to leave an imprint on various fetal organ systems structure and functioning that may increase the risk of degenerative ischemic heart disease (Barker D.J., 1990; Knops et al., 2005; Kaijser et al., 2008), coronary heart disease, CV disease, type 2 diabetes, as well as higher blood pressure (Doyle et al., 2003; Hovi et al., 2007), and impaired glucose regulation (Hovi et al., 2007; Wehkalampi et al., 2011). All these factors may cause mortality from coronary heart disease in adulthood (Barker D.J. and Osmond, 1986; Fewtrell et al., 2001; Knops et al., 2005; Dalziel et al., 2007).

It has been demonstrated that metabolic and CV outcome depends on the timing of malnutrition during fetal life, with the last trimester being a critical period, which can decrease glucose tolerance later in life (Niklasson et al., 2003).

It has also been suggested that early postnatal nutrition permanently affects the major components of the metabolic syndrome, such as hypertension, type II diabetes (mellitus), elevated (basal) blood pressure, increased fasting plasma glucose level, impaired glucose tolerance, dyslipiaemia, obesity, reduced insulin sensitivity, insulin resistance (Barker D.J. et al., 1989; Irving et al., 2000; Newsome et al., 2003; Ekholm et al., 2004; Hofman et al., 2004; Singhal and Lucas, 2004; Knops et al., 2005; Hovi, 2007; Bonamy et al., 2008; Yang S. et al., 2010), myocardial infarction and stroke (Barker D.J., 1990). Vascular, renal, central regulatory factors, and changes in sex hormones were reported to be involved in programming of blood pressure (Bonamy et al., 2005). Interestingly, a diet lower in nutrients favorably programmed later risk for CV diseases (Singhal and Lucas, 2004).

2.4.6.2 Central nervous system and senses

The main part of brain development occurs during the first 40 weeks of gestation and whether this happens inside or outside of the uterus seems to affect brain development (Toulmin et al., 2015). The earlier the birth, the more differences there may be in the wiring of the brain and therefore PT infants may be more at risk of neuro-developmental problems, such as autism and attention deficit disorders (Toulmin et al., 2015). Additionally, immaturity of sucking and swallowing reflexes, which develop until the 34^{th} week of gestation, is often the reason for partial parenteral (intravenously) feeding and feeding via tubing of the newborn. Immaturity of the brain centre for breathing causes respiratory congestion (Tekauc-Golob, 2001).

In addition, peri/intraventricular hemorrhage (bleeding) is a common cause of neonatal morbidity among premature infants and it remains an important cause of cerebral palsy and developmental disability of premature infants. A half of hemorrhages occurs during the first 12 hours and most within the first 3 days after birth (Paneth et al., 1993). Early onset of hemorrhage has been associated with lower gestation, lower birth mass, lack of antenatal steroid administration, male sex, fetal distress and fetal acidosis, amnion inflammation, vaginal delivery, and resuscitation at birth (Wells J.T. and Ment, 1995). Postnatal risk factors associated with late onset hemorrhage are mostly respiratory distress syndrome, complication of respiratory treatment, derangement in blood gas status, and fluctuation in cerebral blood flow (Wells J.T. and Ment, 1995; Babnik et al., 2006).

It has been reported that visual and hearing disorders are more common among PT individuals than expected (Forslund and Bjerre, 1990). This is supported by the fact that, similar to respiratory illnesses, PT infants are susceptible to repeated hospital readmissions for health problems such as vision and hearing impairments (Little, 2009).

2.4.6.3 Respiratory system

The alveoli in the lungs develop by the 25th week of gestation. Surface tension in the alveoli at the first breath has to be sufficient to keep them open. Surfactant (a mixture of phospholipids, lipids, and proteins) increases this surface tension. Due to insufficient production of surfactant in the lung alveoli, PT infant are at risk for collapse of alveoli and the formation of atelectasis (the collapse or closure of the lung resulting in reduced or absent gas exchange), leading to respiratory distress. At the age of 34 to 35 weeks of gestation production of surfactant is adequate to prevent atelectasis (Tekauc-Golob, 2001).

Fetus adapts its growth progress in response to oxygen and nutrient restriction, which may possibly lead to permanent structural and physiological changes in the lungs (Lima et al., 2005). It has been reported that PT infants are susceptible to repeated hospital readmissions especially for respiratory illnesses (due to bronchopulmonary dysplasia, for example) (Romero et al., 1994; Little, 2009), however, other studies reported that preterm birth per se was not associated with poor lung function (Lima et al., 2005).

Oxygen supply to the brain is closely related to the state of circulatory system. It is clear that lack of oxygen, i.e. hypoxia, that can be experienced following a hypoxic-ischemic event such as, for example perinatal asphyxia, the cessation of breathing, or near-drowning cardigenic shock, can be deleterious for an organism (Babnik J., 1988). Nevertheless, the literature rarely describes the impact of hypoxia on heart function of healthy PT infant or older children.

Most of VLBW PT infants require respiratory support during the early part of their life, as they are more prone to lung injury (Anand et al., 2003).

2.4.6.4 Digestive system

PT newborns have a small stomach, reduced gastric emptying and gut peristalsis, and difficulties in sucking and swallowing (Gomella, 2004), which prevent satisfactory oral feeding and may also cause aspiration of food. Intestinal permeability is increased and results in increased macromolecular transport across the epithelium (Gomella, 2004). This may be relevant to the development of necrotizing enterocolitis by allowing bacteria and antigens to penetrate the gut wall (Patole, 2005). Hypoglycemia (i.e. an

abnormally diminished content of glucose in the blood) is very often in PT infants, so it is necessary to carefully coordinate feeding with an intravenous addition of fluids. Most of PT newborns best tolerate mother's milk, as well as premature milk formulas; the smallest premature babies also tolerate fortified breast milk (Tekauc-Golob, 2001).

Epithelial permeability is a significant primary or secondary event in the pathogenesis of several intestinal diseases. Epithelial permeability is determined by the individual's age, concurrent infections, and shielding effect of secretory IgA antibodies provided by breast milk (Brandtzaeg, 2001). Additionally, it seems that frequent short term diseases, like different infections and injuries, present minimal risk for the growth and development of a normally nourished infant. In infants with malnutrition, however, the same diseases can cause growth retardation (Babnik A., 2003).

Individuals born VLBW PT differ in body size, as compared with their peers born at term (Hovi et al., 2007). Thus, it was previously suggested that body size and shape-related symptoms could link eating disorders to preterm birth. Case-control studies have shown that patients with history of obstetric complications and prematurity may be more likely to have eating disorders, like anorexia and bulimia nervosa (Cnattingius et al., 1999). However, Wehkalampi et al. (2010) reported that particularly young adult VLBW women have fewer body size and shape-related symptoms and possibly lower risk for eating disorders.

2.4.6.5 Immune system

Also the function of the immune system depends on the GA of the newborn, therefore sepsis and meningitis are 4-times more common in PT than in FT newborns. The number of T-cells is normal at the age of 30 to 32 weeks, but their functioning is reduced. B-cells are present in bone marrow already in the 12^{th} week of gestation, however, they start producing IgM and IgG at 20 weeks and IgA at 30 weeks (immunoglobulins, also called antibodies, are Y-shape plasma proteins used by the immune system to identify and neutralize pathogens such as bacteria and viruses), all in small quantities. Phagocytes are present, but their function is low, level of immune complement factors is reduced (Tekauc-Golob, 2001). PT newborns have increased need for calcium and iron, as the biggest transition of calcium, iron, and IgG through placenta occurs in the last trimester (Vaughan and Litt, 1992).

After birth, the mucosae of a newborn are bombarded by a large variety of microorganisms and protein antigens (Brandtzaeg, 2001). Enterocytes, cells lining the intestinal wall, play a vital role in antibody-mediated defense of a newborn, as they transfer breast milk-derived maternal immunoglobulins, from the intestinal lumen into

the newborn's body, and thus provide passive systemic immunity in the newborn period.

The best defined effector component of the mucosal immune system is secretory IgA, (dimeric molecule of IgA). It seems that intestinal uptake of secretory IgA antibodies after breast-feeding appears to be of little or no importance in the support of systemic immunity in the neonatal period, except perhaps in the PT infants, as there exists a brief and transient period when the neonatal gut may be capable of the uptake of a range of ingested substances, which is probably more pronounced in PT infants (Weaver et al., 1991).

Relatively good defense against infections confirms that the immune system in PT infants matures rather rapidly (Babnik J., 1988).

2.4.6.6 Urinary system

Due to immaturity, the kidney functions are insufficient, the ability to concentrate and dilute the urine is reduced, and therefore the excretion of toxins is slowed (Tekauc-Golob, 2001). Namely, the majority of nephrons are formed in the third trimester of pregnancy, thus at the time when PT infants are being delivered (Black et al., 2013).

2.4.6.7 Reproductive organs

IUGR and preterm birth can alter organ structure and functioning, which can reduce fertility in women. It was observed that VLBW women displayed a reduced probability of giving birth (Ekholm et al., 2004).

2.4.6.8 Skin and thermoregulation

Water loss from the skin is a major factor in overall water balance and a source of heat loss. Infants of 30 to 33 weeks of gestation have high water losses in the first week of their live (Rutter and Hull, 1979). In extremely PT infants, high water losses are probably transepidermal and the result of a thin, poorly keratinized stratum corneum (Rutter and Hull, 1979). Reduction of skin water loss in these infants may thus increase their chances of survival and their rates of growth (Rutter and Hull, 1979).

PT newborns have significantly increased body surface relative to their body mass, so in a cold environment they lose heat faster and have therefore difficulties in body temperature regulation. Stocks of brown fat, a source of heat in the newborn, are smaller in PT newborns, which diminishes their ability of thermogenesis (Tekauc-Golob, 2001).

3 MATERIAL AND METHODS

The present study, which was the focus of doctoral research project, was entitled “Longitudinal monitoring of growth and development of full-term and preterm infants”, that will be referred to as “Preterms 1987” in the following text. The study was designed by the Group of Anthropology of the Biotechnical Faculty, University of Ljubljana.

The present study used, combined, and analyzed different pre-existing data sources, as well as collected entirely new information that was used exclusively for the purposes of the present study. Pre-existing data sources include the following databases or studies that were performed under the guidance of different collaborators in different institutions:

- the Slovenian perinatal database that includes birth data of all Slovenian newborns;
- data from the study "Preterm birth, preterm babies and their further development", that will be referred to as “Initial study 1987” in the following text, started in 1987 and followed subjects yearly from birth up to the age of 3 and then again at 11 years of their age;
- the SLOfit system, sports-educational records, that are collected yearly in primary and secondary schools across Slovenia; and
- parts of an individual’s general physician (GP) medical record relating to subject’s childhood and adolescence, if available.

In addition, data on anthropometric measures of pregnant women, as well as data on growth and physical development during the first year of infant’s life were collected within the research project “The role of human milk in development of breast fed child's intestinal microbiota” that was performed from 2010 to 2013 and will be referred to as “My Milk” project in the following text.

All these data sources will be presented in detail below, as will the general outline of the present study and its specific protocols.

3.1 ETHICAL CLEARANCE

3.1.1 Ethics approval for the study

The consent of the Ethics Committee of the Republic of Slovenia was sought for the protocol of the study “Preterms 1987”. The approval by the Ethics Committee was gained on July 29, 2011, with the decision number 64/07/2011. The study protocol is in accordance with the Declaration of Helsinki.

In addition, consent of the Ethics Committee of the Republic of Slovenia was also sought for the extended research protocol that included a combined use of previously collected research data from all the data sources stated above, with a special emphasis on those subjects that we failed to contact and consequently failed to obtain their written permission for the participation in the present study. As consent for data collection was already provided by subjects' parents or legal representatives in all previous research studies in question, the Ethics Committee of the Republic of Slovenia approved the extended research protocol on May 20, 2013, with the decision number 76/04/2013.

3.1.2 Subjects' enrollment

Individuals that had already participated in the "Initial study 1987" were sought for and invited to voluntarily enroll to the present study. They were invited to enroll to the study by either electronic mail or Facebook (online social networking service) subgroup. Detailed information on all the enrollment activities for the present study is provided below.

3.1.3 Informed consent

All subjects, with the exception of those presented in paragraph 2 of the Chapter 3.1.1, provided a written informed consent for participation in the study. Informed consent was also obtained from the legal representatives of the subjects in all previous studies that acted as data sources for the present study.

3.1.4 Data protection

The treatment of all research data and their public presentation in written or oral form have been performed in accordance with the ethical standards and the existing law on personal data protection (UL RS, no. 86 / 2004 and supplements). A complete anonymity of subjects has been ensured throughout.

3.2 STUDY DESIGN AND DATA COLLECTION

3.2.1 General outline of the study

The present study was designed as both, prospective and retrospective cohort study.

A prospective approach was applied to study anthropometric variables on a group of pregnant women and their infants, with the purpose of evaluating the existing anthropometric methodology.

Differences in the physical development of premature and FT group of individuals were evaluated by the retrospective approach. For this purpose, birth data, data on physical and motor development of the subjects in their childhood, and data on their health status in childhood were collected. In addition, whenever possible, these data were complemented with data from online questionnaires and anthropometric measurements relating to the current state of the subjects during the study.

Several of the above stated data were collected in different previous studies or databases that have shortly been presented at the beginning of the Methods section. These studies will now be thoroughly presented below.

3.2.2 Overview of the study protocols

3.2.2.1 Research project "My Milk"

The research project entitled "The role of human milk in development of breast fed child's intestinal microbiota" abbreviated "My Milk", was performed by the collaborators of the Biotechnical Faculty University of Ljubljana, Slovenia, the Department of Gastroenterology, Hepatology and Nutrition Neonatology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia, and the Department of Neonatology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia. The project was undertaken from 2010 to 2013.

The study protocol of "My Milk" research project was approved by the Ethics Committee of the Republic of Slovenia on August 11, 2010, with the decision number 32/07/2010. The study protocol is in accordance with the Declaration of Helsinki. The study was also registered at ClinicalTrials.gov (NCT01548313) and was funded by the Slovenian Research Agency (ARRS J4-3606).

Pregnant women (N=175) were enrolled to the project. Their, as well as their newborn children data were collected during the course of the study. They first reported to the laboratory in the 3rd trimester of pregnancy. Thereafter, birth data were collected, which was followed by the second laboratory visit 1 month after delivery, the third laboratory visit 3 months after delivery, and the fourth laboratory visit one year after delivery.

For the pregnant women, the collected data included: data on demography (age, marital status), their anthropometric measures, data on their physical activity, maternal illnesses, allergies, nutritional habits, smoking, bone density determined with ultrasound at the distal third of the radius, and selected blood parameters. Data on pregnancy progress were obtained from their gynecologists' entries into the maternity booklets.

Infants' anthropometric measures were obtained during the second, third, and fourth laboratory visit, thus at the age of 1, 3, and 12 months. In addition, data on infants' anthropometric measures and their development at the age of 6 and 9 months after delivery were obtained from the pediatricians' records.

For the purpose of the present study, the following data from the project "My Milk" were used:
- all anthropometric data of pregnant women, presented in detail below; and
- all anthropometric data of infants during their first year of life, presented in detail below.

These data were used to test the hypotheses 1 and 2, as stated on page 5. We thus evaluated anthropometrical methods that are currently available to assess changes in physical properties of pregnant women (Hypothesis 1), and investigated whether maternal anthropometric characteristics can affect the pattern of growth in FT and premature children during the first year of their life (Hypothesis 2).

3.2.2.2 Research project "Initial study 1987"

The research study entitled "Preterm birth, preterm babies and their further development" now referred to as "Initial study 1987", has started in 1987 by the collaborators of the Unit for neonatal intensive care, Clinical Department of Perinatology, Maternity Hospital of the University Medical Centre Ljubljana, Slovenia, under the coordination of dr. Janez Babnik, MD. The study was performed with the aim to follow growth and development of PT and FT infants.

The growth and development of subjects enrolled into the study was followed in the first three years of their life and again at their 11 years of age (Babnik A., 2003). The subjects that were enrolled in the study included all alive PT infants, born in the period between March 9 and September 9 in 1987 in the Maternity Hospital Ljubljana, Slovenia. The control group consisted of every first FT infant (thus an infant with a GA from 37 to 41 6/7 weeks) born immediately after a PT infant. The final control group was larger than the PT group of infants, because all the FT infants, whose premature peers died in the neonatal period, remained included in the study (Babnik J., 1989).

Parents or legal representatives of the subjects agreed voluntary to participate in the study (Babnik J., 1988). The inclusion criterion was their permanent residence in Slovenia. For all the subjects, the gestational week of pregnancy at birth was determined according to the date of the last menstruation of the mother and actual deviation of the

birth date from the expected date of birth. The equations used for determining the expected date of birth (EDB) and the GA at birth [weeks] were:

$$\text{EDB} = \text{date of last day of menstruation} + 1 \text{ week} + 9 \text{ months} \quad \ldots (1)$$

$$\text{GA at birth [weeks]} = 40 \text{ [weeks]} - (\text{EDB} - \text{actual date of birth}) \quad \ldots (2)$$

Infants with severe lethal malformations were excluded from the study. The protocol of the study was approved by the Slovenian Ethics Committee (project number PORS 09 – 3698).

For the purpose of the study, a questionnaire for their pediatricians was designed, which was filled in at birth and at laboratory visits at the subjects' 1, 2, and 3 years of age and aimed to follow the somatic and neurological development of the subjects. The subjects' data at their 11 years of age were obtained by a questionnaire that was send to their parents (Babnik J., 1988; Babnik A., 2003). Along the course of the study, the smallest PT infants were monitored by pediatricians from the University Gynecological Clinic in Ljubljana, Slovenia. All the other infants were examined by the pediatricians in the regional and local Health care centers in Slovenia (Babnik J., 1989). Any potential changes of the permanent address of participating families were identified with the permission of the Ministry of the Interior (Babnik A., 2003).

The following data were obtained from the study questionnaire: data on morbidity, somatic growth, neurological defects, anamnesis of illnesses, particular chronic illnesses, congenital defects and hearing, hospitalizations, development, and social status of the family. In addition, the development of children was regularly observed with the Denver's developmental screening test (DDST) (Babnik J., 1988).

Data obtained in the "Initial study 1987" are of great importance for the present study, as we continued, upgraded, and deepened the research project from 1987 by contacting the same subjects that were previously enrolled and inviting them to participate in the present study. These, now adult people, provided the information about their current health status and several other information by filling-in the online questionnaires, as presented in detail below.

For the purpose of the present study, the following data from the "Initial study 1987" were adopted:

- order of pregnancy and parity (the number of times a female has given birth) number of PT and stillborn infants in previous pregnancies, number of fetuses in the pregnancy (singleton, twins, triplets);

- mothers age, smoking, illnesses before pregnancy, bleeding or illnesses during pregnancy (hypertension, (pre)eclampsia, and gestational diabetes; Annex A);
- birth date, date of the laboratory visit (at 1, 2, 3 and 11 years);
- GA at birth [weeks], chronological age at 1, 2, 3 [months] and 11 [years] and corrected age at 1, 2 and 3 years [months];
- body length/height [cm], body mass [kg], and head circumference [cm] at birth, 1, 2, and 3 years;
- type of prematurity (VLBW, large premature, FT) and appropriateness of birth mass for GA (SGA, AGA, LGA);
- diagnoses at birth (more in detail in Annex A): fetal distress, respiratory distress, cerebral hemorrhage, peri-ventricular leukomalation, hypoxia, apnoic attacks, hyperbilirubinemia (jaundice), hypoglycemia, cardiac anomalies, kidney anomalies, necrotizing enterocolitis, digestive anomalies, intestinal hernia, blood anemia, and heavier infections;
- medical actions applied at birth: reanimation, artificial ventilation (CPAP), fraction of inspired oxygen >0.4 (F_IO_2), exchange transfusion, transfusion, and ototoxic drugs;
- morbidity at 1, 2, 3 and 11 years (more in detail in Annex A): illnesses of the upper respiratory tract, otitis, pneumonia, obstructive bronchitis, chickenpox, rubella, measles, scarlet fever, gastroenteritis or colitis (Salmonella), acute laryngitis, pharyngeal hypotrophy, intestinal bacteria, urinary tract infection, dermatitis, constipation, and fever), chronic illnesses, rickets, febrile seizures, epilepsy, ventriculomegalia, hemiparesis, hydrocephalus operated, tetraparesis, diplegia, ataxia, cerebral paralysis, and length of potential hospitalizations;
- development observed with Apgar score at 1 and 5 minutes after birth, DDST at 1, 2 and 3 years, Assessment of the psychomotor development for expressing the developmental quotient at 1 and 2 years, and another unpublished questionnaire for detecting disabilities; and
- visual and hearing impairments and medical aids.

These data were used to test the hypotheses 3 to 6, as stated on page 5. We thus evaluated the incidence of illnesses in PT and FT children up to the adolescence (Hypotheses 3), the question whether the altered growth of PT infants can exert consequences further on in childhood, adolescence, and early adulthood (Hypotheses 4), as well as potential long-term differences in physical development of PT and FT children (Hypotheses 5 and 6).

3.2.2.3 Slovenian perinatal database

The Slovenian perinatal database is a national system for documenting birth data of all newborns in Slovenia and is used by all Slovenian maternity hospitals.

Several data are obtained at birth of every newborn, but for the purposes of this thesis the list is too extensive to be presented in detail. The following data from the Slovenian perinatal database were, however, obtained for the purpose of the present study:

- date of birth and GA at birth [weeks];
- birth length [cm], birth mass [kg], head circumference [cm];
- illnesses and other risk factors of the newborn; and
- Apgar scores [1 to 10] at 1 and 5 minutes after birth.

These data were used primarily to update any potentially missing data from the "Initial study 1987" that was presented in Chapter 3.2.2.2 and to supplement the data with anthropometric data between the subjects' ages of 3 and 6.

3.2.2.4 SLOfit system, sports-educational records database

The system of sports-educational records, also named the SLOfit system, was established by the Department of Physical Education, Faculty of Sport, University of Ljubljana, Slovenia. This is a national system for systematic monitoring of physical and motor development of children and youth, which includes all Slovenian primary and secondary schools, thus pupils from the age of 6 (or 7) to the age of 18 (or 19).

The SLOfit system is nowadays legally established within the following Slovenian legislation acts: Article 95 of the Law on primary education, Article 42 of the Law on grammar schools, Article 86 of the Law on Vocational and Technical Education. It was first introduced experimentally on a sample of schools in the period from 1981 to 1985 (approximately 37,000 children were enrolled each year at that time) and it was gradually incorporated in all schools since the school year 1986/87. From 1989/90 it includes almost whole Slovenian population (Jurak et al., 2011; Kovač et al., 2011).

Within the SLOfit system, standardized tests are performed annually (usually every year in April) in primary and secondary schools across the country, on children whose parents provided informed consent for their children's enrollment and subsequent research data processing. Along with data on physical growth, data on the motor capabilities of children are collected, and provide a comprehensive insight into the motor development of individuals and the population. On a yearly basis, the schools send the collected data to the Faculty of Sport, University of Ljubljana, Slovenia, where all the information is processed, evaluated, analyzed, and then resend to schools.

Data collected within the SLOfit system are:
- identification data of the participant;
- body height [cm], body mass [kg], triceps skinfold thickness [mm];
- speed of alternative movements, measured with the speed of touching panels with a hand, also referred to as arm plate tapping;
- explosive power, measured with long jump from the standing position with both feet together, also referred to as standing broad jump [cm];
- coordination of body movements, measured with the speed of walking backwards quadrupedally over the standard polygon, also referred to as polygon backwards [s];
- trunk muscle strength, measured with the number of torso lifts in a minute while lying supine, also referred to as sit-ups;
- forward bend and touch on the bench, also referred to as standing reach touch [cm];
- muscular endurance of the shoulder girdle and arms, measured with the time of hanging with hands on the pole, with head over the pole, also referred to as bent arm hang [s];
- sprint speed, measured with time of 60-meter run [s]; and
- general endurance, measured with time of 600-meter run [s].

A more detailed description of the measuring procedures of the SLOfit system tests was published by Strel et al. (1997). For the purpose of the present study, body height [cm], body mass [kg], triceps skinfold thickness [mm], aerobic test time of 600-meter run [s], anaerobic tests (sit-ups, standing broad jump [cm], bent arm hang [s], and time of 60-meter run [s]), and agility and fine motor tests (arm plate tapping, polygon backwards [s], and standing reach touch [cm]) of our subjects were acquired for each year of schooling from the SLOfit system database. The subjects' data were identified according to their names, birth dates, and school location.

These data were used to test the hypotheses 5 and 6, as stated on page 5.

3.2.2.5 General physician (GP) medical records

An individual's GP medical records are held by a personal physician, and include data recorded at regular systematic examinations that are being carried out during the preschool and primary school period.

Systematic examinations are carried out in children at the age of 1, 3, and 5 years by a family pediatrician, and then in the 1^{st}, 3^{rd}, 6^{th} and 8^{th} grade of primary school (thus at the ages of 6, 8, 11, and 13 years) by the qualified school doctors in local health centers. Systematic examinations are preventive health checks, not intended for treatment, but

are used for physicians to detect and note early illness states. Unlike vaccinations, which are mandatory, systematic examinations are not, but are recommended.

During systematic examinations, physicians note the overall condition of a child (mass, height), check blood pressure, vision, color vision (searching for color blindness), check the posture and spine position, listen to the lungs and heart, look for potential flat feet, and check blood counts. In the higher classes physicians examine the effects of puberty and child's body development.

For those subjects that provided written consent in the present study, health centers and personal physicians were contacted and copies of systematic examination data obtained from individuals' medical record. The participants could also decide to provide copies of their medical records on their own.

For the purpose of the present study, the following data were sought from an individual's medical record:
- body height [cm], body mass [kg], head and chest circumference [cm], all at the time of systematic examinations; and
- any presence of chronic illnesses, medical procedures and medical aids.

These data were used to test hypotheses 3 to 5, as stated on page 5.

3.2.2.6 Online questionnaires about the current state of the subjects

The same subjects enrolled in the "Initial study 1987", were contacted again in 2013 for the purposes of the present study. The aim was to obtain current data on their health status and anthropometric data of these, now adult, people.

Two online websites were created for the purpose of contacting and informing the subjects: an official website of the project (www.nedonosencki1987.si) and a subgroup "(Ne)donošenčki 1987" on Facebook. A detailed description of the study, an informed consent statement for the enrollment of the subjects, instructions for the participation in the study, and questionnaires (Annexes B, C, and D) were available through both of them.

The subjects were sought according to their electronic mail addresses, postal addresses, phone numbers, or Facebook profiles. The subjects, who agreed on enrollment in the study, provided a written informed consent detailing their willingness to provide data for each single data source that was presented above, as well as for anthropometric measurements and questionnaires about their current state.

As twenty-six years have passed since the 1987 study, we predicted a large dropout in number of available participants. Additional subjects born in 1987 were therefore also invited to enroll to the study and the invitations were spread with electronic mail and Facebook invitations.

The subjects were asked to fill-in the online questionnaires about physical activity, well-being and health, demography and, if they had not agreed on laboratory anthropometrical measurements, on their self-acquired basic body measurements. Thus, the new data obtained from the questionnaires were:
- basic demographic data;
- education and profession of the subjects;
- nutritional habits and smoking;
- data on physical activity (standard IPAQ questionnaire); and
- data on diagnosed chronic illnesses, medical aids, and medicines.

In addition, anthropometric data of the subjects were obtained by either reporting to the laboratory of the Group of Anthropology of the Department of Biology, Biotechnical Faculty of the University of Ljubljana, Slovenia, or by the completion of an online questionnaire, for which a detailed description of each measurement was provided to the subjects. In the first case, more anthropometric data (skinfold thicknesses) were obtained, in the second, only the basic anthropometric data were gained (body height, body mass, circumferences and, if available, resting morning blood pressure [mmHg]).

3.3 GENERAL APPROACH TO DATA ANALYSIS

For the purposes of the study, thus, to address all the hypotheses and to assess the differences in growth and development between the PT and FT children, the subjects were classified into subgroups according to the following criteria:

A/ their GA at birth enabled us to classify them as:
- very preterm infants – born before the 32nd gestational week (VPT group),
- moderately preterm infants – born between the 32nd and 36th gestational week (MPT group), and
- full-term infants with GA between 37th and 41st 6/7 week (FT group).

B/ their birth mass enabled us to classify them as:
- infants with very low birth mass, i.e. birth mass under 1,500 g (VLBW group),
- infants with moderate low birth mass, i.e. birth mass between 1,500 and 2,500 g (MLBW group), and
- infants with normal birth mass, i.e. birth mass of 2,500 g or more (NBW group).

As the majority of LBW infants belonged also to the PT group, and the majority of NBW to the FT group, we analyzed only the differences between VPT, MPT, and FT subgroups.

For all types of analysis, the level of 0.05 was adopted as statistically significant. Specific analysis and an exact description of all parameters used for the analysis are presented below and are ordered according to the hypotheses of the present study.

3.4 HYPOTHESES TESTING

3.4.1 Testing of the Hypothesis 1

"The existing anthropometric methods are inadequate for assessing body composition in pregnant women"

A general overview of the used methodology for Hypothesis 1 testing was provided in the Chapter 3.2.2.1, in which the research project "My Milk" was presented. Specific methodology for this purpose is presented below.

3.4.1.1 Specific methodology

Healthy pregnant women volunteers of European origin (N=175) were recruited in approximately the 30^{th} week of singlet pregnancy. They reported for the examination and meeting with the pediatrician and the dietician, and they provided information on their age, GA, and body mass before pregnancy.

Their MBH, current body mass (measured in clothes and barefoot, with mass of clothes later subtracted), six skinfold thicknesses, and four limb circumferences (all specified below) were measured at the time of laboratory visit by the same researcher. A subsample of pregnant women (N=15) was measured in duplicate, in order to assess, how big the influence of a random measurement error on the anthropometric evaluations is.

Their body fat percentage was then calculated from the anthropometric measurements according to different anthropometrical equations (see Tables 2 and 3 and Annex E). The aim of this calculation was to assess, how big the difference between the existing pregnancy specific and pregnancy non-specific methods for body composition assessment is, and consequently to assess the validity of some of the previous studies performed on body composition of pregnant women.

3.4.1.2 Anthropometric measurements

MBH [cm] was measured with a certified medical scale (Seca digital scale 769, Germany) barefoot in the standing position from the heel to the top of the head in Frankfurt horizontal position. Thus, the upper edge of ear hole (auditory meatus) and the lower edge of eye aperture (i.e. the edge of bone, approximately 1 cm below the lower lid) were positioned in a horizontal line. The measurement was performed with the precision of 0.1 cm.

Body mass [kg] was measured with the same medical scale barefoot and in underwear with the precision of 0.1 kg.

Skinfold thicknesses [mm] were measured according to standard instructions (Farmer, 1985; Khalil et al., 1995; Zekan et al., 1999) with the precision of 0.1 mm. Measurements were made in triplicate on the right side of the body with a calibrated certified skinfold caliper (Harpenden, HSB-BI, England), with faces (perpendicular measuring surface) of 6 x 15 mm, exerting a constant pressure of 10 g/mm^2 at all skinfold measurement sites, as proposed by the Committee on Nutritional Anthropometry of the National Research Council (Paxton et al., 1998).

Each fold of skin was firmly lifted up between the thumb and forefinger. The caliper was applied about 1 to 2 cm from the thumb-forefinger. Skinfold thicknesses at the following sites were measured:

- triceps (vertical skinfold, midway between acromion of the scapula and the olecranon of the ulna, over triceps);
- biceps (vertical skinfold, midway between acromion of the scapula and the olecranon of the ulna, over biceps);
- subscapular (oblique skinfold, below and medial to the tip of right scapula);
- iliac crest (horizontal skinfold, above the iliac crest in the midaxillary line);
- front thigh (vertical skinfold, front of thigh at mid-point between the upper end of patella and the mid-point of inguinal ligament); and
- median calf (vertical skinfold, medial skinfold at the largest circumference of the calf).

Triceps skinfold is measured more commonly than any other skinfold, partly because it is easily accessible. It has been closely correlated with percentage of body fat, total body fat, and has often included in studies of fat distribution, but it has also been shown to correlate worse with blood pressure than trunk skinfolds (Lohman et al., 1988).

Biceps skinfold is a measure of subcutaneous adipose tissue and skin thickness on the anterior site of the arm. In combination with other skinfolds it has been proposed as a useful predictor of total body fat (Durnin and Womersly, 1974). It can be useful in obese people, in whom many other skinfold thicknesses cannot be measured.

Subscapular skinfold is a measure of subcutaneous adipose tissue and skin thickness on the posterior site of the torso, it has been described as an important measure of nutritional status, and, combined with other skinfold measurements, it is a predictor of total body fat, blood pressure, and blood lipids (Lohman et al., 1988).

Iliac crest skinfold is commonly used as indicator of body fatness together with other skinfold thicknesses (Durnin and Womersly, 1974) and has been proved useful in the study of subcutaneous adipose tissue distribution, which is important for the assessment of illnesses risk (Lapidus et al., 1984; Larsson et al., 1984).

Front thigh skinfold has demonstrated high correlation with body density, as determined by hydrostatic weighing (Wilmore and Behnke, 1969).

Median calf skinfold samples the adipose tissue in the lower leg region and has been proved important in the prediction of total body fatness and in the evaluation of fat distribution (Lohman et al., 1988).

Circumferences [cm] were measured once on the trunk or on the right side of the body with a non-stretchable narrow measuring tape (fiber glass tape, China) with the precision of 0.1 cm. The following circumferences were obtained:

- wrist (around the wrist, midway between the styloid processus of ulna and pisiform bone);
- upper arm (around triceps and biceps, midway between the acromion of scapula and the olecranon of ulna; this parameter was measured only in the relaxed position in infants and in the relaxed position as well as in the rectangular flexion of the elbow in adults); and
- thigh (around the thigh, midway between the upper end of patella and the mid-point of inguinal ligament).

Wrist circumference is an indicator of limb skeletal growth.

Upper arm circumferences can be used as independent measures or can be combined with skinfold thicknesses to calculate arm muscle and adipose tissue (Gurney and Jelliffe, 1973).

Thigh circumference might facilitate the estimation of body density and can be useful indicator of adiposity or lean body mass, especially for muscle atrophy due to illnesses or injuries (Lohman et al., 1988).

3.4.1.3 Random measurement error for anthropometric parameters

Technical error of measurement (TEM) was calculated according to Gibson (2005) on a subsample of 15 pregnant women, for whom all the variables were measured in duplicate, with the two series of measurements separated by a time gap of 30 minutes. TEM was measured as:

$$TEM = ((\Sigma D^2) / 2N)^{1/2} \quad \ldots (3)$$

where D is the difference between two measurements and N is the number of subjects. The percentage TEM (% TEM) and coefficient of reliability (R) were also calculated according to the suggested protocol (Gibson, 2005):

$$\% TEM = (TEM / mean) * 100 \quad \ldots (4)$$

$$R = 1 - ((TEM)^2 / s^2) \quad \ldots (5)$$

where s^2 is the between-subject variance.

3.4.1.4 Body fat content in pregnant women

Selected anthropometrical measurements were used in twelve anthropometric equations developed for the assessment of body composition of middle-aged women (Equations (6) to (22) in Annex E). Eight direct (Paxton et al., 1998; Slaughter et al., 1988; Deurenberg et al., 1991; Rush et al., 1997; Peterson et al., 2003; Steinkamp et al., 1965) and four indirect (van Raaij et al., 1988; Catalano et al., 1995; Siri, 1961; Brožek et al., 1963) calculations of body fat tissue [%], with different calculations of body density associated with the latter, were applied. The list of anthropometrical measurements used with each of the above stated methods is presented below and in Tables 2 and 3.

Where applicable, body density (BD; [g/cm^3]) was first calculated according to five different equations (Durnin and Womersly, 1974; Jackson et al., 1980; Sloan et al., 1962; Durnin and Rahaman, 1967; Wilmore and Behnke, 1970). Body densities determined with these five equations were in turn used in four indirect equations for the assessment of body fat tissue [%] (van Raaij et al., 1988; Catalano et al., 1995; Siri, 1961; Brožek et al., 1963) (Annex E). Thus, each indirect method resulted in five

different estimates of body density and consequently in five somewhat different body composition assessments.

In total, three pregnancy specific methods (the first one developed for application to pregnant women in the 30th gestational week (van Raaij et al., 1988), the other two developed on a sample of pregnant women in the 30th (Catalano et al., 1995) and 37th (Paxton et al., 1998) gestational week) and nine pregnancy non-specific methods (Slaughter et al., 1988; Deurenberg et al., 1991; Rush et al., 1997; Peterson et al., 2003; Siri, 1961; Brožek et al., 1963; Steinkamp et al., 1965) were applied (Annex E).

Table 2: A list of anthropometric measurements used in anthropometric methods that were compared in the study (Annex E). Pregnancy specific anthropometric methods are written in bold

Preglednica 2: Seznam antropometričnih meritev, ki se jih uporablja pri antropometričnih metodah, ki smo jih primerjali v študiji (Priloga E). Specifične antropometrične metode za uporabo na nosečnicah so napisane s krepkim tiskom

	Equation	(6)	(**7**)	(8)	(9)	(10)	(11)	**(12)**	(13)	(14)	(15)	(16)	**(17)**	(18)	(19)	(20)	**(21)**	(22)
Age [years]				X			X		X									
Body height [cm]				X					X	X								
Body mass [kg]	Pre-pregnancy							X										
	Current			X				X	X	X						X	X	
Skinfold thickness [mm]	Triceps				X	X	X		X		X		X	X				X
	Biceps				X	X		X			X							
	Subscapular				X	X			X		X		X		X			X
	Iliac crest				X	X	X		X		X				X			
	Front thigh						X	X	X									X
	Median calf													X				
Circumference [cm]	Upper arm relax															X		
	Upper arm flex																	
	Wrist							X										
	Thigh															X		
Body density [g/cm^3]		X	X									X					X	

Table 3: A brief presentation of anthropometric methods that were compared in the present study (Annex E). Their type (direct or indirect methods resulting in body fat percentage, as well as methods resulting in body density (BD) are presented), study sample size, subjects' age and ethnic group, as well as comparative methods used in these studies are noted. Pregnancy specific anthropometric methods are written in bold

Preglednica 3: Kratka predstavitev antropometričnih metod, ki smo jih primerjali v tej študiji (Priloga E). Navedene so njihova vrsta (navedene so tako neposredne oz. posredne metode za izračun odstotka telesne maščobe, kot tudi metode za izračun gostote telesa (BD)), velikost vzorca iz raziskav, starost in etnična skupina, kot tudi primerjalne metode, ki so jih uporabili v teh študijah. Specifične antropometrične metode za uporabo na nosečnicah so napisane s krepkim tiskom

Equation	Method type	Sample size	Subjects age or age interval	Ethnic group	Estimation of body density with
(8)	direct	708	7-83	-	underwater weighing
(12)	direct	200	18-35	White (N=42) Black (N=49) Hispanic (N=109)	underwater weighing and deuterium oxide dilution, subjects in the 37th gestational
(13)	direct	321	18-55.6	White	DEXA, deuterium oxide dilution, and underwater weighing
(14) (15)	direct direct	82	18-27	White (N=40), Polynesian (N=42)	isotope dilution ($H_2{}^{18}O$)
(17) (18)	direct direct	136	8-29	White, Black	underwater weighing and deuterium oxide dilution
(20)	direct	817	22-44	White	tritium, helium dilution, and whole body counting of K^{40}
(6)	indirect	37	~ 24.5	-	a combination of equations from other studies
(7)	indirect	40	30.3	White (N=38) Black (N=1) Hispanic (N=1)	underwater weighing and isotope dilution ($H_2{}^{18}O$), subjects in the 30.8th (0.8) gestational week
(16)	indirect	-	-	-	underwater weighing
(21)	indirect	42	28.5	White	chemical analysis of adult human bodies and underwater weighing, developed for women in the 30th
(9)	BD	-	18-34	-	underwater weighing
(10)	BD	272	15-72	-	underwater weighing
(11)	BD	331	18-55	-	underwater weighing
(19)	BD	50	17-25	-	underwater weighing
(22)	BD	128	17.8-47.8	-	underwater weighing

Body mass index (BMI) was calculated according to the equation:

$$\text{BMI [kg/m}^2\text{]} = \text{body mass [kg]} / (\text{body height}^2\ [\text{m}^2]) \quad \ldots (23)$$

3.4.1.5 Specific statistical analysis

For each body location, median of skinfold thickness was first calculated from the three measurements. The median was then adopted as the representative value for skinfold thickness at a given location in all further calculations. Average and SD of each anthropometric variable were then calculated for the sample. SD is a measure that is used to quantify the amount of variation or dispersion of a set of data values.

For each subject, body fat percentage was first calculated separately for each method, than the average (SD) values for each method were calculated from all the individual data. Results on body fat percentages determined with different methods were finally compared with a one-way analysis of variance (ANOVA; VassarStats, Statistical Computation Website).

3.4.2 Testing of the Hypothesis 2

"The pattern of growth of full-term and premature children during the first year of life depends on anthropometric characteristics of mothers."

Selected data from "My Milk" study were used to test the Hypothesis 2. A general overview of the used methodology for Hypothesis 2 testing was provided in the Chapter 3.2.2.1, in which the research project "My Milk" was presented. Specific methodology for this purpose is presented below.

Additionally, selected risk factors for preterm birth were compared between VPT, MPT, and FT infants from "Initial study 1987". A general overview of the used methodology was provided in the Chapter 3.2.2.2, in which the "Initial study 1987" was presented.

3.4.2.1 Specific methodology

To assess the effects of maternal characteristics on infant's growth during the first year of life we compared anthropometric measurements of infants and their mothers from "My Milk".

As described in Chapter 3.4.1.1, healthy pregnant women volunteers of European origin (N=175) were recruited in approximately the 30^{th} week of singlet pregnancy. They reported for the examination and meeting with the pediatrician and the dietician, and they provided information on their age, GA, and PpBM.

Their MBH and current body mass (measured in clothes and barefoot, with mass of clothes later subtracted) were measured at the time of laboratory visit by the same researcher.

To determine whether the pattern of growth in PT and FT infants during the first year of life depends on the anthropometric characteristics of mothers, anthropometric measurements were obtained from infants. After birth, infants´ standard birth data were obtained (body height, birth mass, and head circumference). One, three, and twelve months after birth, those measurements were performed again. In addition, triceps, subscapular and middle thigh skinfold, as well as chest, wrist, and upper arm circumferences were measured in infants at their age of 1 and 12 months.

3.4.2.2 Anthropometric measurements

Infant's body height [cm] was measured by a non-stretchable narrow measuring tape (fiber glass tape, China) with the precision of 0.1 cm. Measurements were performed from the heel to the top of the head. Up to the infant's age of 3 months, measurements were performed in supine position and in standing position at the age of 1 year. Maternal body height was measured as described in Chapter 3.4.1.2.

Infant's body mass [kg] was measured with a certified table medical scale (Seca digital scale 376, Germany) with precision of 5 g. Maternal body mass was measured as described in Chapter 3.4.1.2.

Infant's triceps, subscapular, and front thigh skinfold thicknesses [mm] were measured as described in Chapter 3.4.1.2.

Infant's wrist and relaxed upper arm circumferences [cm] were measured as described in Chapter 3.4.1.2. Head circumference was measured as occipito-frontal circumference around the head, at glabella of the frontal bone and the most distant point of the occipital bone, chest circumference was measured around the thorax, at the mid-point of the sternal bone, both with the precision of 0.1 cm.

3.4.2.3 Maternal anthropometric characteristics and growth-related relative changes of infants´ anthropometric characteristics

PMG was calculated according to the equation:

$$\text{PMG [kg]} = \text{body mass measured once in the last 3 days before delivery [kg]} - \text{PpBM [kg]} \quad \ldots (24)$$

Infants from our study were classified into two or three groups according to the defined cut-off points for maternal physical characteristics. Adjustment for infant's birth mass, height, BMI, circumferences, or skinfold thicknesses was made with exclusion of 5 % of the infants with extreme values, to yield the same initial state in average values of each measurement in the compared groups.

Mothers anthropometric characteristic (MBH, PpBM, PpBMI, PMG) were classified as low or high. Cut-off points were adopted at 168 cm for MBH (Ramakrishnan et al., 1999), 62 kg for PpBM (Ramakrishnan et al., 1999), 25 kg/m^2 for PpBMI (Siega-Riz et al., 2010; WHO, 2004), and 16 kg for PMG (IOM, 1990; Siega-Riz et al., 2010).

Appropriateness of maternal PMG was determined relative to maternal PpBMI according to The Institute of Medicine report from 2009 (Committee on Obstetric Practice, 2013; IOM, 2009). The categories of PMG below, within, or above the recommended values (RV) for PpBMI (RV/PpBMI) were established (Table 4).

Table 4: Appropriateness of maternal pregnancy mass gain (PMG) in singleton or twins pregnancies determined according to recommended values (RV), that are associated with maternal pre-pregnancy BMI (PpBMI) (RV/PpBMI; after IOM, 2009)

Preglednica 4: Primernost pridobljene mase matere v nosečnosti (PMG) z enojčkom ali dvojčki določena glede na priporočene vrednosti (RV), ki so določene glede na prednosečniški ITM matere (PpBMI) (RV/PpBMI; po IOM, 2009)

PMG range [kg]	PpBMI [kg/m^2]			
	<18.5	18.5 – 24.9	25.0 – 30.0	>30.0
pregnant with singleton				
PMG below RV/PpBMI	<12.7	<11.3	<6.8	<5.0
PMG within RV/PpBMI	12.7 – 18.1	11.3 – 15.9	6.8 – 11.3	5.0 – 9.1
PMG above RV/PpBMI	>18.1	>15.9	>11.3	>9.1
pregnant with twins				
PMG below RV/PpBMI		<16.8	<14.1	<11.3
PMG within RV/PpBMI	not available	16.8 – 24.5	14.1 – 22.7	11.3 – 19.1
PMG above RV/PpBMI		>24.5	>22.7	>19.1

All infants were than classified according to each maternal anthropometric characteristic. Their growth patterns of body height, mass, BMI, circumferences, and skinfolds were calculated as relative increases [%] of each anthropometric measurement from birth to their age of 1, 3, and 12 months (body height, body mass, and head circumference) or from 1 to 12 month (skinfolds and other circumferences).

3.4.2.4 Risk factors for preterm birth

In addition, selected risk factors for preterm birth were compared between PT and FT infants from "Initial study 1987" with the aim of enabling better prediction and possible prevention of preterm birth. This part of the analysis was performed in cooperation with the collaborators of the Department of Anthropology, Faculty of Medicine, University of Freiburg, Germany.

As presented in Chapter 3.3, infants were classified according to their GA at birth into VPT, MPT, and FT group.

Potential risk factors for preterm birth (listed below) were recorded:
- order of pregnancy and delivery;
- number of PT and stillborn infants in previous pregnancies;
- multifetal pregnancy;
- illnesses before pregnancy (congenital and acquired heart failure, chronic pulmonary illness, diabetes, epilepsy, cancer, chronic kidney illness, hypertension);
- hypertension of the mother before pregnancy;
- illnesses during pregnancy (hypertensive illnesses: hypertension only during pregnancy, polysimptomatic gestosis, pre-eclampsia, convulsive eclampsia, chronic hypertension), other illnesses in pregnancy);
- bleeding in pregnancy (the first, second, and third trimester, placenta previa);
- maternal age at delivery;
- maternal smoking;
- educational level; and
- maritial status.

Due to large number of potential factors and their low incidence, specific illnesses were combined into meaningful units (Babnik J., 1989).

As data on the incidence of illnesses were primarily collected in yes/no format, no detailed information on diagnosis was available. Both, obstetric history data and anthropometric measures were available in numerical form.

3.4.2.5 Specific statistical analysis

Similar to Chapter 3.4.1.5, for each body location, median of skinfold thickness was first calculated from the three measurements. The median was then adopted as the representative value for skinfold thickness at a given location in all further calculations. Average and SD of each anthropometric variable were then calculated for the sample.

Infants´ anthropometric measurements, classified as presented in Chapter 3.4.2.3 into two or three groups according to maternal anthropometric characteristics, were compared with Student's t-test (Microsoft Office Excel, 2007) or a one-way ANOVA (VassarStats, Statistical Computation Website), respectively.

Frequencies of risk factors for preterm birth between PT and FT infants and between VPT and MPT infants were compared with Chi-square test (Microsoft Office Excel, 2007).

3.4.3 Testing of the Hypothesis 3 and 4

"The susceptibility to illnesses after the period of accelerated growth will be different between full-term and premature children."

"Frequency of illnesses associated with prematurity experienced after a period of accelerated growth will differ between premature and very premature children."

A general overview of the used methodology for Hypothesis 3 and 4 testing was provided in the Chapter 3.2.2, in which the overview of the present study was presented. Specific methodology for this purpose is presented below.

3.4.3.1 Specific methodology

For the purpose of testing the hypotheses 3 and 4, data on health status during the course of the study of participants from research project "Preterms 1987" were collected with an online questionnaire "Well-being, quality of life, and health – Medical aids, Injuries" (presented in detail in Annex B) at the subjects' age of 26 years.

Subjects were asked on their subjective opinion about their health status and health care, and about their previous illnesses, injuries, blood pressure in childhood and later in life, and whether they were wearing glasses or hearing aids. If participants enrolled for the laboratory visit, their blood pressure was measured with automatic blood pressure monitor (Omron M6W device, Japan) after 5 minutes of rest in the sitting position on the left upper arm and according to the manufacturer's instructions.

To supplement data gathered with online questionnaires, data on eventual illnesses in the school age were also obtained from individuals' GP medical records whenever these data were available.

3.4.3.2 Illnesses at birth and in preschool years

In addition, to evaluate the incidence of illnesses, other impairments, and data on neurological development, both, at birth and in the preschool age, data on medical diagnoses and medical aids were collected from the "Initial study 1987" from questionnaires for pediatricians and parents applied at subjects' age of 1, 2, 3, and 11 years, Perinatal database, from individual's GP medical records of participants, and from online questionnaires at their age of 26 years. Due to high number of neonatal illnesses meaningful units were established for easier classification (Babnik J., 1989).

The following recorded diagnoses at birth were collected from the "Initial study 1987" and Perinatal database:

- fetal distress;
- respiratory distress (hyaline membrane illness, transient respiratory distress, primary or secondary atelectasis, pulmonary interstitial emphysema, bronchopulmonary dysplasia, pneumothorax);
- cerebral hemorrhage;
- periventricular leukomalatia;
- hypoxia (lack of oxygen - evaluated according to the symptoms) and apnoeic attacks;
- hyperbilirubinemia (jaundice);
- hypoglycemia;
- blood anemia;
- cardiac, kidney, or digestive anomalies;
- necrotizing enterocolitis;
- intestinal hernia; and
- heavier infections (sepsis, meningitis, pneumonia, omfalitis, disseminated intravascular coagulation).

Similarly, the following recorded medical interventions at birth were collected from the "Initial study 1987" and Perinatal database:

- reanimation mask used;
- ototoxic medicines used;
- artificial ventilation needed (CPAP in days);
- increased fraction of inspired oxygen used (F_IO_2 >0.4; duration in days stated);
- transfusion needed (number stated); and
- exchange transfusion needed (number stated).

Furthermore, data on the following illnesses were obtained with the questionnaires for pediatricians applied at subjects' age of 1, 2, 3, and 11 years:

- infectious illnesses (infection of the upper respiratory tract, otitis, pneumonia, obstructive bronchitis and other infectious illnesses);
- chronic illnesses;
- ventriculomegalia;
- hemiparesis, tetraparesis;
- hydrocephalus operated;
- diplegia;
- ataxia; and
- cerebral palsy.

For the purpose of evaluating vision and hearing disorders at subjects' age of 1, 2, 3, 11, and 26 years, data on whether subjects were wearing glasses or hearing devices were collected with questionnaires for pediatricians during the "Initial study 1987".

Neurological development of the infants was followed-up with Apgar score at 1 and 5 minutes after birth and Assessment of the psychomotor development (APMD) as uncorrected and corrected developmental quotient (Čutarić, 1977). A questionnaire designed to describe neurological and congenital defects, as well as logopedic treatment was completed by infants' pediatricians during the "Initial study 1987" and during systematic health monitoring.

In addition to this assessment, development of infants was observed with the DDST (assessment of socialization, fine and gross motor skills, and speech). DDST had previously been standardized on the population of preschool children in Slovenia in 1984 (Accetto et al., 1988) and published by the Service for labor productivity of Republic of Slovenia as a handbook in 1988 (Babnik J., 1988). Whenever DDST is used on PT infants up to their age of three years, an adjustment of their actual age is used (Babnik J., 1989; 1990). Namely, corrected GA of a child is calculated according to the following equation (Hughes, 1998):

$$\text{Correction factor [years]} = \text{expected birth date} - \text{actual birth date} \quad \ldots (25)$$

$$\text{Corrected GA} = \text{chronological age} - \text{correction factor} \quad \ldots (26)$$

In addition, an overall mental health assessment was also provided by the pediatricians who classified all infants as "healthy", "at risk" (deviation from normal in the neurological and developmental view, no specific diagnosis), "with moderate disability" (manageable cerebral paralysis and retardation, severe behavioral disorders,

convulsions, surgery of hydrocephalus without drastic neurological or developmental problems, decreased hearing, visual impairment and chronic somatic illnesses), or "with severe disability" (any neurological or somatic illnesses that require hospitalization or long-term care, as well as blindness or deafness).

3.4.3.3 Specific statistical analysis

For each specific variable, the number of its cases and the subject number (i.e. the number of all subjects for which data for a specific variable were available) were used to calculate the percentage denoting the frequency of occurrence of a specific variable. Average and SD of selected medical interventions, Apgar scores, and developmental quotients were calculated for each study group.

Frequencies of parametric data denoting incidences of illnesses, tests scores, and injuries between PT and FT infants (Hypothesis 3) as well as between VPT and MPT infants (Hypothesis 4) were compared with Chi-Square test (Microsoft Office Excel 2007).

Numerical data on developmental indicators were compared between PT and FT infants (Hypothesis 3) as well as between VPT and MPT infants (Hypothesis 4) with a one-way ANOVA (VassarStats, Statistical Computation Website).

3.4.4 Testing of the Hypothesis 5

"The consequences of prematurity, such as lower height, lower mass, and smaller physical capacity, will be detected in late childhood and adolescence."

A general overview of the used methodology for Hypothesis 5 testing was provided in the Chapter 3.2.2.2, in which the overview of the present study was presented. Specific methodology for this purpose is presented below.

3.4.4.1 Specific methodology

For the assessment of long term consequences of preterm birth on physical characteristics (such as body height, mass, circumferences, and skinfolds) and physical exercise capacity in late childhood and adolescence, we followed several of these parameters from birth into later life, both in PT and FT group.

Specific data were obtained from the "Initial study 1987", Perinatal database, the SLOfit system records, individual's GP medical records, during laboratory visits, and with online questionnaires.

Those participants, who did not attend the laboratory measurements at their age of 26 years, completed the questionnaire "Anthropometry – Body measurements" (presented in detail in Annex C). For each subject, general instruction on the measuring instruments, best time of measurements, and general advice was first provided in the guidelines of the questionnaire. Female participants were asked to calculate the day of their menstrual cycle, as body composition can vary between different periods of the menstrual cycle. Thereafter, detailed instructions for each single measurement with graphical aids were provided to ensure maximal possible adequacy of measurements.

For all data, subjects' age at a specific measurement was classified into groups with the precision of three months. Thus, four age groups were established within every single year. If needed, these age groups were afterwards consolidated in either half-yearly or yearly periods, so as to enable the optimal analysis.

When data on body height, mass, and triceps skinfold thickness of an individual for a single year were missing, imputation was made by calculating the most appropriate value as the arithmetic mean between the two surrounding values.

BMI [kg/m^2] was calculated according to equation (23).

For body height, mass, and BMI, z-scores were calculated according to WHO standards (2004) and Usher and McLean growth charts (1969), using the following equation:

$$\text{z-score} = (\text{obtained data value} - \text{standard population mean}) / \text{SD} \quad \ldots (27)$$

Z-scores reflect, how many SD above or below the population mean a raw score lies. A z-score of 0 equals the median (50^{th} percentile), and a z-score of ± 2 SD approximately the 98^{th} and 2^{nd} percentile, respectively. Z-scores were proposed as more precise assessments of growth than percentile cut-offs, and are expected to better quantify growth at the extremes of the distribution (Kuczmarski et al., 2002). Also, they were proposed as preferable for statistical comparisons over time, as they enable fewer violations of the underlying assumptions that would occur, if percentiles were compared by parametric statistics (Kuczmarski et al., 2002).

To evaluate the yearly increments of body height in the three study groups (VPT, MPT, and FT), differences between body heights in sequential years were calculated for each individual. In this manner, annual absolute increments of body height were determined. Relative increments were calculated by dividing these absolute yearly increments with each individual's birth length.

For each individual, the age corresponding to the highest increment in body height was determined and adopted as the maximal growth spurt or the so called peak height velocity (PHV). As PHV is an important event in an individual's puberty as indicator of fast maturation of the body (Hägg and Taranger, 1982), this parameter was adopted as important stage in sexual maturation. Average (SD) age at PHV was finally calculated and compared between the three study groups. In addition, for the more precise determination of the onset of sexual maturation, females were asked about their age at menarche onset.

For the assessment of motor skills in late childhood and adolescence, data on body fitness were gathered from the SLOfit system records. Results of eight tests (speed of alternative movements, explosive power, coordination of body movements, trunk muscle strength, forward bend and touch on the bench, muscular endurance of the shoulder girdle and arms, sprint speed, and general endurance) were obtained and standardized separately by comparing each individual's result with population mean (equation (27)) for each test and school year. Mean z-scores for each school year separately for aerobic, anaerobic, and agility and fine motor tests were then calculated.

As body composition is affected by the extent of regular physical activity, the latter, was assessed with a questionnaire "Physical activity and sports clubs" (presented in detail in Annex D), which was based on the International Physical Activity Questionnaires (IPAQ, 2005) adjusted for the purposes of the present study.

3.4.4.2 Anthropometric measurements

In 1987, the newborns were measured right after birth by the midwives according to the standard procedure, which is presented in details below; these data are entered into the Slovenian Perinatal database (Babnik A., 2003).

Birth length [cm] was measured with the measuring tape in the supine position on the side of the body from the heel to the top of the head with minimal precision of 0.5 cm.

Birth mass [kg] was measured with an analog scale for weighing of newborns, with minimal precision of 5 g.

Later on, body height [cm] and body mass [kg] were measured as described in Chapter 3.4.1.2 with the minimal precision of 0.5 cm and 0.5 kg, respectively.

3.4.4.3 Physical activity of subjects

Current physical activity was calculated for each individual according to the Guidelines for data processing and analysis of the IPAQ (2005) and was expressed in metabolic minutes (MET-minutes) per week. MET is an abbreviation for metabolic. MET-minute scores are equivalent to kilocalories for a 60 kilogram person. MET-minutes/day or MET-minutes/week can be presented although the latter is more frequently used and is thus suggested. MET-s are multiples of the resting metabolic rate and a MET-minute is computed by multiplying the MET score of an activity by the minutes performed, considering different weighing factors for walking, cycling, moderate and vigorous physical activity (equations from IPAQ, 2005):

Walking MET = 3.3 * (walking time [minutes per day]) * (walking frequency [days per week]) … (28)

Cycling MET = 6.0 * (cycling time [minutes per day]) * (cycling frequency [days per week]) … (29)

Moderate physical activity MET = 4.0 * (moderate-intensity activity time [minutes per day]) * (moderate-intensity activity frequency [days per week]) … (30)

Vigorous physical activity MET = 8.0 * (vigorous-intensity activity time [minutes per day]) * (vigorous-intensity activity frequency [days per week]) … (31)

Total subjects' physical activity in the last week was calculated as the sum of all different activities performed for transport, housework, and recreation. These values were than evaluated by comparing them with the following recommendations (IPAQ, 2005):

- low physical activity individuals: people, who do not meet the criteria for any of the following groups;
- moderate physical activity individuals: people with any combination of walking, moderate-intensity, or vigorous intensity activities achieving a minimum of 600 MET-min/week; and
- high physical activity individuals: people with any combination of walking, moderate-intensity, or vigorous intensity activities achieving a minimum of 3000 MET-minutes/week.

Finally, the three subject groups (VPT, MPT, and FT) were compared.

3.4.4.4 Specific statistical analysis

Average and SD of each anthropometric variable were calculated for the study groups.

Data on different anthropometric measurements, BMI, z-scores, PHV, age at menarche, SLOfit scores, and physical activity between PT and FT or between VPT, MPT, and FT individuals for each year were compared with Student's t-test (Microsoft Office Excel 2007) or a one-way ANOVA (VassarStats, Statistical Computation Website), respectively.

3.4.5 Testing of the Hypothesis 6

"Distribution of body fat will be different in full-term and premature children."

A general overview of the used methodology for Hypothesis 6 testing was provided in the Chapter 3.2.2.2, in which the overview of the present study was presented. Specific methodology for this purpose is presented below.

3.4.5.1 Specific methodology

For the evaluation of distribution of body fat in PT and FT infants, data on body fat amount in childhood, adolescence, and adulthood were collected from the SLOfit system (triceps skinfold thickness) and laboratory visit (eight skinfold thicknesses and six circumferences) at subjects' age of 26 years. Trunk and limb measurements (presented in detail below) were compared to each other and with body height to evaluate, whether the fat amount differs between these regions.

3.4.5.2 Anthropometric measurements

Body height [cm] was measured as described in Chapter 3.4.1.2 with a certified medical scale (Seca digital scale 799, Germany) or measuring tape at home with the precision of 0.1 cm.

Triceps, biceps, subscapular, iliac crest, front thigh, and median calf skinfold thicknesses [mm] were measured as described in Chapter 3.4.1.2. Supraspinal skinfold thickness was measured as oblique skinfold, above and medial to the iliac spine, abdominal skinfold as horizontal skinfold, 2-3 cm to the right and 1 cm inferior of the umbilicus.

Similar as iliac crest skinfold, supraspinal skinfold is commonly used as indices of body fatness together with other skinfold thicknesses (Durnin and Womersly, 1974) and have

been proved useful in the study of subcutaneous adipose tissue distribution, which is important for the assessment of illnesses risk (Lapidus et al., 1984; Larsson et al., 1984).

Abdominal skinfold has been included in many studies of body fatness and in many regression equations (Lohman et al., 1988) and changes markedly with mass reduction (Després et al., 1985).

Upper arm and thigh circumferences [cm] were measured as described in Chapter 3.4.1.2, but with different measuring tape (fiber glass tape, Rollfix, Hoechstmass, Germany). Waist circumference was measured around the trunk, midway between the lowest edge of the ribs and the highest point of the iliac bone (pelvis), at the end of a normal expiration, hip circumference around the hips, at the level of maximum extension (convex part) of the buttocks, and calf circumference around the calf, at the maximum circumference in a plane perpendicular to the long axis of the calf).

Waist circumference is an anthropometric indicator of deep adipose tissue, it is related to lean body mass (Jackson et al., 1980), and is highly correlated with BMI (Lohman et al., 1988).

Hip circumference (also named buttocks circumference) is a measurement of external pelvic size that reflexes the amount of adipose tissue in that region, which is largely subcutaneous (Lohman et al., 1988) and relates to the lower segment of the body (Lohman et al., 1988).

Calf circumference provides estimates of cross-sectional muscle and adipose tissue of the calf (Lohman et al., 1988).

3.4.5.3 Body fat distribution and content

Fat distribution was determined with the trunk-to-limb skinfold ratios (different number of aggregated skinfold thicknesses; see: “Trunk / limb 1:1”, “2:2”, and “4:4” below) (Monyeki et al., 1999), waist-to-height ratio (WHtR) (Hsieh and Yoshinaga, 1995), waist-to-hip ratio (WHR) (WHO, 2004), and 2:2 trunk-to-limb circumference ratio (see: “Trunk / limb 2:2 C” below):

$$\text{Trunk / limb 1:1} = \text{subscapular skinfold / triceps skinfold} \quad \ldots (32)$$

$$\text{Trunk / limb 2:2} = (\text{subscapular + iliac crest skinfolds}) / (\text{triceps + biceps skinfolds}) \quad \ldots (33)$$

Trunk / limb 4:4 = (subscapular + iliac crest + supraspinal + abdominal skinfolds) / (triceps + biceps + front thigh + median calf skinfolds) … (34)

WHtR = waist circumference [cm] / body height [cm] … (35)

WHR = waist circumference [cm] / hip circumference [cm] … (36)

Trunk / limb 2:2 C = (waist + hip circumference) / (upper arm relaxed + thigh circumference) … (37)

Hip circumference used in conjunction with waist circumference (WHR), it is an indicator of the pattern of subcutaneous adipose tissue distribution (Lohman et al., 1988), with low values being characteristic of women (Lohman et al., 1988).

For childhood, adolescence, and adulthood the percentage of body fat was calculated according to Durnin and Womersly (1974) from triceps skinfold thickness. The equations from which percentage of body fat was calculated were:

Body fat [%] for males = 1.1252 – (0.0625 * log of triceps skinfold thickness) … (38)

and:

Body fat [%] for females = 1.1159 – (0.0648 * log of triceps skinfold thickness) … (39)

Body fat mass [kg] was calculated from body mass and the above presented percentage of body fat:

Body fat mass [kg] = body fat [%] * body mass [kg] / 100 … (40)

As equations (Hume, 1966) and nomograms (Fuchs et al., 1978) for the estimation of lean body mass [kg] were developed for elder age group or for one gender only, lean body mass was calculated by subtracting body fat mass from the total body mass:

Lean body mass [kg] = body mass [kg] – body fat mass [kg] … (41)

3.4.5.4 Specific statistical analysis

Triceps skinfold thickness in SLOfit system was measured once; however, at the laboratory visit it was measured three times. Therefore, for each body location, median of skinfold thicknesses was first calculated from the three measurements. Median was then adopted as the representative value for skinfold thickness at a given location in all further calculations. Average and SD of each anthropometric variable were calculated for the study groups.

Triceps skinfold thickness, percentage of body fat at subjects' ages from 8 to 19 and at 26 years, and body fat distribution ratios at 26 years were compared between the study groups with a one-way ANOVA (VassarStats, Statistical Computation Website).

4 RESULTS

4.1 DATA COLLECTION RESULTS

The sample size varied between the different time points of the study. Hereinafter the main data of the sample are described, separately for both, "My Milk" and "Preterms 1987" projects.

4.1.1 Data from the "My Milk" project

174 women were enrolled to the study. The dropout in sample size was approximately 11 % from the enrollment of the participants up to the laboratory visit performed in the 30th week of pregnancy (N=156) and delivery (N=155), and approximately 13 % up to twelve months after delivery (N=151). The largest dropout was in mothers with FT infants (Tables 5 and 6).

Table 5: The number of participating mothers in the "My Milk" project, presented according to gestational age and gender of their infant

Preglednica 5: Število sodelujočih mater v raziskavi "Moje mleko" glede na gestacijsko starost in spol njihovih otrok

Time point		pre-pregnancy	pregnancy	delivery	1 month	12 months
subject number (N)						
males	PT	2	2	3	3	3
	FT	77	77	77	77	77
females	PT	6	6	5	5	4
	FT	71	71	70	70	67

PT – preterm, FT – full-term

Table 6: The number of participating infants in the "My Milk" project

Preglednica 6: Število sodelujočih dojenčkov v raziskavi "Moje mleko"

Time point		birth	discharge	1 month	3 months	12 months
subject number (N)						
males	PT	6	6	6	6	5
	FT	78	78	78	78	78
females	PT	7	7	7	5	4
	FT	71	71	71	69	68

PT – preterm, FT – full-term

4.1.2 Data from the "Preterms 1987" project

474 subjects were enrolled to the study. All but one FT infants were born as a single fetus, almost all twins and triplets were PT infants. This distribution was significantly different ($p<0.001$) between the study groups (Table 7).

Most of the infants were AGA, but there were significantly more ($p<0.01$) SGA infants in the group of PT infants, and more ($p<0.05$) LGA infants in the group of FT infants (Table 7).

Table 7: The number of participants at birth, presented according to the type of pregnancy and the appropriateness of birth mass for gestational age

Preglednica 7: Število preiskovancev ob rojstvu glede na vrsto nosečnosti in primernost porodne mase glede na gestacijsko starost

		All	Type of pregnancy			Appropriateness of birth mass for gestational age		
	subgoups		singleton	twins	triplets	SGA	AGA	LGA
males	subject number (N, (%))							
	VPT	24	21, (87.5)	0, (0.0)	3, (2.5)	2, (8.3)	22, (91.7)	0, (0.0)
	MPT	90	75, (83.3)	13, (14.5)	2, (2.2)	10, (11.1)	73, (81.1)	7, (7.8)
	FT	141	140, (99.3)	1, (0.7)	0, (0.0)	3, (2.1)	131, (92.9)	7, (5.0)
	Chi-square (p)		**<0.001**	**<0.001**	**<0.001**	**<0.05**	**<0.05**	nsg
females	subject number (N, (%))							
	VPT	20	14, (70.0)	6, (30.0)	0, (0.0)	2, (10.0)	18, (90.0)	0, (0.0)
	MPT	88	74, (84.1)	13, (14.8)	1, (1.1)	11, (12.5)	74, (84.1)	3, (3.4)
	FT	112	112, (100.0)	0, (0.0)	0, (0.0)	7, (6.3)	88, (78.6)	17, (15.3)
	Chi-square (p)		**<0.001**	**<0.001**	NA	nsg	nsg	**<0.01**

VPT – very preterm, MPT – moderately preterm, FT – full-term, AGA – appropriate for gestational age, LGA – large for gestational age, SGA – small for gestational age, NA – not applicable

Six of the initial participants died during the study; 2 males (one at 6 months, one at 13 years) and 4 females (two in the first weeks and two in the first years of life). Eight males and eleven females have moved from Slovenia. For 39 males and 31 females study documentation from laboratory visits that was fulfilled by researchers from the Maternity hospital, was lost after the year of 1990; these subjects were therefore excluded from the present study.

Birth mass (r=0.87) and body length (r=0.88) correlated very well with GA (Figure 4 and 5).

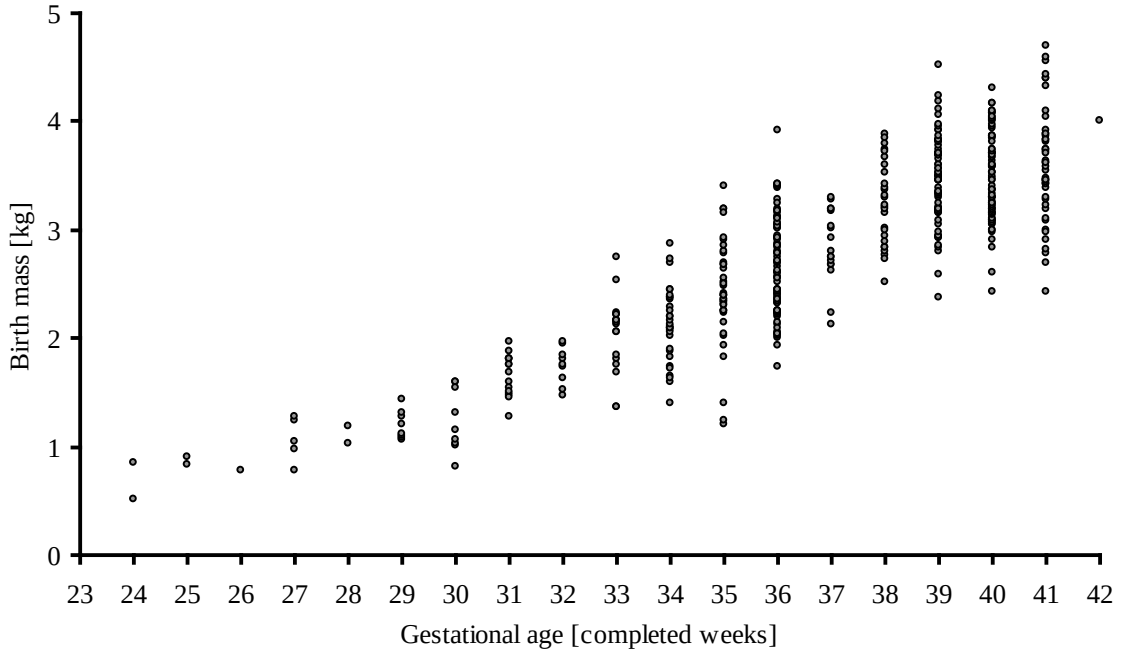


Figure 4: Distribution of birth mass according to gestational age at birth

Slika 4: Porazdelitev porodne mase glede na gestacijsko starost ob rojstvu

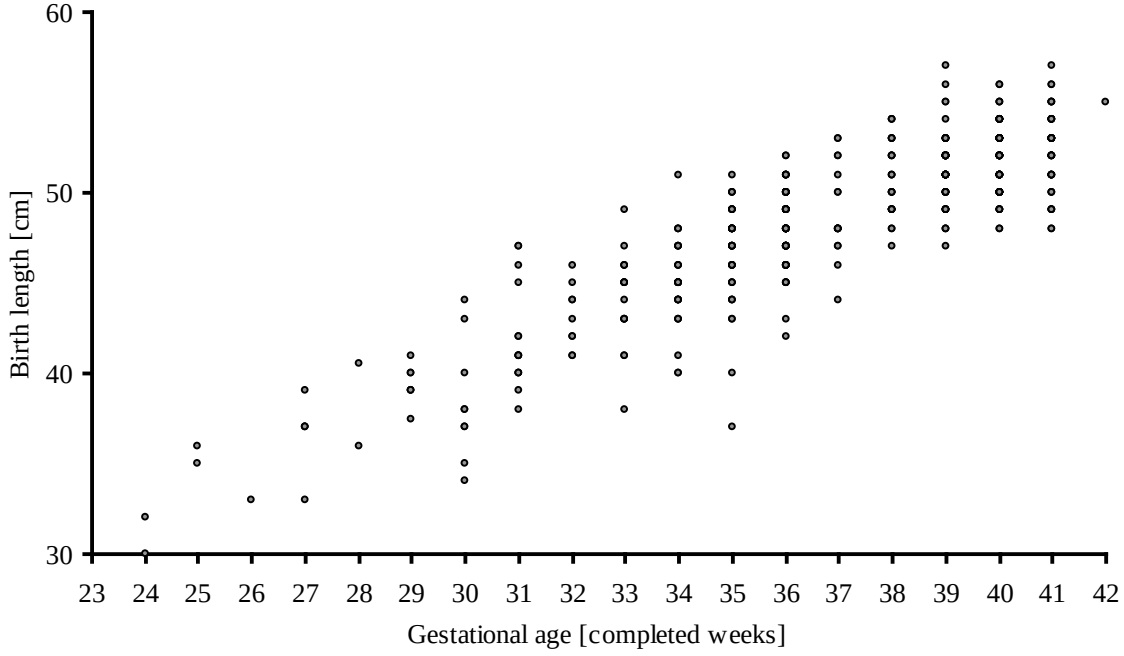


Figure 5: Distribution of birth length according to gestational age at birth

Slika 5: Porazdelitev porodne dolžine glede na gestacijsko starost ob rojstvu

Average (SD) GA at birth was similar between males and females in all three groups (Table 8). Correction factor that were used for the calculation of corrected GA of PT infants up to the age of three years are presented in Table 8.

Table 8: Average (SD) gestational age and the correction factor used for the calculation of corrected age of the participants for all study groups

Preglednica 8: Povprečna (SD) gestacijska starost in korekcijski faktor za starost preiskovancev ob rojstvu za vse raziskovalne skupine

		gestational age [week]	correction factor [years]
average (SD)			
males	VPT	29.5 (1.8)	0.20 (0.04)
	MPT	34.9 (1.2)	0.10 (0.02)
	FT	39.5 (1.2)	NA
females	VPT	28.7 (2.3)	0.22 (0.04)
	MPT	34.9 (1.3)	0.10 (0.02)
	FT	39.5 (1.1)	NA

VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable

There were 439 participants' addresses available in the database of the "Initial study 1987". After searching the recent phonebook and electronic database Facebook, 302 current postal addresses, 121 e-mail addresses, and 83 telephone numbers were identified. When participants could not be reached by telephone number or Facebook, letters of invitation to the present study were sent to postal addresses (N=287), and 88 responses were received. Two subjects rejected to participate, others (N=86) have signed the consent for participation in the study and provided their formal agreement for obtaining their personal data from different databases (Table 9).

Although there were some individuals, who first provided their informed consent, not all of them filled in the questionnaires or provided GP medical records. Nevertheless, a significant amount of data from the above stated databases was obtained, except, of course, for those individuals, who did not provide their consent for the study (Table 10). This was possible because ethics committee approval was also gained for the analysis of data for those subjects who could not be located, as they all provided their informed consent for either the "Initial study 1987" or the SLOfit system, so we were able to obtain further data from the perinatal database and the SLOfit system.

Table 9: The number of signed consent forms and agreements for obtaining personal data from different databases from 26 year old participants

Preglednica 9: Število podpisanih pristopnih izjav in dovoljenj za pridobitev podatkov iz podatkovnih baz, ki so jih zagotovili 26 let stari preiskovanci

		Signed consent forms	Agreement for obtaining data from the perinatal database	SLOfit system	current questionnaires	GP medical records	Written rejections of participation
subject number (N)							
males	VPT	3	3	3	3	3	0
	MPT	15	15	15	15	15	0
	FT	18	18	18	17	17	1
females	VPT	8	8	8	8	8	0
	MPT	20	20	20	20	20	1
	FT	22	24	24	22	22	0

VPT – very preterm, MPT – moderately preterm, FT – full-term, GP – general physician

Table 10: Data obtained from different databases from 26 year old participants

Preglednica 10: Pridobljeni podatki iz podatkovnih baz za 26 let stare preiskovance

Data source:		Perinatal database	SLOfit system	Questionnaires: Demo-graphy	Anthropo-metry	Health	Physical activity	GP medical records
subject number (N)								
males	VPT	24	22	3	2	2	2	1
	MPT	90	78	6	3	6	5	8
	FT	140	125	12	11	11	11	7
females	VPT	20	15	5	4	5	5	4
	MPT	88	66	12	8	12	12	4
	FT	111	97	15	9	14	14	7

VPT – very preterm, MPT – moderately preterm, FT – full-term, GP – general physician

The dropout in sample size was 15 % to 35 % up to the age of three years, the largest dropout was observed in MPT infants.

Data from the SLOfit sports-educational records that included participants at their age of 7 to 20 years were available for approximately 85 % of the initially enrolled participants (84 % of VPT, 81 % of MPT and 88 % of FT); however, for only approximately 65 % of the initially enrolled participants data were obtained in each year during the study (Table 11; 68 % of VPT, 62 % of MPT and 68 % of FT).

At the age of 26 years, approximately 18 % of the initial participants were re-enrolled in the study (Table 11, more details presented in Tables 9 and 10).

Table 11: The number of participants during the study

Preglednica 11: Število preiskovancev v pričujoči raziskavi

Age		birth	disch.	1 mo	3 mo	6 mo	9 mo	1 y	2 y	3 y
subject number (N)										
males	VPT	24	18	0	0	0	0	21	21	19
	MPT	90	65	2	4	4	3	71	69	65
	FT	140	117	3	3	2	2	121	119	107
females	VPT	20	19	0	1	0	0	20	20	17
	MPT	88	65	1	1	0	1	77	61	57
	FT	111	101	3	2	3	2	100	93	85

Age		3.5 y	5 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y
subject number (N)										
males	VPT	0	0	1	12	18	18	19	21	20
	MPT	1	0	6	52	61	65	62	61	66
	FT	1	0	5	85	101	102	99	105	101
females	VPT	0	0	1	12	12	11	12	11	11
	MPT	0	1	4	45	49	56	52	55	56
	FT	1	0	3	70	75	76	73	88	72

Age		14 y	15 y	16 y	17 y	18 y	19 y	20 y	21 y	26 y
subject number (N)										
males	VPT	18	19	13	12	9	8	2	0	3
	MPT	58	56	35	31	29	25	6	2	15
	FT	94	89	55	51	54	35	11	0	18
females	VPT	9	10	9	8	11	7	0	0	8
	MPT	49	46	38	31	26	22	5	0	20
	FT	71	69	52	35	30	40	11	1	22

VPT – very preterm, MPT – moderately preterm, FT – full-term, disch. – discharge from the hospital, mo – months, y – years

4.2 RESULTS OF HYPOTHESES TESTING

4.2.1 Results of Hypothesis 1 testing

We hypothesized that the existing anthropometric methods are inadequate for assessing body composition in pregnant women. In addition, we expected that pregnancy specific anthropometric methods will provide rather similar results on body composition of pregnant women, whereas pregnancy non-specific anthropometric methods will differ from the pregnancy specific methods by certain amounts. Results were published in Robič et al. (2013).

The measurements were performed on 147 women of average 30.5 (4.3) years of age, and GA of 31.6 (2.8) weeks of pregnancy (range: 26 to 37 weeks). The average values of their body mass before pregnancy, body mass at the time of measurement, and body height, as well as skinfold thicknesses and limb circumferences are presented in Table 12.

% TEM for the measurements of skinfold thicknesses was 5.3 (1.8) %, for other measurements 0.9 (0.2) %. R for the measurements of skinfold thicknesses was 0.998 (0.002), for other obtained measurements 0.997 (0.037) (Table 12).

Table 12: Results of anthropometric measurements from 147 pregnant women in the present study. Average (SD) measurement outcomes, percentage technical error of a measurement (% TEM), and coefficient of reliability (R)

Preglednica 12: Rezultati antropometričnih meritev 147 nosečnic v pričujoči raziskavi. Prikazani so povprečja (SD) meritev, tehnična napaka meritve v odstotkih (% TEM) in koeficient zanesljivosti (R)

Anthropometric measurement	average (SD)	% TEM	R
Age [years]	30.5 (4.3)		
Body height [cm]	167.3 (6.0)		
Pre-pregnancy body mass [kg]	62.7 (10.2)		
Current body mass [kg]	73.0 (11.0)		
Triceps skinfold thickness [mm]	19.2 (7.3)	5.3	0.999
Biceps skinfold thickness [mm]	9.4 (4.4)	7.3	0.994
Subscapular skinfold thickness [mm]	16.6 (7.0)	3.3	0.999
Iliac crest skinfold thickness [mm]	31.9 (8.4)	4.4	0.997
Front thigh skinfold thickness [mm]	40.3 (13.0)	3.7	0.999
Median calf skinfold thickness [mm]	18.4 (7.2)	7.7	0.998
Upper arm relax circumference [cm]	29.0 (3.3)	1.0	0.993
Upper arm flex circumference [cm]	30.1 (3.2)	0.7	0.997
Wrist circumference [cm]	15.9 (0.9)	0.7	0.921
Thigh circumference [cm]	55.9 (5.2)	1.1	0.998

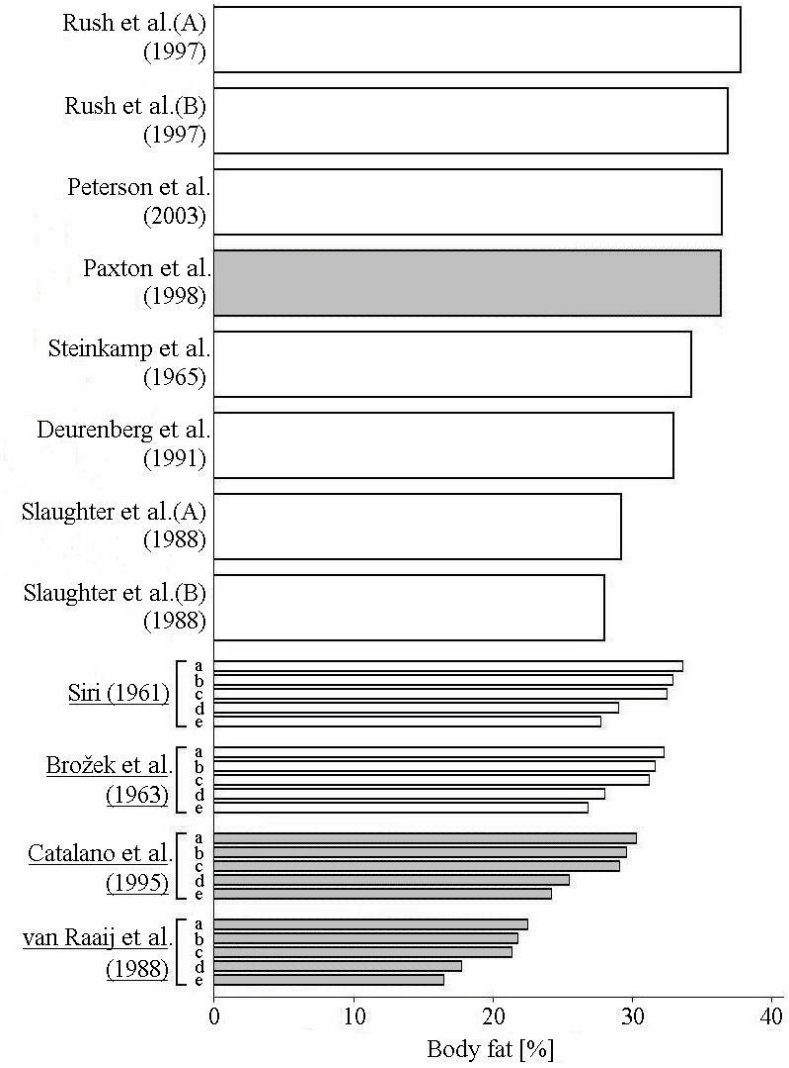
The estimations of body fat percentage for the same sample of pregnant women varied dramatically ($p<0.0001$), both, statistically and meaningfully, according to the equation used. They ranged from 16 (5) % up to 38 (4) % (Figure 6), depending on the method used.

Pregnancy non-specific direct anthropometric methods of Rush et al. (A and B) (1997), Peterson et al. (2003), Steinkamp et al. (1965), Deurenberg et al. (1991), and Slaughter et al. (A and B) (1988) resulted in the estimated body fat content of 38 (4) %, 37 (4) %, 36 (5) %, 34 (6) %, 33 (5) %, 29 (7) %, and 28 (8) %, respectively. Pregnancy non-specific indirect anthropometric methods of Siri (1961) and Brožek et al. (1963) resulted in body fat content of 28 (5) % to 34 (5) %, and 27 (5) % to 32 (4) %, respectively, depending on the selected method for body density calculation (Figure 6).

A pregnancy specific direct anthropometric method of Paxton et al. (1998) resulted in body fat content of 36 (6) %. Pregnancy specific indirect anthropometric methods of Raaij et al. (1988) and Catalano et al. (1995) resulted in body fat content of 16 (5) % to 23 (5) %, and 24 (6) % to 30 (5) %, respectively, depending on the selected method for body density calculation (Figure 6).

The analysis was also performed on more selected sample of 96 women of average 30.4 (4.2) years of age, and GA of 31.8 (1.7) weeks of pregnancy (range: 29 to 34 weeks) and the results were practically the same, which proofs that a wide range of GA in the present study is not the reason for a wide range of results on body fat content.

Furthermore, these large differences in body composition assessment persisted regardless of the women's stature. Namely, the range between the minimal and maximal values of body fat percentage, as assessed by different anthropometric methods, were 23 (2), 23 (3), and 24 (4) units for women with low, normal, and high PpBMI, respectively, (Figure 7) and there was no statistical difference ($p=0.185$) between the 3 groups.



Letters on the Y-axis: a – Sloan et al. (1962), b – Durnin and Rahaman (1967), c – Wilmore and Behnke (1970), d – Durnin and Womersly (1974), e – Jackson et al. (1980)

Figure 6: Estimates of body fat percentage for the same sample of 147 pregnant women. Both, direct and indirect (underlined) anthropometric methods for body composition assessment are presented. Pregnancy specific methods are marked grey. Two different equations obtained from the same reference are marked with (A) and (B)

Slika 6: Ocene odstotka maščobnega tkiva izračunane za vzorec 147 nosečnic. Prikazane so tako neposredne kot posredne (podčrtane) antropometrične metode za ocenjevanje sestave telesa. Metode, specifično razvite za nosečnice, so označene s sivo bravo. Dve različni enačbi iz istega vira sta označeni z (A) in (B)

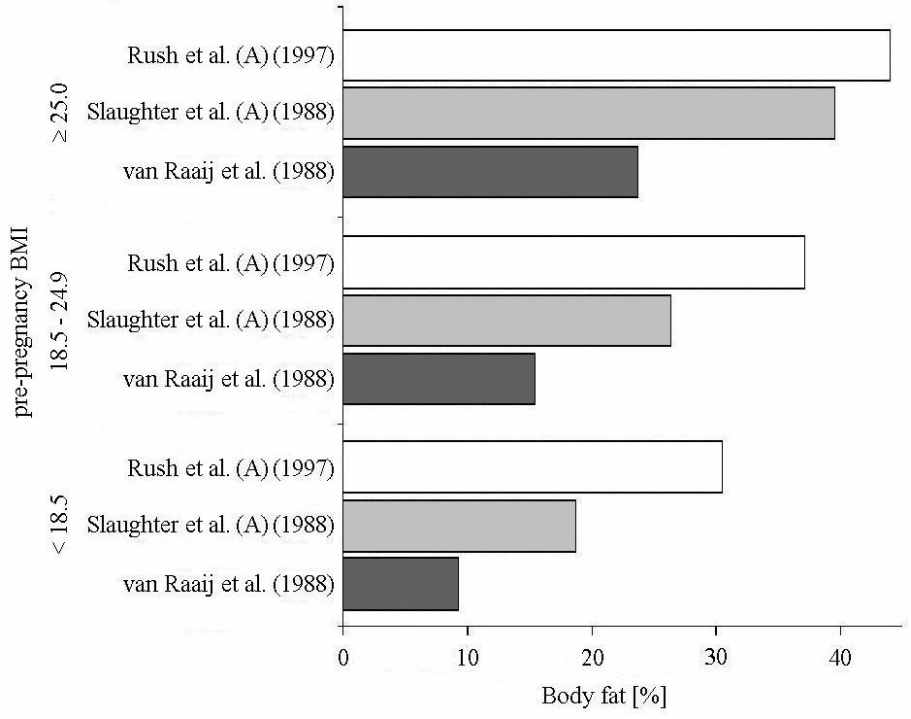


Figure 7: Estimates of body fat percentage obtained with three different anthropometric methods for women with low (<18.5 kg/m^2, N=8), normal (18.5-24.9 kg/m^2, N=116), and high (≥25.0 kg/m^2, N=25) pre-pregnancy BMI

Slika 7: Ocene odstotka maščobnega tkiva pridobljene po treh različnih antropometrijskih enačbah za ženske z nizkim (<18.5 kg/m^2, N=8), normalnim (18.5-24.9 kg/m^2, N=116) in visokim (≥25.0 kg/m^2, N=25) ITM-jem pred nosečnostjo

4.2.2 Results of Hypothesis 2 testing

We hypothesized that the pattern of growth of full-term and premature children during the first year of life depends on anthropometric characteristics of mothers.

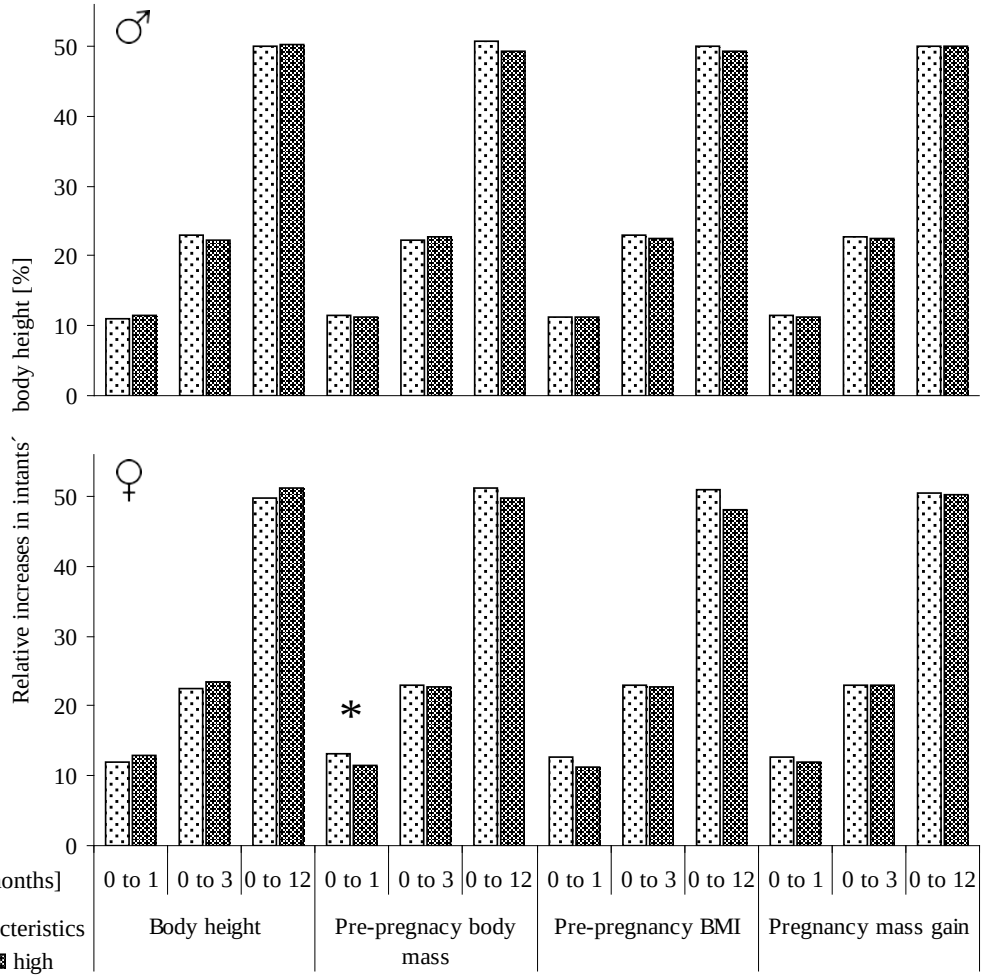
4.2.2.1 Effects of maternal anthropometric characteristics on infants' growth pattern

Infants (N=154) were classified according to maternal anthropometric characteristics and were then compared. Due to small (N=9) sample of PT infants in the "My Milk" study, they were not classified according to their GA at birth.

4.2.2.1.1 Effects on infants´ body height

Absolute values of infants´ body height, being an indicator of skeletal growth, from birth up to 1 year of age for both, males and females that were used for further calculation of relative increases in infants´ body height are presented in Annex F and Figure 8.

Before the adjustment for infant's body height at birth, the results revealed that maternal physical characteristics did not affect body height at birth in female infants. However, increased body height at birth was observed in male infants of mothers with higher MBH, higher PpBM, higher PMG, and higher RV/PpBMI (thus to high maternal PMG according to PpBMI) (not presented in Tables and Annexes).



* – p<0.05

Figure 8: Relative increases in infants´ body height [%] calculated with respect to birth height, according to classification by maternal body height (cut-off point at 168 cm), pre-pregnancy body mass (cut-off point at 62 kg), pre-pregnancy BMI (cut-off point at 25 kg/m^2), and pregnancy mass gain (cut-off point at 16 kg)

Slika 8: Relativna povečanja dojenčkove telesne višine [%] izračunana glede na porodno višino, glede na razdelitev po materini telesni višini (mejna vrednost pri 168 cm), prednosečniški telesni masi (mejna vrednost pri 62 kg), prednosečniškem ITM-jem (mejna vrednost pri 25 kg/m^2) in pridobljeni masi v nosečnosti (mejna vrednost pri 16 kg)

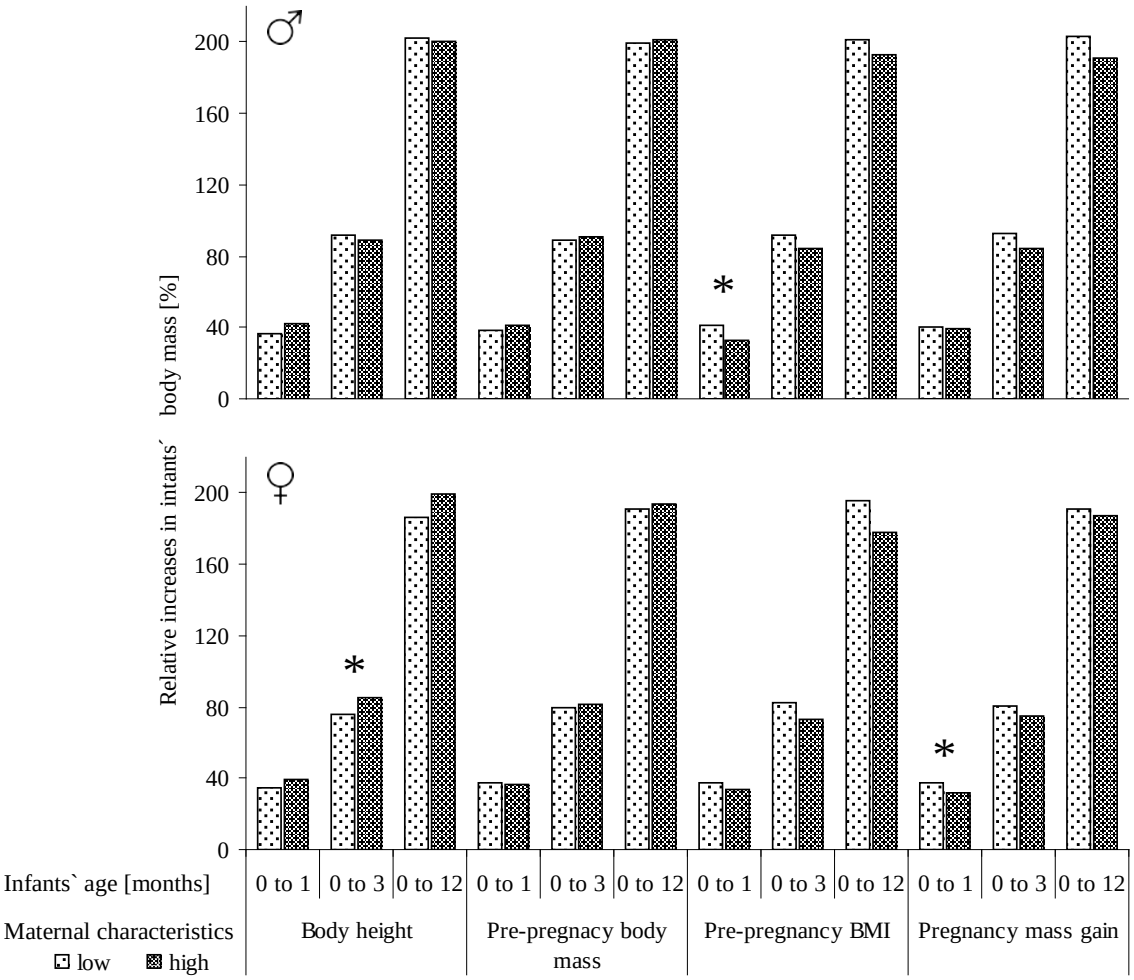
For female infants, relative increases in body height from birth up to 1 month of age was significantly diminished by higher maternal PpBM (Annex F and Figure 8), but was not affected during the first year of life by other maternal anthropometric characteristics. For male infants, relative increases in body height from birth up to 12 months of age were not affected by any of the maternal characteristics.

4.2.2.1.2 Effects on infants´ body mass

Absolute values of infants´ body mass, being an indicator of overall growth of the body, from birth up to 1 year of age for both, males and females that were used for further calculation of relative increases in infants´ body mass, are presented in Annex G and Figure 9.

Before the adjustment for infant's body mass at birth, enlarged body mass at birth was observed in infants of mothers with higher PMG and higher RV/PpBMI. Enlarged body mass at birth was also observed in male infants of mothers with higher MBH and higher PpBM (not presented in Tables and Annexes).

For male infants, relative increases in body mass from birth up to 1 month of age were significantly diminished by the higher maternal PpBMI and higher RV/PpBMI, the same trend was in infants of mothers with higher MBH. From birth to 3 months the relative increases tend to be smaller in males from mothers with higher PMG and higher RV/PpBMI. Relative increases in body mass of female infants from birth up to 3 months, and most likely ($p=0.08$) also up to 12 months of age were enlarged by maternal MBH, but were diminished by higher maternal PpBMI and higher RV/PpBMI up to 1 month of age. The later was also likely to enlarge ($p=0.08$) infants body mass also up to 3 months of age. There was also a trend for the maternal PpBMI to decrease ($p=0.07$) relative increases of infant's body mass up to 12 months of age (Annex G and Figure 9).



* – p<0.05

Figure 9: Relative increases in infants´ body mass [%] calculated with respect to birth mass, according to classification by maternal body height (cut-off point at 168 cm), pre-pregnancy body mass (cut-off point at 62 kg), pre-pregnancy BMI (cut-off point at 25 kg/m^2), and pregnancy mass gain (cut-off point at 16 kg)

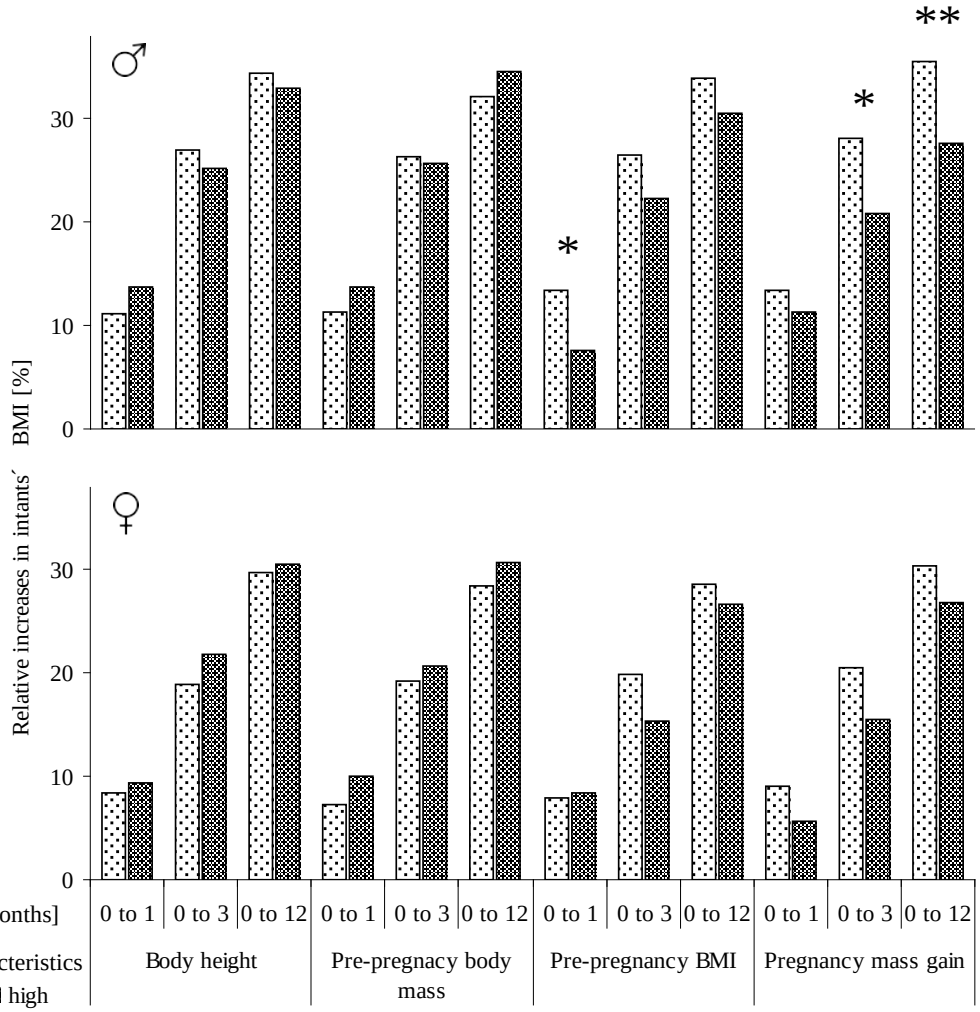
Slika 9: Relativna povečanja dojenčkove telesne mase [%] izračunana glede na porodno maso, glede na razdelitev po materini telesni višini (mejna vrednost pri 168 cm), prednosečniški telesni masi (mejna vrednost pri 62 kg), prednosečniškem ITM-jem (mejna vrednost pri 25 kg/m^2) in pridobljeni masi v nosečnosti (mejna vrednost pri 16 kg)

4.2.2.1.3 Effects on infants´ BMI

Absolute values of infants´ BMI, being an indicator of the appropriateness of body mass relative to body height, from birth up to 1 year of age, for both, males and females that were used for further calculation of relative increases in infants´ BMI, are presented in Annex H and Figure 10.

Before the adjustment for infant's BMI at birth, the results demonstrated that enlarged BMI at birth was observed in infants of mothers with higher PMG, higher RV/PpBMI.

The same trend was observed in infants of mothers with higher PpBMI. Lower BMI at birth was also observed in female infants of mothers with higher MBH (not presented in Tables and Annexes).



* – p<0.05, ** – p<0.01

Figure 10: Relative increases in infants´ BMI [%] calculated with respect to birth BMI, according to classification by maternal body height (cut-off point at 168 cm), pre-pregnancy body mass (cut-off point at 62 kg), pre-pregnancy BMI (cut-off point at 25 kg/m^2), and pregnancy mass gain (cut-off point at 16 kg)

Slika 10: Relativna povečanja dojenčkovega ITM-ja [%] izračunana glede na porodni ITM, glede na razdelitev po materini telesni višini (mejna vrednost pri 168 cm), prednosečniški telesni masi (mejna vrednost pri 62 kg), prednosečniškem ITM-jem (mejna vrednost pri 25 kg/m^2) in pridobljeni masi v nosečnosti (mejna vrednost pri 16 kg)

For male infants, relative increase in BMI from birth up to 1 month of age was diminished by higher maternal PpBMI, up to 12 months of age it was diminished by higher maternal PMG. In female infants, higher RV/PpBMI diminished the relative

increase in infants BMI from birth up to 3 months of age. The same trend was observed in infants from mothers with higher maternal PMG (Annex H and Figure 10).

4.2.2.1.4 Effects on infants´ circumferences, skinfold thickness and body fat amount

In addition, we also analyzed the effects of maternal anthropometric characteristics on infants´ increase in head circumferences, being an indicator of the central nervous system growth, wrist circumference, being an indicator of limb skeletal growth, chest circumference, being an indicator of trunkal skeletal growth, upper arm circumference, triceps and front thigh skinfold thickness, being the indicators of the limb fat tissue, subscapular skinfold thickness, being an indicator of the trunk fat tissue, and total infants´ body fat amount, calculated according to equations of Durnin and Womersly (1974) and Siri (1961).

Absolute values, which were used for further calculation of relative increases, and relative increases of these parameters from birth up to 1 year of age, are presented in the Annexes I to L.

Before the adjustment for infant's head circumference at birth, the results demonstrated that maternal physical characteristics did not affect head circumference at birth in female infants. However, enlarged head circumference at birth was observed in male infants of mothers with higher PMG and higher RV/PpBMI (not presented in Tables and Annexes).

For female infants, relative increases in head circumference from birth up to 12 months of age were significantly enlarged by maternal PpBM, which may also play a role ($p=0.08$) in male infants (Annex I). For the same parameter for female infants, maternal MBH may also play a role ($p=0.06$) in the first 3 months (Annex I).

Before the adjustment for infant's other circumferences at 1 month of age, maternal PpBM and PpBMI were associated with larger upper arm and wrist circumferences at the age of 1 month in female infants. Maternal MBH and PpBM were associated with larger upper arm and chest circumferences at the age of 1 month in male infants (not presented in Tables and Annexes).

For male infants, higher maternal MBH seems to diminish the relative increases in upper arm circumference from 1 to 12 months of age (Annex J), as in infants of mothers with lower MBH enlargement was larger. Relative increases in upper arm circumference of female infants were significantly enlarged by maternal PpBMI (Annex J), which in males also tended to enlarge relative increases in upper arm circumference

in the same way. Infants' relative increases in wrist and chest circumferences from 1 to 12 months of males and females were not significantly affected by maternal anthropometric parameters (Annex J).

Before the adjustment for infant's skinfold thicknesses at 1 month of age, maternal physical characteristics did not affect skinfold thicknesses and body fat percentage at 1 month of age in both, male and female infants (not presented in Tables and Annexes).

Relative increase in infants' subscapular skinfold thickness from 1 to 12 months of age, for both, males and females, was not affected by any of the maternal anthropometric parameters (Annex K). For male infants, relative increase in triceps skinfold thickness from 1 to 12 months was not affected by maternal anthropometric parameters. For females, higher maternal PpBMI caused significantly slower enlargement of triceps and front thigh skinfold thickness (Annex K). Maternal MBH tends to diminish relative increases in front thigh skinfold thickness from 1 to 12 months.

Similar to the above, relative increase in body fat percentage from 1 to 12 months for females, was significantly higher in infants with mothers having lower PpBMI. For male infants, relative increase in body fat percentage was not affected by any of the maternal anthropometric parameters (Annex L).

4.2.2.2 Risk factors for preterm birth

Strong maternal risk factors for preterm birth (in the following Tables comparison between PT and FT infants is marked as "PT vs. FT") were multifetal pregnancy ($p<0.001$), pregnancy illnesses (unfortunately, illnesses were not specified in the existing database of the "Initial study 1987") ($p<0.001$), bleeding during pregnancy ($p<0.001$), smoking ($p<0.01$), preterm birth ($p<0.01$) and stillbirth ($p<0.05$) history, university education ($p<0.05$) (Table 13), and maternal age at delivery ($p<0.05$) (Annex M, Figure 11). Pregnancy illnesses and bleeding during pregnancy also caused more ($p<0.001$) VPT than MPT births (in the following Tables the latter comparison is marked as "VPT vs. MPT") (Table 13).

Significantly more ($p<0.05$) PT (especially VPT, $p<0.01$) than FT infants were born to women younger than 21 and older than 35 years. This conclusion is based on significant p-values of Chi-square test, which was performed separately for each study group between the number of mothers in each age group) (Annex M, Figure 11).

Other analyzed risk factors (marital status, pre-pregnancy illnesses, and previous abortions) were of similar incidence in all groups (Table 13).

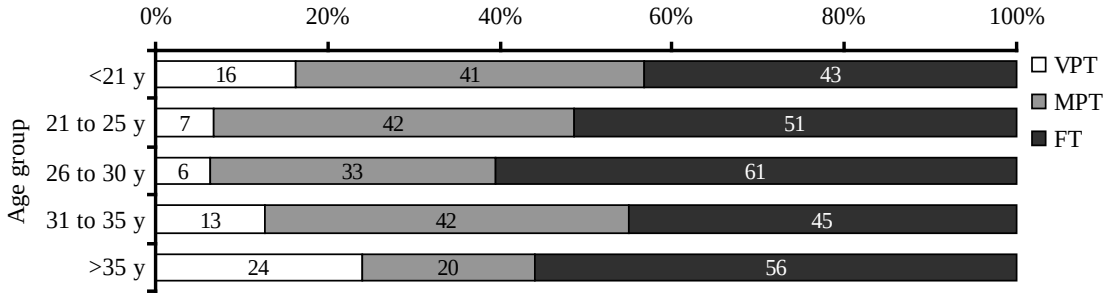
Table 13: Maternal risk factors for preterm birth

Preglednica 13: Rizični dejavniki matere za prezgodnji porod otroka

Risk factor	Pregnancy with twins or triples	Pregnancy illnesses	Bleeding during pregnancy	Previous preterm births	Previous stillbirths	Previous abortions
subject number (N (%))						
VPT	9 (20.5)	30 (68.2)	17 (38.6)	4 (9.3)	2 (4.7)	15 (34.9)
MPT	29 (16.3)	71 (39.9)	20 (11.2)	27 (15.2)	8 (4.5)	47 (26.4)
FT	1 (0.4)	14 (5.6)	16 (6.4)	13 (5.2)	3 (1.2)	62 (24.7)
Chi-square (p)						
overall	**<0.001**	**<0.001**	**<0.001**	**<0.01**	nsg	nsg
PT vs. FT	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.05**	nsg
VPT vs. MPT	nsg	**<0.001**	**<0.001**	nsg	nsg	nsg

Risk factor	Pre-pregnancy illnesses	Hyper-tension	Smoking	Primary school education	University education	Marital status - married
subject number (N (%))						
VPT	4 (9.1)	4 (9.1)	18 (41.9)	13 (29.5)	4 (9.1)	33 (75.0)
MPT	12 (6.7)	35 (19.7)	64 (36.0)	42 (23.6)	32 (18.0)	137 (77.0)
FT	14 (5.6)	65 (25.9)	57 (22.7)	54 (21.5)	59 (23.5)	210 (83.7)
Chi-square (p)						
overall	nsg	**<0.05**	**<0.01**	nsg	nsg	nsg
PT vs. FT	nsg	**<0.05**	**<0.001**	nsg	**<0.05**	nsg
VPT vs. MPT	nsg	nsg	nsg	nsg	nsg	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term



VPT – very preterm, MPT – moderately preterm, FT – full-term, y – years

Figure 11: Proportions of preterm and full-term infants according to mothers' age at delivery

Slika 11: Delež nedonošenškov in donošenčkov glede na starost matere ob rojstvu otroka

4.2.3 Results of Hypothesis 3 and 4 testing

We hypothesized that the susceptibility to illnesses after the period of accelerated growth will be different between full-term and premature children and that the frequency of illnesses associated with prematurity experienced after a period of accelerated growth will differ between premature and very premature children.

4.2.3.1 Illnesses and injuries in youth and adulthood

According to self-assessment of participants, in all three groups they were on average of the same health, they were similarly taking care of their own health, and had similarly level of stress in their life.

Average (SD) systolic blood pressure at the age of 26 years, measured in the sitting position on the left upper arm in the morning at home or during a laboratory visit, was 115 (8) in VPT, 115 (10) in MPT, and 126 (18) in FT, average diastolic blood pressure was 65 (5) in VPT, 68 (8) in MPT, and 78 (13) in FT. There were no statistically significant differences in blood pressure between the three study groups.

CV illnesses were practically absent in all participants, who fulfilled the questionnaire at the age of 26 years. Therefore, we cannot make any final conclusions on the potential differences in the incidence of CV illnesses between the study groups (Table 14).

Although it seems that, according to self-assessment of participants, more FT infants were wearing glasses in youth and adulthood than PT infants, the difference between the groups was not statistically significant (Table 14). Other stated aids, treatments, and illnesses were rare and none of these health problems, for which we could make the final conclusions, was statistically different between PT and FT or between VPT and MPT infants (Table 14).

Table 14: Health status in youth and adulthood. The stated percentage of ill persons was calculated relative to those persons in a particular subject group, for which data were available (in Table 11)

Preglednica 14: Zdravstveno stanje v mladostništvu in odraslosti. Prikazani odstotek obolelih oseb je izračunan glede na tiste osebe v posamezni skupini, za katere so bili podatki dosegljivi (v Preglednici 11)

Health status	All	Diabetes type I	Diabetes type II	Diabetes in the family	Elevated blood sugar	Hyper-tension	Other CV illnesses
subject number (N, (%))							
VPT	7	0, (0.0)	0, (0.0)	2, (28.6)	0, (0.0)	0, (0.0)	1, (14.3)
MPT	18	0, (0.0)	0, (0.0)	7, (38.9)	2, (11.1)	0, (0.0)	0, (0.0)
FT	25	0, (0.0)	0, (0.0)	10, (40.0)	0, (0.0)	1, (4.0)	0, (0.0)
Chi-square (p)							
overall		NA	NA	nsg	NA	NA	NA
PT vs. FT		NA	NA	nsg	NA	NA	NA
VPT vs. MPT		NA	NA	nsg	NA	NA	NA

Health status	Glasses	Hearing aid	Speech therapy	Orthopedic aid	Physiotherapy treatment	Orthodontic braces
subject number (N, (%))						
VPT	3, (42.9)	0, (0.0)	0, (0.0)	0, (0.0)	1, (14.3)	2, (28.6)
MPT	7, (38.9)	0, (0.0)	2, (11.1)	0, (0.0)	1, (5.6)	2, (11.1)
FT	17, (68.0)	0, (0.0)	3, (12.0)	1, (4.0)	3, (12.0)	5, (20.0)
Chi-square (p)						
overall	nsg	NA	NA	NA	NA	nsg
PT vs. FT	nsg	NA	NA	NA	NA	nsg
VPT vs. MPT	nsg	NA	NA	NA	NA	nsg

Health status	Allergies	Asthma	Epilepsy	NM illnesses	Digestive illnesses	Other
subject number (N, (%))						
VPT	2, (28.6)	1, (14.3)	1, (14.3)	1, (14.3)	1, (14.3)	1, (14.3)
MPT	6, (33.3)	3, (16.7)	0, (0.0)	0, (0.0)	2, (11.1)	3, (16.7)
FT	7, (28.0)	2, (8.0)	0, (0.0)	0, (0.0)	0, (0.0)	1, (4.0)
Chi-square (p)						
overall	nsg	NA	NA	NA	NA	NA
PT vs. FT	nsg	NA	NA	NA	NA	NA
VPT vs. MPT	nsg	NA	NA	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, CV – cardiovascular, NM – neuromuscular, NA – not applicable

Additionally, we obtained and analyzed the data on injuries experienced in PT and FT individuals either in youth and adulthood. The frequencies of selected injuries were too rare for statistical analysis or provided similar results for all three study groups, except for the injuries of joints, as FT infants experienced those injuries more often ($p<0.05$) than their PT peers (Table 15).

Table 15: Injuries experienced in youth and adulthood. The stated percentage of injured persons was calculated relative to those persons in a particular subject group, for which data were available (in Table 11)

Preglednica 15: Poškodbe v mladostništvu in odraslosti. Prikazani odstotek poškodovanih oseb je izračunan glede na tiste osebe v posamezni skupini, za katere so bili podatki dosegljivi (v Preglednici 11)

Injuries	All	All injured	Injury of bones	Injury of joints	Injury of muscles	Brain concussion	Other
subject number (N, (%))							
VPT	7	4, (57.1)	3, (75.0)	1, (25.0)	0, (0.0)	1, (25.0)	0, (0.0)
MPT	18	9, (50.0)	3, (33.3)	3, (33.3)	1, (11.1)	2, (22.2)	4, (44.4)
FT	25	19, (76.0)	6, (31.6)	14, (73.7)	2, (10.5)	2, (10.5)	3, (15.8)
Chi-square (p)							
overall		nsg	nsg	nsg	NA	NA	NA
PT vs. FT		nsg	nsg	**<0.05**	NA	NA	NA
VPT vs. MPT		nsg	nsg	nsg	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable

4.2.3.2 Illnesses at birth and in preschool years

In contrast to FT, there were several illnesses evident in PT infants ($p<0.001$) at birth, as almost all (98 %) VPT and 69 % of MPT, but only 56 % of FT infants were born with at least one illness at birth. In infants with illnesses at birth, on average 2.4 (1.3), 1.6 (1.0), and 1.2 (0.7) different illnesses were recorded per infant for VPT, MPT, and FT infants, respectively.

Statistically significant differences between the PT and FT infants were observed in the frequencies of dystocia ($p<0.001$), with the highest levels observed in the FT group, followed by respiratory distress ($p<0.001$), apnoeic attacks ($p<0.001$), hyperbili-rubinemia ($p<0.001$), infections ($p<0.001$), hypoxia ($p<0.01$), and finally cerebral hemorrhage ($p<0.05$), with the highest levels in the PT group (Table 16, Figure 12).

Periventricular leukomalatia, hypoglycemia, necrotizing enterocolitis, heart, intestinal, and kidney anomalies, and cosmetic defects were too rare for further conclusions (Table 16, Figure 12).

Table 16: Infant's illnesses at birth. The stated percentage of affected infants was calculated relative to all births in a particular subject group

Preglednica 16: Obrojstni medicinski zapleti dojenčkov. Prikazani odstotek dojenčkov s težavami je izračunan glede na vse dojenčke rojene v posamezni skupini

Illness	Dystocia	Fetal distress	Respiratory distress	Apnoeic attacks	hypoxia	Cerebral hemorrhage
subject number (N, (%))						
VPT	10, (22.7)	3, (6.8)	17, (38.6)	14, (31.8)	3, (6.8)	5, (11.4)
MPT	62, (34.8)	6, (3.4)	21, (11.8)	1, (0.6)	13, (7.3)	5, (2.8)
FT	121, (48.2)	10, (4.0)	2, (0.8)	0, (0.0)	5, (2.0)	2, (0.8)
Chi-square (p)						
overall	**<0.001**	nsg	**<0.001**	**<0.001**	**<0.05**	**<0.001**
PT vs. FT	**<0.001**	nsg	**<0.001**	**<0.001**	**<0.01**	**<0.05**
VPT vs. MPT	nsg	nsg	**<0.001**	**<0.001**	nsg	**<0.05**

Illness	Periventricular leukomalatia	Hyperbili-rubinemia	Hypo-glycemia	Necrotising enterocolitis	Heart anomalies	Intestinal anomalies
subject number (N, (%))						
VPT	1, (2.3)	27, (61.4)	0, (0.0)	3, (6.8)	3, (6.8)	0, (0.0)
MPT	0, (0.0)	63, (35.4)	2, (1.1)	0, (0.0)	2, (1.1)	2, (1.1)
FT	0, (0.0)	17, (6.8)	1, (0.4)	0, (0.0)	0, (0.0)	1, (0.4)
Chi-square (p)						
overall	NA	**<0.001**	NA	NA	NA	NA
PT vs. FT	NA	**<0.001**	NA	NA	NA	NA
VPT vs. MPT	NA	**<0.01**	NA	NA	NA	NA

Illness	Intestinal hernia	Kidney anomalies	Cosmetic defects	Infections
subject number (N, (%))				
VPT	4, (9.1)	1, (2.3)	3, (7.3)	11, (25.0)
MPT	1, (0.6)	2, (1.1)	0, (0.0)	10, (5.6)
FT	0, (0.0)	3, (1.2)	0, (0.0)	0, (0.0)
Chi-square (p)				
overall	NA	NA	NA	**<0.001**
PT vs. FT	NA	NA	NA	**<0.001**
VPT vs. MPT	NA	NA	NA	**<0.001**

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable

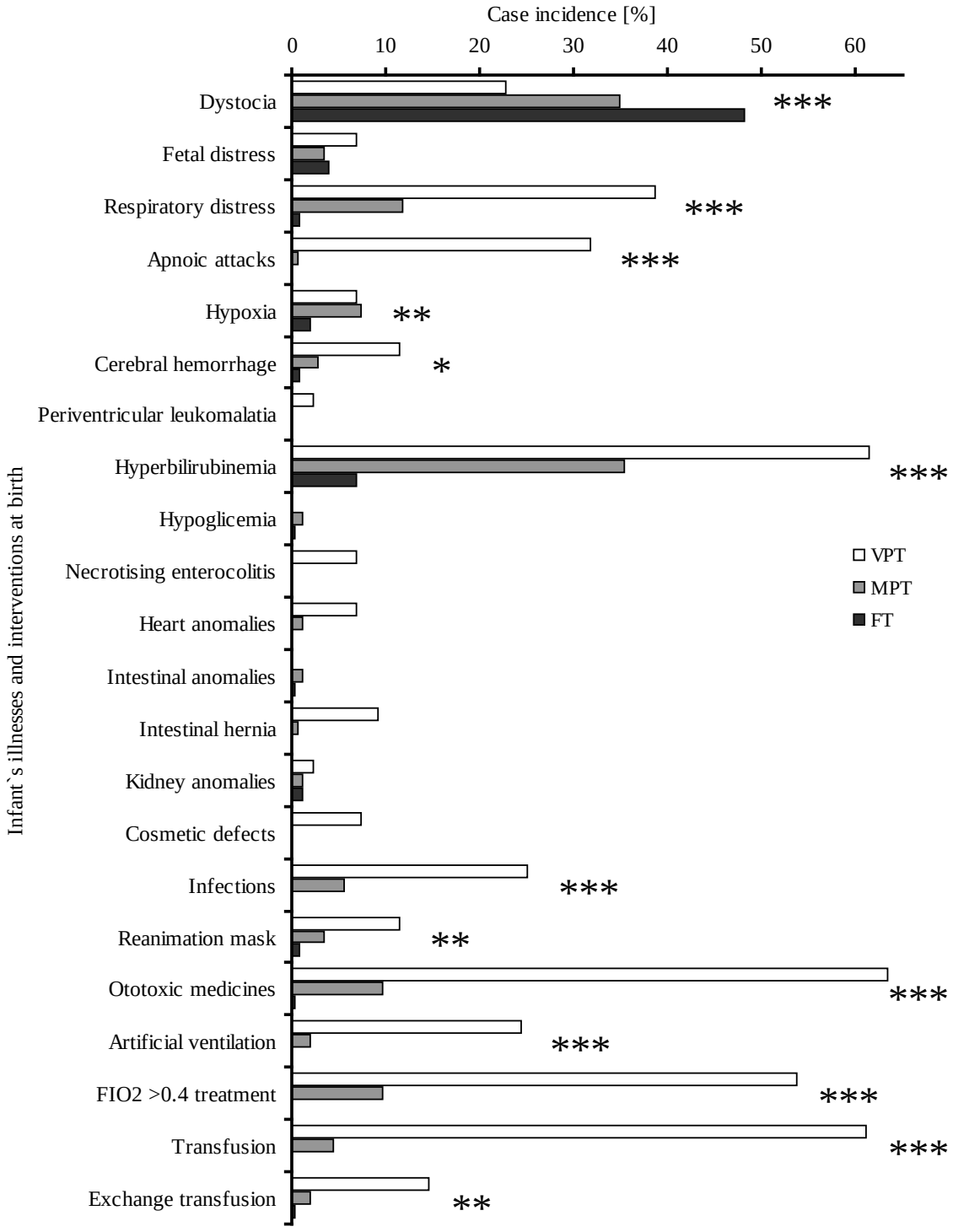
Similarly, all interventions at birth (the use of reanimation mask, ototoxic medicines, artificial ventilation, addition of oxygen (F_IO_2), transfusions, and exchange transfusions) were significantly more often ($p<0.001$) in VPT and MPT, than in FT infants (Table 17, Figure 12).

Table 17: Interventions on infants at birth. The stated percentage of sick infants was calculated relative to all births in a particular subject group

Preglednica 17: Obrojstne intervencije na dojenčkih. Prikazani odstotek dojenčkov s težavami je izračunan glede na vse dojenčke rojene v posamezni skupini

Interventions	Reanimation mask	Ototoxic medicines	Artificial ventilation [days]	F_IO_2 >0.4 [days]	Transfusion [Number]	Exchange transfusion [Number]
subject number (N, (%))						
VPT	5, (11.4)	26, (63.4)	10, (24.4)	22, (53.7)	25, (61.0)	6, (14.6)
MPT	6, (3.4)	15, (9.6)	3, (1.9)	15, (9.6)	7, (4.5)	3, (1.9)
FT	2, (0.8)	1, (0.4)	0, (0.0)	0, (0.0)	0, (0.0)	1, (0.4)
average value (SD)						
VPT			30.4 (25.7)	8.7 (14.7)	2.1 (1.6)	1.5 (0.8)
MPT			25.7 (21.2)	6.5 (10.4)	2.0 (1.5)	1.0 (0.0)
FT			NA	NA	NA	1.0 (0.0)
Chi-square (p)						
overall	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PT vs. FT	**<0.01**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.01**
VPT vs. MPT	**<0.05**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable



VPT – very preterm, MPT – moderately preterm, FT – full-term, F_IO_2 – fraction of inspired oxygen, * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$

Figure 12: Infant's illnesses and interventions at birth. The stated percentage of affected infants was calculated relative to all births in a particular subject group

Slika 12: Obrojstni medicinski zapleti in intervencije dojenčkov. Prikazani odstotek dojenčkov s težavami je izračunan glede na vse dojenčke rojene v posamezni skupini

Apart from medical problems at birth, illnesses (including infectious illnesses) were also reported for all subject groups in their childhood (Tables 18 and 19).

Blood anemia was more often ($p<0.001$) experienced in VPT and MPT, than in FT infants at the age of 1 year, while rickets was of similar incidence between the study groups at the age of 1 year (Table 18). Febrile seizures and epilepsy were too rare for further conclusions.

Table 18: Children's illnesses in the first three years of life. The stated percentage of affected children was calculated relative to those children in a particular subject group, for which data were available (in Table 11)

Preglednica 18: Otroške bolezni v prvih treh letih življenja. Prikazani odstotek otrok s težavami je izračunan glede na tiste otroke v posamezni skupini, za katere so bili podatki dosegljivi (v Preglednici 11)

Illness	Blood anemia				Rickets		
Age [years]	birth	1	2	3	1	2	3
subject number (N, (%))							
VPT	0, (0.0)	28, (68.3)	3, (7.3)	1, (2.9)	4, (9.8)	0, (0.0)	0, (0.0)
MPT	3, (1.7)	51, (35.4)	9, (6.9)	6, (5.2)	6, (4.1)	2, (1.5)	0, (0.0)
FT	1, (0.4)	45, (20.5)	17, (8.1)	4, (2.5)	11, (5.0)	5, (2.4)	0, (0.0)
Chi-square (p)							
overall	NA	**<0.001**	nsg	NA	nsg	NA	NA
PT vs. FT	NA	**<0.001**	nsg	NA	nsg	NA	NA
VPT vs. MPT	NA	**<0.001**	nsg	NA	nsg	NA	NA

Illness	Febrile seizures			Epilepsy		
Age [years]	1	2	3	1	2	3
subject number (N, (%))						
VPT	1, (2.4)	1, (2.4)	0, (0.0)	1, (2.4)	1, (2.4)	0, (0.0)
MPT	3, (2.1)	5, (3.8)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)
FT	7, (3.2)	5, (2.4)	0, (0.0)	3, (1.4)	1, (0.5)	1, (0.6)
Chi-square (p)						
overall	NA	NA	NA	NA	NA	NA
PT vs. FT	NA	NA	NA	NA	NA	NA
VPT vs. MPT	NA	NA	NA	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable

Pneumonia was more often ($p<0.001$) experienced in VPT and MPT, than in FT infants at the age of 1 year, while upper respiratory tract infections and otitis were more often ($p<0.05$) in FT infants at the age of 2 and 3 years (Table 19), as compared to PT infants. As other childhood infectious illnesses and symptoms were much less frequent than those stated above, only the number of cases for each study group is presented below (Table 19).

Table 19: Children's infectious illnesses and symptoms in the first three years of life. The stated percentage of affected children was calculated relative to those children in a particular subject group, for which data were available (in Table 11)

Preglednica 19: Nalezljive otroške bolezni in simptomi v prvih treh letih življenja. Prikazani odstotek otrok s težavami je izračunan glede na tiste otroke v posamezni skupini, za katere so bili podatki dosegljivi (v Preglednici 11)

Infectious illness	Upper respiratory tract infection			Otitis		
Age [years]	1	2	3	1	2	3
subject number (N, (%))						
VPT	25, (61.0)	22, (53.7)	17, (48.6)	13, (31.7)	13, (31.7)	3, (8.6)
MPT	85, (58.6)	86, (65.6)	72, (62.6)	42, (29.0)	53, (40.5)	33, (28.7)
FT	139, (62.9)	157, (74.4)	119, (73.0)	72, (32.6)	98, (46.2)	54, (33.1)
Chi-square (p)						
overall	nsg	**<0.05**	**<0.05**	nsg	nsg	**<0.05**
PT vs. FT	nsg	**<0.05**	**<0.05**	nsg	nsg	nsg
VPT vs. MPT	nsg	nsg	nsg	nsg	nsg	**<0.05**

Infectious illness	Pneumonia			Obstructive bronchiolitis		
Age [years]	1	2	3	1	2	3
subject number (N, (%))						
VPT	12, (29.3)	7, (17.1)	5, (14.3)	11, (26.8)	3, (7.3)	5, (14.7)
MPT	15, (10.3)	17, (13.0)	6, (5.2)	23, (15.9)	25, (19.1)	12, (10.4)
FT	18, (8.1)	25, (11.8)	14, (8.6)	37, (16.7)	40, (18.9)	20, (12.3)
Chi-square (p)						
overall	**<0.001**	nsg	nsg	nsg	nsg	nsg
PT vs. FT	**<0.05**	nsg	nsg	nsg	nsg	nsg
VPT vs. MPT	**<0.01**	nsg	nsg	nsg	nsg	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term

continued

continuation of Table 19.

Children's infectious illnesses and symptoms in the first three years of life. The stated percentage of affected children was calculated relative to those children in a particular subject group, for which data were available (in Table 11)

Infectious illness Group:	VPT				MPT				FT			
Age [years]	1	2	3	4-11	1	2	3	4-11	1	2	3	4-11
subject number (N)												
Chickenpox	1	1	5	13	4	3	17	45	7	13	22	62
Rubella	2	1	1	2	0	2	5	9	4	1	6	9
Measles	0	0	0	4	0	1	0	3	0	3	0	4
Scarlet fever	0	1	2	2	0	1	2	7	0	2	7	9
Gastroenteritis or colitis (Salmonella)	4	0	0		9	11	1		17	14	1	
Acute laryngitis	0	2	0		1	2	0		1	1	1	
Pharyngeal hypotrophy	0	0	2		0	0	4		0	0	2	
Intestinal bacteria	0	0	2		0	0	4		0	0	2	
Urinary tract infection	2	1	0		7	2	1		3	3	2	
Dermatitis	0	0	0		1	1	0		1	2	1	
Constipation	0	1	0		0	0	1		1	0	0	
Fever	0	0	2		4	3	4		6	5	1	

VPT – very preterm, MPT – moderately preterm, FT – full-term

Congenital intestinal illnesses (hernia and other malformations), genital illnesses (undescended testicle, constricted foreskin, hypospadia), musculoskeletal illnesses (limb and foot arch malformations), heart, and skin / mucosa malformations, and cystic kidney illness were rare (Table 20) in childhood and youth.

Table 20: Incidence of congenital malformations in the three study groups. Intestinal, genital, musculoskeletal, and cystic kidney illnesses, heart malformations, and skin and mucosa malformations in childhood and youth are presented

Preglednica 20: Incidenca prirojenih napak v vseh treh raziskovalnih skupinah. Predstavljene so črevesne, genitalne, mišičnoskeletne napake, cistična bolezen ledvic, nepravilnosti srca ter nepravilnosti kože in sluznice v otroštvu in mladostništvu

Malformation	All	Intestinal	Genital	Muscular-skeletal	Kidney	Heart	Skin and mucosa
subject number (N)							
VPT	29	10	1	0	0	0	0
MPT	86	14	5	8	2	0	0
FT	134	6	16	3	1	1	1

VPT – very preterm, MPT – moderately preterm, FT – full-term

Additionally, the start of obligatory vaccination was at approximately 5.6 (2.3) months of age in PT infants, while in FT infants at the age of 4.2 (1.9) months ($p<0.01$). The age at the onset of vaccination in VPT infants was even later at 7.3 (2.1) months. Kindergarten enrollment was earlier ($p<0.01$) in MPT and FT infants (at 2.4 (1.5) and 2.6 (1.5) years of age, respectively) than in VPT infants (at 3.5 (1.8) years of age).

Among the chronic diseases allergies (food allergy in 3 cases, drug allergy, neurodermatitis) and immune deficits (3 cases) were the most common, but they were still too rare for further conclusions.

Furthermore, several neurological disorders, such as hydrocephalus, cerebral palsy, diplegia, and hemiparesis seem to be more often in PT infants, but as they were very rare in general, only the number of cases is presented below (Table 21).

Table 21: Neurological disorders at the age of 1 to 3 years

Preglednica 21: Nevrološke nepravilnosti v starosti 1 do 3 let

Neurolog. disorder	VPT			MPT			FT		
Age [years]	1	2	3	1	2	3	1	2	3
subject number (N)									
Cerebral palsy	3	3	2	1	1	1	0	0	0
Diplegia	3	2	0	0	0	0	0	0	0
Hemiparesis	2	0	1	1	1	1	0	0	0
Hydrocephalus	0	0	0	1	1	1	0	0	0

VPT – very preterm, MPT – moderately preterm, FT – full-term, Neurolog. – Neurological

The results of developmental indicators, such as Apgar score at 1 and 5 minutes (for both p<0.001) and APMD (uncorrected developmental quotient (p<0.001)), were significantly worse in PT than in FT infants (Table 22). Corrected developmental quotient was worse (<0.05) in VPT than in FT infants at the age of 1 and worse (p<0.01) in VPT than in MPT at the age of two years (Table 22).

Table 22: Apgar score at birth and developmental quotient at the age of 1 and 2 years

Preglednica 22: Vrednost Apgar ob rojstvu in razvojni količnik v starosti 1 in 2 let

	Apgar score		Uncorrected developmental quotient		Corrected developmental quotient	
Age	1 min	5 min	1 y	2 y	1 y	2 y
subject number (N)						
VPT	43	41	37	38	37	38
MPT	177	178	115	94	116	94
FT	251	251	167	130	167	130
average (SD)						
PT	7.5 (2.3)	8.3 (1.3)	93.0 (13.4)	97.0 (13.2)	105.4 (13.3)	103.7 (13.0)
VPT	5.2 (2.3)	6.9 (1.3)	82.1 (13.8)	88.9 (12.6)	101.9 (15.2)	99.3 (13.8)
MPT	8.1 (1.9)	8.7 (1.1)	96.5 (11.3)	100.3 (11.9)	106.5 (12.5)	105.5 (12.3)
FT	8.7 (1.3)	9.1 (0.8)	108.3 (10.6)	103.3 (11.4)	108.4 (10.5)	103.4 (11.3)
t-test (p)						
PT vs. FT	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0111**	0.4104
one-way ANOVA (p)[a]						
overall	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0095**	**0.0284**
Tukey HSD post hoc (p)						
VPT vs. MPT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	nsg	**<0.01**
VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.05**	nsg
MPT vs. FT	nsg	**<0.05**	**<0.01**	nsg	nsg	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, min – minutes, y – years, [a] – ANOVA performed for VPT, MPT, and FT

An additional indicator of neurological development, DDST, was performed more successfully ($p<0.05$) in FT than in MPT and VPT infants at the age of 1 year, and was more often performed questionably ($p<0.05$) in VPT infants (unfinished tests not included in these two categories). The majority of differences between PT and FT infants was observed in fine and gross motor skills (Table 23).

Table 23: Results of Denver's developmental screening test (DDST). Number of successful and questionable performances overall at different infants' ages (above). Number of successful performances for the two components of the test at different infants' ages (below). Any unfinished tests are not included. The stated percentage of children was calculated relative to those children in a particular subject group, for which data were available (in Table 11)

Preglednica 23: Rezultati Denverjevega razvojnega presejalnega testa (DDST). Število uspešno in vprašljivo opravljenih celotnih testov v različnih otrokovih starostih (zgoraj). Število uspešnih rezultatov za dve komponenti testa v različnih otrokovih starostih (spodaj). Nedokončani testi niso vključeni. Prikazani odstotek otrok je izračunan glede na tiste otroke v posamezni skupini, za katere so bili podatki dosegljivi (v Preglednici 11)

Results of DDST	Successful performance			Questionable performance		
Age [years]	1	2	3	1	2	3
subject number (N, (%))						
VPT	28, (75.7)	32, (86.5)	26, (74.3)	7, (18.9)	2, (5.4)	2, (5.7)
MPT	87, (90.6)	85, (94.4)	74, (85.1)	6, (6.3)	2, (2.2)	4, (4.6)
FT	125, (93.3)	106, (93.0)	89, (93.7)	8, (6.0)	4, (3.5)	3, (3.2)
Chi-square (p)						
overall	**<0.01**	nsg	**<0.05**	**<0.05**	NA	NA
PT vs. FT	nsg	nsg	**<0.05**	nsg	NA	NA
VPT vs. MPT	**<0.05**	nsg	nsg	**<0.05**	NA	NA

Results of DDST	Fine motor skills			Gross motor skills		
Age [years]	1	2	3	1	2	3
subject number (N, (%))						
VPT	35, (94.6)	33, (89.2)	26, (81.3)	29, (78.4)	33, (89.2)	23, (71.9)
MPT	92, (95.8)	87, (96.7)	74, (88.1)	87, (90.6)	85, (94.4)	71, (84.5)
FT	131, (97.8)	108, (94.7)	82, (97.6)	127, (94.8)	110, (96.5)	81, (96.4)
Chi-square (p)						
overall	nsg	nsg	**<0.05**	**<0.01**	nsg	**<0.001**
PT vs. FT	nsg	nsg	**<0.01**	**<0.05**	nsg	**<0.01**
VPT vs. MPT	nsg	nsg	nsg	nsg	nsg	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable

Overall mental health assessment, chosen by the scientists from the Maternity hospital, has shown that healthy infants more often belong to the ($p<0.001$) FT group, infants at risk were more frequent ($p<0.05$) in PT (especially in VPT) infants, while infants with moderate or severe disabilities were less frequent in all study groups and only the number of cases for each study group is presented below (Table 24).

Table 24: Results of mental health assessment, with subjects classified into: healthy, at risk, moderate disability, and severe disability group. The stated percentage of children was calculated relative to those children in a particular subject group, for which data were available (in Table 11)

Preglednica 24: Rezultati ocene mentalnega zdravja s preiskovanci uvrščenimi v sledeče skupine: zdrav, rizičen, lažja prizadetost, težka prizadetost. Prikazani odstotek otrok je izračunan glede na tiste otroke v posamezni skupini, za katere so bili podatki dosegljivi (v Preglednici 11)

Mental health	Healthy			At risk		
Age [years]	1	2	3	1	2	3
subject number (N, (%))						
VPT	30, (73.2)	34, (85.0)	26, (76.5)	9, (22.0)	3, (7.5)	6, (17.6)
MPT	136, (93.8)	127, (96.2)	109, (94.8)	7, (4.8)	2, (1.5)	4, (3.5)
FT	220, (98.2)	206, (96.7)	158, (96.9)	4, (1.8)	5, (2.3)	3, (1.8)
Chi-square (p)						
overall	**<0.001**	**<0.01**	**<0.001**	**<0.001**	nsg	**<0.001**
PT vs. FT	**<0.001**	nsg	**<0.05**	**<0.01**	nsg	**<0.05**
VPT vs. MPT	**<0.001**	**<0.05**	**<0.01**	**<0.001**	**<0.05**	**<0.01**

Mental health	VPT			MPT			FT		
Age [years]	1	2	3	1	2	3	1	2	3
subject number (N)									
moderate disability	1	2	2	2	1	1	0	2	2
severe disability	1	1	0	0	2	1	0	0	0

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term

Visual impairment was more often ($p<0.05$) evident in PT than in FT group at the age of 2 years and wearing glasses at 11 years of age was more frequent ($p<0.05$) in VPT and MPT, than in FT infants (Table 25), which is in contrast to self-reports at the age of 26 years, presented in Chapter 4.2.3.1. Hearing impairment up to eleven years of age was less frequent in all study groups (Table 25).

Table 25: Children's visual or hearing impairment in the first three years of life and wearing glasses or hearing aids at the age of 11 years. The stated percentage of affected children was calculated relative to those children in a particular subject group, for which data were available (in Table 11)

Preglednica 25: Otroške nepravilnosti vida in sluha v prvih treh letih življenja in nošenje očal ali slušnega aparata v starosti 11 let. Prikazani odstotek otrok s težavami je izračunan glede na tiste otroke v posamezni skupini, za katere so bili podatki dosegljivi (v Preglednici 11)

	Visual impairment				Hearing impairment			
Age [years]	1	2	3	11	1	2	3	11
subject number (N, (%))								
VPT	1, (2.4)	2, (4.9)	2, (5.9)	12, (36.4)	0, (0.0)	0, (0.0)	1, (2.9)	0, (0.0)
MPT	4, (2.8)	5, (3.8)	7, (6.1)	17, (17.5)	4, (2.8)	1, (0.8)	0, (0.0)	0, (0.0)
FT	4, (1.8)	2, (0.9)	3, (1.8)	19, (12.8)	0, (0.0)	0, (0.0)	1, (0.6)	1, (0.7)
Chi-square (p)								
overall	NA	nsg	nsg	**<0.01**	NA	NA	NA	NA
PT vs. FT	NA	**<0.05**	nsg	**<0.05**	NA	NA	NA	NA
VPT vs. MPT	NA	nsg	nsg	**<0.05**	NA	NA	NA	NA

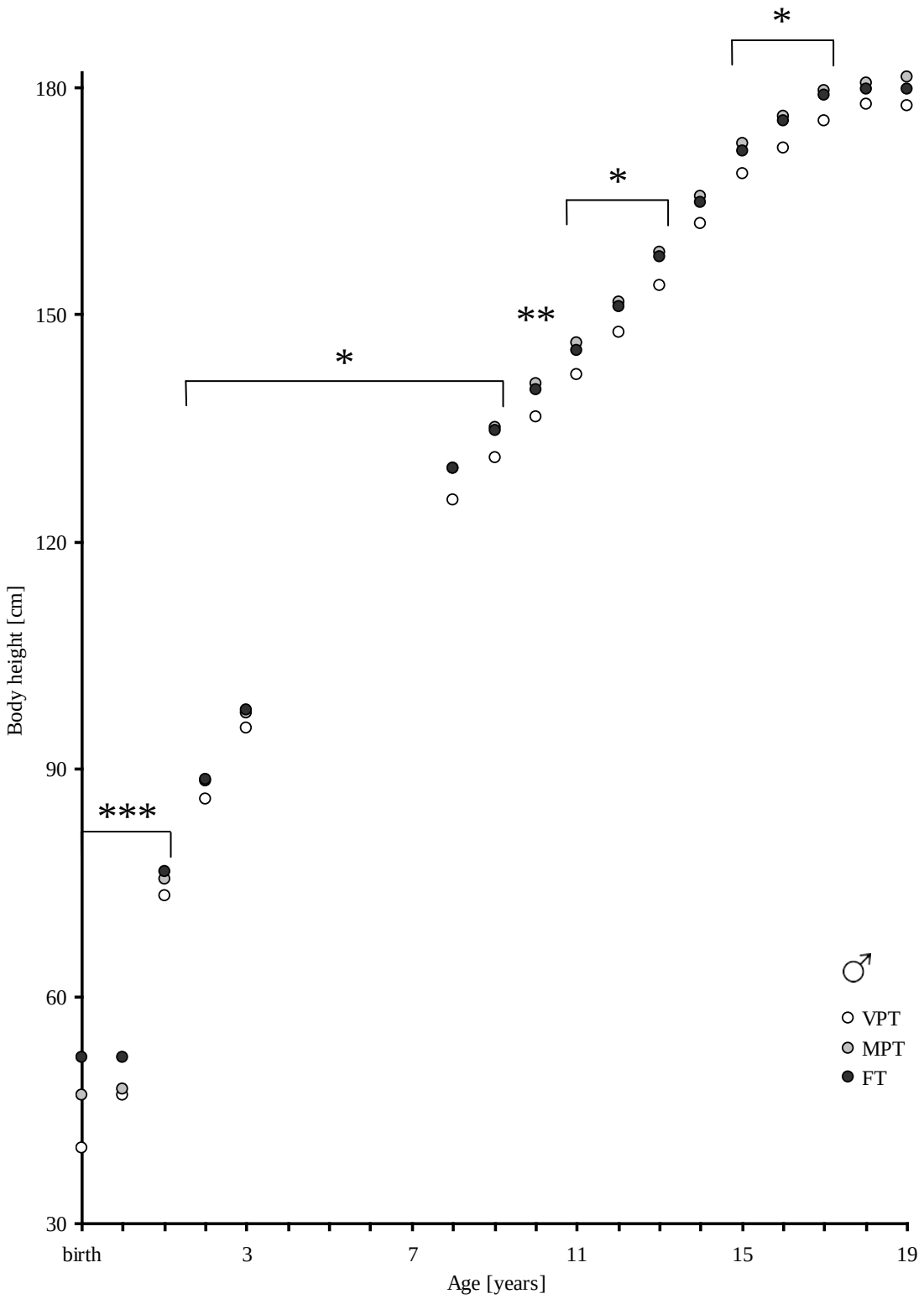
PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable

4.2.4 Results of Hypothesis 5 testing

We hypothesized that the potential consequences of prematurity, such as lower height, lower mass, and lower capacity of physical exercise, will be detected in late childhood and adolescence.

4.2.4.1 Body height of preterm and full-term infants

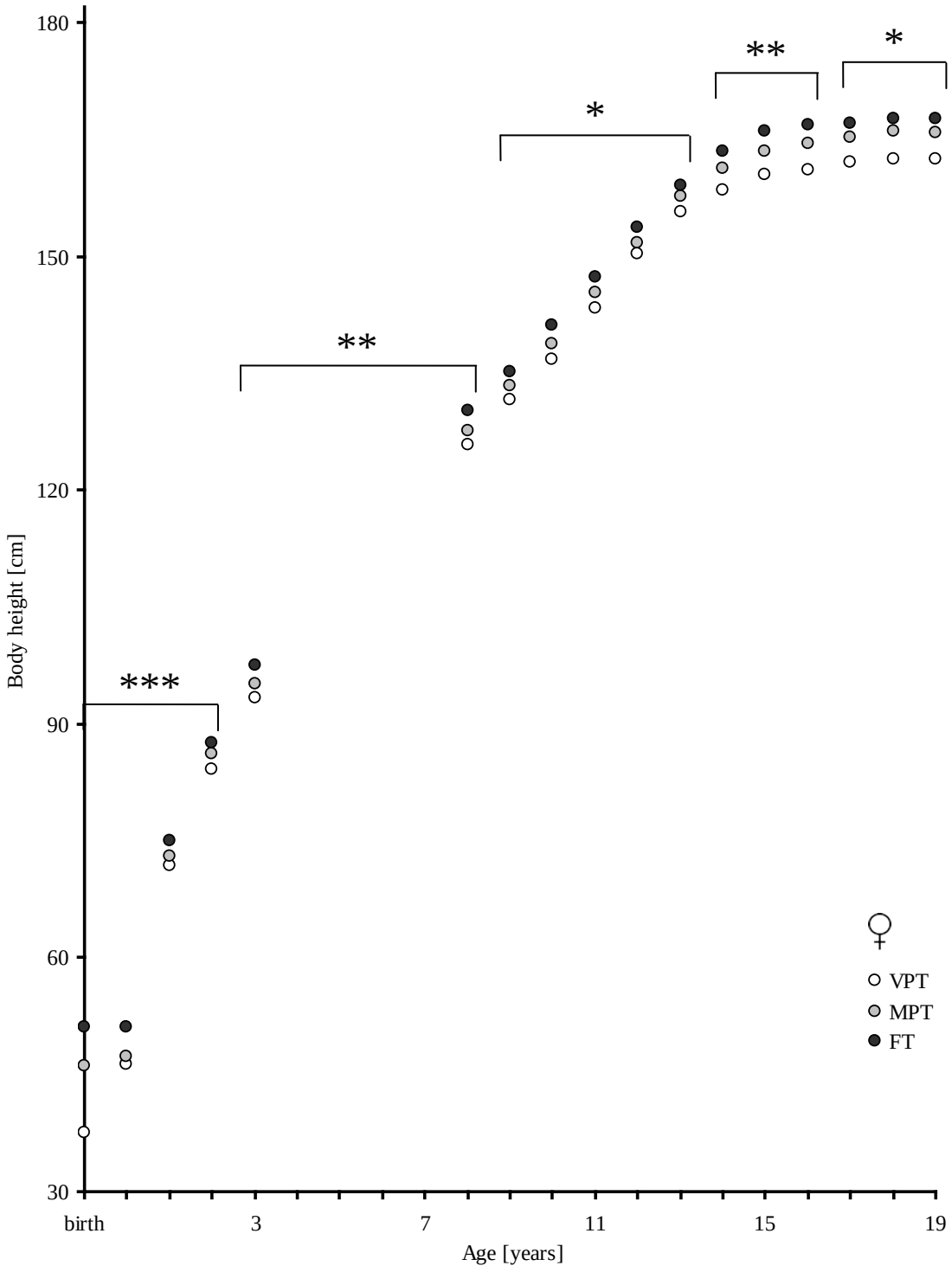
Body height in males was significantly lower ($p<0.05$) in PT infants (VPT and MPT combined) than in FT individuals up to the age of 2 years, at 3 years it seems similar ($p=0.06$). However, as evident from Annex N and Figure 13, VPT were significantly shorter ($p<0.05$) than MPT and FT individuals also up to the age of 13 and between 15 and 17 years, the same trend ($p=0.097$) is seen also at 14 and 19 years of age (Annex N, Figure 13). In females, the difference in body height between PT and FT individuals persisted into the adulthood ($p<0.05$), mostly because of the large differences between VPT females, as compared to their MPT and FT peers, except for the ages of 11 to 13 years (Annex N, Figure 14).



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – p<0.05, ** – p<0.01, *** – p<0.001

Figure 13: Body height [cm] in males from birth to the age of 19 years

Slika 13: Telesna višina [cm] moških od rojstva do starosti 19 let



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – p<0.05, ** – p<0.01, *** – p<0.001

Figure 14: Body height [cm] in females from birth to the age of 19 years

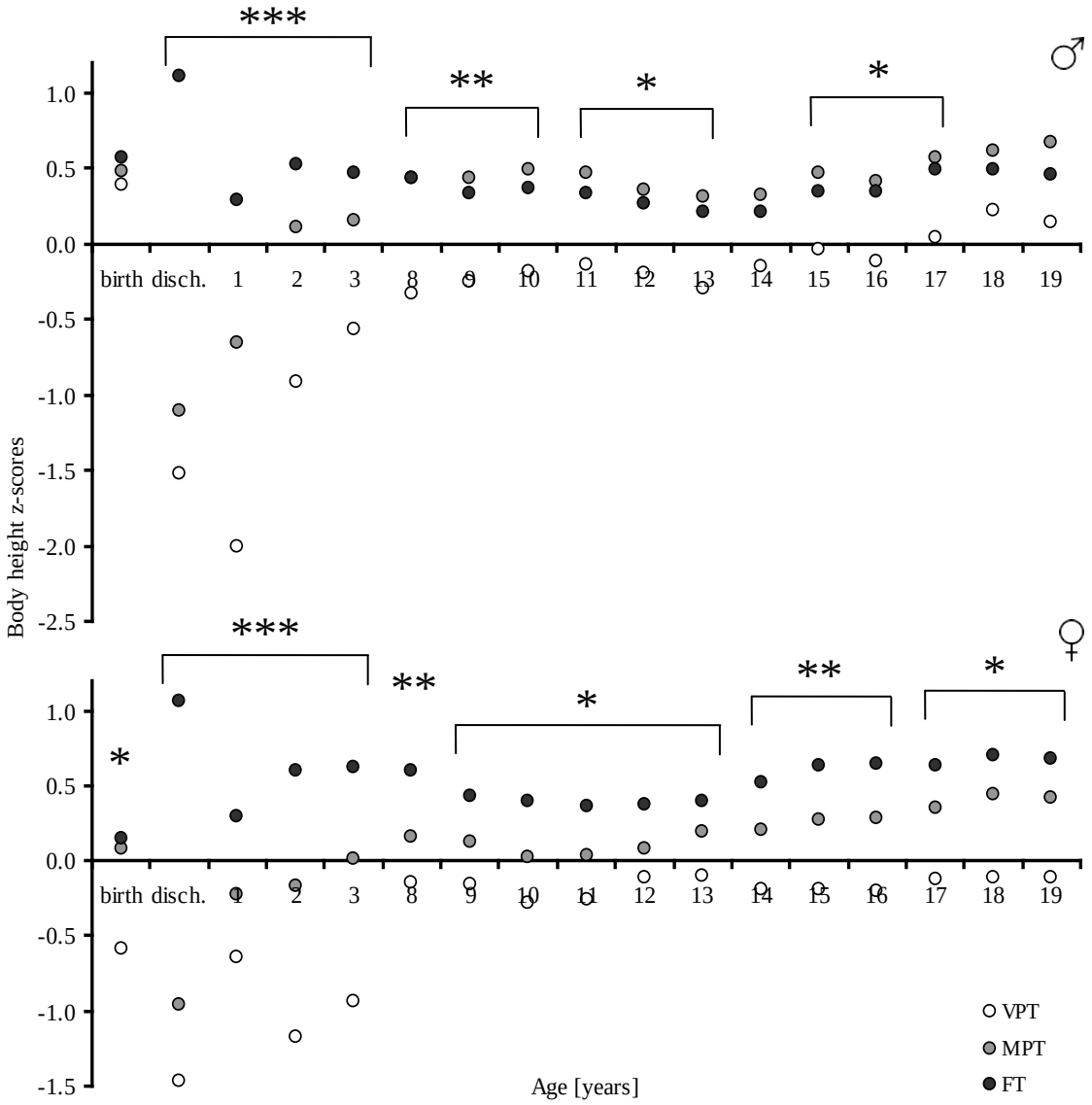
Slika 14: Telesna višina [cm] žensk od rojstva do starosti 19 let

After calculating z-scores for body height (Annex N, Figure 15), which are statistical measurements of scores' relationship to the mean of a standard normal distribution, it can be concluded that VPT females are shorter than MPT and FT females at birth and PT females remain shorter than their FT peers through their whole life. PT males are shorter than their peers from discharge up to the age of 3 years and VPT males are shorter than MPT and FT peers up to 17 years of age. FT individuals are taller than the average of the WHO height standards (WHO, 2004), while VPT females remain shorter than the WHO height standards also in adulthood (Annex N, Figure 15).

As evident from Annex N, relative increases in body height demonstrate that VPT individuals grow faster ($p<0.05$) than their peers up to the age of 12 years, VPT males also from 13 to 18 years (Annex N). VPT females reach their final body height earlier then MPT and FT peers, as they stop growing at 17 to 18 years. PT individuals grow faster ($p<0.05$) than their peers up to the age of 13 years, in males also from 13 to 17 years. PT individuals have higher PHV than FT individuals (Annex N, Figure 16).

When the uncorrected age is considered, VPT females (N=10) experience PHV earlier ($p=0.02$) than FT (N=72) females (11.1 (0.6) vs. 11.5 (1.2) years, respectively). MPT females (N=62) experienced PHV at 11.4 (1.0) years of age on average, which is similar to FT individuals. No statistically significant difference ($p=0.71$) in age at PHV was observed between VPT (N=19), MPT (N=54), and FT (N=81) males (13.6 (1.4), 13.6 (0.9), and 13.4 (1.1) years, respectively) (Figure 17).

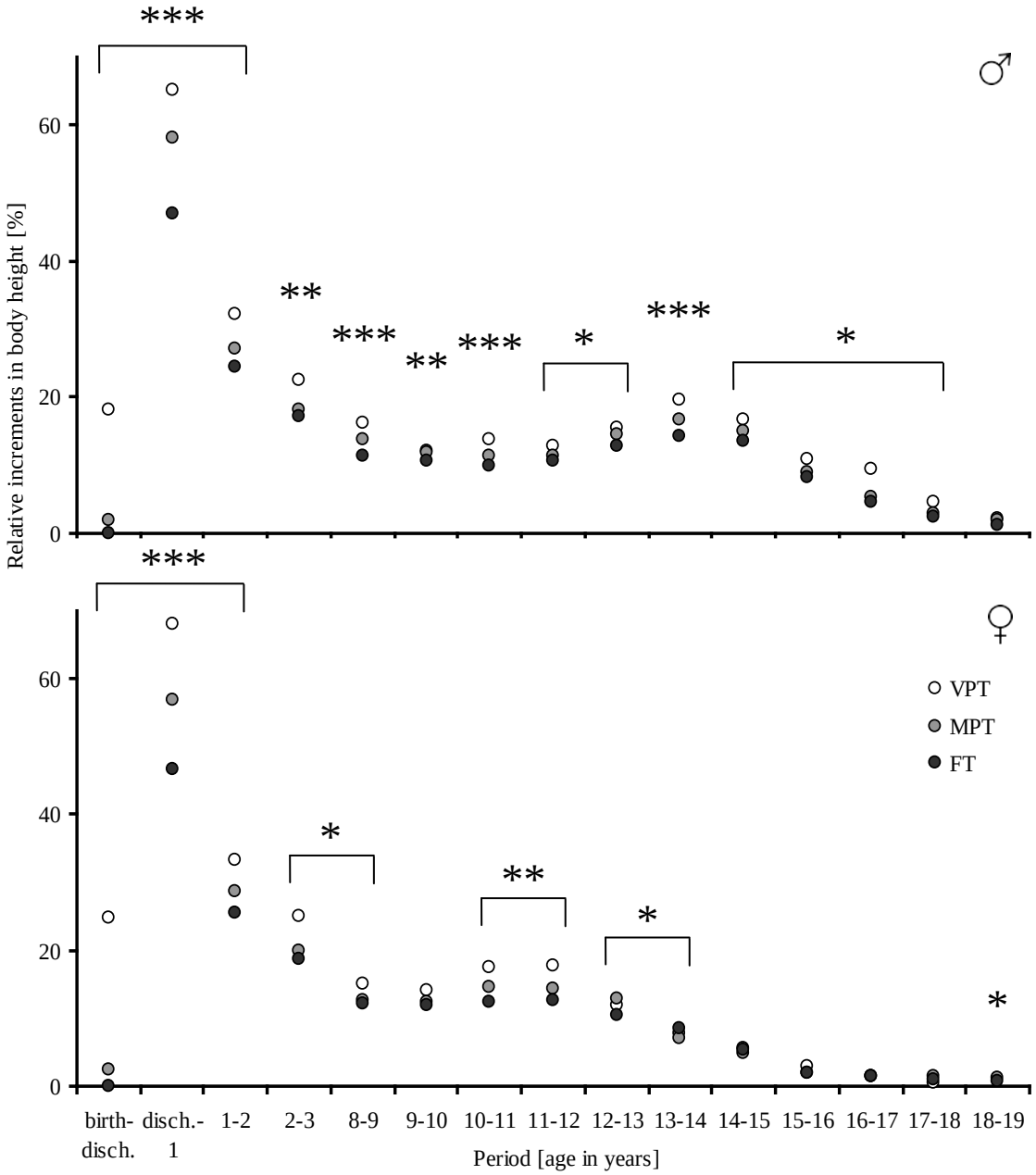
When the corrected age is considered, VPT females experience PHV earlier ($p<0.01$) than FT females (10.8 (0.5) vs. 11.5 (1.2) years, respectively), MPT females experienced PHV at 11.3 (1.0) years on average, which is similar to FT individuals. No statistically significant difference ($p=0.94$) in age at PHV was observed between VPT, MPT, and FT males (13.4 (1.4), 13.5 (0.9), and 13.4 (1.1) years, respectively) (Figure 17).



VPT – very preterm, MPT – moderately preterm, FT – full-term, disch. – discharge, * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$

Figure 15: Body height z-scores from birth to the age of 19 years

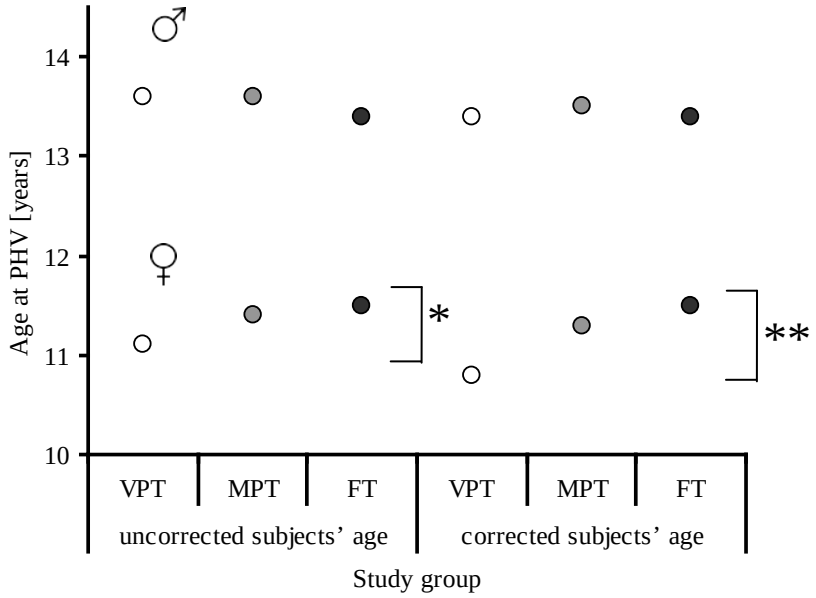
Slika 15: Z-vrednosti telesne višine preiskovancev od rojstva do starosti 19 let



VPT – very preterm, MPT – moderately preterm, FT – full-term, disch. – discharge, * – p<0.05, ** – p<0.01, *** – p<0.001

Figure 16: Relative increases in body height [%] from birth to the age of 19 years calculated with respect to birth height

Slika 16: Relativna povečanja telesne višine [%] preiskovancev od rojstva do starosti 19 let izračunana glede na porodno višino



VPT – very preterm, MPT – moderately preterm, FT – full-term, disch. – discharge, * – $p<0.05$, ** – $p<0.01$

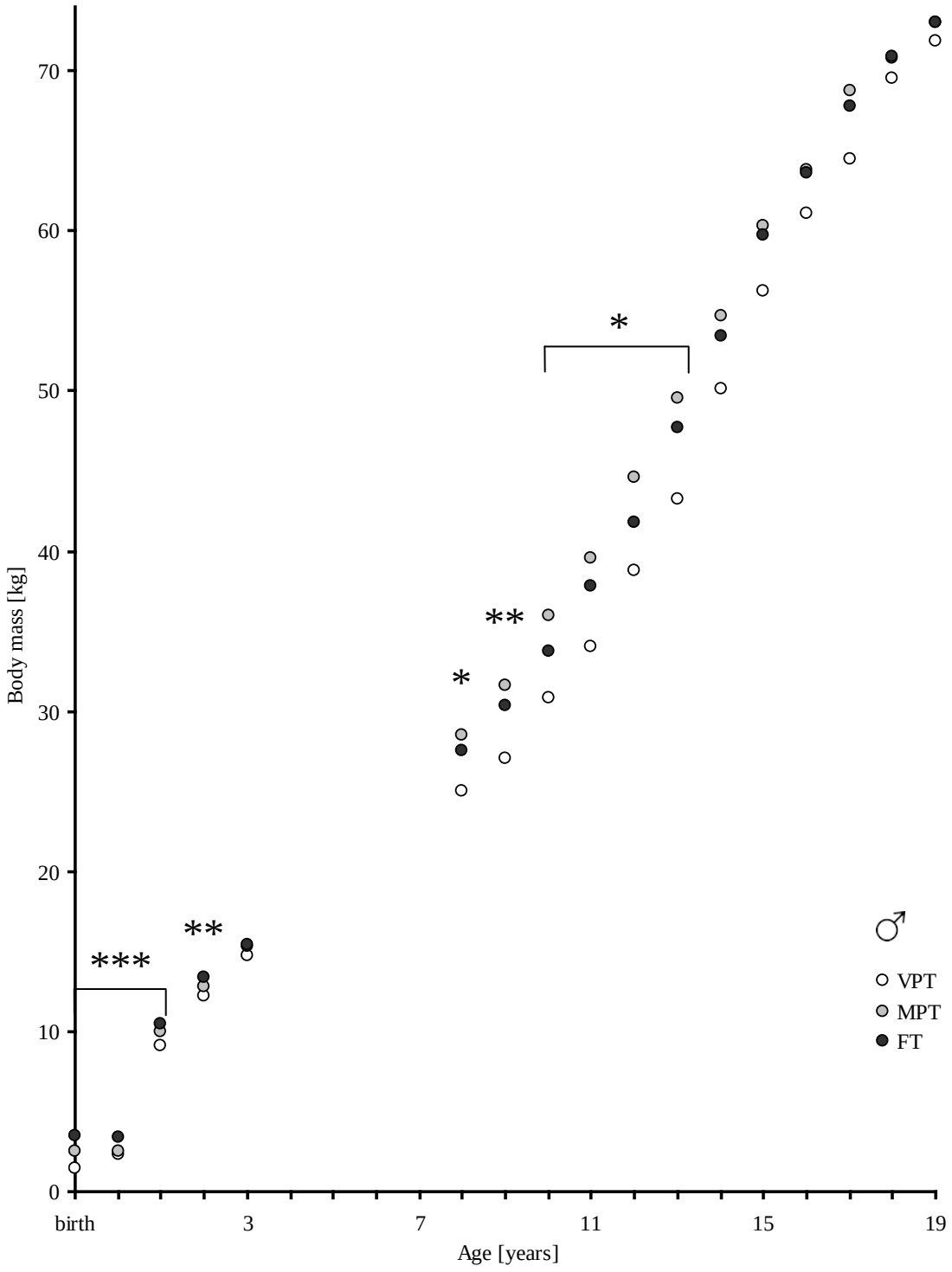
Figure 17: Age at peak height velocity (PHV; [years]) for all study groups calculated for uncorrected and corrected subjects' age

Slika 17: Starost ob rastnem sunku (PHV; [leta]) za vse raziskovalne skupine izračunana za nekorigirano in korigirano starost preiskovancev

4.2.4.2 Body mass of preterm and full-term infants

For males, body mass was statistically lower ($p<0.01$) in PT than in FT infants from birth up to 2 years of age. Significant differences in body mass between VPT and their MPT and FT individuals were observed also between 8 and 13 years of age ($p<0.05$), with VPT individuals being lighter than peers and MPT were heavier ($p<0.05$) than VPT peers. (Annex O, Figure 18).

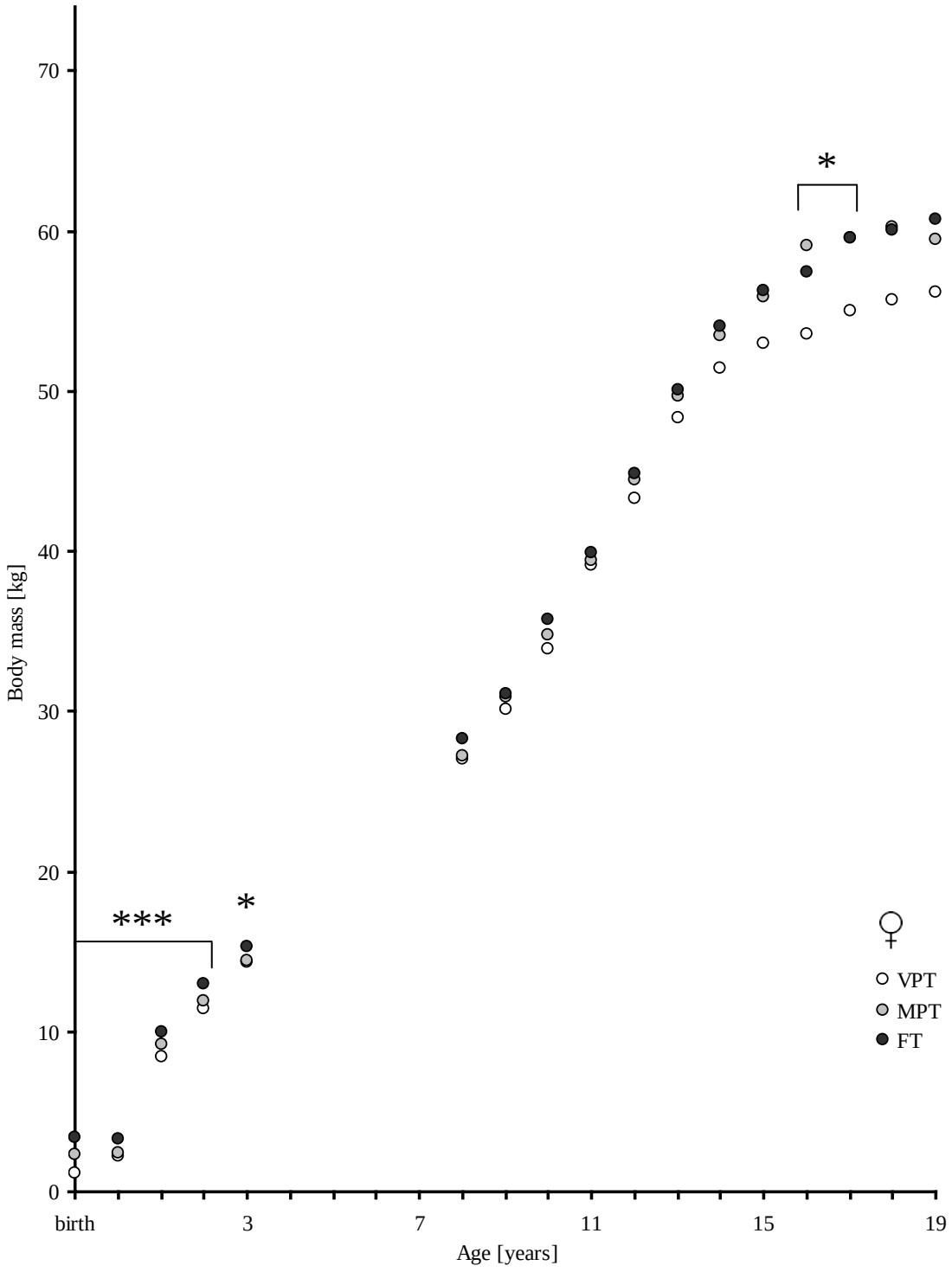
In females, the difference in body mass between PT and FT individuals persisted from birth up to 3 years. VPT females were lighter than MPT and FT peers also at 16 and 17 years of age (Annex O, Figure 19).



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – p<0.05, ** – p<0.01, *** – p<0.001

Figure 18: Body mass [kg] in males from birth to the age of 19 years

Slika 18: Telesna masa [kg] moških od rojstva do starosti 19 let

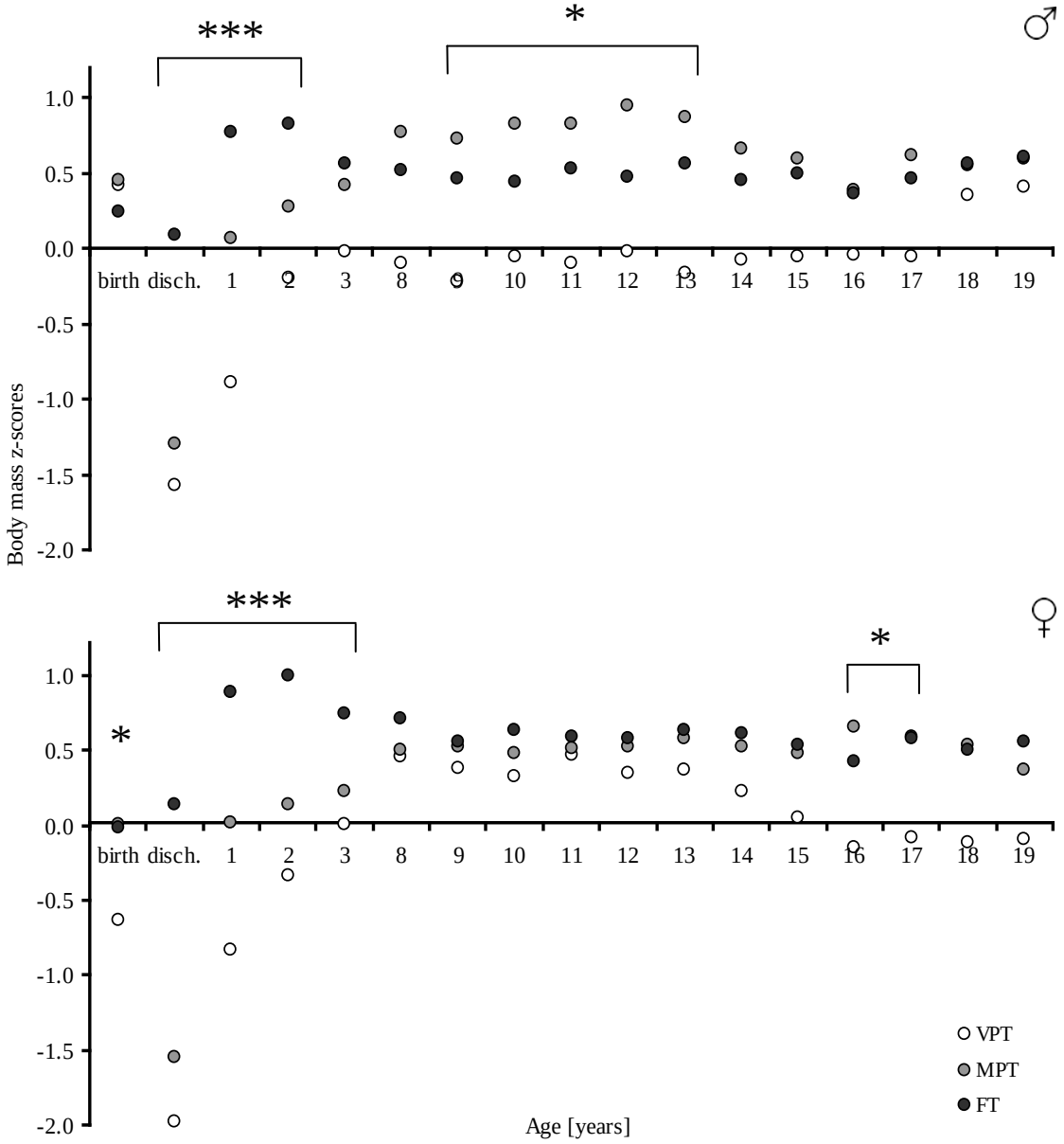


VPT – very preterm, MPT – moderately preterm, FT – full-term, * – p<0.05, ** – p<0.01, *** – p<0.001

Figure 19: Body mass [kg] in females from birth to the age of 19 years

Slika 19: Telesna masa [kg] žensk od rojstva do starosti 19 let

After calculating z-scores for body mass (Annex O, Figure 20), it can be concluded that VPT males remain lighter ($p<0.05$) than the average population through their puberty, VPT females in the first years and in late adolescence. FT individuals are heavier than the average of WHO mass standard, while MPT individuals catch-up in mass successfully by the age of 1 year (Annex O, Figure 20).



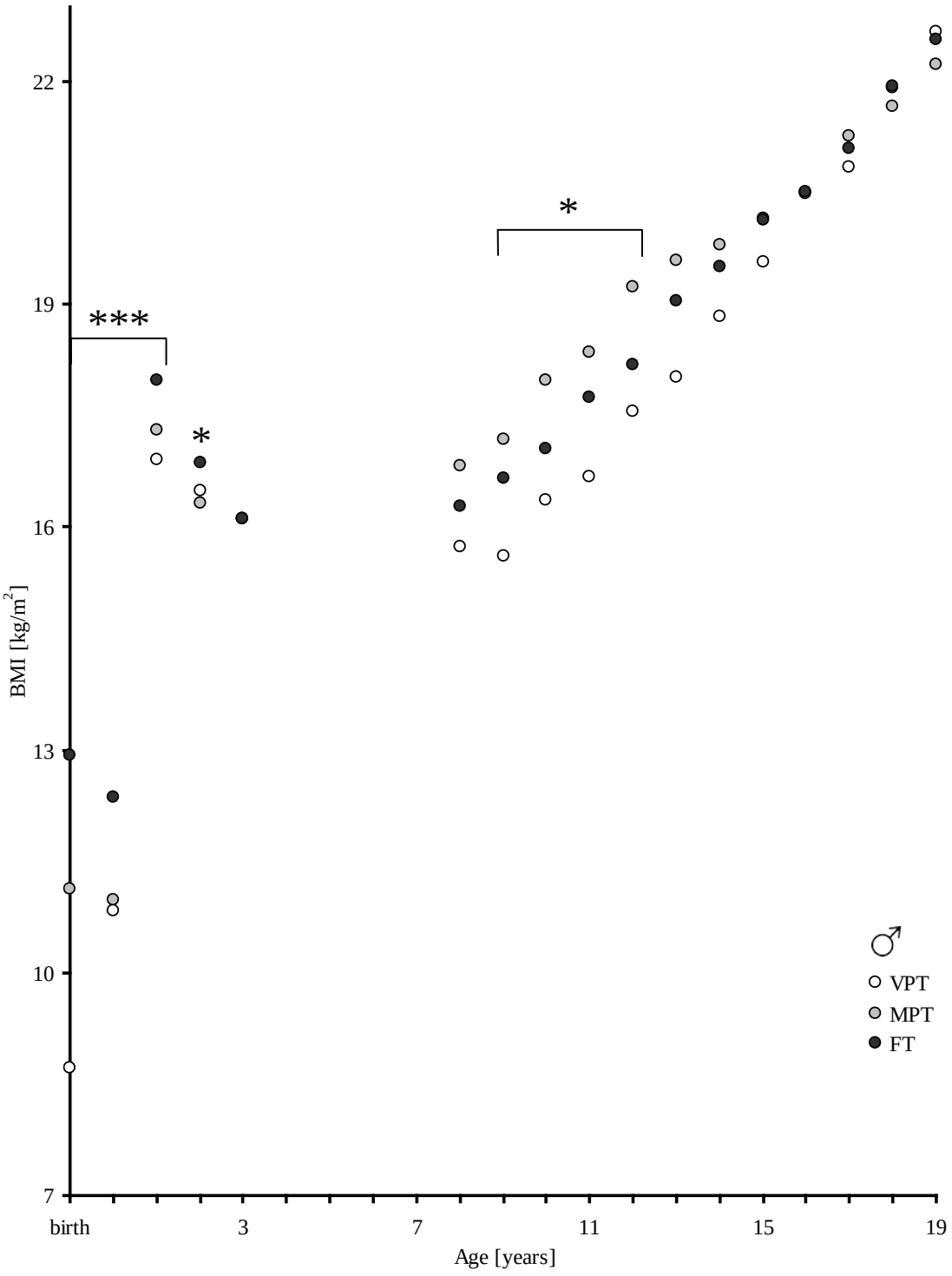
VPT – very preterm, MPT – moderately preterm, FT – full-term, disch. – discharge, * – $p<0.05$, *** – $p<0.001$

Figure 20: Body mass z-scores from birth to the age of 19 years

Slika 20: Z-vrednosti telesne mase preiskovancev od rojstva do starosti 19 let

4.2.4.3 BMI of preterm and full-term infants

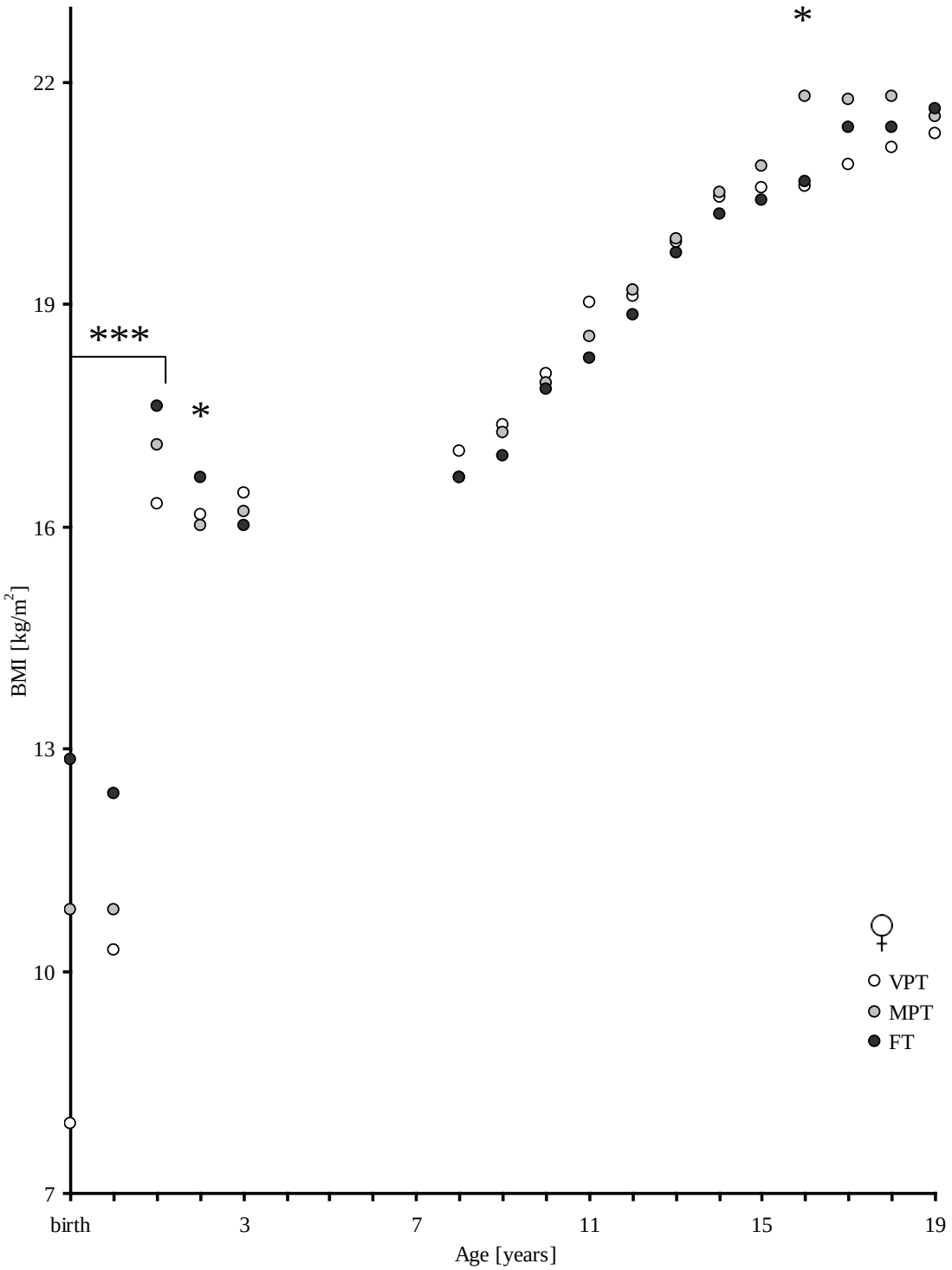
BMI was significantly lower ($p<0.05$) in PT than in FT infants from birth up to 2 years of age for both, males and females, with the lowest values in VPT individuals (Annex P, Figures 21 and 22). PT females had higher BMI than FT peers at 16 years of age. VPT males had lower ($p<0.05$) BMI than their peers at 9 and 11 years, and lower than MPT at 10 and 12 years (Annex P, Figure 22).



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – p<0.05, *** – p<0.001

Figure 21: BMI [kg/m^2] in males from birth to the age of 19 years

Slika 21: ITM [kg/m^2] moških od rojstva do starosti 19 let

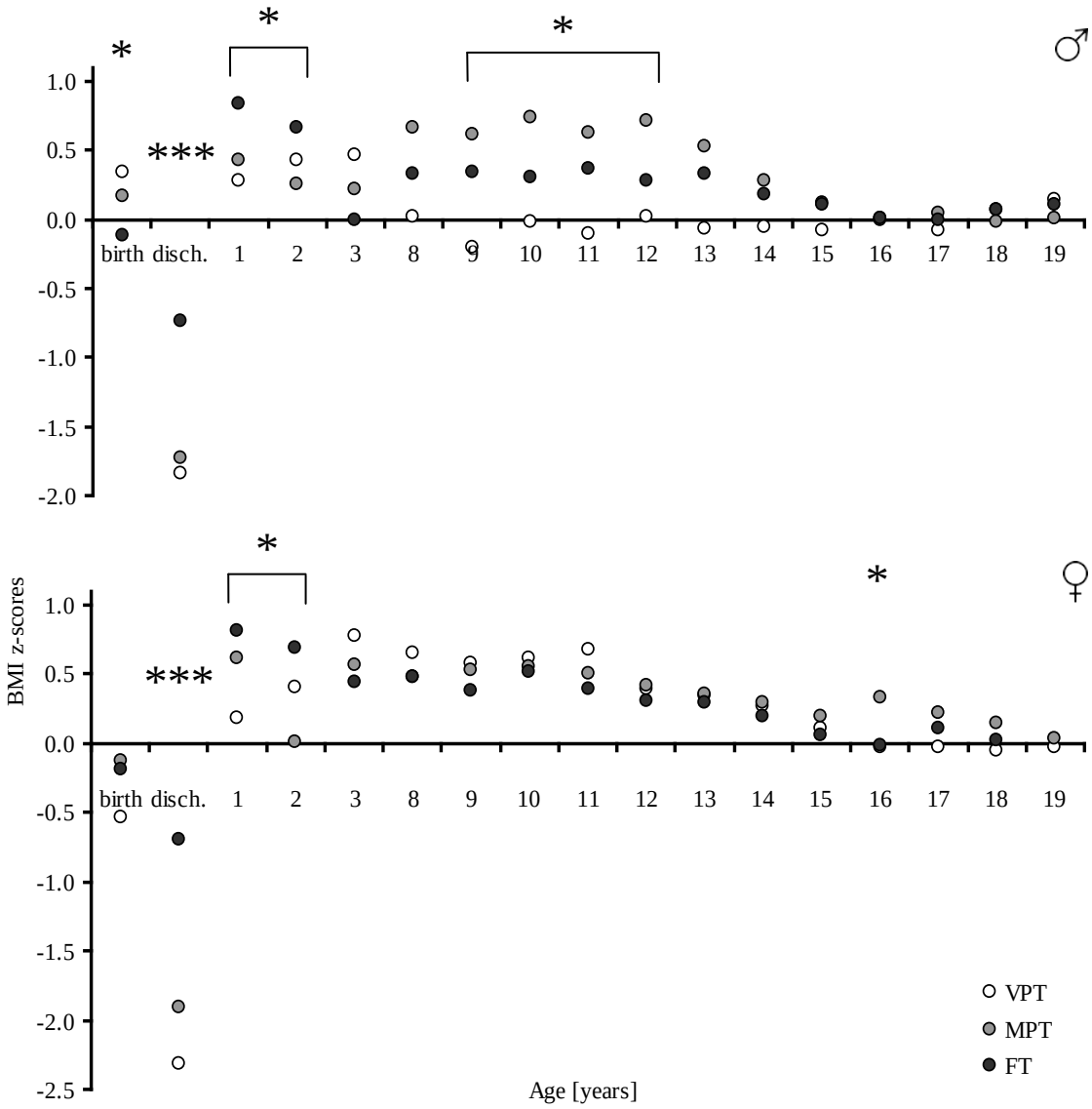


VPT – very preterm, MPT – moderately preterm, FT – full-term, * – p<0.05, *** – p<0.001

Figure 22: BMI [kg/m^2] in females from birth to the age of 19 years

Slika 22: ITM [kg/m^2] žensk od rojstva do starosti 19 let

Also, after calculating z-scores for BMI (Annex P, Figure 23) it can be observed that FT individuals have higher BMI than their PT peers from birth up to 2 years of age. Later on, significantly lower ($p<0.05$) BMI in VPT males can be observed from 9 to 12 years than in peers. PT females had higher BMI than FT peers at 16 years of age (Annex P, Figure 23).



VPT – very preterm, MPT – moderately preterm, FT – full-term, disch. – discharge, * – $p<0.05$, *** – $p<0.001$

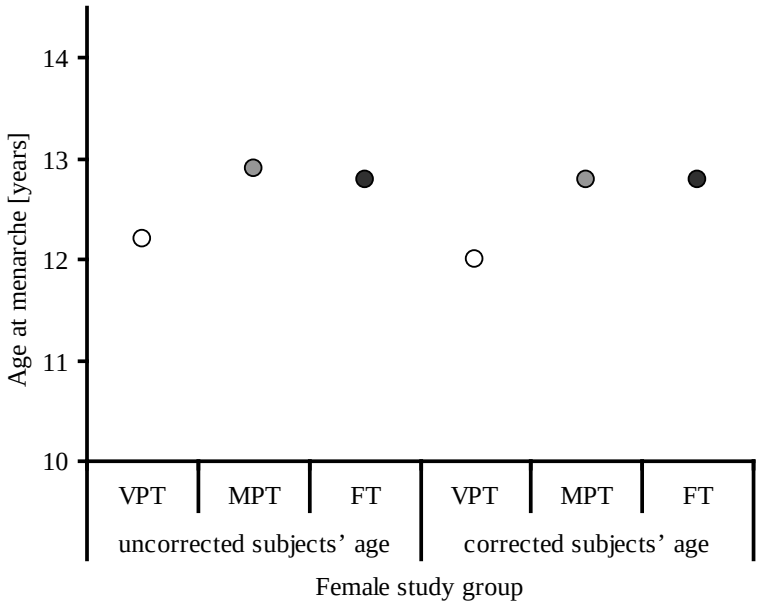
Figure 23: BMI z-scores from birth to the age of 19 years

Slika 23: Z-vrednosti ITM-ja preiskovancev od rojstva do starosti 19 let

4.2.4.4 Age at menarche of preterm and full-term female infants

Although the sample of VPT females (N=5) was too small for final conclusions, they tend (p=0.18) to experience menarche earlier (12.2 (1.3) years) than their MPT (N=12) and FT (N=15) peers (12.9 (1.3) and 12.8 (1.3) years, respectively) (Figure 24), with age expressed as the uncorrected age.

When the corrected age is considered, the tendency is even stronger: VPT females tend (p=0.12) to experience menarche earlier (12.0 (1.3) years) than their MPT and FT peers (12.8 (1.3) and 12.8 (1.3) years, respectively) (Figure 24).



VPT – very preterm, MPT – moderately preterm, FT – full-term

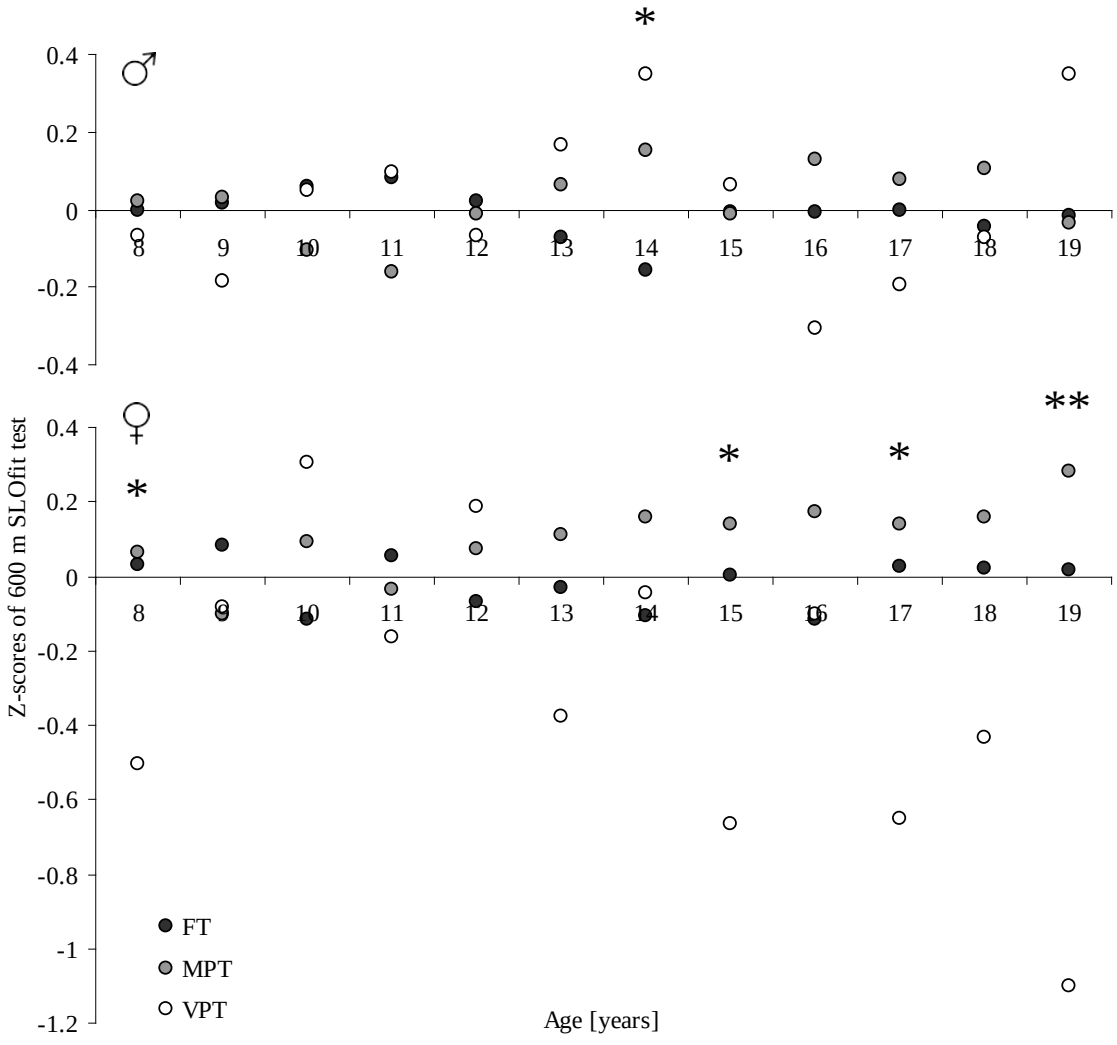
Figure 24: Age at menarche [years] for all female study groups, calculated for uncorrected and corrected subjects´ age

Slika 24: Starost ob menarhi [leta] v vseh skupinah žensk izračunana za nekorigirano in korigirano starost preiskovancev

4.2.4.5 Capacity of physical exercise and motor skills of preterm and full-term infants

Absolute values, z-scores, and statistics results of SLOfit tests performed during schooling are presented in the Annexes Q to S and Figures 25 to 27.

The results of general endurance (aerobic) test (Annex Q, z-scores presented in Figure 25) were similar between VPT, MPT, and FT males, except at the age of 14, when PT males ran faster at 600 m ($p<0.05$) than their FT peers (146.4 (20.9) s and 155.6 (28.6) s, respectively). VPT females were statistically slower ($p<0.05$) than their MPT and FT peers at the age of 8, 15, 17, and 19 years of age, the same trend ($p=0.06$) was seen at the age of 18 years.



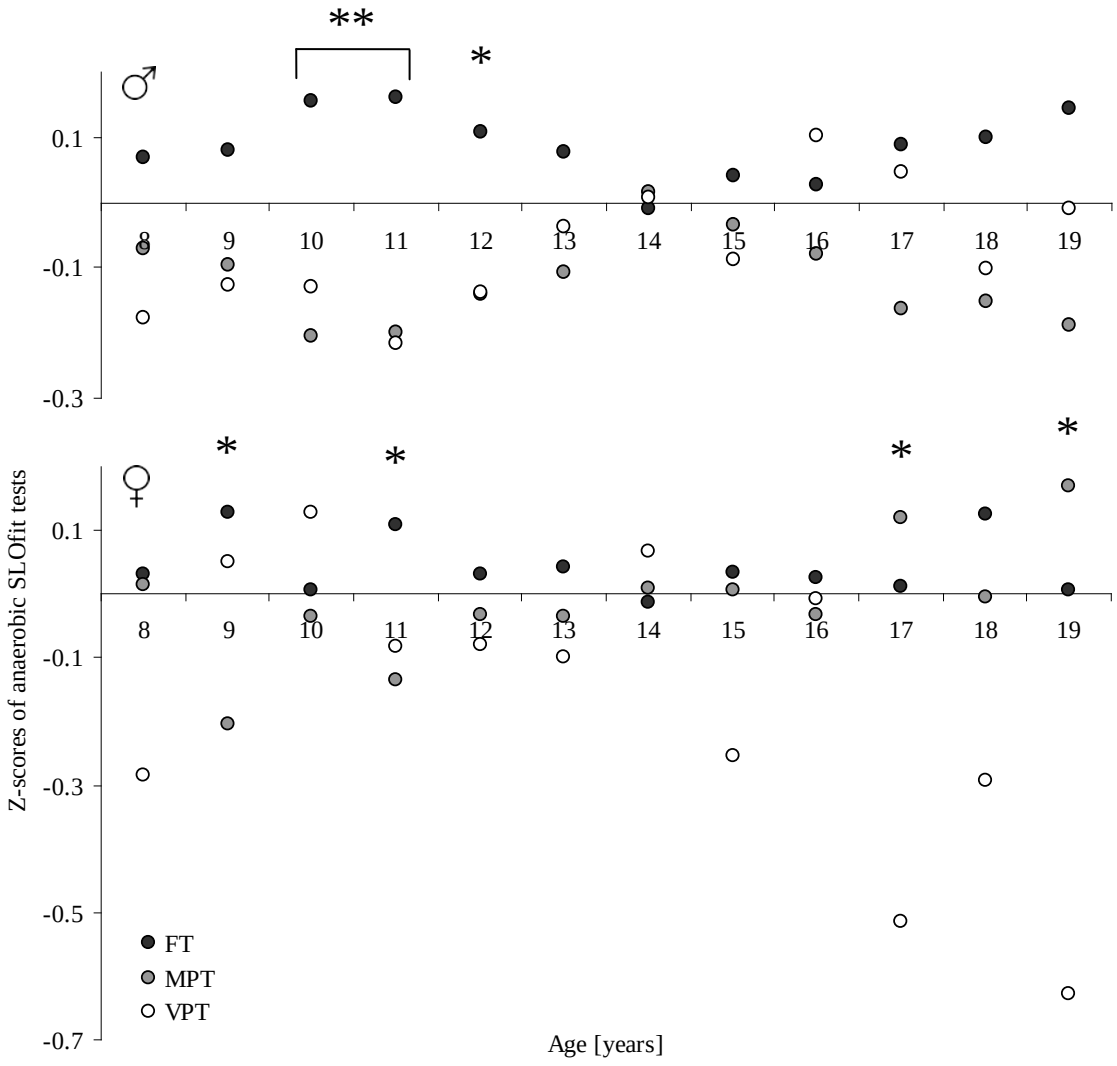
VPT – very preterm, MPT – moderately preterm, FT – full-term, * – $p<0.05$, ** – $p<0.01$

Figure 25: Z-scores of aerobic general endurance SLOfit test from the age of 8 to 19 years

Slika 25: Z-vrednosti SLOfit aerobnega testa splošne vzdržljivosti preiskovancev v starosti 8 do 19 let

Anaerobic SLOfit tests (Annex R, z-scores presented in Figure 26) were mostly performed worse by PT than by FT individuals, which is supported by statistical differences at the age of puberty and at the end of growth (more in detail below).

Sprint speed was lower ($p<0.05$) in PT than in FT males from the age of 10 to 12 years, the same trend seems to be also present at the age of 8 and 13 years ($p=0.06$ and 0.07, respectively). PT females were statistically slower in running at 60 m at the age of 9 years and, as it seems ($p=0.07$), also at 18 years. VPT females were slower ($p<0.05$) than their MPT and FT peers at the ages of 8 and from 17 to 19 years of age.



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – $p<0.05$, ** – $p<0.01$

Figure 26: Average z-scores of all anaerobic SLOfit tests from the age of 8 to 19 years

Slika 26: Povprečne z-vrednosti vseh aerobnih SLOfit testov preiskovancev v starosti 8 do 19 let

Explosive power was significantly lower ($p<0.05$) in PT males than in their FT peers from the age of 8 to 13 years and at 15 and 17 years of age (with the lowest values in VPT observed at 11 years), the same trend ($p=0.08$) was also evident at 19 years of age. In females, the same difference was present at the ages of 9, 11, 15, and 19 years, with the lowest values in VPT individuals at 19 years of age. The same trend ($p=0.06$) was also evident at the age of 12 years.

Better ($p<0.05$) trunk muscle strength was evident in FT males than in their PT peers (with the lowest values observed in VPT individuals) at the ages of 10, 11, 12, and 18 years, and, as it seems, also at the ages of 8 and 19 years ($p=0.05$ and 0.07, respectively). In females, the same trend was evident at the ages of 17 ($p=0.09$) and 19 ($p<0.05$) years.

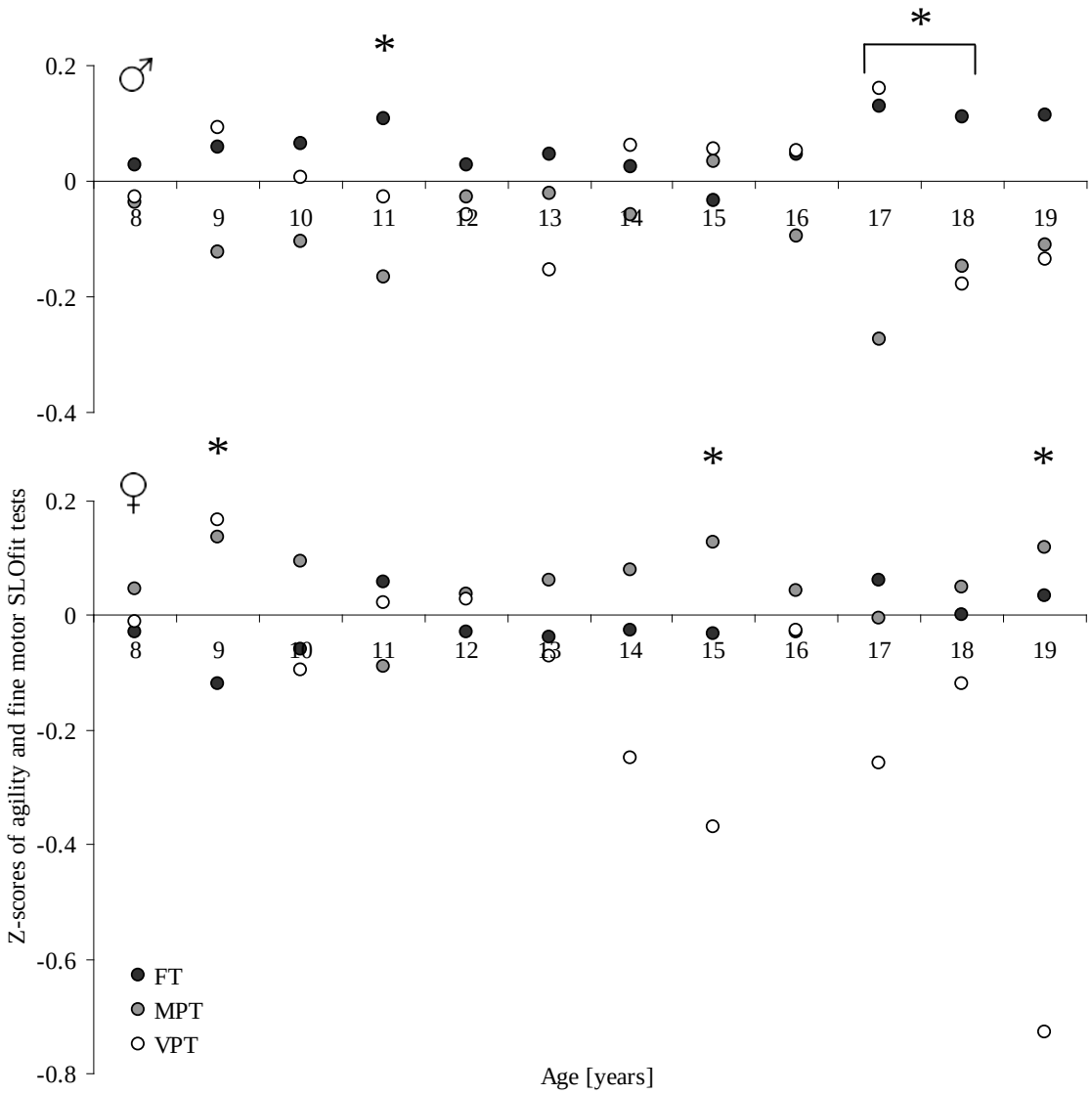
Muscular endurance of the shoulder girdle and arms was worse ($p<0.05$) in PT males than in FT peers, with the lowest values in MPT individuals at the ages of 10 and 11 years and with the longest duration in VPT males at 8 years of age. The same trend was also observed at 10 and 12 years ($p=0.07$) of age. However, at the age of 14 years, PT males most likely improved ($p=0.07$). PT females tended to hang less time on the pole at 9 and 11 years ($p=0.07$ and 0.09, respectively) than their FT peers, with VPT females hawing the worst ($p<0.05$) scores at 17 years of age.

Agility and fine motor SLOfit tests (Annex S, z-scores presented in Figure 27) were mostly performed better in PT individuals up to puberty (which was especially evident in females). Later on, FT peers performed better.

Coordination of body movements was worse ($p<0.05$) in MPT males than in their VPT and FT peers at the ages of 10, 11, 14, and 17 years. The same trend seems to be present at 9 and 18 years ($p=0.09$). In contrary, PT females, especially MPT females, had better coordination ($p<0.05$) at the ages of 9 and 10 years than FT peers. Later on FT females improved and tended to be better than VPT peers at the ages of 15 and 19 years.

Similar to above, forward bend and touch on the bench tended to be performed better in FT males ($p=0.07$) at the age of 11 and 17 years and in PT females ($p<0.05$) at the age of 9 years. However, in puberty FT females improved (at the ages of 15 and 19) and performed better ($p<0.05$) than their VPT peers.

PT females had faster speed of alternative movements ($p<0.05$) than their FT peers at the ages from 13 to 16 years, while VPT males were slower in arm plate tapping than their MPT and FT peers at 18 and 19 years of age ($p<0.05$).



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – $p<0.05$

Figure 27: Average z-scores of all agility and fine motor SLOfit tests from the age of 8 to 19 years

Slika 27: Povprečne z-vrednosti vseh testov gibljivosti in fine motorike iz SLOfit sistema preiskovancev v starosti 8 do 19 let

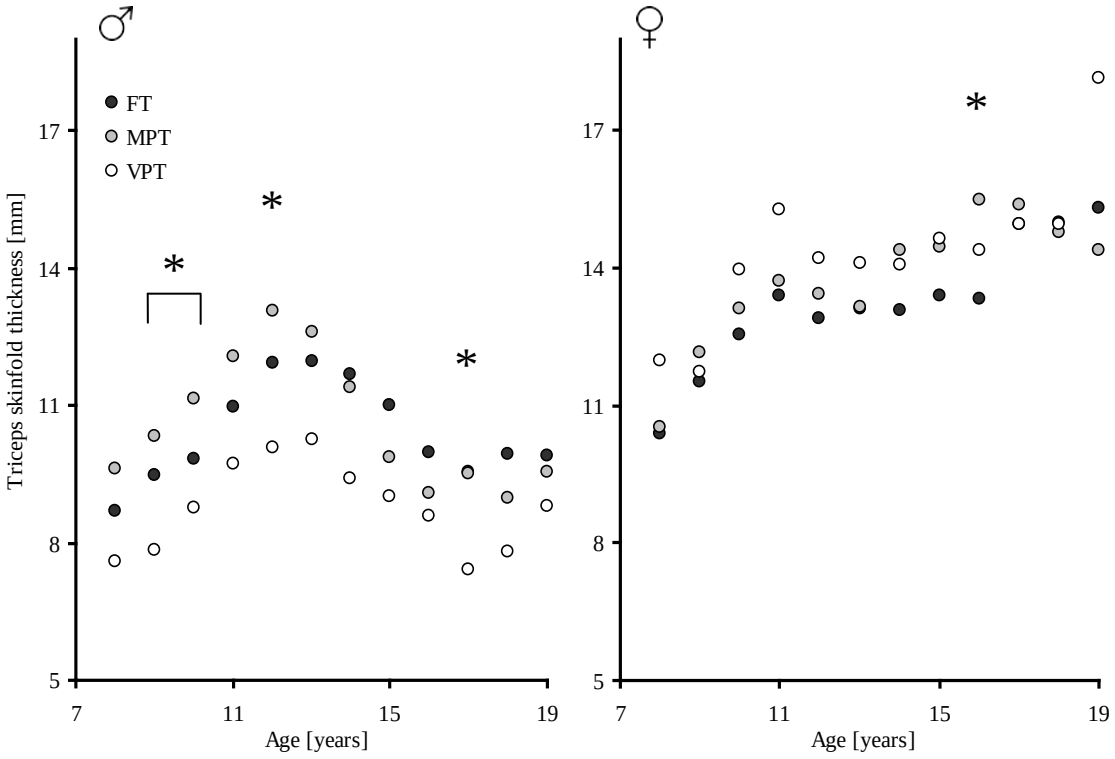
Average (SD) physical activity of VPT, MPT, and FT individuals (N=7, 17, and 24, respectively) was 6602 (5772), 7328 (4627), 5882 (4000) MET-minutes/week, respectively. As the sample was small, standard deviation is very large, and as from the results was evident that many participants didn't fulfilled the questions properly and very overestimated their physical activity, we cannot compare current physical activity between the PT and FT individuals at the age of 26.

4.2.5 Results of Hypothesis 6 testing

We hypothesized that distribution of body fat will be different in full-term and premature children.

In males, triceps skinfold thickness was similar between PT and FT individuals between 8 and 19 years of age. In VPT it was lower ($p<0.05$) than in MPT and FT individuals at the ages of 9, 12, and 17 years (the highest values in MPT at 9 and 10 years), the same trend seems to be also from 8 to 15 and at 18 years (Annex T, Figure 28).

In females, triceps skinfold thickness was higher in PT ($p<0.05$) than in FT individuals at the age of 16 years, the same trend ($p=0.09$) seemed to be also present at 14 years of age. At 19 years of age, triceps skinfold thickness seemed to be higher in VPT females than in their peers (Annex T, Figure 28).



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – $p<0.05$

Figure 28: Triceps skinfold thickness [mm] from the age of 8 to 19 years

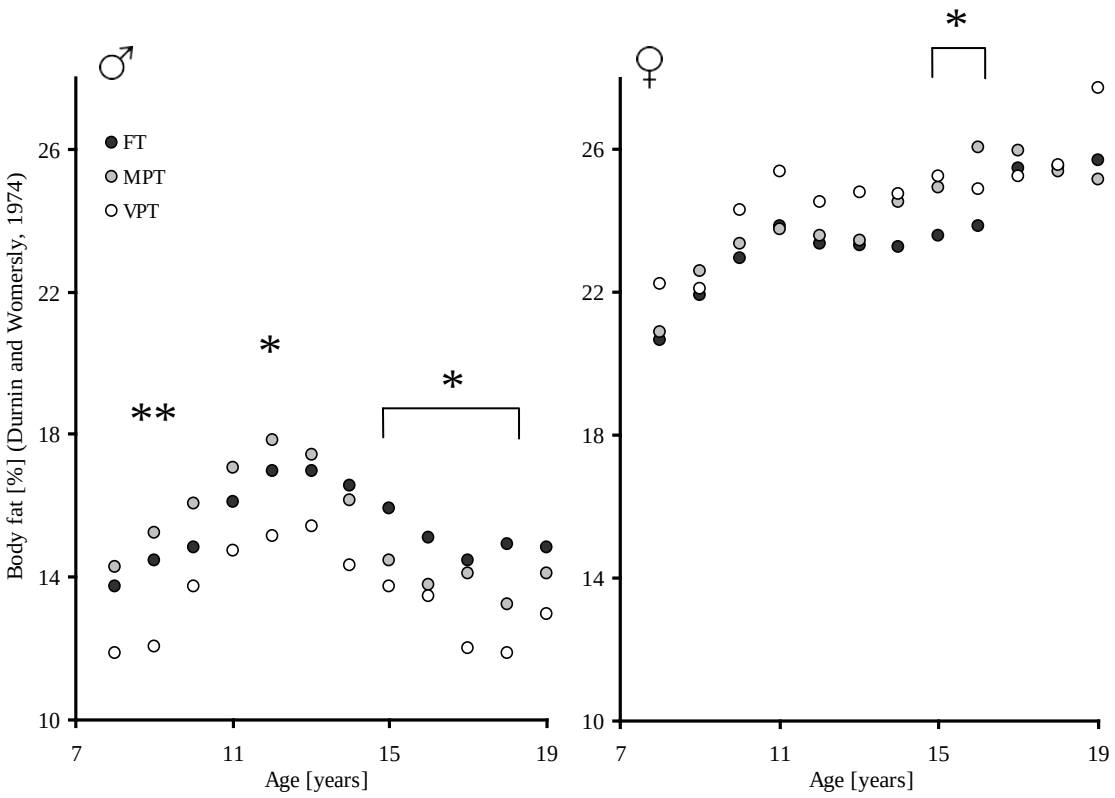
Slika 28: Debelina kožne gube tricepsa [mm] preiskovancev v starosti 8 do 19 let

As the final sample was small, we could not compare skinfold thicknesses at eight body sites, circumferences at six body sites, and distribution of body fat between the PT and

FT individuals at the age of 26 years. Absolute values of those measurements are nevertheless presented in the Annexes U and V.

Percentage of body fat, estimated according to the equations of Durnin and Womersly (1974) and Siri (1961), was higher ($p<0.05$) in FT males than in their PT peers at the ages of 15, 16, and 18 years, and was lower in VPT males ($p<0.05$) than in their MPT and FT peers at the ages of 9, 12, and 17 years. The same trend was seen at the ages from 8 to 15 years and at 18 years of age (Annex W, Figure 29).

PT females had higher ($p<0.05$) percentage of body fat at the ages of 15 and 16 years than their FT peers, which is also demonstrated in higher ($p<0.01$) values of body fat percentage in MPT females, as compared to FT individuals at the age of 16 years. The same trend was also seen at 14 years of age ($p=0.06$) and in higher values of body fat percentage in VPT females, as compared to their MPT and FT peers at the age of 19 years ($p=0.07$) (Annex W, Figure 29).



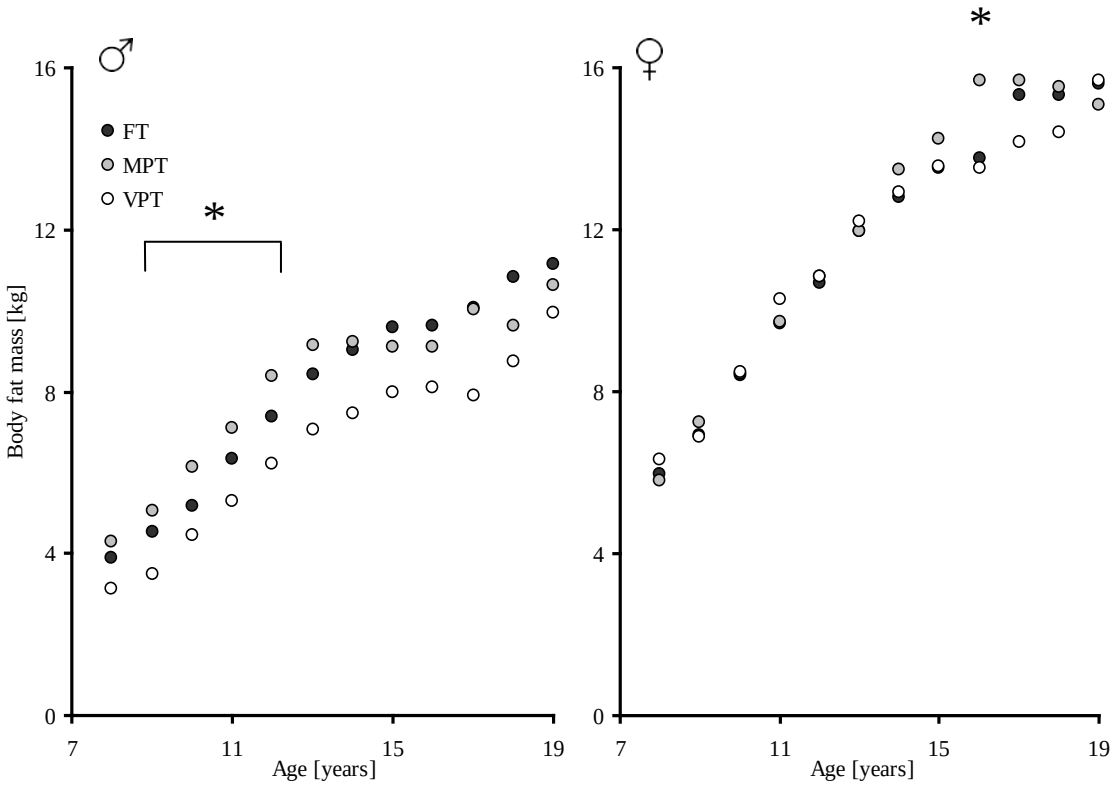
VPT – very preterm, MPT – moderately preterm, FT – full-term, * – $p<0.05$, ** – $p<0.01$

Figure 29: Percentage of body fat from the age of 8 to 19 years calculated according to the equations of Durnin and Womersly (1974) and Siri (1961)

Slika 29: Odstotek telesnega maščobnega tkiva preiskovancev v starosti 8 do 19 let, izračunan po enačbah Durnin in Womersly (1974) in Siri (1961)

In males, body fat mass did not differ between PT and FT individuals; however, in VPT males it was lower ($p<0.05$) than in MPT and FT individuals at the ages of 9 to 12 years. The same trend was also seen at 8 years of age and from 13 to 17 years of age (Annex X, Figure 30).

In females, body fat mass was higher in PT than in FT individuals at the age of 16 years, but it did not differ between VPT and MPT or FT individuals from 8 to 19 years of age (Annex X, Figure 30).



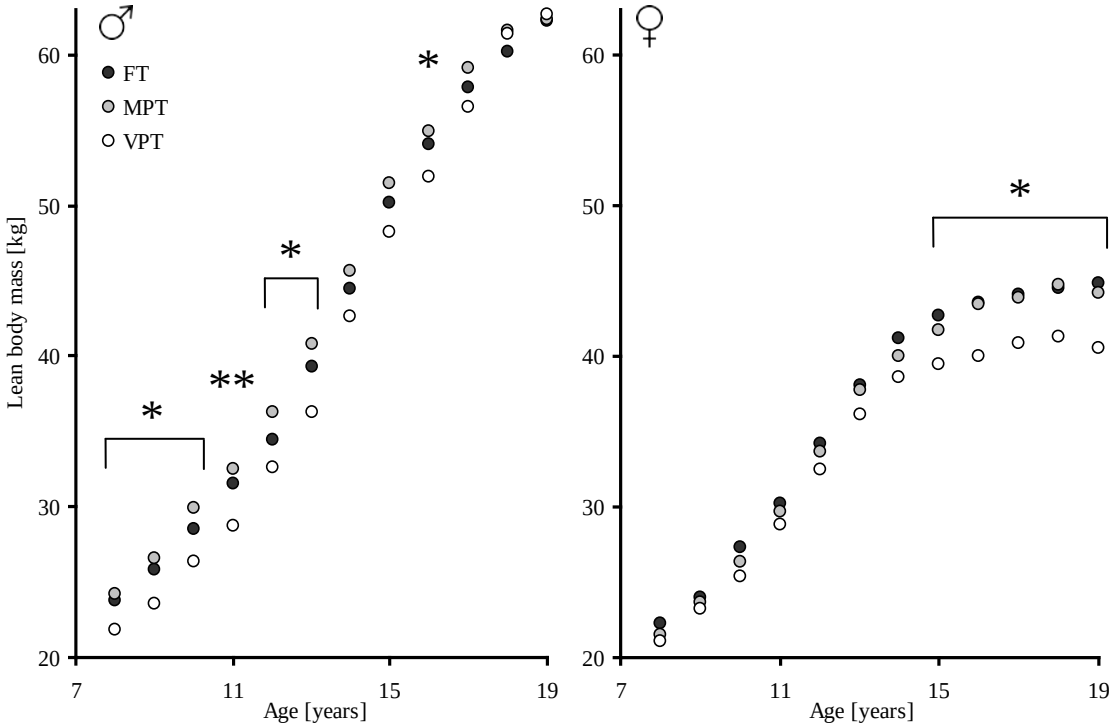
VPT – very preterm, MPT – moderately preterm, FT – full-term, * – $p<0.05$

Figure 30: Body fat mass [kg] from the age of 8 to 19 years

Slika 30: Masa telesnega maščobnega tkiva [kg] preiskovancev v starosti 8 do 19 let

Lean body mass did not differ between PT and FT males. However, in VPT males it was lower ($p<0.05$) than in MPT and FT individuals from 8 to 13 years (with the highest values in MPT from 10 to 12 years of age) and at 16 years of age (Annex Y, Figure 31).

In females, lean body mass was similar in PT and FT individuals, although a trend towards smaller lean body mass in PT females could be seen at 8, 10, 14, and 15 years of age ($p=0.06$, 0.06, 0.06, and 0.07, respectively). In VPT females lean body mass was lower ($p<0.05$) than in their MPT and FT peers after the age of 15 years (Annex Y, Figure 31).



VPT – very preterm, MPT – moderately preterm, FT – full-term, * – $p<0.05$, ** – $p<0.01$

Figure 31: Lean body mass [kg] from the age of 8 to 19 years

Slika 31: Pusta telesna masa [kg] preiskovancev v starosti 8 do 19 let

5 DISCUSSION

As preterm birth (PT; <37th weeks gestation) and low birth mass were proposed to impair growth and development, increase prenatal, childhood, and adult morbidity and mortality, affect the onset of sexual maturity and physical characteristics in later life, and as physical characteristics of pregnant women and their infants may be related, the aim of the present thesis was to investigate, whether the existing anthropometric methods are adequate for assessing body composition in pregnant women; whether the pattern of growth of PT and full-term (FT) infants during the first year of life depends on anthropometric characteristics of their mothers; whether the susceptibility and frequency of illnesses after the period of accelerated growth is different between PT and FT children; whether the potential consequences of prematurity (lower body height, body mass, and capacity of physical exercise) are detected after childhood; and whether the distribution of body fat is different in PT and FT individuals. We therefore extended the systematic monitoring of physical and motor development of children and adolescents in Slovenia into a combination of prospective and retrospective research study, with a general title of "Preterms 1987". Anthropometric measurements were performed on pregnant women and used in anthropometric equations for the estimation of body fat percentage. Their infants were classified according to maternal physical characteristics and relative increases between the groups were compared. Furthermore, anthropometric measurements, data on health problems at birth and further on in life were obtained from participants born in 1987 from the Slovenian perinatal database, a part of the individual's medical records, the SLOfit system, at laboratory visits, and with questionnaires of the now 26-year-old subjects. The subjects were classified into very PT (VPT), moderate PT (MPT), and FT groups, and their data were compared between the groups.

The main findings of this study are that:

- currently known anthropometric methods are not reliable for the determination of body fat percentage of pregnant women;
- maternal pre-pregnancy mass, pre-pregnancy body mass index (PpBMI), pregnancy mass gain (PMG), and the appropriateness of maternal PMG according to her pre-pregnancy BMI affect the growth of an infant during the first year of life;
- the majority of previously reported risk factors for PT birth were also the cause for PT (especially for very PT (VPT)) birth in our sample;
- a lot of illnesses and applied interventions at birth and in childhood are more often in PT, especially in VPT children, as compared to their FT peers; neurological and motor development is worse in PT than in FT infants from birth and during childhood;

- body height and mass increase faster in the first years of life in VPT individuals than in FT peers, but are still hindered in VPT males up to the age of 17 years. In VPT females the same difference persists into the adulthood. Body mass and BMI are lower in PT than in FT individuals up to 13 years of age, later on body mass stays lower, but BMI higher in VPT females, as compared to their FT peers;
- FT individuals perform aerobic and most anaerobic tests better than PT individuals; the exception is muscular endurance of the shoulder girdle and arms, which is of better performance in VPT males. Before puberty, PT females perform the agility and fine motor tests better than their FT peers; however, PT males perform the same tests worse than their FT peers;
- VPT females experience peak height velocity (PHV) earlier than their FT peers and a similar trend is also observed with an earlier onset of menarche;
- VPT males have lower triceps skinfold thickness, fat mass, and calculated body fat percentage than their FT peers after puberty. However, triceps skinfold thickness and body fat percentage are higher in FT than in PT females after puberty; and that
- lean body mass is similar in PT and FT individuals during schooling, but it is lower in VPT individuals than in MPT and FT peers after the age of 8.

5.1 DISCUSSION RELATED TO HYPOTHESIS 1

We hypothesized that the existing anthropometric methods are inadequate for assessing body composition in pregnant women. In addition, we expected that pregnancy specific anthropometric methods will provide rather similar results on body composition of pregnant women, whereas pregnancy non-specific anthropometric methods will differ from the pregnancy specific methods by certain amounts.

The results of the present study (Robič et al., 2013) demonstrate that current knowledge does not yet allow us to select the most appropriate anthropometric method for a reliable determination of body fat percentage of pregnant women.

Namely, the present study focused on the evaluation of three pregnancy specific and nine pregnancy non-specific anthropometric methods. We focused on anthropometric methods, because they are relatively simple (as they are based on measurements of skinfold thicknesses and sometimes combined with circumferences or body mass), they are inexpensive, can be performed routinely outside laboratories, are safe for pregnant women, fetus and newborn, and can be therefore used repeatedly over time even during pregnancy.

The estimations of body fat percentage were supposed to give more or less similar results. However, the present results revealed huge differences between the estimations

on the same sample of pregnant women. Namely, different anthropometric methods for estimating body fat percentage gave results that varied by more than 20 units. Currently it is thus practically impossible to reliably determine nutritional status of a pregnant woman, as different methods result in the same woman being classified as either undernourished (<21.0 % of body fat), normally nourished (21.0 % to 29.5 %), or even over nourished (>29.5 %) according to cut-off points for general population of middle-aged women (Zdešar Kotnik and Golja, 2012).

As revealed by the present study, factors underlining the discrepancies between body composition results obtained by different methods are several; at least some of them are pointed out and discussed below.

Siri (1959), Brožek et al. (1963), and Steinkamp et al. (1965) developed their methods approximately half a century ago, when the physical characteristics of the population were, to a certain extent, different than today (Flegal et al., 1988; Bodzsár and Susanne, 1998; Cole, 2003), which may limit the applicability of these methods nowadays. If we were to select one of these methods as preferential, the method of Steinkamp et al. (1965) would be the most likely choice, as it is based on the measurements of limb circumferences, which are non-linearly related to body fat percentage; as the body composition does not change linearly over time, this seems appropriate for a solid estimation of body composition.

The methods of Slaughter et al. (1988) and Rush et al. (1997) were developed for calculation of body fat percentage in non-pregnant women. Women in their samples were younger (8 to 29, and 18 to 27 years, respectively) than women in the present study. As body fat usually accumulates throughout life, the weighing factors for different variables in these two anthropometric equations would likely change to a certain extent, if they were developed for a somewhat older population, such as ours. Therefore, the results obtained by these two methods on our sample yielded values that would be somewhat different, if the equations were developed on women of about 30 years of age. In addition, these two methods use simple linear correlations to either BMI (Rush et al., 1997) or sum of skinfold thicknesses (Slaughter et al., 1988; Rush et al., 1997). Similar to the above, a linear approach does not seem to be a sufficiently precise method. Furthermore, BMI is not an appropriate method for the estimation of body fat percentage because by its definition, it does not distinguish between fat and lean body mass (Zdešar Kotnik and Golja, 2012). This issue is even more important in pregnant women, where, in addition to fat and lean body mass, fetus mass and mass of the amniotic fluid represent a more or less unknown part of the total body mass of the mother. Last but not least, as compared to the majority of other pregnancy non-specific methods, Rush et al. (1997) developed their method on a somewhat smaller sample of

82 subjects (42 White and 40 Polynesian women), who very likely had different body composition already due to different ethnic origin (Deurenberg et al., 1998; Deurenberg and Deurenberg-Yap, 2003).

Deurenberg et al. (1991) developed their anthropometric equation on a sample of non-pregnant women with a large range of ages (7 to 83 years). Such sample selection most likely widened its applicability, however, similar to the above, the method is also a linear correlation between subjects age and their BMI on one, and body fat percentage on the other side. In turn, the same methodological drawbacks as discussed before are introduced with this method.

The method of Peterson et al. (2003) was developed on a larger sample of 321 subjects and on six different body measurements. They used accurate comparative methods for estimation of body composition (DEXA, deuterium dilution, and underwater weighing), and the equation is a sum of non-linear relations, which, as presented above, seems to be a good choice. The largest weighing factor in the equation of Peterson et al. (2003) is BMI, which can be problematic for reasons discussed above.

One would assume that at least pregnancy specific anthropometric methods would yield rather similar results; however the present study clearly demonstrated that estimates of body composition lie on the extreme ends of the body composition results spectrum; this is a very concerning fact on its own, that calls for a thorough and detailed evaluation of the existing anthropometric methods developed for pregnant women.

The method of Paxton et al. (1998) was developed on pregnant women in the 37^{th} week of pregnancy or later, which is on average 5 weeks later in pregnancy than our study was performed. Body fat usually accumulates throughout pregnancy; therefore the results of body fat percentage obtained by this method on our sample have likely yielded values that were somewhat different than the real values for our sample. Furthermore, the largest weighing factor in the equation of Paxton et al. (1998) is body mass, which can result in discrepancies especially in the second half of pregnancy, due to relative contributions of mothers and fetal tissues to total body mass.

The methods of van Raaij et al. (1988) and Catalano et al. (1995) were developed for (van Raaij et al., 1988) or on (Catalano et al., 1995) pregnant women in approximately the 30^{th} week of pregnancy, which is quite similar to the GA of the subjects in our study. However, both methods were developed on rather small samples of 42 and 40 subjects, respectively. Although Catalano et al. (1995) used accurate comparative methods for estimation of body composition (isotope dilution and underwater weighing), they did not distinguish between White, Black, and Hispanic women (N=38,

1, and 1, respectively), who may have had somewhat different body composition (Deurenberg et al., 1998; Deurenberg and Deurenberg-Yap, 2003) not only due to pregnancy changes.

Pregnancy non-specific anthropometric methods differ from the pregnancy specific methods by different amounts, which are much larger than expected. The results rejected the hypothesis that pregnancy specific anthropometric methods provide rather similar results on body composition of pregnant women.

The calculated indicators of measurement precision (% TEM, R) of the present study demonstrated that anthropometric measuring procedure, if applied correctly, is precise and reliable (Table 12). It has thus been confirmed that random measurement errors in anthropometry can be minimized by personnel training, use of standardized techniques, and precise, correctly calibrated instruments (Gibson, 2005), and are therefore not a significant source of the observed differences in different anthropometric methods.

The results of the present study call for a standardization against a suitable golden standard and for examination of reliability of existing anthropometric methods for body composition assessment (especially for pregnant women). A thorough analysis of factors causing the major variations between the results has to be performed to minimize the discrepancies.

When we use body composition as feedback information of health status or nutritional status of an individual, it is important to keep in mind that at present body composition results do vary greatly depending on the anthropometric methodology used.

Our hypothesis $H_0 1$ was therefore rejected and working hypothesis $H_W 1$ was accepted.

5.2 DISCUSSION RELATED TO HYPOTHESIS 2

We hypothesized that the pattern of growth of full-term and premature children during the first year of life depends on anthropometric characteristics of mothers.

A number of studies have identified parental fatness, high birth mass (Parsons et al., 1999), infants' excess mass gain during postnatal life, social factors, timing or rate of maturation, physical activity, and dietary factors (Parsons et al., 1999) as risk factors for obesity (Chandler-Laney et al., 2013) and development of CV diseases (Barker D.J. et al., 1993) during childhood and adulthood. This effect of birth mass may be mediated by maternal pre-pregnancy obesity (Whitaker, 2004; Catalano and Ehrenberg, 2006; Dubois and Girard, 2006), and/or excess PMG (Oken et al., 2008). In 2009, the Institute

of Medicine (IOM, 2009) also highlighted both, high PpBMI of mothers and excess PMG, as significant contributors to infant's development.

5.2.1 Effects of maternal anthropometric characteristics on infants' growth pattern

Prior to discussing the corresponding results, it is worth stating the representativeness of the study sample. Namely, in the "My Milk" study, the number of participating infants was similar for both genders and approximately 8 % of all the participating infants were born preterm, which is similar to the Slovenian population average. We can therefore conclude that the sampling was representative.

The results of the present study demonstrate that enlarged newborns' body height and mass at birth were observed in male infants of mothers with higher MBH, higher PpBM, higher PMG, and higher RV/PpBMI (meaning to high maternal PMG according to PpBMI). The latter two maternal characteristics also enlarged body mass at birth in female infants and BMI at birth in both, male and female infants. The same pattern seems to be present also in infants of mothers with higher PpBMI.

In contrast to the present study, the majority of other studies have reported only absolute or z-score values for infants' anthropometric measurements and only a few studies the changes in anthropometric characteristics observed at different ages were reported, which only allows us to describe the infants' growth patterns.

In a study from 1986 on approximately 10,000 children from New York (USA) the authors reported that high PMG is related to increased birth mass and therefore to a decreased prematurity rate (Singer et al., 1968). High maternal PMG was also associated with better growth and performance in the infants first year of life (Singer et al., 1968). The authors therefore hypothesized that the abandonment of keeping PMG during pregnancy to a minimum might significantly reduce the incidence of prematurity and its attendant mortality and morbidity (Singer et al., 1968).

Similarly, in a study from 1984, pre-pregnancy mass-for-height status and PMG were positively related to infant birth mass (Taper et al., 1984).

After sample standardization, performed by excluding 5 % of the infants with extreme values so as to gain the same initial average values for each measurement, the results of the present study pointed out that during the first year of life, higher MBH tended to diminish relative increases of male infants' mass from birth up to 1 month of age. It also

enlarged relative increases of female infants' mass from birth up to 3 months of age (with a similar trend lasting up to 12 months of age).

Higher maternal PpBM diminished relative increases of female infant's height within the first month of life, while in male infants no differences were observed. It also enlarged relative increases in head circumference for both genders; however, no effects were observed on relative increases in infants' mass and BMI.

Higher maternal PpBMI diminished relative increases in male and female infants' mass from birth up to 1 month of age (with a similar trend lasting up to 12 months of age), in male infants' BMI from birth up to 1 month of age, and in triceps and front thigh skinfold thickness within the first year of life. However, it enlarged relative increases in upper arm circumference within the first year of life for both genders.

Higher maternal PMG tended to diminish relative increases in male infants' mass from birth up to 3 months of age and in male and, to a smaller extent, in female infants' BMI up to 12 months of age.

Higher RV/PpBMI diminished relative increases in male and female infants' mass from birth up to 1 month of age (and most likely up to 3 months of age), and BMI from birth up to 3 months of age in female infants.

In the present study, relative increases in body height of infants from birth up to 12 months of age were not affected by any of the maternal characteristics, except in female infants, where higher maternal PpBM acted as presented above.

Similar to our study, Heerman et al. (2014) recently measured 499 mother–FT child pairs between the years 2007 and 2012 from birth up to 1 year of life. Their findings, however, are not entirely in line with the present study. In the study of Heerman et al. (2014) maternal PpBMI and the interaction between PpBMI and maternal PMG showed significant positive association with infants' growth trajectory through the first year of life (the latter was adjusted for the estimated GA, exclusive breast-feeding for the first 6 months of life, maternal age, number of previous pregnancies, maternal smoking, hypertension, depression, insurance type, and gestational diabetes). The combined effect of excess maternal PMG and pre-pregnancy obesity resulted in higher infant birth mass, rapid mass gain in the first 3 months of life (which is directly in contrast to the results of the present study), with a sustained increased mass throughout the first year of life (Heerman et al., 2014). However, the effect of PMG on infants mass gain did not reach statistical significance (Heerman et al., 2014), as it tended in the present study.

Similarly to the results of Heerman et al. (2014), the positive interaction between high maternal PpBMI and high PMG were reported to result in rapid infant mass gain (Li N. et al., 2013).

The effect of parental BMI on anthropometric characteristics of their infants was studied in 912 children born between 1928 and 2008 in USA. Their mass and length were measured from birth up to 3.5 years of age, BMI was calculated, and then infants were classified according to parental BMI (Linabery et al., 2012). Infants' BMI curves were significantly different between the maternal BMI categories (a more gradual increase in BMI was observed with age in infants of obese mothers in contrast to not obese mothers). Infants of obese mothers also had greater BMI at birth and between 1.5 and 3.5 years of age than those of overweight and normal mass mothers (Linabery et al., 2012). It has been suggested that infants of obese mothers may encounter a BMI rebound earlier and at a higher value, placing them at greater risk for later obesity (Williams S.M. and Goulding, 2009). Knight et al. (2007) also reported that association between maternal and infants BMI persisted at each measured time point from birth up to 2 years of infants' age. Additionally, maternal BMI, at delivery and in later infancy, had a stronger influence on infants' BMI growth than paternal BMI, suggesting that mass control in reproductive age women may be of particular benefit for preventing excess infant BMI (Linabery et al., 2012).

In an Egyptian study on mother-infants pairs (N=782) from 2011, correlation tests between maternal and neonatal physical characteristics revealed that for both, male and female infants, combined maternal mass and height had a significant positive correlation with infant’s birth mass, length, BMI, and head circumference, while maternal BMI had significant positive effect only on birth mass, length, and BMI (Hassan et al., 2011). Similar results were observed when analyzing data for female infants separately. For male infants, all maternal anthropometric measurements demonstrated a significant positive correlation with birth mass and length (Hassan et al., 2011).

Not only in developed, but also in developing countries, effects on growth pattern in the first months and years of life were observed (Iannotti et al., 2009; Varela-Silva et al., 2009; Yilgwan et al., 2012; Hanieh et al., 2014). In Ha Nam province (rural Vietnam), rate of PMG in 1,258 women was significantly associated with infant (N=965) mass, length, and infant mass gain velocity during the first 6 months of life (Hanieh et al., 2014). In Yucatan (Mexico), 206 Maya children were followed up till the age of 5 years. Less than 30 % of mothers were higher than 150 cm and their children were more than twice as likely to be overweight in the first years of life, as compared to children whose mothers were shorter than 150 cm (Varela-Silva et al., 2009). In Nigeria, 318 infants were measured after a complete physical examination at birth and at 6 weeks postnatal

(Yilgwan et al., 2012). A decreased mass gain within the first 6 weeks of life was observed in infants of more educated and lighter mothers with lower blood pressure. In Peru, 232 infants were followed up from birth up to 12 months of age and their anthropometric measurements were investigated for different maternal characteristics. Significant predictors of growth and body composition throughout infancy were maternal height, mass in the early pregnancy, and the altitude of the region of maternal origin. No associations were found for maternal education, asset ownership, or sanitation and hygiene factors (Iannotti et al., 2009).

Stettler et al. (2005) have demonstrated that increased mass gain during the first week of life in healthy formula-fed European American infants was associated with overweightness 2-3 decades later. This may be related to the programming of the developing brain or the endocrine system of the young infant (Stettler et al., 2005).

Another recent work has provided evidence that infancy is a critical period of child development where rapid mass gain and altered adiposity can shift a child's growth trajectory toward a more obese phenotype in childhood and into adulthood (Taveras et al., 2011). Rapid mass gain in the first 3 to 6 months of life has been associated with both, a predicted prevalence of childhood obesity of 40 % at the age of 3 years and with the development of obesity and its metabolic consequences in early adulthood (Taveras et al., 2011).

In contrary to these findings, however, some other studies did not observed any association between maternal physical characteristics and infants' growth pattern, including changes in body mass and height during the first year of life (Taper et al., 1984; Chandler-Laney et al., 2013). For example, in 47 FT infants from Oklahoma (USA), growth patterns between 0-3 months, 3-6 months, and 6-12 months were calculated (Chandler-Laney et al., 2013). In contrast to the above presented studies, none of the maternal characteristics was observed to be associated with infants' mass-for-length z-scores (Chandler-Laney et al., 2013).

Several growth parameters were also measured in 120 infants from Virginia (USA) from birth up to 11 years of age and were investigated for effects of pre-pregnancy mass-for-height status, PMG, demographic factors, and smoking. In contrast to the above presented studies, the authors concluded that maternal factors were not highly predictive of infant growth and that other factors in the early infant environment may play a more significant role in determining infant growth patterns (Taper et al., 1984).

In addition to data presented above, the present study also investigated body circumferences. Our results revealed that in female infants head circumference at birth

was not affect by maternal physical characteristics. In contrast, increased head circumference at birth was observed in male infants of mothers with higher PMG and higher RV/PpBMI. Higher maternal PpBM and PpBMI were also positively associated with upper arm and wrist circumferences at the age of 1 month in female infants, and maternal MBH and PpBM with upper arm and chest circumferences at the age of 1 month in male infants.

For our female infants, relative increases in head circumference from birth up to 12 months of age were positively affected by maternal PpBM, and a similar trend was observed in male infants. For the same parameter in female infants, maternal MBH seems to also play a role in the first 3 months.

For male infants in the present study, higher maternal body height tended to diminish relative increases in upper arm circumference observed from 1 to 12 months of age. In addition, in the present study, increases in upper arm circumference of female infants in the same time period as stated above were significantly associated with maternal PpBMI and a similar trend was observed in male infants. Infants' relative increases in wrist and chest circumferences in the period from 1 to 12 months of age, of both, males and females, were not significantly affected by maternal anthropometric parameters.

It is almost impossible to compare these results to the results of other studies, as studies of the effects of maternal characteristics on neonatal circumferences are almost nonexistent. It was the Egyptian study from 2011 in which maternal mass and height positively correlated with infant's birth head circumference (Hassan et al., 2011).

In addition, the study of Bouthoorn et al. (2012) included 3,383 Dutch FT children from Rotterdam (a so called Generation R Study from 2002 to 2006) and evaluated some physical and socioeconomic factors as well as head circumference in early childhood. At 1, 3, and 6 months of age, children of mothers with low education had smaller head circumference than of those with high education. Birth mass, GA, and parental height were positively associated with head circumference difference at 6 months, while child's length and mass at 1 and 3 months of age could only partially explain a smaller head circumference at these ages. It therefore seems that head circumference in the first 6 months of life could be mainly explained by pregnancy-related factors, such as birth mass and GA and less with post-natal factors (length and mass gain).

In the present study, maternal physical characteristics did not affect absolute values and relative increases of skinfold thicknesses, nor body fat percentage of infants at 1 month. For female infants, higher maternal PpBMI significantly diminished relative increases of triceps and front thigh skinfold thickness in the period from 1 to 12 months of age.

For female infants in the present study, relative increase in body fat percentage from 1 to 12 months of age was significantly higher in infants from mothers having lower PpBMI. For male infants, relative increase in body fat percentage in the same time period was not affected by any of the maternal anthropometric parameters.

Our results are partially in accordance with previous studies in which, however, subcutaneous fat of infants at birth was only rarely related to different maternal physical and socio-demographic factors in the past (Whitelaw, 1976; Udall et al., 1978). For example, 265 FT infants from London (UK) of obese mothers were significantly fatter than the infants of non-obese mothers. There was a highly significant positive correlation between maternal triceps thickness and the infant's sum of skinfold thicknesses (Whitelaw, 1976). Udall et al. (1978) reported that obese mothers had FT infants (N=109) with significantly increased skinfold thicknesses, as compared with infants of non-obese mothers. Similarly, Neggers et al., (1995) reported that an increase in maternal PpBMI from the 10^{th} to the 90^{th} percentile resulted in a 12-15 % increase in various infants' skinfold thicknesses. This effect on infants' body fat was thus larger than the one of any other maternal characteristic. Multiple regression analysis showed that both PpBMI and PMG were associated with increased infants' subcutaneous fat. On the contrary, in a study from 1984, PpBMI status and PMG were not predictive of triceps skinfold measurements (Taper et al., 1984).

Similarly to body circumferences, only a few studies investigated the effect of maternal gestational factors and PMG on body composition and fat distribution during infancy (Chandler-Laney et al., 2013). One of them is a study, in which body composition was determined with DEXA in 47 FT infants from Oklahoma (USA) at birth and at 3, 6, and 12 months of age (Chandler-Laney et al., 2013). Interestingly, maternal age was associated with greater trunk fat mass, while maternal pre-pregnancy BMI and total fat mass tend to be positively associated with infant's lean body mass at 12 months (Chandler-Laney et al., 2013).

Based on the results of our study, it can be concluded that increases in infants´ body height and head circumference in the first year of life are more affected by mother's pre-pregnancy characteristics (thus by genetics) in contrast to infants´ mass and BMI in the first year of life, which are affected by both, mother's physical characteristics before pregnancy and their changes during pregnancy (thus by the intrauterine environment). Pregnant women should therefore be attentive on their PpBM status and pregnancy-associated body mass changes.

Due to this results, our hypothesis $H_0 2$ was rejected and working hypothesis $H_W 2$ was accepted.

5.2.2 Risk factors for preterm birth

The initial study sample ("Initial study 1987"), which was analyzed, was representative for the Slovenian population. Namely, the sample was larger than the proposed sample size for a single country for the selected type of study (according to the recommendations of European Food Safety Authority, the latter is approximately 260 participants (EFSA, 2014)). Additionally, childhood mortality within the sample was similar to general mortality rates in Slovenia (which was 13 deaths up to 5 years of age in 1,000 live births; data for Slovenia in 1987 (WDI, 2014)).

In searching for risk factors for preterm delivery in Slovenia, Blejec (1990) has already evaluated the impact of certain risk factors (including maternal age of less than 20 or more than 34 years, single marital status, smoking, spontaneous and induced abortion, history of preterm delivery and stillbirth) and the impact of certain diseases in pregnancy (including gestosis, uro-infections, threatening premature abortion, and some other diseases) on preterm birth. He observed that the chances of preterm birth increased especially with gestosis and threatened preterm birth or stillbirth in previous pregnancies. The influence of factors such as age, marital status, education, and spontaneous or artificial abortions in previous pregnancies did not exert a significant impact on preterm delivery in his study (Blejec, 1990).

In addition to above, in our present study, pregnancy with twins or triplets, pregnancy illnesses, bleeding during pregnancy, previous preterm births or stillbirths, smoking, and maternal age at delivery of less than 21 and more than 35 years were all more frequent in the group of mothers, who delivered preterm.

In our study multiple pregnancies resulted in 15 % to 20 % of preterm births (MPT and VPT, respectively), which is in line with the observations of Slattery and Morrison (2002), Lumley (2003), and Goldenberg et al. (2008). The overall increased incidence of multiple pregnancies in the last 30 years is largely a result of increased use of reproductive medicine, such as assisted conception technologies, which increased the number of interventions to deliver twins early in the third trimester with iatrogenic induction of labor or caesarean section (Slattery and Morrison, 2002).

Pregnancy illnesses were present in 40 % to 70 % of women who delivered preterm (MPT and VPT births, respectively), which is close to the observations of other studies. Goldenberg et al. (2000), for example, reported that up to 80 % of women, who deliver before the 30^{th} week of gestation, have evidence of bacterial infection, as compared to only 30 % of those, who deliver after 37 weeks of gestation. Similarly, data from

Germany suggest that approximately 40 % of all preterm births are initialized by infections (Mylonas, 2012).

From 10 % to 40 % of preterm (MPT and VPT, respectively) births occurred after maternal bleeding during pregnancy. The study of Yang J. et al. (2004) investigated the relation between self-reported vaginal bleeding during pregnancy and preterm birth in a prospective cohort of 2,829 pregnant women between 1995 and 2000 in North Carolina. The association between vaginal bleeding and preterm birth was not very strong. Frequent and massive bleeding was associated with approximately twofold increase in risk for preterm birth, PPROM, and preterm labor. In contrast, bleeding in the second trimester only, in a single episode, on a single day, and with less total blood loss was not associated with any category of preterm birth (Yang J. et al., 2004).

Previous preterm births occurred in 10 % to 15 % (MPT and VPT, respectively) and previous stillbirths in 5 % of women, who experienced preterm birth in our study. A previous history of preterm birth was reported to be the strongest risk factor (Bakketeig et al., 1979; Lang et al., 1996; Porter et al., 1997; Gardosi and Francis, 2000; Williams C.E.C.S. et al., 2000; Slattery and Morrison, 2002; Winkvist et al., 1998; Wilcox et al., 2007; Little, 2009) for recurrence of preterm birth in the next gestation, especially for early spontaneous preterm birth (Mercer et al., 1999). Preterm birth has also been associated with second trimester stillbirths and, in contrast to our results, with history of two or more induced or spontaneous abortions (Lang et al., 1996; Selling et al., 2006).

Mothers who were smoking (data on whether before or during pregnancy not available) were more at risk to deliver preterm than non-smokers (42 % vs. 23 %, respectively; $p<0.01$), which is similar to the results of several other studies, which were studying influences of smoking in pregnant women (Voigt et al., 2006; Salihu and Wilson, 2007; Bergmann et al., 2008; Goldenberg et al., 2008).

Furthermore, deviation of fetal growth from the expected pattern was previously associated with spontaneous preterm delivery (Morken et al., 2006). In the present study, the reasons for preterm birth were probably similar as predicted before, but additional data, such as data on morphological changes of the placenta, volume of maternal intervillous space, utero-placental blood flow, volume of fetal capillaries, carboxy-haemoglobin, or catecholamine levels, would be needed to speculate on the more precise causes of preterm birth.

In the present study, maternal age of less than 21 and more than 35 years influenced the duration of pregnancy. These results are similar to results of other previous studies, as incidence of preterm birth in white women was reported to be the lowest between 20-24

years of age, and increased in adolescent (less than 18 years of age) and late (greater than 30 years of age) pregnancies (Meis et al., 1995; Lang et al., 1996; Porter et al., 1997; Gardosi and Francis, 2000; Williams C.E.C.S. et al., 2000; Slattery and Morrison, 2002; Selling et al., 2006; PerkinElmer, 2009; Schure et al., 2012; Bird, 2014).

In our study, gestational hypertension was more frequent in women, who delivered at term, which is in contrast to results of other studies, where hypertensive disorders during pregnancy were reported to be associated with an increased risk of preterm birth and IUGR and were also described as a leading cause of maternal mortality (Roberts et al., 2003; Thomas and Duarte-Gardea, 2013).

It is well known that socio-economic factors are one of the major causes of preterm birth and that later on in life also affect the development of children. As detected by the present study, in the Slovenian socio-economic environment, one of the very important socio-economic factors affecting preterm birth is maternal education, which played a large role in preterm birth also in other studies (e.g. Astolfi and Zonta, 1999). Among women who gave birth to VPT infants in our study, the majority had only primary or secondary school education, and only 9 % higher education.

Other risk factors in our study (thus, marital status, pre-pregnancy illnesses, and previous abortions) were of similar incidence in all groups (Table 13). As proven in a large study on 4,700 PT infants and their parents from 17 European countries, including Slovenia, marital status and the corresponding social support provided by the father, being an important parameter for psychological welfare, do not influence the incidence of preterm birth (Zeitlin et al., 2001). This is not surprising, as non-married status before the first birth would often mean only, that the preterm birth simply surprised the couple, before they could get married (Babnik J., 1990). Therefore, single women do not constitute a special risk group for preterm delivery. As mentioned before, preterm birth was also associated with a history of two or more induced or spontaneous abortions (Lang et al., 1996; Selling et al., 2006; Swingle et al., 2009).

5.3 DISCUSSION RELATED TO HYPOTHESES 3 AND 4

We hypothesized that the susceptibility to illnesses after the period of accelerated growth will be different between full-term and premature children and that the frequency of illnesses associated with prematurity experienced after a period of accelerated growth will differ between premature and very premature children.

5.3.1 Illnesses and injuries in youth and adulthood

As reported previously, preterm birth may cause some health problems in childhood and early adulthood (Selling et al., 2006), but data on health status of premature and FT individuals in later periods of life are lacking. Our results on systolic and diastolic blood pressure of participants at the age of 26 years were similar between the VPT, MPT, and FT groups, yet the sample size is limited, therefore the results are rather inconclusive. CV illnesses were practically absent in our participants and consequently no final conclusions on the potential differences in the incidence of CV illnesses between the PT and FT individuals, neither between VPT and MPT individuals can be made.

According to numerous studies, the medical and social consequences of preterm birth may persist into adult life (Little, 2009). The mechanisms underlying the early origin of adult disease hypothesis are unclear, but it has been suggested that the fetus adapts to poor nutrition in uterus. This adaptation, however, may become detrimental, leading to overweightness, obesity, and type II diabetes after birth, when nutrition is affluent (Evensen et al., 2008). Long-term consequences of early nutrition and growth could also explain previous theories, such as the fetal origins hypothesis (which proposed the association between LBW with later CV diseases; Barker D.J. et al., 1993) and the common soil hypothesis (which considered early nutrition an underlying factor for the development of CV diseases and non-insulin dependent diabetes mellitus) (Pettitt et al., 1997).

Nowadays, convincing epidemiologic evidences link perinatal effects, preterm birth, and hypertension later in life exists, in contrast to a rather common genetic explanation for hypertension (Bonamy et al., 2008). Singhal and Lucas (2004) have published numerous articles on long-term consequences of early nutrition. They reported that if PT infants were randomly assigned to human milk in contrast to formula for just the first four weeks of life (and for insulin resistance for just the first two weeks of life), milk-fed preterms had a better prognosis for blood lipid profile, blood pressure, leptin, and insulin resistance at the age of 13-16 years, than formula-fed preterms. It has therefore been suggested that growth acceleration induced by nutrient-enriched diet may result in insulin resistance and increased blood pressure later on in life (Singhal and Lucas, 2004).

Normal aortic size and structure are important for efficient blood circulation. Vascular functions depend both, on the elastic properties of the aorta, as well as on its size. It has been observed that preterm birth exerts lasting adverse effects on growth and development of the aorta (Bonamy et al., 2008), and that very PT birth may be associated with persistent, general aortic narrowing (Bonamy et al., 2008). Indeed, at 5 years of age, VPT children had narrower aortic lumen than their FT peers (a difference of 16 % in the thoracic and 19 % in the abdominal aorta was reported). In addition, an altered endothelial function has been proposed as a pathophysiological mechanism linking LBW and increased blood pressure (Evensen et al., 2008). Indeed, PT adolescents had higher systolic and diastolic blood pressure than their FT peers (Bonamy et al., 2008).

In contrast to data presented above, some other studies reported that SGA individuals did not have increased prevalence of any of CV risk factors (Evensen et al., 2008).

According to self-assessment, significantly more PT individuals may experience psychological stress during childhood, adolescence, and at 19 years of age, than their FT individuals (recent study on 30 PT and 30 FT individuals; UK Essays, 2013). However, levels of mental health, scores regarding self-esteem, and quality of life were of similar frequencies between the two groups (Tideman et al., 2001). According to self-assessment in our study, participants in all three groups (VPT, MPT, and FT) at the age of 26 years had on average the same physical health and reported similar level of stress in their life.

PT children and VLBW infants have been reported to experience neuro-sensory deficits or impairments (blindness, deafness, and cerebral palsy) more often than FT individuals (Romero et al., 1994; Slattery and Morrison, 2002; Ekholm et al., 2004; Little, 2009). The period of accelerated growth is therefore undoubtedly useful for the development of nervous system (Casey P.H. et al., 2006). In our study, according to self-assessment, more FT than PT infants wore glasses in youth and adulthood. Other stated health aids, treatments, and illnesses were rare in our subjects, therefore results are inconclusive.

Allergies were of similar frequency in our study groups. This is in line with the findings of Liem et al. (2007), who reported, using a large population database, that prematurity or LBW do not play a role in the occurrence of food allergies. Immaturity of the gastrointestinal tract or immune response which are both experienced by PT infants, therefore, does not seem to change the risk for development of food allergies (Liem et al., 2007). Similar findings were reported in the study about PT infants and food allergies from Manitoba, Alberta, and Canada in 1995 (Kumar R. et al., 2008). Whether early exposure to food antigens may protect premature children by increasing the

immune tolerance to these antigens remains an open question. However, Crump et al. (2011a) suggested, using data from a large national cohort study from the 80`s in Sweden, that low GA at birth, independent of fetal growth, is associated with a decreased risk of allergic rhinitis in young adulthood (25 to 37 years of age).

According to some studies, preterm birth is associated with increased risk of asthma. Been et al. (2014) identified 30 studies between 1995 and 2013 that investigated the association between preterm birth and asthma in more than 1,500,000 children. Cumulative data suggested that 13.7 % of PT infants developed asthma during childhood, as compared to only 8.3 % of FT infants. Actually, MPT infants were 50 % more likely to develop asthma, than FT infants, and VPT infants were three times more prone to asthma than FT infants (Been et al., 2014). Similar findings were reported by Goyal et al. (2011), who studied 7,925 infants born in 2007 in Philadelphia (USA). By 18 months, 8.3 % had been diagnosed with asthma. In their study, MPT birth was associated with significant increases in persistent asthma diagnoses, inhaled corticosteroid use, and numbers of acute respiratory visits, in comparison to FT birth. VPT birth was associated with increases in asthma diagnoses and inhaled corticosteroid use (Goyal et al., 2011).

Crump et al. (2011b) conducted a study on 630,090 infants, born from 1973 through 1979, and excluded individuals with cerebral palsy, inflammatory diseases of the central nervous system, cerebral-vascular disease, and brain tumors (Crump et al., 2011b). In Swedish adults aged 25 to 37 years, preterm birth, including late preterm birth, was strongly associated with epilepsy (odd ratio of 4.98) (Crump et al., 2011b).

In the present study, the frequencies of the majority of selected injuries that were experienced either in youth or in adulthood were similar between all three study groups, with the exception of joint injuries, which were experienced more often in FT, than in PT individuals (Table 15). Similar to our results, a recent study performed on more than 2,000,000 participants, for which data were analyzed from birth to 23 years of age, no consistent risk pattern between preterm birth and unintentional injuries (including falls, transport injuries, and other injuries) in childhood, adolescence, or young adulthood was reported (Calling et al., 2012).

Although, in our study we had no data on hormone levels at birth and prevalence of cancer, it is worth mentioning a study, in which associations between preterm birth and breast cancer were investigated (Ekbom et al., 2000; Kaijser et al., 2003). Namely, in the early postnatal period, extremely PT infants have been reported (Sedin et al., 1985) to have high levels of estrogens in their blood, with estrogens being the fundamental hormones in breast cancer etiology. In a study of women born between 1925 and 1932

in Sweden, the authors reported VPT birth to constitute a strong risk factor for adult breast cancer (Ekbom et al., 2000). Similar was reported in a study on 474,156 women born after 1935 in Denmark (Melbye et al., 1999). However, a study performed later did not confirm those findings and suggested that preterm birth can be ruled out as a risk factor for breast cancer (Kaijser et al., 2003). Additionally, increased levels of estrogens during pregnancy of the mother were suggested to influence subsequent breast cancer risk in their infants (Trichopoulos, 1990). Similar to the above, however, in a later study neither preterm birth nor LBW have been associated with an increased risk for breast cancer in offspring (Kaijser et al., 2003).

Thus, we were not able to refute the null hypotheses $H_0$3 and $H_0$4, which may be due to either small differences between the samples, substantial variability, or small sample size.

5.3.2 Illnesses at birth and in preschool years

In the last trimester of pregnancy, the fetus receives immunoglobulins G through the placenta that protect it from bacteria. With breastfeeding the infants also receive immunoglobulins A that protect their intestinal mucosa (Vaughan and Litt, 1992). PT infants, especially if they are LBW infants, are less physiologically and metabolically mature than FT infants (Engle et al., 2007) and have less mature immune system (Vaughan and Litt, 1992). Therefore, they are more susceptible to infections in the neonatal period and suffer from many diseases, of which some can greatly affect the physical development. It is therefore understandable that PT infants require many more medical interventions for their survival in the neonatal period than their FT peers (Babnik J., 1989). Also, serious illnesses of the newborn (such as respiratory distress, cerebral hemorrhage (Usher, 1981), severe infections), which are conditioned by his immaturity and require intensive treatment methods (such as mechanical ventilation, frequent transfusions due to numerous donations, exchange transfusion at severe jaundice, or therapy septic diseases) are risk factors for subsequent worse child's development (Babnik J., 1989). Respiratory difficulties, hyperbilirubinemia, patent ductus arteriosus, hematological disorders, and metabolic disturbances (e.g. hypocalcaemia and hypoglycemia) are also frequent in PT infants (Usher, 1981).

In our study, in the period from birth up to the entrance to school, PT infants were more often sick than FT infants, however, dystocia was most often observed in the FT group, which is expected due to a larger size of newborns. Nevertheless, there exist only a few previous studies (e.g. Norwitz et al., 2007) that describe the association between preterm birth and dystocia. As larger infants typically have a higher risk for perinatal problems, prolonged labor, cephalopelvic disproportion, and shoulder dystocia are not

surprisingly increased in post-term infants (Norwitz et al., 2007), which is in line with our findings.

In our study, respiratory distress, apnoeic attacks, hypoxia, hyperbilirubinemia (Annex A), infections, cerebral hemorrhage, and intestinal hernia were more often experienced in PT than in FT group. Intestinal congenital malformations were also reported in childhood and youth for PT subjects in our study. Fetal distress was of similar incidence between the groups. Periventricular leucomalatia, hypoglycemia, heart anomalies, kidney anomalies, intestinal anomalies, necrotizing enterocolitis, and cosmetic defects were too rare for statistical analysis to be performed (Table 16).

As presented above, respiratory distress syndrome is a major cause of morbidity and mortality in PT infants; it presents immediately or soon after birth with worsening respiratory distress (Fraser et al., 2004). If untreated, infants may become fatigued, apnoeic, and hypoxic, which may progress to respiratory failure and may need assisted ventilation (Fraser et al., 2004). Treatment with artificial ventilation saves lives of seriously ill newborns; however, the opinions about its impact on later development are conflicting. Namely, extremely poor outcomes of assisted ventilation in ELBW children were reported (Rothberg et al., 1983). In contrast, the Swedish authors reported relatively good development of PT infants who required assisted ventilation (Blennow et al., 1986). Among the infants who were included in the present study, artificial ventilation seems to represent a relatively low risk for future disability (Babnik J., 1990).

Infant apnoea is defined as a pause in breathing lasting for more than 20 seconds, or lasting less than 20 seconds, but associated with cyanosis, marked pallor, hypotonia, or bradycardia. According to the reports, recurrent episodes of apnoea are common in PT infants (Henderson-Smart and De Paoli, 2010). Also, the lower the GA at birth, the longer the apnoea continues, which suggests that immaturity plays a major causative role (Henderson-Smart, 1981). Although recurrent apnoea can occur spontaneously and can be attributed to prematurity alone, it can also be provoked or made more severe when combined with infections, hypoxaemia, or intracranial pathology (Henderson-Smart and De Paoli, 2010).

Complimentary to the above, a few studies investigated lung functions in LBW (Anand et al., 2003; Lima et al., 2005; Evensen et al., 2008) and PT infants (Štucin Gantar et al., 2002). It has been suggested that VPT children may have poorer lung function and may therefore be less physically active (Štucin Gantar et al., 2002), which was confirmed also in our results on physical activity performance (in Chapter 5.4.3). The authors suggested that increased levels of albumin in the gastric aspirate, which was taken

immediately after birth, may contribute to the development of the respiratory distress syndrome in PT infants. Other factors, such as the influence of bilirubin, meconium, and inflammatory mediators did not seem to play a role (Štucin Gantar et al., 2002).

Similar to the results of our study, jaundice and hyperbilirubinemia were reported to occur more commonly and were more prolonged among MPT infants than among FT infants. It has been suggested that MPT infants may have a lower concentration of UDP-glucuronosyltransferase (Sarici et al., 2004), which is an enzyme that transforms small lipophilic molecules (such as steroids, bilirubin, hormones, and drugs) into water-soluble, excretable metabolites, as compared to FT infants. Visual jaundice was seen in 60 % of FT and in 80 % of PT infants (Cohen S.M., 2006). In addition, MPT infants are more likely to have significantly elevated bilirubin concentrations one week after birth than FT infants (Sarici et al., 2004; Engle et al., 2007).

The general opinion is that PT infants are more susceptible to various infections due to immature immune defense mechanism (Babnik J., 1988). It was reported that PT infants have deficiencies in both, innate and adaptive immunity, as well as in the interaction between them (Melville and Moss, 2013). Compared to FT infants, the immune system of PT infants has less monocytes and neutrophils, impaired ability of these cells to kill pathogens, and a lower production of cytokines, which limits T-cell activation and reduces the ability to fight against bacteria and viruses (Melville and Moss, 2013). We therefore recorded the incidence of infectious illnesses in the first years of life in PT infants and compared it to the incidence in the control group. It is worth noting, however, that no data on specific infectious diagnosis at birth was available. Similar to the results of our study, neonatal infections were reported as a frequent complication among ELBW PT infants and were associated with short-term sequelae and an increased risk of death (Stoll et al., 2004).

Brain injury is a problem of enormous importance in the PT infant and includes a variety of neuropathologic lesions, including periventricular leukomalacia, germinal matrix-intraventricular hemorrhage, posthemorrhagic hydrocephalus, and several patterns of neuronal injury (Volpe, 2001). Intracranial hemorrhage was reported to have enormous potential impact on morbidity, mortality, and long-term neurodevelopmental outcome in PT infant (Bassan, 2009). PT infants primarily bleed into the germinal matrix and not in the cortical mantle or white matter, suggesting that there is an intrinsic weakness in the germinal matrix vasculature, as compared to the other brain regions (Ballabh, 2010). Endothelial tight junctions, basement membrane, pericytes, and astrocyte end-feet ensheathing the blood vessels are in the blood brain barrier, and immaturity or weakness of any of these components can potentially cause fragility of germinal matrix vasculature (Ballabh, 2010). The majority of authors (e.g. Papile et al.,

1983; Williamson et al., 1982) report about 20 to 30 % incidence of disabled children, who suffered from brain hemorrhage. Periventricular leukomalacia is the major neuropathologic form of brain injury (Volpe, 2001), it is the main determinant for cerebral palsy in PT infants, and mainly occurs in VLBW infants and between 24 and 34 weeks of GA (van Haastert et al., 2008). After following up 59 PT infants up to the age of 7.5 years, the association between periventricular leukomalacia and gross motor outcome was strong (van Haastert et al., 2008).

Anomalies of heart, intestine (including enterocolitis and intestinal hernia, which are presented in more detail later), and kidneys were also previously reported more often in PT than in FT infants. It is a congenital heart defect that is a major cause of mortality and disability of perinatal origin. After studying the association between preterm birth and different congenital heart defects (anomalies of the venous return, atrioventricular junctions and valves, ventricular outflow tract, extrapericardial arterial trunks, functional univentricular hearts, and ventricular septal defect) in more than 300,000 infants, Laas et al. (2012) observed a higher risk of preterm birth in newborns with those defects, which was essentially due to spontaneous preterm birth. Similar findings were reported in an older study by Dees et al. (2000).

In our sample, urinary tract defects were too rare for final conclusions. However, some previous studies have confirmed the difference in prevalence of kidney abnormalities between PT and FT infants (Drukker and Guignard, 2002; Black et al., 2013). The majority of nephrons are formed in the third trimester of pregnancy, thus at the time when PT infants are being delivered. It is suggested that glomeruli in the outer renal cortex may be formed towards the end of pregnancy (in PT infants maybe even in the extra-uterine environment), as morphologically abnormal glomeruli (with a cystic Bowman's space) are often observed in PT infants (Black et al., 2013). Renal maldevelopment in PT and SGA infants has also been related to serious medical problems in adult life, including hypertension (Drukker and Guignard, 2002).

Necrotizing enterocolitis is one of the most severe gastrointestinal emergencies in VLBW PT infants, affecting 7 % to 14 % of these infants (Lin et al., 2008). The inflammatory cascade promotes the spread of bacteria or toxin, which results in ischemia, necrosis, and sometimes perforation. Pathogenic florae attach to the epithelial cells of PT infants much more easily than to those of FT infants, and some studies indicated that commensal bacteria from probiotics inhibit or reduce inflammatory signaling in intestinal epithelia. Namely, after 6 weeks of eating probiotics, the incidence of death or necrotizing enterocolitis was reduced (Lin et al., 2008; Deshpande et al., 2010; AlFaleh et al., 2011).

Fetuses that show signs of distress (such as gross disturbances of fetal heart rate during labor, passage of meconium, signs of fetal asphyxia) are likely to be in a poor condition at birth and to need special attention. In an older study, the relation between fetal distress and the subsequent condition at birth was studied in 2,791 pregnancies. Fetal distress was defined as a heart rate >160 or <120/min between uterine contractions, with or without meconium-stained liquor; the latter may be an early sign of fetal distress (De Souza et al., 1975). The reduction in birth scores was greater in the presence of meconium-stained liquor and abnormal fetal heart rate than in meconium-stained liquor alone (De Souza et al., 1975). Ananth and Vintzileos (2006) recently showed that fetal distress, combined with pre-eclampsia, SGA, and placental abruption, is the main condition in more than a half of all medically indicated PT births (Ananth and Vintzileos, 2006).

Hypoglycemia is defined as blood glucose levels <40 mg/dl and is a more frequent complication in PT than in FT infants (Zanardo et al., 1999; Laptook and Jackson, 2006). Although the risk magnitude for the MPT infant is not well characterized, it may approach 10 % to 15 % (Laptook and Jackson, 2006) or even 35 % (Zanardo et al., 1999) of all PT infants. Although there exists a continued uncertainty regarding the definition of hypoglycemia in FT and PT infants, there is a uniform recognition of glucose as the primary substrate for cerebral metabolism (Laptook and Jackson, 2006). Hypoglycemia may therefore lead to later central nervous system damage (Zanardo et al., 1999; Wang M.L. et al., 2004).

Because diagnoses of different neonatal diseases (such as respiratory distress, cerebral hemorrhage, hypoxia, hyperbilirubinemia, and anemia) do not say much about the difficulty of disease, we also collected the number of medical procedures, which were necessary for the survival of an infant. As seen in Table 17, almost all procedures (i.e. the use of reanimation mask, ototoxic medicines, artificial ventilation, addition of oxygen (F_IO_2), transfusions, and exchange transfusions) were observed in the VPT and MPT groups and only a few FT infants needed infusion, reanimation mask, or ototoxic medicines for a short time (Babnik J., 1988).

In the present study, not only data on medical problems at birth, but also data on illnesses in childhood (including infectious illnesses) were obtained for all subject groups (Tables 18 and 19). Our results identified different incidences of some of the selected illnesses in first years of life between PT and FT infants that will be presented below.

Blood anemia was more often experienced in VPT and MPT, than in FT infants at the age of 1 year, while rickets was of similar incidence between the study groups at the age

of 1 year (Table 18). Epilepsy and febrile seizures were too rare for any further conclusions.

All neonates experience a decline in circulating red blood cells during the first weeks of life (Strauss, 2010). As, during the third trimester of pregnancy fetal red cell production switches from hepatic to marrow erythropoiesis (Von Kohorn and Ehrenkranz, 2009), ELBW and VPT infants are deprived of most of the iron transported from the mother and most of the in-uterus fetal erythropoiesis (Strauss, 2010). Extrauterine body growth is rapid during the first months of life and red blood cell production by neonatal marrow must increase proportionally. It is widely accepted that the life span of neonatal red blood cell is shorter than that of adult red blood cells, due to several developmental differences in metabolic and membrane characteristics (Strauss, 2010). Therefore, within the first few weeks of life multiple red blood cell transfusions are often given to PT infants (Strauss, 2010).

PT infants are at risk of metabolic bone disease during the initial period of life, due to an inadequate supply of phosphorus and calcium. The worst disturbances have been reported in the most immature infants receiving diets lowest in mineral, such as human milk without supplements (Wharton and Bishop, 2003). In rickets, the biochemical evidence of disturbed mineral metabolism is present and is followed by a reduced bone mineralization. The latter may be caught up during infancy and childhood (Wharton and Bishop, 2003). In our study, 9 % of PT and 5 % of FT children experienced rickets, despite the fact that PT infants are usually fed only parenteral in a much larger percentage than FT (Babnik J., 1990). The beginning of the dentition, which was delayed in VPT for 2.7 months, as compared to FT children (not presented in the results), is thus a reflection of PT birth (11 weeks preterm on average) and is an indirect evidence that rickets is not a large problem for PT infants.

Febrile seizures are the most common type of seizure in children. Genetic susceptibility to seizures is different according to the type of febrile seizure and subsequent epilepsy (Herrgård et al., 2006). VPT children (N=59) have been reported to have increased rate of febrile seizures, as compared to FT infants (N=60) (Herrgård et al., 2006). Symptomatic epilepsy in PT children may be characterized by neonatal seizures, major neurological disabilities, and early onset of epilepsy. However, in some other studies, no cascade from initial injury via febrile seizures to epilepsy could be shown during the follow-up of 16 years (Herrgård et al., 2006).

The general opinion is that LBW and PT infants are often ill after discharge and often need hospitalization. During the first years of life PT infants are less protected from bacteria, respiratory pathways are sensible and react very quickly to infects, therefore

pneumonia occurs more often than in FT peers. Inflammation of respiratory pathways can spread through the throat and Eustachian tube into the middle ear. In our study, some infectious illnesses, such us upper respiratory tract infections (which included naso-pharyngitis, tonsillitis, and bronchitis) and middle ear infection (otitis) were more common in MPT and FT infants (~65 % and ~30 %, respectively), as compared to VPT infants (~50 % and ~10 %, respectively) at the age of 2 and 3 years. This is probably due to earlier enrollment of MPT and FT infants into kindergartens, as compared to VPT infants, where they get more often in touch with respiratory infections. In contrast to these illnesses, pneumonia was more often experienced in VPT and MPT, than in FT infants at the age of 1 year. In the present study, obstructive bronchiolitis was of similar incidence in all three groups.

After monitoring 37 VLBW children Termini et al. (1990) observed that by the first 18 months, 45 % infants suffer from upper respiratory infections, 49 % from ear infections, 12 % from bronchiolitis, and that during this time 25 % of children were re-hospitalized. Similarly, Mitchell and Najak (1989) reported a 27 % incidence of re-hospitalization in this group of children. VLBW children were 6-times more likely to be hospitalized due to respiratory infections than FT children (Mitchell and Najak, 1989). Kitchen et al. (1990) performed a follow-up of the development of 197 VLBW children for 5 years and compared them with 47 FT infants. They observed that respiratory problems were experienced by 40 % of premature children and 19 % of FT children, ear infection by 15 % of PT infants, and 18 % also experienced asthma. In 5 years, on average 1.7 hospitalizations per VLBW child were reported and 0.5 per FT child (Kitchen et al., 1990).

Interestingly, after studying the relationship between childhood illnesses, in particular diarrhea, and growth increments in length and mass in a 13-month birth cohort of 276 rural Mexican children (Condon-Paoloni et al., 1977), the authors observed that children with frequent diarrhea in the first three years of life may suffer deficits in mass gain of 5 %. If, at the same time, they also suffer from growth failure due to malnutrition, the combined deficit can reach 10 %.

Apart from illnesses presented above, other childhood infectious illnesses and symptoms were much less frequent in our sample, which prevents from any further conclusions to be made. To sum up, a relatively good defense against infections confirms that the immune system in PT infants matures rather rapidly and that there is no reason to delay a mandatory vaccination (Babnik J., 1988), like some would expect.

Congenital anomalies (also referred to as birth defects) affect an estimated 1 in 33 infants and can be defined as structural or functional anomalies, including metabolic

disorders, which are present at the time of birth (WHO, 2014). In the majority of studies, congenital defects were reported to be more common in PT infants, mainly due to a larger number of inguinal hernias and undescended testicles (Kitchen et al., 1990; Termini et al., 1990). In our study, all VPT infants with birth defect in the first year of life experienced an inguinal hernia. Frequent inguinal hernia is probably caused by abnormal lower abdominal wall closure (Babnik J., 1988). Similar data were presented by Termini et al. (1990), who reported that a quarter of all hospital admissions of VLBW infants occur due to operations and that the proportion of hernoplastics is 70 %. After 5 years of follow-up of VLBW children, Kitchen et al. (1990) reported that 40 % of them were operated at least once, in comparison to 20 % of FT infants that were operated in the same time period. Similarly, thirty percent of 37 ELBW PT infants were noted to develop inguinal hernias (Harper et al., 1975; Boocock and Todd, 1985), which were more often experienced by male infants (Peevy et al., 1986). However, especially with VPT birth, the exact incidence of inguinal hernia is related to GA, (Kumar V.H. et al., 2002).

In our study, congenital genital and musculoskeletal illnesses, heart, and skin / mucosa malformations, and cystic kidney illness were rare in childhood and youth. Temtamy et al. (1998) studied the incidence of congenital malformations among 3,000 infants (not classified according to GA) in Egypt. The prevalence of congenital malformations was approximately 3.2 % (Temtamy et al., 1998). Similar incidence was reported by Honein et al. (2009). In their sample, the congenitally malformed neonates (N=95) had central nervous system anomalies (29.5 %), musculoskeletal anomalies (20.0 %), genetic syndromes (13.7 %), genital system anomalies (8.4 %), miscellaneous anomalies (6.3 %), cleft lip and/or cleft palate (5.3 %), chromosomal aberrations (4.2 %), congenital heart disease (3.2 %), ear, face, and neck anomalies (2.1 %), conjoined twins (1.1 %), gastrointestinal anomalies (1.1 %), and urinary tract anomalies (1.1 %) (Temtamy et al., 1998). After studying different congenital malformations, Honein et al. (2009) reported that PT infants were more than twice as likely to have major birth defects as FT infants, and VPT infants had an overall prevalence of birth defects 2.3 times that of MPT infants.

In our study, developmental indicators, such as Apgar score at 1 and 5 minutes after birth (which reflects vitality of a child immediately after birth) and developmental quotient, were significantly worse in PT than in FT infants (Table 22). Corrected developmental quotient was worse in VPT than in FT infants at the age of 1 year, and worse than in MPT at the age of 2 years.

In 1952, at the 27th Annual Congress of Anesthetists, Virginia Apgar introduced an infant scoring system, as a method for comparison “of the results of obstetric practices,

types of maternal pain relief and the effects of resuscitation" (Apgar, 1953). Apgar score evaluates color, heart rate, grimace, muscle tone, and respiratory effort of a newborn. Among the components, respiratory effort, muscle tone, and reflex activity correlated well with one another; heart rate correlated less well; and color, the least in PT infants (Apgar, 1953). These findings pointed to the limited use of the Apgar score in PT infants (Hegyi et al., 1998). However, a recent study called into question 4 of the 5 parameters used, when Apgar scores are applied to PT infants, and recommended the use of an improved delivery room score that is supposed to decrease variability among medical care professionals, with the aim to accurately reflect the clinical status of PT infants (Bashambu et al., 2012).

In the present study, neurological disorders such as hydrocephalus, cerebral palsy, diplegia, and hemiparesis were very rare in general; however, all the cases were observed in the PT group. Cerebral palsy was observed in 4 PT infants (Table 21) with an average birth mass of 1,230 g and GA of 30 weeks (not presented in the results). Previously, cerebral palsy was associated with PT birth, growth retardation, and asphyxia at birth, although most children with these risk factors may not have neurological disorders, and conversely, more than 75 % of children with cerebral palsy may not have a history of risk factors (NIOH, 1985). By multivariate analysis of perinatal risk factors Nelson and Ellenberg (1986) demonstrated that events at childbirth play only a small role in the causes of cerebral palsy, a greater role, however, was attributed to genetic factors and events during fetal growth and development. One third of children with cerebral palsy were born preterm and incidence of cerebral palsy in VLBW children was 13 % (Nelson and Ellenberg 1985).

In Slovenia, a risk register of newborns exists, which records risk factors for later development, and tries to identify as many children, who will become disabled later on in life, as possible (Babnik J., 1990). Since 1960, however, children are being checked with Denver's developmental screening test (DDST), which was also recommend by the American Academy of Pediatrics for laboratory work. All screening tests need to be comprehensible, simple, economically justifiable, reasonable, reliable, and repeatable (Dworkin, 1989). Frankenburg et al. (1988) pointed out that only 15 % of pediatricians regularly use the DDST in only 10 % of children, despite the fact, that the test has already proved to be successful in the early identification of children with developmental problems. They reported that the sensitivity of DDST is 100 % in the identification of severely disabled children, and 92 % in the detection of questionable development (Frankenburg et al., 1988). In contrast, Elliman et al. (1985) reported that, if the corrected age was taken into account for PT infants testing, the majority of PT infants successfully completed the test, despite the fact that during more precise developmental checks (Griffiths Scales), the backlogs were detected. Therefore, it was

recommended that in the DDST on PT infants actual rather than corrected age should be used. It is worth noting that in the first year of life, the assessment of child's development is rather rough, and that the whole child's psychosomatic and motor development can be assessed only by combining the results of DDST with the results of psychologists' research (Babnik J., 1988). To sum up, Dworkin (1989) cited the opinion of British Joint Working Party on Child Health Surveillance, which advised against the use of any screening test development.

In the present study, another indicator of mental health chosen by the scientists from the Maternity hospital Ljubljana, Slovenia, demonstrated that approximately 78 % of PT infants and 97 % of infants in the FT group were evaluated by pediatricians as healthy. More children were at risk for mental disability in the PT group (22 %, 7.5 %, and 17.6 % at the ages of 1, 2, and 3 years, respectively), in comparison to their FT peers (1.8 %, 2.3 %, and 1.8 %, at the ages of 1, 2, and 3 years, respectively) (Table 24). A comparison of frequencies of moderately and severely disabled children was not performed due to small frequencies in all study groups.

Increased prevalence of medical disabilities in VPT and MPT children raised concerns on whether they would be having difficulties in coping with adult life (Moster et al., 2008; McGowan et al., 2011). In their study on 1,726 children (PT and FT), Palfrey et al. (1987) reported early specific developmental problems they identified. They followed speech disorders, learning ability, emotional disturbances, mental retardation, sensory and general illness. They observed that at least 50 % of the illnesses, such as Down syndrome, cerebral palsy, neurological and other illnesses, injuries of eyes and ears, and mental retardation, are being diagnosed by the age of 3 years with 90 % certainty, but it is usually necessary to follow-up children for more than 6 years from birth. During monitoring of 58 children with GA of 27 to 28 weeks and birth mass of approximately 1,050 g, Yu et al. (1984) observed that 85 % of these children experienced normal development, and 74 % in the group of 35 children with GA of 24 to 26 weeks. Kitchen et al. (1987) found that the assessment of development of 98 ELBW children at the age of 2 years is too pessimistic with regard to their later development and that many children (33 %) overgrow their functional disturbances.

In our study, visual impairment was more often in PT than in FT group at the age of 2 years and wearing glasses at 11 years of age was more frequent in VPT and MPT, than in FT infants (Table 25). Hearing impairments up to 11 years of age were too rare in all study groups for any final conclusions.

Visual impairments are common in PT infants and occur due to peripheral (retina/optic nerve) problems and to a widespread involvement of visual pathways at different levels

of cerebral structures (Madan et al., 2005; Fazzi et al., 2012). They may result from the exposure of immature visual system to early visual stimulation, from nutritional deficits, and from systemic diseases or complications associated with PT birth (Fazzi et al., 2012). Retinopathy of prematurity is the most frequent visual impairment after PT birth and is defined as a vision-threatening disease associated with abnormal retinal vascular development (Blencowe et al., 2013b). Madan et al. (2005) have suggested that between 22 and 34 weeks of GA subplate neurons provide their synaptic contact site for axons ascending from the thalamus and other cortical sites. Therefore, in VPT infants the cortical plate has not even developed and subplate neurons function as a holding region for these afferent ascending pathways.

Prematurity is a commonly quoted risk factor for acquired hearing loss. Postulated neonatal causes of hearing loss in PT infants may be hypoxic-ischemic injury to the brainstem, prolonged respirator care, hemorrhage into the inner ear, bilirubin or aminoglycoside antibiotic toxicity, cytomegalovirus infection, acoustic trauma to the cochlear hair cells, or combinations of these factors (Bergman et al., 1985). Exchange transfusions may decrease the risk of hearing loss (Bergman et al., 1985). In various VLBW or PT populations the prevalence of high frequency hearing loss among survivors ranges from 0 % to 4 % (Marlow E.S. et al., 2000). Jiang et al. (2001) studied brainstem auditory evoked responses on 70 PT VLBW infants when reaching term (37 to 42 week of postconceptional age) and compared the results with those of FT term infants. Approximately 25 % of PT VLBW infants had peripheral and/or central hearing impairment at term, which obviously connects unfavourable perinatal factors with hearing impairment.

In the study of Marlow N. et al. (2005) 6 % of 6 year old VPT children were wearing hearing aids, and 4 % had mild hearing loss, as compared to 1 % of FT controls. Similar was reported in the Swedish cohort on 11 year old VPT children (Farooqi et al., 2006) and in the study of Doyle et al. (2001a) on 14 year old ELBW children. In adulthood, only 1.3 % of ELBW young adults, versus less than 1 % of controls were wearing hearing aids, although a higher proportion was reported having hearing impairments (Saigal and Doyle, 2008).

Until the preschool and school years, emotional problems, learning and speech disabilities, and hyperactivity cannot be diagnosed with certainty (Babnik J., 1988). Based on these facts, one can say that with detailed follow-up performed by the age of 3 years in the present study, only severe neurological impairments and mental retardation could have been diagnosed with certainty, while the diagnosis of hearing and sight impairments were unreliable.

5.4 DISCUSSION RELATED TO HYPOTHESIS 5

We hypothesized that the potential consequences of prematurity, such as lower height, lower mass, and lower capacity of physical exercise, will be detected in late childhood and adolescence.

5.4.1 Body height, mass, and body mass index

The intrauterine growth is the fastest during the last trimester of pregnancy (Vaughan and Litt, 1992) and a fetus with more time in the uterus gains more body mass. VPT infants are thus exposed to extrauterine life during a period that is normally characterized by rapid intrauterine growth. To survive, their energy expenditure shifts from growth-promoting actions to survival strategies, in order to cope with increased requirements of unintended postnatal life. Therefore, extrauterine growth retardation is often the result (Wit et al., 2006). However, PT birth may not be always the reason for growth retardation of a child, as physical characteristics and growth depend on GA at birth and birth mass. It, however, seems that growth retardation before term age impairs future physical growth (Hadders-Algra and Touwen, 1990).

The altered growth of PT infants in their childhood seems to be reflected in some of the physical characteristics (Cooper R.L. et al., 1996). Namely, data from epidemiological studies from the developed countries have shown a direct association between birth dimensions and some of the physical characteristics of people in their later life (Oken et al., 2003). Birth mass and length, as well as bone mass of adolescents may be independently positively associated with height, BMI, and sum of skinfolds in young adults (Adair, 2007). According to Euser et al. (2005), in VPT infants, mass gain before the 32nd week of gestation was positively associated with adult body height. It has also been reported that the attained height, which is inversely associated with risk of disease, can strongly associate with birth length (Whitaker et al., 1998; Slattery and Morrison, 2002; Dusick et al., 2003; Eide et al., 2005; Ong, 2006). In addition, adult body mass is a function of height, girth, and tissue mass and distribution (Stein et al., 2007). Each of these measures has an independent association with the risk for CV disease and may have specific associations with early development (Stein et al., 2007).

The results of the present study demonstrate that at birth PT infants were on average 6.4 cm shorter than FT infants, but the difference between the two groups at one year of age was only 1.5 to 2.1 cm (data for males and females, respectively). VPT infants at birth were on average 11.8 to 13.4 cm shorter (data for males and females, respectively) than FT infants, and by 1 year of age the difference between the two groups was only 3.1 cm. Similar to our study, researchers from Arkansas followed-up PT LBW infants during their first year of life (Casey P.H. et al., 1990). In contrast to our results and quite

surprisingly, they did not notice any catch-up growth up to the age of one year. The reason for the discrepancies between their and the present study is likely the fact that they analyzed data from PT infants using their corrected age and they consequently concluded that PT LBW infants have different patterns of growth than their FT NBW counterparts, if corrected age in PT individuals is used for the analysis (Casey P.H. et al., 1990).

After the comparison of present results with Usher and McLean growth charts (1969), as well as with the American growth standards (WHO, 2004), and the calculation of z-scores for body height, one can see that PT infants' body height at birth was below the average of a standard population, which is expected, as they were younger than the average newborns. At discharge, thus, when the ages of PT and FT infants were more similar, one would expect similar body height in both groups. However, this was not the case, as PT infants' body height still remained 1 SD below the average of a standard population. This difference can thus be associated directly with preterm birth and is most likely associated with medical conditions PT infants have experienced.

After discharge, body height was significantly lower in PT males than in their FT peers up to the age of 2 years. VPT infants grew even slower than MPT infants, who obviously recovered from PT birth, grew faster up to 2 years of age and caught-up the FT group by that time. As evident from relative increases in body height, VPT infants on average grew faster than FT infants in the first years of life, but still stayed below the average height, which is evident especially in females. The growth of our FT infants could be matched precisely with the growth of Finnish infants, as at the age of two years the FT males from the present study were 88.7 (3.3) cm tall and the Finnish infants 88 cm tall (Piekkala et al., 1989).

Our results demonstrate that in the first years of life VPT infants gain body height faster than their peers. Catch-up growth is evident from higher relative increases in body height, which is particularly obvious in VPT individuals, as compared to the other two groups. In comparison to their FT peers, the afterward growth of VPT individuals seems to be limited by their early prematurity, which is evident especially from their body height, as the differences in body height between VPT and FT individuals persist into adulthood.

Kitchen et al. (1989) reported that in VLBW infants both, poor growth up to the age of two as well as poor growth up to the age of five, result in similar outcomes, and that perinatal factors have no significant impact on growth in that period (Kitchen et al., 1989). However, other researchers reported that post-discharge growth failure contributed to poorer growth outcomes among VLBW and ELBW individuals (Sices et

al., 2007; Rotteveel et al., 2008) and was associated with poorer motor outcomes, regardless on whether it occurred early after discharge or later in infancy (Sices et al., 2007). Also, SGA children were reported to be at increased risk for short stature (the height below the 10^{th} percentile) (Paz et al., 1993).

Although nowadays several studies suggest that rapid and early catch-up growth is the main factor affecting the risk of adverse body composition and metabolic profile (Hales and Ozanne, 2003), there is growing evidence indicating an independent effect of GA on liver fat content and also blood pressure in adulthood (Thomas E.L. et al., 2012).

Furthermore, our results demonstrate that body mass was statistically lower in PT males than in their FT peers from birth up to 2 years of age. In addition, VPT males were lighter than MPT and FT peers up to 2 years of age, and also between the age of 8 and 12 years. PT and FT females had different body mass from birth up to 3 years of age, with VPT females being lighter than MPT and FT peers also between the ages of 16 and 17. Although at discharge PT infants were on average 900 g lighter than their FT peers, they successfully reduced that difference by the age of one year. Namely, at birth, PT infants were on average 1.2 kg lighter than FT infants, but the remaining difference in body mass at one year of age was 0.8 kg only. Also, at birth VPT infants were on average 2.1 to 2.2 kg lighter (data for males and females, respectively) than FT infants, but at the age of 1 year the difference in body mass between the two groups was only 1.4 kg. Similar to body size/length, body mass of our FT infants was similar to Finnish infants, as at 2 years of age our infants weighted 13.3 (1.5) kg on average and the Finnish 12.9 kg (Piekkala et al., 1989). In addition, the z-scores calculation enables us to conclude that VPT males remain lighter than the average WHO (2004) population through their whole life, which is also true for VPT females after the age of 16 years, but not before and during puberty. Finally, our FT individuals were on average heavier than the WHO mass standards and MPT individuals caught-up in mass successfully with the WHO standard group by the age of one.

It has been observed that very immature or severely ill newborns, which are treated with mechanical ventilation and parenteral food for a long time, often have postnatal growth retardation (Babnik J., 1989). After the recovery and with sufficient caloric diet they grow faster than FT or healthy infants and their growth curve approaches the values of their genetic predisposition (Babnik J., 1989). However, data on height from our study enable us to conclude that the earlier an infant is born, the larger are the negative effect of preterm birth, which in the long term affects their growth potential.

In our study, BMI was lower in PT than in FT infants from birth up to 2 years of age for both, males and females. Later on, higher BMI in MPT individuals than in their VPT

peers was observed, which was especially prominent at the ages from 9 to 12 years. As MPT males of our study gained more body mass in adolescence then their peers, their BMI was higher in adolescence, as compared to their peers. Interestingly, according to the existing literature, this difference was more often observed in females (Euser et al., 2008), yet our PT and FT females had practically similar BMI, both in childhood and adolescence (with the only exception at 16 years of age).

Similar to our study, Dutch Project on Preterm and SGA (POPS) cohort followed up 94 % of 1,338 live born infants from 1983 (VPT and/or VLBW) to young adulthood (Verloove-Vanhorick et al., 1986). The POPS cohort included those, who were VPT, ELBW, or both (Verloove-Vanhorick et al., 1986). They reported that postnatal mass gain, which was accelerated sooner, as well as late infancy mass gain, although the latter to a lesser extent, were associated with higher BMI z-scores at 19 years of age (Euser et al., 2005). The authors suggested that the altered fat distribution, determined with subscapular-to-triceps ratio, at term age, which was noted in PT born infants, might have persisted into adulthood, which might have in turn contributed to a less favorable CV disease risk profile (Euser et al., 2005).

Studies reported that height and mass of FT and post-term individuals at 18 years of age were independent of GA, most likely because in both groups the maturing process of pregnancy has been completed (Eide et al., 2005). In PT infants, however, the positive associations of birth length and mass with adult height and mass were weaker than in FT individuals, indicating that maternal or pregnancy-related factors may influence an individual's growth potential (Eide et al., 2005). Data on which such proposition was based on were provided by Bhargava et al. in 1995. Namely, body mass and height were recorded in LBW/SGA and NBW children up to 14 (N=252 and 176, respectively) and 16 years of age (Saigal et al., 2001). Despite of the evident catch-up growth, which was observed between the age of 8 and puberty, ELBW (Saigal et al., 2001) and SGA (Bhargava et al., 1995) children stayed shorter and lighter than their NBW peers (Saigal et al., 2001). In addition, LBW males lagged significantly behind their controls in all physical growth parameters untill 14 years of age, while LBW females had a physical growth comparable to controls after the age of 11 years (Bhargava et al., 1995). Similar data were reported in Melbourne, where significant catch-up growth was described in ELBW between 8 and 14 years of age, but they nevertheless stayed lighter than their NBW peers (Doyle, 2000).

However, there also exist studies that could not find any significant differences in physical characteristics between PT and FT individuals later on in life. In Poland, for example, information on physical characteristics was collected from 155 PT and FT menstruating females with defective vision. No significant differences in body height,

mass, and BMI were observed between the two groups, but there was a tendency towards a robust body stature in PT subjects (Umławska, 2007). Similarly, Bhargava et al. (1995) reported similar mass, height, and head circumference for PT and FT controls at 11 years of age.

In addition to the above, variations in body proportions, such as the ratio of leg to trunk lengths, were suggested to have their origin in childhood and were considered independent predictors of the risk of later morbidity and mortality (Stein et al., 2007).

Finally, although there is still little understanding of the heterogeneity of these effects (Currie and Vogl, 2012), research in the past decades has shown that health shocks in early-life have long-term effects on adults in both, the developed and developing world.

Recently, physical development, growth, and infant mortality were associated with famine and starvation exposure in prenatal and early postnatal life (Stein et al., 2007). People born during famine suffered from increased risk of obesity, schizophrenia, metabolic syndrome, hypertension, fecundity, and reduced adult height (Song, 2013). A number of studies also demonstrated that prenatal exposure to famine can influence the health and well-being of children and may even have an "intergenerational" effect. Such reports were made for famine in 1982 in China (Song, 2013; Kim et al., 2014), the Netherlands from 1944 to 1946 (Lumey et al., 2009), and Ethiopia in 1984 (Dercon and Porter, 2014).

Song (2013) suggested two kinds of intergenerational effects of mothers' prenatal famine exposure on the risk of infant mortality of their children: low prenatal famine severity significantly reduced infant mortality risk whereas high famine severity increased it. It was also reported that the epigenetic effects of parents' malnutrition (through both female and male line) extend to their children, which demonstrates further perpetuation of growth programming (Kim et al., 2014).

Indeed, individuals born in China during famine had significant decreased body height by 2.7 cm and mass by 3.03 kg, as compared to individuals who did not experience the famine (Meng and Qian, 2009).

Similarly, individuals who were exposed to Ethiopian famine in uterus or in the first 3 years of life were on average 3.9 cm shorter than their controls at approximately 20 years of age (Dercon and Porter, 2014). Children who were aged 1 to 3 years at the peak of the famine were also significantly shorter by at least 5 cm than older and unaffected peers (Dercon and Porter, 2014).

A significant relationship between famine exposure during early gestation and increased adult (height-adjusted) mass was also seen in a Dutch cohort of 1,116 females born during the famine in 1944-1946 (Lumey, 1998) and the same was described for 300,000 males born in the same period, when they were recruited for military (Ravelli et al., 1976). It was suggested that this observed body mass increase may be due to a change in metabolic efficiency of these individuals, due to an increase in nutritional intake, or due to lower levels of physical activity. However, it is also possible that diet and prenatal or early postnatal environment interact to produce changes in fetal brain in appetite and mass control, which may have permanent effects (Lumey, 1998). It has been suggested that nutritional deprivation may affect the differentiation of hypothalamic centers regulating food intake and growth (Ravelli et al., 1976). In contrast, increased food availability produces excess fat accumulation in an individual growing to its predetermined size (Ravelli et al., 1976).

After studying 359 men and women born in 1945-1946 to mothers exposed to famine during pregnancy the researchers observed increased adiposity in females aged approximately 58 years (Lumey et al., 2009). They observed an association between prenatal undernutrition and elevated total cholesterol concentrations, triglycerides (Lumey et al., 2009), and blood pressure (Stein et al., 2006). In males, the same pattern was not observed. The increases in total cholesterol and LDL cholesterol were independent of BMI, waist circumference, and midthigh circumference. The increase in triglycerides was independent of midthigh circumference but was attenuated with control for either BMI or waist circumference (Lumey et al., 2009). In addition, exposure to famine during gestation was suggested to cause the development of hypertension in adulthood (Stein et al., 2006).

5.4.2 Peak height velocity and age at menarche of preterm and full-term infants

Sexual maturation requires a lot of energy. Metabolic status of the body is reported to the central nervous system by substances produced by adipose tissue and peptides produced in the digestive tract. Adipocytes secrete a peptide hormone leptin (that is encoded on the gene LEP), which is involved in the establishment of energy homeostasis and regulates numerous neuroendocrine systems, including hypothalamus-pituitary-gonad axis. To be precise, the receptors for leptin are on the front of the pituitary gland, but not in the hypothalamus. It is known that mutations on a gene LEP, which inhibit the secretion of sex hormones (Martos-Moreno et al., 2010), cause severe obesity, morbid obesity with hypogonadism, or type 2 diabetes mellitus.

Studies report that leptin level is low in prepubescent children, while it constantly increases in pubertal females. Females with higher BMI or fat content have higher leptin

concentrations than other females (Argente et al., 1997; Martos-Moreno et al., 2010). Less is known on whether leptin is a signal for the onset of puberty and if a critical level of leptin is required for the puberty to start.

Apart from leptin, adipocytes also secrete peptides adiponectin (it is secreted from mature adipocytes) and resistin (produced in adipose tissue and liver). The effects these peptides may have on the maturation and fertility has also not yet been described (Martos-Moreno et al., 2010).

Preterm birth may potentially affect metabolic status in childhood and puberty (van Weissenbruch and Delemarre-van de Waal, 2006; Yermachenko and Dvornyk, 2014). This estimation has now been confirmed by our results, which demonstrate, that the onset of sexual maturation in females is earlier in VPT than in FT individuals. Namely, VPT females experienced PHV approximately 5 months earlier than FT and MPT females. For males, no statistically significant difference for the same parameter was observed between VPT, MPT, and FT group, regardless of whether uncorrected or corrected age was considered in the analysis (Figure 17). It has been reported that prematurity *per se* is also associated with advanced pubertal growth (Fewtrell et al., 2001; Wehkalampi et al., 2011). This observation is supported by our results, as our PT individuals had higher PHV than FT individuals (Figure 16).

Similar to our results, the components of pubertal growth (i.e. the age at the start of pubertal growth spurt and PHV, the onset of sexual maturity) seemed to appear sooner in PT individuals (Bhargava et al., 1995; Umławska, 2007; Ahmed et al., 2009; Wehkalampi et al., 2010; Biro et al., 2012). Additionally, the interval between PHV and menarche was suggested to be shorter in LBW than in control females (approximately 1.0 and 1.6 years for LBW and controls, respectively), which may be an important factor underlying the ultimate shorter stature observed in LBW females (Bhargava et al., 1995).

In Finland, the age at PHV in 128 PT LBW children was on average 0.8 years lower than in FT children, and was 0.9 years lower in PT VLBW children, as compared to the controls (Wehkalampi et al., 2011). In the neighboring Sweden, the majority (87 %) of 252 SGA individuals, who experienced full catch-up growth within the first 2 years of their life, attained puberty at a normal or slightly earlier age. Other 13 % of SGA, who remained below 2 standard deviations in body mass throughout childhood, reached puberty somewhat early (Albertsson-Wikland and Karlberg, 1994).

In contrast to the above, Canadian researchers reported that 25 PT LBW males were significantly older at PHV, as compared with 71 FT NBW controls (14.2 (0.5) and 13.6

(0.6) years for PT LBW and FT NBW males, respectively), suggesting that the PT males may reach sexual maturity later. Age at PHV in females was similar in 16 PT LBW and 56 FT NBW individuals (12.8 (0.7) and 12.5 (0.8) years for PT LBW and FT NBW females, respectively) (Erlandson et al., 2011). This sample size, however, was not as large as in the previously mentioned Scandinavian studies or in our study.

As described in Chapter 2.4.4, the menarche is a sign that a female is sexually mature. The natural selection has ensured that the female body is large enough (having body mass of at least 48 kg and hip width of a minimum of 24 cm) for delivery prior the conception and that enough body fat (a minimum of 17 %) for provision of energy is stored for both, pregnancy and childbirth (Bogin, 1999).

When we investigated the age at menarche, the results of our study revealed that VPT females tended to experience menarche approximately 10 months earlier than their MPT and FT peers. When the corrected age was considered, the tendency was even stronger (Figure 24). However, the sample of VPT females in our study was too small (N=5) for any significant final conclusions to be made.

In a study performed in India, pubertal changes (pubic hair and genitalia development) were recorded up to 14 years of age in 252 LBW and 176 FT AGA children. The authors reported that onset of menarche occurred 6 months earlier in PT and 12 months earlier in SGA females (Bhargava et al., 1995). This, however, was not the case for males, as the sequence of pubertal changes in males was almost similar in all groups (Bhargava et al., 1995). Similar results were also reported from Sweden, where SGA females born in 1973-1977 (N=100) were 5 months younger than FT NBW females (N=688) at the onset of puberty and menarche (Persson et al., 1999). Also, the information on the age of menarche was collected from 155 females born with defective vision (with 22 % of them born prematurely) in Poland (Umławska, 2007). Blind females reached pubertal age 2 months earlier than the partially sighted (at 13.31 and 13.44 years, respectively) and the PT females entered puberty 6 months earlier than their FT peers (at 12.93 and 13.42 years, respectively), irrespective of the degree of defect. The authors therefore suggested that the mechanisms responsible for earlier onset of puberty in PT and LBW individuals seem to play an important role in sexual maturation in females with visual impairment (Umławska, 2007).

Results from Boynton-Jarrett et al. (2011) suggest that low maternal PMG is associated with earlier age at menarche of the daughter. Namely, higher maternal PMG increased the age at menarche of the daughter (Boynton-Jarrett et al., 2011). The authors suggested that the intrauterine environment may be an important factor for the timing of menarche in daughters. Insulin resistance and hyperinsulinemia were proposed as two

of the possible mechanisms linking LBW or PT birth and early age at menarche. Namely, they are both associated with altered adrenal function and elevated levels of androgens (Neville and Walker, 2005). Hyperinsulinemia was associated with IUGR and premature pubarche (i.e. the first appearance of pubic hair) (Boynton-Jarrett et al., 2011). Insulin resistance or metabolic syndrome, which is a consequence of obesity (especially of visceral fat amount), are both characterized by increased insulin levels (Holly et al., 1989) that reduce the level of globulins that bind steroid sex hormones and consequently increase the availability of sex hormones (Ahmed et al., 2009; Biro et al., 2012), which could lead to earlier sexual maturation. It is also worth noting that the production of sex hormones results from pathways of fat metabolism. A greater amount of fat tissue or its different distribution in the body may therefore cause larger or earlier synthesis of sex hormones, which would in turn lead to earlier maturation (de Ridder et al., 1990, 1992).

Menarche was also suggested to be affected by the nutritional status and growth patterns during early childhood. This was observed in a study of 2,083 women born in Brazil in 1982 (Mesa et al., 2010). Females, who experienced rapid growth in mass-for-age z-score from birth up to 2 years of age and in mass-for-age or height-for-age z-scores from the age of 2 to 3.5 years, were more prone to early menarche onset occurring before the age of 12 years (Mesa et al., 2010).

In contrast to the above, some studies did not describe any significant associations between prematurity and age at menarche (van Weissenbruch and Delemarre-van de Waal, 2006; Hui et al., 2012; Szwed and Kosińska, 2012; Shim et al., 2013). In an Indian cohort, for example, 180 LBW infants were divided into PT SGA, FT SGA, and PT AGA and were compared with FT AGA infants (Chaudhari et al., 2008). The parameters studied were subjects' age at menarche and testicular volume determined with orchidometer. No significant differences in sexual maturity and onset of menarche were observed between the study and control groups (Chaudhari et al., 2008).

Also in contrast to our results, Szwed and Kosińska (2012) demonstrated a considerable variation of age at menarche in 527 Polish PT females. The latest crossing of the puberty threshold was observed in VPT females, where the age at menarche was postponed by 2 years (it was observed at 14 years of age) in comparison with FT females. Average appearance of menarche was observed in MPT females at 13 years of age (Szwed and Kosińska, 2012). Moreover, a later onset of menarche was also observed in PT LBW females. The same trend of the later onset of puberty was also observed in Asian (Hui et al., 2012) and Scandinavian (Fledelius, 1982) adolescent females. In 3,963 males and 3,403 females in a population-representative Chinese birth cohort the associations of GA and PT birth with the age at the onset of puberty (as

determined in accordance with Tanner stage II for breast or genitalia development) were analyzed (Hui et al., 2012). In this study PT females were reported to reach puberty about 4 months later than FT females (both groups were adjusted for mother' age of menarche).

Apart from the factors presented above, further research on other possible determinants of the timing of puberty, such as maternal constitution, infant and childhood exposures to endocrine disruptors, tempo of infant's growth, and infections that affect the gonadotropic axis, were proposed to be performed in future (Hui et al., 2012). Further improvements from our study could in future be achieved by increasing the sample size of VPT individuals and by using a longitudinal method for determining menarche onset, as self-report onset of menarche may sometimes be questionable. In addition, gaining new knowledge on this topic is particularly important, because early maturation may be involved in the pathway that links VLBW PT birth with adult CV disease risk (Wehkalampi et al., 2011).

5.4.3 Capacity of physical exercise and motor skills of preterm and full-term infants

Aerobic and anaerobic exercises differ in the duration and intensity of muscular contractions involved, as well as in how energy is generated within the muscle. Aerobic exercise is physical exercise that depends primarily on the aerobic energy-generating processes (thus on aerobic metabolism). "Solely aerobic" exercise is low-intensive enough, not to generate lactate, so that all carbohydrate is aerobically turned into energy. Generally, light-to-moderate intensity activities that are sufficiently supported by aerobic metabolism can be performed by a healthy person for extended periods of time (McArdle et al., 2010). Anaerobic exercise occurs when there is not sufficient oxygen present, for example in strength training and short-distance running. In almost all conditions, anaerobic metabolic processes are accompanied by aerobic processes, because the anaerobic metabolism must supplement the aerobic system, when the energy demands exceed the aerobic system's capacity.

Aerobic capacity is the functional capacity of cardiorespiratory system and refers to the maximum amount of oxygen consumed by the body during exercise of maximal intensity. It is a function of cardiorespiratory performance and the maximum ability to remove and utilize oxygen from the blood. To measure maximal aerobic capacity, a so called VO_2 max test has to be performed, in which the participant undergoes progressively more strenuous exercise (usually on a treadmill or cycle ergometer), from low intensity exercise through to exhaustion.

In our study, 600-meter run was used to test our subjects' capacity of aerobic exercise or general endurance. The three experimental groups, thus VPT, MPT, and FT males achieved similar results throughout the tested period, except at the age of 14, when PT males ran faster than their FT peers. In contrast, VPT females had statistically worse general endurance than their MPT and FT peers during most of the time.

Similar to our females, aerobic capacity was significantly reduced in 15 VPT children at the age of 8 years, when measured with a graded treadmill exercise test, and motor competence with the Movement Assessment Battery for Children or Movement ABC (M'ABC) (Takken et al., 2015), within which the following groups of skills were investigated: manual dexterity, ball skills, and static/dynamic balance (Henderson and Sugden, 1992). In Norway, 75 VPT individuals born in 1982 and 1991 were compared with their FT peers at 11, 18 (Clemm et al., 2012), and 25 (Clemm et al., 2014) years of age by using pulmonary function tests and standardized incremental maximal running exercise treadmill test at 800 to 1,000 m, using a modified Bruce protocol (Cumming et al., 1978 as in Bruce et al., 1973). On average, measures of aerobic capacity for VPT and FT individuals were in the same range, whereas the average running distance was reduced for approximately 10 % in VPT individuals (both genders combined) (Clemm et al., 2012). However, FT males had significantly higher mean peak of attainable oxygen consumption (VO_2 max; $ml*kg^{-1}*min^{-1}$) than PT males (53.7 and 49.3, respectively), whereas there was no such difference between FT and PT females (42.9 and 42.0, respectively) (Clemm et al., 2012). A reduced speed of running seemed to be an underlying problem of VPT individuals (Husby et al., 2013). Also, at approximately 17.5 years of age, 53 Canadian ELBW and FT adolescents were assessed by a pediatric physiotherapist and completed a self-assessment fitness and activity questionnaire (Rogers et al., 2005). ELBW males and females had lower aerobic capacity and reported less sports participation, lower physical activity level (aerobic fitness 495 and 423 vs. 529 and 442, respectively), and poorer coordination, as compared with FT control subjects (Rogers et al., 2005).

When it comes to anaerobic performance, our results demonstrate that anaerobic tests were performed worse by PT than by FT individuals. Sprint speed was significantly lower in PT than in FT males both, before and during puberty. PT females, especially VPT individuals, were slower than their MPT and FT peers during adolescence in this test. Explosive power was significantly lower in PT males and VPT females than in FT peers throughout the adolescence. Trunk muscle strength was higher in FT males than in PT peers, both before and after puberty, with the lowest values in VPT individuals. In females, the same trend was evident at 17 and 19 years of age. Muscular endurance of the shoulder girdle and arms was lower in PT males, than in FT peers, with the lowest values in MPT individuals, both before and during puberty. Before puberty, MPT

females were able to hang less time on the pole, than VPT and FT peers, but later on VPT females have the worst scores.

Previously mentioned 17.5 years old 53 Canadian ELBW and FT adolescents were also tested with muscular function and dynamic muscle endurance tests (Rogers et al., 2005). The ELBW group scored lower than control subjects on grip strength, with overall better scores in males than in females. ELBW also scored lower than the control group on lower limb strength in vertical jump and leg power. There were overall gender differences, with males having more leg power and higher vertical jump than the females. ELBW could do fewer sit-ups and partial curl-ups than the control teens, and males performed better than females at both tests (Rogers et al., 2005). ELBW teens had less lower back flexibility, and had tighter hamstrings (Rogers et al., 2005). In another study, lower extremity muscle strength was also significantly reduced in 15 VPT children at the age of 8 years, when measured with a hand-held dynamometer (Takken et al., 2015). No further similar anaerobic test have been performed in other studies, therefore at this time we can not compare our results with further similar data from other studies.

As presented in the Results chapter of this thesis, agility and fine motor SLOfit tests were mostly performed better in FT males than in PT peers. In FT females, however, these tests were performed better than in PT only after puberty, which suggests that earlier PHV and sexual maturation in PT cause a faster motor development and therefore better performance of these tests before FT females are entering puberty and surpassing the PT peers. Coordinaton of body movements was worse in MPT males than in their VPT and FT peers. In contrary, PT females, especially MPT females, were significantly better than FT females before puberty. Later on PT, especially VPT, females stagnated and tended to be worse than FT peers, who surpassed them. Forward bend and touch on the bench tended to be better in FT than in PT males. PT females, however, performed this test better than FT peers before puberty, but in puberty PT females regressed and performed worse than their FT peers. Speed of alternative movements was lower in VPT males than in their MPT and FT peers at 18 and 19 years of age; however, PT females were faster than their FT peers after puberty.

Interestingly, Piper et al. (1989) suggested that gross motor development of PT individuals matures according to conceptional, rather than chronological age, but that fine motor development may be adversely affected by very early birth. They also suggested that this delay in motor development may be associated with the development of other sensory-motor systems such as vision. Early lags in fine motor development may be indicator of later handedness and more subtle cognitive and learning disorders (Piper et al., 1989). It was also reported that together with cognitive and behavioral

problems, minor motor problems are by now the most dominant neuro-developmental sequele in PT (Bos et al., 2013) and VLBW (Ornstein et al., 1991) children, with the prevalence reported of up to 50 % to 70 %.

After the examination of corticomotor development in 151 Australian children at the ages of 10 to 13 years born between 25th and 41st completed week of gestation, it was reported that with every week of reduced gestation, corticomotor excitability is reduced, which remains evident in late childhood as poorer motor skill development, particularly manual dexterity (Pitcher et al., 2012). There are a few studies, which have reported problems in motor skills in VLBW children at preschool (Forslund and Bjerre, 1989, N=44 PT infants) and school age (Marlow N. et al., 1989, N=53 ELBW infants; additional data reported in a review article by Moreira et al., 2014).

There have also been few reports on impaired motor skills in VLBW adolescents (Powls et al., 1995; N=53 VLBW infants) and young adults (Husby et al., 2013). The assessments were performed with the M'ABC (Henderson and Sugden, 1992). In Norway, VLBW and SGA adolescents were reported to have an increased risk of motor problems, as compared with control children. Namely, 54 VLBW, 59 FT SGA, and 83 control children (with birth mass higher than 10th centile at term) were assessed at the age of 14 in a population based study (Evensen et al., 2004). Approximately 26 % VLBW children and approximately 15 % SGA children had motor problems, as compared with controls (4 %). There were no sex differences in motor problems in the VLBW group, but for SGA children, an increased risk of motor problems was evident in manual dexterity for males (Evensen et al., 2004). After another examination of these individuals at the age of 23 years, the researchers reported about an overall poorer fine and gross motor skills, as compared with controls (Evensen et al., 2004). Finally, a recent longitudinal study indicates that VLBW children have not outgrown their motor problems when entering adulthood (Husby et al., 2013). ELBW and FT 17.5 year-old Canadian adolescents were tested with flexibility tests. ELBW teens were less flexible than the control teens on measurements of forward bend and touch on the bench, as well as right and left popliteal angle. There were no gender differences in the results of this test, but females had better flexibility than males in right and left popliteal angle (Rogers et al., 2005).

Additional risk factors for impaired fine motor skills that have been reported for VPT children include IUGR, inflammatory conditions, and bronchopulmonary dysplasia (Bos et al., 2013).

When it comes to calculating physical activity according to IPAQ for the subjects participating in our study at the age of 26, no final conclusions can be made, as the

sample size was rather small. Therefore, a comparison of the current physical activity between the PT and FT individuals could not be made reliably. There are, however, some data on this topic available from other countries, which are presented below.

In Norway, leisure-time physical activity was similarly and positively associated with exercise capacity in PT and FT adolescents alike, although participation was lower among PT children (Clemm et al., 2012). Also in other studies, VLBW adults exercised less during their leisure time, than FT adults (Kajantie et al., 2010; Kaseva et al., 2012). These differences in the capacity of physical activity may be related to the interaction of effects of PT birth on the motor system, together with a more inactive lifestyle. Therefore, encouragement of more often participation in physical activities from early childhood onwards might be important for PT children.

As discussed later in Chapter 5.5.2, VLBW subjects may have lower lean body mass than their FT peers (Hovi et al., 2007). It is known, however, that the amount of lean body mass has implications for glucose uptake and physical capacity for work and exercise (Wells J.C.K. et al., 2007). This seems to underlie the difference in conditioning leisure-time physical activity. However, it is difficult to distinguish between cause and consequence. Lower muscle strength, exercise capacity, and poorer motor coordination, all present from childhood onwards, are likely to make physical activity less rewarding, resulting in physical inactivity, which aggravates the slower development of motor skills and contributes to the lower muscle and lean body mass (Kaseva et al., 2012).

In contrast, the agility and fine motor tests, which are on average better performed in PT than in FT children, this could be due to their early maturation. The latter can result in a more mature body and thus in highly developed fine motor skills for the same age, as compared to FT children, who are not yet in the same stage of body maturation. As evident from the results of the present study, the difference in maturation between PF and FT individuals was especially prominent in females.

Our hypothesis $H_0$5 was therefore rejected and selected issues of working hypothesis H_W5 were accepted.

5.5 DISCUSSION RELATED TO HYPOTHESIS 6

We hypothesized that distribution of body fat will be different in full-term and premature individuals.

The results of the present study demonstrate that body fat amount between 9 and 18 years of age seems to depend on both, GA and gender, as VPT males had lower triceps skinfold thickness, fat mass, and calculated percentage of body fat (based on the triceps skinfold thickness) than their FT peers. In contrast, however, PT females had higher triceps skinfold thickness and percentage of body fat than their FT peers. Lean body mass was similar in PT and FT individuals; however, it was lower in VPT individuals than in MPT and FT peers, which was evident in males up to the age of 16 years and in females after the 15 years of age.

5.5.1 Distribution of body fat in preterm and full-term individuals

In the present study, data on the calculated values for fat distribution between the torso and limbs, which were obtained on the basis of skinfold thicknesses at eight body sites and circumferences at six body sites, are also presented in Annexes U and V. It has to be noted, however, that only a very small sample could have been obtained for the age of 26 years, which prevented us against making any final conclusions regarding the distribution of body fat between PT and FT subjects.

The existing data on changes in body composition in PT children during the first decade of life are still controversial (Gianni et al., 2008).

There exist a few studies, which found no associations between prematurity and body fat distribution. For example, Euser et al. (2005) found that in VPT infants, mass gain before the 32nd week of gestation and birth mass were not associated with fat distribution at the age of 19 years. Similarly, Ezzahir et al. (2005) suggested that catch-up growth may not be problematic for different distribution of body fat, if it takes place early in life. They therefore speculated that PT individuals are not at risk for unfavorable fat distribution, because, according to reports (Gianni et al. 2008), catch-up growth can be achieved for the majority of PT children within the first year of life.

PT children were nevertheless suggested as being at risk for altered regional adiposity (Gianni et al., 2008), as some studies (Uthaya et al., 2005) have established that PT children show a pattern of more fat deposition on the trunk relative to the extremities, depending on mass gain in infancy. For example, Gianni et al. (2008) observed no difference in the fat amount on the trunk between PT and FT infants, but fat amount on the limbs was lower at school age (4.8 to 6.6 years) in 45 LBW PT children than in FT

children. In addition, increased earlier postnatal and, to a lesser extent, late infancy mass gain was associated with abdominal fat at age 19 years (Euser et al., 2005). A greater postnatal mass gain was also associated with a higher adult waist circumference. Also, fetal mass gain was positively associated with waist circumference, but only when it was unadjusted for adult body height, which indicated that the increase in waist circumference with higher birth mass reflected not solely an increase in visceral fat, but mainly an increase in body size (Euser et al., 2005). Te Velde et al. (2003) reported that LBW individuals may be related to a higher adult subcutaneous fat mass and a more abdominal distribution of subcutaneous fat.

In some studies, LBW and growth in the first two years of age have been associated with higher waist-to-hip and subscapular-to-triceps ratios (Fall et al., 1995; Li H. et al., 2003; Euser et al., 2005) and with more truncal and abdominal fat pattern, but only after adjusting for adult BMI (Law et al., 1992; Fall et al., 1995; Barker M. et al., 1997). It has been pointed out that adjustment for body size in fetal origins studies should always be interpreted cautiously, although this might influence some adult disease outcomes (Lucas et al., 1999). Euser et al. (2005), however, rejected the adjustment for current BMI in analyses with fat mass and fat distribution as outcomes. They proposed that if correction for current body proportions is applied, an index independent of body fat should be used.

Last but not least, SGA status was shown to positively affect trunk fat mass content in PT children (Gianni et al., 2008). This suggests that fetal under-nutrition may play a role in the development of body composition changes in terms of altered regional adipose tissue distribution (Gianni et al., 2008).

Thus, although still disputable, growth during early infancy may be a critical predictor of subsequent body composition and trunk fat distribution (Chandler-Laney et al., 2013). PT children tend to gain mass more rapidly during the early postnatal period, which seems to lead to greater central fat deposition than on the extremities (Ong, 2006). Excess mass gain during the first, but not the second 6 months of life, has also been associated with relatively greater trunk fat among 234 individuals between 4 and 20 years of age (Chomto et al., 2008). Children, who experienced catch-up growth between birth and 2 years of age, were fatter and had more central fat distribution even at the age of five years (Ong et al., 2000). It was therefore suggested that mechanisms that signal and regulate early catch-up growth in the postnatal period may be involved in the associations between the small size at birth and risks for disease in adulthood (Ong et al., 2000).

Thus, we were not able to refute the null hypothesis $H_0$6, which may be due to either small differences between the samples, substantial variability, or small sample size.

5.5.2 Body fat and lean body mass in preterm and full-term individuals

Results of the present study demonstrate that PT and FT males had similar triceps skinfold thickness and body fat mass during schooling. However, PT males had lower percentage of body fat than their FT peers at the ages of 15, 16, and 18 years (Annex W, Figure 29). In VPT males, triceps skinfold thickness at 9, 10, 12, and at 17 years (mean difference of 2.4 mm; Annex T, Figure 28), body fat mass from 9 to 12 years (mean difference of 1.8 kg; Annex X, Figure 30), and percentage of body fat at 9, 12, and 17 years of age (Annex W) were significantly lower than in MPT and FT individuals.

In contrast to males, PT females had higher triceps skinfold thickness (mean difference of 2 mm) and body fat mass (mean difference of 1.4 kg) at and above the age of 16, and higher body fat percentage at the ages of 15 and 16 (mean difference of 2.2 units) than their FT peers. The MPT and FT females consequently differ significantly at the age of 16 years.

Our findings of body composition in PT females are in line with the results of Euser et al. (2005), who observed increased total and subcutaneous adiposity at the age of 19 years, as demonstrated by skinfold thickness measurements (Euser et al., 2005). Also similar to our PT males, the lack of adiposity was reported by others (Peralta-Carcelen et al., 2000; Fewtrell et al., 2004; Uthaya et al., 2005; Gianni et al., 2008; Johnson et al., 2012), who observed a significantly lower fat mass in PT children, as compared to FT children. Gianni et al. (2008) assessed body fat amount and total body fat mass index at the ages of 5 to 7 on 45 PT LBW infants, and found no differences in body composition variables between males and females for the PT children. They, however, used DEXA scanning, which can give results with rather different accuracy then skinfold thickness measurements. There are several studies, which studied adiposity in PT and FT individuals, but did not separate the participants by gender (Peralta-Carcelen et al., 2000; Fewtrell et al., 2004; Uthaya et al., 2005; Johnson et al., 2012). Fewtrell et al. (2004) studied 497 PT LBW children between the ages of 8 and 12, which is similar to our study. They used both DEXA and skinfold thicknesses measurements. PT children (not separated by gender) had lower fat mass and fat free mass. In their systematic review and meta-analysis Johnson et al. (2012) evaluated body composition of 733 VPT VLBW infants from eight studies and found less fat mass than in FT infants, when reaching term. Their overall results suggested that PT infants had less fat mass, but a greater total body fat percentage at term than FT infants. Daly-Wolfe (2012) reported that MPT infants (N=28) developed increased body fat percentage as they approached

term corrected age, as compared to FT infants, which they evaluated with mid-arm circumference. In SGA infants up to 4 years of age body fat percentage appeared to be relatively higher than in their AGA peers (Hediger et al., 1998). Peralta-Carcelen et al. (2000) measured 53 ELBW VPT individuals (with mean birth mass of 849 g and GA of 28 weeks,) at the age of 15 years, not separated by gender. They observed significantly lower body fat mass in 53 ELBW VPT, as compared to 53 NBW FT (13.1 (8.8) and 17.2 (9.6) kg, respectively), but no significant differences in the percentage of body fat (23.1 (11.0) % and 26.0 (10.7) %, respectively). Their SD was very large, likely due to the analysis of both genders combined, and therefore any potential differences most likely could not have been detected. Uthaya et al. (2005) reported a significant decrease in subcutaneous adipose tissue and an increase in intra-abdominal adiposity in 38 VPT infants assessed at term by means of magnetic resonance imaging. Adair (2007) reported that birth mass and length were inversely associated with the subscapular to triceps ratio in males only.

In contrast to the above, some studies found that body fat amount in PT infants is similar to that of FT infants. For example, Rawlings et al. (1999) studied 125 PT LBW infants with DEXA scans at corrected age of 12 months and taking into account their gender, and they observed that PT infants had similar fat mass and body fat percentage than FT controls.

It has been reported that during puberty lean body mass increases for approximately 50 %, with the highest increase in muscle mass for approximately 120 % (Molnar, 2005). In the present study we demonstrated that lean body mass was similar in PT and FT individuals. However, it was lower ($p<0.05$) in VPT males than in MPT and FT peers from 8 to 16 years and also lower ($p<0.05$) in VPT females than in MPT and FT peers after the age of 15 years (Annex Y, Figure 31).

In line with our findings, Peralta-Carcelen et al. (2000) observed lower lean body mass in 53 ELBW VPT individuals at the age of 15, with both genders combined. If we look at younger individuals, Rawlings et al. (1999) found that during the first year of life, infants born before the 34^{th} week of gestation had lower amount of lean body mass than FT infants. Also, meta-analysis of Johnson et al. (2012) demonstrated that PT infants at term had much less lean body mass than FT infants. Hovi et al. (2007) reported lower lean body mass in 163 adult VLBW subjects (18 to 27 years of age) than in their FT peers. Also, in SGA infants of 2 to 47 months of age, the discrepancies in mass between SGA and infants with AGA were primarily attributable to differences in lean body mass (muscularity), with fat tissue being less affected (Hediger et al., 1998).

Singhal et al. (2003) suggested that fetal programming of lean body mass amount can present a link between the birth mass and lean body mass in adolescence, but not between birth mass and fat tissue mass. The associations between birth mass and muscle mass later in life has also been reported by others (te Velde et al., 2004). It is worth noting that less lean tissue mass has immediate implication in terms of functional reserve and susceptibility to illnesses and has far-reaching consequences for health in later life (Johnson et al., 2012). In a young population, birth mass is indeed associated with lean body mass, diastolic blood pressure, total cholesterol, the ratio between total cholesterol, serum HDL concentrations, and bone mineral content (te Velde et al., 2004).

The findings from Euser et al. (2005) support the connection between preterm birth and increased risk of metabolic imbalance and complications, including glucose intolerance, in PT children and young adults (Daly-Wolfe, 2012), as increased intra-abdominal adiposity may be the main cause of illness severity (Uthaya et al., 2005). Evidence of causal pathways linking accelerated postnatal growth with increased total and subcutaneous adiposity, and illness severity with altered adipose tissue exists, so the associations between small size at birth and later disease could exist (Uthaya et al., 2005). Fat mass and fat distribution affect reproductive function and present risks of disordered metabolism (Wells J.C.K. et al., 2007). It has been speculated (i.e. “thrifty phenotype hypothesis”) that in LBW children, alterations of body composition may be a key factor in increasing the susceptibility to a diabetogenic environment, although the mechanisms leading to the metabolic reprogramming are not clear yet (Tappy, 2006).

Body composition in childhood (with an emphasis on the quantity of adipose tissue) has also been proposed to affect the functioning of endocrine glands in adulthood (Rutter and Hull, 1979). Early growth patterns may thus induce long-term effects on body composition, e.g. by impacting the hormonal pathways that in turn regulate childhood growth (Wells J.C.K. et al., 2007). In addition, as mentioned before, greater amount of fat tissue or its different distribution in the body can cause larger or earlier synthesis of sex hormones, which can, in turn, lead to earlier maturation (de Ridder et al., 1990, 1992). As PT individuals seem to have more abdominal fat distribution, this could also lead to pronounced and earlier sex hormone synthesis, which could explain earlier sexual maturation of PT individuals and younger age at reaching their final height, which could be a direct cause for adult PT individuals being smaller than FT peers.

5.6 GENERAL DISCUSSION AND FURTHER RECOMMENTADIONS

Our results demonstrated that physical characteristics of mothers influence their child growth patterns during the first year of life, therefore we would recommend that women should wait with conception until they have achieved a normal mass to improve their pregnancy outcome and should also during pregnancy be attentive on their pregnancy-associated body mass changes.

We proved that the existing methodology to assess anthropometric characteristics of pregnant women is rather questionable. It is recommended to have in mind all the possible limitations of the existing equations when assessing the body composition of pregnant women or, even more recommended, to consider not using the equations for evaluation of body fat percentage. By comparing the raw anthropometric data (skinfold thicknesses, circumferences, body mass) the inaccuracies of equations can be avoided.

We also demonstrated that selected differences in physical characteristics of FT and PT individuals from childhood up to early adulthood exist. PT, especially VPT and female, individuals were smaller, lighter, tended to have higher BMI, higher amount of subcutaneous fat tissue, less lean body mass, and worse performance of aerobic and aerobic physical exercise tests than their FT peers. However, agility and fine motor tests were performed better by PT individuals up to their puberty, which seemed to occur earlier (especially in females) than in FT individuals. This indicates the potential of PT individuals to show comparable or even better results in certain aspects of motor development than their FT peers. In this light, we would recommend to parents to encourage their children in sports activities in order to exploit their full potential in development, which appears to be present in spite of their prematurity.

In future, Slovenian perinatal database and SLOfit system data should systematically be connected in one database to gather the information on prematurity status of all children in our schools. With such a combined databases we could avoid the problems with small sample size and come to even firmer and more informative conclusions.

These results provided a meaningful and broad insight into the processes of growth and physical development of PT individuals. We therefore believe that the results of the present doctoral thesis will be useful for further research in auxology and neonatology. Finally, in the view of increasingly alarming data on body mass and obesity (in 1997 the WHO declared obesity as an epidemic of modern time), our results can also be used to work preventively against abdominal obesity and, in particular, CV disorders in adulthood.

6 CONCLUSION

Based on the results of our research we came to the following conclusions:

- The currently existing anthropometric methods are not reliable for the estimation of body fat percentage (BFP) of pregnant women, as their results vary by 22 units, depending on the method used.

- Maternal pre-pregnancy mass, pre-pregnancy body mass index (BMI), pregnancy mass gain (PMG), and the appropriateness of maternal PMG according to her pre-pregnancy BMI affect the growth of an infant during the first year of life, as high values of these maternal parameters diminish relative increases of infants body height, mass, BMI, skinfold thicknesses and BFP.

- The majority of previously reported risk factors for preterm (PT) birth were also the cause for PT (especially for very PT (VPT)) birth in our sample; these are multifetal pregnancy, illnesses and bleeding during pregnancy, smoking, preterm birth and stillbirth in previous pregnancies, and maternal age at delivery less than 21 and more than 35 years.

- The majority of illnesses and applied interventions at birth and in childhood are more often in PT, especially in VPT children, as compared to their FT peers, except for infections, which are more often in moderately PT (MPT) and FT infants; after birth and during childhood, neurological and motor development is also worse in PT than in FT infants.

- Body height increases faster in the first years of life in VPT individuals, as compared to their FT peers, but stays hindered in VPT males up to 17 years of age and in VPT females into the adulthood. Body mass and BMI are lower in PT (especially in VPT) than in FT individuals up to 13 years of age, later on body mass remains lower in VPT females; however, BMI of VPT females is higher than in their FT peers at 16 years of age.

- FT individuals perform aerobic general endurance test and the majority of anaerobic tests (sprint speed, explosive power, and trunk muscle strength) better than PT individuals; the exception is muscular endurance of the shoulder girdle and arms, which was better in VPT males. Just before puberty, PT females perform the agility and fine motor tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) better than their FT peers, which

may be related to earlier sexual maturation of VPT females; however, PT males perform the same tests worse than their FT peers.

- VPT females experience peak height velocity approximately 5 months earlier than their FT peers and the same trend is present for the onset of menarche, which is observed approximately 10 months earlier in VPT females. No similar differences related to sexual maturation were observed in males.

- After puberty, VPT males have lower triceps skinfold thickness, fat mass, and calculated BFP than their FT peers. In females, however, triceps skinfold thickness and BFP are higher in PT than in FT peers after puberty.

- Lean body mass is similar in PT and FT individuals during schooling; however, it is lower in VPT individuals than in MPT and FT peers after the age of 8 years.

7 SUMMARY

7.1 SUMMARY

Preterm birth (PT; <37th weeks gestation) and low birth mass may impair growth and development, increase prenatal, childhood, and adult morbidity and mortality, and affect physical characteristics later on in life. Full-term (FT) and PT infants may have different patterns of growth, as the period of accelerated (catch-up) growth may be incomplete in PT individuals. Disproportional changes in height and mass may modify body composition in childhood (e.g. result in higher abdominal fat accumulation especially in females), which has been proposed to affect the functioning of endocrine glands in adulthood. Increased amount of body fat or its distribution seems to induce earlier appearance of pubertal components (e.g. age at pubertal growth spurt, peak height velocity (PHV), the onset of sexual maturity), as the production of sex hormones results from fat metabolism pathways. Prenatal development and early childhood therefore seem to be the critical periods for child's growth and development, since the long-term regulation of energy metabolism is still being established in this period.

In addition, physical characteristics of pregnant women and their infants are undoubtedly related to a certain extent; therefore some studies used an anthropometrical approach in pregnancy to evaluate different prenatal effects on child growth and morbidity. The problem is, however, that the majority of mathematical equations for the evaluation of body composition have been developed for use on men or non-pregnant women. Equations for pregnant women are rare and often neglect the specificity of tissue composition in pregnancy, which can lead to inconsistent results. In the view of increasingly alarming data on body mass and obesity, the evaluation of existing anthropometric methods is therefore crucial to enable reliable body composition assessment, which can in turn be used to work preventively against abdominal obesity and, in particular, cardiovascular disorders in adulthood.

We hypothesized that the existing anthropometric methods are inadequate for assessing body composition in pregnant women (H_W1); that the pattern of growth of FT and PT infants during the first year of life depends on anthropometric characteristics of mothers (H_W2); that the susceptibility and frequency of illnesses after the period of accelerated growth is different between PT and FT children (H_W3, H_W4); that the potential consequences of prematurity (lower height, mass, and capacity of physical exercise) will be detected after childhood (H_W5); and that distribution of body fat will be different in PT and FT individuals (H_W6). To test these hypotheses, we extended systematic monitoring of physical and motor development of children and adolescents in Slovenia into a combination of prospective and retrospective study, general entitled “Preterms 1987”. The study gained approval from the Slovenian Ethics Committee.

(H_W1) Anthropometric measurements were performed on 147 healthy pregnant women of approximately 31 years of age and 32 weeks of gestation, enrolled into the study "My Milk". Their body height (MBH), mass, three body circumferences, and six skinfold thicknesses were obtained. Measurements were used in five different anthropometric equations for the estimation of body density, and twelve equations for the estimation of body fat percentage. The results varied remarkable, statistically and meaningfully, from 16 % to 38 % of body fat for the same sample, depending on the method used. Pregnancy non-specific methods resulted in body fat estimates between 27 % and 38 %, and pregnancy specific methods in body fat estimates between 16 % and 30 %.

(H_W2) Infants (N=154) were classified according to maternal MBH, pre-pregnancy mass (PpBM), pre-pregnancy body mass index (PpBMI), pregnancy mass gain (PMG), and appropriateness of PMG determined relative to the recommended values according to maternal PpBMI (RV/PpBMI). Their body height, mass, four circumferences, and three skinfold thicknesses from birth up to 12 months of age were measured, and relative increases of the measurements were compared. In female infants, relative increase in body height was diminished by higher maternal PpBM. Relative increases in infants' body mass were diminished by higher maternal PpBMI, RV/PpBMI, and in males also by higher PMG, however, in females higher MBH enlarged their relative increase in body mass. Relative increases in BMI were diminished by higher maternal PpBMI and PMG in male infants and by higher RV/PpBMI in female infants. In females, higher maternal PpBMI diminished relative increases in skinfold thicknesses and body fat percentage; however, higher maternal PpBM and PpBMI enlarged relative increases in infants' circumferences. Additionally, 474 infants were classified as very PT (VPT; $<32^{nd}$ week of gestation), moderately PT (MPT; 32^{nd} to 36^{th} week of gestation), or FT group. The identified risk factors for PT (especially for VPT) birth were: multiple births, illnesses and bleeding during pregnancy, smoking, PT birth and stillbirth history, higher education of mothers, and maternal age of less than 21 and more than 35 years.

(H_W3, H_W4) Data from 474 participants were obtained from the Slovenian perinatal database, a part of the individual's medical records, at laboratory visits, and with a questionnaire of the now 26-year-old persons. Blood pressure, frequencies of wearing glasses, and injuries experienced provided similar results between PT and FT group. The injuries of joints were more often in PT than in FT individuals. Additionally, at birth and in childhood more VPT infants experienced health problems, as compared to FT, with the exception of upper respiratory tract and ear infections, which were more often in MPT and FT infants. The latter was probably due to earlier inclusion of FT in kindergartens. During the first 2 years of life, the indicators of mental health and development were worse in PT (especially in VPT) infants, as compared to FT infants.

(H_W5) When it comes to physical characteristics, body height was lower in PT than in FT males up to 2 years of age. In addition, VPT males were shorter than their peers up to 17 years of age and in VPT females the same difference persisted into the adulthood. Body mass and BMI were lower in PT (especially in VPT) than in FT individuals up to 13 years of age. VPT females had a lower body mass and a higher BMI than FT peers also at 16 and 17 years of age. Aerobic general endurance test was performed better in PT than in FT males at 14 years; however, VPT females had worse endurance than their peers. Anaerobic tests (sprint speed, explosive power, and trunk muscle strength) were mostly performed worse by PT than by FT individuals; the exception was muscular endurance of the shoulder girdle and arms, which was better in VPT males. Agility and fine motor tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) were performed better in PT females up to puberty; however, PT males performed the same tests worse than their FT peers. Additionally, VPT females experienced PHV and, as it seems, menarche earlier (5 and 10 months, respectively) than their peers; no similar differences were observed in males. It is thus earlier maturation that could explain the observed good physical performance of PT females in the period, in which their FT peers have not yet reached puberty.

(H_W6) Triceps skinfold thickness and percentage of body fat were lowest in VPT males at 9, 12, and 17 years of age, and the highest in MPT males at 9 and 10 years of age. In females, the same two parameters were higher in PT (especially in VPT) than in FT peers after the age of 15 years. Lean body mass was lower in VPT individuals than in their peers after the age of 8 years. Body fat mass was lower in VPT males than in their peers between 8 and 13 years of age, and higher in PT females than in FT peers at 16 years of age.

Our results clarified that the child growth patterns during the first year of life are influenced by the physical characteristics of their mothers and also that the existing methodology currently available to assess anthropometric characteristics of pregnant women is rather questionable. Furthermore, the research work clearly identified selected differences in physical characteristics of FT and PT individuals from childhood up to early adulthood, which provided a meaningful and broad insight into the processes of growth and physical development of PT individuals. On the basis of our results, we have thus accepted the working hypotheses (H_W1) and (H_W2), as well as the selected issues of hypothesis (H_W5). According to our knowledge, the present study is likely the most extensive longitudinal study in the research field of growth and development of PT infants. We therefore believe that the results of the present doctoral thesis will be useful for further research in auxology and neonatology.

7.2 POVZETEK

Prezgodnji porod (pred 37. gestacijskim tednom, šteto od prvega dne zadnje menstruacije) in nizka porodna masa oslabita rast in razvoj, povečata tveganje za prenatalno obolevnost in umrljivost v otroštvu ter predvidoma povečata tveganje za bolezni v odrasli dobi. Epidemiološke študije iz razvitih držav so pokazale neposredno povezavo med obrojstnimi merami in telesnimi značilnostmi ljudi kasneje v življenju (npr. med porodno dolžino in odraslo višino). Donošeni (FT) in nedonošeni (PT) dojenčki imajo različne vzorce rasti. Pri PT otrocih je za zgodnje obdobje po rojstvu skoraj vedno značilna počasna rast, temu obdobju pa pri večini sledi obdobje pospešene rasti (oz. tako imenovana catch-up rast), s katero lahko nadoknadijo zamujeno in dohitijo vrstnike. Vendar je ta rast pri PT otrocih pogosto nepopolna in zato lahko ostanejo nižji in lažji od njihovih vrstnikov v otroštvu, adolescenci in celo v odrasli dobi. Čeprav je obdobje pospešene rasti nedvomno koristno za razvoj živčnega sistema, pa domnevajo, da je povezano tudi z neželenimi metabolnimi tveganji pri odraslih (denimo z debelostjo, diabetesom tipa 2, povišanim krvnim tlakom in tveganjem za bolezni srca in ožilja). Namreč, nesorazmerne spremembe v višini in masi, ki jih včasih lahko opazimo pri PT otrocih (pri čemer je povečevanje mase pogosto hitrejše od povečevanja telesne višine), lahko spremenijo sestavo telesa (pri čemer predvidoma lahko pride do večjega kopičenja maščobnega tkiva na trebuhu, v primerjavi z okončinami, kar je zlasti izrazito pri dekletih), kar posledično predvidoma lahko vpliva na delovanje endokrinih žlez v odraslosti. Povečana količina telesne maščobe ali njena spremenjena razporeditev bi torej lahko povzročili zgodnejše pojavljanje komponent pubertetne rasti (denimo starosti ob začetku in vrhu pubertetnega rastnega sunka, največji hitrosti rasti (PHV) ter spolni zrelosti). Proizvodnja spolnih hormonov namreč poteka po poteh maščobnega metabolizma in zato bi večja količina maščobnega tkiva ali njegova drugačna porazdelitev v telesu predvidoma lahko povzročila večjo ali zgodnejšo sintezo spolnih hormonov, kar bi posledično vodilo v zgodnejše spolno dozorevanje. Očitno je torej, da sta tako prenatalni razvoj, kot zgodnje otroštvo, kritični obdobji za otrokovo nadaljnjo rast in razvoj, saj se dolgoročna regulacija energijskega metabolizma takrat še vedno vzpostavlja.

Zgoraj predstavljena dejstva razkrivajo nujnost novih raziskav na tem področju, zlasti v luči vedno bolj zaskrbljujočih podatkov o neustrezni telesni masi posameznikov; v letu 1997 je namreč Svetovna zdravstvena organizacija debelost razglasila za epidemijo sodobnega časa. Z rednim spremljanjem in ovrednotenjem zgodnjih kazalcev odraslih telesnih značilnosti bi predvidoma lahko delovali preventivno proti negativnim posledicam prezgodnjega rojstva in torej potencialno tudi proti trebušni debelosti ter nekaterim srčno-žilnim (CV) in kostno-mišičnim boleznim v odrasli dobi.

Znano je, da telesne značilnosti nosečnic (denimo telesna višina, masa in sestava telesa) lahko napovedujejo nekatere od telesnih značilnosti njihovih otrok ob rojstvu in deloma tudi kasneje v življenju. Študije, ki so se do sedaj ukvarjale z antropometrijo nosečnic, so bile večinoma izvedene na majhnih ali izbranih vzorcih, rezultati pridobljeni na večjih vzorcih pa so bili največkrat pridobljeni zgolj z vprašalniki, zato so ti podatki lahko precej netočni ali, v najslabšem primeru, nepravilni. Istočasno bolj prefinjene metode za določanje sestave telesa (na primer ultrazvočna diagnostika, bioelektrična impedanca, metoda absorpcije in odboja infrardeče svetlobe) zahtevajo uporabo okorne, drage in zato pogosto nedostopne opreme, nekatere sicer zanesljive metode pa so lahko tudi nevarne za plod. Nadalje, večina danes obstoječih matematičnih enačb za oceno sestave telesa je bila razvitih s pomočjo antropometričnih meritev, opravljenih na moških ali ne-nosečih ženskah, in le nekaj avtorjev je antropometrično metodologijo dejansko prilagodilo uporabi na nosečnicah. Poleg tega obstoječa metodologija za določanje sestave telesa pri nosečnicah pogosto zanemarja specifičnost sestave tkiv med nosečnostjo, zato obstaja precejšnja verjetnost, da lahko različni metodološki pristopi vodijo do precej različnih raziskovalnih zaključkov. Ovrednotenje in optimizacija obstoječih antropometričnih metod sta zato ključnega pomena za zanesljivo oceno povezav med morfološkimi značilnostmi staršev in njihovih otrok ter za njihovo nadaljnjo interpretacijo.

Raziskave sledenja FT in PT otrok od rojstva do zgodnje odrasle dobe so zelo redke. Takšne študije namreč longitudinalno sledijo istim ljudem, kar je logistično težavno, saj zahteva pripravljenost preiskovancev in raziskovalcev, da neprekinjeno sodelujejo oz. dosledno delajo v zelo dolgem časovnem obdobju. Vzorec preiskovancev se s časom posledično neizogibno zmanjšuje, kar vpliva na kakovost raziskovalnih zaključkov. Zaradi predanega dela raziskovalcev, ki delujejo na področju neonatologije, in zaradi sistematičnega spremljanja telesnega in gibalnega razvoja otrok in mladostnikov v Sloveniji, smo imeli edinstveno priložnost za razširitev obstoječih podatkov v kombinacijo prospektivne in retrospektivne raziskave, ki smo jo poimenovali "Nedonošenčki 1987". Soglasje za izvedbo raziskave smo pred začetkom raziskave pridobili od Komisije Republike Slovenije za medicinsko etiko (Št. 64/07/2011).

V naši raziskavi smo predpostavili, da so obstoječe antropometrične metode neustrezne za oceno sestave telesa pri nosečnicah ter da bodo za nosečnice prilagojene antropometrične metode pokazale precej podobne rezultate sestave telesa, medtem ko se bodo rezultati antropometričnih metod prilagojenih za ne-nosečnice znatno razlikovali od za nosečnice prilagojenih metod (H_W1); da je vzorec rasti FT in PT dojenčkov v prvem letu življenja odvisen od antropometričnih značilnosti mater (H_W2), da se dovzetnost za bolezni po obdobju pospešene rasti razlikuje med FT in PT otroki in da se pogostost bolezni razlikuje med VPT (zelo nedonošeni - rojeni pred 32. tednom

nosečnosti) in MPT (zmerno nedonošeni - rojeni med 32. in 36. tednom nosečnosti) otroki (H_W3, H_W4); da bomo morebitne posledice prezgodnjega rojstva, kot so nižja telesna višina, manjša masa in manjša zmogljivost za telesno vadbo, zaznali tudi v poznem otroštvu in mladostništvu (H_W5), ter da se porazdelitev telesne maščobe razlikuje med FT in PT otroki (H_W6).

(H_W1) Za testiranje prve hipoteze smo uporabili prospektiven pristop k antropometričnim meritvam, ki smo jih opravili na 147 zdravih nosečnicah povprečne starosti 31 let in povprečno v 32. gestacijskem tednu nosečnosti, ki so bile vključene v študijo "Moje mleko". Od preiskovank smo pridobili podatke o točnem tednu nosečnosti, telesni višini (MBH), masi, obsegih zapestja, nadlahti in stegna, ter debelini kožnih gub na tricepsu, bicepsu, pod lopatico, nad grebenom črevnice, na sprednji strani stegna in na notranji strani goleni. Izbrane antropometrične meritve smo uporabili v dvanajstih neposrednih in posrednih antropometričnih enačbah razvitih za oceno sestave telesa žensk v srednjih letih. Kjer je bilo potrebno, smo gostoto telesa najprej izračunali po petih različnih enačbah.

Ocene za odstotek telesne maščobe za isti vzorec nosečnic so variirale tako statistično kot pomensko glede na enačbo, ki smo jo uporabili. Ocene telesnega maščevja so se tako za isti vzorec preiskovank razvrstile v razpon od 16 % do 38 % telesne maščobe, odvisno od uporabljene metode. Za ne-nosečnice prilagojene neposredne antropometrične metode so pokazale vsebnost telesne maščobe med 28 % in 38 %, posredne metode pa med 27 % in 34 %, odvisno od izbrane metode za izračun gostote telesa. Za nosečnice prilagojena neposredna metoda je pokazala 36 % vsebnosti telesne maščobe, posredni antropometrični metodi pa med 16 % in 30 %, spet odvisno od izbrane metode za izračun gostote telesa. Te razlike v ocenah telesne sestave so bile prisotne ne glede na postavo žensk, saj so bili razponi vrednosti za odstotek telesne maščobe 23, 23 in 24 enot za ženske z nizkim, normalnim, in visokim prednosečniškim indeksom telesne mase (PpBMI).

(H_W2) Za testiranje druge hipoteze smo uporabili prospektiven pristop k antropometričnim meritvam, ki smo jih opravili na dojenčkih prej omenjenih nosečnic. Po porodu smo dodatno pridobili podatke o materini prednosečniški (PpBM) masi ter podatke o dojenčkovi porodni masi, višini in obsegu glave. En, tri in dvanajst mesecev po rojstvu smo navedene antropometrične meritve ponovili, dodatno pa smo v starosti 1 in 12 mesecev pri dojenčkih izmerili tudi tri obsege in tri debeline kožnih gub. Iz podatkov smo izračunali odstotek telesne maščobe. Dojenčke smo razvrstili glede na materino MBH, PpBM, PpBMI, pridobljeno maso med nosečnostjo (PMG) (mejne vrednosti za navedene spremenljivke so bile postavljene na 168 cm, 62 kg, 25 kg/m^2 in 16 kg) in ustreznost materine PMG glede na PpBMI (razmejitvene meje so prikazane v

Tabeli 4; RV/PpBMI). Nato smo primerjali relativne prirastke spremenljivk med posameznimi časovnimi točkami meritev.

Relativni prirastek telesne višine deklic od rojstva do starosti enega meseca starosti je pomembno zavirala materina višja PpBM, vendar pa nanj v prvem letu življenja niso vplivale druge materine antropometrične značilnosti. Pri dečkih na relativni prirastek telesne višine od rojstva do starosti 12 mesecev ni vplivala nobena od materinih telesnih značilnosti. Višja materina PpBMI in RV/PpBMI sta pomembno zavirala relativni prirastek telesne mase dečkov od rojstva do starosti enega meseca. Od rojstva do starosti treh mesecev se je relativni prirastek telesne mase nagibal k nižjim vrednostim pri dečkih mater z višjo PMG in RV/PpBMI. Relativni prirastek telesne mase deklic od rojstva do starosti treh mesecev je povečala višja materina MBH, od rojstva do starosti enega meseca pa zavirala materina PpBMI in RV/PpBMI. Relativni prirastek BMI-ja dečkov od rojstva do starosti enega meseca je zaviral višji materin PpBMI, do 12 mesecev pa zavirala višja materina PMG. Pri deklicah je povišana RV/PpBMI zavirala relativni prirastek dojenčkovega BMI-ja od rojstva do starosti treh mesecev. Višja materina PpBM je pomembno povečala relativni prirastek obsega glave deklic od rojstva do starosti 12 mesecev. Opazili smo trend, da je pri dečkih večja materina MBH zavirala relativni prirastek obsega nadlakti v starosti od enega do 12 mesecev. Relativni prirastek obsega nadlakti je bil bistveno večji pri deklicah mater z višjim PpBMI-jem. Antropometrični parametri mater niso vplivali na relativna prirastka obsegov zapestja in prsnega koša v starosti od nega do 12 mesecev. Na relativni prirastek v debelini podlopatične kožne gube dojenčkov v starosti od enega do 12 mesecev ni vplival noben materin antropometrični parameter. Pri dečkih na relativne prirastke tricepsne, sprednje stegenske kožne gube in odstotka telesne maščobe v starosti od enega do 12 mesecev prav tako ni vplival noben materin antropometrični parameter, pri deklicah pa je višji materin PpBMI povzročil manjše prirastke teh dveh kožnih gub in odstotka telesne maščobe.

Poleg navedenega smo analizirali tudi dejavnike tveganja za prezgodnji porod. V ta namen smo uporabili retrospektivni pristop za obdelavo podatkov iz slovenske perinatalne baze, pridobljenih iz dokumentov študije "Prvotna raziskava 1987" Enote za intenzivno nego novorojenčkov, Kliničnega oddelka za perinatologijo, Porodnišnice Univerzitetnega kliničnega centra, Ljubljana. Perinatalna baza je sistem za dokumentiranje rojstnih podatkov (denimo porodne dolžine, mase in obsega glave) vseh novorojenčkov v Sloveniji in se uporablja po vseh slovenskih porodnišnicah.

474 novorojenčkov smo tako razvrstili v skupine VPT, MPT in FT. Močni materini dejavniki tveganja za prezgodnja rojstva so bili: mnogoplodna nosečnost, bolezni in krvavitve v nosečnosti (bolj pogosto pri VPT kot pri MPT), kajenje, nedonošenčki in

mrtvorojeni v predhodnih nosečnostih, višja izobrazba matere in starost nosečnice pod 21 in nad 35 let (velja predvsem za VPT). Ostali analizirani dejavniki tveganja za prezgodnji porod (zakonski stan, prednosečniške bolezni in splavi v predhodnih nosečnostih) so imeli podobno pojavnost v vseh skupinah.

(H_W3, H_W4) Za testiranje tretje in četrte hipoteze smo raziskovalne podatke preiskovancev pridobili iz slovenske perinatalne baze, iz dela osebnih zdravstvenih kartotek, če so bili na voljo, in s spletnim vprašalnikom za preiskovance v starosti 26 let. Osebni zdravstveni kartoni se hranijo pri osebnih zdravnikih in so sestavljeni iz podatkov, zapisanih na rednih sistematskih pregledih, ki se izvajajo v predšolskem in osnovnošolskem obdobju. V "Prvotno raziskavo 1987" je bilo vključenih 474 oseb. Skoraj vsi PT dojenčki so bili dvojčki ali trojčki. Šest od začetnih udeležencev je umrlo v času študije, 19 se jih je preselilo iz Slovenije, za 70 začetnih udeležencev pa po letu 1990 študijska dokumentacija iz laboratorijskih obiskov ni bila več dosegljiva; te osebe so bile zato izključene iz naše študije. Pri starosti 26 let se je 86 oseb od prvotnih udeležencev s podpisom soglasja za sodelovanje v raziskavi ponovno vključilo v študijo "Nedonošenčki 1987", dve osebi sta sodelovanje zavrnili.

Med skupinami VPT, MPT in FT ni bilo statistično značilnih razlik v krvnem tlaku, izmerjenem v sedečem položaju zjutraj, na levi nadlahti, pri preiskovancih doma ali med laboratorijskim obiskom. V starosti 26 let so bile CV bolezni praktično odstotne pri vseh udeležencih, ki so izpolnili vprašalnik. Ni bilo razlik med skupinami v nošenju očal ali drugih zdravstvenih pripomočkov, zdravljenja in bolezni so bili redki in nobena od obstoječih zdravstvenih težav ni pokazala razlik med PT in FT ali med VPT in MPT preiskovanci. Frekvence izbranih poškodb v otroštvu, mladosti in odraslosti so bile podobne v vseh treh študijskih skupinah, razen poškodb sklepov, ki so jih PT posamezniki izkusili pogosteje kot njihovi FT vrstniki.

Analizirali smo tudi pogostost bolezni ob rojstvu in v predšolskih letih. Številne bolezni so bile zabeležene pri PT dojenčkih ob rojstvu, saj so se skoraj vsi (98 %) VPT in 69 % MPT, vendar le 56 % FT dojenčkov rodili z vsaj eno boleznijo ali zdravstveno težavo. Več PT kot FT dojenčkov je doživelo dihalno stisko, apnejo, hiperbilirubinemijo (vzrok za zlatenico), okužbe, možgansko krvavitev ali hipoksijo. Nasprotno, več FT kot PT dojenčkov je doživelo distocijo. Nekrotizirajoči enterokolitis, periventrikularna levkomalacija, hipoglikemija, črevesne, srčna in ledvične anomalije in kozmetične napake so bili redki v študijskih skupinah. Podobno so bili bolj pogosti uporaba reanimacijske maske, ototoksična zdravila, umetna ventilacija, dodajanje kisika, transfuzija in izmenjalna transfuzija pri VPT in MPT, kot pri FT dojenčkih. Krvna anemija in pljučnica sta bili pogostejši pri VPT in MPT, kot pri FT dojenčkih v starosti 1 leta, rahitis je imel podobno pojavnost med študijskimi skupinami v starosti 1 in 2 let,

medtem ko so okužbe zgornjih dihalnih poti in otitis bili bolj pogosti pri FT, kot pri PT dojenčkih v starosti 2 in 3 let. Zadnje je bilo predvidoma opaženo zaradi zgodnejšega vpisa MPT in FT otrok v vrtec (pri 2,4 (1,5) in 2,6 (1,5) letih), v primerjavi z VPT otroci (pri 3,5 (1,8) letih) in s tem zgodnejše izpostavljenosti nalezljivim boleznim. Druge bolezni, kot vročinski krči, epilepsija, druge otroške nalezljive bolezni in simptomi, prirojene črevesne bolezni (hernije, druge malformacije), genitalne bolezni (nespuščena moda, zožena kožica, hipospadija), mišičnoskeletne bolezni (malformacije okončin in stopalnega loka), malformacije srca, kože in sluznice ter cistična bolezen ledvic so bile preredke za analizo. Prevladujoče kronične bolezni so bile alergije (npr. alergija na hrano, zdravila, nevrodermatitis), ki so bile enakomerno zastopane v vseh skupinah. Rezultati razvojnih kazalnikov kot sta Apgar test po 1 in 5 minutah po rojstvu in nekorigirani razvojni količnik so bili precej slabši pri PT (zlasti VPT) kot pri FT dojenčkih v starosti 1 in 2 let. Denverski razvojni presejalni test je bil bolj uspešen pri FT kot pri PT dojenčkih v starosti 1 leta in bolj pogosto ovrednoten kot »vprašljiv« pri VPT dojenčkih. Večino razlik med PT in FT dojenčkih smo opazili v fini in grobi motorični zmogljivosti. Duševno zdravi dojenčki so bolj pogosto pripadali skupini FT dojenčkov, »še rizični« dojenčki so bili bolj pogosti v PT (še posebej VPT) skupini, medtem ko so »lažje« ali »težje prizadeti« dojenčki bili redki v vseh študijskih skupinah. Slabovidnost v otroštvu je bila bolj pogosto zabeležena v PT, kot pri FT skupini pri starosti 2 let, pogostost nošenja očal pri 11 letih pa je bila pogostejša pri VPT in MPT, kot pri FT otrocih, kar je v nasprotju s samoporočanjem pri starosti 26 let. Okvare sluha so bile redke v vseh študijskih skupinah.

(H_W5) Za testiranje pete hipoteze smo raziskovalne podatke retrospektivno pridobili iz slovenske perinatalne baze, iz sistema športno-vzgojnih kartonov (SLOfit sistem), iz dela osebnih zdravstvenih kartonov, ter prospektivno s spletnim vprašalnikom in na laboratorijskih obiskih pri starosti preiskovancev 26 let. SLOfit sistem je bil zasnovan za sistematično vsakoletno spremljanje telesnega in gibalnega razvoja otrok v osnovnih in srednjih šolah (v starosti od 6 do 19 let) v Sloveniji in zagotavlja celovit vpogled v motorični razvoj posameznikov in populacije. Podatki SLOfit sistema so bili na voljo za približno 65 % naših preiskovancev.

Telesna višina pri PT moških je bila precej nižja kot pri FT posameznikih do starosti 2 let. Vendar so bili VPT bistveno nižji kot MPT in FT posamezniki tudi do starosti 13 let ter med 15 in 17 letom, podoben trend pa je bilo opaziti tudi pri starosti 14 in 19 let. Pri ženskah se je razlika v telesni višini med PT in FT posamezniki nadaljevala v odraslost, predvsem zaradi velikih razlik med VPT ženskami v primerjavi z njihovimi MPT in FT vrstnicami. Relativni prirastek v telesni višini dokazuje, da PT (zlasti VPT) posamezniki rastejo hitreje kot njihovi vrstniki do starosti 12 let, VPT moški tudi med 13 in 18 letom. VPT ženske dosežejo svojo končno telesno višino prej, kot MPT in FT vrstnice.

Telesna masa pri PT moških je bila statistično manjša kot pri FT posameznikih od rojstva do 2 let, VPT pa so bili lažji od MPT in FT posameznikov tudi med 8 in 13 letom. Pri ženskah je podobna razlika v telesni masi med PT in FT posameznicami vztrajala od rojstva do 3 let, VPT ženske pa so bile lažje od MPT in FT vrstnic tudi pri 16 in 17 letih. Podobno kot pri telesni masi, je bil tudi BMI pri PT precej nižji, kot pri FT posameznikih od rojstva do 2 let starosti pri obeh spolih, z najnižjimi vrednostmi pri VPT posameznikih. VPT moški so imeli nižji BMI, kot njihovi vrstniki pri starosti 9 in 11 let, in nižjega kot MPT pri 10 in 12 letih, PT ženske pa so pri starosti 16 let imele višji BMI, kot FT vrstnice.

PT imajo višji PHV kot FT posamezniki in to ne glede na to, ali upoštevamo korigirano ali nekorigirano starost. VPT ženske dosežejo PHV pet mesecev prej, kot MPT in FT ženske (nekorigirano pri 11,1 (0,6), 11.5 (1.2) in 11,4 (1,0) letih), med VPT, MPT in FT moškimi pa ni bilo statistično značilnih razlik v starosti ob PHV (nekorigirano pri 13,6 (1,4), 13,6 (0,9) in 13,4 (1,1) letih). Čeprav je bil vzorec VPT žensk (N=5) premajhen za dokončne sklepe, so se rezultati upoštevajoč nekorigirano starost nagibali v smer, da VPT ženske menarho (prvo menstruacijo) doživijo deset mesecev prej kot njihove MPT in FT vrstnice. Ob upoštevanju korigirane starosti, je bil ta trend še močnejši (12,0 (1,3) let, 12,8 (1,3) in 12,8 (1,3) let).

Če pogledamo zmogljivost za telesno vadbo, so bili rezultati aerobnega SLOfit testa splošne vzdržljivosti (teka na 600 m) podobni pri VPT, MPT, in FT moških, razen pri starosti 14 let, ko so PT moški tekli hitreje kot njihovi FT vrstniki (146,4 (20,9) s in 155,6 (28,6) s). VPT ženske so bile počasnejše od svojih MPT in FT vrstnic pri starostih 8, 15, 17, in 19 let. Rezultati anaerobnih SLOfit testov so bili večinoma slabši pri PT, kot pri FT posameznikih. Hitrost sprinta (tek na 60 m) je bila nižja pri PT, kot pri FT moških v starosti od 10 do 12 let. PT ženske so bile pri starosti 9 let statistično počasnejše, pri tem so bile VPT ženske počasneje, kot njihove MPT in FT vrstnice pri starosti 8 in od 17 do 19 let. Eksplozivna moč (skok v daljino z mesta) je bila bistveno slabša pri PT moških, kot pri njihovih FT vrstnikih v starosti od 8 do 13 let in pri 15 in 17 letih (z najnižjimi vrednostmi pri VPT posameznikih pri 11 letih). Pri ženskah je bila enaka razlika prisotna pri starostih 9, 11, 15 in 19 let, z najnižjimi vrednostmi pri VPT posameznicah pri 19 letih. Moč mišic trupa (dvigi trupa iz ležečega v sedeči položaj) je bila večja pri FT v primerjavi s PT moškimi (najnižje vrednosti so zabeležene pri VPT posameznikih) pri starostih 10, 11, 12 in 18 let. Pri ženskah je bil prisoten podoben trend v starosti 17 in 19 let. Mišična vzdržljivost ramenskega obroča in rok (vesa v zgibi) je bila slabša pri PT moških, kot pri FT vrstnikih, vendar so bili rezultati presenetljivo najslabši pri MPT posameznikih v starosti od 10 do 11 let in najboljši pri VPT moških pri starosti 8 let. PT ženske so pri vesi v zgibi dosegale slabše rezultate kot FT vrstnice pri 9 in 11 letih, VPT ženske pa so imele najslabše rezultate pri 17 letih. Pri

SLOfit testih spretnosti in fine motorike so PT posamezniki večinoma dosegli boljše rezultate od FT vrstnikov v času do njihove pubertete (zlasti ženske), kasneje pa so boljše rezultate pri teh testih dosegli FT vrstniki. Koordinacija telesnih gibov (hoja štirinožno nazaj čez standardni poligon) je bila slabša pri MPT moških, kot pri njihovih VPT in FT vrstnikih pri starostih 10, 11, 14 in 17 let. Nasprotno pa so bile PT ženske, predvsem MPT posameznice, boljše kot FT vrstnice pri starosti 9 in 10 let, v starosti 15 in 19 let pa so FT ženske izboljšale rezultate napram VPT vrstnicam. Podobno kot pri prejšnjem testu, so bili rezultati predklona naprej z dotikom prečke boljši pri FT moških v starosti od 11 do 17 let in pri PT ženskah v starosti 9 let, vendar pa so v puberteti FT posameznice dosegle boljše rezultate (v starosti od 15 do 19 let) od svojih VPT vrstnic. PT ženske so imele višjo hitrost alternativnih gibov (izmenični dotiki plošče z rokami – tapkanje), kot njihove FT vrstnice pri starosti od 13 do 16 let, VPT moški pa so bili počasnejši od svojih MPT in FT vrstnikov pri 18 in 19 letih. To nakazuje na prisotnost potenciala nedonošenčkov, da dosežejo podobne ali celo boljše rezultate kot donošenčki, zato je priporočljivo spodbujati nedonošenčke k telesni aktivnosti, da bi ta potencial lahko popolnoma izkoristili.

Kot prikazano v nadaljevanju, naj bi zelo nedonošeni posamezniki imeli manjšo pusto telesno maso kot njihovi donošeni vrstniki. Znano pa je, da količina puste telesne mase vpliva na privzem glukoze in zmožnost za telesno aktivnost. Nižja mišična moč, zmogljivost za vadbo in slabša motorična koordinacija so verjetno vzrok, da je telesna dejavnost manj privlačna. To se lahko nadalje odraža v telesni nedejavnosti, ki še otežuje že tako počasnejši razvoj motoričnih sposobnosti ter prispeva k nižji mišični in pusti telesni masi. V nasprotju s tem, v povprečju bolje izvedeni gibljivostni in fino-motorični testi pri PT kot pri FT preiskovancih imajo lahko vzrok v zgodnejšem dozorevanju PT posameznikov. Slednje lahko povzroči bolj razvito telo in s tem bolj razvite fino-motorične sposobnosti pri isti starosti, v primerjavi z FT posamezniki, ki še niso v isti fazi razvoja telesa. Kot je razvidno iz rezultatov te študije je bila razlika v spolnem dozorevanju med PT in FT posamezniki vidna še posebej pri ženskah.

(H_W6) Za testiranje šeste hipoteze smo, podobno kot za testiranje pete hipoteze, podatke pridobili iz SLOfit sistema (debelino tricepsne kožne gube) in na laboratorijskih obiskih pri starosti preiskovancev 26 let (debeline kožnih gub in izbrane telesne obsege).

Zaradi majhnega vzorca nismo mogli primerjati drugih debelin kožnih gub, obsegov in porazdelitve telesne maščobe med PT in FT posamezniki v starosti 26 let.

Pri moških preiskovancih je bila debelina tricepsne kožne gube podobna pri PT in FT posameznikih v starosti med 8 in 19 let, najnižje vrednosti so bile zabeležene pri VPT posameznikih v starostih 9, 12 in 17 let in najvišje vrednosti pri MPT posameznikih pri

9 in 10 letih. Pri ženskah je bila debelina tricepsne kožne gube pri PT višja, kot pri FT posameznicah pri starosti 16 let. Odstotek telesne maščobe je bil višji pri FT moških, kot pri njihovih PT vrstnikih v starostih 15, 16 in 18 let in je bil nižji pri VPT moških, kot pri njihovih MPT in FT vrstnikih v starosti 9, 12 in 17 let. PT ženske so imele višji odstotek telesne maščobe pri starosti 15 in 16 let, kot njihove FT vrstnice, podoben trend pa je bilo opaziti tudi pri VPT ženskah, pri katerih so bili odstotki telesne maščobe višji, kot pri njihovih MPT in FT vrstnicah pri starosti 19 let. Pri moških preiskovancih ni bilo razlike v masi telesne maščobe med PT in FT posamezniki, bila pa je nižja pri VPT moških, kot pri MPT in FT posameznikih pri starosti od 9 do 12 let. Pri ženskah je bila masa telesne maščobe višja pri PT, kot FT posameznicah v starosti 16 let, vendar pa razlik med VPT in MPT ali FT posameznicami v starosti med 8 in 19 let ni bilo. Tudi v pusti telesni masi ni bilo razlik med PT in FT posamezniki, vendar je bila pri VPT moških manjša, kot v MPT in FT posameznikih v starosti med 8 in 13 let (najvišje vrednosti so bile dosežene pri MPT posameznikih v starosti od 10 do 12 let) in pri 16 letih. Pri ženskah smo lahko opazili trend nižje puste telesne mase pri PT posameznicah pri starostih 8, 10, 14 in 15 let, z najnižjimi vrednostmi pri VPT ženskah od starosti 15 let naprej.

Če povzamemo, rezultati doktorske disertacije pojasnjujejo, da fizične značilnosti mater vplivajo na vzorce rasti njihovih otrok v prvem letu življenja in da metodologija, ki je trenutno na voljo za oceno antropometričnih značilnosti nosečnic, ni zanesljiva. Nadalje, raziskovalno delo je izpostavilo nekatere razlike v fizičnih lastnostih PT in FT posameznikov od otroštva do zgodnje odrasle dobe, kar prinaša smiseln in širok vpogled v procese rasti in telesnega razvoja. Glede na naše rezultate lahko sprejmemo delovni hipotezi (H_W1), (H_W2) in posamezne dele hipoteze (H_W5). Po našem vedenju je pričujoča študija verjetno najbolj obsežna longitudinalna študija na področju raziskav rasti in razvoja PT posameznikov. kar jih je bilo do sedaj izvedenih, zato verjamemo, da bodo rezultati doktorske disertacije nedvomno koristni za nadaljnje raziskave v neonatologiji in avksologiji.

7.3 ZUSAMMENFASSUNG

Frühgeburt (<37. Schwangerschaftswoche) und niedrige Geburtsmasse beeinträchtigen Wachstum und Entwicklung, pränatale, Kinder- und Erwachsenen Morbidität und Mortalität und beeinträchtigen physiologische Eigenschaften später im Leben. Termingeborene (FT) und Frühgeborene (PT) Kleinkinder können unterschiedliche Wachstumsmuster haben und die Zeit des beschleunigten Wachstums scheint unvollständig in PT Kindern. Unverhältnismäßige Veränderungen in der Höhe und Masse modifizieren die Körperzusammensetzung in der Kindheit (z. B. ergeben höhere Fettansammlungen am Bauch, vor allem bei Frauen), was die Funktionsweise der

endokrinen Drüsen im Erwachsenenalter beeinträchtigen könnte. Eine erhöhte Menge an Körperfett oder deren Verteilung scheinen früheres Auftreten von Komponenten der Pubertät zu induzieren (Alter beim pubertären Wachstumsschub (PHV), Wachstumsgeschwindigkeit, der Eintritt der Geschlechtsreife), da sich die Produktion von Sexualhormonen aus dem Fettstoffwechsel ergibt. Pränatale Entwicklung und Kleinkindentwicklung scheinen daher kritische Phasen für Wachstum und Entwicklung zu sein, da die langfristige Regelung des Energiestoffwechsels in diesem Zeitraum festgelegt wird.

Da physische Eigenschaften der Schwangeren einige der Eigenschaften der Kinder bei der Geburt und im späteren Leben beeinflussen können, haben sich einige Studien mit Schwangerschaftanthropometrie befassten, aber diese verwendeten meist mathematische Gleichungen für die Bewertung der Körperzusammensetzung, entwickelt an Männern oder nicht-schwangeren Frauen. Dabei wird für Schwangere die Spezifität der Gewebezusammensetzung häufig vernachlässigt und insgesamt existieren nur wenige Gleichungen für schwangere Frauen, was zu inkonsistenten Ergebnissen führen kann. Im Hinblick auf zunehmende gesundheitsgefährdende Körpermasse und Fettsucht, ist die Bewertung der bestehenden Methoden für eine zuverlässige Bewertung der Körperzusammensetzung entscheidend, was wiederum für Präventive gegen abdominale Fettleibigkeit und Herz-Kreislaufkrankheiten im Erwachsenenalter verwendet werden kann.

Wir stellten die Hypothesen auf, dass die bestehenden anthropometrischen Methoden für die Schätzung der Körperzusammensetzung bei Schwangeren unzureichend sind (H_W1), dass das Wachstumsmuster von PT und FT Kleinkinder während des ersten Lebensjahres von anthropometrischen Eigenschaften der Mütter abhängt (H_W2), dass sich die Anfälligkeit und die Häufigkeit der Erkrankungen nach der Phase des PHV zwischen FT und PT Personen unterscheiden (H_W3, H_W4), dass man die möglichen Folgen der PT (geringere Körperhöhe, Masse und Kapazität der körperlichen Bewegung) in der späten Kindheit und im Jugendalter erkennen kann (H_W5), und dass die Verteilung von Körperfett in PT und FT Personen unterschiedlich sein können (H_W6). Um diese Hypothesen zu testen, erweiterten wir die systematische Überwachung der körperlichen und motorischen Entwicklung von Schülern in Slowenien in einer Kombination von prospektiver und retrospektiver Studie, allgemein "Preterms 1987" genannt, mit Genehmigung von der slowenischen Ethikkommission.

(H_W1) Anthropometrische Messungen wurden an 147 gesunden Schwangeren aus der Studie „My Milk“ im Alter von etwa 31 Jahren und in der 32. Schwangerschaftswoche durchgeführt. Ihre Körperhöhe, Masse, drei Umfänge und sechs Hautfaltendicken wurden gemessen. Die Messungen wurden in, wenn bevor notwendig, fünf verschiedenen anthropometrischen Gleichungen zur Schätzung der Körperdichte und

zwölf Gleichungen für Körperfettanteil benutzt. Die Schätzungen für Körperfettanteil variierten für dieselbe Probe von Frauen methodenabhängig von 16 % bis 38 %. Schwangerschafts-unspezifische Methoden führten zum Körperfettgehalt zwischen 27 % und 38 % und schwangerschafts-spezifische Methoden zwischen 16 % und 30 %.

(H_W2) Säuglinge (N=154) wurden nach der mütterlichen Körpergröße (MBH), nach der Masse (PpBM) und dem Körpermassenindex vor der Schwangerschaft (PpBMI), nach der Schwanger-schaftsgewichtszunahme (PMG), und der Angemessenheit der PMG bestimmt in Bezug auf die empfohlenen Werte für mütterlichen PpBMI (RV/PpBMI). Ihre Körperhöhe, Masse, vier Umfänge und drei Hautfaltendicken von der Geburt bis zum Alter von 12 Monaten wurden gemessen und relative Zunahmen der Messungen verglichen. Relative Zunahme der Körperhöhe wurde bei Mädchen durch höhere mütterliche PpBM gehemmt. Relative Erhöhung der Körpermasse wurde durch höhere mütterliche PpBMI, RV/PpBMI und bei Jungen auch PMG gehemmt, jedoch bei Mädchen erhöhte eine höhere MBH ihre relative Zunahme der Körpermasse. Relative Zunahme des BMI wurde durch höhere mütterliche PpBMI und PMG bei Jungen und durch höhere RV/PpBMI in Mädchen gehemmt. Bei Mädchen, hat höher PpBMI die Relative Zunahmen der Hautfaltendicken und des Körperfettanteiles gehemmt, aber höhere PpBM und PpBMI erhöhten relative Zunahmen der Umfänge. Zusätzlich wurden 474 Neugeborenen als sehr frühe PT (VPT; <32. Schwangerschaftswoche), mäßig frühe PT (MPT; 32. bis 36. Schwangerschaftswoche) oder FT klassifiziert. Rie Risikofaktoren für Frühgeburt waren (insbesondere für VPT) Mehrlingsgeburten, Krankheiten und Blutungen während der Schwangerschaft, sowie Rauchen, vorangegangene Früh- und Totgeburten, Schulbildung und Alter der Mutter unter 21 und über 35 Jahre.

(H_W3, H_W4) Die Daten von 474 Teilnehmern erhielten wir aus der slowenischen perinataler Datenbank, einem Teil der individuellen Patientenakten, bei Laborbesuchen, und mit einem Fragebogen der inzwischen 26-jährigen Personen. Der Blutdruck, Frequenz des Brillentragens und von erlebten Verletzungen gaben ähnliche Ergebnisse für alle Gruppen, mit Ausnahme der Gelenkenverletzungen die häufiger in PT als in FT Personen waren. Weiterhin, bei der Geburt und in der Kindheit, mehrere PT als FT Säuglinge erlebten die meisten gesundheitliche Probleme; jedoch waren Infektionen der oberen Atemwege und der Ohren häufiger in MPT und FT Säuglingen, wahrscheinlich aufgrund der früheren Aussetzung gegenüber Infektionsherden im Kindergarten. In den ersten zwei Jahren waren Indikatoren der psychischen Entwicklung schlechter in PT (insbesondere in VPT) als in FT Kindern.

(H_W5) Aus der Analyse der physischen Eigenschaften geht hervor, dass die Körperhöhe niedriger in PT als in FT Jungen mit bis zu 2 Jahren war, VPT Männer waren kleiner als

ihre Altersgenossen bis zu 17 Jahren und bei VPT Frauen blieb der Unterschied auch im Erwachsenenalter erhalten. Die Körpermasse und der BMI waren niedriger in PT (vor allem in VPT) als bei FT Personen bis 13 Jahren, VPT Mädchen hatten eine niedrigere Körpermasse und einen höheren BMI mit 16 und 17 Jahren als ihre FT Altersgenossinnen. Der Aerober Test allgemeiner Ausdauer wurde besser von PT als von FT männlichen 14-jährigen durchgeführt; jedoch waren VPT Mädchen grundsätzlich langsamer als ihre Altersgenossen. Beim Anaeroben Tests (Sprintgeschwindigkeit, Explosivkraft, Rumpfmuskelkraft) haben die PT größtenteils schlechter als die FT Personen abgeschnitten, jedoch war die Kraftausdauer des Schultergürtels und der Arme besser bei den VPT Männern. Die Beweglichkeits- und Feinmotoriktests (Koordination der Körperbewegungen, Vornüberbeugung und Berührung der Bank, Geschwindigkeit der alternativen Bewegungen) haben bis zur Pubertät PT Frauen besser durchgeführt als FT, PT Männern waren jedoch schlechter als ihre Altersgenossen. Weiterhin erlebten VPT Frauen ihren PHV und anscheinend auch den Eintritt der Menarche früher (5 bzw. 10 Monate) als ihre Altersgenossen. Bei den Männern konnte kein Unterschied festgestellt werden. Diese frühere sexuelle Reifung könnte die Erklärung für gute Leistung der PT Frauen in der Zeit sein, bis FT Altersgenossinnen die Pubertät erreichten.

(H_W6) VPT Männer hatten die niedrigsten Triceps Hautfaltendicke und Körperfettanteil Werte mit 9, 12 und 17 Jahren und die höchsten Werte in MPT mit 9 und 10 Jahren. Bei Frauen waren dieselben zwei Parameter höher in PT (vor allem in VPT) als in FT Altersgenossinnen nach 15 Jahren. Fettfreie Masse war niedriger bei VPT Personen als in Altersgenossen nach 8 Jahren. Körperfettmasse war niedriger in VPT Männern als in Altersgenossen zwischen 8 und 13 Jahren und höher in PT Frauen als in ihren FT Altersgenossinnen mit 16 Jahren.

Unsere Ergebnisse verdeutlichen, dass die Wachstumsmuster der Kinder während der ersten Lebensjahre von den physikalischen Eigenschaften der Mütter beeinflusst werden und dass die derzeit zur Verfügung stehenden anthropometrischen Methoden für die Schätzung der Körperzusammensetzung für schwangere Frauen ziemlich bedenklich sind. Außerdem nannte die Forschungsarbeit einige Unterschiede in den physischen Eigenschaften der FT und PT Personen von der Kindheit bis zum frühen Erwachsenenalter, und bietet damit einen sinnvollen, neuen und breiten Einblick in die Prozesse des Wachstums und der körperlichen Entwicklung. Somit übernehmen wir Arbeitshypothesen (H_W1) und (H_W2), sowie auch einige Teile der Hypothese (H_W5). Nach unserer Kenntnis ist die vorliegende Studie die wohl umfangreichste Langzeitstudie im Forschungsbereich der Wachstums- und Entwicklungsprozesse von PT Säuglingen. Wir glauben deswegen, dass die Ergebnisse der Doktorarbeit daher zweifellos nützlich für die weitere Forschung in der Auxologie und Neonatologie sind.

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ANNEXES

Annex A

Description of the diseases and health conditions of pregnant women, newborns and children (data from Goodwin, 2012)

Opisi bolezni in zdravstvenih stanj nosečnic, novorojenčkov in otrok (podatki povzeti po Goodwin, 2012)

DIPLEGIA

Diplegia is the most common cause of crippling in children, specifically in children with cerebral palsy or injury of the spinal cord. There is no set course of progression for people with diplegia. Symptoms may get worse but the neurological part does not change. The primary parts of the brain that are affected by diplegia are the ventricles, fluid filled sacs in the brain, and the wiring from the center of the brain to the cerebral cortex. Causes are also degeneration of the cerebral neurons and problems in the upper motor neuron system. The term refers to any bodily area, such as the face, arms, or legs.

ECLAMPSIA AND PRE-ECLAMPSIA (preeclampsia)

Eclampsia and pre-eclampsia are collectively called Hypertensive disorder of pregnancy and toxemia of pregnancy. Eclampsia (Greek, "shining forth") is an acute and life-threatening complication of pregnancy, usually in a patient who has developed pre-eclampsia. Eclampsia includes seizures and coma that happen during pregnancy but are not due to preexisting or organic brain disorders. Typical signs are pregnancy-induced hypertension, proteinuria, cerebral signs (nausea, vomiting, headaches, and cortical blindness), other organ symptoms (abdominal pain, liver failure, pulmonary edema, and oliguria), placental bleeding or abruption. Pre-eclampsia is characterized by high blood pressure and significant amounts of protein in the urine of a pregnant woman. If untreated, it can develop into eclampsia. Blood pressure elevation can damage the maternal endothelium, kidneys, and liver, with the release of vasoconstrictive factors being a consequence of the original damage. It may develop anytime during pregnancy after 20^{th} gestational weeks up to 6^{th} week after delivery. Apart from Caesarean section and induction of labor, there is no known cure.

FETAL DISTRESS

This refers to the presence of signs in a pregnant woman, before or during delivery, that suggest that the fetus may not be well. It includes decreased movement felt by the mother, meconium in the amniotic fluid, increased or decreased fetal heart rate, especially during and after a contraction, decreased variability in the fetal heart rate, and biochemical signs, assessed by collecting a small sample of fetus's blood from a scalp. The possible causes include breathing problems, abnormal position and presentation of the fetus, multiple births, shoulder dystocia, umbilical cord prolapse, nuchal cord, placental abruption, premature closure of the fetal ductus arteriosus, uterine rupture, intrahepatic cholestasis of pregnancy, or a liver disorder during pregnancy. This diagnosis leads the obstetrician to recommend rapid delivery.

continued

Description of the diseases and health conditions of pregnant women, newborns and children

GESTATIONAL DIABETES (or gestational diabetes mellitus)

This is when women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy, especially during their third trimester. It is caused when the insulin receptors do not function properly due to pregnancy-related factors, such as the presence of human placental lactogen that interferes with susceptible insulin receptors, which causes inappropriately elevated blood sugar levels. Diagnostic tests detect inappropriately high levels of glucose in blood samples. It affects 3-10% of pregnancies, so may be a natural phenomenon, which is a treatable condition. If unmanaged it can lead to development of type 2 diabetes mellitus after pregnancy, pre-eclampsia, and Caesarean section; their infants have increased risk for LGA, low blood sugar, and jaundice, seizures or still birth, and are prone to developing childhood obesity, with type 2 diabetes later in life. Women manage their blood glucose levels with a modified, moderate exercise, some require antidiabetic drugs.

HEMIPARESIS

This is weakness of the entire left or right side of the body and the most severe form of paralysis. Hemiparesis (and hemiplegia) can be caused by congenital causes, trauma, tumors, or stroke. People with hemiparesis often have difficulties maintaining their balance due to limb weaknesses leading to an inability to properly shift body mass. This makes performing everyday activities such as dressing, eating, grabbing objects, or using the bathroom more difficult.

HYPERBILIRUBINEMIA (jaundice)

This is a yellowish pigmentation of the skin, sclerae (whites of the eyes), and other mucous membranes caused by high blood bilirubin levels, which subsequently causes increased levels of bilirubin in the extracellular fluid. Concentration of bilirubin in blood plasma is normally below 25 µmol/l, a concentration higher than approx. 50 µmol/l leads to jaundice (French word “jaune” means yellow). Neonatal jaundice is usually harmless and is often seen in infants around the second day after birth, lasting until 8^{th} day in FT and 14^{th} day in PT births. Causes for neonatal jaundice include normal physiologic jaundice, jaundice due to formula supplementation, and hemolytic disorders. Serum bilirubin normally drops to a low level without any intervention required. In cases where bilirubin rises higher, a brain-damaging condition known as kernicterus can occur, leading to significant disability.

HYPOXIA

(lack of oxygen - evaluated according to the symptoms)

This condition is deprivation of adequate oxygen supply of a body or a region of the body. Although hypoxia is often a pathological condition, variations in arterial oxygen concentrations can be part of the normal physiology (during hypoventilation, training, or strenuous physical exercise). Generalized hypoxia occurs in healthy people when they ascend to high altitude or when breathing mixtures of gasses with a low oxygen content. Hypoxia is also a serious consequence of PT birth in the neonate. The main cause for this is that the lungs of the human fetus develop as the last organ during pregnancy. To assist the lungs to distribute oxygenated blood throughout the body, infants at risk of hypoxia are often placed inside an incubator capable of providing continuous positive airway pressure.

continued

Description of the diseases and health conditions of pregnant women, newborns and children

JAUNDICE (see Hyperbilirubinemia)

OTITIS

This is a general term for inflammation or infection of the ear. It is subdivided into the external otitis (swimmer's ear), middle ear infection (infection behind the ear drum), and internal otitis (labyrinthitis, dizziness is a common symptom). The inflammation may be caused by infection, allergy, or other causes. Usually effective treatment are ear drops.

PLACENTA PREVIA

This is an obstetric complication in which the placenta is inserted partially or wholly in lower uterine segment, which can occur in at the end of the first trimester, but usually during the second or third. Risk factors for placenta previa are previous placenta previa, caesarean delivery, myomectomy or endometrium damage, previous pregnancies, especially closely spaced pregnancies due to uterine damage, alcohol, nicotine, and cocaine use during pregnancy, women`s age less than 20 and higher than 35 years, large placenta from twins or erythroblastosis, nationality, and placental pathology. It causes maternal (antepartum hemorrhage, malpresentation, abnormal placentation, postpartum hemorrhage, and puerperal sepsis) and fetal (IUGR, premature delivery, death) complications. It affects approximately 0.4 to 0.5% of all labors.

PRE-ECLAMPSIA (see Eclampsia)

RESPIRATORY DISTRESS

This is difficulty in breathing and the psychological experience associated with such difficulty, even if there is no physiological basis for experiencing such distress. It occurs in connection with acute respiratory distress syndrome, a serious reaction to injuries to the lung, or prematurity as developmental insufficiency of surfactant production and structural immaturity in the lungs. Infant respiratory distress syndrome can result from a genetic problem with the production of surfactant associated proteins. It can manifest as hyaline membrane illness, transient respiratory distress, primary or secondary atelectasis, pulmonary interstitial emphysema, bronchopulmonary dysplasia, or pneumothorax. It affects about 1% of newborn infants and is the leading cause of death in preterm infants. To mothers who are about to deliver prematurely can be given glucocorticoids, which speed the production of surfactant. It is treated with oxygen given with a continuous airway pressure, intravenous fluids administered to stabilize the blood sugar, blood salts, and blood pressure, or with an endotracheal tube and intermittent breaths given by a mechanical device.

RICKETS

This is defective calcification or mineralization of bones before epiphyseal closure due to deficiency or impaired metabolism of vitamin D, phosphorus, or calcium, which can lead to fractures and deformations. Rickets is among the most frequent childhood diseases in many developing countries. Although it can occur in adults, the majority of cases occur in children suffering from severe malnutrition, usually resulting from famine or starvation during the early stages of childhood.

Annex B

Questionnaire “Well-being, quality of life, and health”

Vprašalnik “Počutje, kvaliteta življenja in zdravje”

The questionnaire was classified into four parts. Each part aimed to provide specific information, which is summarized below.

Part 1: Well-being and quality of life
- any confirmed levels of disability;
- evaluation of subjects current health status;
- information on how subjects take care of their health;
- information on how often subjects feel tense, stressed, or under high pressure; and
- information on how subjects manage with this tension, stress and pressures.

Part 2: Diseases
- the diseases or abnormalities that were diagnosed at birth (accurate description or name of the disease or abnormality and reactions): cerebral hemorrhage, hip dysplasia, congenital malformations, anomalies, respiratory distress, chronic lung disease, anemia, hyperbilirubinemia, congenital anomalies of vision or hearing…;
- the chronic diseases (accurate description or name of the disease, the age at which the disease was diagnosed, and what are the countermeasures used (prevention, medications...): allergies, diabetes type I or type II, hypertension, other cardiovascular diseases, asthma, epilepsy, neuromuscular diseases, chronic intestinal diseases…;
- elevated blood sugar levels at any time in the past; and
- if anyone of subjects close or wider relatives has/had diabetes (diabetes type I or II).

Part 3: Medical aids and specialized treatments
- were the subjects in the past or currently treated by any medical specialist (a detailed description or type of the treatment, age at the beginning and end of the medication); and
- were the subjects in the past or currently using any of the items listed below, or experiencing medical treatments by any medical specialists (a detailed description or type of the treatment, age at the beginning and end of the medication): orthopedic devices, orthodontic devices, wearing glasses, hearing devices, treatment at physical therapist or at the speech therapist.

Part 4: Injuries
- any previously experienced injuries; and
- information on the type of injury, year of injury, cause or situation of injury, any interruption of regular physical activity or training because of injury, any repetition of these injuries, and data on whether the subjects still experience any problems because of the injury.

Annex C

Questionnaire “Anthropometry – Body measurements”

Vprašalnik “Antropometrija – Meritve telesa”

This questionnaire provided detailed instructions (summarized below) to the participants on how to perform body measurements at home with some help from another person. After the first question on their gender, the participants provided data on their day of the menstrual cycle (females only), blood pressure, and eight body measurements. Illustrations of the measurements enabeling a better understanding of the instructions were also provided within the questionnaire.

The day of the menstrual cycle:
The correct day was determined by counting all days from (and including) the first day of the last menstrual cycle, up to the day of fulfillment of the questionnaire. If the subjects had no menstrual periods, they provided the reason.

Systolic and diastolic blood pressure [mmHg]:
The measurement was performed in the morning, as soon as the subjects got up, on the naked stretched left upper arm at the level of the heart. Five minutes before the measurement the subjects sat relaxed, with no eating, drinking or smoking. During the measurement the subjects were instructed not to speak, laugh, or move. The rubber hose from the upper arm cuff was positioned on the front side in the direction of the fold of the elbow and the lower edge of the cuff was instructed to be 2 to 3 cm above the elbow fold.

Body height [cm]:
The height was measured along the vertical wall, standing in an upright position, with relaxed hands, with knees and heels together, and with heels touching the wall. The subjects aligned the head so that the horizontal line between the upper edge of the ear hole and the lower edge of the orbita was obtained. The person helping to the subject placed a firm straight object with a right angle to the wall above the subject’s head and touched the highest point of the head with it. The precision of the measurement was set to 0.5 cm.

Body mass [kg]:
If an analog scale was used, it was first checked so that the scale cursor demonstrated zero kilograms in an unloaded condition. The subjects stepped barefoot on the scale and waited until the pointer on a scale stabilized. The precision of the measurement was set to 0.5 kg.

Head circumference [cm]:
The person helping to the subject surrounded the head of the subject with a flexible, unstreachable measuring tape, by positioning it 1 to 2 cm above the eyebrows at the forehead and over the most convex part of the head on the back of the head. The measuring tape had to be positioned tightly against the scalp. The precision of the measurement was set to 0.1 cm.

continued

continuation of Annex C.

Questionnaire “Anthropometry – Body measurements”

Waist circumference [cm]:
In a standing position, the subjects found the highest point of the iliac bone and the lower edge of the lowest rib. Exactly in the middle between these two points the person helping to the subject surrounded the torso with a measuring tape. The precision of the measurement was set to 0.1 cm.

Hip circumference [cm]:
The subject was in a standing position, the person helping to the subject was kneeling on the side of the subject. At the level of the most protruding point of the buttocks the person helping to the subject surrounded the subjects hips with the measuring tape. The precision of the measurement was set to 0.1 cm.

Upper arm circumferences in relaxed and flexed position [cm]:
The subjects bent the right arm at the elbow to the right angle. The person helping to the subjects measured the length of the arm from the top of the shoulder to the tip of the elbow with the measuring tape, calculated half of the length value, and marked the calculated point on the skin with a marker. At the marked level, the person helping to the subject surrounded the subjects upper arm with the measuring tape. First, the circumference of subjects upper arm was measured when the arm was relaxed and positioned next to a thigh, then when the subjects upper arm was bent at the elbow to the right angle and the muscles (biceps) were flexed. The precision of the measurement was set to 0.1 cm.

Middle thigh circumference [cm]:
The subject was standing upright and the person helping to the subject first measured the length of the right thigh with the measuring tape from the hip crease (on the front of the leg, midway between the hips and crotch) to the upper edge of the patella, then calculated half of the length value, and marked the calculated point on the skin with a marker. At the marked level, the person helping to the subject surrounded the thigh with the measuring tape. The precision of the measurement was set to 0.1 cm.

The online form, which was provided to the subjects, was complemented with ratio calculations performed from the measurements presented above and with cut-off points for a particular parameter that became visible after the subjects entered their data.This was for the participants to get some feedback information on their blood pressure, body mass index, waist-to-height ratio, and waist-to-hip ratio.

Annex D

Questionnaire “Physical activity and sports clubs”

Vprašalnik “Telesna dejavnost in športni klubi”

The questionnaire “Physical activity and sports clubs” was the International Physical Activity Questionnaire (IPAQ; http://www.ipaq.ki.se/ipaq.htm) adjusted for the purposes of our study. After the first question on the subjects ability for physical activity, the questionnaire was classified into five parts. Each part consisted of one or a few questions, which are summarized below.

Part 1: Physical activity related to work out of home:

- information on whether the subjects currently have a job, do any unpaid work, or educate themselves outside their home; and
- during the last week, on how many days the subjects performed vigorous or moderate physical activities or walking as a part of their work for at least 10 minutes at a time, as weel as information on how much time the subjects usually spent performing this activities in a day.

Part 2: Physical activity related to travel or transport

- during the last week, on how many days did the subjects travel by bicycle or walk for at least 10 minutes at a time to get from place to place, and how much time they usually spent performing these activities in a day.

Part 3: Housework, house maintenance, and caring for family

- during the last week, on how many days the subjects performed vigorous or moderate physical activities in the garden or backyard or inside their home for at least 10 minutes at a time, and how much time they usually spent performing these activities in a day.

Part 4: Recreation, sport, and leisure-time physical activity

- during the last week, on how many days they performed vigorous or moderate physical activities or walk in their leisure time for at least 10 minutes at a time, and how much time they usually spent performing these activities in a day (organized training in sports clubs was not included); and
- if the subjets were performing sports in their leisure time for at least 10 minutes at a time, they also provided information on their sports discipline (organized training in sports clubs was not included).

Part 5: Sports clubs

- have the subjects been in the past (or are currently) members of a sports club; and
- if yes, the subjects provided information on their sports discipline, the age at which they started (and stopped) with trainings, and on how many hours per week they train(ed).

Annex E

Different anthropometric equations developed for the assessment of body composition of middle-aged women (BD – body density, BF – body fat)

Različne antropometrijske enačbe za ocenjevanje sestave telesa žensk v srednjih letih (BD – gostota telesa, BF – telesno maščobno tkivo)

Brožek et al. (1963): BF [%] = 100 * ((4.57 / BD [g/cm^3]) – 4.142) … (6)

Catalano et al. (1995): BF [%] = (518.57 / BD [g/cm^3]) – 476.3 … (7)

Deurenberg et al. (1991): BF [%] = (1.2 * current BMI [kg/m^2]) + (0.23 * age [years]) – 5.4 … (8)

Durnin and Rahaman (1967): BD [g/cm^3] = 1.1581 – (0.072 * log of sum of 4 skinfolds) … (9)

Durnin and Womersly (1974): BD [g/cm^3] = 1.1599 – (0.0717 * log of sum of 4 skinfolds) … (10)

Jackson et al. (1980): BD [g/cm^3] = 1.0994921 – (0.0009929 * sum of 3 skinfolds [mm]) + (0.0000023 * * square of sum of 3 skinfolds [mm^2]) – (0.0001392 * age [years]) … (11)

Paxton et al. (1998): BF [%] = (0.4 * current mass [kg]) + (0.16 * biceps skinfold [mm]) + (0.15 * thigh front skinfold [mm]) – (0.09 * wrist circumference [cm]) + (0.1 * (current – – pre-pregnancy mass [kg])) … (12)

Peterson et al. (2003): BF [%] = 22.18945 + (0.06368 * age [years]) + (0.60404 * pregnancy BMI [kg/m^2]) – (0.1452 * height [cm]) + (0.30919 * sum of 4 skinfolds [mm]) – – (0.00099562 * square of sum of 4 skinfolds [mm^2]) … (13)

Rush et al. (1997): A/ BF [%] = (72.66 * log of current BMI) – 64.88 … (14)
B/ BF [%] = 23.25 + (0.177 * sum of 4 skinfolds [mm]) … (15)

Siri (1961): BF [%] = (495 / BD [g/cm^3]) – 450 … (16)

Slaughter et al. (1988): A/ BF [%] = 9.7 + (0.546 * (triceps + subscapular skinfold [mm])) … (17)
B/ BF [%] = 5.1 + (0.61 * (triceps + median calf skinfold [mm])) … (18)

Sloan et al. (1962): BD [g/cm^3] = 1.0764 – (0.0008 * iliac crest skinfold [mm]) – (0.00088 * subscapular skinfold [mm]) … (19)

Steinkamp et al. (1965): BF [%] = ((1.176 * upper arm relax circumference [cm]) + (0.635 * thigh circumference [cm]) – 44.255) / current body mass [kg]) * 100 … (20)

van Raaij et al. (1988): BF [%] = 100 * (current mass [kg] / 100 * ((510.8 / BD [g/cm^3]) – 476.5)) / / current mass [kg]) … (21)

Wilmore and Behnke (1970): BD [g/cm^3] = 1.06234 – (0.00068 * subscapular skinfold [mm]) – (0.00039 * triceps skinfold [mm]) – (0.00025 * thigh front skinfold [mm]) … (22)

Annex F

Absolute values [cm] and relative increases [%] in infants´ body height from birth up to 1 year of age

Absolutne vrednosti [cm] in relativna povečanja [%] dojenčkove telesne višine od rojstva do starosti enega leta

Absolute values of infants´ body height [cm]

Absolutne vrednosti dojenčkove telesne višine [cm]

Infants´ body height [cm]				
Time point	Birth	1 month	3 months	12 months
subject number (N)				
males	82	82	82	82
females	72	72	72	72
average (SD)				
males	51.6 (2.6)	57.4 (2.7)	63.3 (2.9)	77.3 (2.7)
females	50.3 (2.0)	56.5 (2.7)	61.7 (2.1)	75.6 (2.9)

Relative increases in infants´ body height [%] calculated with respect to birth height, according to maternal body height (MBH)

Relativna povečanja dojenčkove telesne višine [%] izračunana glede na porodno višino, glede na telesno višino matere (MBH)

Relative increases in infants´ body height [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
MBH < 168 cm	30	30	30	39	39	39
MBH ≥ 168 cm	45	45	45	33	33	33
average (SD)						
MBH < 168 cm	11.1 (5.0)	22.9 (3.9)	49.9 (7.6)	12.0 (4.3)	22.4 (4.8)	49.8 (7.1)
MBH ≥ 168 cm	11.6 (3.9)	22.4 (5.6)	50.2 (5.8)	12.9 (4.6)	23.4 (4.9)	51.3 (7.5)
t-test (p)						
overall	0.3327	0.3352	0.4253	0.2197	0.2012	0.1898

continued

continuation of Annex F.

Absolute values [cm] and relative increases [%] in infants´ body height from birth up to 1 year of age

Relative increases in infants´ body height [%] calculated with respect to birth height, according to maternal pre-pregnancy body mass (PpBM)

Relativna povečanja dojenčkove telesne višine [%] izračunana glede na porodno višino, glede na prednosečniško telesno maso matere (PpBM)

Relative increases in infants´ body height [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBM < 62 kg	31	31	31	38	38	38
PpBM ≥ 62 kg	47	47	47	34	34	34
average (SD)						
PpBM < 62 kg	11.6 (4.5)	22.3 (4.4)	50.7 (6.7)	13.3 (4.6)	23.0 (4.2)	51.2 (6.9)
PpBM ≥ 62 kg	11.2 (4.2)	22.8 (5.3)	49.4 (7.0)	11.5 (4.1)	22.7 (5.6)	49.7 (7.6)
t-test (p)						
overall	0.3399	0.3116	0.2067	**0.0427**	0.4036	0.2056

Relative increases in infants´ body height [%] calculated with respect to birth height, according to maternal pre-pregnancy BMI (PpBMI)

Relativna povečanja dojenčkove telesne višine [%] izračunana glede na porodno višino, glede na prednosečniški ITM matere (PpBMI)

Relative increases in infants´ body height [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBMI < 25 kg/m^2	68	68	68	59	59	59
PpBMI ≥ 25 kg/m^2	14	14	14	13	13	13
average (SD)						
PpBMI < 25 kg/m^2	11.3 (4.3)	22.9 (5.0)	50.0 (7.2)	12.7 (4.4)	22.9 (4.0)	51.0 (7.0)
PpBMI ≥ 25 kg/m^2	11.2 (4.6)	22.4 (5.3)	49.3 (7.2)	11.2 (4.6)	22.8 (8.0)	48.2 (8.1)
t-test (p)						
overall	0.4501	0.3786	0.3745	0.1451	0.4766	0.1017

continued

continuation of Annex F.

Absolute values [cm] and relative increases [%] in infants´ body height from birth up to 1 year of age.

Relative increases in infants´ body height [%] calculated with respect to birth height, according to maternal pregnancy mass gain (PMG)

Relativna povečanja dojenčkove telesne višine [%] izračunana glede na porodno višino, glede na pridobljeno maso matere v nosečnosti (PMG)

Relative increases in infants´ body height [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG < 16 kg	57	57	57	52	52	52
PMG ≥ 16 kg	23	23	23	19	19	19
average (SD)						
PMG < 16 kg	11.4 (4.3)	22.8 (4.8)	49.9 (6.7)	12.6 (4.3)	23.0 (5.5)	50.6 (7.8)
PMG ≥ 16 kg	11.3 (4.3)	22.6 (5.6)	50.0 (7.9)	11.9 (4.9)	22.9 (2.8)	50.3 (5.6)
t-test (p)						
overall	0.4671	0.4491	0.4750	0.2791	0.4672	0.4358

Relative increases in infants´ body height [%] calculated with respect to birth height, categorized according to the appropriateness of maternal pregnancy mass gain (PMG) determined relative to the recommended values according to maternal pre-pregnancy BMI (RV/PpBMI; in Table 4)

Relativna povečanja dojenčkove telesne višine [%] izračunana glede na porodno višino, glede na ustreznost pridobljene mase matere v nosečnosti (PMG) glede na priporočene vrednosti glede na prednosečniški ITM matere (RV/PpBMI; v Preglednici 4)

Relative increases in infants´ body height [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG below RV/PpBMI	13	13	13	19	19	19
PMG within RV/PpBMI	40	40	40	27	27	27
PMG above RV/PpBMI	21	21	21	25	25	25
average (SD)						
PMG below RV/PpBMI	12.4 (3.1)	24.9 (4.7)	53.0 (6.4)	12.9 (4.4)	23.9 (3.6)	50.9 (7.1)
PMG within RV/PpBMI	11.5 (4.7)	22.3 (5.1)	49.7 (7.3)	12.4 (4.3)	22.0 (5.3)	50.7 (8.8)
PMG above RV/PpBMI	10.9 (4.4)	22.6 (5.0)	49.5 (5.9)	12.1 (4.8)	23.2 (5.3)	50.0 (5.7)
one-way ANOVA (p)						
overall	0.6510	0.2630	0.2740	0.8510	0.4330	0.9000

Annex G

Absolute values [kg] and relative increases [%] in infants´ body mass from birth up to 1 year of age

Absolutne vrednosti [kg] in relativna povečanja [%] dojenčkove telesne mase od rojstva do starosti enega leta

Absolute values of infants´ body mass [kg]

Absolutne vrednosti dojenčkove telesne mase [kg]

Infants´ body mass [kg]				
Time point	Birth	1 month	3 months	12 months
subject number (N)				
males	83	83	83	83
females	70	70	70	70
average (SD)				
males	3.4 (0.5)	4.8 (0.7)	6.5 (0.8)	10.1 (1.0)
females	3.2 (0.5)	4.4 (0.6)	5.8 (0.7)	9.3 (1.0)

Relative increases in infants´ body mass [%] calculated with respect to birth mass, according to maternal body height (MBH)

Relativna povečanja dojenčkove telesne mase [%] izračunana glede na porodno maso, glede na telesno višino matere (MBH)

Relative increases in infants´ body mass [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
MBH < 168 cm	31	31	31	37	37	37
MBH ≥ 168 cm	47	47	47	35	33	33
average (SD)						
MBH < 168 cm	36.8 (15.2)	91.9 (28.6)	202.3 (46.1)	34.6 (12.0)	75.6 (18.8)	186.1 (36.7)
MBH ≥ 168 cm	42.1 (17.3)	89.3 (21.0)	200.2 (37.9)	38.9 (12.5)	85.5 (22.5)	199.4 (39.7)
t-test (p)						
overall	0.0839	0.3235	0.4123	0.0763	**0.0240**	0.0750

continued

continuation of Annex G.

Absolute values [kg] and relative increases [%] in infants´ body mass from birth up to 1 year of age

Relative increases in infants´ body mass [%] calculated with respect to birth mass, according to maternal pre-pregnancy body mass (PpBM)

Relativna povečanja dojenčkove telesne mase [%] izračunana glede na porodno maso, glede na prednosečniško telesno maso matere (PpBM)

Relative increases in infants´ body mass [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBM < 62 kg	31	31	31	36	36	36
PpBM ≥ 62 kg	48	48	48	34	34	34
average (SD)						
PpBM < 62 kg	38.3 (16.6)	88.9 (28.1)	199.2 (39.5)	37.0 (10.6)	79.2 (18.0)	191.0 (34.5)
PpBM ≥ 62 kg	41.0 (16.7)	90.7 (22.9)	201.7 (43.9)	36.3 (14.1)	81.3 (24.1)	193.8 (42.7)
t-test (p)						
overall	0.2447	0.3791	0.3996	0.4077	0.3387	0.3810

Relative increases in infants´ body mass [%] calculated with respect to birth mass, according to maternal pre-pregnancy BMI (PpBMI)

Relativna povečanja dojenčkove telesne mase [%] izračunana glede na porodno maso, glede na prednosečniški ITM matere (PpBMI)

Relative increases in infants´ body mass [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBMI < 25 kg/m^2	69	69	69	57	57	57
PpBMI ≥ 25 kg/m^2	14	14	14	13	13	13
average (SD)						
PpBMI < 25 kg/m^2	41.2 (16.9)	91.7 (24.6)	201.6 (40.8)	37.3 (12.6)	82.0 (21.3)	195.6 (40.1)
PpBMI ≥ 25 kg/m^2	32.8 (13.4)	84.0 (28.4)	193.2 (51.1)	33.7 (11.0)	72.6 (18.9)	178.1 (27.1)
t-test (p)						
overall	**0.0419**	0.1491	0.2523	0.1722	0.0747	0.0697

continued

continuation of Annex G.

Absolute values [kg] and relative increases [%] in infants´ body mass from birth up to 1 year of age

Relative increases in infants´ body mass [%] calculated with respect to birth mass, according to maternal pregnancy mass gain (PMG)

Relativna povečanja dojenčkove telesne mase [%] izračunana glede na porodno maso, glede na pridobljeno maso matere v nosečnosti (PMG)

Relative increases in infants´ body mass [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG < 16 kg	53	53	53	49	49	49
PMG ≥ 16 kg	24	24	24	19	19	19
average (SD)						
PMG < 16 kg	40.4 (16.0)	92.3 (25.3)	202.7 (38.1)	37.1 (10.6)	80.3 (19.3)	191.2 (34.2)
PMG ≥ 16 kg	38.9 (18.5)	84.4 (21.7)	191.2 (47.9)	32.1 (12.1)	74.6 (18.9)	187.3 (39.9)
t-test (p)						
overall	0.3549	0.0971	0.1327	**0.0477**	0.1369	0.3449

Relative increases in infants´ body mass [%] calculated with respect to birth mass, categorized according to the appropriateness of maternal pregnancy mass gain (PMG) determined relative to the recommended values according to maternal pre-pregnancy BMI (RV/PpBMI; in Table 4) (NA – not applicable)

Relativna povečanja dojenčkove telesne mase [%] izračunana glede na porodno maso, glede na ustreznost pridobljene mase matere v nosečnosti (PMG) glede na priporočene vrednosti glede na prednosečniški ITM matere (RV/PpBMI; v Preglednici 4) (NA – se ne uporablja)

Relative increases in infants´ body mass [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG below RV/PpBMI	12	12	12	17	17	17
PMG within RV/PpBMI	40	40	40	26	26	26
PMG above RV/PpBMI	18	18	18	24	24	24
average (SD)						
PMG below RV/PpBMI	50.8 (11.6)	106.3 (18.6)	222.8 (40.0)	39.7 (9.7)	85.6 (19.7)	196.0 (32.6)
PMG within RV/PpBMI	39.9 (18.7)	90.7 (25.5)	205.9 (41.3)	37.3 (10.9)	80.4 (19.4)	195.1 (44.6)
PMG above RV/PpBMI	35.7 (13.1)	87.0 (23.2)	195.7 (37.7)	31.0 (11.2)	72.6 (16.8)	182.7 (26.0)
one-way ANOVA (p)						
overall	**0.0500**	0.0834	0.2030	**0.0259**	0.0836	0.3810
Tukey HSD post hoc (p)						
below vs. within RV/PpBMI	nsg	NA	NA	nsg	NA	NA
below vs. above RV/PpBMI	**<0.01**	NA	NA	**<0.05**	NA	NA
within vs. above RV/PpBMI	nsg	NA	NA	nsg	NA	NA

Annex H

Absolute values [kg/m^2] and relative increases [%] in infants´ BMI from birth up to 1 year of age

Absolutne vrednosti [kg/m^2] in relativna povečanja [%] dojenčkovega ITM-ja od rojstva do starosti enega leta

Absolute values of infants´ BMI [kg/m^2]

Absolutne vrednosti dojenčkovega ITM-ja [kg/m^2]

Infants´ BMI [kg/m^2]				
Time point	Birth	1 month	3 months	12 months
subject number (N)				
males	81	81	81	81
females	70	70	70	70
average (SD)				
males	12.79 (1.03)	14.38 (1.52)	16.03 (1.62)	17.00 (1.46)
females	12.72 (1.21)	13.76 (1.37)	15.18 (1.69)	16.39 (1.37)

Relative increases in infants´ BMI [%] calculated with respect to birth BMI, according to maternal body height (MBH)

Relativna povečanja dojenčkovega ITM-ja [%] izračunana glede na porodni ITM, glede na telesno višino matere (MBH)

Relative increases in infants´ BMI [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
MBH < 168 cm	32	32	32	35	35	35
MBH ≥ 168 cm	49	49	49	33	33	33
average (SD)						
MBH < 168 cm	11.2 (11.3)	27.1 (16.6)	34.4 (15.3)	8.4 (9.7)	19.0 (12.9)	29.7 (12.4)
MBH ≥ 168 cm	13.8 (11.4)	25.2 (12.4)	33.1 (12.5)	9.3 (11.0)	21.9 (14.0)	30.6 (12.3)
t-test (p)						
overall	0.1610	0.2843	0.3324	0.3596	0.1949	0.3809

continued

continuation of Annex H.

Absolute values [kg/m^2] and relative increases [%] in infants´ BMI from birth up to 1 year of age

Relative increases in infants´ BMI [%] calculated with respect to birth BMI, according to maternal pre-pregnancy body mass (PpBM)

Relativna povečanja dojenčkovega ITM-ja [%] izračunana glede na porodni ITM, glede na prednosečniško telesno maso matere (PpBM)

Relative increases in infants´ BMI [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBM < 62 kg	32	32	32	36	36	36
PpBM ≥ 62 kg	49	49	49	34	34	34
average (SD)						
PpBM < 62 kg	11.3 (11.5)	26.3 (16.1)	32.2 (14.0)	7.3 (6.9)	19.2 (11.4)	28.5 (13.0)
PpBM ≥ 62 kg	13.7 (11.2)	25.7 (12.8)	34.5 (13.3)	10.0 (12.9)	20.6 (15.7)	30.6 (12.2)
t-test (p)						
overall	0.1810	0.4312	0.2242	0.1349	0.3307	0.2420

Relative increases in infants´ BMI [%] calculated with respect to birth BMI, according to maternal pre-pregnancy BMI (PpBMI)

Relativna povečanja dojenčkovega ITM-ja [%] izračunana glede na porodni ITM, glede na prednosečniški ITM matere (PpBMI)

Relative increases in infants´ BMI [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBMI < 25 kg/m^2	65	65	65	54	54	54
PpBMI ≥ 25 kg/m^2	14	14	14	13	13	13
average (SD)						
PpBMI < 25 kg/m^2	13.4 (11.0)	26.6 (14.4)	34.0 (13.6)	8.0 (10.0)	19.9 (12.3)	28.6 (11.6)
PpBMI ≥ 25 kg/m^2	7.6 (11.0)	22.3 (13.5)	30.6 (13.8)	8.4 (11.5)	15.4 (16.4)	26.7 (8.3)
t-test (p)						
overall	**0.0406**	0.1536	0.1976	0.4428	0.1388	0.2876

continued

continuation of Annex H.

Absolute values [kg/m^2] and relative increases [%] in infants´ BMI from birth up to 1 year of age

Relative increases in infants´ BMI [%] calculated with respect to birth BMI, according to maternal pregnancy mass gain (PMG)

Relativna povečanja dojenčkovega ITM-ja [%] izračunana glede na porodni ITM, glede na pridobljeno maso matere v nosečnosti (PMG)

Relative increases in infants´ BMI [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG < 16 kg	55	55	55	50	50	50
PMG ≥ 16 kg	22	22	22	19	19	19
average (SD)						
PMG < 16 kg	13.4 (12.0)	28.2 (14.8)	35.6 (14.0)	9.0 (9.1)	20.6 (12.9)	30.4 (13.3)
PMG ≥ 16 kg	11.3 (10.3)	20.8 (11.5)	27.7 (10.2)	5.7 (10.2)	15.5 (10.7)	26.8 (10.3)
t-test (p)						
overall	0.2424	**0.0188**	**0.0095**	0.1020	0.0659	0.1446

Relative increases in infants´ BMI [%] calculated with respect to birth BMI, categorized according to the appropriateness of maternal pregnancy mass gain (PMG) determined relative to the recommended values according to maternal pre-pregnancy BMI (RV/PpBMI; in Table 4) (NA – not applicable)

Relativna povečanja dojenčkovega ITM-ja [%] izračunana glede na porodni ITM, glede na ustreznost pridobljene mase matere v nosečnosti (PMG) glede na priporočene vrednosti glede na prednosečniški ITM matere (RV/PpBMI; v Preglednici 4) (NA – se ne uporablja)

Relative increases in infants´ BMI [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG below RV/PpBMI	12	12	12	17	17	17
PMG within RV/PpBMI	39	39	39	26	26	26
PMG above RV/PpBMI	19	19	19	23	23	23
average (SD)						
PMG below RV/PpBMI	18.9 (12.4)	32.2 (12.8)	36.7 (13.3)	10.2 (10.8)	22.3 (11.9)	32.1 (12.8)
PMG within RV/PpBMI	12.1 (11.6)	27.3 (14.3)	36.0 (14.0)	9.6 (8.5)	21.6 (10.2)	30.2 (12.5)
PMG above RV/PpBMI	11.9 (8.9)	23.6 (12.5)	30.3 (10.5)	4.7 (8.9)	13.8 (13.3)	26.1 (7.8)
one-way ANOVA (p)						
overall	0.1500	0.2340	0.2450	0.1060	**0.0389**	0.2170
Tukey HSD post hoc (p)						
below vs. within RV/PpBMI	NA	NA	NA	NA	nsg	NA
below vs. above RV/PpBMI	NA	NA	NA	NA	nsg	NA
within vs. above RV/PpBMI	NA	NA	NA	NA	nsg	NA

Annex I

Absolute values [cm] and relative increases [%] in infants´ head circumference from birth up to 1 year of age

Absolutne vrednosti [cm] in relativna povečanja [%] dojenčkovega obsega glave od rojstva do starosti enega leta

Absolute values of infants´ head circumference [cm]

Absolutne vrednosti dojenčkovega obsega glave [cm]

Infants´ head C [cm]				
Time point	Birth	1 month	3 months	12 months
subject number (N)				
males	83	83	83	83
females	67	67	67	67
average (SD)				
males	35.0 (1.4)	38.8 (1.1)	41.8 (1.1)	47.1 (1.1)
females	34.2 (1.5)	37.7 (1.1)	40.5 (1.1)	46.1 (1.3)

C – circumference

Relative increases in infants´ head circumference [%] calculated with respect to birth head circumference, according to maternal body height (MBH)

Relativna povečanja dojenčkovega obsega glave [%] izračunana glede na porodni obseg glave, glede na telesno višino matere (MBH)

Relative increases in infants´ head C [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
MBH < 168 cm	34	34	34	37	37	37
MBH ≥ 168 cm	49	49	49	30	30	30
average (SD)						
MBH < 168 cm	11.0 (3.7)	19.6 (4.2)	35.1 (5.6)	9.8 (3.8)	17.9 (4.2)	34.1 (5.5)
MBH ≥ 168 cm	10.9 (3.3)	19.2 (3.9)	34.6 (5.0)	10.8 (3.4)	19.4 (4.0)	35.6 (5.1)
t-test (p)						
overall	0.4751	0.3113	0.3362	0.1105	0.0571	0.1265

C – circumference

continued

continuation of Annex I.

Absolute values [cm] and relative increases [%] in infants´ head circumference from birth up to 1 year of age

Relative increases in infants´ head circumference [%] calculated with respect to birth head circumference, according to maternal pre-pregnancy body mass (PpBM)

Relativna povečanja dojenčkovega obsega glave [%] izračunana glede na porodni obseg glave, glede na prednosečniško telesno maso matere (PpBM)

Relative increases in infants´ head C [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBM < 62 kg	34	34	34	35	35	35
PpBM ≥ 62 kg	49	49	49	32	32	32
average (SD)						
PpBM < 62 kg	10.2 (3.3)	18.5 (3.7)	33.8 (5.1)	9.4 (3.5)	17.6 (4.0)	33.4 (4.7)
PpBM ≥ 62 kg	11.5 (3.5)	19.9 (4.1)	35.5 (5.3)	11.1 (3.5)	19.7 (4.1)	36.1 (5.7)
t-test (p)						
overall	0.0512	0.0503	0.0808	**0.0302**	**0.0214**	**0.0195**

C – circumference

Relative increases in infants´ head circumference [%] calculated with respect to birth head circumference, according to maternal pre-pregnancy BMI (PpBMI)

Relativna povečanja dojenčkovega obsega glave [%] izračunana glede na porodni obseg glave, glede na prednosečniški ITM matere (PpBMI)

Relative increases in infants´ head C [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PpBMI < 25 kg/m^2	69	69	69	54	54	54
PpBMI ≥ 25 kg/m^2	14	14	14	13	13	13
average (SD)						
PpBMI < 25 kg/m^2	10.9 (3.4)	19.3 (3.8)	34.6 (5.1)	10.2 (3.6)	18.6 (4.3)	34.6 (5.4)
PpBMI ≥ 25 kg/m^2	11.1 (3.7)	19.6 (4.8)	35.8 (6.1)	10.1 (3.7)	18.5 (3.8)	35.2 (5.5)
t-test (p)						
overall	0.4247	0.4005	0.2121	0.4604	0.4672	0.3630

C – circumference

continued

continuation of Annex I.

Absolute values [cm] and relative increases [%] in infants´ head circumference from birth up to 1 year of age

Relative increases in infants´ head circumference [%] calculated with respect to birth head circumference, according to maternal pregnancy mass gain (PMG)

Relativna povečanja dojenčkovega obsega glave [%] izračunana glede na porodni obseg glave, glede na pridobljeno maso matere v nosečnosti (PMG)

Relative increases in infants´ head C [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG < 16 kg	54	54	54	49	49	49
PMG ≥ 16 kg	24	24	24	19	19	19
average (SD)						
PMG < 16 kg	10.8 (3.2)	19.2 (3.9)	34.5 (5.1)	10.5 (3.9)	18.7 (4.3)	34.9 (5.3)
PMG ≥ 16 kg	10.5 (3.4)	18.9 (3.6)	34.6 (5.1)	10.0 (2.9)	18.2 (4.0)	34.2 (5.5)
t-test (p)						
overall	0.3670	0.3821	0.4589	0.3171	0.3333	0.3183

C – circumference

Relative increases in infants´ head circumference [%] calculated with respect to birth head circumference, categorized according to the appropriateness of maternal pregnancy mass gain (PMG) determined relative to the recommended values according to maternal pre-pregnancy BMI (RV/PpBMI; in Table 4)

Relativna povečanja dojenčkovega obsega glave [%] izračunana glede na porodni obseg glave, glede na ustreznost pridobljene mase matere v nosečnosti (PMG) glede na priporočene vrednosti glede na prednosečniški ITM matere (RV/PpBMI; v Preglednici 4)

Relative increases in infants´ head C [%]	Males			Females		
Age period [months]	0 to 1	0 to 3	0 to 12	0 to 1	0 to 3	0 to 12
subject number (N)						
PMG below RV/PpBMI	14	14	14	18	18	18
PMG within RV/PpBMI	40	40	40	24	24	24
PMG above RV/PpBMI	25	25	25	25	25	25
average (SD)						
PMG below RV/PpBMI	12.1 (3.6)	20.3 (4.1)	35.7 (5.3)	10.5 (4.0)	18.8 (4.0)	34.7 (5.0)
PMG within RV/PpBMI	11.0 (3.7)	19.4 (4.0)	35.0 (5.6)	10.7 (4.1)	19.0 (4.9)	35.4 (6.1)
PMG above RV/PpBMI	10.4 (3.0)	19.1 (3.7)	34.2 (4.5)	9.6 (2.8)	18.0 (3.6)	34.1 (5.0)
one-way ANOVA (p)						
overall	0.3480	0.6700	0.6960	0.5290	0.6600	0.6810

C – circumference

Annex J

Absolute values [cm] and relative increases [%] in infants´ upper arm, wrist, and chest circumferences from 1 to 12 months of age

Absolutne vrednosti [cm] in relativna povečanja [%] dojenčkovih obsegov nadlakti, zapestja in prsnega koša od 1 do 12 mesecev starosti

Absolute values of infants´ upper arm, wrist, and chest circumferences [cm]

Absolutne vrednosti dojenčkovih obsegov nadlakti, zapestja in prsnega koša [cm]

Infants´ C [cm]	upper arm		wrist		chest	
Time point	1 month	12 months	1 month	12 months	1 month	12 months
subject number (N)						
males	84	84	84	84	82	82
females	70	70	70	70	70	70
average (SD)						
males	12.3 (1.1)	16.1 (2.0)	9.2 (0.9)	11.6 (1.3)	38.0 (2.0)	48.1 (3.0)
females	11.9 (1.0)	15.3 (1.1)	9.0 (0.8)	11.1 (0.8)	37.2 (1.7)	46.5 (2.1)

C – circumferences

Relative increases in infants´ upper arm, wrist, and chest circumferences [%] calculated with respect to circumferences at 1 month, according to maternal body height (MBH)

Relativna povečanja dojenčkovih obsegov nadlakti, zapestja in prsnega koša [%] izračunana glede na obsege pri 1 mesecu, glede na telesno višino matere (MBH)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ C [%]	upper arm	wrist	chest	upper arm	wrist	chest
subject number (N)						
MBH < 168 cm	32	34	31	37	38	38
MBH ≥ 168 cm	48	50	45	32	32	32
average (SD)						
MBH < 168 cm	34.7 (23.3)	28.7 (23.5)	26.5 (7.4)	27.9 (12.5)	24.2 (12.7)	25.3 (6.4)
MBH ≥ 168 cm	28.5 (11.0)	26.1 (11.3)	27.5 (9.8)	30.4 (14.0)	24.6 (10.3)	24.6 (6.2)
t-test (p)						
overall	0.0565	0.2541	0.3197	0.2220	0.4452	0.3095

C – circumferences

continued

continuation of Annex J.

Absolute values [cm] and relative increases [%] in infants´ upper arm, wrist, and chest circumferences from 1 to 12 months of age

Relative increases in infants´ upper arm, wrist, and chest circumferences [%] calculated with respect to circumferences at 1 month, according to maternal pre-pregnancy body mass (PpBM)

Relativna povečanja dojenčkovih obsegov nadlakti, zapestja in prsnega koša [%] izračunana glede na obsege pri 1 mesecu, glede na prednosečniško telesno maso matere (PpBM)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ C [%]	upper arm	wrist	chest	upper arm	wrist	chest
subject number (N)						
PpBM < 62 kg	34	34	32	37	37	37
PpBM ≥ 62 kg	50	50	46	33	31	33
average (SD)						
PpBM < 62 kg	30.1 (12.8)	24.3 (10.4)	26.3 (6.7)	28.8 (12.5)	25.4 (11.2)	24.7 (6.2)
PpBM ≥ 62 kg	32.0 (20.2)	29.1 (20.5)	27.3 (10.0)	28.9 (14.0)	24.8 (10.6)	25.2 (6.3)
t-test (p)						
overall	0.3158	0.1075	0.3034	0.4836	0.4029	0.3731

C – circumferences

Relative increases in infants´ upper arm, wrist, and chest circumferences [%] calculated with respect to circumferences at 1 month, according to maternal pre-pregnancy BMI (PpBMI)

Relativna povečanja dojenčkovih obsegov nadlakti, zapestja in prsnega koša [%] izračunana glede na obsege pri 1 mesecu, glede na prednosečniški ITM matere (PpBMI)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ C [%]	upper arm	wrist	chest	upper arm	wrist	chest
subject number (N)						
PpBMI < 25 kg/m^2	70	70	69	57	57	57
PpBMI ≥ 25 kg/m^2	14	14	13	12	12	13
average (SD)						
PpBMI < 25 kg/m^2	29.8 (11.8)	25.7 (11.3)	27.0 (9.4)	29.7 (13.5)	25.6 (11.1)	24.9 (6.6)
PpBMI ≥ 25 kg/m^2	38.2 (33.9)	34.5 (33.8)	25.7 (7.3)	26.4 (11.1)	21.6 (10.2)	25.1 (4.5)
t-test (p)						
overall	0.0513	**0.0403**	0.3193	0.2182	0.1275	0.4591

C – circumferences

continued

continuation of Annex J.

Absolute values [cm] and relative increases [%] in infants´ upper arm, wrist, and chest circumferences from 1 to 12 months of age

Relative increases in infants´ upper arm, wrist, and chest circumferences [%] calculated with respect to circumferences at 1 month, according to maternal pregnancy mass gain (PMG)

Relativna povečanja dojenčkovih obsegov nadlakti, zapestja in prsnega koša [%] izračunana glede na obsege pri 1 mesecu, glede na pridobljeno maso matere v nosečnosti (PMG)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ C [%]	upper arm	wrist	chest	upper arm	wrist	chest
subject number (N)						
PMG < 16 kg	58	58	56	51	51	51
PMG ≥ 16 kg	26	26	26	18	18	18
average (SD)						
PMG < 16 kg	32.8 (19.2)	28.8 (19.3)	27.2 (10.2)	28.3 (12.7)	24.6 (12.1)	24.7 (5.5)
PMG ≥ 16 kg	27.7 (12.5)	23.6 (10.7)	25.9 (6.1)	31.5 (14.3)	25.0 (9.8)	26.3 (8.0)
t-test (p)						
overall	0.1083	0.1048	0.2727	0.1842	0.4497	0.1693

C – circumferences

Relative increases in infants´ upper arm, wrist, and chest circumferences [%] calculated with respect to circumferences at 1 month, categorized according to the appropriateness of maternal pregnancy mass gain (PMG) determined relative to the recommended values according to maternal pre-pregnancy BMI (RV/PpBMI; in Table 4)

Relativna povečanja dojenčkovih obsegov nadlakti, zapestja in prsnega koša [%] izračunana glede na obsege pri 1 mesecu, glede na ustreznost pridobljene mase matere v nosečnosti (PMG) glede na priporočene vrednosti glede na prednosečniški ITM matere (RV/PpBMI; v Preglednici 4)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ C [%]	upper arm	wrist	chest	upper arm	wrist	chest
subject number (N)						
PMG below RV/PpBMI	15	15	15	19	19	19
PMG within RV/PpBMI	40	40	39	26	26	26
PMG above RV/PpBMI	29	29	28	24	24	24
average (SD)						
PMG below RV/PpBMI	28.4 (13.1)	25.2 (9.2)	26.5 (7.5)	28.9 (15.3)	26.1 (14.0)	24.6 (5.9)
PMG within RV/PpBMI	31.6 (10.6)	27.7 (12.0)	28.5 (11.0)	29.5 (12.6)	24.0 (11.9)	24.5 (6.1)
PMG above RV/PpBMI	32.2 (25.7)	27.4 (25.2)	24.5 (6.1)	28.9 (12.3)	24.2 (8.9)	26.2 (6.6)
one-way ANOVA (p)						
overall	0.7717	0.8871	0.2124	0.9901	0.7952	0.5152

C – circumferences

Annex K

Absolute values [mm] and relative increases [%] in infants´ triceps, subscapular, and front thigh skinfold thickness calculated from 1 to 12 months of age

Absolutne vrednosti [mm] in relativna povečanja [%] dojenčkovih debelin kožnih gub na tricepsu, pod lopatico in na stegnu od 1 do 12 mesecev starosti

Absolute values of infants´ triceps, subscapular, and front thigh skinfold thickness [mm]

Absolutne vrednosti dojenčkovih debelin kožnih gub na tricepsu, pod lopatico in na stegnu [mm]

Infants´ SFT [mm]	triceps		subscapular		front thigh	
Time point	1 month	12 months	1 month	12 months	1 month	12 months
subject number (N)						
males	84	84	84	84	84	84
females	69	69	69	69	69	69
average (SD)						
males	7.3 (1.8)	8.3 (1.8)	6.5 (1.4)	5.9 (1.2)	12.2 (3.0)	13.6 (2.5)
females	7.0 (1.3)	8.4 (2.1)	6.7 (1.5)	6.0 (1.5)	12.2 (2.3)	14.0 (3.0)

SFT – skinfold thicknesses

Relative increases in infants´ triceps, subscapular, and front thigh skinfold thickness [%] calculated with respect to skinfold thickness at 1 month, according to maternal body height (MBH)

Relativna povečanja dojenčkovih debelin kožnih gub na tricepsu, pod lopatico in na stegnu [%] izračunana glede na debelino kožnih gub pri 1 mesecu, glede na telesno višino matere (MBH)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ SFT [%]	triceps	subscapular	front thigh	triceps	subscapular	front thigh
subject number (N)						
MBH < 168 cm	34	34	34	37	38	38
MBH ≥ 168 cm	50	50	50	30	31	31
average (SD)						
MBH < 168 cm	18.9 (41.0)	-3.5 (22.1)	23.6 (37.2)	23.7 (41.2)	-8.9 (24.1)	19.2 (35.2)
MBH ≥ 168 cm	20.1 (32.0)	-6.2 (24.7)	13.7 (30.3)	23.1 (28.9)	-9.4 (16.3)	15.9 (25.3)
t-test (p)						
overall	0.4428	0.3059	0.0930	0.4722	0.4608	0.3314

SFT – skinfold thicknesses

continued

continuation of Annex K.

Absolute values [mm] and relative increases [%] in infants´ triceps, subscapular, and front thigh skinfold thickness calculated from 1 to 12 months of age

Relative increases in infants´ triceps, subscapular, and front thigh skinfold thickness [%] calculated with respect to skinfold thickness at 1 month, according to maternal pre-pregnancy body mass (PpBM)

Relativna povečanja dojenčkovih debelin kožnih gub na tricepsu, pod lopatico in na stegnu [%] izračunana glede na debelino kožnih gub pri 1 mesecu, glede na prednosečniško telesno maso matere (PpBM)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ SFT [%]	triceps	subscapular	front thigh	triceps	subscapular	front thigh
subject number (N)						
PpBM < 62 kg	34	34	34	37	37	37
PpBM ≥ 62 kg	50	50	50	32	32	32
average (SD)						
PpBM < 62 kg	21.7 (37.0)	-3.9 (22.4)	19.3 (35.1)	24.8 (39.5)	-9.0 (22.2)	20.9 (31.4)
PpBM ≥ 62 kg	18.2 (35.1)	-5.9 (24.6)	16.6 (32.5)	20.0 (32.8)	-9.3 (19.4)	14.0 (30.5)
t-test (p)						
overall	0.3312	0.3486	0.3628	0.2917	0.4750	0.1782

SFT – skinfold thicknesses

Relative increases in infants´ triceps, subscapular, and front thigh skinfold thickness [%] calculated with respect to skinfold thickness at 1 month, according to maternal pre-pregnancy BMI (PpBMI)

Relativna povečanja dojenčkovih debelin kožnih gub na tricepsu, pod lopatico in na stegnu [%] izračunana glede na debelino kožnih gub pri 1 mesecu, glede na prednosečniški ITM matere (PpBMI)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ SFT [%]	triceps	subscapular	front thigh	triceps	subscapular	front thigh
subject number (N)						
PpBMI < 25 kg/m^2,	70	70	70	56	56	56
PpBMI ≥ 25 kg/m^2	14	14	14	13	13	13
average (SD)						
PpBMI < 25 kg/m^2,	21.1 (34.4)	-6.1 (22.5)	16.6 (32.8)	26.1 (37.3)	-8.4 (21.6)	20.8 (31.9)
PpBMI ≥ 25 kg/m^2	12.1 (42.0)	0.1 (29.2)	23.0 (37.1)	7.4 (28.9)	-12.4 (17.5)	4.1 (22.9)
t-test (p)						
overall	0.1965	0.1869	0.2580	**0.0475**	0.2677	**0.0398**

SFT – skinfold thicknesses

continued

continuation of Annex K.

Absolute values [mm] and relative increases [%] in infants´ triceps, subscapular, and front thigh skinfold thickness calculated from 1 to 12 months of age

Relative increases in infants´ triceps, subscapular, and front thigh skinfold thickness [%] calculated with respect to skinfold thickness at 1 month, according to maternal pregnancy mass gain (PMG)

Relativna povečanja dojenčkovih debelin kožnih gub na tricepsu, pod lopatico in na stegnu [%] izračunana glede na debelino kožnih gub pri 1 mesecu, glede na pridobljeno maso matere v nosečnosti (PMG)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ SFT [%]	triceps	subscapular	front thigh	triceps	subscapular	front thigh
subject number (N)						
PMG < 16 kg	58	58	58	51	51	51
PMG ≥ 16 kg	26	26	26	18	18	18
average (SD)						
PMG < 16 kg	22.3 (39.0)	-3.6 (25.6)	20.6 (33.6)	20.5 (37.3)	-11.0 (20.6)	15.4 (29.3)
PMG ≥ 16 kg	13.5 (26.4)	-8.4 (18.6)	11.2 (32.7)	28.5 (34.0)	-4.0 (21.1)	24.2 (35.3)
t-test (p)						
overall	0.1493	0.1974	0.1184	0.2145	0.1124	0.1519

SFT – skinfold thicknesses

Relative increases in infants´ triceps, subscapular, and front thigh skinfold thickness [%] calculated with respect to skinfold thickness at 1 month, categorized according to the appropriateness of maternal pregnancy mass gain (PMG) determined relative to the recommended values according to maternal pre-pregnancy BMI (RV/PpBMI; in Table 4)

Relativna povečanja dojenčkovih debelin kožnih gub na tricepsu, pod lopatico in na stegnu [%] izračunana glede na debelino kožnih gub pri 1 mesecu, glede na ustreznost pridobljene mase matere v nosečnosti (PMG) glede na priporočene vrednosti glede na prednosečniški ITM matere (RV/PpBMI; v Preglednici 4)

Relative increases in	Males (1 to 12 months)			Females (1 to 12 months)		
infants´ SFT [%]	triceps	subscapular	front thigh	triceps	subscapular	front thigh
subject number (N)						
PMG below RV/PpBMI	15	15	15	19	19	19
PMG within RV/PpBMI	40	40	40	26	26	26
PMG above RV/PpBMI	29	29	29	24	24	24
average (SD)						
PMG below RV/PpBMI	15.0 (22.4)	-11.4 (24.9)	16.2 (32.1)	30.3 (49.2)	-11.9 (23.1)	20.4 (36.7)
PMG within RV/PpBMI	25.7 (40.3)	-1.9 (24.2)	22.7 (35.7)	20.0 (28.5)	-9.1 (19.2)	18.9 (26.4)
PMG above RV/PpBMI	13.5 (34.0)	-6.3 (22.1)	11.6 (30.5)	19.3 (32.7)	-7.0 (21.2)	14.3 (31.7)
one-way ANOVA (p)						
overall	0.3249	0.3910	0.3872	0.5683	0.7418	0.7873

SFT – skinfold thicknesses

Annex L

Absolute values [%] and relative increases [%] in infants´ body fat from 1 to 12 months of age

Absolutne vrednosti [%] in relativna povečanja [%] dojenčkovega telesnega maščobnega tkiva od 1 do 12 mesecev starosti

Absolute values of infants´ body fat [%] calculated according to equations of Durnin and Womersly (1974) and Siri (1961)

Absolutne vrednosti dojenčkovega telesnega maščobnega tkiva [%] izračunane po enačbah Durnin in Womersly (1974) ter Siri (1961)

Infants´ body fat [%]		
Time point	1 month	12 months
subject number (N)		
males	84	84
females	69	69
average (SD)		
males	11.7 (3.0)	13.3 (2.6)
females	16.3 (2.2)	18.4 (2.9)

continued

continuation of Annex L.

Absolute values [%] and relative increases [%] in infants´ body fat from 1 to 12 months of age

Relative increases in infants´ body fat [%] calculated with respect to body fat at 1 month, according to low or high maternal body height (cut-off point at 168 cm), pre-pregnancy body mass (cut-off point at 62 kg), pre-pregnancy BMI (cut-off point at 25 kg/m^2), pregnancy mass gain (cut-off point at 16 kg), and according to the appropriateness of maternal pregnancy mass gain determined relative to the recommended values according to maternal pre-pregnancy BMI (in Table 4)

Relativna povečanja dojenčkovega telesnega maščobnega tkiva [%] izračunana glede na maščobno tkivo pri 1 mesecu, glede na nizko ali visoko telesno višino (razmejeno pri 168 cm), prednosečniško telesno maso (razmejeno pri 62 kg), prednosečniški ITM matere (razmejeno pri 25 kg/m^2), pridobljeno maso matere v nosečnosti (razmejeno pri 16 kg) in glede na ustreznost pridobljene mase matere v nosečnosti glede na priporočene vrednosti glede na prednosečniški ITM matere (v Preglednici 4)

Relative increases in infants´ body fat [%]	Males (1 to 12 months)				
Maternal anthropometric parameter	body height	pre-pregnancy body mass	pre-pregnancy BMI	pregnancy mass gain	appropriateness of mass gain
subject number (N)					
low	34	34	70	58	15
appropriate					40
high	50	50	14	26	29
average (SD)					
low	19.3 (42.0)	21.8 (37.3)	25.8 (54.3)	27.4 (60.1)	15.0 (23.3)
appropriate					33.6 (67.8)
high	26.2 (58.7)	24.6 (60.9)	11.4 (41.5)	14.5 (27.8)	13.8 (34.4)
t-test or ANOVA (p)					
overall	0.2772	0.4054	0.1746	0.1498	0.2406

Relative increases in infants´ body fat [%]	Females (1 to 12 months)				
Maternal anthropometric parameter	body height	pre-pregnancy body mass	pre-pregnancy BMI	pregnancy mass gain	appropriateness of mass gain
subject number (N)					
low	38	37	63	51	19
appropriate					26
high	31	30	14	18	24
average (SD)					
low	13.6 (25.1)	15.4 (22.6)	16.6 (22.4)	12.7 (22.2)	17.8 (27.7)
appropriate					12.8 (18.1)
high	15.2 (18.7)	13.0 (21.8)	4.6 (20.3)	18.9 (22.7)	13.1 (22.5)
t-test or ANOVA (p)					
overall	0.3868	0.3329	**0.0406**	0.1563	0.7273

Annex M

Proportions of preterm and full-term infants according to mothers' age at delivery (VPT – very preterm, MPT – moderately preterm, FT – full-term)

Delež nedonošenčkov in donošenčkov glede na starost matere ob rojstvu otroka (VPT – zelo prezgodaj rojeni, MPT – zmerno prezgodaj rojeni, FT – donošeni)

Age group [years]	All	<21	21 to 25	26 to 30	31 to 35	>35
subject number (N, (%))						
VPT	43	6, (16.2)	12, (6.7)	10, (6.3)	9, (12.7)	6, (24.0)
MPT	178	15, (40.5)	75, (41.9)	53, (33.1)	30, (42.3)	5, (20.0)
FT	251	16, (43.2)	92, (51.4)	97, (60.6)	32, (45.1)	14, (56.0)
average mothers' age (SD)						
VPT	27.3 (6.4)					
MPT	26.3 (4.9)					
FT	26.8 (4.6)					
one-way ANOVA (p)						
overall averages	0.4110					
Chi-square (p) between mothers` age groups						
VPT	**<0.01**					
MPT	**<0.05**					
FT	**<0.05**					

Annex N

Absolute values [cm], z-scores, and relative increases [%] of body height

Absolutne vrednosti [cm], z-vrednosti in relativna povečanja [%] telesne višine preiskovancev

Absolute values of body height [cm]

Absolutne vrednosti telesne višine [cm] preiskovancev

Age		birth	discharge	1 year	2 years	3 years	8 years
subject number (N)							
males	VPT	24	18	21	21	19	12
	MPT	90	65	65	67	65	52
	FT	139	117	109	111	106	85
females	VPT	19	19	20	19	17	12
	MPT	88	65	72	60	57	45
	FT	111	101	91	89	85	70
average (SD)							
males	PT	45.5 (4.2)	47.6 (2.1)	74.9 (3.3)	87.9 (3.6)	97.0 (4.6)	129.0 (6.2)
	VPT	40.1 (3.6)	47.0 (1.7)	73.3 (3.1)	86.1 (3.0)	95.5 (3.7)	125.5 (6.4)
	MPT	47.0 (3.1)	47.8 (2.1)	75.5 (3.2)	88.4 (3.7)	97.4 (4.8)	129.8 (6.0)
	FT	51.9 (2.1)	52.0 (2.0)	76.4 (2.9)	88.7 (3.3)	97.8 (4.0)	129.7 (5.8)
females	PT	44.7 (4.2)	47.1 (2.1)	72.9 (3.6)	85.7 (3.6)	94.7 (6.1)	127.2 (5.3)
	VPT	37.7 (3.7)	46.3 (1.6)	71.9 (3.3)	84.1 (2.8)	93.3 (3.7)	125.8 (3.6)
	MPT	46.2 (2.4)	47.3 (2.2)	73.1 (3.7)	86.2 (2.9)	95.1 (6.7)	127.5 (5.6)
	FT	51.1 (2.1)	51.1 (2.2)	75.0 (3.3)	87.6 (3.7)	97.5 (3.7)	130.1 (5.3)
t-test (p)							
males PT vs. FT		**<0.0001**	**<0.0001**	**<0.001**	**0.0466**	0.0501	0.2243
males VPT vs. peers[a]		**<0.0001**	**<0.0001**	**<0.001**	**<0.001**	**0.0186**	**0.0088**
females PT vs. FT		**<0.0001**	**<0.0001**	**<0.0001**	**<0.001**	**<0.001**	**0.0012**
females VPT vs. peers[a]		**<0.0001**	**<0.0001**	**0.0038**	**<0.001**	**0.0069**	**0.0220**
one-way ANOVA (p)[b]							
males		**<0.0001**	**<0.0001**	**<0.001**	**0.0068**	0.0926	0.0605
females		**<0.0001**	**<0.0001**	**<0.0001**	**<0.001**	**0.0013**	**0.0057**
Tukey HSD post hoc (p)							
males	VPT vs. MPT	**<0.01**	nsg	**<0.01**	**<0.05**	NA	NA
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	NA	NA
	MPT vs. FT	**<0.01**	**<0.01**	nsg	nsg	NA	NA
females	VPT vs. MPT	**<0.01**	nsg	nsg	**<0.01**	nsg	nsg
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.05**
	MPT vs. FT	**<0.01**	**<0.01**	**<0.05**	nsg	nsg	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Absolute values of body height [cm]

Age		9 years	10 years	11 years	12 years	13 years	14 years
subject number (N)							
males	VPT	18	20	21	22	20	19
	MPT	69	71	69	70	70	66
	FT	106	109	112	115	112	106
females	VPT	12	13	12	12	13	14
	MPT	57	61	61	60	59	58
	FT	86	90	90	93	88	85
average (SD)							
males	PT	134.4 (7.0)	140.0 (7.2)	145.3 (7.6)	150.7 (8.0)	157.3 (8.9)	164.9 (8.9)
	VPT	131.1 (6.8)	136.6 (7.2)	142.2 (8.0)	147.7 (8.6)	153.8 (9.5)	162.0 (10.3)
	MPT	135.2 (6.9)	141.0 (7.0)	146.2 (7.3)	151.6 (7.6)	158.3 (8.4)	165.7 (8.4)
	FT	134.6 (5.8)	140.1 (6.1)	145.4 (6.2)	151.0 (6.8)	157.6 (8.0)	164.8 (8.6)
females	PT	133.0 (5.9)	138.4 (5.9)	144.9 (6.4)	151.5 (6.4)	157.3 (5.9)	160.7 (5.3)
	VPT	131.6 (4.3)	136.8 (4.1)	143.3 (4.9)	150.4 (5.4)	155.7 (5.3)	158.5 (4.2)
	MPT	133.3 (6.2)	138.7 (6.2)	145.3 (6.7)	151.7 (6.6)	157.7 (6.0)	161.2 (5.5)
	FT	135.1 (6.3)	141.2 (6.5)	147.4 (7.0)	153.8 (7.3)	159.2 (6.9)	163.4 (6.0)
t-test (p)							
males PT vs. FT		0.3816	0.4436	0.4581	0.3837	0.4142	0.4819
males VPT vs. peers[a]		**0.0081**	**0.0064**	**0.0125**	**0.0165**	**0.0194**	0.0698
females PT vs. FT		**0.0154**	**0.0027**	**0.0119**	**0.0194**	**0.0390**	**0.0016**
females VPT vs. peers[a]		0.0616	**0.0334**	0.0603	0.1103	0.0628	**0.0069**
one-way ANOVA (p)[b]							
males		**0.0469**	**0.0323**	0.0586	0.0878	0.0997	0.2740
females		0.0651	**0.0126**	0.0522	0.0990	0.1270	**0.0037**
Tukey HSD post hoc (p)							
males	VPT vs. MPT	**<0.05**	**<0.01**	NA	NA	NA	NA
	VPT vs. FT	**<0.05**	**<0.05**	NA	NA	NA	NA
	MPT vs. FT	nsg	nsg	NA	NA	NA	NA
females	VPT vs. MPT	NA	nsg	NA	NA	NA	nsg
	VPT vs. FT	NA	**<0.05**	NA	NA	NA	**<0.01**
	MPT vs. FT	NA	**<0.05**	NA	NA	NA	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Absolute values of body height [cm]

Age		15 years	16 years	17 years	18 years	19 years	26 years
subject number (N)							
males	VPT	19	18	13	11	9	2
	MPT	64	46	37	36	27	3
	FT	102	77	69	59	41	10
females	VPT	13	13	12	12	7	4
	MPT	53	48	35	30	23	8
	FT	78	60	51	47	42	7
average (SD)							
males	PT	171.7 (8.4)	175.0 (7.5)	178.5 (6.7)	180.0 (6.5)	180.4 (6.7)	181.8 (6.5)
	VPT	168.7 (9.6)	172.0 (7.7)	175.5 (6.9)	177.8 (6.6)	177.6 (7.9)	177.7 (10.4)
	MPT	172.6 (7.8)	176.1 (7.2)	179.5 (6.4)	180.7 (6.3)	181.4 (6.1)	184.5 (1.3)
	FT	171.7 (8.0)	175.6 (6.8)	179.0 (6.2)	179.8 (6.1)	179.8 (5.9)	179.8 (7.2)
females	PT	162.9 (5.4)	163.7 (5.4)	164.4 (5.4)	165.0 (5.7)	165.1 (5.0)	164.0 (7.4)
	VPT	160.4 (4.1)	161.1 (4.0)	162.1 (3.4)	162.4 (3.5)	162.5 (2.9)	158.7 (4.8)
	MPT	163.5 (5.5)	164.4 (5.5)	165.2 (5.8)	166.0 (6.1)	165.9 (5.2)	166.6 (7.3)
	FT	166.0 (5.7)	166.9 (5.9)	167.1 (6.1)	167.7 (6.3)	167.3 (6.3)	169.9 (5.1)
t-test (p)							
males PT vs. FT		0.4891	0.3008	0.3438	0.4358	0.3292	0.3048
males VPT vs. peers[a]		**0.0438**	**0.0173**	**0.0265**	0.1167	0.0966	NA
females PT vs. FT		**<0.001**	**0.0012**	**0.0117**	**0.0171**	**0.0374**	**0.0238**
females VPT vs. peers[a]		**0.0028**	**0.0031**	**0.0096**	**0.0069**	**0.0260**	NA
one-way ANOVA (p)[b]							
males		0.1800	0.0999	0.1420	0.3950	0.2520	NA
females		**0.0010**	**0.0018**	**0.0212**	**0.0229**	0.0808	NA
Tukey HSD post hoc (p)							
females	VPT vs. MPT	nsg	nsg	nsg	nsg	NA	NA
	VPT vs. FT	**<0.01**	**<0.01**	**<0.05**	**<0.05**	NA	NA
	MPT vs. FT	nsg	nsg	nsg	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Body height z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Z-vrednosti telesne višine izračunane glede na Usher in McLean (1969) in WHO (2004) standarde

Age		birth	discharge	1 year	2 years	3 years	8 years
subject number (N)							
males	VPT	24	18	21	21	19	12
	MPT	90	65	65	67	65	52
	FT	139	117	109	111	106	85
females	VPT	19	19	20	19	17	12
	MPT	88	65	72	60	56	45
	FT	111	101	91	89	85	70
average (SD) standard values [cm]							
males		34.6 (1.5) 51.7 (1.9)	49.9 (1.9)	75.7 (2.4) 80.2 (2.6)	87.1 (3.1) 90.4 (3.3)	96.1 (3.7) 98.6 (3.9)	127.3 (5.6)
females		34.6 (1.5) 51.7 (1.9)	49.1 (1.9)	71.4 (2.6) 75.8 (2.8)	85.7 (3.2) 89.1 (3.4)	95.1 (3.8) 97.7 (4.0)	126.6 (5.8)
average z-scores (SD)							
males	PT	0.46 (1.48)	-1.20 (1.08)	-0.98 (1.44)	-0.14 (1.19)	-0.01 (1.22)	0.30 (1.11)
	VPT	0.39 (1.71)	-1.53 (0.88)	-2.01 (1.18)	-0.92 (0.89)	-0.57 (0.93)	-0.33 (1.13)
	MPT	0.48 (1.42)	-1.11 (1.12)	-0.65 (1.37)	0.11 (1.17)	0.16 (1.26)	0.44 (1.07)
	FT	0.57 (1.02)	1.11 (1.06)	0.29 (1.19)	0.53 (1.08)	0.47 (1.08)	0.43 (1.04)
females	PT	-0.04 (1.22)	-1.07 (1.09)	-0.31 (1.05)	-0.41 (1.16)	-0.21 (1.01)	0.10 (0.92)
	VPT	-0.58 (1.55)	-1.47 (0.86)	-0.65 (1.10)	-1.17 (1.56)	-0.94 (0.99)	-0.15 (0.62)
	MPT	0.08 (1.11)	-0.96 (1.13)	-0.22 (1.02)	-0.16 (0.88)	0.01 (0.91)	0.16 (0.97)
	FT	0.15 (1.03)	1.06 (1.17)	0.30 (0.91)	0.60 (1.16)	0.62 (0.98)	0.60 (0.92)
t-test (p)							
males PT vs. FT		0.2354	**<0.0001**	**<0.0001**	**<0.0001**	**0.0024**	0.2243
males VPT vs. peers[a]		0.2873	**<0.0001**	**<0.0001**	**<0.0001**	**<0.001**	**0.0088**
females PT vs. FT		0.1158	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0012**
females VPT vs. peers[a]		**0.0049**	**<0.0001**	**0.0015**	**<0.0001**	**<0.0001**	**0.0220**
one-way ANOVA (p)[b]							
males		0.7337	**<0.0001**	**<0.0001**	**<0.0001**	**0.0001**	0.0605
females		**0.0332**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0058**
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	nsg	**<0.01**	**<0.01**	**<0.05**	NA
	VPT vs. FT	NA	**<0.01**	**<0.01**	**<0.01**	**<0.01**	NA
	MPT vs. FT	NA	**<0.01**	**<0.01**	nsg	nsg	NA
females	VPT vs. MPT	**<0.05**	nsg	nsg	**<0.01**	**<0.01**	nsg
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.05**
	MPT vs. FT	nsg	**<0.01**	nsg	**<0.01**	**<0.05**	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Body height z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Age		9 years	10 years	11 years	12 years	13 years	14 years
subject number (N)							
males	VPT	18	20	21	22	20	19
	MPT	69	71	69	70	70	66
	FT	106	109	112	115	112	106
females	VPT	12	13	12	12	13	14
	MPT	57	61	61	60	59	58
	FT	86	90	90	93	88	85
average (SD) standard values [cm]							
males		132.6 (6.0)	137.8 (6.4)	143.1 (6.7)	149.1 (7.1)	156.0 (7.5)	163.2 (7.7)
females		132.5 (6.1)	138.6 (6.4)	145.0 (6.6)	151.2 (6.9)	156.4 (6.9)	159.8 (6.9)
average z-scores (SD)							
males	PT	0.29 (1.17)	0.35 (1.13)	0.32 (1.13)	0.23 (1.13)	0.18 (1.18)	0.21 (1.16)
	VPT	-0.25 (1.14)	-0.19 (1.13)	-0.14 (1.19)	-0.19 (1.22)	-0.29 (1.27)	-0.15 (1.34)
	MPT	0.43 (1.15)	0.50 (1.09)	0.46 (1.08)	0.36 (1.07)	0.31 (1.13)	0.32 (1.09)
	FT	0.34 (0.96)	0.37 (0.96)	0.34 (0.92)	0.27 (0.95)	0.21 (1.06)	0.21 (1.12)
females	PT	0.08 (0.97)	-0.03 (0.92)	-0.01 (0.97)	0.05 (0.93)	0.14 (0.86)	0.13 (0.77)
	VPT	-0.16 (0.71)	-0.28 (0.63)	-0.25 (0.75)	-0.11 (0.78)	-0.10 (0.77)	-0.19 (0.61)
	MPT	0.13 (1.01)	0.02 (0.97)	0.04 (1.01)	0.08 (0.96)	0.19 (0.87)	0.21 (0.79)
	FT	0.43 (1.01)	0.40 (1.02)	0.36 (1.06)	0.38 (1.06)	0.40 (1.00)	0.53 (0.87)
t-test (p)							
males PT vs. FT		0.3816	0.4436	0.4581	0.3837	0.4142	0.4819
males VPT vs. peers[a]		**0.0081**	**0.0064**	**0.0125**	**0.0165**	**0.0194**	0.0698
females PT vs. FT		**0.0154**	**0.0027**	**0.0119**	**0.0194**	**0.0390**	**0.0016**
females VPT vs. peers[a]		0.0616	**0.0334**	0.0603	0.1103	0.0628	**0.0069**
one-way ANOVA (p)[b]							
males		**0.0469**	**0.0323**	0.0586	0.0878	0.0997	0.2740
females		0.0651	**0.0126**	0.0522	0.0990	0.1270	**0.0037**
Tukey HSD post hoc (p)							
males	VPT vs. MPT	**<0.05**	**<0.01**	NA	NA	NA	NA
	VPT vs. FT	**<0.05**	**<0.05**	NA	NA	NA	NA
	MPT vs. FT	nsg	nsg	NA	NA	NA	NA
females	VPT vs. MPT	NA	nsg	NA	NA	NA	nsg
	VPT vs. FT	NA	**<0.05**	NA	NA	NA	**<0.01**
	MPT vs. FT	NA	nsg	NA	NA	NA	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Body height z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Age		15 years	16 years	17 years	18 years	19 years	26 years
subject number (N)							
males	VPT	19	18	13	11	9	2
	MPT	64	46	37	36	27	3
	FT	102	77	69	59	41	10
females	VPT	13	13	12	12	7	4
	MPT	53	48	35	30	23	8
	FT	78	60	51	47	42	7
average (SD) standard values [cm]							
males		169.0 (7.8)	172.9 (7.8)	175.2 (7.6)	176.1 (7.5)	176.5 (7.3)	176.5 (7.3)
females		161.7 (6.8)	162.5 (6.8)	162.9 (6.6)	163.1 (6.6)	163.2 (6.5)	163.2 (6.5)
average z-scores (SD)							
males	PT	0.35 (1.07)	0.27 (0.96)	0.43 (0.88)	0.52 (0.86)	0.54 (0.92)	0.72 (0.89)
	VPT	-0.04 (1.24)	-0.11 (0.98)	0.04 (0.91)	0.22 (0.89)	0.14 (1.08)	0.16 (1.42)
	MPT	0.46 (1.00)	0.41 (0.92)	0.57 (0.84)	0.61 (0.85)	0.67 (0.84)	1.10 (0.18)
	FT	0.34 (1.02)	0.35 (0.87)	0.49 (0.82)	0.49 (0.81)	0.45 (0.80)	0.51 (0.97)
females	PT	0.18 (0.80)	0.18 (0.79)	0.23 (0.82)	0.28 (0.86)	0.30 (0.77)	0.12 (1.14)
	VPT	-0.19 (0.61)	-0.20 (0.58)	-0.12 (0.51)	-0.11 (0.53)	-0.11 (0.44)	-0.69 (0.73)
	MPT	0.27 (0.82)	0.28 (0.81)	0.35 (0.87)	0.44 (0.92)	0.42 (0.81)	0.53 (1.12)
	FT	0.64 (0.84)	0.65 (0.87)	0.64 (0.92)	0.70 (0.96)	0.69 (0.98)	1.03 (0.78)
t-test (p)							
males PT vs. FT		0.4891	0.3008	0.3438	0.4358	0.3292	0.3048
males VPT vs. peers[a]		**0.0438**	**0.0173**	**0.0265**	0.1167	0.0966	0.2788
females PT vs. FT		**<0.001**	**0.0012**	**0.0117**	**0.0171**	**0.0374**	**0.0238**
females VPT vs. peers[a]		**0.0028**	**0.0031**	**0.0096**	**0.0069**	**0.0260**	**0.0063**
one-way ANOVA (p)[b]							
males		0.1800	0.0999	0.1420	0.3950	0.2506	NA
females		**0.0010**	**0.0018**	**0.0211**	**0.0226**	0.0800	NA
Tukey HSD post hoc (p)							
females	VPT vs. MPT	nsg	nsg	nsg	nsg	NA	NA
	VPT vs. FT	**<0.01**	**<0.01**	**<0.05**	**<0.05**	NA	NA
	MPT vs. FT	nsg	nsg	nsg	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Relative increases in body height [%] calculated with respect to birth height

Relativna povečanja telesne višine [%] izračunana glede na porodno višino

Age period		birth to disch.	disch. to 1 years	1 to 2 years	2 to 3 years	8 to 9 years
subject number (N)						
males	VPT	18	18	21	18	12
	MPT	65	57	55	56	52
	FT	116	106	82	82	82
females	VPT	18	18	18	16	9
	MPT	65	58	51	46	44
	FT	101	89	69	66	69
average (SD)						
males	PT	5.4 (9.5)	59.5 (10.0)	28.6 (7.0)	19.3 (6.4)	14.2 (5.3)
	VPT	18.3 (11.6)	65.2 (10.8)	32.3 (7.4)	22.5 (8.3)	16.2 (5.3)
	MPT	1.8 (4.6)	58.2 (9.2)	27.2 (6.4)	18.3 (5.3)	13.7 (5.3)
	FT	0.0 (0.8)	47.0 (6.0)	24.6 (6.4)	1.71 (5.4)	11.3 (3.9)
females	PT	7.2 (12.0)	59.4 (10.2)	29.9 (8.4)	21.3 (7.3)	13.1 (2.9)
	VPT	24.8 (13.3)	68.0 (8.3)	33.3 (8.0)	25.1 (8.6)	15.0 (3.9)
	MPT	2.3 (5.0)	56.8 (9.3)	28.7 (8.2)	20.0 (6.5)	12.7 (2.5)
	FT	0.0 (1.3)	46.7 (7.9)	25.4 (7.5)	18.7 (5.6)	12.1 (2.9)
t-test (p)						
males PT vs. FT		**<0.0001**	**<0.0001**	**<0.001**	**0.0096**	**<0.001**
males VPT vs. peers[a]		**<0.0001**	**<0.0001**	**<0.0001**	**<0.001**	**0.0026**
females PT vs. FT		**<0.0001**	**<0.0001**	**<0.001**	**0.0122**	**0.0398**
females VPT vs. peers[a]		**<0.0001**	**<0.0001**	**<0.001**	**<0.001**	**0.0047**
one-way ANOVA (p)[b]						
males		**<0.0001**	**<0.0001**	**<0.0001**	**0.0017**	**<0.001**
females		**<0.0001**	**<0.0001**	**<0.001**	**0.0022**	**0.0238**
Tukey HSD post hoc (p)						
males	VPT vs. MPT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	nsg
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
	MPT vs. FT	nsg	**<0.01**	nsg	nsg	nsg
females	VPT vs. MPT	**<0.01**	**<0.01**	nsg	**<0.01**	**<0.05**
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.05**
	MPT vs. FT	nsg	**<0.01**	nsg	nsg	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Relative increases in body height [%] calculated with respect to birth height

Age period		9 to 10 years	10 to 11 years	11 to 12 years	12 to 13 years	13 to 14 years
subject number (N)						
males	VPT	18	20	21	20	19
	MPT	69	69	66	69	65
	FT	103	107	109	109	106
females	VPT	11	11	11	11	12
	MPT	56	60	59	58	57
	FT	84	86	89	87	83
average (SD)						
males	PT	12.0 (3.1)	12.0 (3.9)	11.8 (4.2)	14.8 (5.7)	17.3 (5.6)
	VPT	12.2 (4.0)	13.8 (4.4)	12.8 (3.3)	15.5 (6.3)	19.6 (6.6)
	MPT	11.9 (2.9)	11.5 (3.6)	11.4 (4.4)	14.5 (5.5)	16.6 (5.1)
	FT	10.7 (3.2)	9.9 (2.9)	10.6 (3.7)	12.9 (4.6)	14.2 (4.2)
females	PT	12.6 (4.6)	15.1 (4.4)	14.9 (5.1)	12.8 (4.9)	7.2 (4.5)
	VPT	14.1 (5.5)	17.4 (4.9)	17.8 (6.3)	12.0 (4.9)	7.9 (5.6)
	MPT	12.4 (4.4)	14.7 (4.2)	14.3 (4.7)	12.9 (4.9)	7.0 (4.3)
	FT	11.8 (3.6)	12.4 (3.3)	12.6 (3.8)	10.6 (4.2)	8.5 (4.7)
t-test (p)						
males PT vs. FT		**0.0039**	**<0.0001**	**0.0185**	**0.0058**	**<0.0001**
males VPT vs. peers[a]		0.0998	**<0.0001**	**0.0191**	0.0550	**<0.001**
females PT vs. FT		0.1004	**<0.0001**	**<0.001**	**0.0013**	**0.0386**
females VPT vs. peers[a]		0.0505	**<0.001**	**<0.001**	0.3618	0.4986
one-way ANOVA (p)[b]						
males		**0.0319**	**<0.0001**	**0.0401**	**0.0315**	**<0.0001**
females		0.1899	**<0.0001**	**<0.001**	**0.0119**	0.1502
Tukey HSD post hoc (p)						
males	VPT vs. MPT	nsg	**<0.01**	nsg	nsg	**<0.01**
	VPT vs. FT	nsg	**<0.01**	**<0.05**	nsg	**<0.01**
	MPT vs. FT	nsg	nsg	nsg	nsg	nsg
females	VPT vs. MPT	NA	nsg	**<0.05**	nsg	NA
	VPT vs. FT	NA	**<0.01**	**<0.01**	nsg	NA
	MPT vs. FT	NA	nsg	nsg	nsg	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex N.

Absolute values [cm], z-scores, and relative increases [%] of body height

Relative increases in body height [%] calculated with respect to birth height

Age period		14 to 15 years	15 to 16 years	16 to 17 years	17 to 18 years	18 to 19 years
subject number (N)						
males	VPT	19	18	13	11	9
	MPT	63	46	36	35	24
	FT	100	75	66	58	38
females	VPT	12	11	11	11	5
	MPT	51	46	35	28	19
	FT	77	58	48	45	37
average (SD)						
males	PT	15.4 (5.3)	9.6 (6.1)	6.5 (5.3)	3.3 (3.6)	2.0 (3.3)
	VPT	16.7 (6.2)	10.9 (6.7)	9.5 (7.0)	4.5 (3.9)	2.1 (3.4)
	MPT	15.0 (5.0)	9.1 (5.8)	5.4 (4.1)	2.9 (3.5)	2.0 (3.3)
	FT	13.5 (5.4)	8.3 (4.7)	4.7 (3.9)	2.5 (3.1)	1.2 (3.1)
females	PT	5.0 (4.4)	2.0 (3.3)	1.4 (2.5)	1.1 (2.7)	0.7 (3.1)
	VPT	5.6 (4.8)	2.8 (2.6)	1.4 (3.4)	0.5 (3.4)	0.0 (5.8)
	MPT	4.9 (4.3)	1.8 (3.4)	1.4 (2.2)	1.4 (2.3)	1.2 (2.0)
	FT	5.3 (4.3)	1.9 (2.6)	1.4 (1.9)	1.0 (1.3)	0.6 (1.1)
t-test (p)						
males PT vs. FT		**0.0089**	0.0760	**0.0214**	0.1189	0.1567
males VPT vs. peers[a]		**0.0216**	**0.0418**	**<0.001**	**0.0368**	0.3159
females PT vs. FT		0.3884	0.3997	0.4237	0.3852	0.4371
females VPT vs. peers[a]		0.3551	0.1538	0.4869	0.1462	**0.0228**
one-way ANOVA (p)[b]						
males		**0.0249**	0.1535	**0.0022**	0.1972	0.6209
females		0.8272	0.5672	0.9901	0.4397	0.0822
Tukey HSD post hoc (p)						
males	VPT vs. MPT	nsg	NA	**<0.01**	NA	NA
	VPT vs. FT	**<0.05**	NA	**<0.01**	NA	NA
	MPT vs. FT	nsg	NA	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex O

Absolute values [kg] and z-scores of body mass

Absolutne vrednosti [kg] in z-vrednosti telesne mase preiskovancev

Absolute values of body mass [kg]

Absolutne vrednosti telesne mase [kg] preiskovancev

Age		birth	discharge	1 year	2 years	3 years	8 years
subject number (N)							
males	VPT	24	21	21	20	19	12
	MPT	90	78	73	63	64	52
	FT	140	120	120	99	110	85
females	VPT	20	20	20	19	17	12
	MPT	88	79	75	54	59	45
	FT	111	103	100	80	86	70
average (SD)							
males	PT	2.26 (0.68)	2.48 (0.33)	9.8 (1.4)	12.7 (1.8)	15.2 (2.3)	27.9 (6.3)
	VPT	1.41 (0.34)	2.36 (0.20)	9.1 (1.3)	12.3 (1.7)	14.7 (1.9)	25.0 (5.1)
	MPT	2.49 (0.55)	2.52 (0.35)	10.0 (1.3)	12.8 (1.8)	15.3 (2.4)	28.6 (6.4)
	FT	3.49 (0.45)	3.35 (0.41)	10.5 (1.2)	13.3 (1.5)	15.4 (1.8)	27.5 (5.1)
females	PT	2.11 (0.62)	2.37 (0.31)	9.1 (1.2)	11.8 (1.4)	14.4 (1.8)	27.2 (4.9)
	VPT	1.15 (0.32)	2.20 (0.13)	8.5 (1.2)	11.5 (1.5)	14.4 (1.7)	27.0 (5.1)
	MPT	2.33 (0.43)	2.42 (0.33)	9.2 (1.2)	11.9 (1.4)	14.5 (1.8)	27.3 (4.9)
	FT	3.37 (0.46)	3.26 (0.44)	9.9 (1.3)	13.0 (1.7)	15.3 (2.0)	28.3 (4.6)
t-test (p)							
males PT vs. FT		**<0.0001**	**<0.0001**	**<0.0001**	**0.0040**	0.2616	0.3426
males VPT vs. peers[a]		**<0.0001**	**<0.0001**	**<0.0001**	**0.0114**	0.0943	**0.0421**
females PT vs. FT		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0023**	0.1023
females VPT vs. peers[a]		**<0.0001**	**<0.0001**	**<0.0001**	**0.0039**	0.1152	0.2814
one-way ANOVA (p)[b]							
males		**<0.0001**	**<0.0001**	**<0.0001**	**0.0116**	0.4180	0.1286
females		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0180**	0.4450
Tukey HSD post hoc (p)							
males	VPT vs. MPT	**<0.01**	nsg	**<0.01**	nsg	NA	NA
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	NA	NA
	MPT vs. FT	**<0.01**	**<0.01**	nsg	nsg	NA	NA
females	VPT vs. MPT	**<0.01**	**<0.05**	**<0.05**	nsg	nsg	NA
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	**<0.01**	nsg	NA
	MPT vs. FT	**<0.01**	**<0.01**	**<0.05**	**<0.05**	nsg	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex O.

Absolute values [kg] and z-scores of body mass

Absolute values of body mass [kg]

Age		9 years	10 years	11 years	12 years	13 years	14 years
subject number (N)							
males	VPT	18	20	21	22	20	19
	MPT	69	71	69	70	70	66
	FT	106	109	112	115	112	107
females	VPT	12	13	12	12	13	14
	MPT	57	61	61	60	59	58
	FT	86	90	90	93	88	85
average (SD)							
males	PT	30.7 (7.2)	34.9 (8.1)	38.3 (8.9)	43.2 (10.5)	48.2 (11.7)	53.7 (11.4)
	VPT	27.1 (5.6)	30.9 (6.6)	34.0 (7.3)	38.8 (9.5)	43.3 (11.2)	50.1 (11.7)
	MPT	31.7 (7.2)	36.0 (8.1)	39.6 (8.9)	44.6 (10.5)	49.6 (11.6)	54.7 (11.1)
	FT	30.4 (6.3)	33.7 (7.0)	37.8 (8.3)	41.8 (8.9)	47.7 (11.0)	53.4 (11.1)
females	PT	30.8 (6.3)	34.6 (7.6)	39.4 (8.3)	44.3 (9.5)	49.4 (9.7)	53.1 (9.9)
	VPT	30.1 (5.4)	33.9 (5.9)	39.1 (6.0)	43.3 (5.4)	48.3 (6.9)	51.5 (6.2)
	MPT	30.9 (6.5)	34.8 (7.9)	39.4 (8.7)	44.5 (10.2)	49.7 (10.2)	53.5 (10.6)
	FT	31.1 (5.5)	35.7 (7.1)	39.9 (7.9)	44.8 (9.2)	50.0 (9.6)	54.1 (9.3)
t-test (p)							
males PT vs. FT		0.3738	0.1424	0.3433	0.1425	0.3864	0.4370
males VPT vs. peers[a]		**0.0098**	**0.0159**	**0.0117**	**0.0314**	**0.0268**	0.0800
females PT vs. FT		0.3732	0.1699	0.3475	0.3551	0.3438	0.2621
females VPT vs. peers[a]		0.3082	0.2396	0.4068	0.3135	0.2819	0.1882
one-way ANOVA (p)[b]							
males		**0.0308**	**0.0132**	**0.0296**	**0.0263**	0.0867	0.2850
females		0.8700	0.5810	0.9200	0.8660	0.8260	0.6350
Tukey HSD post hoc (p)							
males	VPT vs. MPT	**<0.01**	**<0.01**	**<0.01**	**<0.05**	NA	NA
	VPT vs. FT	nsg	nsg	nsg	nsg	NA	NA
	MPT vs. FT	nsg	nsg	nsg	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex O.

Absolute values [kg] and z-scores of body mass

Absolute values of body mass [kg]

Age		15 years	16 years	17 years	18 years	19 years	26 years
subject number (N)							
males	VPT	19	18	13	11	9	2
	MPT	64	46	37	36	27	3
	FT	103	78	69	59	41	11
females	VPT	13	13	12	11	7	4
	MPT	53	48	35	30	23	8
	FT	78	60	50	46	41	9
average (SD)							
males	PT	59.4 (11.5)	63.0 (10.9)	67.6 (10.5)	70.5 (9.6)	72.7 (10.6)	81.4 (18.2)
	VPT	56.3 (12.1)	61.1 (11.2)	64.5 (9.0)	69.6 (10.7)	71.8 (12.7)	70.8 (8.8)
	MPT	60.4 (11.2)	63.8 (10.9)	68.7 (10.6)	70.8 (9.4)	73.0 (10.1)	88.5 (20.8)
	FT	59.7 (11.5)	63.6 (10.4)	67.8 (10.8)	70.9 (11.5)	73.1 (10.1)	79.3 (11.6)
females	PT	55.3 (9.4)	57.9 (9.8)	58.4 (8.9)	59.0 (10.2)	58.7 (7.9)	61.0 (11.0)
	VPT	53.0 (6.0)	53.5 (6.8)	55.0 (8.3)	55.7 (8.2)	56.2 (4.9)	60.3 (9.0)
	MPT	55.9 (10.0)	59.1 (10.2)	59.6 (8.9)	60.3 (10.8)	59.4 (8.6)	61.4 (12.5)
	FT	56.3 (9.2)	57.5 (7.6)	59.6 (7.3)	60.1 (7.6)	60.7 (9.1)	62.5 (4.3)
t-test (p)							
males PT vs. FT		0.4291	0.3728	0.4679	0.4253	0.4440	0.3591
males VPT vs. peers[a]		0.0910	0.1654	0.1228	0.3503	0.3714	0.1418
females PT vs. FT		0.2740	0.3894	0.2386	0.2861	0.1664	0.4390
females VPT vs. peers[a]		0.1238	**0.0344**	**0.0313**	0.0560	0.1217	0.4076
one-way ANOVA (p)[b]							
males		0.3870	0.6220	0.4650	0.9280	0.9480	NA
females		0.5010	0.1200	0.1780	0.2840	0.4340	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex O.

Absolute values [kg] and z-scores of body mass

Body mass z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Z-vrednosti telesne mase izračunane glede na Usher in McLean (1969) in WHO (2004) standarde

Age		birth	discharge	1 year	2 years	3 years	8 years
subject number (N)							
males	VPT	24	21	21	20	19	12
	MPT	90	78	73	63	64	52
	FT	140	120	120	99	110	85
females	VPT	20	20	20	19	17	12
	MPT	88	79	75	54	59	45
	FT	111	103	100	80	86	70
average (SD) standard values [kg]							
males		0.85 (0.10) 3.51 (0.48)	3.3 (0.6)	9.6 (1.2) 10.5 (1.2)	12.2 (1.4) 12.9 (1.6)	14.3 (1.9) 15.0 (2.0)	25.4 (4.1)
females		0.85 (0.10) 3.51 (0.48)	3.2 (0.5)	8.9 (1.2) 9.8 (1.3)	11.5 (1.5) 12.3 (1.7)	13.9 (1.9) 14.6 (2.3)	25.0 (4.7)
average z-scores (SD)							
males	PT	0.45 (1.40)	-1.36 (0.56)	-0.15 (1.23)	0.16 (1.17)	0.32 (1.22)	0.61 (1.53)
	VPT	0.42 (1.24)	-1.57 (0.34)	-0.89 (1.07)	-0.20 (1.05)	-0.02 (0.97)	-0.10 (1.24)
	MPT	0.46 (1.45)	-1.30 (0.59)	0.07 (1.19)	0.28 (1.19)	0.42 (1.28)	0.77 (1.55)
	FT	0.25 (0.90)	0.09 (0.68)	0.77 (0.99)	0.82 (1.08)	0.57 (0.95)	0.51 (1.23)
females	PT	-0.13 (1.13)	-1.65 (0.63)	-0.18 (1.05)	0.00 (0.92)	0.16 (0.88)	0.47 (1.05)
	VPT	-0.66 (1.15)	-2.00 (0.25)	-0.85 (1.01)	-0.36 (0.97)	-0.01 (0.84)	0.43 (1.09)
	MPT	-0.01 (1.10)	-1.56 (0.67)	0.00 (1.00)	0.12 (0.88)	0.21 (0.90)	0.48 (1.05)
	FT	-0.03 (0.98)	0.12 (0.87)	0.87 (1.08)	0.98 (1.13)	0.73 (1.03)	0.70 (0.97)
t-test (p)							
males PT vs. FT		0.0840	**<0.0001**	**<0.0001**	**<0.001**	0.0566	0.3426
males VPT vs. peers[a]		0.2470	**<0.0001**	**<0.0001**	**<0.0001**	**<0.001**	0.1023
females PT vs. FT		0.2455	**<0.0001**	**<0.0001**	**<0.0001**	**0.0001**	0.1023
females VPT vs. peers[a]		**0.0051**	**<0.0001**	**<0.0001**	**<0.001**	**0.0204**	0.2814
one-way ANOVA (p)[b]							
males		0.3843	**<0.0001**	**<0.0001**	**0.0001**	0.0816	0.1280
females		**0.0362**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0009**	0.4450
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	nsg	**<0.01**	nsg	NA	NA
	VPT vs. FT	NA	**<0.01**	**<0.01**	**<0.01**	NA	NA
	MPT vs. FT	NA	**<0.01**	**<0.01**	nsg	NA	NA
females	VPT vs. MPT	**<0.05**	**<0.05**	**<0.01**	nsg	nsg	NA
	VPT vs. FT	**<0.05**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	NA
	MPT vs. FT	nsg	**<0.01**	**<0.01**	**<0.01**	nsg	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continuation of Annex O.

Absolute values [kg] and z-scores of body mass

Body mass z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Age		9 years	10 years	11 years	12 years	13 years	14 years
subject number (N)							
males	VPT	18	20	21	22	20	19
	MPT	69	71	69	70	70	66
	FT	106	109	112	115	112	107
females	VPT	12	13	12	12	13	14
	MPT	57	61	61	60	59	58
	FT	86	90	90	93	88	85
average (SD) standard values [kg]							
males		28.1 (4.9)	31.2 (5.8)	34.6 (6.0)	38.9 (6.0)	44.3 (6.1)	50.6 (6.2)
females		28.2 (5.4)	31.9 (6.3)	36.2 (6.5)	41.2 (6.5)	46.0 (6.6)	50.1 (6.7)
average z-scores (SD)							
males	PT	0.53 (1.46)	0.64 (1.39)	0.61 (1.48)	0.72 (1.76)	0.64 (1.92)	0.50 (1.83)
	VPT	-0.21 (1.14)	-0.06 (1.13)	-0.09 (1.22)	-0.02 (1.58)	-0.16 (1.84)	-0.08 (1.89)
	MPT	0.73 (1.48)	0.83 (1.40)	0.83 (1.49)	0.95 (1.75)	0.87 (1.89)	0.66 (1.79)
	FT	0.47 (1.28)	0.44 (1.20)	0.53 (1.38)	0.48 (1.48)	0.56 (1.81)	0.46 (1.79)
females	PT	0.48 (1.17)	0.44 (1.20)	0.49 (1.28)	0.48 (1.46)	0.52 (1.47)	0.45 (1.47)
	VPT	0.36 (1.01)	0.31 (0.94)	0.45 (0.93)	0.33 (0.84)	0.35 (1.04)	0.21 (0.93)
	MPT	0.50 (1.21)	0.46 (1.26)	0.50 (1.34)	0.51 (1.56)	0.56 (1.55)	0.51 (1.58)
	FT	0.53 (1.03)	0.61 (1.13)	0.57 (1.22)	0.56 (1.41)	0.61 (1.45)	0.60 (1.39)
t-test (p)							
males PT vs. FT		0.3738	0.1424	0.3433	0.1425	0.3864	0.4370
males VPT vs. peers[a]		**0.0098**	**0.0159**	**0.0117**	**0.0314**	**0.0268**	0.0800
females PT vs. FT		0.3732	0.1699	0.3475	0.3551	0.3438	0.2621
females VPT vs. peers[a]		0.3082	0.2396	0.4068	0.3135	0.2819	0.1882
one-way ANOVA (p)[b]							
males		**0.0306**	**0.0133**	**0.0297**	**0.0264**	0.0867	0.2850
females		0.8700	0.5810	0.9200	0.8660	0.8260	0.6350
Tukey HSD post hoc (p)							
males	VPT vs. MPT	**<0.01**	**<0.01**	**<0.01**	**<0.05**	NA	NA
	VPT vs. FT	nsg	nsg	nsg	nsg	NA	NA
	MPT vs. FT	nsg	nsg	nsg	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex O.

Absolute values [kg] and z-scores of body mass

Body mass z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Age		15 years	16 years	17 years	18 years	19 years	26 years
subject number (N)							
males	VPT	19	18	13	11	9	2
	MPT	64	46	37	36	27	3
	FT	103	78	69	59	41	11
females	VPT	13	13	12	11	7	4
	MPT	53	48	35	30	23	8
	FT	78	60	50	46	41	9
average (SD) standard values [kg]							
males		56.6 (6.3)	61.3 (6.4)	64.8 (6.4)	67.3 (6.4)	69.2 (6.4)	74.8 (6.6)
females		52.8 (6.8)	54.7 (6.9)	55.7 (6.9)	56.7 (6.9)	57.0 (6.9)	61.3 (7.1)
average z-scores (SD)							
males	PT	0.45 (1.82)	0.27 (1.71)	0.44 (1.64)	0.50 (1.50)	0.55 (1.66)	1.00 (2.75)
	VPT	-0.06 (1.92)	-0.04 (1.74)	-0.05 (1.41)	0.35 (1.67)	0.41 (1.99)	-0.61 (1.34)
	MPT	0.60 (1.78)	0.39 (1.70)	0.61 (1.70)	0.55 (1.46)	0.60 (1.57)	2.08 (3.15)
	FT	0.50 (1.83)	0.36 (1.62)	0.46 (1.69)	0.56 (1.79)	0.60 (1.57)	1.38 (2.78)
females	PT	0.37 (1.38)	0.47 (1.42)	0.39 (1.29)	0.33 (1.48)	0.24 (1.15)	-0.04 (1.56)
	VPT	0.03 (0.89)	-0.17 (0.99)	-0.11 (1.20)	-0.14 (1.19)	-0.11 (0.71)	-0.14 (1.27)
	MPT	0.46 (1.47)	0.64 (1.48)	0.57 (1.29)	0.52 (1.56)	0.35 (1.24)	0.01 (1.76)
	FT	0.51 (1.35)	0.40 (1.11)	0.56 (1.05)	0.49 (1.11)	0.54 (1.33)	0.16 (0.60)
t-test (p)							
males PT vs. FT		0.4291	0.3728	0.4679	0.4253	0.4440	0.3591
males VPT vs. peers[a]		0.0910	0.1654	0.1228	0.3503	0.3714	0.1418
females PT vs. FT		0.2740	0.3894	0.2386	0.2861	0.1664	0.4390
females VPT vs. peers[a]		0.1238	**0.0344**	**0.0313**	0.0560	0.1217	0.4076
one-way ANOVA (p)[b]							
males		0.3870	0.6220	0.4650	0.9280	0.9513	NA
females		0.5010	0.1200	0.1780	0.2840	0.4319	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex P

Absolute values [kg/m^2] and z-scores of BMI

Absolutne vrednosti [kg/m^2] in z-vrednosti ITM-ja preiskovancev

Absolute values of BMI [kg/m^2]

Absolutne vrednosti ITM-ja [kg/m^2] preiskovancev

Age		birth	discharge	1 year	2 years	3 years	8 years
subject number (N)							
males	VPT	24	18	21	20	19	12
	MPT	90	65	65	62	64	52
	FT	139	117	109	93	107	85
females	VPT	19	19	20	19	17	12
	MPT	88	65	72	51	57	45
	FT	111	101	91	76	85	70
average (SD)							
males	PT	10.62 (1.72)	10.94 (0.93)	17.20 (1.66)	16.36 (1.56)	16.11 (1.84)	16.62 (2.71)
	VPT	8.71 (1.29)	10.83 (1.07)	16.92 (2.05)	16.48 (1.72)	16.11 (1.85)	15.74 (1.96)
	MPT	11.12 (1.44)	10.97 (0.90)	17.30 (1.51)	16.32 (1.52)	16.12 (1.85)	16.83 (2.84)
	FT	12.93 (1.05)	12.37 (0.99)	17.97 (1.66)	16.86 (1.50)	16.01 (1.67)	16.27 (2.14)
females	PT	10.31 (1.61)	10.70 (1.03)	16.93 (1.54)	16.07 (1.51)	16.26 (3.10)	16.73 (2.19)
	VPT	7.93 (1.07)	10.29 (0.76)	16.30 (1.61)	16.22 (1.79)	16.46 (1.41)	17.01 (2.41)
	MPT	10.82 (1.19)	10.83 (1.08)	17.11 (1.49)	16.01 (1.41)	16.20 (3.45)	16.68 (2.12)
	FT	12.85 (1.07)	12.40 (1.09)	17.63 (1.97)	16.66 (1.52)	16.02 (1.54)	16.64 (2.08)
t-test (p)							
males PT vs. FT		**<0.0001**	**<0.0001**	**<0.001**	**0.0151**	0.4798	0.1882
males VPT vs. peers[a]		**<0.0001**	**0.0002**	**0.0203**	0.3245	0.4925	0.1548
females PT vs. FT		**<0.0001**	**<0.0001**	**0.0042**	**0.0073**	0.2663	0.4209
females VPT vs. peers[a]		**<0.0001**	**<0.0001**	**0.0047**	0.2686	0.2751	0.2884
one-way ANOVA (p)[b]							
males		**<0.0001**	**<0.0001**	**0.0045**	0.0886	0.9230	0.2520
females		**<0.0001**	**<0.0001**	**0.0061**	0.0573	0.7620	0.8560
Tukey HSD post hoc (p)							
males	VPT vs. MPT	**<0.01**	nsg	nsg	NA	NA	NA
	VPT vs. FT	**<0.01**	**<0.01**	**<0.05**	NA	NA	NA
	MPT vs. FT	**<0.01**	**<0.01**	nsg	NA	NA	NA
females	VPT vs. MPT	**<0.01**	nsg	nsg	NA	NA	NA
	VPT vs. FT	**<0.01**	**<0.01**	**<0.01**	NA	NA	NA
	MPT vs. FT	**<0.01**	**<0.01**	nsg	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex P.

Absolute values [kg/m^2] and z-scores of BMI

Absolute values of BMI [kg/m^2]

Age		9 years	10 years	11 years	12 years	13 years	14 years
subject number (N)							
males	VPT	18	20	21	22	20	19
	MPT	69	71	69	70	70	66
	FT	106	109	112	115	112	106
females	VPT	12	13	12	12	13	14
	MPT	57	61	61	60	59	58
	FT	86	90	90	93	88	85
average (SD)							
males	PT	16.85 (2.80)	17.61 (2.88)	17.96 (2.95)	18.82 (3.30)	19.24 (3.21)	19.58 (2.87)
	VPT	15.61 (1.94)	16.37 (1.95)	16.67 (2.04)	17.56 (2.52)	18.02 (2.51)	18.84 (2.29)
	MPT	17.17 (2.91)	17.96 (3.01)	18.35 (3.09)	19.22 (3.43)	19.59 (3.31)	19.79 (3.00)
	FT	16.65 (2.47)	17.05 (2.55)	17.75 (2.89)	18.18 (2.79)	19.05 (3.20)	19.51 (2.89)
females	PT	17.29 (2.72)	17.97 (3.21)	18.64 (3.25)	19.17 (3.43)	19.87 (3.32)	20.50 (3.32)
	VPT	17.37 (2.62)	18.07 (2.90)	19.03 (2.65)	19.11 (1.72)	19.85 (1.97)	20.44 (1.86)
	MPT	17.27 (2.77)	17.94 (3.29)	18.56 (3.37)	19.18 (3.69)	19.88 (3.56)	20.51 (3.60)
	FT	16.95 (2.20)	17.86 (2.73)	18.27 (2.76)	18.86 (3.07)	19.70 (3.27)	20.23 (3.18)
t-test (p)							
males PT vs. FT		0.3015	0.0732	0.3104	0.0661	0.3357	0.4312
males VPT vs. peers[a]		**0.0273**	0.0516	**0.0254**	0.0685	0.0503	0.1314
females PT vs. FT		0.1973	0.4061	0.2175	0.2717	0.3688	0.3043
females VPT vs. peers[a]		0.3473	0.4162	0.2377	0.4501	0.4675	0.4572
one-way ANOVA (p)[b]							
males		0.0688	**0.0227**	0.0602	**0.0252**	0.1400	0.4370
females		0.6910	0.9620	0.6530	0.8300	0.9450	0.8750
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	**<0.05**	NA	**<0.05**	NA	NA
	VPT vs. FT	NA	nsg	NA	nsg	NA	NA
	MPT vs. FT	NA	nsg	NA	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex P.

Absolute values [kg/m^2] and z-scores of BMI

Absolute values of BMI [kg/m^2]

Age		15 years	16 years	17 years	18 years	19 years	26 years
subject number (N)							
males	VPT	19	18	13	11	9	2
	MPT	64	46	37	36	27	3
	FT	102	77	69	59	41	11
females	VPT	13	13	12	12	7	4
	MPT	53	48	35	30	23	8
	FT	78	60	50	46	41	9
average (SD)							
males	PT	20.02 (2.78)	20.50 (2.67)	21.16 (2.54)	21.72 (2.40)	22.33 (3.00)	24.51 (4.50)
	VPT	19.56 (2.37)	20.51 (2.49)	20.84 (1.86)	21.91 (2.32)	22.67 (2.74)	22.37 (0.18)
	MPT	20.15 (2.89)	20.49 (2.77)	21.27 (2.76)	21.66 (2.46)	22.22 (3.12)	25.95 (5.73)
	FT	20.13 (2.84)	20.51 (2.66)	21.09 (2.75)	21.93 (3.41)	22.56 (2.63)	25.72 (4.79)
females	PT	20.81 (3.07)	21.55 (3.13)	21.55 (2.61)	21.60 (3.10)	21.49 (2.45)	22.73 (3.91)
	VPT	20.58 (1.93)	20.59 (2.26)	20.90 (2.85)	21.12 (2.81)	21.31 (2.01)	24.09 (4.58)
	MPT	20.86 (3.31)	21.81 (3.30)	21.77 (2.53)	21.80 (3.24)	21.54 (2.60)	22.05 (3.66)
	FT	20.41 (3.12)	20.65 (2.26)	21.39 (2.55)	21.38 (2.52)	21.64 (3.16)	21.68 (1.77)
t-test (p)							
males PT vs. FT		0.3948	0.4865	0.4510	0.3615	0.3606	0.2595
males VPT vs. peers[a]		0.1998	0.4953	0.3454	0.4648	0.4047	0.1467
females PT vs. FT		0.2235	**0.0470**	0.3812	0.3563	0.3461	0.1660
females VPT vs. peers[a]		0.4794	0.4832	0.3804	0.3413	0.3142	0.0964
one-way ANOVA (p)[b]							
males		0.7010	0.9990	0.8800	0.9120	0.8610	NA
females		0.7190	0.1020	0.5760	0.7280	0.9608	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex P.

Absolute values [kg/m^2] and z-scores of BMI

BMI z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Z-vrednosti ITM-ja izračunane glede na Usher in McLean (1969) in WHO (2004) standarde

Age		birth	discharge	1 year	2 years	3 years	8 years
subject number (N)							
males	VPT	24	18	21	20	19	12
	MPT	90	65	65	62	64	52
	FT	139	117	109	93	107	85
females	VPT	19	19	20	19	17	12
	MPT	88	65	72	51	57	45
	FT	111	101	91	76	85	70
average (SD) standard values [kg/m^2]							
males		7.1 (0.5) 13.3 (1.4)	13.4 (1.4)	16.8 (1.4) 16.3 (1.4)	16.0 (1.3) 15.9 (1.3)	15.6 (1.3) 15.5 (1.3)	15.7 (1.7)
females		7.1 (0.5) 13.3 (1.3)	13.3 (1.3)	16.4 (1.3) 15.9 (1.5)	15.7 (1.4) 15.6 (1.4)	15.4 (1.4) 15.3 (1.5)	15.7 (2.0)
average z-scores (SD)							
males	PT	0.21 (1.47)	-1.75 (0.66)	0.40 (1.18)	0.29 (1.18)	0.28 (1.96)	0.54 (1.60)
	VPT	0.34 (1.69)	-1.84 (0.77)	0.28 (1.46)	0.43 (1.25)	0.47 (1.42)	0.03 (1.15)
	MPT	0.17 (1.41)	-1.73 (0.64)	0.44 (1.08)	0.25 (1.16)	0.22 (2.09)	0.66 (1.67)
	FT	-0.12 (0.78)	-0.74 (0.71)	0.84 (1.19)	0.67 (1.15)	0.39 (1.06)	0.33 (1.26)
females	PT	-0.20 (1.15)	-2.00 (0.80)	0.53 (1.01)	0.12 (1.71)	0.62 (2.21)	0.52 (1.09)
	VPT	-0.53 (1.12)	-2.32 (0.59)	0.18 (1.06)	0.41 (1.13)	0.78 (0.97)	0.66 (1.21)
	MPT	-0.13 (1.15)	-1.90 (0.83)	0.62 (0.99)	0.02 (1.88)	0.57 (2.47)	0.48 (1.07)
	FT	-0.19 (0.85)	-0.69 (0.84)	0.82 (1.31)	0.69 (1.08)	0.45 (1.10)	0.47 (1.02)
t-test (p)							
males PT vs. FT		**0.0129**	**<0.0001**	**0.0054**	**0.0185**	0.3080	0.1882
males VPT vs. peers[a]		0.0814	**<0.001**	0.0701	0.3973	0.3418	0.1548
females PT vs. FT		0.4768	**<0.0001**	**0.0452**	**0.0085**	0.2607	0.4209
females VPT vs. peers[a]		0.0644	**<0.0001**	**0.0248**	0.4920	0.2602	0.2884
one-way ANOVA (p)[b]							
males		0.0678	**<0.0001**	**0.0341**	0.0964	0.7180	0.2520
females		0.2857	**<0.0001**	0.0811	**0.0344**	0.7410	0.8560
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	nsg	nsg	NA	NA	NA
	VPT vs. FT	NA	**<0.01**	nsg	NA	NA	NA
	MPT vs. FT	NA	**<0.01**	nsg	NA	NA	NA
females	VPT vs. MPT	NA	nsg	NA	nsg	NA	NA
	VPT vs. FT	NA	**<0.01**	NA	nsg	NA	NA
	MPT vs. FT	NA	**<0.01**	NA	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continuation of Annex P.

Absolute values [kg/m^2] and z-scores of BMI

BMI z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Age		9 years	10 years	11 years	12 years	13 years	14 years
subject number (N)							
males	VPT	18	20	21	22	20	19
	MPT	69	71	69	70	70	66
	FT	106	109	112	115	112	106
females	VPT	12	13	12	12	13	14
	MPT	57	61	61	60	59	58
	FT	86	90	90	93	88	85
average (SD) standard values [kg/m^2]							
males		16.0 (1.9)	16.4 (2.1)	16.9 (2.3)	17.5 (2.4)	18.2 (2.6)	19.0 (2.8)
females		16.1 (2.2)	16.6 (2.4)	17.2 (2.7)	18.0 (2.8)	18.8 (3.0)	19.6 (3.1)
average z-scores (SD)							
males	PT	0.45 (1.47)	0.58 (1.37)	0.46 (1.28)	0.55 (1.37)	0.40 (1.23)	0.21 (1.02)
	VPT	-0.20 (1.02)	-0.01 (0.93)	-0.10 (0.88)	0.02 (1.05)	-0.07 (0.97)	-0.06 (0.82)
	MPT	0.61 (1.53)	0.74 (1.43)	0.63 (1.34)	0.72 (1.43)	0.53 (1.27)	0.28 (1.07)
	FT	0.34 (1.30)	0.31 (1.21)	0.37 (1.26)	0.28 (1.16)	0.33 (1.23)	0.18 (1.03)
females	PT	0.54 (1.24)	0.57 (1.34)	0.53 (1.20)	0.42 (1.22)	0.36 (1.11)	0.29 (1.07)
	VPT	0.58 (1.19)	0.61 (1.21)	0.68 (0.98)	0.40 (0.61)	0.35 (0.66)	0.27 (0.60)
	MPT	0.53 (1.26)	0.56 (1.37)	0.50 (1.25)	0.42 (1.32)	0.36 (1.19)	0.29 (1.16)
	FT	0.39 (1.00)	0.52 (1.14)	0.40 (1.02)	0.31 (1.10)	0.30 (1.09)	0.20 (1.03)
t-test (p)							
males PT vs. FT		0.3015	0.0732	0.3104	0.0661	0.3357	0.4312
males VPT vs. peers[a]		**0.0273**	0.0516	**0.0254**	0.0685	0.0503	0.1314
females PT vs. FT		0.1973	0.4061	0.2175	0.2717	0.3688	0.3043
females VPT vs. peers[a]		0.3473	0.4162	0.2377	0.4501	0.4675	0.4572
one-way ANOVA (p)[b]							
males		0.0688	**0.0227**	0.0602	**0.0252**	0.1400	0.4370
females		0.6910	0.9620	0.6530	0.8300	0.9450	0.8750
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	**<0.05**	NA	**<0.05**	NA	NA
	VPT vs. FT	NA	nsg	NA	nsg	NA	NA
	MPT vs. FT	NA	nsg	NA	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex P.

Absolute values [kg/m^2] and z-scores of BMI

BMI z-scores calculated according to Usher and McLean (1969) and WHO (2004) standards

Age		15 years	16 years	17 years	18 years	19 years	26 years
subject number (N)							
males	VPT	19	18	13	11	9	2
	MPT	64	46	37	36	27	3
	FT	102	77	69	59	41	11
females	VPT	13	13	12	12	7	4
	MPT	53	48	35	30	23	8
	FT	78	60	50	46	41	9
average (SD) standard values [kg/m^2]							
males		19.8 (2.9)	20.5 (3.0)	21.1 (3.2)	21.7 (3.2)	22.2 (3.2)	24.0 (3.2)
females		20.2 (3.3)	20.7 (3.4)	21.0 (3.5)	21.3 (3.5)	21.4 (3.6)	23.0 (3.6)
average z-scores (SD)							
males	PT	0.07 (0.96)	0.00 (0.89)	0.02 (0.80)	0.01 (0.75)	0.04 (0.94)	0.16 (1.41)
	VPT	-0.08 (0.82)	0.00 (0.83)	-0.08 (0.58)	0.07 (0.73)	0.15 (0.86)	-0.51 (0.06)
	MPT	0.12 (1.00)	0.00 (0.92)	0.05 (0.86)	-0.01 (0.77)	0.01 (0.97)	0.61 (1.79)
	FT	0.11 (0.98)	0.00 (0.89)	0.00 (0.86)	0.07 (1.07)	0.11 (0.82)	0.54 (1.50)
females	PT	0.18 (0.93)	0.25 (0.92)	0.16 (0.75)	0.09 (0.89)	0.02 (0.68)	-0.08 (1.09)
	VPT	0.12 (0.58)	-0.03 (0.66)	-0.03 (0.82)	-0.05 (0.80)	-0.03 (0.56)	0.30 (1.27)
	MPT	0.20 (1.00)	0.33 (0.97)	0.22 (0.72)	0.14 (0.92)	0.04 (0.72)	-0.27 (1.02)
	FT	0.06 (0.95)	-0.01 (0.80)	0.11 (0.73)	0.02 (0.72)	0.07 (0.88)	-0.37 (0.49)
t-test (p)							
males PT vs. FT		0.3948	0.4865	0.4510	0.3615	0.3606	0.2595
males VPT vs. peers[a]		0.1998	0.4953	0.3454	0.4648	0.4047	0.1467
females PT vs. FT		0.2235	**0.0470**	0.3812	0.3563	0.4144	0.1660
females VPT vs. peers[a]		0.4957	0.2550	0.2088	0.3118	0.3980	0.0964
one-way ANOVA (p)[b]							
males		0.7010	0.9990	0.8800	0.9120	0.8630	NA
females		0.7190	0.1020	0.5760	0.7280	0.9600	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex Q

Aerobic general endurance SLOfit test (600-meter run [s]) from the age of 8 to 19 years

Aerobni SLOfit test splošne vzdržljivosti (tek na 600 m [s]) preiskovancev v starosti 8 do 19 let

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	193.2 (34.1)	180.6 (30.7)	170.6 (28.4)	167.6 (30.9)	162.3 (25.6)	155.2 (22.5)
	VPT	195.5 (26.1)	185.7 (31.6)	167.3 (12.9)	162.1 (19.4)	163.4 (25.2)	153.1 (19.2)
	MPT	192.6 (36.0)	179.1 (30.6)	171.5 (31.4)	169.3 (33.6)	161.9 (26.0)	155.9 (23.5)
	FT	193.4 (29.4)	179.6 (30.6)	167.1 (26.2)	162.5 (25.7)	161.1 (26.4)	159.7 (31.2)
females	PT	203.8 (29.8)	194.6 (32.3)	180.4 (31.6)	179.7 (31.6)	168.3 (27.5)	165.3 (24.8)
	VPT	217.1 (31.1)	194.2 (33.1)	175.2 (29.0)	182.7 (26.7)	165.6 (21.6)	175.4 (26.9)
	MPT	200.8 (29.0)	194.7 (32.5)	181.4 (32.3)	179.1 (32.8)	168.9 (28.7)	163.3 (24.1)
	FT	201.7 (27.7)	189.2 (27.6)	187.6 (26.8)	176.4 (26.1)	172.8 (28.4)	166.8 (25.2)
t-test (p)							
males PT vs. FT		0.4811	0.4105	0.1888	0.1154	0.3781	0.1362
males VPT vs. peers[a]		0.4007	0.2049	0.4138	0.3304	0.3724	0.2195
females PT vs. FT		0.3489	0.1473	0.0742	0.2525	0.1645	0.3613
females VPT vs. peers[a]		**0.0477**	0.3795	0.1467	0.2780	0.2610	0.0986
one-way ANOVA (p)[b]							
males		0.9608	0.7100	0.5740	0.3030	0.9310	0.5080
females		0.2470	0.5780	0.2869	0.7430	0.5850	0.3200

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex Q.

Aerobic general endurance SLOfit test (600-meter run [s]) from the age of 8 to 19 years

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	4
	MPT	56	56	34	31	29	22
	FT	94	90	55	51	53	33
females	VPT	9	10	9	8	11	5
	MPT	49	46	38	31	26	18
	FT	68	69	49	35	27	27
average (SD)							
males	PT	146.4 (20.9)	143.2 (24.1)	136.0 (23.3)	135.3 (23.0)	132.0 (20.2)	131.6 (23.7)
	VPT	142.6 (11.8)	141.8 (21.9)	143.3 (32.6)	140.8 (27.8)	135.1 (21.1)	124.5 (4.5)
	MPT	147.6 (23.1)	143.7 (24.9)	133.3 (18.5)	133.1 (21.0)	131.0 (20.2)	132.9 (25.5)
	FT	155.6 (28.6)	143.6 (25.9)	136.5 (23.0)	135.3 (32.7)	134.5 (25.6)	132.5 (20.5)
females	PT	163.7 (24.5)	172.4 (31.3)	166.3 (24.2)	170.7 (20.6)	173.8 (24.2)	180.4 (33.6)
	VPT	168.3 (16.3)	193.1 (33.5)	172.8 (28.5)	188.0 (14.3)	184.2 (26.5)	212.4 (54.0)
	MPT	162.8 (25.8)	167.9 (29.3)	164.7 (23.3)	166.3 (19.8)	169.4 (22.2)	171.6 (19.8)
	FT	170.1 (29.7)	172.2 (31.3)	173.3 (33.7)	169.5 (33.7)	172.8 (26.3)	179.4 (26.1)
t-test (p)							
males PT vs. FT		**0.0106**	0.4666	0.4644	0.4990	0.3105	0.4397
males VPT vs. peers[a]		0.0588	0.3828	0.1201	0.2368	0.4103	0.2383
females PT vs. FT		0.0955	0.4830	0.1231	0.4242	0.4373	0.4536
females VPT vs. peers[a]		0.4464	**0.0136**	0.3774	**0.0251**	0.0568	**0.0040**
one-way ANOVA (p)[b]							
males		0.0541	0.9560	0.4120	0.7342	0.7950	0.7797
females		0.3672	0.0677	0.3910	0.1325	0.2550	**0.0198**
Tukey HSD post hoc (p)							
females	VPT vs. MPT	NA	NA	NA	NA	NA	**<0.01**
	VPT vs. FT	NA	NA	NA	NA	NA	**<0.05**
	MPT vs. FT	NA	NA	NA	NA	NA	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex R

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

Anaerobni testi SLOfit sistema (hitrost sprinta, eksplozivna moč, moč mišic trupa ter mišična vzdržljivost ramenskega obroča in rok) preiskovancev v starosti 8 do 19 let

SLOfit test of sprint speed (60-meter run [10^{-1} s])

SLOfit test hitrosti sprinta (tek na 60 m [10^{-1} s])

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	126.3 (10.7)	119.9 (11.9)	115.5 (12.7)	111.7 (12.0)	108.7 (11.5)	105.6 (12.1)
	VPT	129.0 (12.7)	122.0 (8.9)	116.1 (9.4)	111.7 (6.1)	109.4 (6.4)	105.6 (6.8)
	MPT	125.6 (10.2)	119.2 (12.7)	115.4 (13.5)	111.7 (13.4)	108.5 (12.8)	105.6 (13.3)
	FT	123.5 (10.7)	118.3 (12.0)	112.0 (9.8)	108.3 (9.6)	106.1 (9.5)	103.1 (10.3)
females	PT	129.5 (12.2)	124.0 (10.5)	117.3 (10.4)	113.5 (9.5)	109.8 (8.6)	105.6 (7.5)
	VPT	136.0 (12.8)	123.3 (10.2)	117.7 (6.0)	115.2 (8.5)	110.7 (8.2)	106.2 (6.7)
	MPT	128.0 (11.7)	124.1 (10.7)	117.3 (11.2)	113.1 (9.8)	109.7 (8.7)	105.4 (7.6)
	FT	128.0 (10.4)	120.1 (8.5)	117.4 (7.6)	112.2 (11.5)	108.8 (9.2)	105.7 (9.7)
t-test (p)							
males PT vs. FT		0.0613	0.1902	**0.0166**	**0.0185**	**0.0463**	0.0676
males VPT vs. peers[a]		0.0730	0.1295	0.1583	0.2178	0.1561	0.2855
females PT vs. FT		0.2344	**0.0107**	0.4896	0.2519	0.2386	0.4656
females VPT vs. peers[a]		**0.0155**	0.3030	0.4452	0.2106	0.2845	0.4136
one-way ANOVA (p)[b]							
males		0.1864	0.4710	0.1012	0.1138	0.2281	0.3290
females		0.0987	0.0682	0.9901	0.6620	0.7280	0.9640

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

SLOfit test of sprint speed (60-meter run [10^{-1} s])

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	4
	MPT	56	56	34	31	29	24
	FT	94	90	55	51	53	33
females	VPT	9	10	9	8	11	6
	MPT	49	46	38	31	26	20
	FT	68	69	49	35	27	29
average (SD)							
males	PT	97.9 (8.6)	93.8 (7.2)	88.6 (6.7)	87.7 (8.2)	88.3 (11.5)	88.3 (9.8)
	VPT	97.8 (6.2)	94.9 (7.4)	88.5 (8.8)	87.8 (9.2)	86.0 (7.6)	83.0 (2.4)
	MPT	97.9 (9.3)	93.4 (7.1)	88.6 (5.8)	87.6 (7.9)	89.0 (12.4)	89.2 (10.3)
	FT	99.2 (12.0)	92.9 (8.7)	88.9 (7.9)	86.9 (8.2)	85.8 (7.5)	86.6 (9.6)
females	PT	102.6 (8.5)	103.5 (8.6)	101.9 (7.2)	101.7 (8.1)	105.2 (8.2)	106.8 (12.1)
	VPT	102.2 (9.4)	104.7 (9.4)	103.2 (7.4)	107.5 (10.3)	107.9 (8.8)	118.2 (16.2)
	MPT	102.7 (8.4)	103.3 (8.6)	101.6 (7.1)	100.2 (6.9)	104.0 (7.8)	103.4 (8.4)
	FT	103.5 (8.6)	102.7 (8.2)	102.5 (7.5)	103.4 (9.9)	102.3 (6.5)	107.5 (13.4)
t-test (p)							
males PT vs. FT		0.2172	0.2380	0.4107	0.3385	0.1096	0.2469
males VPT vs. peers[a]		0.3687	0.1814	0.4510	0.3991	0.3872	0.1754
females PT vs. FT		0.2693	0.2965	0.3457	0.2128	0.0659	0.4185
females VPT vs. peers[a]		0.3733	0.2644	0.3304	**0.0486**	**0.0279**	**0.0113**
one-way ANOVA (p)[b]							
males		0.7370	0.6150	0.9740	0.9140	0.3309	0.3927
females		0.8190	0.7730	0.7710	0.0893	0.1140	**0.0385**
Tukey HSD post hoc (p)							
females	VPT vs. MPT	NA	NA	NA	NA	NA	**<0.05**
	VPT vs. FT	NA	NA	NA	NA	NA	nsg
	MPT vs. FT	NA	NA	NA	NA	NA	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

SLOfit test of explosive power (standing broad jump [cm])

SLOfit test eksplozivne moči (skok v daljino z mesta [cm])

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	133.2 (19.6)	140.3 (21.3)	152.1 (23.5)	159.5 (23.0)	165.9 (22.6)	174.2 (24.6)
	VPT	129.9 (21.2)	141.3 (18.1)	153.4 (21.5)	155.6 (18.4)	165.7 (19.0)	174.7 (21.9)
	MPT	134.0 (19.4)	140.1 (22.3)	151.8 (24.2)	160.8 (24.2)	165.9 (23.9)	174.0 (25.6)
	FT	138.5 (17.8)	147.1 (17.7)	161.5 (17.7)	169.2 (19.0)	175.8 (19.9)	181.8 (21.5)
females	PT	123.0 (16.1)	133.3 (15.5)	144.7 (15.4)	149.8 (16.1)	159.7 (16.8)	168.0 (20.7)
	VPT	120.9 (20.5)	137.4 (14.9)	145.4 (13.8)	151.4 (11.2)	159.8 (13.8)	166.9 (21.6)
	MPT	123.5 (15.2)	132.2 (15.6)	144.5 (15.8)	149.4 (17.1)	159.7 (17.4)	168.3 (20.7)
	FT	125.6 (17.7)	138.2 (13.3)	147.1 (16.6)	158.2 (18.9)	164.0 (17.5)	170.1 (20.5)
t-test (p)							
males PT vs. FT		**0.0464**	**0.0106**	**0.0012**	**0.0011**	**0.0009**	**0.0125**
males VPT vs. peers[a]		0.1140	0.2592	0.2046	**0.0222**	0.0990	0.2337
females PT vs. FT		0.2055	**0.0245**	0.1893	**0.0031**	0.0649	0.2787
females VPT vs. peers[a]		0.2492	0.3587	0.4524	0.2836	0.3241	0.3562
one-way ANOVA (p)[b]							
males		0.1957	0.0688	**0.0095**	**0.0062**	**0.0078**	0.0810
females		0.6510	0.0776	0.6711	**0.0228**	0.3180	0.8260
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	nsg	nsg	nsg	NA
	VPT vs. FT	NA	NA	nsg	**<0.05**	nsg	NA
	MPT vs. FT	NA	NA	nsg	nsg	nsg	NA
females	VPT vs. MPT	NA	NA	NA	nsg	NA	NA
	VPT vs. FT	NA	NA	NA	nsg	NA	NA
	MPT vs. FT	NA	NA	NA	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

SLOfit test of explosive power (standing broad jump [cm])

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	24
	FT	94	90	55	51	53	34
females	VPT	9	10	9	8	11	7
	MPT	49	46	38	31	26	22
	FT	68	69	49	35	27	39
average (SD)							
males	PT	190.1 (24.1)	198.0 (28.2)	211.0 (23.7)	217.1 (25.3)	220.3 (27.3)	215.2 (30.5)
	VPT	188.6 (25.2)	196.6 (26.9)	209.1 (25.5)	218.9 (24.3)	212.6 (26.1)	212.0 (17.6)
	MPT	190.6 (24.0)	198.5 (28.9)	211.7 (23.3)	216.4 (26.0)	222.7 (27.6)	216.0 (33.2)
	FT	194.7 (24.8)	207.7 (24.8)	213.8 (24.9)	227.0 (24.6)	225.7 (22.0)	225.2 (26.4)
females	PT	175.3 (17.9)	171.4 (23.4)	170.3 (22.2)	173.9 (21.9)	173.9 (17.8)	170.3 (28.0)
	VPT	177.8 (14.9)	169.1 (21.6)	171.1 (15.3)	165.4 (12.8)	169.9 (11.9)	157.4 (44.5)
	MPT	174.9 (18.5)	171.9 (23.9)	170.2 (23.7)	176.1 (23.3)	175.7 (19.7)	174.4 (20.2)
	FT	177.9 (19.2)	178.4 (19.3)	175.6 (19.6)	173.5 (20.7)	174.4 (18.5)	174.1 (17.4)
t-test (p)							
males PT vs. FT		0.1140	**0.0099**	0.2793	**0.0283**	0.1469	0.0830
males VPT vs. peers[a]		0.2264	0.1240	0.2939	0.3023	0.0792	0.2237
females PT vs. FT		0.2192	**0.0350**	0.1109	0.4692	0.4633	0.2467
females VPT vs. peers[a]		0.4311	0.1718	0.3879	0.1215	0.1985	**0.0303**
one-way ANOVA (p)[b]							
males		0.4620	0.0647	0.7990	0.1570	0.3213	0.3667
females		0.6779	0.1810	0.4730	0.4489	0.6780	0.1734

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

SLOfit test of trunk muscle strength (sit-ups [N])

SLOfit test moči mišic trupa (dvigi trupa iz ležečega v sedeči položaj [N])

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	28.5 (6.0)	31.5 (8.8)	34.1 (9.1)	35.9 (9.7)	40.2 (7.4)	42.5 (9.2)
	VPT	25.8 (6.6)	29.4 (10.6)	32.1 (6.3)	34.3 (7.1)	38.1 (7.5)	42.7 (7.4)
	MPT	29.2 (5.8)	32.1 (8.1)	34.7 (9.6)	36.4 (10.3)	40.9 (7.3)	42.5 (9.7)
	FT	29.1 (7.2)	32.0 (8.0)	36.6 (6.5)	38.7 (8.2)	41.7 (7.9)	43.9 (10.3)
females	PT	27.3 (8.0)	29.8 (7.9)	34.7 (7.7)	36.4 (8.2)	39.7 (8.5)	43.2 (8.7)
	VPT	25.0 (9.6)	30.3 (8.9)	35.3 (6.2)	38.7 (8.7)	40.0 (5.9)	45.0 (11.5)
	MPT	27.8 (7.6)	29.7 (7.7)	34.6 (8.0)	35.9 (8.1)	39.6 (9.0)	42.9 (8.1)
	FT	27.1 (6.0)	30.8 (8.2)	33.3 (6.3)	37.4 (7.6)	39.6 (7.8)	43.8 (8.0)
t-test (p)							
males PT vs. FT		0.3066	0.3343	**0.0161**	**0.0194**	0.0921	0.1780
males VPT vs. peers[a]		0.0512	0.1029	**0.0253**	0.0528	**0.0305**	0.3835
females PT vs. FT		0.4408	0.2290	0.1084	0.2413	0.4780	0.3445
females VPT vs. peers[a]		0.1485	0.4784	0.2632	0.2102	0.4419	0.2699
one-way ANOVA (p)[b]							
males		0.2651	0.4490	**0.0452**	0.0794	0.1430	0.6530
females		0.5080	0.7430	0.4514	0.4270	0.9890	0.6860
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	nsg	NA	NA	NA
	VPT vs. FT	NA	NA	**<0.05**	NA	NA	NA
	MPT vs. FT	NA	NA	nsg	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

SLOfit test of trunk muscle strength (sit-ups [N])

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	25
	FT	94	90	55	51	53	34
females	VPT	9	10	9	8	11	6
	MPT	49	46	38	31	26	22
	FT	68	69	49	35	27	39
average (SD)							
males	PT	47.0 (9.7)	49.6 (10.9)	52.1 (9.0)	51.8 (8.5)	52.9 (11.2)	50.3 (10.7)
	VPT	46.2 (8.8)	47.6 (7.5)	55.1 (6.8)	54.4 (8.5)	52.2 (9.3)	50.7 (4.1)
	MPT	47.2 (10.0)	50.2 (11.8)	51.0 (9.5)	50.8 (8.5)	53.1 (11.9)	50.2 (11.8)
	FT	47.8 (10.7)	49.3 (11.4)	53.4 (9.6)	52.9 (11.0)	56.6 (9.7)	54.1 (9.5)
females	PT	46.3 (8.5)	47.1 (10.1)	47.9 (8.6)	46.1 (10.3)	48.2 (9.4)	48.6 (9.0)
	VPT	46.6 (10.9)	45.1 (8.6)	48.2 (10.0)	44.0 (10.8)	48.3 (10.3)	43.0 (8.3)
	MPT	46.2 (8.1)	47.6 (10.5)	47.8 (8.3)	46.7 (10.3)	48.2 (9.2)	50.1 (8.7)
	FT	46.3 (8.4)	45.8 (10.6)	47.1 (8.2)	49.3 (10.0)	50.1 (8.8)	48.7 (10.0)
t-test (p)							
males PT vs. FT		0.3031	0.4358	0.2401	0.3023	**0.0471**	0.0661
males VPT vs. peers[a]		0.2985	0.2308	0.1765	0.2240	0.1947	0.3457
females PT vs. FT		0.4875	0.2349	0.3263	0.0895	0.2098	0.4840
females VPT vs. peers[a]		0.4629	0.3435	0.3931	0.1444	0.3896	0.0646
one-way ANOVA (p)[b]							
males		0.8220	0.6760	0.3160	0.4943	0.2425	0.3233
females		0.9901	0.6130	0.8960	0.3288	0.7230	0.2717

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

SLOfit test of muscular endurance of the shoulder girdle and arms (bent arm hang [s])

SLOfit test mišične vzdržljivosti ramenskega obroča in rok (vesa v zgibi [s])

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	29.3 (19.9)	32.9 (26.9)	36.1 (27.1)	36.4 (31.7)	40.1 (32.8)	43.7 (32.6)
	VPT	39.5 (23.1)	40.3 (28.6)	50.0 (24.0)	46.4 (34.4)	51.0 (31.2)	49.3 (28.0)
	MPT	26.8 (18.5)	30.7 (26.2)	32.3 (26.8)	33.2 (30.4)	36.3 (32.7)	42.0 (33.8)
	FT	29.7 (21.4)	37.7 (26.6)	44.6 (28.9)	48.8 (32.6)	42.9 (29.0)	43.3 (28.5)
females	PT	25.7 (18.9)	23.9 (19.2)	28.6 (20.2)	27.4 (18.4)	33.2 (22.1)	32.5 (22.5)
	VPT	26.7 (20.6)	32.5 (32.4)	38.6 (23.2)	26.3 (19.8)	31.0 (15.3)	25.5 (14.9)
	MPT	25.5 (18.7)	21.7 (13.9)	26.7 (19.2)	27.6 (18.3)	33.6 (23.3)	33.9 (23.5)
	FT	26.3 (19.6)	29.4 (22.9)	31.2 (22.5)	32.3 (22.9)	31.5 (21.2)	37.4 (25.1)
t-test (p)							
males PT vs. FT		0.4491	0.1152	**0.0213**	**0.0052**	0.2698	0.4649
males VPT vs. peers[a]		**0.0404**	0.2185	0.0738	0.3297	0.0703	0.1834
females PT vs. FT		0.4330	0.0659	0.2368	0.0866	0.3199	0.1171
females VPT vs. peers[a]		0.4535	0.1724	0.0819	0.2658	0.4223	0.0831
one-way ANOVA (p)[b]							
males		0.1610	0.1990	**0.0076**	**0.0113**	0.1390	0.6420
females		0.9700	0.0938	0.1847	0.3900	0.8390	0.2770
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	**<0.05**	nsg	NA	NA
	VPT vs. FT	NA	NA	nsg	nsg	NA	NA
	MPT vs. FT	NA	NA	nsg	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

SLOfit test of muscular endurance of the shoulder girdle and arms (bent arm hang [s])

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	25
	FT	94	90	55	51	53	31
females	VPT	9	10	9	8	11	7
	MPT	49	46	38	31	26	21
	FT	68	69	49	35	27	38
average (SD)							
males	PT	50.4 (31.4)	51.9 (30.0)	54.3 (27.2)	51.1 (27.9)	59.3 (27.2)	50.2 (29.8)
	VPT	53.4 (29.9)	57.9 (31.1)	62.2 (24.8)	59.1 (26.5)	67.2 (26.8)	60.7 (39.4)
	MPT	49.4 (32.1)	49.8 (29.7)	51.3 (27.8)	48.0 (28.2)	56.9 (27.3)	47.7 (27.4)
	FT	43.5 (27.3)	49.0 (29.3)	54.6 (29.2)	56.1 (27.2)	62.5 (28.0)	56.5 (30.2)
females	PT	38.8 (24.0)	36.0 (23.6)	34.6 (25.0)	32.6 (20.5)	30.0 (18.6)	31.0 (19.1)
	VPT	38.7 (22.7)	26.2 (17.2)	39.0 (25.4)	17.6 (13.5)	25.0 (18.4)	21.4 (20.1)
	MPT	38.9 (24.4)	38.1 (24.4)	33.5 (25.1)	36.5 (20.4)	32.1 (18.6)	34.2 (18.1)
	FT	35.0 (24.3)	36.1 (23.9)	37.9 (22.9)	32.3 (19.3)	35.4 (25.5)	32.5 (20.3)
t-test (p)							
males PT vs. FT		0.0656	0.2690	0.4842	0.1932	0.2942	0.2083
males VPT vs. peers[a]		0.1467	0.1171	0.1447	0.2399	0.2455	0.2659
females PT vs. FT		0.1848	0.4916	0.2475	0.4745	0.1623	0.3818
females VPT vs. peers[a]		0.4028	0.0860	0.3597	**0.0118**	0.1128	0.0690
one-way ANOVA (p)[b]							
males		0.2830	0.4880	0.4980	0.3439	0.5350	0.4631
females		0.6712	0.3570	0.6560	0.0536	0.4120	0.3201

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

Average z-scores of all anaerobic SLOfit tests

Povprečne z-vrednosti vseh anaerobnih testov iz SLOfit sistema

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	-0.09 (0.66)	-0.10 (0.81)	-0.19 (0.85)	-0.20 (0.80)	-0.14 (0.78)	-0.09 (0.76)
	VPT	-0.18 (0.65)	-0.13 (0.71)	-0.13 (0.57)	-0.22 (0.51)	-0.14 (0.56)	-0.04 (0.49)
	MPT	-0.07 (0.67)	-0.09 (0.84)	-0.21 (0.92)	-0.20 (0.88)	-0.14 (0.85)	-0.11 (0.83)
	FT	0.07 (0.71)	0.08 (0.69)	0.15 (0.68)	0.16 (0.72)	0.11 (0.73)	0.08 (0.73)
females	PT	-0.04 (0.77)	-0.15 (0.72)	-0.01 (0.71)	-0.12 (0.65)	-0.04 (0.80)	-0.05 (0.75)
	VPT	-0.28 (1.02)	0.05 (0.85)	0.13 (0.63)	-0.08 (0.56)	-0.08 (0.64)	-0.10 (0.72)
	MPT	0.02 (0.70)	-0.20 (0.68)	-0.03 (0.73)	-0.13 (0.67)	-0.03 (0.83)	-0.04 (0.76)
	FT	0.03 (0.70)	0.13 (0.68)	0.01 (0.71)	0.11 (0.72)	0.03 (0.77)	0.04 (0.84)
t-test (p)							
males PT vs. FT		0.0810	0.0543	**0.0013**	**0.0008**	**0.0137**	0.0638
males VPT vs. peers[a]		0.1781	0.2252	0.2270	0.1025	0.1891	0.4093
females PT vs. FT		0.2962	**0.0105**	0.4527	**0.0243**	0.2939	0.2547
females VPT vs. peers[a]		0.0999	0.3976	0.2668	0.3328	0.3657	0.3344
one-way ANOVA (p)[b]							
males		0.3370	0.2740	**0.0099**	**0.0072**	0.0885	0.2930
females		0.4380	**0.0370**	0.7820	0.1400	0.8500	0.7830
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	nsg	nsg	NA	NA
	VPT vs. FT	NA	NA	nsg	nsg	NA	NA
	MPT vs. FT	NA	NA	nsg	nsg	NA	NA
females	VPT vs. MPT	NA	nsg	NA	NA	NA	NA
	VPT vs. FT	NA	nsg	NA	NA	NA	NA
	MPT vs. FT	NA	nsg	NA	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex R.

Anaerobic SLOfit tests (sprint speed, explosive power, trunk muscle strength, and muscular endurance of the shoulder girdle and arms) from the age of 8 to 19 years

Average z-scores of all anaerobic SLOfit tests

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	25
	FT	94	90	55	51	53	35
females	VPT	9	10	9	8	11	7
	MPT	49	46	38	31	26	22
	FT	68	69	49	35	27	40
average (SD)							
males	PT	0.01 (0.71)	-0.05 (0.68)	-0.03 (0.73)	-0.10 (0.75)	-0.14 (0.86)	-0.15 (0.83)
	VPT	0.01 (0.59)	-0.09 (0.64)	0.10 (0.62)	0.05 (0.64)	-0.10 (0.54)	-0.01 (0.39)
	MPT	0.01 (0.75)	-0.03 (0.70)	-0.08 (0.77)	-0.16 (0.79)	-0.15 (0.94)	-0.19 (0.91)
	FT	-0.01 (0.80)	0.04 (0.78)	0.03 (0.84)	0.09 (0.79)	0.10 (0.65)	0.15 (0.70)
females	PT	0.02 (0.74)	-0.04 (0.83)	-0.03 (0.77)	-0.01 (0.73)	-0.09 (0.73)	-0.02 (0.78)
	VPT	0.07 (0.45)	-0.25 (0.67)	-0.01 (0.72)	-0.51 (0.59)	-0.29 (0.73)	-0.63 (0.98)
	MPT	0.01 (0.79)	0.01 (0.86)	-0.03 (0.79)	0.12 (0.71)	-0.01 (0.72)	0.17 (0.61)
	FT	-0.01 (0.79)	0.03 (0.76)	0.03 (0.72)	0.01 (0.76)	0.12 (0.63)	0.01 (0.70)
t-test (p)							
males PT vs. FT		0.4260	0.2234	0.3625	0.1155	0.0664	0.0597
males VPT vs. peers[a]		0.4861	0.2927	0.3089	0.4116	0.3334	0.4800
females PT vs. FT		0.4093	0.3027	0.3620	0.4463	0.1108	0.4353
females VPT vs. peers[a]		0.3927	0.1450	0.4875	**0.0183**	0.0626	**0.0081**
one-way ANOVA (p)[b]							
males		0.9820	0.7230	0.7320	0.3560	0.3200	0.2640
females		0.9520	0.5630	0.9360	0.0956	0.2460	**0.0386**
Tukey HSD post hoc (p)							
females	VPT vs. MPT	NA	NA	NA	NA	NA	**<0.05**
	VPT vs. FT	NA	NA	NA	NA	NA	nsg
	MPT vs. FT	NA	NA	NA	NA	NA	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex S

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

Testi gibljivosti in fine motorike iz SLOfit sistema (koordinacija telesnih gibov, predklon naprej z dotikom prečke in hitrost alternativnih gibov) preiskovancev v starosti 8 do 19 let

SLOfit test of coordination of body movements (polygon backwards [10^{-1} s])

SLOfit test koordinacije telesnih gibov (poligon nazaj [10^{-1} s])

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	184.5 (42.7)	172.1 (52.6)	151.2 (49.4)	149.7 (53.6)	132.4 (40.1)	123.8 (36.0)
	VPT	171.4 (39.4)	168.1 (52.7)	132.4 (32.4)	127.8 (34.4)	125.3 (32.4)	119.7 (20.5)
	MPT	187.6 (43.2)	173.2 (52.9)	156.3 (52.1)	156.5 (56.8)	134.8 (42.4)	125.1 (39.5)
	FT	187.4 (44.2)	162.5 (40.5)	139.0 (36.1)	130.9 (33.3)	126.8 (32.3)	118.2 (28.6)
females	PT	211.2 (55.8)	177.7 (40.0)	154.5 (32.9)	153.6 (31.2)	137.8 (34.8)	126.9 (28.5)
	VPT	206.6 (45.1)	186.1 (33.1)	171.2 (40.3)	150.0 (32.3)	135.6 (26.3)	130.3 (25.0)
	MPT	212.2 (58.3)	175.7 (41.5)	151.2 (30.6)	154.4 (31.3)	138.3 (36.5)	126.3 (29.3)
	FT	216.3 (59.5)	192.1 (52.4)	165.2 (39.6)	145.2 (40.3)	140.6 (48.0)	128.1 (28.1)
t-test (p)							
males PT vs. FT		0.3485	0.0851	**0.0274**	**0.0022**	0.1471	0.1194
males VPT vs. peers[a]		0.1107	0.4440	0.1059	0.1181	0.3004	0.4363
females PT vs. FT		0.3128	**0.0403**	**0.0417**	0.0895	0.3455	0.4061
females VPT vs. peers[a]		0.3370	0.4849	0.1498	0.4638	0.3814	0.3692
one-way ANOVA (p)[b]							
males		0.4742	0.3600	**0.0170**	**0.0007**	0.3360	0.4050
females		0.8550	0.1727	0.0568	0.3790	0.9090	0.8880
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	**<0.05**	**<0.05**	NA	NA
	VPT vs. FT	NA	NA	nsg	nsg	NA	NA
	MPT vs. FT	NA	NA	nsg	**<0.05**	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex S.

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

SLOfit test of coordination of body movements (polygon backwards [10^{-1} s])

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	25
	FT	94	90	55	51	53	33
females	VPT	9	10	9	8	11	7
	MPT	49	46	38	31	26	21
	FT	68	69	49	35	27	38
average (SD)							
males	PT	111.9 (30.8)	103.3 (24.0)	98.4 (19.5)	99.3 (27.3)	97.6 (20.6)	101.3 (31.0)
	VPT	99.0 (14.6)	99.6 (15.5)	96.9 (15.9)	88.2 (15.8)	94.4 (19.9)	97.2 (13.9)
	MPT	116.0 (33.5)	104.5 (26.3)	99.0 (20.9)	103.6 (29.7)	98.6 (21.1)	102.3 (34.0)
	FT	110.7 (24.0)	105.6 (20.8)	95.7 (16.1)	92.0 (17.0)	91.9 (18.4)	93.4 (22.9)
females	PT	121.3 (23.0)	120.8 (25.4)	116.1 (22.7)	120.7 (24.1)	115.8 (17.8)	115.6 (22.3)
	VPT	128.1 (25.3)	137.8 (26.6)	108.7 (14.2)	121.3 (23.1)	119.7 (19.4)	130.0 (21.1)
	MPT	120.1 (22.6)	117.1 (23.8)	117.8 (24.1)	120.5 (24.7)	114.2 (17.2)	110.9 (21.1)
	FT	121.4 (24.0)	120.8 (36.9)	117.0 (24.3)	113.8 (18.8)	113.3 (14.3)	113.1 (18.4)
t-test (p)							
males PT vs. FT		0.3922	0.2539	0.2246	0.0583	0.0860	0.1246
males VPT vs. peers[a]		**0.0211**	0.1537	0.4967	0.1193	0.4891	0.4969
females PT vs. FT		0.4978	0.4980	0.4247	0.0895	0.2748	0.3057
females VPT vs. peers[a]		0.1860	**0.0404**	0.1455	0.3027	0.1370	**0.0130**
one-way ANOVA (p)[b]							
males		0.0646	0.5720	0.7070	**0.0359**	0.3407	0.4767
females		0.6450	0.1810	0.5670	0.4072	0.5430	0.0785
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	NA	nsg	NA	NA
	VPT vs. FT	NA	NA	NA	nsg	NA	NA
	MPT vs. FT	NA	NA	NA	nsg	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex S.

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

SLOfit test of forward bend and touch on the bench [cm]

SLOfit test predklona naprej z dotikom prečke [cm]

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	40.6 (5.3)	41.5 (7.2)	41.1 (8.4)	41.7 (7.2)	42.5 (6.6)	42.5 (7.3)
	VPT	39.0 (4.9)	42.2 (8.9)	39.1 (10.8)	41.5 (8.3)	41.9 (7.1)	41.6 (7.4)
	MPT	40.9 (5.4)	41.2 (6.7)	41.6 (7.7)	41.7 (6.9)	42.7 (6.5)	42.8 (7.3)
	FT	41.5 (7.4)	42.0 (6.3)	42.2 (6.5)	43.1 (6.3)	41.9 (6.8)	42.8 (7.5)
females	PT	43.3 (6.1)	45.7 (5.6)	45.8 (6.3)	45.9 (5.8)	47.1 (6.9)	50.0 (6.7)
	VPT	41.6 (9.1)	46.0 (6.6)	43.6 (8.0)	45.9 (5.9)	45.7 (8.1)	48.4 (5.4)
	MPT	43.6 (5.4)	45.6 (5.4)	46.2 (5.9)	45.8 (5.9)	47.4 (6.7)	50.3 (6.9)
	FT	44.0 (7.4)	43.9 (5.9)	46.2 (6.5)	46.2 (6.9)	47.6 (7.3)	50.7 (7.0)
t-test (p)							
males PT vs. FT		0.2001	0.2870	0.1406	0.0748	0.2891	0.3930
males VPT vs. peers[a]		0.1264	0.3845	0.0588	0.2452	0.4279	0.2299
females PT vs. FT		0.2716	**0.0445**	0.3467	0.3632	0.3439	0.2558
females VPT vs. peers[a]		0.1363	0.2128	0.0976	0.4667	0.2135	0.1587
one-way ANOVA (p)[b]							
males		0.4649	0.7350	0.2540	0.3510	0.7760	0.7620
females		0.5310	0.2314	0.4339	0.9400	0.7210	0.5670

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex S.

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

SLOfit test of forward bend and touch on the bench [cm]

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	24
	FT	94	90	55	51	53	34
females	VPT	9	10	9	8	11	6
	MPT	49	46	38	31	26	20
	FT	68	69	49	35	27	37
average (SD)							
males	PT	42.8 (7.4)	45.0 (8.4)	45.1 (8.0)	44.1 (8.6)	46.6 (9.9)	46.3 (7.2)
	VPT	42.9 (6.3)	44.5 (7.4)	48.2 (6.7)	49.7 (7.0)	48.6 (9.1)	48.7 (6.1)
	MPT	42.8 (7.7)	45.2 (8.8)	44.0 (8.3)	42.0 (8.2)	45.9 (10.2)	45.7 (7.5)
	FT	43.7 (7.7)	43.7 (8.4)	45.5 (7.9)	47.8 (8.5)	48.6 (8.4)	46.6 (10.7)
females	PT	50.8 (7.3)	51.4 (7.5)	51.5 (6.8)	51.6 (9.4)	51.8 (9.2)	51.7 (11.7)
	VPT	49.1 (10.7)	47.4 (10.5)	50.3 (9.8)	49.9 (11.9)	51.7 (10.9)	43.7 (16.1)
	MPT	51.1 (6.6)	52.2 (6.5)	51.7 (6.0)	52.0 (8.8)	51.9 (8.6)	54.1 (9.3)
	FT	51.6 (7.5)	52.2 (7.6)	53.0 (7.2)	53.5 (7.1)	52.3 (6.2)	53.1 (6.3)
t-test (p)							
males PT vs. FT		0.2434	0.1548	0.4058	**0.0211**	0.1424	0.4557
males VPT vs. peers[a]		0.4174	0.4471	0.0871	0.0653	0.3913	0.2680
females PT vs. FT		0.2779	0.2780	0.1494	0.1643	0.4045	0.2714
females VPT vs. peers[a]		0.1883	**0.0260**	0.1979	0.1786	0.4428	**0.0048**
one-way ANOVA (p)[b]							
males		0.7840	0.5730	0.2700	**0.0036**	0.4267	0.7796
females		0.6387	0.1520	0.5060	0.5099	0.9700	**0.0331**
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	NA	**<0.01**	NA	NA
	VPT vs. FT	NA	NA	NA	nsg	NA	NA
	MPT vs. FT	NA	NA	NA	nsg	NA	NA
females	VPT vs. MPT	NA	NA	NA	NA	NA	**<0.05**
	VPT vs. FT	NA	NA	NA	NA	NA	**<0.05**
	MPT vs. FT	NA	NA	NA	NA	NA	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex S.

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

SLOfit test of speed of alternative movements (arm plate tapping [N])

SLOfit test hitrosti elternativnih gibov (izmenični dotiki plošče z rokami – tapkanje [N])

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	24.0 (5.0)	26.6 (4.4)	30.3 (5.1)	32.9 (5.0)	35.7 (5.6)	38.3 (5.4)
	VPT	23.8 (3.4)	27.9 (3.7)	30.7 (5.5)	32.2 (5.0)	34.8 (7.6)	36.9 (5.6)
	MPT	24.1 (5.3)	26.2 (4.6)	30.2 (5.1)	33.1 (5.0)	36.0 (4.7)	38.8 (5.3)
	FT	24.5 (3.7)	27.1 (4.5)	30.2 (5.0)	33.3 (4.4)	36.2 (4.4)	38.8 (4.7)
females	PT	25.6 (3.8)	28.4 (4.8)	31.6 (4.2)	33.5 (4.6)	37.5 (4.7)	40.4 (4.4)
	VPT	25.8 (4.6)	29.3 (3.7)	32.9 (3.8)	34.3 (3.3)	38.0 (3.7)	40.5 (4.5)
	MPT	25.5 (3.6)	28.2 (5.0)	31.3 (4.3)	33.3 (4.9)	37.3 (4.9)	40.4 (4.4)
	FT	24.7 (4.4)	27.6 (4.1)	31.0 (4.2)	33.9 (4.8)	36.6 (4.4)	39.0 (4.4)
t-test (p)							
males PT vs. FT		0.2498	0.2547	0.4736	0.2897	0.2252	0.2874
males VPT vs. peers[a]		0.3506	0.1397	0.3523	0.1865	0.1191	0.0537
females PT vs. FT		0.1221	0.1376	0.2022	0.2961	0.1251	**0.0378**
females VPT vs. peers[a]		0.2891	0.1497	0.0898	0.3408	0.2179	0.2741
one-way ANOVA (p)[b]							
males		0.7869	0.2840	0.9280	0.6560	0.4770	0.2740
females		0.5010	0.4310	0.3669	0.7140	0.4700	0.2070

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex S.

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

SLOfit test of speed of alternative movements (arm plate tapping [N])

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	24
	FT	94	90	55	51	53	35
females	VPT	9	10	9	8	11	7
	MPT	49	46	38	31	26	22
	FT	68	69	49	35	27	39
average (SD)							
males	PT	41.9 (6.2)	44.0 (6.4)	45.9 (5.7)	47.6 (6.0)	48.5 (4.9)	47.6 (5.8)
	VPT	40.5 (6.4)	43.6 (7.1)	45.0 (5.7)	46.4 (5.9)	46.0 (3.8)	44.8 (3.2)
	MPT	42.3 (6.2)	44.1 (6.2)	46.3 (5.8)	48.1 (6.1)	49.3 (4.9)	48.3 (6.1)
	FT	41.9 (6.2)	44.3 (7.0)	46.6 (7.5)	48.3 (6.2)	50.1 (5.9)	49.9 (6.3)
females	PT	42.6 (4.5)	44.1 (5.4)	44.7 (4.3)	46.0 (6.0)	46.6 (5.6)	46.2 (7.9)
	VPT	41.1 (2.9)	43.2 (4.5)	43.2 (4.1)	44.0 (6.8)	46.1 (4.8)	43.3 (6.6)
	MPT	42.9 (4.7)	44.3 (5.5)	45.1 (4.3)	46.5 (5.7)	46.9 (6.0)	47.1 (8.2)
	FT	41.3 (4.8)	42.4 (4.8)	43.1 (4.9)	45.0 (4.3)	45.5 (5.2)	45.9 (3.9)
t-test (p)							
males PT vs. FT		0.4794	0.3837	0.3059	0.3054	0.0976	0.0688
males VPT vs. peers[a]		0.1573	0.3555	0.2283	0.1768	**0.0253**	**0.0465**
females PT vs. FT		0.0660	**0.0363**	**0.0449**	0.2152	0.1992	0.4162
females VPT vs. peers[a]		0.2966	0.4898	0.3312	0.1915	0.4827	0.0980
one-way ANOVA (p)[b]							
males		0.5640	0.9220	0.7410	0.6454	0.1261	0.1523
females		0.1888	0.1680	0.1360	0.3553	0.6470	0.3199

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex S.

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

Average z-scores of all agility and fine motor SLOfit tests

Povprečne z-vrednosti vseh testov gibljivosti in fine motorike iz SLOfit sistema

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	18	19	21	20
	MPT	51	60	65	61	60	66
	FT	83	101	102	100	104	101
females	VPT	10	12	11	12	11	11
	MPT	45	49	56	52	55	56
	FT	67	74	73	73	85	72
average (SD)							
males	PT	-0.04 (0.69)	-0.07 (0.78)	-0.08 (0.76)	-0.13 (0.77)	-0.03 (0.77)	-0.05 (0.77)
	VPT	-0.03 (0.47)	0.09 (0.80)	0.00 (0.58)	-0.03 (0.62)	-0.06 (0.86)	-0.15 (0.62)
	MPT	-0.04 (0.74)	-0.12 (0.77)	-0.10 (0.81)	-0.17 (0.81)	-0.03 (0.74)	-0.02 (0.81)
	FT	0.03 (0.70)	0.06 (0.66)	0.06 (0.59)	0.11 (0.61)	0.03 (0.66)	0.05 (0.64)
females	PT	0.03 (0.62)	0.14 (0.68)	0.06 (0.66)	-0.07 (0.63)	0.04 (0.65)	0.04 (0.73)
	VPT	-0.01 (0.65)	0.17 (0.53)	-0.10 (0.83)	0.02 (0.50)	0.03 (0.55)	-0.07 (0.66)
	MPT	0.05 (0.62)	0.14 (0.72)	0.10 (0.63)	-0.09 (0.65)	0.04 (0.68)	0.06 (0.75)
	FT	-0.03 (0.77)	-0.12 (0.73)	-0.06 (0.76)	0.06 (0.75)	-0.03 (0.75)	-0.04 (0.78)
t-test (p)							
males PT vs. FT		0.2950	0.1133	0.0730	**0.0100**	0.2782	0.1689
males VPT vs. peers[a]		0.4420	0.2828	0.4870	0.4244	0.3466	0.1487
females PT vs. FT		0.3109	**0.0172**	0.1578	0.1425	0.2945	0.2765
females VPT vs. peers[a]		0.4777	0.2021	0.3232	0.4550	0.4460	0.3737
one-way ANOVA (p)[b]							
males		0.8650	0.2570	0.2900	0.0501	0.8290	0.4820
females		0.8620	0.1070	0.4380	0.5010	0.8640	0.7300

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex S.

Agility and fine motor SLOfit tests (coordination of body movements, forward bend and touch on the bench, and speed of alternative movements) from the age of 8 to 19 years

Average z-scores of all agility and fine motor SLOfit tests

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	18	19	13	12	9	6
	MPT	56	56	34	31	29	25
	FT	94	90	55	51	53	35
females	VPT	9	10	9	8	11	7
	MPT	49	46	38	31	26	22
	FT	68	69	49	35	27	40
average (SD)							
males	PT	-0.03 (0.71)	0.04 (0.72)	-0.05 (0.72)	-0.15 (0.81)	-0.15 (0.70)	-0.12 (0.67)
	VPT	0.06 (0.53)	0.06 (0.64)	0.05 (0.57)	0.16 (0.51)	-0.18 (0.46)	-0.14 (0.33)
	MPT	-0.06 (0.76)	0.03 (0.75)	-0.10 (0.77)	-0.27 (0.87)	-0.15 (0.76)	-0.11 (0.73)
	FT	0.02 (0.71)	-0.03 (0.72)	0.05 (0.70)	0.13 (0.60)	0.11 (0.67)	0.11 (0.74)
females	PT	0.03 (0.70)	0.04 (0.65)	0.03 (0.62)	-0.06 (0.82)	0.00 (0.73)	-0.09 (0.94)
	VPT	-0.25 (0.63)	-0.37 (0.50)	-0.02 (0.68)	-0.26 (0.98)	-0.12 (0.87)	-0.73 (1.07)
	MPT	0.08 (0.70)	0.13 (0.65)	0.04 (0.61)	0.00 (0.78)	0.05 (0.68)	0.12 (0.83)
	FT	-0.03 (0.74)	-0.03 (0.76)	-0.03 (0.78)	0.06 (0.58)	0.00 (0.58)	0.03 (0.50)
t-test (p)							
males PT vs. FT		0.3164	0.2607	0.2389	**0.0267**	**0.0355**	0.0970
males VPT vs. peers[a]		0.3528	0.3584	0.3853	0.2052	0.2079	0.3056
females PT vs. FT		0.3347	0.2869	0.3448	0.2379	0.4995	0.2506
females VPT vs. peers[a]		0.1406	**0.0432**	0.4562	0.1397	0.2619	**0.0024**
one-way ANOVA (p)[b]							
males		0.7400	0.8090	0.6330	**0.0293**	0.1960	0.4320
females		0.4110	0.1120	0.8940	0.5210	0.7880	**0.0173**
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	NA	nsg	NA	NA
	VPT vs. FT	NA	NA	NA	nsg	NA	NA
	MPT vs. FT	NA	NA	NA	nsg	NA	NA
females	VPT vs. MPT	NA	NA	NA	NA	NA	**<0.01**
	VPT vs. FT	NA	NA	NA	NA	NA	**<0.05**
	MPT vs. FT	NA	NA	NA	NA	NA	nsg

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex T

Triceps skinfold thickness [mm] from the age of 8 to 19 years

Debelina kožne gube triceps [mm] preiskovancev v starosti 8 do 19 let

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	20	21	22	20
	MPT	51	68	71	69	70	70
	FT	83	107	111	114	117	113
females	VPT	10	12	13	13	13	14
	MPT	45	58	62	62	61	60
	FT	67	81	87	87	90	85
average (SD)							
males	PT	9.2 (4.3)	9.8 (4.4)	10.6 (4.9)	11.5 (4.9)	12.4 (5.9)	12.1 (6.0)
	VPT	7.6 (2.7)	7.8 (3.3)	8.8 (3.1)	9.7 (3.5)	10.1 (4.0)	10.3 (4.5)
	MPT	9.6 (4.5)	10.3 (4.6)	11.1 (5.2)	12.1 (5.2)	13.1 (6.2)	12.6 (6.3)
	FT	8.7 (3.1)	9.5 (3.6)	9.8 (4.1)	11.0 (4.6)	11.9 (5.1)	11.9 (5.3)
females	PT	10.8 (4.0)	12.1 (4.5)	13.3 (5.7)	14.0 (6.2)	13.6 (5.9)	13.3 (5.4)
	VPT	12.0 (5.6)	11.8 (4.9)	14.0 (6.2)	15.3 (6.3)	14.2 (5.5)	14.1 (4.4)
	MPT	10.5 (3.6)	12.2 (4.4)	13.1 (5.6)	13.7 (6.2)	13.5 (6.0)	13.2 (5.7)
	FT	10.4 (3.8)	11.5 (4.8)	12.6 (4.9)	13.4 (5.2)	12.9 (5.1)	13.1 (5.8)
t-test (p)							
males PT vs. FT		0.3793	0.3757	0.2167	0.2591	0.3185	0.4442
males VPT vs. peers[a]		0.0944	**0.0225**	0.0698	0.0636	**0.0332**	0.0713
females PT vs. FT		0.2740	0.2317	0.1954	0.2490	0.2140	0.3979
females VPT vs. peers[a]		0.1122	0.4862	0.2224	0.1443	0.2430	0.2663
one-way ANOVA (p)[b]							
males		0.1610	**0.0487**	**0.0491**	0.0999	0.0718	0.2580
females		0.4699	0.7350	0.6060	0.5350	0.6560	0.8220
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	**<0.05**	**<0.05**	NA	NA	NA
	VPT vs. FT	NA	nsg	nsg	NA	NA	NA
	MPT vs. FT	NA	nsg	nsg	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex T.

Triceps skinfold thickness [mm] from the age of 8 to 19 years

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	19	19	17	13	10	8
	MPT	65	63	45	36	35	27
	FT	110	106	82	71	60	40
females	VPT	14	13	13	12	12	7
	MPT	59	55	50	37	30	21
	FT	83	77	62	52	48	42
average (SD)							
males	PT	10.9 (5.1)	9.7 (4.5)	9.0 (3.8)	9.0 (4.4)	8.7 (4.4)	9.4 (5.0)
	VPT	9.4 (4.1)	9.0 (4.0)	8.6 (2.9)	7.4 (1.7)	7.8 (3.8)	8.8 (5.6)
	MPT	11.4 (5.4)	9.9 (4.7)	9.1 (4.1)	9.5 (4.9)	9.0 (4.6)	9.5 (4.9)
	FT	11.7 (5.7)	11.0 (5.1)	10.0 (5.4)	9.6 (4.0)	9.9 (3.9)	9.9 (3.9)
females	PT	14.3 (5.8)	14.5 (4.9)	15.3 (4.6)	15.3 (4.7)	14.8 (4.7)	15.3 (5.5)
	VPT	14.1 (4.5)	14.7 (4.5)	14.4 (5.3)	15.0 (6.0)	15.0 (4.4)	18.1 (8.2)
	MPT	14.4 (6.1)	14.5 (5.0)	15.5 (4.5)	15.4 (4.3)	14.8 (4.8)	14.4 (4.1)
	FT	13.1 (5.8)	13.4 (5.7)	13.3 (4.9)	15.0 (4.9)	15.0 (4.8)	15.3 (5.5)
t-test (p)							
males PT vs. FT		0.2016	0.0608	0.0926	0.2186	0.1094	0.3822
males VPT vs. peers[a]		0.0521	0.0921	0.1428	**0.0398**	0.0975	0.2833
females PT vs. FT		0.0889	0.1100	**0.0124**	0.3619	0.4406	0.4958
females VPT vs. peers[a]		0.3925	0.3019	0.4715	0.4508	0.4830	0.0752
one-way ANOVA (p)[b]							
males		0.2530	0.1410	0.2731	0.2160	0.2320	0.8031
females		0.3970	0.4690	0.0621	0.9040	0.9820	0.2931

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex U

Skinfold thicknesses [mm] at eight body sites and three trunk-to-limb skinfold thickness ratios at the age of 26 years

Debelina kožnih gub [mm] preiskovancev na osmih mestih telesa in tri razmerja kožnih gub trup-okončine v starosti 26 let

SFT site		Triceps	Biceps	Subscapular	Iliac crest	Supraspinal	Abdominal
subject number (N)							
males	VPT	1	1	1	1	1	1
	MPT	1	1	1	1	1	1
	FT	5	5	5	5	5	5
females	VPT	1	1	1	1	1	1
	MPT	2	2	2	2	2	2
	FT	1	1	1	1	1	1
average (SD)							
males	VPT	5.1 (-)	4.2 (-)	11.7 (-)	20.5 (-)	7.4 (-)	15.4 (-)
	MPT	6.3 (-)	3.4 (-)	8.8 (-)	11.2 (-)	5.2 (-)	13.3 (-)
	FT	15.4 (10.1)	6.6 (4.0)	18.0 (12.4)	25.7 (13.1)	14.6 (10.0)	19.6 (12.5)
females	VPT	19.4 (-)	8.2 (-)	19.3 (-)	24.2 (-)	17.8 (-)	21.0 (-)
	MPT	12.6 (4.0)	5.6 (2.4)	11.7 (4.8)	13.0 (7.3)	6.1 (0.5)	16.6 (6.6)
	FT	11.7 (-)	4.4 (-)	9.8 (-)	16.8 (-)	8.2 (-)	15.2 (-)

SFT site, ratio		Thigh front	Median calf	Trunk / limb 1:1 SFT	Trunk / limb 2:2 SFT	Trunk / limb 4:4 SFT
subject number (N)						
males	VPT	1	1	1	1	1
	MPT	1	1	1	1	1
	FT	5	5	5	5	5
females	VPT	1	1	1	1	1
	MPT	2	2	2	2	2
	FT	1	1	1	1	1
average (SD)						
males	VPT	8.8 (-)	4.0 (-)	2.29 (-)	3.46 (-)	2.49 (-)
	MPT	7.3 (-)	5.1 (-)	1.40 (-)	2.06 (-)	1.74 (-)
	FT	23.9 (15.9)	13.3 (8.7)	1.27 (0.49)	2.10 (0.32)	1.44 (0.26)
females	VPT	30.2 (-)	18.3 (-)	0.98 (-)	1.58 (-)	1.08 (-)
	MPT	24.6 (5.3)	14.7 (3.0)	1.70 (0.08)	1.32 (0.20)	0.81 (0.13)
	FT	17.3 (-)	14.5 (-)	0.71 (-)	1.65 (-)	1.04 (-)

VPT – very preterm, MPT – moderately preterm, FT – full-term, SFT – skinfold thickness

Annex V

Body circumferences [cm] at six body sites and their ratios at the age of 26 years

Obsegi telesa [cm] preiskovancev na šestih mestih telesa in njihova razmerja v starosti 26 let

C site		Upper arm relax	Upper arm flex	Waist	Hip	Thigh	Calf
subject number (N)							
males	VPT	2	2	2	1	2	1
	MPT	3	3	3	3	3	1
	FT	10	10	11	9	10	5
females	VPT	4	4	4	4	4	1
	MPT	6	6	6	6	5	2
	FT	7	7	6	6	7	1
average (SD)							
males	VPT	30.2 (0.3)	33.4 (0.9)	82.3 (1.8)	90.9 (-)	51.0 (1.4)	35.3 (-)
	MPT	33.4 (4.6)	35.7 (5.0)	91.0 (17.1)	102.5 (12.5)	52.8 (3.6)	35.9 (-)
	FT	33.3 (3.9)	35.6 (3.5)	85.7 (17.9)	103.9 (10.7)	56.2 (6.7)	40.1 (5.4)
females	VPT	28.2 (3.7)	29.2 (3.3)	76.3 (15.9)	97.5 (6.2)	50.7 (5.4)	37.8 (-)
	MPT	25.4 (2.7)	27.2 (2.3)	71.6 (9.7)	95.5 (5.3)	48.7 (6.4)	33.1 (0.9)
	FT	26.5 (1.7)	28.3 (1.6)	72.8 (6.5)	97.8 (4.6)	52.8 (3.8)	39.2 (-)

C ratio	Males			Females		
	Waist C / Height	Waist C / hip C	Trunk / limb 2:2 C	Waist C / Height	Waist C / hip C	Trunk / limb 2:2 C
subject number (N)						
VPT	1	1	1	3	4	4
MPT	2	3	3	5	6	5
FT	8	9	9	3	6	6
average (SD)						
VPT	0.49 (-)	0.92 (-)	2.12 (-)	0.52 (0.09)	0.78 (0.12)	2.20 (0.11)
MPT	0.49 (0.13)	0.88 (0.11)	2.24 (0.13)	0.44 (0.07)	0.75 (0.08)	2.27 (0.24)
FT	0.50 (0.10)	0.83 (0.12)	2.13 (0.13)	0.43 (0.01)	0.75 (0.06)	2.06 (0.08)

VPT – very preterm, MPT – moderately preterm, FT – full-term, C – circumference

Annex W

Percentage of body fat from the age of 8 to 19 years calculated according to the equations of Durnin and Womersly (1974) and Siri (1961)

Odstotek telesnega maščobnega tkiva preiskovancev v starosti 8 do 19 let izračunan po enačbah Durnin in Womersly (1974) ter Siri (1961)

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	20	21	22	20
	MPT	51	68	71	69	70	69
	FT	81	107	110	113	117	113
females	VPT	10	12	13	13	13	14
	MPT	45	58	62	62	61	60
	FT	67	81	87	87	90	85
average (SD)							
males	PT	13.8 (4.9)	14.6 (5.0)	15.5 (4.9)	16.5 (5.0)	17.1 (5.6)	17.0 (5.8)
	VPT	11.9 (4.2)	12.0 (4.8)	13.6 (4.3)	14.7 (4.4)	14.9 (5.2)	14.9 (5.9)
	MPT	14.3 (5.0)	15.2 (4.9)	16.1 (5.0)	17.1 (5.0)	17.8 (5.5)	17.4 (5.7)
	FT	13.8 (3.8)	14.5 (4.0)	14.8 (4.5)	16.1 (4.6)	17.0 (4.8)	17.0 (4.8)
females	PT	21.1 (4.5)	22.5 (4.7)	23.5 (5.2)	24.1 (5.7)	23.7 (5.5)	23.7 (5.0)
	VPT	22.3 (5.2)	22.1 (5.0)	24.3 (4.9)	25.4 (5.4)	24.6 (5.1)	24.8 (3.9)
	MPT	20.9 (4.4)	22.6 (4.7)	23.4 (5.2)	23.8 (5.8)	23.6 (5.6)	23.4 (5.2)
	FT	20.7 (4.4)	21.9 (4.5)	23.0 (4.8)	23.8 (4.6)	23.4 (4.5)	23.3 (5.4)
t-test (p)							
males PT vs. FT		0.4593	0.4345	0.1300	0.2813	0.3868	0.4998
males VPT vs. peers[a]		0.0543	**0.0069**	0.0747	0.0559	**0.0304**	0.0764
females PT vs. FT		0.2842	0.2143	0.2375	0.3985	0.3238	0.3235
females VPT vs. peers[a]		0.1555	0.4719	0.2134	0.1469	0.2240	0.1619
one-way ANOVA (p)[b]							
males		0.2158	**0.0253**	0.0724	0.1203	0.0704	0.3064
females		0.5810	0.6910	0.6480	0.5750	0.7320	0.6100
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	**<0.01**	NA	NA	NA	NA
	VPT vs. FT	NA	**<0.05**	NA	NA	NA	NA
	MPT vs. FT	NA	nsg	NA	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex W.

Percentage of body fat from the age of 8 to 19 years calculated according to the equations of Durnin and Womersly (1974) and Siri (1961)

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	19	19	17	13	10	8
	MPT	65	63	45	36	35	27
	FT	110	106	82	71	60	40
females	VPT	14	13	13	12	12	7
	MPT	59	55	50	37	30	21
	FT	83	77	62	52	48	42
average (SD)							
males	PT	15.7 (5.6)	14.3 (5.1)	13.7 (4.3)	13.5 (4.7)	12.9 (5.5)	13.8 (5.3)
	VPT	14.0 (5.6)	13.7 (4.5)	13.5 (3.7)	12.0 (2.5)	11.9 (5.0)	12.9 (5.7)
	MPT	16.1 (5.6)	14.5 (5.3)	13.8 (4.5)	14.1 (5.1)	13.2 (5.6)	14.1 (5.2)
	FT	16.5 (5.1)	15.8 (5.2)	15.0 (4.5)	14.4 (4.8)	14.9 (4.6)	14.9 (4.7)
females	PT	24.6 (5.0)	25.0 (4.3)	25.8 (3.8)	25.8 (3.9)	25.4 (3.8)	25.8 (3.9)
	VPT	24.7 (3.9)	25.2 (4.1)	24.9 (4.4)	25.3 (4.8)	25.6 (4.0)	27.7 (5.0)
	MPT	24.5 (5.3)	24.9 (4.4)	26.1 (3.6)	26.0 (3.6)	25.4 (3.7)	25.2 (3.4)
	FT	23.3 (5.3)	23.6 (5.4)	23.9 (4.5)	25.5 (4.0)	25.5 (3.9)	25.7 (4.2)
t-test (p)							
males PT vs. FT		0.1442	**0.0168**	**0.0243**	0.1479	**0.0226**	0.1933
males VPT vs. peers[a]		0.0519	0.0927	0.1404	**0.0457**	0.0745	0.1947
females PT vs. FT		0.0599	**0.0450**	**0.0045**	0.3343	0.4516	0.4665
females VPT vs. peers[a]		0.2622	0.2265	0.4802	0.3655	0.4733	0.0900
one-way ANOVA (p)[b]							
males		0.1520	0.1140	0.1392	0.2600	0.1020	0.5820
females		0.2970	0.2340	**0.0225**	0.7870	0.9840	0.3600
Tukey HSD post hoc (p)							
females	VPT vs. MPT	NA	NA	nsg	NA	NA	NA
	VPT vs. FT	NA	NA	nsg	NA	NA	NA
	MPT vs. FT	NA	NA	**<0.01**	NA	NA	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex X

Body fat mass [kg] from the age of 8 to 19 years

Masa telesnega maščobnega tkiva [kg] preiskovancev v starosti 8 do 19 let

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	20	21	22	20
	MPT	51	68	71	69	70	69
	FT	81	106	108	111	115	112
females	VPT	10	12	13	12	12	13
	MPT	45	57	61	61	60	59
	FT	67	81	87	87	90	85
average (SD)							
males	PT	4.1 (2.2)	4.7 (2.6)	5.8 (3.1)	6.7 (3.4)	7.9 (4.1)	8.7 (4.5)
	VPT	3.1 (1.6)	3.5 (2.1)	4.5 (2.3)	5.3 (2.7)	6.2 (3.3)	7.1 (3.9)
	MPT	4.3 (1.9)	5.1 (2.7)	6.1 (3.5)	7.1 (4.1)	8.4 (4.7)	9.1 (4.7)
	FT	3.9 (1.7)	4.6 (2.2)	5.2 (2.6)	6.3 (3.1)	7.4 (3.6)	8.4 (4.2)
females	PT	5.9 (2.1)	7.2 (2.7)	8.5 (3.5)	9.8 (4.0)	10.9 (4.5)	12.0 (4.5)
	VPT	6.3 (2.8)	6.9 (2.8)	8.5 (3.3)	10.3 (3.6)	10.9 (3.2)	12.2 (3.0)
	MPT	5.8 (1.9)	7.2 (2.7)	8.5 (3.5)	9.7 (4.1)	10.9 (4.7)	12.0 (4.7)
	FT	6.0 (2.1)	6.9 (2.6)	8.4 (3.2)	9.7 (3.4)	10.7 (3.8)	12.0 (4.6)
t-test (p)							
males PT vs. FT		0.3249	0.2930	0.0757	0.2244	0.1795	0.3459
males VPT vs. peers[a]		0.0594	**0.0147**	**0.0482**	**0.0359**	**0.0348**	0.0548
females PT vs. FT		0.4183	0.2949	0.4631	0.3952	0.3916	0.4825
females VPT vs. peers[a]		0.2578	0.4139	0.4820	0.3049	0.4644	0.4277
one-way ANOVA (p)[b]							
males		0.1700	**0.0368**	**0.0218**	0.0581	**0.0404**	0.1560
females		0.7340	0.7950	0.9960	0.8730	0.9630	0.9830
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	**<0.05**	**<0.05**	NA	**<0.05**	NA
	VPT vs. FT	NA	nsg	nsg	NA	nsg	NA
	MPT vs. FT	NA	nsg	nsg	NA	nsg	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex X.

Body fat mass [kg] from the age of 8 to 19 years

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	19	19	17	13	10	8
	MPT	65	63	45	36	35	27
	FT	107	103	77	68	58	40
females	VPT	14	13	13	12	12	7
	MPT	58	53	48	35	30	21
	FT	82	75	57	47	43	40
average (SD)							
males	PT	8.8 (4.4)	8.8 (4.4)	8.8 (4.1)	9.5 (4.7)	9.4 (5.0)	10.5 (5.4)
	VPT	7.5 (3.9)	8.0 (4.0)	8.1 (3.1)	7.9 (2.8)	8.7 (5.1)	10.0 (6.7)
	MPT	9.2 (4.5)	9.1 (4.6)	9.1 (4.4)	10.0 (5.1)	9.6 (5.0)	10.6 (5.1)
	FT	9.0 (4.3)	9.6 (4.3)	9.6 (3.7)	10.1 (4.6)	10.8 (4.7)	11.2 (4.5)
females	PT	13.4 (4.8)	14.1 (4.6)	15.2 (4.6)	15.3 (4.3)	15.2 (4.5)	15.2 (3.9)
	VPT	12.9 (3.4)	13.6 (3.6)	13.5 (4.0)	14.1 (4.8)	14.4 (4.0)	15.7 (3.8)
	MPT	13.5 (5.2)	14.2 (4.8)	15.7 (4.7)	15.7 (4.2)	15.5 (4.8)	15.1 (4.0)
	FT	12.8 (4.7)	13.5 (4.9)	13.8 (3.9)	15.3 (3.7)	15.3 (3.8)	15.6 (4.3)
t-test (p)							
males PT vs. FT		0.3795	0.1264	0.1203	0.2521	0.0703	0.2726
males VPT vs. peers[a]		0.0610	0.0934	0.0905	0.0588	0.1554	0.2984
females PT vs. FT		0.2316	0.2339	**0.0331**	0.4826	0.4572	0.3624
females VPT vs. peers[a]		0.4488	0.4332	0.1916	0.1415	0.2250	0.4324
one-way ANOVA (p)[b]							
males		0.2910	0.3290	0.3260	0.2950	0.2990	0.7873
females		0.7060	0.6980	0.0506	0.5210	0.7350	0.8871

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

Annex Y

Lean body mass [kg] from the age of 8 to 19 years

Pusta telesna masa [kg] preiskovancev v starosti 8 do 19 let

Age		8 years	9 years	10 years	11 years	12 years	13 years
subject number (N)							
males	VPT	12	18	20	21	22	20
	MPT	51	68	71	69	70	69
	FT	81	106	108	111	115	112
females	VPT	10	12	13	12	12	13
	MPT	45	57	61	61	60	59
	FT	67	81	87	87	90	85
average (SD)							
males	PT	23.8 (4.5)	25.9 (4.9)	29.1 (5.3)	31.6 (5.8)	35.4 (6.9)	39.7 (7.8)
	VPT	21.9 (3.6)	23.6 (3.6)	26.4 (4.4)	28.8 (4.8)	32.6 (6.5)	36.2 (7.6)
	MPT	24.2 (4.6)	26.5 (5.0)	29.9 (5.3)	32.5 (5.8)	36.2 (6.9)	40.7 (7.6)
	FT	23.8 (3.7)	25.8 (4.4)	28.6 (5.0)	31.5 (5.7)	34.4 (5.9)	39.3 (7.7)
females	PT	21.4 (3.5)	23.6 (3.9)	26.2 (4.6)	29.6 (4.9)	33.4 (5.7)	37.4 (6.0)
	VPT	21.1 (2.9)	23.2 (2.8)	25.4 (2.8)	28.9 (2.9)	32.5 (3.5)	36.1 (4.6)
	MPT	21.5 (3.6)	23.7 (4.1)	26.4 (4.9)	29.7 (5.2)	33.6 (6.1)	37.7 (6.2)
	FT	22.3 (2.8)	24.0 (3.5)	27.3 (4.5)	30.2 (5.3)	34.1 (6.3)	38.0 (6.0)
t-test (p)							
males PT vs. FT		0.4853	0.4535	0.2151	0.4417	0.1415	0.3499
males VPT vs. peers[a]		**0.0468**	**0.0134**	**0.0127**	**0.0091**	**0.0411**	**0.0236**
females PT vs. FT		0.0609	0.2651	0.0615	0.2262	0.2319	0.2641
females VPT vs. peers[a]		0.2080	0.2901	0.1261	0.2359	0.2112	0.1461
one-way ANOVA (p)[b]							
males		0.1990	0.0537	**0.0182**	**0.0321**	**0.0363**	0.0665
females		0.2880	0.7670	0.2410	0.6620	0.6390	0.5490
Tukey HSD post hoc (p)							
males	VPT vs. MPT	NA	NA	**<0.01**	**<0.01**	**<0.05**	NA
	VPT vs. FT	NA	NA	nsg	nsg	nsg	NA
	MPT vs. FT	NA	NA	nsg	nsg	nsg	NA

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, NA – not applicable, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT

continued

continuation of Annex Y.

Lean body mass [kg] from the age of 8 to 19 years

Age		14 years	15 years	16 years	17 years	18 years	19 years
subject number (N)							
males	VPT	19	19	17	13	10	8
	MPT	65	63	45	36	35	27
	FT	107	103	77	68	58	40
females	VPT	14	13	13	12	12	7
	MPT	58	53	48	35	30	21
	FT	82	75	57	47	43	40
average (SD)							
males	PT	45.0 (8.1)	50.7 (8.4)	53.9 (7.4)	58.4 (7.4)	61.5 (7.1)	62.5 (7.0)
	VPT	42.6 (8.7)	48.3 (9.0)	51.1 (6.0)	56.6 (6.6)	61.4 (6.9)	62.7 (7.8)
	MPT	45.7 (7.8)	51.5 (8.1)	54.9 (7.7)	59.1 (7.6)	61.5 (7.2)	62.4 (6.9)
	FT	44.4 (8.0)	50.1 (8.9)	54.1 (8.0)	57.8 (7.5)	60.2 (7.9)	62.2 (7.1)
females	PT	39.7 (5.8)	41.3 (5.4)	42.7 (5.7)	43.1 (5.2)	43.8 (6.5)	43.3 (5.3)
	VPT	38.6 (3.4)	39.4 (2.9)	40.0 (3.6)	40.8 (4.2)	41.3 (5.0)	40.5 (3.1)
	MPT	40.0 (6.3)	41.7 (5.8)	43.4 (5.9)	43.9 (5.3)	44.8 (6.9)	44.2 (5.6)
	FT	41.2 (5.8)	42.7 (5.7)	43.6 (4.7)	44.1 (4.5)	44.6 (4.6)	44.8 (5.7)
t-test (p)							
males PT vs. FT		0.3109	0.3243	0.4465	0.3446	0.2000	0.4382
males VPT vs. peers[a]		0.1240	0.1273	**0.0491**	0.2168	0.3956	0.4346
females PT vs. FT		0.0645	0.0679	0.1883	0.1607	0.2621	0.1243
females VPT vs. peers[a]		0.0975	**0.0423**	**0.0109**	**0.0162**	**0.0289**	**0.0319**
one-way ANOVA (p)[b]							
males		0.3110	0.3300	0.2139	0.5350	0.7020	0.9802
females		0.2240	0.1420	0.0723	0.1000	0.1660	0.1623

PT – preterm, VPT – very preterm, MPT – moderately preterm, FT – full-term, [a] – MPT and FT, [b] – ANOVA performed for VPT, MPT, and FT