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Growth from birth to adolescence, and the relationship between physical and general health status in Lithuanian preterm newborns (a longitudinal study)

DOCTORAL DISSERTATION

Medical and Health Sciences,
Medicine (M 001)

VILNIUS 2025

The dissertation was prepared between 2016 and 2024 at the Department of Anatomy, Histology and Anthropology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University.

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Neišnešiotų Lietuvos naujagimių augimas nuo gimimo iki paauglystės, fizinės ir bendros sveikatos būklės sąsajos (longitudinis tyrimas)

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DISSERTATION AT A GLANCE				
This study aimed to evaluate the body size at birth of Lithuanian newborns based on gestational age (GA) and sex and to perform a longitudinal analysis of the physical status, growth dynamics, and health outcomes of preterm-born children depending on GA and birth weight (BW).				
STUDY DESIGN	**Cross-Sectional Population-Based Study**		**Retrospective Longitudinal Study**	
STUDY PERIOD	1995-2015	2001-2015	2000-2015	
COHORT SIZE	618,235	423,999	467	
RESEARCH OBJECTIVES	BW/length by GA and sex	Head Circumference (HC) by GA and sex	Growth patterns (weight, length, BMI) by GA and BW groups	Multisystem Health Consequences related to birth
MAIN METHODS	GAMLSS LMST		SITAR	Negative binomial regression Upset visualisation method Nonparametric tests
DEFENDED STATEMENTS	GA- and sex-adjusted population-based references for BW and length, compared to global standards, more accurately reflect the neonatal size and health status of Lithuanian newborns (**Paper I**)	GA- and sex-adjusted population-based references for neonatal HC, compared to global standards, more precisely represent the specific features of the neonatal HC of the Lithuanian population (**Paper II**)	Birth-related variables significantly impact longitudinal growth trajectories in Lithuanian preterm infants (**Paper III**)	Lithuanian preterm-born individuals face complex long-term health challenges affecting different organ systems and depending on birth-related factors (**Paper IV**)
CONCLUSIONS	Regional GA- and sex-adjusted population-based neonatal references, compared to the global standard IG-21, reveal distinct differences in the Lithuanian neonatal weight and length. Specifically, IG-21 substantially underestimates the prevalence of SGA and overestimates the prevalence of LGA in Lithuanian newborns, particularly in term and post-term gestations. These regional references better capture the unique growth patterns of the Lithuanian population, highlighting the discrepancies in the classification of at-risk newborns.	Global standards such as IG-21 effectively evaluate neonatal HC in early gestations. However, in later gestations, the neonatal HC in Lithuanian newborns deviates from global standards, as the GA- and sex-adjusted population-based references demonstrate consistently larger HC values. These references better capture the specific characteristics of Lithuanian newborns by reflecting regional growth patterns not accounted for by global standards.	BW strongly influences sustained growth deficits in Lithuanian preterm infants, while GA dynamically shapes BMI trajectories, increasing the obesity risk in early preterm groups. Boys, compared to girls, face greater long-term challenges in weight and BMI.	Lithuanian preterm-born individuals exhibit a substantial burden of multimorbidity, with the highest prevalence of disease manifestations occurring before age 7. Lower BW is strongly associated with greater susceptibility to multimorbidity and a broader spectrum of conditions across multiple ICD-10 chapters. The unique and complex comorbidity patterns underscore the need for personalised, multidisciplinary care to address their intricate health trajectories.

ABBREVIATIONS

AGA	Appropriate for gestational age
AR	Adiposity rebound
BCT	Box-Cox t (BCT) distribution
BW	Birth weight
CI	Confidence interval
CV	Coefficient of variation
ELBW	Extremely low birth weight
GA	Gestational age
GAMLSS	Generalised additive models for location, scale, and shape
HC	Head circumference
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IG-21	International Foetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st)
IQR	Interquartile range
IRRs	Incidence rate ratios
IUGR	Intrauterine growth restriction
LGA	Large for gestational age
LMS	*Lambda-Mu-Sigma* method
LMST	*Lambda-Mu-Sigma-Tau* method
M	Mean
N	Count
SD	Standard deviation
SE	Standard error
SGA	Small for gestational age
SITAR	SuperImposition by Translation and Rotation
VLBW	Very low birth weight
WHO	World Health Organization

CONTENTS

LIST OF SCIENTIFIC PAPERS

This dissertation is based on the following research papers, referred to in the text by their Roman numerals.

I. **Morkuniene R,** Cole TJ, Jakimaviciene EM, Isakova J, Bankauskiene A, Drazdiene N, Basys V, Tutkuviene J (2023). *Regional References vs. International Standards for Assessing Weight and Length by Gestational Age in Lithuanian Neonates.* Front. Pediatr. 11:1173685. Published 2023 June 14.
doi:10.3389/fped.2023.1173685
Author's contribution: Prepared raw data for analysis; Performed part of the calculations; Analysed and interpreted the data; Took the lead in writing the manuscript.

II. **Morkuniene R**, Tutkuviene J, Cole TJ, Jakimaviciene EM, Isakova J, Bankauskiene A, Drazdiene N, Basys V. *Neonatal Head Circumference by Gestation Reflects Adaptation to Maternal Body Size: Comparison of Different Standards*. Sci Rep 12, 11057 (2022). Published 2022 June 30.
doi:10.1038/s41598-022-15128-3
Author's contribution: Prepared raw data for analysis; Performed part of the calculations; Analysed and interpreted the data; Took the lead in writing the manuscript.

III. **Morkuniene R**, Cole TJ, Levuliene R, Suchomlinov A, Tutkuviene J. *The Associations of Preterm Birth and Low Birth Weight with Childhood Growth Curves between Birth and 12 Years: A Sitar-Based Longitudinal Analysis***.** Ann. Hum. Biol.
Accepted for publication 2025 February 21.
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Author's contribution: Collected, analysed, and interpreted the data and took the lead in writing the manuscript.

IV. **Morkuniene R**, Levuliene R, Gegzna V, Jakimaviciene EM, Tutkuviene J. *Surviving Prematurity: Retrospective Longitudinal Study of Multisystem Consequences in Preterm-Born Individuals from Infancy to Adolescence.* BMC Pediatr 25, 46 (2025).
Published 2025 January 18.
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Author's contribution: Collected, analysed, and interpreted the data; Performed part of the calculations; Took the lead in writing the manuscript.

PREAMBLE

The doctoral dissertation is presented for defence as a compilation of research articles, with some sections quoted verbatim from previous publications listed at the bottom of the dissertation.

The dissertation comprises interconnected parts, contributing to a comprehensive analysis of growth and health outcomes in Lithuanian preterm infants of different gestation and birth weight.

Initially, the birth weight and length patterns by GA and sex in Lithuanian newborns have been analysed, and population-based birth weight and length reference values and curves for Lithuanian newborns have been constructed and compared against international standards. Subsequently, the distribution and variation of head circumference in Lithuanian newborns by GA and sex have been analysed, population-based head circumference reference values and curves have been developed for Lithuanian newborns, stratified by gestational age and sex, and those have been compared to international standards. Following this, the longitudinal growth outcomes in Lithuanian preterm infants have been evaluated, with growth patterns (height, weight, BMI) analysed across the gestational age and birth weight groups until 12 years. Lastly, the dissertation has examined the multisystem health consequences in Lithuanian individuals born preterm, from infancy to adolescence, focusing how birth-related factors impact the complexity of health conditions and the interrelationships among different disorders.

1. INTRODUCTION

1.1. Research Problem and Relevance of the Study

Prematurity remains a significant global health challenge with an estimated 13.4 million preterm births (<37 gestational weeks) reported in 2020 (1). Despite tangible advancements in healthcare, preterm birth rates have shown little change over the past decade contributing to nearly 1 million neonatal deaths annually and leaving millions more with lifelong disabilities (2,3). Furthermore, neonatal conditions remain the leading global cause of lost human capital, a trend unchanged since 1990 (3).

The assessment of the growth and health status of preterm newborns relies on various growth standards and reference charts that are essential for clinical practice to enable accurate diagnosis and informed decision-making. However, no global consensus exists on the most suitable growth standards for preterm infants. Controversies persist regarding the use of intrauterine charts (4–6) versus postnatal growth charts (7,8), customised versus population-based references (9–12), and regional versus global standards (6,13–19). For instance, although the Intergrowth-21st (IG-21) consortium proposed adopting a single international growth standard the rising evidence of physiological and ethnic variability increasingly challenges the applicability of a 'one-size-fits-all' approach (13–15).

In Lithuania, birth weight and length evaluation relied on outdated, unadjusted, and empirical centiles derived from the incomplete population data collected between 1998 and 2002 (20). Moreover, no population-based references for neonatal head circumference have existed until now, leaving the assessments reliant on international references with limited local applicability. These limitations highlight the urgent need for updated, region-specific growth references to improve the accuracy and relevance of clinical assessments.

This need is particularly critical given that preterm newborns face heightened risks of postnatal growth failure most commonly followed by a catch-up growth in the first 2–3 years. Moreover, they are likely to typically achieve lower adult height than their term-born peers (21–23). A smaller birth weight (BW) prolongs the compensatory growth period (21), while being small for gestational age (SGA) further increases the risks of adverse perinatal outcomes (24–26). Notably, extremely preterm survivors (< 26 gestational weeks) often remain shorter and lighter when reaching adulthood, with an elevated BMI (27). While an estimated shorter final height is associated with a decreasing gestational age (GA) (28), some studies suggest that by

adulthood, preterm-born individuals—including those born very, moderately, and late preterm—may achieve adult size, pubertal timing, and a peak height velocity comparable to their term-born peers (29,30).

Thus, the findings vary significantly across studies regarding the age at which preterm-born children catch up with their peers in terms of their pace and rate of growth, pubertal timing, and sex-related differences (22,31,32). These inconsistencies driven by the classification methods (e.g., GA vs. BW), study duration, and debates over the optimal growth rates (33,34) highlight the need for further longitudinal research as most of the existing studies are cross-sectional and frequently isolate GA or BW, thus leaving a gap in understanding their combined impact on growth and health outcomes (35).

The developmental origins of health and disease framework highlight the profound impact of fetal life on health across the lifespan (36). In childhood, preterm newborns are at a higher risk of neurodevelopmental impairments, including cerebral palsy (37–41), autism spectrum disorders, and cognitive or academic challenges (40–50), with the severity strongly linked to GA (51). Additionally, they are prone to an increased susceptibility to conditions such as bronchopulmonary dysplasia, asthma (52–63), and digestive dysfunctions (59). Later in life, preterm individuals are more prone to cardiovascular diseases, including hypertension and ischemic heart disease (64,65), as well as to endocrine and metabolic disorders such as metabolic syndrome and hypothyroidism (64,66–71), and renal impairment (72–74). While extensive research focuses on individual organ systems, the interplay between these conditions and the cumulative burden of multimorbidity remains underexplored. Additionally, most studies focus on extremely preterm infants, with limited attention to late preterm and sub-optimal BW groups (75–81). Longitudinal research studies emphasise short-term outcomes (up to 7 years) (40,52,56,69,70), leaving gaps in understanding health trajectories into adolescence and adulthood (48,82–86).

Therefore, to address these gaps, the overall aim of this study was to evaluate the body size at birth of Lithuanian newborns based on GA and sex and to perform a longitudinal analysis of the physical condition, growth dynamics, and health outcomes of preterm newborns, depending on GA and BW. This doctoral dissertation is based on four published research articles. **Paper I** analyses the birth weight and length patterns in Lithuanian newborns by GA and sex, constructs the population-based birth weight and length reference values and curves for Lithuanian newborns according to GA and sex and compares them against global standards. **Paper II** analyses the distribution and variation of head circumference in Lithuanian newborns by GA and sex, develops population-based head circumference reference values

and curves for Lithuanian newborns, stratified by GA and sex, and compares them to global standards. **Paper III** evaluates longitudinal growth outcomes in preterm Lithuanian infants from infancy to adolescence based on the analysis of growth patterns according to GA and BW. **Paper IV** explores multisystem health consequences in Lithuanian preterm-born individuals, from infancy to adolescence, focusing on the influence of birth-related factors on health condition complexity and the interrelationships among different disorders.

1.2. Research Aims

This study has aimed to evaluate the body size at birth of Lithuanian newborns based on GA and sex, and to perform a longitudinal analysis of the physical condition, growth dynamics, and health outcomes in preterm-born children, depending on GA and BW.

1.3. Research Objectives

1. To analyse the birth weight and length patterns in the Lithuanian newborn population by GA and sex, and to compare these findings with international standards (**Paper I**).
2. To analyse the distribution and variation of head circumference in the Lithuanian newborn population by GA and sex, and to compare these findings with international standards (**Paper II**).
3. To evaluate longitudinal growth outcomes in preterm Lithuanian infants from infancy to adolescence based on the analysis of growth patterns (height, weight, BMI) by GA and BW groups (**Paper III**).
4. To explore the multisystem health consequences in Lithuanian preterm-born individuals, from infancy to adolescence by analysing the impact of birth-related factors on health condition complexity and interrelationships among different disorders (**Paper IV**).

1.4. Scientific Novelty

Until recently, the body size indices of Lithuanian newborns, specifically birth weight and length, were assessed based on GA and sex-specific centiles derived from the national data on 164,662 newborns born between 1998 and 2002 (20). This study upgrades these references by applying globally approved statistical methods (LMS) to create smoothed and contemporary centiles for birth weight and length (87).

In addition, this is the first study that comprehensively evaluates neonatal head circumference in Lithuanian newborns, stratified by GA and sex, and presents the first regional, population-based references for neonatal head circumference in Lithuanian newborns.

This study represents the first effort in Lithuania to analyse growth and health trajectories in preterm-born children from infancy to adolescence, employing the most sophisticated longitudinal growth study methods (SITAR) (88). It offers a comprehensive perspective on the growth outcomes of different GA and BW groups, addressing a gap in research that is likely to focus on short-term effects.

The findings reveal novel interrelationships among birth-related factors and long-term multisystem health consequences, contributing to a deeper understanding of the cumulative burden of prematurity and informing clinical and public health practices.

1.5. Practical Value of the Study

This study provides updated, population-based neonatal reference values and curves for birth weight and length, and newly developed national references for neonatal head circumference, stratified by GA and sex, offering a more precise tool for assessing neonatal size in the Lithuanian population. These references improve the identification of growth abnormalities and enhance clinical decision-making by better reflecting local population characteristics.

By extensively analysing infancy to adolescence, this study offers valuable insights into long-term growth dynamics and multisystem health consequences in preterm-born individuals. The findings not only emphasize the importance of early identification of at-risk individuals but also highlight the role of birth-related factors in shaping growth and health outcomes. These results contribute to a more comprehensive understanding of prematurity-related challenges, reinforce the need for personalised, multidisciplinary healthcare approaches, and offer practical recommendations for managing long-term health in preterm survivors.

1.6. Defended Statements

1. Gestational age- and sex-adjusted population-based references for BW and length more accurately reflect the Lithuanian newborns' neonatal size and health status compared to global standards (**Paper I**).

2. Gestational age- and sex-adjusted population-based references for neonatal head circumference, compared to global standards, more precisely represent the specific features of the neonatal HC of the Lithuanian population (**Paper II**).
3. Birth-related variables significantly impact longitudinal growth trajectories in Lithuanian preterm infants (**Paper III**).
4. Lithuanian preterm-born individuals face complex long-term health challenges that affect different organ systems depending on birth-related factors (**Paper IV**).

2. LITERATURE REVIEW

2.1. Assessment of Neonatal Body Size: Indicators, Standards, and Challenges

The health status of a newborn is reflected in its body size at birth. An accurate assessment of birth weight (BW), length, and head circumference (HC) using appropriate standards plays a crucial role in both clinical care and in preventing adverse growth-related outcomes (89).

The classification of the neonatal body size highlights two groups of infants at a higher risk for adverse outcomes: Small for Gestational Age (SGA) and Large for Gestational Age (LGA) (90). The SGA group, defined as BW below the 10^{th} centile, comprises constitutionally small infants and those with intrauterine growth restriction (IUGR). In contrast, the LGA group, defined as BW above the 90^{th} centile, most commonly indicates excessive growth due to maternal factors (91,92).

Apart from BW and length, HC, there is a routine pediatric measurement and a proxy for brain size (93) that indirectly reflect fetal brain growth and are key health indicators , particularly in preterm infants. Greater HC at birth and faster postnatal head growth are associated with better neurocognitive outcomes, while smaller HC is linked to increased risks of intellectual, behavioural, and cardiovascular disorders (94–101).

From a clinical perspective, aiming to reduce health risks related to birth size requires preventive care, monitoring for complications, and fostering optimal neurodevelopment through appropriate early nutrition. An accurate size classification at birth remains particularly challenging for preterm infants, a highly heterogeneous group. Growth standards and reference charts are indispensable tools to be deployed in this process to support clinical assessments and informed decision-making.

However, no global consensus has been achieved on optimal growth standards for preterm infants. On the one hand, commonly used intrauterine charts (6) tend to be controversial for infants with very low birth weight (VLBW) (4,5), on the other hand, postnatal charts better reflect longitudinal growth (8) but are influenced by clinical practices (7). The debate extends to customised (11,12) vs population-based references (9), with critics questioning the utility of customisation (9,10).

Similar discussions arise regarding regional versus global growth standards (6,16–19). The World Health Organization (WHO) child growth standards introduced in 2006 have faced criticism for their applicability across diverse populations (102,103). In 2008, the International Foetal and Newborn

Growth Consortium for the 21st Century (INTERGROWTH-21st, IG-21) proposed universal standards for fetal and neonatal growth but has found limited support due to the rising evidence of physiological variations between countries and ethnic groups (13–15,17,18). These challenges highlight the need for region-specific growth references that account for the characteristics of local population.

2.2. Growth Dynamics and Long-Term Outcomes in Preterm Infants

Preterm infants, especially those born very preterm (<32 weeks) or with very low birth weight (VLBW), face heightened risks of medical and developmental challenges, including growth restriction with long-lasting effects into adulthood. Recent studies have established links between the body parameters of preterm newborns at birth, postnatal growth restriction, and subsequent growth failure, highlighting significant short- and long-term health implications (21–23).

Preterm-born individuals frequently experience early postnatal growth failure, followed by a catch-up growth within the first 2–3 years. Despite this, they typically achieve lower adult height than their term-born peers (22). A smaller birth weight (BW) extends the compensatory growth period (21) while being small for gestational age (SGA) further increases the risks of adverse perinatal outcomes (24–26). Extremely preterm survivors (<26 weeks) tend to remain shorter and lighter into adulthood, with an elevated BMI (27). Moreover, a shorter final height is associated with a decreasing GA, particularly among very preterm-born women (28). In contrast, some studies suggest that very, moderately, and late preterm-born individuals, by adulthood, may achieve adult size, pubertal timing, and peak height velocity comparable to their term-born peers (29,30).

Significant variability exists in the timing and pace of catch-up growth, pubertal milestones, and sex-related differences among preterm-born children (22,31,32). These inconsistencies, driven by classification methods (e.g., GA vs. BW), study duration, and debates over optimal growth rates (33,34), underscore the need for longitudinal research that integrates both variables. Most current studies are cross-sectional, limiting the understanding of the combined effects of GA and BW on growth and health outcomes (35).

An accurate analysis of human growth, particularly among preterm infants, requires robust longitudinal statistical methods to address its variability and complexity (104–107). Growth models are crucial not only in capturing population-wide trends but also in accounting for individual variability (88,108–110). However, traditional models most commonly

struggle with the unique growth trajectories of preterm infants. In contrast, the SITAR (SuperImposition by Translation And Rotation) model has emerged as a valuable tool to be used in studying these patterns (88). By aligning individual growth curves with a population-average curve and adjusting for differences in growth timing and intensity, SITAR provides a nuanced understanding of growth dynamics, making it particularly effective for analysing preterm infant growth trajectories.

2.3. Multisystem Health Consequences and Long-Term Morbidity in Preterm Infants

Referring to the developmental origins of the health and disease framework, emphasis is laid on adverse fetal programming that significantly impacts childhood and adulthood health with particular vulnerability observed in the brain, cardiovascular, liver, kidney, and respiratory systems (36). Exposed prematurely to environmental factors, preterm newborns, due to their immature physiology, face increased risks of cardiovascular diseases such as hypertension, ischemic heart disease (64,65), endocrine and metabolic disorders, including congenital hypothyroidism and metabolic syndrome (64,66–71), respiratory conditions such as bronchopulmonary dysplasia and asthma (52–63), as well as digestive and renal dysfunctions, including necrotising enterocolitis (59) and renal impairment (72–74). Neurodevelopmental impairments, including cerebral palsy (37–41), autism spectrum disorders, and cognitive or academic challenges (40–50) are strongly associated with prematurity the severity of which correlates to GA (51).

Despite extensive research studies of individual organ systems, the interplay between the mentioned conditions in preterm survivors remains underexplored. Multimorbidity characterised by the coexistence of multiple chronic conditions reflects shared embryological origins and highlights the cumulative health burden faced by this population (77–79). Even though current research disproportionately emphasises extremely or very low BW preterm infants (80,81), the gaps in understanding the outcomes of late preterm or suboptimal BW groups are obvious (75,76). Furthermore, longitudinal studies tend to focus on short-term outcomes (up to 5–7 years) (40,52,56,69,70) while there are only a few recent studies with a focus extending into adolescence or adulthood (48,82–86).

Even though traditional classifications such as SGA, AGA (appropriate for gestational age, BW between the 10^{th} and 90^{th} centile), and LGA combine birth weight (BW) and gestational age (GA), they may obscure

the independent effects of these variables. By examining BW and GA separately, our study disentangles their distinct impacts: BW reflects cumulative fetal energy reserve (83), while GA captures developmental timing and intrauterine exposures. This approach offers a more nuanced understanding of prematurity-related health challenges from both evolutionary (111) and developmental perspectives (112).

In summary, the review of the published literature confirms the importance of neonatal body size metrics for assessing health, particularly in preterm infants. First, substantial research has established the significance of BW, length, and HC as key indicators of neonatal growth and neurodevelopment. Second, ongoing debates persist regarding the optimal growth standards with controversies over the applicability of intrauterine versus postnatal charts, population-based versus customised references, and regional versus global standards. Many studies highlight the limitations of IG-21 and WHO standards, emphasising the need for region-specific references. Third, most longitudinal studies track health outcomes until early childhood, limiting insights into adolescent and adult health risks. Moreover, the existing research primarily focuses on single-system morbidities, leaving gaps in understanding cumulative health burdens and multimorbidity across different prematurity subcategories. Therefore, this dissertation aims to fill in these gaps by developing updated, population-specific neonatal growth references for Lithuania, conducting a comprehensive longitudinal analysis of growth patterns in preterm infants, and exploring the long-term multisystem health consequences of prematurity with a focus laid on the independent effects of BW and GA.

3. RESEARCH DESIGN AND METHODS

3.1. Ethical Approval

The Lithuanian Bioethics Committee approved the study (Permission No. 57, latest update as of 2017-02-06). It was conducted following the relevant ethical guidelines and regulations, including the principles of the Declaration of Helsinki.

3.2. Research Design Overview

This study comprises two complementary parts: (1) a cross-sectional analysis of neonatal anthropometry in the Lithuanian population and (2) a retrospective longitudinal investigation of growth and health outcomes in preterm-born individuals. The cross-sectional component analyses birth weight, length, and head circumference patterns in Lithuanian newborns by GA and sex, establishes national birth weight, length, and head circumference references based on a population-based dataset and compares them against global standards. The longitudinal study follows a cohort of preterm-born individuals from infancy through adolescence, analysing growth trajectories and multisystem health consequences.

3.3. Cross-Sectional Population-Based Study on Lithuanian Neonatal Weight, Length and HC by GA and Sex

3.3.1. Study Design and Cohort Selection

This part of the study examined anonymised data from the Lithuanian Medical Data of Births provided by the Health Information Center of the Institute of Hygiene based in Vilnius, Lithuania.

The analysis of birth weight (BW) and length was based on the data registered between 1995 and 2015. This dataset included all singleton liveborn newborns from 22 to 42 completed weeks of gestational age (GA). For neonatal HC, the data spanning from 2001 to 2015 were used, taking into consideration the fact that HC measurements were introduced in Lithuanian birth records starting only from 2001, and covering liveborn singletons from 24 to 42 completed weeks of GA. To carry out further comparative analysis, the GA ranges were selected to match those used in the IG-21 global standards

Both datasets excluded multiple births, stillbirths, newborns with undetermined sex, major congenital malformations, syndromes, or incomplete data (for sex, GA, BW, birth length, or head circumference). Additionally, other cases removed from the analysis were key anthropometric indices (weight, length or HC) falling outside ±3 standard deviations (SD) from the mean (M), based on WHO standards (113).

The final sample included 618,235 newborns to be examined for BW and length analysis and 423,999 newborns for HC analysis. The detailed sampling procedures and exclusion criteria for BW/length and HC are illustrated in flow diagrams, **Figures 1-2**, respectively.

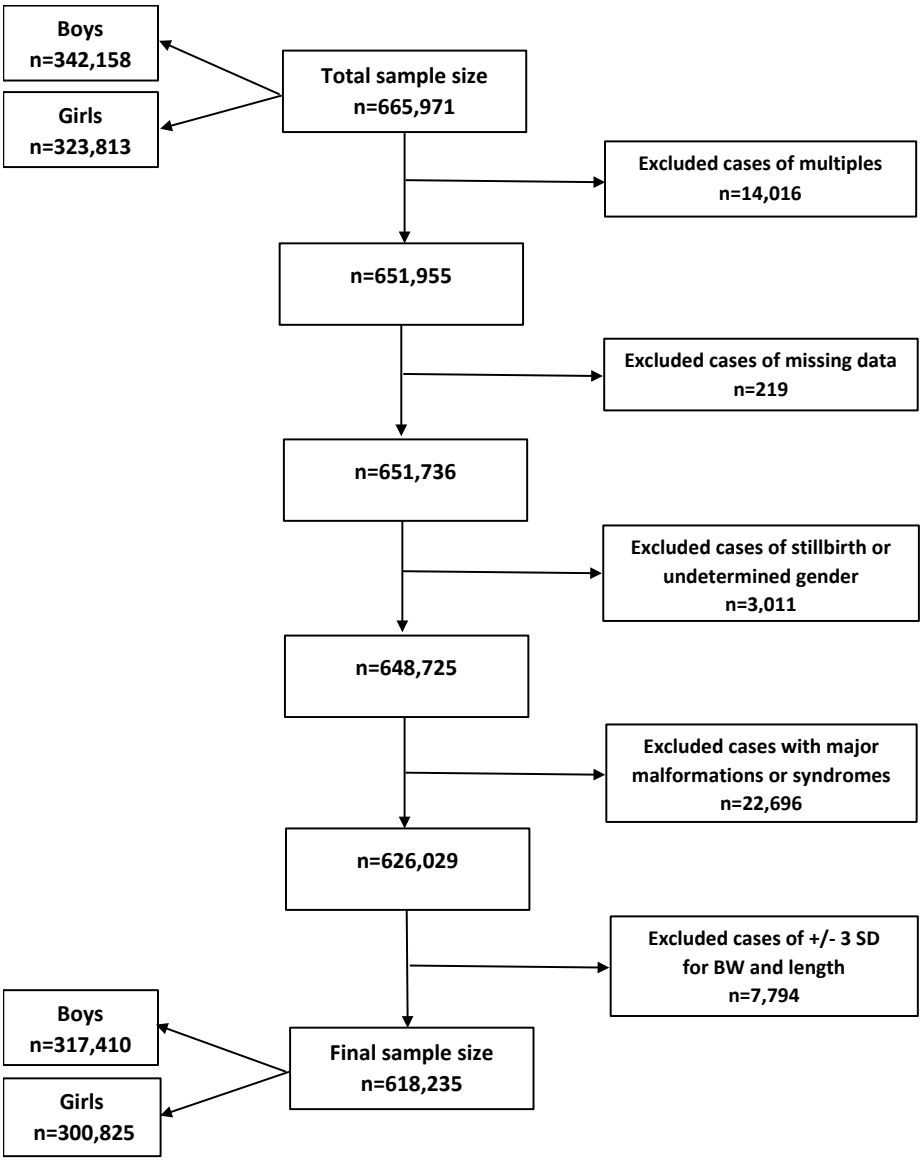

Figure 1. Flow diagram representing the sampling procedure and exclusion criteria for neonatal BW/length. BW – birth weight, n – number, SD – standard deviation.

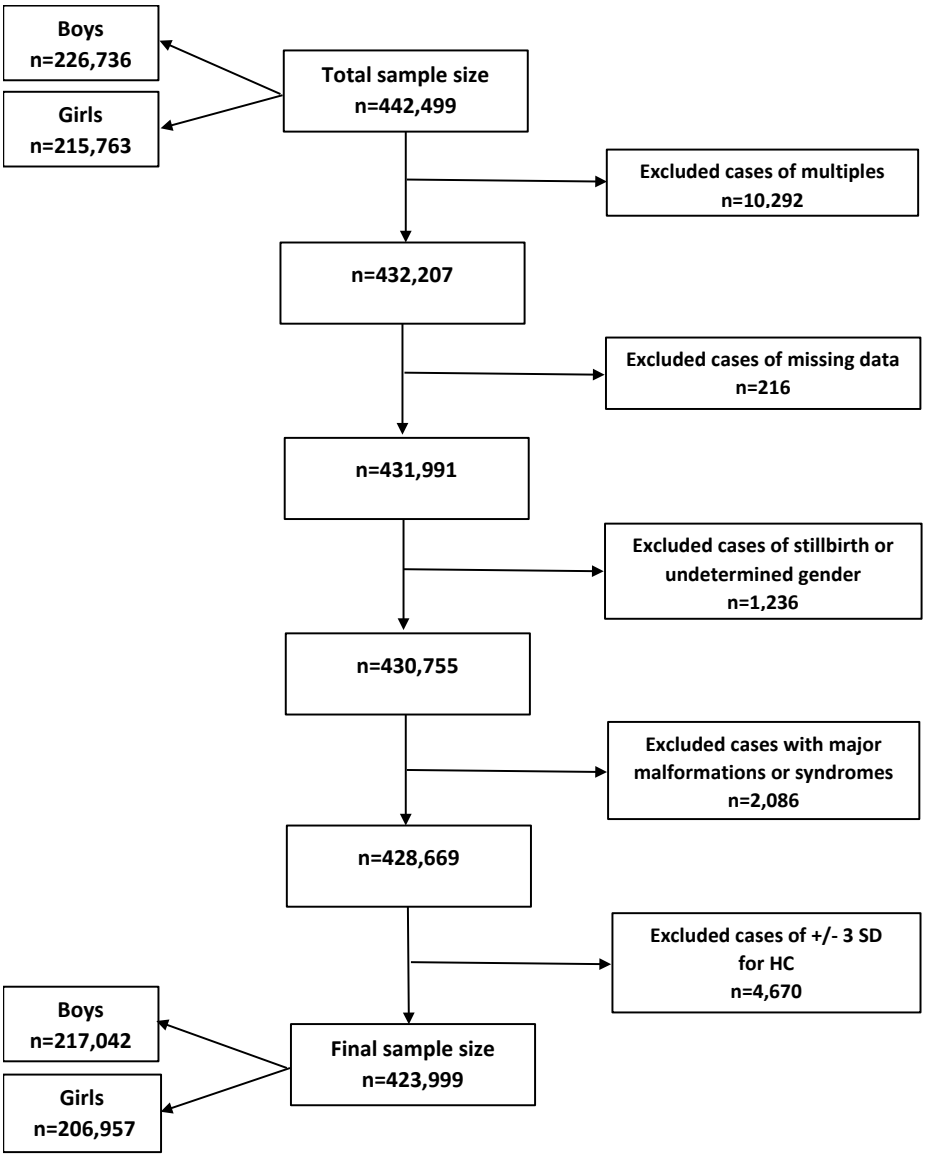

Figure 2. Flow diagram representing the sampling procedure and exclusion criteria for neonatal HC. HC - head circumference, n – number, SD – standard deviation.

3.3.2. Estimation of Growth Reference Centiles by LMST Method

The LMS (Lambda-Mu-Sigma) method estimates growth reference centiles by adjusting for skewness in the data distribution using a power transformation (87). The extended LMST (Lambda-Mu-Sigma-Tau) method

(114) incorporates both skewness and leptokurtosis, using the Box-Cox t (BCT) distribution to account for excess kurtosis that the LMS method cannot address. The BCT distribution applies a power transformation, $Y\nu$, to normalise the data, with the transformed values following a truncated t-distribution defined by degrees of freedom (τ). This distribution is characterised by four parameters—μ (median), σ (scale or variability), ν (skewness), and τ (kurtosis)—which together describe the location, spread, symmetry, and tail heaviness of the data.

The statistical analysis was conducted using SPSS 22.0, EXCEL, and R software. Generalised additive models for location, scale, and shape (GAMLSS) were employed to estimate smoothed reference centiles and curves for BW, length, and HC applying the LMST method (BCT distribution) to model skewness and kurtosis (87,114). Separate models were fitted for each sex and measurement. Descriptive statistics and centiles (3^{rd}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 97^{th}) were calculated by GA and sex. Data analysis was performed using the GAMLSS package (version 4.3-3) in R 4.0.3 (www.r-project.org) (115).

For a comparative analysis, the IG-21 standards presented centiles for both sexes by each gestational week and day (e.g., 30+0, 30+1), whereas GA was recorded in the present study as complete gestational weeks (e.g., 30, 31). To align with IG-21, the mean values for BW, length, and HC for each completed week in the present study were compared with the midpoint day (e.g., 30+3) of the corresponding week in IG-21. The validity of this alignment procedure was mathematically verified. The differences between mean values were assessed using a t-test, with the statistical significance defined as $p<0.05$.

The main centiles (3^{rd}, 10^{th}, 50^{th}, 90^{th}, and 97^{th}) for BW and length and (3^{rd}, 50^{th}, and 97^{th}) for HC were compared with corresponding values from the IG-21 standards (16,18). The coefficient of variation (CV) was computed for HC and used in conducting comparative analyses with foreign studies (116). Z-scores were also calculated for BW, length, and HC using IG-21 as a reference (16,18). For BW, the frequency and percentage of neonates classified as small for gestational age (SGA, BW $<10^{th}$ centile) and large for gestational age (LGA, BW $>90^{th}$ centile) were determined and compared using the cut-off values from both the references of this study and IG-21.

3.4. Retrospective Longitudinal Study on Lithuanian Preterm-Born Individuals

3.4.1. Study Design and Cohort Selection

The longitudinal part of the dissertation was constructed based on the data collected retrospectively from paper-based medical records accessible at two of the largest primary health care centres in Vilnius, Lithuania, and their affiliates. The study included 467 preterm-born individuals (GA 22–36 weeks; 238 girls, 229 boys; 384 singletons, 86 twins) born between 2000 and 2015. Detailed health histories were documented from birth to adolescence, including birth-related variables such as sex, BW, and GA.

The longitudinal growth patterns were compared with those of the control group of term-born individuals (GA 37–42 weeks) born in 1996, whose data was sourced from the Department of Anatomy, Histology, and Anthropology. Although the preterm (2000–2015) and term (1996) cohorts were born years apart, the representatives of both categories reached adolescence under similar environmental, socioeconomic, and nutritional conditions. Growth data were collected within the same region and healthcare system, reducing the variability from systemic factors. Anthropometric measurements of height (or length up to the age of two) and weight were collected longitudinally, allowing for the calculation of BMI. All the individuals with at least one measurement were included in the analysis.

Height (length up to two years) and weight data were collected from birth to 18 years; however, for further analysis, the interval up to 12 years was selected due to insufficient measurements in groups beyond this age to enable comparative analysis. Data were collected monthly for the first year, three times annually for the second and third years, and twice a year thereafter. In all, 16,159 measurements were recorded, with a median of 17 measurements per child; the interquartile range was (IQR) 13-21.

The growth patterns of weight, length, and BMI were analysed across three BW groups (Low, Low-normal, and Normal) and three GA groups (Early preterm, Late preterm, and Term). **Table 1** shows the distribution of individuals in these groups, stratified by sex.

Table 1. Number of children in the gestational and birth weight groups by sex.

Sex	**Birth weight** / **Gestational age**	**Low** (<2500 g)	**Low-normal** (2500 to <3000 g)	**Normal** (3000 to <4000 g)	**Total**
Boy	Early preterm (<34 weeks)	67	1	0	**68**
	Late preterm (34 to <37 weeks)	67	70	24	**161**
	Term (37 to <42 weeks)	2	12	226	**240**
	Total (boys)	**136**	**83**	**250**	**469**
Girl	Early preterm (<34 weeks)	75	3	0	**78**
	Late preterm (34 to <37 weeks)	71	68	21	**160**
	Term (37 to <42 weeks)	5	33	205	**243**
	Total (girls)	**151**	**104**	**226**	**481**
Total	Early preterm (<34 weeks)	142	4	0	**146**
	Late preterm (34 to <37 weeks)	138	138	45	**321**
	Term (37 to <42 weeks)	7	45	431	**483**
	Total	**287**	**187**	**476**	**950**

The analysis of multisystem health consequences was carried out based on 1,818 first-time diagnoses from birth until the time of the study, documented for preterm-born individuals according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (117). Recurrent or re-diagnosed conditions were excluded to emphasise the time of the disease onset within each ICD-10 disease chapter. The disease chapters included in the analysis are presented in detail in Supplementary Table 1, **Paper IV**.

To identify the distinct contributions of BW and GA on long-term health outcomes, these variables were analysed independently rather than combined into categories such as SGA/AGA/LGA. A long-term health complexity in preterm-born individuals was examined across the BW categories as follows: "Extremely and very low" (< 1000 – 1500) g, "Low" [1500 – 2500) g, "Sub-optimal" [2500 – 3000) g, "Normal" [3000 – 4000) g. GA categories were defined in weeks as “Extremely and very preterm” (22 – 32), "Moderate preterm" [32 – 34), and "Late preterm" [34 – 37).

To carry out statistical analysis, the diseases were categorised by the ICD-10 disease chapters, with the age intervals set at [0-3], (3-7], (7-12], (12-18], and [0-18] years. Round and square brackets denote an excluded or included endpoint of a time interval, respectively.

3.4.2. SITAR Model Analysis on Longitudinal Growth Patterns (Weight, Length, BMI) of Lithuanian Preterm-Born Individuals

The SITAR model (SuperImposition by Translation And Rotation) (88) was applied to obtain the mean curves for height, weight, and BMI across GA and BW groups of boys and girls from birth to 12 years. SITAR, a mixed-effects model incorporating a cubic spline mean curve, adjusts the mean curve to individual data using three subject-specific random effects (88,118,119). It is a shape-invariant model so that individuals are assumed to have the same shape of the growth curve subject to three transformations: 1) shift the curve up/down (size parameter), 2) shift it left/right (timing or tempo), 3) stretch/shrink the age scale (intensity or velocity). The effect of covariates can be included in the SITAR model as fixed effects, i.e. the model can include separate fixed effects for each SITAR parameter (119,120).

The corrected postnatal age was used in the analysis: Corrected postnatal age = chronological age (years) + (gestation weeks - 40) * 7 / 365.25. This adjustment was applied to all children, including term-born, to ensure

continuity between term and preterm growth trajectories, particularly around the ages of one and two. To avoid negative ages, nine months (i. e. 3/4 years) were added to the corrected postnatal age, resulting in a postconceptual age scale.

Outliers with standardised residuals exceeding 4 in absolute value were excluded. Degrees of freedom (d.f.) for the cubic spline, controlling smoothness were selected to minimise the Bayesian Information Criterion (BIC). A logarithmic transformation of age-improved model fit, and reduced models (omitting timing random effects) were used where convergence issues occurred.

Separate SITAR models were fitted for boys and girls due to sex differences in growth patterns, particularly around puberty. Initially, we explored the models that included both the GA and BW groups as covariates; however, we analysed these variables separately aiming to avoid collinearity and seeking to assess their etiological effects independently. Therefore, separate models for GA and BW groups were fitted by sex. Timing random effects were omitted when required for model convergence. The timing of adiposity rebound (AR) was derived as the age at the lowest BMI point on the modelled mean BMI curves.

The analysis was performed in R version 4.4.1 using the SITAR package (version 1.4.0) (121). The results were visualised with the ggplot2 package (version 3.5.1).

3.4.3. Statistical Analysis of Longitudinal Health Consequences in Lithuanian Preterm-Born Individuals

The statistical analysis aimed to examine morbidity incidence and distribution across prematurity sub-categories from birth to adolescence, evaluate the impact of birth-related factors on the mean number of diseases and the ICD-10 disease chapters per child, and explore the complexity of health conditions and their interrelationships among ICD-10 disease chapters.

To describe the distribution of children into GA and BW groups, the data was summarised by counts and percentages (Supplementary Table 2, **Paper IV**). The counts and percentages of all diseases were calculated for age intervals across GA and BW groups. Further, the diagnoses were categorised by the ICD-10 chapters to analyse the morbidity structure and distribution within sub-categories. Comparative analyses for GA and BW groups were conducted using Fisher's exact test, with morbidity rates for the general Lithuanian pediatric population calculated from official health statistics databases (122,123).

The Poisson and negative binomial regression models with logarithmic link functions (124) were applied to model the mean number of diseases and the ICD-10 disease chapters per an individual. Due to low disease counts per child in smaller age intervals, modelling was performed for the entire age range [0, 18] in years. Regression models included sex, GA, and BW groups as covariates, adjusting for confounders to identify significant predictors of morbidity. Overdispersion was observed, leading to the selection of the negative binomial regression as the final model.

The results were presented as incidence rate ratios (IRRs) derived from exponentiated regression coefficients. IRRs describe the multiplicative change in the mean disease count for a unit increase in continuous variables or relative to a reference category for categorical variables (125). For instance, an IRR for sex (reference: girls) indicates the ratio of mean diseases for boys compared to girls.

The heat maps were used to illustrate the percentages of individuals diagnosed with varying disease counts by GA and BW. A Fisher's exact test was used to compare the percentages across sub-categories, with visualisations generated using the ggplot2 package in R.

An UpSet graph was employed to analyse the intersections of the ICD-10 disease chapters, highlighting comorbidity patterns. This visualisation technique analysed the sets and their intersections (126). The R package UpSetR (127) created the visualisation, including only the intersections with frequencies greater than one for clarity.

4. RESULTS

4.1. Gestational Age- and Sex-Adjusted Population-Based References for Lithuanian Newborn BW and Length

4.1.1. BW and Length Patterns by GA and Sex

The sample size of our study increased sharply with GA, ranging from fewer than 50 neonates at 22–24 weeks to over 140,000 at term for each sex. The mean BW of boys exceeded that of girls by approximately 50–100 g at preterm gestations and by 100–180 g at term and post-term periods. Similarly, the difference in the mean birth length between sexes varied from 0.1 to 0.6 cm during the preterm period and increased to 0.6–0.8 cm at later gestations (**Table 2**).

Table 2. BW (g) and length (cm) of Lithuanian newborns by sex and GA. n – count, SD – standard deviation.

BOYS (n = 317,410)					**GA (in weeks)**	**GIRLS (n = 300,825)**				
Count (n)	**Weight (g)**		**Length (cm)**			**Count (n)**	**Weight (g)**		**Length (cm)**	
	Mean	**SD**	**Mean**	**SD**			**Mean**	**SD**	**Mean**	**SD**
1*	915.0	-	37.0	-	**22**	8	635.3	111.0	29.0	3.2
12	706.9	115.0	31.8	2.2	**23**	13	649.9	83.2	30.9	1.9
38	773.0	109.0	33.2	3.0	**24**	46	715.0	96.3	33.0	2.6
93	849.3	121.6	33.7	2.8	**25**	82	798.0	105.5	33.6	2.2
136	966.9	144.7	35.4	2.4	**26**	139	892.4	157.3	34.7	2.8
196	1106.9	181.0	37.0	2.8	**27**	174	1028.6	187.9	36.3	3.3
304	1229.3	193.9	38.1	2.9	**28**	239	1181.3	237.4	37.9	3.0
291	1375.5	235.2	39.8	2.9	**29**	255	1314.2	236.0	39.2	3.1
445	1542.7	243.4	41.4	2.8	**30**	405	1485.8	253.2	40.9	3.1
488	1756.5	263.3	42.9	2.9	**31**	431	1662.7	298.7	42.3	3.0
849	1946.9	288.2	44.3	2.6	**32**	720	1886.5	309.4	44.0	2.8
1,116	2152.2	326.1	45.6	2.6	**33**	909	2061.3	325.4	45.0	2.7
1,877	2381.1	351.6	46.8	2.5	**34**	1,609	2289.8	355.2	46.3	2.5
2,858	2585.0	354.1	47.8	2.3	**35**	2,421	2482.8	355.9	47.4	2.3
5,592	2772.3	368.8	48.9	2.3	**36**	4,967	2679.1	360.8	48.5	2.2
13,141	3124.5	404.4	50.7	2.2	**37**	11,219	3009.5	393.0	50.1	2.1
33,850	3363.7	417.5	51.7	2.1	**38**	29,873	3224.0	407.3	51.1	2.1
68,016	3540.8	413.1	52.5	2.1	**39**	63,919	3397.1	405.0	51.8	2.1
144,625	3670.0	421.4	53.0	2.1	**40**	141,902	3519.9	405.9	52.3	2.1
40,947	3773.0	425.0	53.5	2.2	**41**	39,209	3609.1	415.1	52.7	2.1
2,535	3774.2	492.0	53.4	2.4	**42**	2,285	3594.3	449.3	52.6	2.3

*An actual case that does not exceed the critical deviation from BW/length.

4.1.2. Smoothed Gestational Age- and Sex-Adjusted Centile Curves for BW and Length

Our study constructed the 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves according to GA and sex for BW and length of Lithuanian newborns (**Figures 3–6**). The variability of BW rose with GA for both sexes. In contrast, the variability of birth length fell with the increasing gestation, and negative skewness in the distribution was evident (**Figures 3–6**).

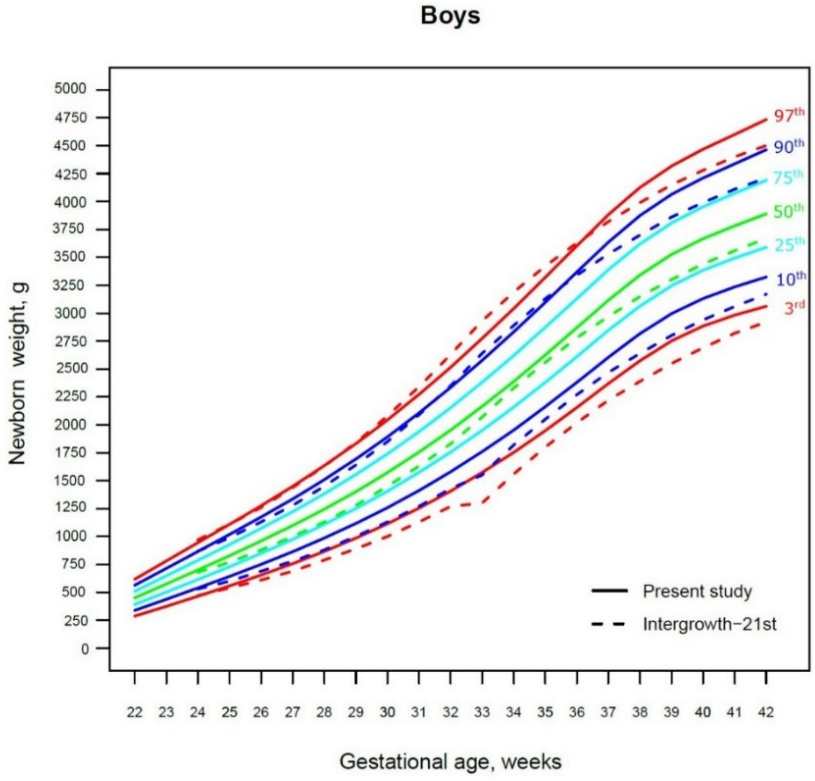

Figure 3. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for BW (g) in Lithuanian boys and the 3rd, 10th, 50th, 90th and 97th centiles for IG-21.

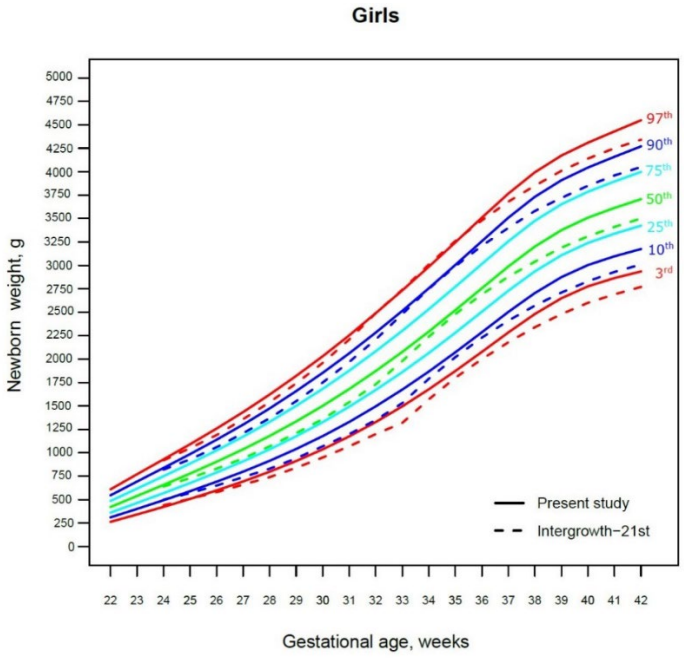

Figure 4. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for BW (g) in Lithuanian girls and the 3rd, 10th, 50th, 90th and 97th centiles for IG-21.

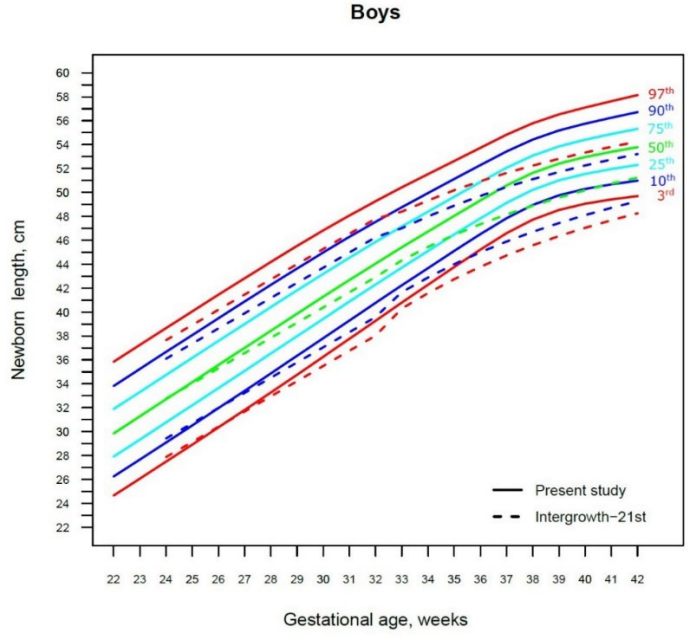

Figure 5. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for birth length (cm) in Lithuanian boys and the 3rd, 10th, 50th, 90th and 97th centiles for IG-21.

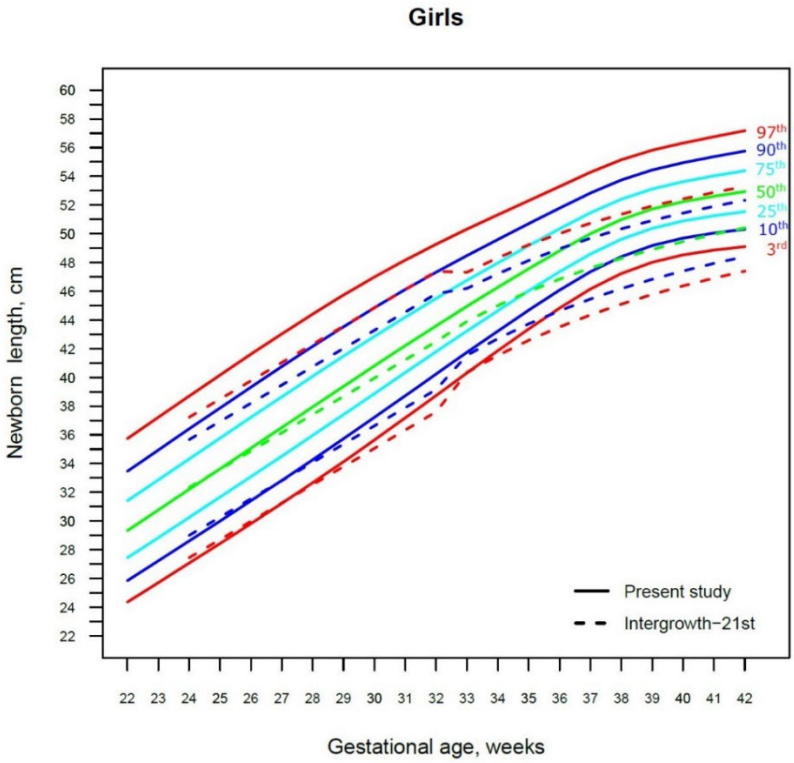

Figure 6. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for birth length (cm) in Lithuanian girls and the 3rd, 10th, 50th, 90th and 97th centiles for IG-21.

Tables 3 and 4 demonstrate the values of smoothed gestational age- and sex-adjusted centiles (3rd–97th) for BW/length of Lithuanian newborns. The LMS parameters for BW and length by GA and sex are presented in Supplementary Tables 1 and 2, **Paper I**, respectively.

Table 3. Smoothed centiles for Lithuanian BW (g) by GA and sex.

BOYS							GA (in weeks)	GIRLS						
Birth weight centiles								Birth weight centiles						
3	10	25	50	75	90	97		3	10	25	50	75	90	97
288	339	391	450	510	564	618	**22**	264	312	363	422	486	546	610
375	438	503	575	649	716	783	**23**	342	402	465	539	618	693	770
465	539	615	701	788	867	946	**24**	424	494	569	657	750	838	930
558	643	730	829	928	1019	1109	**25**	509	590	677	778	885	987	1092
655	751	850	960	1073	1174	1276	**26**	598	691	789	904	1025	1140	1259
758	865	975	1098	1223	1337	1450	**27**	694	798	909	1038	1173	1302	1435
867	986	1108	1245	1383	1509	1634	**28**	798	914	1038	1181	1331	1474	1622
985	1117	1251	1402	1555	1694	1832	**29**	912	1041	1177	1335	1501	1657	1820
1114	1258	1406	1572	1740	1892	2044	**30**	1037	1179	1328	1501	1682	1854	2031
1254	1412	1574	1756	1939	2106	2272	**31**	1176	1330	1492	1680	1877	2062	2254
1407	1579	1755	1953	2153	2335	2515	**32**	1328	1495	1670	1872	2084	2283	2489
1573	1759	1950	2165	2381	2578	2773	**33**	1496	1674	1861	2077	2303	2515	2733
1753	1954	2159	2389	2621	2832	3042	**34**	1677	1867	2066	2294	2532	2756	2986
1948	2162	2380	2625	2873	3097	3320	**35**	1872	2072	2281	2521	2771	3005	3246
2156	2381	2612	2871	3132	3369	3604	**36**	2077	2287	2505	2756	3016	3259	3509
2370	2605	2846	3116	3389	3636	3882	**37**	2285	2503	2729	2989	3257	3509	3766
2575	2817	3064	3341	3621	3874	4126	**38**	2481	2704	2936	3201	3476	3732	3994
2752	2996	3246	3526	3808	4064	4318	**39**	2649	2875	3109	3376	3652	3909	4173
2884	3132	3385	3668	3953	4211	4468	**40**	2776	3004	3240	3509	3786	4044	4309
2983	3236	3494	3783	4074	4338	4600	**41**	2865	3097	3338	3612	3896	4159	4429
3062	3323	3590	3889	4190	4463	4734	**42**	2935	3175	3423	3706	3998	4270	4548

Table 4. Smoothed centiles for Lithuanian birth length (cm) by GA and sex.

BOYS							GA (in weeks)	GIRLS						
Birth length centiles								Birth length centiles						
3	10	25	50	75	90	97		3	10	25	50	75	90	97
24.7	26.2	27.9	29.8	31.9	33.8	35.8	**22**	24.4	25.8	27.4	29.3	31.4	33.5	35.7
26.1	27.7	29.3	31.3	33.3	35.2	37.3	**23**	25.7	27.2	28.8	30.8	32.9	34.9	37.2
27.5	29.1	30.8	32.7	34.7	36.7	38.7	**24**	27.1	28.6	30.2	32.2	34.3	36.4	38.7
28.9	30.5	32.2	34.1	36.2	38.1	40.1	**25**	28.4	30.0	31.7	33.6	35.8	37.9	40.2
30.4	32.0	33.6	35.6	37.6	39.5	41.4	**26**	29.8	31.4	33.1	35.1	37.2	39.3	41.6
31.8	33.4	35.1	37.0	39.0	40.9	42.8	**27**	31.2	32.8	34.5	36.5	38.7	40.8	43.0
33.3	34.9	36.5	38.4	40.4	42.3	44.2	**28**	32.7	34.3	36.0	37.9	40.1	42.2	44.4
34.8	36.3	38.0	39.9	41.8	43.6	45.5	**29**	34.1	35.7	37.4	39.4	41.5	43.5	45.7
36.3	37.8	39.4	41.3	43.2	45.0	46.8	**30**	35.6	37.2	38.9	40.8	42.9	44.8	47.0
37.8	39.3	40.9	42.7	44.5	46.3	48.1	**31**	37.2	38.7	40.3	42.2	44.2	46.1	48.2
39.3	40.8	42.3	44.1	45.9	47.5	49.3	**32**	38.7	40.2	41.8	43.6	45.5	47.3	49.3
40.8	42.2	43.7	45.4	47.1	48.8	50.4	**33**	40.3	41.7	43.2	44.9	46.8	48.5	50.3
42.3	43.7	45.1	46.7	48.4	50.0	51.5	**34**	41.9	43.2	44.6	46.3	48.0	49.6	51.3
43.8	45.1	46.5	48.0	49.6	51.1	52.6	**35**	43.4	44.7	46.0	47.6	49.2	50.7	52.3
45.2	46.5	47.8	49.3	50.9	52.3	53.7	**36**	44.8	46.1	47.4	48.8	50.3	51.8	53.3
46.6	47.8	49.1	50.6	52.1	53.4	54.8	**37**	46.1	47.4	48.6	50.0	51.5	52.8	54.3
47.7	49.0	50.2	51.6	53.1	54.4	55.8	**38**	47.2	48.4	49.6	51.0	52.4	53.8	55.1
48.5	49.8	51.0	52.4	53.9	55.2	56.5	**39**	48.0	49.2	50.4	51.7	53.1	54.4	55.8
49.1	50.3	51.5	53.0	54.4	55.7	57.1	**40**	48.5	49.7	50.9	52.2	53.6	54.9	56.3
49.4	50.7	52.0	53.4	54.9	56.2	57.6	**41**	48.9	50.0	51.3	52.6	54.0	55.4	56.8
49.7	51.0	52.3	53.8	55.3	56.7	58.1	**42**	49.1	50.3	51.5	52.9	54.4	55.8	57.2

4.1.3. Comparison of BW and Length Centiles Between Lithuanian and IG-21 Standards Across Gestational Ages

The Lithuanian 3rd, 50th and 97th BW centiles by sex and gestation closely matched those of the IG-21 standards at extremely early gestations (24–27 weeks), particularly for boys and at the 97th centile (**Figures 3 and 4**). However, with the increasing gestation, especially after 37 weeks, the gap between Lithuanian and IG-21 centiles widened to nearly one centile channel or two-thirds of an SD (**Figures 3 and 4**). At term, the IG-21 median corresponded to the Lithuanian 25th centile (the difference of ~200 g), while the IG-21 97th centile aligned with the Lithuanian 90th (difference of ~350 g). At the 3rd centile, the differences were more pronounced among term newborns (37–40 gestational weeks) at 200 g, compared to 100 g in the post-term period (**Figures 3 and 4**).

For birth length, the IG-21 median and lower centiles were close to the Lithuanian centiles at early gestations, while the higher centiles differed by almost a full centile channel, i.e., 1.0–1.5 cm (**Figures 5 and 6**). In late preterm (34–36 weeks), the differences became more pronounced across all centiles, widening to nearly two centile channels. The IG-21 97th centile corresponded to the Lithuanian 50th, while the IG-21 median aligned with the Lithuanian 10th. At term, the differences at the 50th and 97th centiles reached 3–4 cm, while at the 3rd centile the differences were smaller by approximately 2 cm (**Figures 5 and 6**).

4.1.4. Comparison of SGA and LGA Prevalence Across Gestations Using Lithuanian and IG-21 Standards

A total of 9.7 % (30,859) boys were classified as small for gestational age (SGA) based on the Lithuanian 10th centile, compared to 4.1 % based on the IG-21 10th centile, less than half the prevalence (**Table 5**). Similarly, for girls, the prevalence of SGA was 10.1 % (30,439) using the Lithuanian centile versus 4.4 % with IG-21. Both instruments showed the highest SGA prevalence among very and late preterm and post-term gestations for both sexes. Moreover, the older the GA, the larger the discrepancy between the studies. At extremely preterm gestations (24-27 weeks), IG-21 underestimated SGA by up to 3.1% in boys and 6.9% in girls. The largest SGA discrepancies were observed at term and post-term gestations, reaching 6.9% for boys and 8.1% for girls (**Table 5**). The 10th centile curves (**Figures 3 and 4**) illustrate these discrepancies, with the IG-21 10th centile aligning closely with the

Lithuanian 3rd centile until 32 weeks and remaining slightly higher at later gestations.

In contrast, the prevalence of large for gestational age (LGA) was 10.1 % (31,972) for boys based on the Lithuanian 90th centile, compared to 20.7 % using the IG-21 90th centile, i.e. more than double (**Table 5**). For girls, LGA prevalence was 9.9 % (29,810) with the Lithuanian centile versus 19.1% with IG-21. The differences were particularly pronounced in extremely preterm (4.4–8 %) and term/post-term periods, with discrepancies of 4.8–12.4% more prominent for boys. The 90th centile curves (**Figures 3 and 4**) highlight these differences, showing the 90th centile near the Lithuanian 75th centile at extremely preterm and term gestations, with a gap of almost one centile channel post-term.

Table 5. Prevalence of Small for Gestational Age (SGA, birth weight <10th centile) and Large for Gestational Age (LGA, birth weight >90th centile) according to the present study's Lithuanian reference and INTERGROWTH-21st (IG-21) by sex and gestational age (GA).

BOYS								GA (in weeks)	GIRLS							
Present study				IG-21					Present study				IG-21			
SGA		LGA		SGA		LGA			SGA		LGA		SGA		LGA	
0	0.0%	9	23.7%	0	0.0%	9	23.7%	**24**	1	2.2%	7	15.2%	1	2.2%	7	15.2%
3	3.2%	10	10.8%	1	1.1%	10	10.8%	**25**	1	1.2%	3	3.7%	0	0.0%	7	8.5%
5	3.7%	11	8.1%	3	2.2%	17	12.5%	**26**	11	7.9%	8	5.8%	7	5.0%	15	10.8%
13	6.6%	17	8.7%	7	3.6%	32	16.3%	**27**	21	12.1%	9	5.2%	9	5.2%	23	13.2%
31	10.2%	16	5.3%	10	3.3%	33	10.9%	**28**	24	10.0%	31	13.0%	14	5.9%	44	18.4%
36	12.4%	23	7.9%	19	6.5%	36	12.4%	**29**	31	12.2%	21	8.2%	15	5.9%	39	15.3%
55	12.4%	31	7.0%	23	5.2%	37	8.3%	**30**	44	10.9%	27	6.7%	22	5.4%	56	13.8%
46	9.4%	38	7.8%	18	3.7%	47	9.6%	**31**	58	13.5%	30	7.0%	36	8.4%	51	11.8%
85	10.0%	71	8.4%	35	4.1%	62	7.3%	**32**	73	10.1%	77	10.7%	28	3.9%	102	14.2%
123	11.0%	107	9.6%	42	3.8%	71	6.4%	**33**	97	10.7%	75	8.3%	49	5.4%	89	9.8%
188	10.0%	164	8.7%	102	5.4%	129	6.9%	**34**	166	10.3%	135	8.4%	112	7.0%	135	8.4%
321	11.2%	200	7.0%	199	7.0%	164	5.7%	**35**	285	11.8%	141	5.8%	233	9.6%	161	6.7%
762	13.6%	315	5.6%	443	7.9%	349	6.2%	**36**	633	12.7%	277	5.6%	496	10.0%	338	6.8%
1,293	9.8%	1,366	10.4%	653	5.0%	2,001	15.2%	**37**	1,094	9.8%	1,090	9.7%	647	5.8%	1,630	14.5%
3,195	9.4%	3,761	11.1%	1,370	4.0%	6,719	19.8%	**38**	2,946	9.9%	3,164	10.6%	1,472	4.9%	5,562	18.6%
5,928	8.7%	7,130	10.5%	2,248	3.3%	14,617	21.5%	**39**	5,976	9.3%	6,622	10.4%	2,619	4.1%	12,983	20.3%
14,231	9.8%	14,527	10.0%	5,482	3.8%	32,460	22.4%	**40**	14,561	10.3%	14,179	10.0%	5,594	3.9%	28,251	19.9%
4,085	10.0%	3,964	9.7%	1,811	4.4%	8,561	20.9%	**41**	4,026	10.3%	3,734	9.5%	1,798	4.6%	7,582	19.3%
459	18.1%	207	8.2%	283	11.2%	461	18.2%	**42**	391	17.1%	170	7.4%	207	9.1%	352	15.4%
30,859	9.7%	31,967	10.1%	12,749	4.1%	65,815	20.7%	**Total**	30,439	10.1%	29,800	9.9%	13,359	4.4%	57,427	19.1%

4.2. Gestational Age- and Sex-Adjusted Population-Based References for Lithuanian Neonatal HC

4.2.1. HC Patterns by GA and Sex

The study sample size increased significantly with GA, from fewer than 50 neonates at 24 weeks to nearly 100,000 at term for each sex (**Table 6**). The mean HC of boys exceeded that of girls by 0.5–0.8 cm across all gestational weeks. Conversely, the SD and CV for HC decreased markedly with the increasing GA (**Table 6**).

Table 6. Comparison of head circumference (HC) of Lithuanian newborns by sex and gestational age (GA) and the IG-21 reference (16,18). n – count, M – mean, SD – standard deviation, CV - coefficient of variation, defined as standard deviation / mean.

GA (in weeks)	PRESENT STUDY				INTERGROWTH – 21st				Mean difference LT – IG-21
	n	M	SD	CV	n	M	SD	CV	
BOYS									
24	28	23.0	1.0	0.043	3	22.7	1.6	0.070	0.3
25	71	23.6	1.4	0.059	10	23.6	1.6	0.068	0.0
26	89	24.5	1.4	0.057	13	24.5	1.6	0.065	0.0
27	124	25.5	1.5	0.059	12	25.4	1.6	0.063	0.1
28	211	26.6	1.7	0.064	19	26.3	1.6	0.061	0.3
29	190	27.5	1.7	0.062	19	27.2	1.6	0.059	0.3
30	303	28.5	1.7	0.060	25	28.1	1.6	0.057	0.4
31	306	29.7	1.7	0.057	37	28.9	1.6	0.055	0.8
32	533	30.6	1.6	0.052	52	29.8	1.6	0.054	0.8
33	744	31.5	1.6	0.051	33	31.1	1.3	0.042	0.4
34	1,305	32.3	1.5	0.046	48	31.7	1.3	0.041	0.6
35	1,977	33.0	1.5	0.045	127	32.2	1.3	0.040	0.8
36	3,682	33.5	1.5	0.045	322	32.7	1.2	0.037	0.8
37	9,651	34.3	1.5	0.044	848	33.2	1.2	0.036	1.1
38	24,745	34.9	1.4	0.040	2,032	33.7	1.2	0.036	1.2
39	51,027	35.3	1.4	0.040	2,985	34.1	1.1	0.032	1.2
40	93,843	35.5	1.4	0.039	2,532	34.5	1.1	0.032	1.0
41	27,226	35.8	1.4	0.039	1,147	34.9	1.1	0.032	0.9
42	987	35.8	1.5	0.042	204	35.2	1.1	0.031	0.6

GA (in weeks)	PRESENT STUDY				INTERGROWTH – 21st				Mean difference LT – IG-21
	n	M	SD	CV	n	M	SD	CV	
GIRLS									
24	40	22.2	1.3	0.059	3	22.5	1.6	0.071	-0.3
25	65	23.1	1.3	0.056	7	23.4	1.6	0.068	-0.3
26	98	23.7	1.6	0.068	7	24.3	1.6	0.066	-0.6
27	122	25.0	1.7	0.068	11	25.1	1.6	0.064	-0.1
28	153	26.2	1.9	0.073	16	26.0	1.6	0.062	0.2
29	168	27.0	1.7	0.063	22	26.9	1.6	0.059	0.1
30	248	28.2	1.8	0.064	24	27.8	1.6	0.058	0.4
31	274	29.0	1.7	0.059	33	28.7	1.6	0.056	0.3
32	454	30.4	1.7	0.056	43	29.6	1.6	0.054	0.8
33	610	31.1	1.6	0.051	17	30.7	1.3	0.042	0.4
34	1,066	31.9	1.5	0.047	65	31.3	1.2	0.038	0.6
35	1,635	32.5	1.5	0.046	111	31.9	1.2	0.038	0.6
36	3,183	33.1	1.5	0.045	293	32.3	1.2	0.037	0.8
37	8,078	33.8	1.4	0.041	798	32.8	1.1	0.034	1.0
38	21,708	34.3	1.4	0.041	1,783	33.2	1.1	0.033	1.1
39	48,487	34.8	1.4	0.040	2,849	33.6	1.1	0.033	1.2
40	93,307	35.0	1.3	0.037	2,486	33.9	1.1	0.032	1.1
41	26,354	35.2	1.3	0.037	1,180	34.2	1.0	0.029	1.0
42	907	35.3	1.4	0.040	218	34.5	1.0	0.029	0.8

4.2.2. Smoothed Gestational Age- and Sex-Adjusted Centile Curves for HC of Lithuanian Newborns

The smoothed 3rd, 10th, 25th, 50th, 75th, 90th and 97th gestational age- and sex-adjusted centile curves for HC of Lithuanian newborns are presented in **Figures 7 and 8**. The variability of HC decreases with the increasing GA while the negative skewness in the distribution is evident from wider gaps observed between the lower centiles compared to the upper centiles.

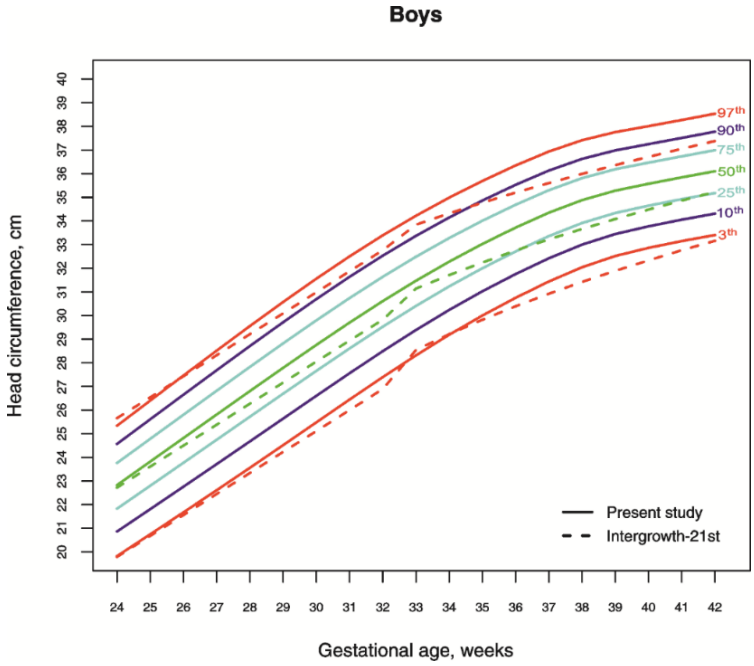

Figure 7. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for HC (cm) in Lithuanian neonate boys and the 3rd, 50th and 97th centiles for IG-21 (16,18).

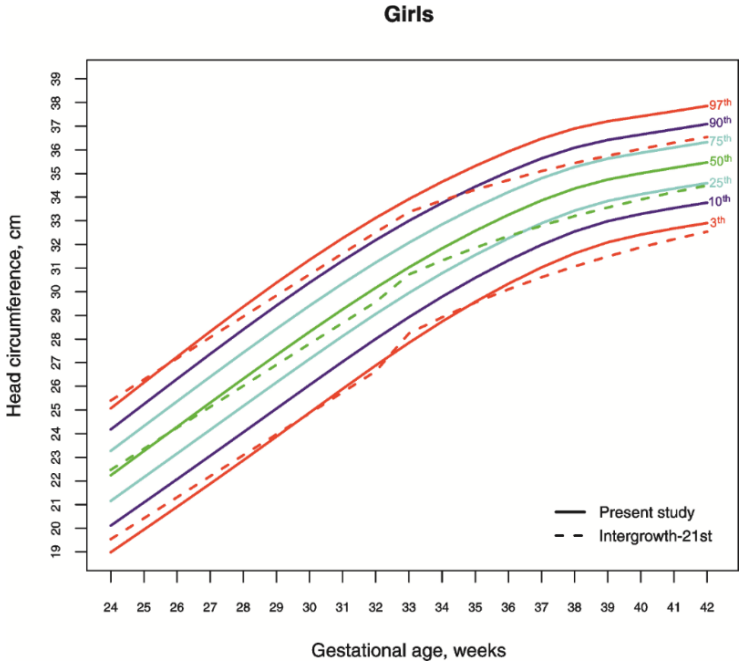

Figure 8. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for HC (cm) in Lithuanian neonate girls and the 3rd, 50th and 97th centiles for IG-21 (16,18).

4.2.3. Comparison of Lithuanian and IG-21 HC Centiles Across Gestational Ages

The mean HC of Lithuanian preterm and term newborns was consistently greater than the corresponding values outlined in the IG-21 standards (16,18), starting from 31 weeks for boys and 32 weeks for girls, with the disparity increasing with GA (**Table 6**). This pattern was further reflected in gestational age- and sex-adjusted Z-scores for HC based on IG-21 standards, which showed a similar trend (Supplementary Figure 2, **Paper II**).

The comparison of the 3rd, 50th and 97th Lithuanian HC centiles by GA and sex to those of the IG-21 standards confirmed the pattern observed in **Table 6**. There was a close agreement at earlier gestations, however the gap widened with the increasing gestation, primarily in the higher centiles (**Figures 7 and 8**). At the 3rd percentile, differences in term newborns (37-40 weeks) ranged from 0.5 to 0.75 cm, decreasing to less than 0.5 cm in the post-term period. The differences in the 50th and 97th centiles varied between 1 and 1.5 cm (**Figures 7 and 8**).

4.3. Longitudinal Growth Outcomes in Lithuanian Preterm-Born Children by GA and BW from Infancy to Adolescence

4.3.1. Growth Trajectories in Preterm-Born Children (SITAR Model Performance)

To explore the growth trajectories in preterm-born children, SITAR models were fitted to height, weight, and BMI from birth to 12 years (Table 2, **Paper III**), each adjusted separately for GA group and tBW group in boys and girls. The models incorporating log-transformed age provided better fits, with degrees of freedom ranging from 6 to 8. The SITAR models demonstrated a good fit, explaining 72% to 92% of the variance in growth patterns, with the highest accuracy observed for weight (92% for girls, 90% for boys).

4.3.2. Height Growth Patterns by GA and BW

Significant differences in the SITAR mean height models from birth to 12 years were observed among GA and BW groups, stratified by sex (**Table 7**). On average, early preterm boys and girls were 0.9 cm shorter than their term counterparts. Furthermore, low BW girls and boys were significantly shorter by 1.4 cm than their normal BW peers.

Despite these differences, the mean height curves across the groups (**Figure 9**) remained closely aligned throughout childhood. The differences became more pronounced between the ages between 9 and 12, where group offsets persisted but growth trajectories remained parallel without evidence of divergence

Table 7. Significant mean differences between GA and BW groups in the SITAR height model for the period from birth to 12 years. CI – confidence interval.

Covariate	Sex	Effect	SITAR parameter	Coefficient (95% CI) (cm)	Standard Error (cm)	p-value
GA group	Girls	Early preterm	a (size)	-0.92 (-1.49; -0.34)	0.29	0.002
		Late preterm		0.08 (-0.37; 0.53)	0.23	0.7
	Boys	Early preterm	a (size)	-0.89 (-1.48; -0.29)	0.30	0.003
		Late preterm		0.09 (-0.34; 0.53)	0.22	0.7
BW group	Girls	Low	a (size)	-1.45 (-1.90; -0.99)	0.23	<0.001
		Low-normal		-0.35 (-0.86; 0.15)	0.26	0.2
	Boys	Low	a (size)	-1.43 (-1.88; -0.99)	0.23	<0.001
		Low-normal		-0.18 (-0.71; 0.34)	0.27	0.5

References: Term GA group; Normal BW group.

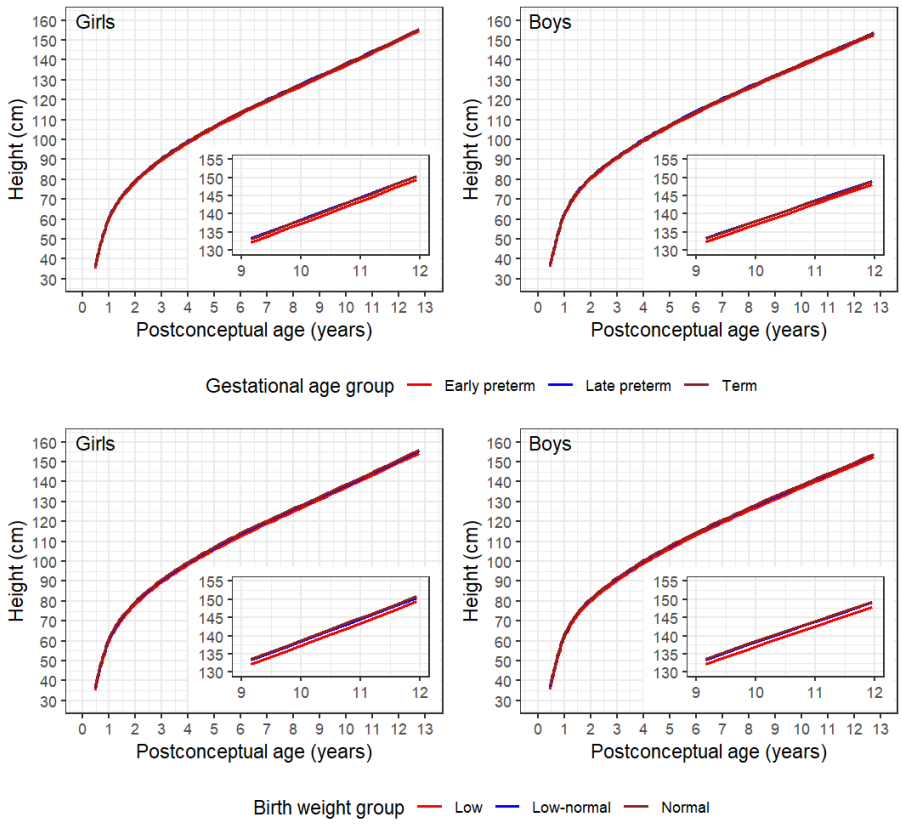

Figure 9. Mean SITAR height curves for the GA and BW groups.

4.3.3. Weight Growth Patterns by GA and BW

Across the entire study period (0–12 years), significant effects of GA and BW on weight size and intensity were observed with less pronounced differences in girls compared to boys (**Table 8**). On average, boys in the early preterm group were 0.8 kg lighter than their term peers (95% CI: -1.19 to -0.48), compared to 0.3 kg for girls (95% CI: -0.50 to -0.07). Similarly, in the low BW group, boys were 1.0 kg lighter than their normal BW counterparts (95% CI: -1.26 to -0.73), compared to 0.5 kg for girls (95% CI: -0.62 to -0.29), showing a significant sex difference. Also, GA and BW significantly impacted growth intensity in boys, with the early preterm group showing 4% and the low BW group showing 3.7% less intense growth spurts compared to their term and normal BW counterparts.

The mean weight curves for girls and boys illustrate more pronounced differences between the GA and BW groups (**Figure 10**) than those observed

for height (**Figure 9**). The curves for girls were closely aligned across groups throughout childhood, indicating a smaller effect of GA and BW on weight development in girls. In contrast, for boys, the curves diverged more noticeably across groups, particularly after age 9, with preterm and lower BW boys growing more slowly than their term and normal BW peers. The insets highlight these patterns, showing much larger differences for boys than girls, particularly for early preterm and low BW compared to other groups.

Table 8. Significant GA and BW group mean differences in the SITAR weight model from birth to 12 years. CI – confidence interval.

Covariate	Sex	Effect	SITAR parameter	Coefficient (95% CI)	Standard Error	p-value
GA group	Girls	Early preterm	a (size)	-0.29 (-0.50; -0.07)	0.11	0.009
		Late preterm		-0.07 (-0.24; 0.09)	0.09	0.4
	Boys	Early preterm	a (size)	-0.83 (-1.19; -0.48)	0.18	<0.001
		Late preterm		-0.26 (-0.53; -0.01)	0.13	0.05
		Early preterm	c (intensity)	-0.040 (-0.068; -0.012)	0.01	0.005
		Late preterm		-0.005 (-0.025; 0.015)	0.01	0.6
BW group	Girls	Low	a (size)	-0.46 (-0.62; -0.29)	0.09	<0.001
		Low-normal		-0.15 (-0.34; 0.04)	0.10	0.1
	Boys	Low	a (size)	-1.00 (-1.26; -0.73)	0.14	<0.001
		Low-normal		-0.30 (-0.61; 0.02)	0.160	0.07
		Low	c (intensity)	-0.037 (-0.058; -0.016)	0.011	0.001
		Low-normal		-0.006 (-0.030; -0.019)	0.013	0.7

References: Term GA; Normal BW. Coefficients: size – kg, intensity – fractional.

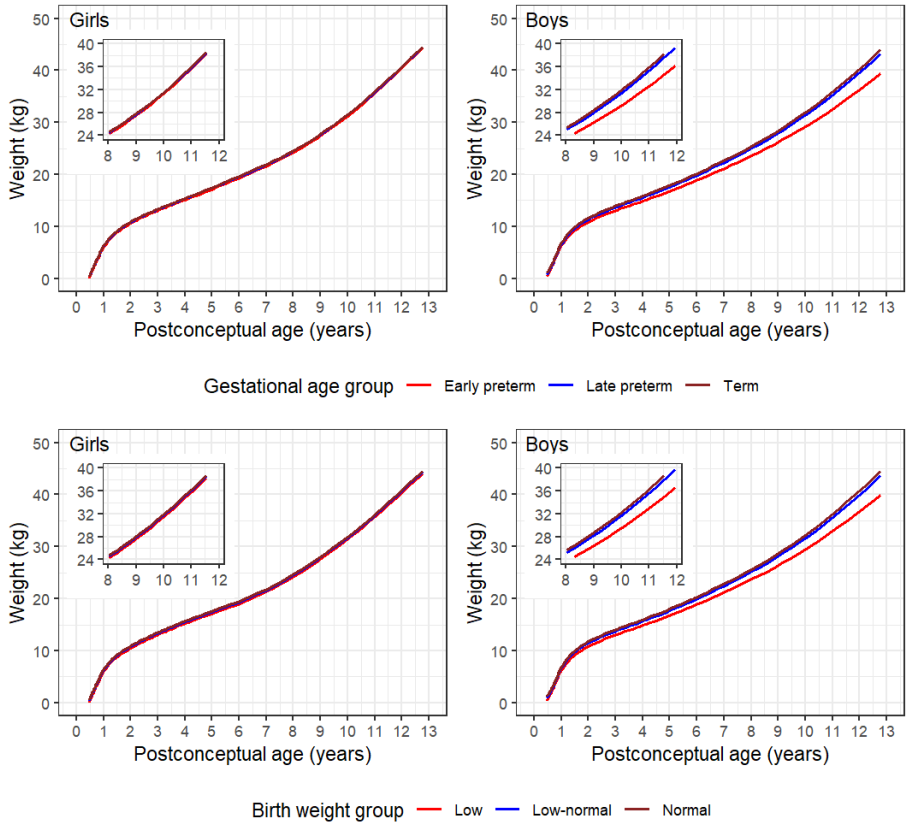

Figure 10. Mean SITAR weight curves for the GA and BW groups.

4.3.4. BMI Growth Patterns by GA and BW

Over the entire 12-year study period, significant effects of GA and BW on the BMI size and the timing were observed with mean BMI being smaller for the early/late preterm GA and low/low-normal BW groups, by 0.8/0.3 kg/m2 in girls and 0.9/0.6 kg/m2 in boys (**Table 9**). Similarly, the timing was earlier in two preterm groups, by 0.11/0.08 units in both sexes, and to a lesser extent in the BW groups, by 0.08/0.05 units. A negative timing coefficient indicates an earlier growth spurt where the fractional coefficient can be multiplied by 100 and viewed as a percentage difference. The larger effect for GA than BW is because the timing effect is a shift on the age scale and hence corresponds directly to GA.

The mean BMI curves for the GA and BW groups in girls and boys highlight distinct trends in the BMI development across the groups (**Figure 11**). The early preterm children are initially lower than the late

preterm and term children, with an earlier adiposity peak and earlier adiposity rebound (AR). AR occurred earlier in the early/late preterm GA groups compared to term, by 10.2/5.3 months in boys and 7.8/7.8 months in girls (Supplementary Table 1, **Paper III**). However, after the age of 9 or 10 the GA curves cross and the early preterm becomes relatively higher, which is what the earlier AR predicts. Similarly, the AR timing was earlier in the low/low-normal BW groups compared to normal BW, by 7.6/5.2 months in boys and 5.2/0.0 months in girls (Supplementary Table 1, **Paper III**). As for the BW curves, the low BW group is consistently lower than the other two groups until the curves merge at around age 12.

Table 9. Significant GA and BW group mean differences in the SITAR BMI model from birth to 12 years. CI – confidence interval.

Covariate	Sex	Effect	SITAR parameter	Coefficient (95% CI)	Standard Error	p-value
GA group	Girls	Early preterm	a (size)	-0.77 (-1.05; -0.48)	0.14	<0.001
		Late preterm		-0.46 (-0.68; -0.24)	0.11	<0.001
		Early preterm	b (timing)	-0.110 (-0.123; -0.089)	0.007	<0.001
		Late preterm		-0.080 (-0.095; -0.070)	0.009	<0.001
	Boys	Early preterm	a (size)	-0.81 (-1.13; -0.49)	0.16	<0.001
		Late preterm		-0.60 (-0.83; -0.36)	0.11	<0.001
		Early preterm	b (timing)	-0.120 (-0.136; -0.098)	0.010	<0.001
		Late preterm		-0.078 (-0.091; -0.065)	0.007	<0.001
BW group	Girls	Low	a (size)	-0.81 (-1.03; -0.58)	0.11	<0.001
		Low-normal		-0.22(-0.47; 0.03)	0.13	0.09
		Low	b (timing)	-0.069 (-0.085; -0.054)	0.009	<0.001
		Low-normal		-0.028 (-0.046; -0.011)	0.008	0.001
	Boys	Low	a (size)	-0.92 (-1.17; -0.68)	0.13	<0.001
		Low-normal		-0.48 (-0.77; -0.19)	0.15	0.001
		Low	b (timing)	-0.078 (-0.094; -0.062)	0.008	<0.001
		Low-normal		-0.054 (-0.073; -0.036)	0.010	<0.001

References: Term GA group; Normal BW group. Coefficients: size – kg, intensity, timing – fractional.

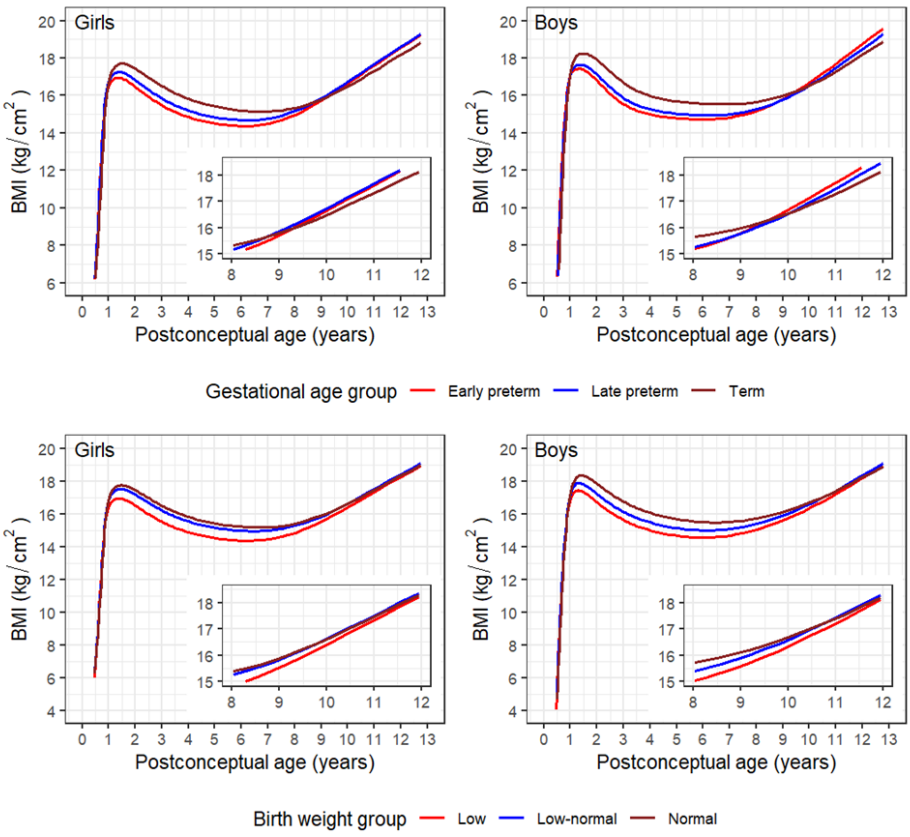

Figure 11. Mean SITAR BMI curves for the GA and BW groups.

4.4. Multisystem Health Consequences in Lithuanian Preterm-Born Individuals from Infancy to Adolescence

4.4.1. Incidence and Distribution of Morbidity Across Prematurity Sub-Categories from Birth to Adolescence

The mean number of diseases acquired from birth to age 18, categorized by BW and GA, revealed a distinct trend: a lower BW was consistently associated with a higher disease burden. The "Extremely and very low" and "Low" BW categories had the highest mean disease counts (4.6), with standard deviations of 2.6 and 3.2, respectively. "Sub-optimal" BW individuals showed slightly lower values (4.24 ± 2.8) while the "Normal" BW group exhibited the lowest mean disease count (3.2 ± 2.2).

In the GA groups, "Moderate preterm" children demonstrated the highest mean number of diseases (4.55 ± 2.82), followed by "Late preterm" (4.33 ± 3.08) and "Extremely and very preterm" (4.28 ± 2.73). While lower BW demonstrated a more pronounced association with higher disease counts, the relationship within the GA groups was less distinct, suggesting BW as a stronger determinant of overall morbidity compared to GA.

The distribution of diseases across age intervals by the BW and GA categories is summarised in **Tables 10 and 11**. Most diagnoses occurred within the first three years (47.5%) and preschool years (32.7%), with 80.2% of all 1818 diagnoses arising by age 7.

A lower BW correlated with a higher disease incidence (**Table 10**), with the "Low" BW group accounting for 51.8% of diagnoses, while the "Sub-optimal" and "Normal" BW groups contributed 29.2% and 6.8%, respectively. The "Extremely and very low" BW group had the highest proportion of diagnoses but was limited by a small sample size.

In the GA groups, "Late preterm" individuals had the most diagnoses overall. However, the "Extremely and very preterm" and the "Moderate preterm" groups bore a greater proportional burden in early life, underscoring their heightened morbidity risk (**Table 11**).

Table 10. The distribution of diseases diagnosed at different age intervals from birth to adolescence across various BW categories. The first row shows the frequency in numbers while the second presents the row percentages.

Birth weight category	**Number of ICD-10 diseases diagnosed**				
	[0-3]	**(3-7]**	**(7-12]**	**(12-18]**	**Total**
Extremely and very low	126 56.8	73 32.9	21 9.5	2 0.9	**222**
Low	451 47.9	298 31.6	149 15.8	44 4.7	**942**
Sub-optimal	223 42.1	183 34.5	84 15.8	40 7.5	**530**
Normal	63 50.8	40 32.3	14 11.3	7 5.6	**124**
Total	**863** **47.5**	**594** **32.7**	**268** **14.7**	**93** **5.1**	**1,818** **100**

Round and square brackets denote an excluded or included endpoint of a time interval, respectively.

Table 11. Distribution of diseases diagnosed at different age intervals from birth to adolescence across various GA categories. The first row shows the frequency in numbers while the second presents the row percentages.

Gestational age category	Number of ICD-10 diseases diagnosed				
	[0-3]	(3-7]	(7-12]	(12-18]	Total
Extremely and very preterm	153 55.8	80 29.2	33 12.0	8 2.9	**274**
Moderate preterm	173 53.6	99 30.7	41 12.7	10 3.1	**323**
Late preterm	537 44.0	415 34.0	194 15.9	75 6.1	**1,221**
Total	**863** **47.5**	**594** **32.7**	**268** **14.7**	**93** **5.1**	**1,818** **100**

Round and square brackets denote an excluded or included endpoint of a time interval, respectively.

The structure of diagnoses (N=1818) among the ICD-10 disease chapters from birth to adolescence revealed that the most prevalent category was eye and adnexa conditions (almost 17%) (Tables 3-4, **Paper IV**). Following this, congenital malformations and certain infectious diseases were the following most frequent categories (around 10-11%). A third group, comprising respiratory, endocrine, nutritional, metabolic, mental, behavioural, and neurodevelopmental disorders (8-9 %), accounted for similar proportions in the overall structure of diagnoses. However, this high prevalence in some cases is somewhat misleading as these diseases are also prevalent in the general pediatric population (refer to **Table 12** and further discussion below).

The timing of different condition categories was analysed across four age periods (Tables 3-4, **Paper IV**), focusing on the most frequent ICD-10 chapters. The blood and immune system disorders were almost exclusively diagnosed in the 0–3 age period (up to 90%). A similar pattern was observed for congenital malformations (ranging from 55% in higher BW and GA groups to 80% in lower BW and GA groups) and digestive system diseases, with over half of the cases manifesting during this period (equally to all the GA and BW groups). Eye and adnexa diseases were common throughout childhood, with similar prevalence in the 0–3 and 3–7 age groups. Respiratory diseases and certain infections peaked in the 3–7 age group, with a significant portion of cases occurring during this interval (from 45% to 80%).

Some conditions showed later peaks (Tables 3-4, **Paper IV**). Endocrine and metabolic disorders were primarily diagnosed in the 0–3 age group but exhibited a second notable increase during school-age years (7–12).

Similarly, mental and behavioural disorders were most commonly diagnosed in the 3–7 age group, but higher BW and GA groups saw a secondary peak during school years (7–12). Adolescence (12–18 years) contributed relatively fewer diagnoses but included some late-onset cases within the categories of nervous system diseases, skin conditions, and the musculoskeletal system.

This disease chapter-based perspective highlights the variability in the timing across conditions, with most diagnoses concentrated in early childhood. A detailed distribution of newly diagnosed cases across the ICD-10 disease chapters by GA categories in subsequent age intervals is presented in Table 3, **Paper IV**, and by BW categories in Table 4, **Paper IV**.

Further, the differences in morbidity prevalence from 0 to 18 years across the ICD-10 disease chapters among prematurity sub-categories were identified (**Table 12**), and the incidence of the most common specific diseases or health conditions within these chapters was calculated (**Table 13**). The following sections highlight the most common conditions in the study population, focusing on those that mostly exceed 30% prevalence. Importantly, some of these conditions such as refractive errors and some other diseases are also prevalent in the general population, as discussed further below.

Table 12. Morbidity across different ICD-10 disease chapters distributed according to GA and BW categories of our study (the first row shows the number of children while the second row shows the percentage in the GA and BW category), and morbidity of the Lithuanian pediatric population (included for comparison, compiled according to (122,123)) from 0 to 18 years.

Disease Chapter	Gestational age categories			Birth weight categories				Total (for the chapter) in our study (n=417)	Total (for the chapter) in the Lithuanian pediatric population (n=556 620)
	Extremely and very preterm (n=64)	Moderate preterm (n=71)	Late preterm (n=282)	Extremely and very low (n=48)	Low (n=205)	Sub-optimal (n=125)	Normal (n=39)		
A00-B99 - Certain infectious and parasitic diseases	21 32.8	23 32.4	119 42.2	20 41.7	74 36.1	57 45.6	12 30.8	**163** **39.1*** **	**81,107** **14.6**
C00-D49 - Neoplasms	5 7.8	8 11.3	19 6.7	6 12.5	18 8.8	7 5.6	1 2.6	**32** **7.7*** **	**10,015** **1.8**
D50-D89 - Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (° BW)	13 20.3	20 28.2	68 24.1	12 25.0	55 26.8	31 24.8	3 7.7	**101** **24.2*** **	**12,555** **2.3**
E00-E89 - Endocrine, nutritional and metabolic diseases	16 25.0	25 35.2	82 29.1	14 29.2	64 31.2	35 28.0	10 25.6	**123** **29.5*** **	**62,505** **11.2**
F01-F99 - Mental, Behavioral and Neurodevelopmental disorders	16 25.0	25 35.2	80 28.4	13 27.1	63 30.7	34 27.2	11 28.2	**121** **29.1*** **	**43,720** **7.8**
G00-G99 - Diseases of the nervous system	9 14.1	6 8.5	33 11.7	7 14.6	22 10.7	16 12.8	3 7.7	**48** **11.5*** **	**15,881** **2.8**
H00-H59 - Diseases of the eye and adnexa	36 56.3	41 57.4	142 50.4	29 60.4	110 53.7	64 51.2	16 41.0	**219** **52.5*** **	**171,310** **30.8**
H60-H95 - Diseases of the ear and mastoid process	4 6.3	3 4.2	4 1.4	3 6.3	4 2.0	4 3.2	0 0.0	**11** **2.6*** **	**46,349** **8.3**

Disease Chapter	Gestational age categories			Birth weight categories				Total (for the chapter) in our study (n=417)	Total (for the chapter) in the Lithuanian pediatric population (n=556 620)
	Extremely and very preterm (n=64)	Moderate preterm (n=71)	Late preterm (n=282)	Extremely and very low (n=48)	Low (n=205)	Sub-optimal (n=125)	Normal (n=39)		
I00-I99 - Diseases of the circulatory system	0 0.0	1 1.4	10 3.5	0 0.0	5 2.5	5 4.0	1 2.6	**11** **2.6**	**18,801** **3.4**
J00-J99 - Diseases of the respiratory system	23 35.9	23 32.4	80 28.4	20 41.7	61 29.8	38 30.4	7 17.9	**126** **30.2*****	**322,052** **57.9**
K00-K95 - Diseases of the digestive system	21 32.8	17 23.9	76 27.0	17 35.4	51 24.9	35 28.0	11 28.2	**114** **27.3***	**183,997** **33.1**
L00-L99 - Diseases of the skin and subcutaneous tissue	9 14.1	14 19.7	51 18.1	5 10.4	39 19.0	25 20.0	5 12.8	**74** **17.7***	**74,953** **13.5**
M00-M99 - Diseases of the musculoskeletal system and connective tissue (° BW, GA)	9 14.1	12 16.9	71 25.2	8 16.7	48 23.4	27 21.6	9 23.1	**92** **22.1*****	**60,376** **10.8**
N00-N99 - Diseases of the genitourinary system	9 14.1	13 18.3	43 15.2	6 12.5	35 17.1	19 15.2	5 12.8	**65** **15.6*****	**25,428** **4.6**
P00-P96 - Certain conditions originating in the perinatal period	5 7.8	5 7.0	18 6.4	4 8.3	15 7.3	7 5.6	2 5.1	**28** **6.7*****	**10,693** **1.9**
Q00-Q99 - Congenital malformations, deformations and chromosomal abnormalities (* BW)	29 45.3	27 38.0	92 32.6	22 45.8	82 40.0	37 29.6	7 17.9	**148** **35.5*****	**55,649** **10**
Total (the number of cases in all disease chapters)	225	263	988	186	746	441	103	**1,476**	-

p-value ° <0.1, * <0.05, ** <0.01, *** <0.00; BW and GA in the brackets shows which comparisons were significant. The asterisks in the "Total (for the chapter) in our study" column indicate statistically significant differences in morbidity prevalence between our study cohort and the general pediatric population in Lithuania.

Table 13. Most common morbidities and health conditions of the study population from birth to 18 years, classified under ICD-10.

No.	Diagnosis	ICD-10 code	Number of children	Percentage, %	Disease Chapter
1.	**Hypermetropia**	H52.0	158	**37.9**	H00-H59 - Diseases of the eye and adnexa
2.	**Varicella (chickenpox)**	B01	137	**32.9**	A00-B99 - Certain infectious and parasitic diseases
3.	**Specific developmental disorders of speech and language**	F80	112	**26.9**	F01-F99 - Mental, Behavioral and Neurodevelopmental disorders
4.	**Rickets, active**	E55.0	90	**21.6**	E00-E89 - Endocrine, nutritional and metabolic diseases
5.	**Anemia, unspecified**	D64.9	82	**19.7**	D50-D89 - Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
6.	**Umbilical hernia**	K42	74	**17.7**	K00-K95 - Diseases of the digestive system
7.	**Postural kyphosis**	M40.0	67	**16.1**	M00-M99 - Diseases of the musculoskeletal system and connective tissue
8.	**Congenital deformities of feet**	Q66	63	**15.1**	Q00-Q99 - Congenital malformations, deformations and chromosomal abnormalities
9.	**Astigmatism**	H52.2	61	**14.6**	H00-H59 - Diseases of the eye and adnexa
10.	**Hypertrophy of adenoids**	J35.2	61	**14.6**	J00-J99 - Diseases of the respiratory system
11.	**Congenital malformations of cardiac septa**	Q21	61	**14.6**	Q00-Q99 - Congenital malformations, deformations and chromosomal abnormalities
12.	**Asthma**	J45	57	**13.7**	J00-J99 - Diseases of the respiratory system
13.	**Atopic dermatitis**	L20	56	**13.4**	L00-L99 - Diseases of the skin and subcutaneous tissue
14.	**Myopia**	H52.1	48	**11.5**	H00-H59 - Diseases of the eye and adnexa
15.	**Hemangioma, any site**	D18.0	26	**6.2**	C00-D49 - Neoplasms
16.	**Allergic rhinitis**	J30	24	**5.8**	J00-J99 - Diseases of the respiratory system
17.	**Urinary tract infection, site not specified**	N39.0	22	**5.3**	N00-N99 - Diseases of the genitourinary system
18.	**Nonorganic enuresis**	F98.0	19	**4.6**	F01-F99 - Mental, Behavioral and Neurodevelopmental disorders
19.	**Scarlatina**	A38	18	**4.3**	A00-B99 - Certain infectious and parasitic diseases
20.	**Obesity**	E66	18	**4.3**	E00-E89 - Endocrine, nutritional and metabolic diseases

Eye and adnexa conditions were the most prevalent, affecting more than half of the study population, with 1.5 times higher prevalence in the "Extremely and very low" BW group compared to the "Normal" group (**Table 12**). The most common cases were those of hypermetropia in almost 38% of the cases, astigmatism in almost 15%, and myopia in around 12% of the cases (**Table 13**).

Certain infectious diseases affected 39% of the preterm population without significant differences between prematurity sub-categories – in these cases, varicella accounted for 33% (**Tables 12-13**). Congenital malformations were diagnosed in almost 36% of preterm children, among them the most common were congenital deformities of feet in around 15% of the cases and congenital malformations of cardiac septa in nearly 15% of the cases. These conditions were significantly more prevalent in the "Extremely and very low" (almost 46%) and "Low" (40%) BW categories than in the "Sub-optimal" (almost 30%) and "Normal" (nearly 18%) groups ($p<0.05$) (**Tables 12-13**).

High incidences (almost 30%) were also observed in respiratory diseases with lower morbidity in higher BW groups (**Table 12**). The most common cases in this chapter were hypertrophy of adenoids in almost 15%, asthma in nearly 14%, and allergic rhinitis in 6% of the cases (**Table 13**). Endocrine, nutritional, and metabolic diseases accounted for almost 30% and were similarly distributed across the analysed groups, with active rickets found in nearly 22% and most prevalent obesity in 4% of the cases (**Tables 12-13**).

Moreover, mental, behavioural, and neurodevelopmental disorders were observed in almost 30% of the preterm population and were relatively evenly distributed across sub-categories, with specific developmental disorders of speech and language accounting for nearly 27%, ranking third overall in prevalence (**Tables 12-13**). Notably, anaemia affected almost one-fifth of the study population, with the "Normal" BW group showing a significantly lower incidence of blood and immune disorders compared to lower BW groups ($p<0.1$) (**Tables 12-13**).

Although statistically significant results of morbidity analysis were modest, the more severely premature groups exhibited a higher prevalence of diagnoses across the majority of ICD-10 disease chapters. This pattern was more distinct when analysing the disease percentage distribution by BW rather than GA, except for the musculoskeletal and connective tissue diseases, where "Late preterm" infants showed a higher incidence ($p<0.1$) (**Table 12**). Moreover, the total cumulative morbidity was particularly pronounced when comparing the study population to the general Lithuanian pediatric population (**Table 12**) which is further explored in the discussion.

4.4.2. Impact of Birth-Related Factors for The Mean Number of Diseases and the ICD-10 Disease Chapters Per Child

The primary goal of the negative binomial regression analysis was to determine the effect of birth-related variables on the mean number of diseases per child between the ages of 0 and 18. The results showed that the mean number of diseases per child is 34% greater for individuals from the "Sub-optimal" BW group, 50% greater for the "Low" BW group and 77% greater for the "Extremely and very low" BW group comparing to "Normal" BW individuals (**Table 14**). This results in the conclusion that lower BW is a significant risk factor for a larger number of diseases acquired from birth till adolescence.

Conversely, the analysis found that the other two factors considered (sex and GA category) were not significant. This outcome justified a sex-neutral approach in the analysis. The non-significance of the GA group may be attributed to the grouping into three intervals, which was necessary due to the limited number of cases for certain gestational weeks.

Similarly, when modelling the mean number of ICD-10 disease chapters per child within the same age range (**Table 15**), confirmed that lower BW is associated with a broader spectrum of health issues across ICD-10 chapters, reinforcing its role as a critical factor in long-term morbidity.

Table 14. The influence of sex, birth weight and gestational age categories on certain separate disease incidence from birth to 18 years by negative binomial regression outcomes. CI – confidence interval.

Factor	Coef.	p-value	IRR and 95% CI	
			IRR	95% CI
Sex (girl)	-0.0192	0.7715	0.9810	(0.8615, 1.1170)
Birth weight group (Sub-optimal)	0.2899	0.0279 *	1.3363	(1.0331, 1.7326)
Birth weight group (Low)	0.4061	0.0020 **	1.5009	(1.1619, 1.9437)
Birth weight group (Extremely and very low)	0.5726	0.0039 **	1.7728	(1.2042, 2.6150)
Gestational age group (Moderate pre-term)	-0.0527	0.5890	0.9487	(0.7839, 1.1479)
Extremely and very preterm	-0.2195	0.1257	0.8029	(0.6065, 1.0612)

p-value * <0.05, ** <0.01, *** <0.001

Table 15. The influence of sex, birth weight and gestational age categories on the incidence of different ICD-10 disease chapters from birth to 18 years by negative binomial regression outcomes. CI – confidence interval.

Factor	Coef.	p-value	IRR and 95% CI	
			IRR	95% CI
Sex (girl)	-0.0036	0.95136	0.9964	(0.8875, 1.1188)
Birth weight group (Sub-optimal)	0.2904	0.0161 *	1.3369	(1.0591, 1.7005)
Birth weight group (Low)	0.3496	0.0037 **	1.4185	(1.1248, 1.8028)
Birth weight group (Extremely and very low)	0.5730	0.0014 **	1.7735	(1.2512, 2.5231)
Gestational age group (Moderate pre-term)	-0.0025	0.7701	0.9749	(0.8219, 1.1545)
Extremely and very preterm	-0.2155	0.0961	0.8062	(0.6236, 1.0361)

p-value * <0.05, ** <0.01, *** <0.00

4.4.3. Health Condition Complexity and Interrelationships Among Disorders Across Different ICD-10 Disease Chapters

Lower birth weights (BW) and greater prematurity were associated with a higher number of diagnosed diseases per child from birth to age 18. This pattern is clearly illustrated in the distribution of disease counts across the GA and BW categories (**Figure 12**).

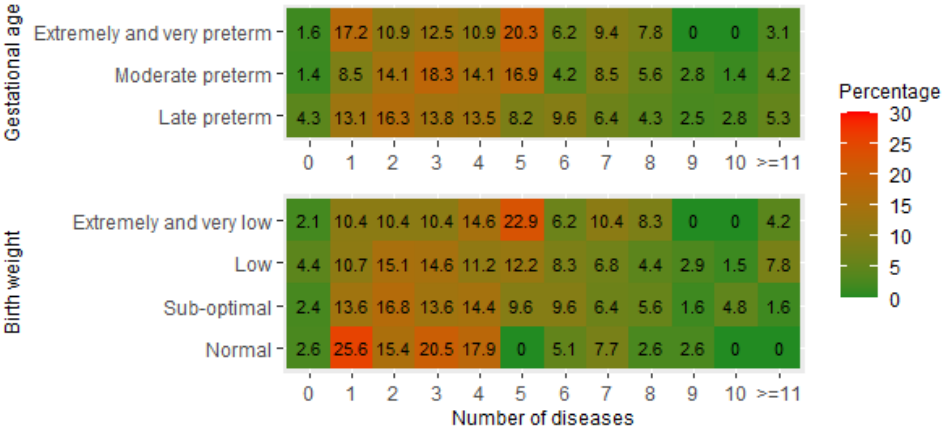

Figure 12. The percentage of individuals diagnosed with varying numbers of certain separate diseases from birth to age 18, categorised by GA and BW (represented by heat maps).

Individuals with lower birth weights and greater prematurity were more likely to have diagnoses involving multiple ICD-10 disease chapters from birth to age 18. This trend is highlighted in the frequency distribution of the disease chapters per child (**Figure 13**). In general, the heatmaps revealed that lower GA and lower BW were associated with an increased likelihood of having multiple diseases and disease chapters, with a more pronounced trend observed in BW categories.

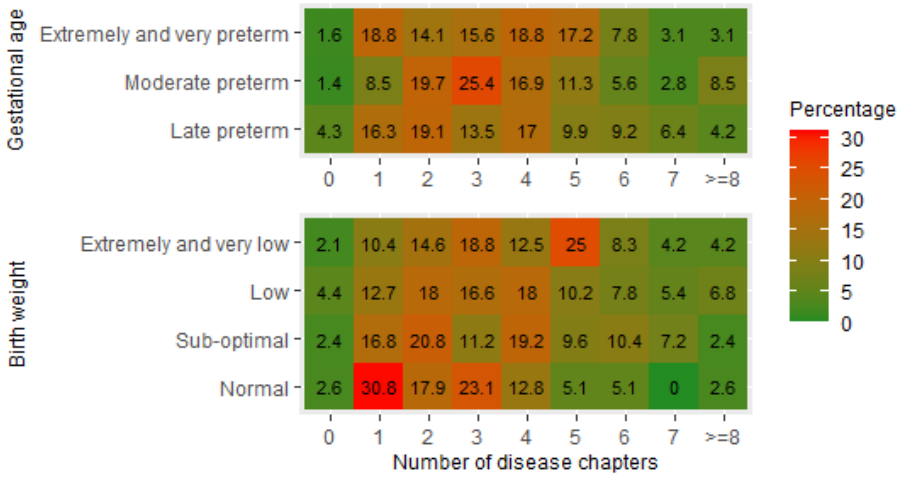

Figure 13. The percentage of individuals diagnosed with varying numbers of ICD-10 disease chapters from birth to age 18, categorised by GA and BW (represented by heat maps).

However, Fisher's exact test revealed no significant differences in disease counts across GA groups. Nevertheless, the differences were significant between "Extremely and very low" and "Normal" BW groups ($p<0.05$) and between "Low" and "Normal" BW groups ($p<0.05$). **Figure 12** shows that in the "Extremely and very low" BW group, individuals with five or more diseases make up 52%, in the "Low" BW group 44%, while in the "Normal" BW group only 18%. In terms of the ICD-10 disease chapters, the only significant differences were found between "Extremely and very low" and "Normal" BW groups ($p<0.05$) and between "Low" and "Normal" ($p<0.05$) BW groups. **Figure 13** illustrates that in the "Extremely and very low" BW group, individuals with five or more ICD-10 disease chapters make up 41.7%, in the "Low" group 30.2%, while in the "Normal" BW group only 12.8%.

Moreover, to explore the relationships and overlaps among different ICD-10 disease chapters, the UpSet graph in **Figure 14** was utilised. This

graph effectively visualises the individual intersections of diagnosed ICD-10 disease chapters, providing insights into the mostly unique patterns of comorbidities with 300 combinations detected in total. Only cases with a frequency greater than one were included in the graph. The UpSet graph provides an overview of the distribution and intersections of ICD-10 disease chapters, with horizontal bars showing the number of cases in each chapter. The central matrix uses filled and empty dots to highlight the chapter's involvement in comorbidities. For example, it reveals that seven individuals have diagnoses in the H00-H59 (eye and adnexa diseases) and A00-B99 (infectious diseases) chapters without overlapping with other chapters.

However, there were few frequently recurring variations of the co-morbid disease chapters. Thus, the vast majority of cases (84.7%) in the preterm population were highly individual and unique variations of the interrelations among the disease chapters which have been found to occur at single frequencies and are not reflected in this graph.

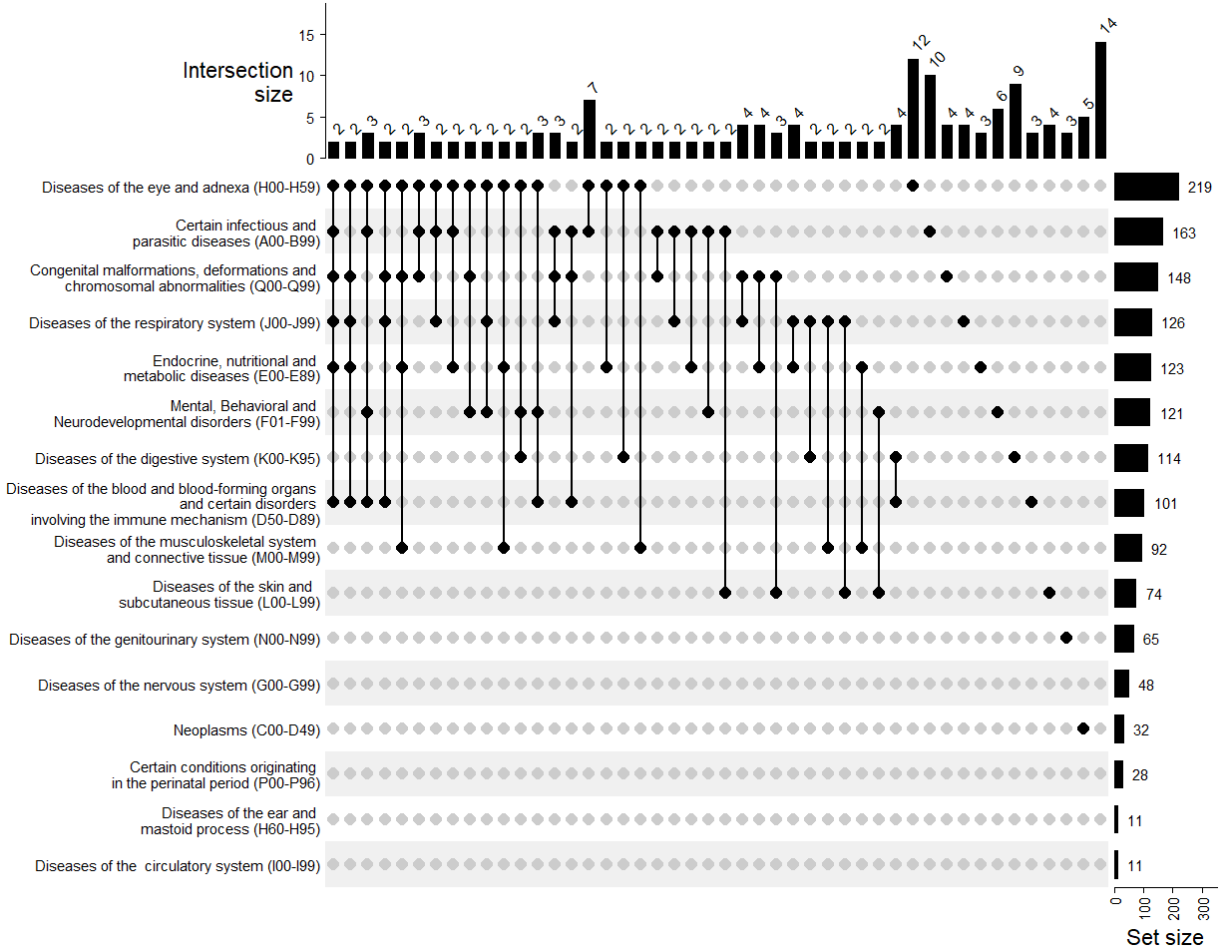

Figure 14. Combination variants of different interrelated ICD-10 disease chapters provided by the Upset graph. The horizontal bars on the right side represent the cases observed in each ICD-10 disease chapter. Filled dots in the central matrix indicate the participation in a given intersection linked by vertical lines within the respective column. The vertical bars at the top of the graph quantify the cases within each intersection, highlighting specific instances such as twelve individuals having diagnoses exclusively in the H00-H59 (Diseases of the eye and adnexa) chapter.

5. DISCUSSION

Preterm birth is a multifaceted phenomenon with profound implications for growth, development, and health outcomes across the lifespan. This discussion synthesises key findings from our research, examining how population-specific factors, birth-related variables, and longitudinal health trajectories shape the experiences of preterm-born individuals. By integrating anthropometric assessments, growth patterns, and multisystem health outcomes, this study highlights the interplay between early-life factors and long-term morbidity, emphasising the importance of personalised and regionalised approaches in healthcare and public health interventions.

5.1. BW and Length: Regional Insights and Clinical Implications

BW and length centiles are essential to assessing an infant's physical status and guiding clinical decision-making. The choice between global standards and regional, population-specific references remains debated (128,129). Our findings support the use of regional population-based growth curves which more accurately reflect the characteristics of Lithuanian newborns than the global standard IG-21. At term, IG-21 significantly underestimates or overestimates the prevalence of SGA and LGA, with differences exceeding a factor of two.

The observed discrepancies between Lithuanian and IG-21 centiles for BW and length align closely with those seen for HC. The better agreement at extremely preterm gestations reflects the smaller biological variability at early gestational ages, as previously discussed for HC. However, these parallels should be interpreted cautiously as IG-21 data for <37 weeks gestation relied on a modest sample size (16) (**Figures 3–6**).

As GA increases, the variability becomes more population-specific, with disparities widening after 34 weeks, particularly at term, similar to HC findings. Noteworthy, the mean BW and length values for term Lithuanian neonates exceeded IG-21 centiles, reinforcing the role of regional maternal and genetic factors in shaping neonatal anthropometry. Likewise, other studies from different continents also found their regional neonatal reference charts to be significantly different from the neonatal standards provided by IG-21 (15,128,130–133). These parallels underscore the need for regional references across all neonatal anthropometric indices, especially for term newborns.

The categorisation of newborns as SGA or LGA based on regional versus global standards highlights the clinical implications of misclassification. Our study showed that using IG-21 significantly alters the tails of BW distribution, affecting the identification of at-risk neonates. For example, the prevalence of SGA and LGA among Lithuanian term newborns differed dramatically between IG-21 and regional standards (**Table 4**). Similar to the HC discussion, such misclassification could lead to over- or underestimation of clinical risks, underscoring the importance of contextually appropriate charts for clinical practice.

Importantly, the ability to evaluate SGA and LGA prevalence across all gestational ages provides valuable insights into fetal development. Early growth phases dominated by cellular hyperplasia (first 16 weeks) are particularly vulnerable to irreversible damage when disrupted, leading to severe neurological and systemic sequelae (25,134). In contrast, hypertrophic growth phases beyond 32 weeks are more resilient, with better prognoses for SGA neonates if hypoxic-ischemic encephalopathy is avoided as these processes are typically reversible.

Indeed, while newborns with BW below the 10^{th} centile (mild hypotrophy) may reflect normal biological or ethnic variability, neonates with BW below the 3^{rd} centile (severe hypotrophy) face significantly higher risks of adverse outcomes and require greater clinical attention. Accurate SGA classification, particularly at extreme gestations, is crucial for informing prognosis and guiding timely interventions.

The comprehensive inclusion of all births in our dataset, regardless of maternal socioeconomic or ethnic background, strengthens the generalizability of our findings. However, this inclusivity may also explain some of the discrepancies with IG-21 which included only low-risk pregnancies from highly controlled environments (16). Ethnic differences within Lithuania, where 15% of the population belongs to minority groups, may have also played a role. However, our previous studies found minimal BW differences among ethnic groups when maternal education levels were comparable (135). This suggests that socioeconomic factors, rather than ethnicity alone, likely account for discrepancies in neonatal size.

One limitation of our references is their applicability to postnatal growth monitoring in preterm infants as they do not account for the initial weight loss and fluid shifts typical in the first weeks of life (5,136). This rationale highlights why another part of this dissertation focuses on longitudinal data, aiming to create growth curves which more accurately reflect these dynamics.

The findings of our study, consistent with the HC discussion, highlight significant discrepancies between regional references and IG-21 standards, particularly at later gestations. Regional population-based references more accurately capture the anthropometric characteristics of Lithuanian newborns, providing critical tools for identifying SGA and LGA neonates and guiding clinical interventions. In contrast, global standards like IG-21 require validation before widespread implementation as their use may misrepresent the prevalence of at-risk neonates and compromise clinical decision-making. By adopting regional standards, healthcare professionals can better address the needs of vulnerable infant populations and enhance neonatal outcomes.

5.2. Population-Specific Variability and Clinical Implications of Neonatal HC Assessment

As with BW and length, monitoring neonatal HC requires precise tools to ensure accurate growth and neurodevelopmental assessment (137). Recent discussions highlight whether global standards or region-specific references are more suitable for diverse populations (138–140). Our findings reveal that HC variability is most pronounced between the populations of late preterm and term gestations where the variability within the populations (141–144) is at its lowest (Table 2, **Paper II**). This suggests that population-specific factors play a greater role in determining neonatal HC as GA increases.

The coefficient of variation (CV) and standard deviation (SD) for HC provide insights into within-population variability. Consistent with previous studies (141–144), CVs were highest in extremely preterm gestations and decreased progressively with GA, indicating narrower HC variability closer to term (Table 2, **Paper II**). Early gestational HC displays greater biological flexibility due to reduced constraints from maternal pelvic size, while at later gestations, HC becomes increasingly shaped by maternal anthropometry, particularly pelvic dimensions (145).

These findings support the hypothesis that neonatal HC is anthropometrically limited by maternal pelvic size—a phenomenon termed the "evolutionary bottleneck" (146). The human pelvis represents an evolutionary compromise between bipedal locomotion and the need to accommodate highly encephalised neonates during childbirth (147). Studies have shown that females with larger heads tend to deliver neonates with larger HC as they possess birth canals better suited to accommodate such neonates (145). Furthermore, taller women with more oval pelvic inlets are better able

to accommodate larger fetal heads (145), a relationship supported by the work of R. G. Tague's findings on pelvic inlet dimensions and stature (148).

Variations in the pelvic shape, which is geographically structured (149), further explain the observed HC differences between populations. For instance, Lithuanian women, being among the tallest globally with an average height of 167.6 cm (150), exhibit neonatal HC values similar to Finnish women (166.5 cm), however, significant differences emerge when compared to shorter populations such as Indonesians (154.4 cm) (Table 2, **Paper II**). These findings underscore the critical role of maternal height and pelvic size in influencing neonatal HC (145). This possible relationship between neonatal HC (cm) at term (40 weeks of gestation) and average women's height figures (141–144) across the compared countries is presented in Figure 3, **Paper II**.

While global standards like IG-21 provide useful benchmarks for extremely preterm neonates, their application at later gestations is less reliable. For example, the IG-21 10th percentile aligns closely with the Lithuanian 3rd percentile in extremely preterm neonates but diverges significantly at term, potentially underestimating the prevalence of microcephaly (**Figures 7 and 8**). Similarly, the IG-21 97th percentile overestimates macrocephaly in Lithuanian term neonates by more than 1 cm. These discrepancies highlight the need for regional validation of IG-21 standards, particularly in term and post-term populations (129,151–158).

The limitations of IG-21 at later gestations are further reflected in centile misclassification. Brazil's data revealed similarities with IG-21 trajectories at the 3rd percentile until term, but other studies identified a substantial misclassification of microcephaly and infant birth size using IG-21 standards (156). The modest sample size for <37 weeks gestation in IG-21 (18) underscores the need for caution when applying these standards and explains the "wave" observed at 33 gestational weeks in the IG-21 centile curves (**Figures 7 and 8**).

Inappropriate HC standards can result in significant clinical consequences, such as unnecessary interventions or missed diagnoses (159). Regional references are crucial for predicting higher percentiles in moderate to late preterm and term neonates where population variability is most pronounced. For instance, while the CDC HC curves (160) show smaller gaps than IG-21, they still fail to capture population-specific characteristics as effectively as regional standards.

The overestimation of macrocephaly above the 97th centile and the underestimation of microcephaly below the 3rd centile observed in our study underscore the importance of accurate centile classification. Misclassification

can have far-reaching consequences for clinical decision-making, particularly in late preterm and term populations (159).

Our findings emphasise that neonatal HC is a reflection of growth and neurodevelopment and a result of evolutionary adaptation to maternal anthropometry. Over generations, neonatal HC and body size have adapted to maternal pelvic dimensions, reflecting a balance between genetic inheritance, environmental conditions, and the physical constraints of childbirth (146,147). Regional references provide a more precise assessment of neonatal HC, accounting for these population-specific factors, and are, therefore, critical for an accurate evaluation and the identification of potential clinical pathologies.

5.3. Longitudinal Growth Patterns of Preterm-Born Individuals by GA and BW

This longitudinal study has applied the SITAR model to analyse growth trajectories in height, weight, and BMI among children born preterm, offering insights into how GA and BW shape growth patterns from birth to 12 years. The results highlight the dynamic interplay between GA and BW, with distinct long-term implications for growth and development.

Our findings underscore the significant influence of BW on long-term growth outcomes, surpassing the effects of GA, particularly for height and weight. Children with low BW exhibited consistently greater deficits in height and weight than those born early preterm, indicating that BW serves as a more robust determinant of adverse growth outcomes. For instance, low BW girls and boys were, on average, 1.4 cm shorter and 0.5/1.0 kg lighter than their normal BW peers, compared to 0.9 cm and 0.3/0.8 kg deficits among early preterm girls and boys. These findings align with previous research showing that extremely low BW (ELBW) children often remain smaller and lighter throughout childhood and adolescence, with growth deficits persisting into adulthood (161–163).

While BW was dominantly influencing height and weight, GA played a more dynamic role in BMI trajectories. Early preterm children exhibited sharper BMI increases post-adiposity rebound (AR), particularly among boys, suggesting that GA contributes more dynamically to BMI growth patterns. These findings reveal distinct pathways through which BW and GA influence different growth parameters, supporting the hypothesis that BW reflects in utero energy reserves more directly than GA, with potential long-term implications for growth and energy allocation (111,112).

BMI trajectories in early childhood follow a characteristic pattern: a rapid increase in the first year, a decline to a nadir around age 6, and

a subsequent rise in a phase termed adiposity rebound (AR). Studies report that preterm infants experience early AR (before age 5) at significantly higher rates, reaching up to 54% in some cohorts (38). This early timing is associated with an increased BMI and a heightened risk of developing obesity and cardiometabolic conditions later in life (164–166).

In our study, term-born children exhibited later AR timing compared to preterm groups, aligning with findings that preterm children often undergo earlier AR. Notably, the magnitude of AR differed markedly between the GA and BW groups. In the GA groups, early preterm children experienced an earlier AR characterised by a sharp BMI increase post-AR, surpassing term-born peers by ages 9–9.5, signalling a higher risk for overweight and future obesity (164). Conversely, in the BW groups, AR timing was more consistent, but the magnitude of the BMI increase was less pronounced. This stability suggests that the BW groups may follow healthier BMI trajectories, avoiding the sharp rises observed in early preterm children.

The literature indicates that delayed AR (occurring at or after 7 years) offers protective benefits, reducing excessive weight gain, lowering the risk of obesity, and providing opportunities to reverse childhood obesity (167,168). The earlier AR observed in preterm groups, especially in those with low BW, highlights the need for early interventions targeting preterm children to mitigate long-term health risks.

Moreover, boys exhibited more pronounced long-term growth deficits when compared to girls, particularly in weight. Specifically, low BW boys weighed 1.0 kg less than their normal BW peers, low BW girls weighed only less than 0.5 kg compared to normal BW girls, with confidence intervals confirming a significant sex difference. Similarly, boys experienced less intense growth spurts, with 3.7% lower growth intensity in the low BW group. Consistent with earlier studies, these results suggest boys may be more vulnerable to adverse growth outcomes (23), however, conflicting research indicates no significant differences in pubertal timing between preterm boys and girls (29). These controversial findings indicate the need for further research to explore how these vulnerabilities manifest across different stages of development.

The SITAR model's ability to account for individual variations in size, timing, and intensity provided a robust framework for analysing growth trajectories. The large sample size and extended follow-up period has further strengthened the study's generalizability. However, a retrospective nature of the study has led to certain limitations, particularly regarding the pubertal stage. While the SITAR model adjusts for pubertal timing and intensity through its random effects, direct data on pubertal stages could provide

additional insights into growth dynamics during the observed period. Future studies extending into late adolescence and adulthood could better capture these developmental processes and their implications for long-term health.

Additionally, this study focused on infant sex, GA, and BW as primary variables for growth modelling due to their well-established relevance in determining growth trajectories. While other potential covariates, such as maternal age and maternal education attainment, may influence growth outcomes, their adjustment would likely have minimal impact in this analysis, as the same infants are being compared for both BW and GA. The study's primary focus on preterm-specific and birth-related variables aligns with its objectives. However, larger cohorts including more extremely preterm and extremely low BW infants would strengthen the findings and improve their applicability to the most vulnerable populations. Future research could also incorporate a broader range of covariates in studies with more heterogeneous populations to provide additional insights into growth determinants.

Clinically, this part of the study highlights the complex interplay between BW, GA, and sex in shaping long-term growth outcomes. While BW predominantly determines height and weight, GA demonstrates a dynamic influence on BMI trajectories, particularly post-AR. These findings highlight the heterogeneity of preterm populations and the need for individualised growth monitoring and interventions to optimise developmental outcomes.

5.4 Multisystem Health Outcomes in Preterm-Born Individuals: The Impact of Birth-Related Factors on Health Complexity and Disorder Interrelationships from Infancy to Adolescence

Our study revealed a complex pattern of multimorbidity in preterm-born survivors from infancy through adolescence, with the highest disease burden occurring from birth to preschool age. A lower BW was strongly associated with a higher mean number of diseases by age 18 (4.6 in the "Extremely and very low" BW group vs. 3.2 in the "Normal" group), along with a broader range of ICD-10 health issues. In contrast, GA-related differences in mean disease numbers were less pronounced, underscoring the greater role of BW as a determinant of long-term health outcomes. While most studies on preterm morbidity focus on risk assessment (85,86), they rarely quantify the cumulative disease burden longitudinally. Our findings bridge this gap, offering a detailed timeline of disease progression in preterm-born individuals, continuously tracked from birth to adolescence, and underscoring the critical need for targeted interventions.

Morbidity in preterm children was markedly higher compared to the general Lithuanian pediatric population aged 0-18 in 2019, with statistically significant differences observed in the prevalence of many ICD-10 disease chapters (**Table 12**, compiled according to (122,123)). Although the most common conditions in preterm children included eye and adnexa diseases, respiratory conditions, and certain infectious diseases, the greatest disparities compared to the general pediatric population were noted in blood and immune disorders which were over ten times more prevalent. Neoplasms, nervous system diseases, mental disorders, congenital malformations, and genitourinary diseases were 3–4 times more prevalent in the preterm population. Certain infectious diseases and endocrine and metabolic disorders were 2.5 times more frequent, and musculoskeletal and eye conditions were nearly twice as common. The prevalence of skin and subcutaneous tissue diseases was comparable between the groups. In contrast, respiratory and digestive diseases were less prevalent, and ear and mastoid disorders were three times less frequent. The detailed structure of diagnoses within these categories is discussed below.

Eye and adnexa diseases affected over half of preterm-born individuals, compared to almost 31% in the general population (122,123). In the general pediatric population, eye disorders ranked third in prevalence after respiratory and digestive diseases. Hypermetropia was over three times more common in premature children (almost 38%) than in the general population (about 13% (122,123)) and over eight times higher than the global prevalence (4.6% (169)). This high rate may reflect either physiological hyperopia in children aged 5-7 years (169), or pathological refractive error, as the ICD-10 classification does not distinguish between the two. In contrast, myopia, which is never physiological in children, was nearly twice as prevalent in preterm children (almost 12%) compared to the general population (about 7% (170)). Similarly, astigmatism in preterm infants (approximately 15%) was comparable to other studies (about 14% (171)), indicating that astigmatism is more common in preterm-born children (170,172). In Lithuania, national guidelines recommend regular ophthalmological follow-ups for preterm infants, particularly those with ELBW or severe prematurity, to screen for conditions like retinopathy of prematurity (ROP) (173,174). A higher prevalence of visual problems in preterm children in our study likely reflects this proactive monitoring, whereas undiagnosed conditions in term-born children may underestimate their prevalence.

Certain infectious diseases were the second most prevalent in the preterm population, occurring almost three times as frequently as in the general pediatric population (about 40% vs. 15%). A similar retrospective

longitudinal study highlighted the increased risk of long-term infectious morbidity in preterm individuals, with each additional week of gestation reducing this risk (175). Preterm newborns' susceptibility to infections may stem from immature immune systems, inadequate passive immunity, or delayed vaccination schedules (176–178). Varicella (B01) was the second most common disease in the preterm cohort, reflecting the optional nature of varicella vaccination in Lithuania's national immunisation program (179). Higher varicella rates in preterm-born children may reflect actual incidence and proactive follow-up, potentially amplifying diagnosis rates compared to term-born peers, and underscoring the importance of vaccination strategies for preterm infants.

Congenital malformations affected almost 36% of the preterm population, over three times higher than the 10% prevalence in the general pediatric population (10% (122,123)). This finding aligns with a prospective study reporting congenital anomalies in 33% of preterm infants, compared to only about 5% in full-term infants (180), however, it focused only on the malformations diagnosed within the first month of life. Consistent with the follow-up study up to 5 years (181), cardiac septal malformations (Q21) were among the most common, occurring in almost 15% of preterm children - more than four times the prevalence of congenital circulatory system malformations (Q20-Q28) in the general pediatric population (about 3%) (122,123).

Respiratory diseases, though common in preterm children (about 30%), were less prevalent compared to the general Lithuanian pediatric population where they represented the leading disease chapter (close to 58% (122,123)). Even though Lithuania has no specific national policies mandating delayed child care or school entry for preterm-born children, this may be related to delayed kindergarten and school entry for preterm-born children (182), potentially reducing exposure to communicable respiratory illnesses (183). However, chronic respiratory conditions, such as bronchial asthma, were significantly more common in preterm children (almost 14%) compared to the overall prevalence in Lithuanian children (close to 5%) (122,123). These findings are consistent with longitudinal studies indicating a heightened risk of asthma persisting into adolescence (184,185).

Endocrine, nutritional, and metabolic diseases were nearly three times more prevalent in preterm children (almost 30%) compared to the general pediatric population (about 11% (122,123)). This increased prevalence aligns with the findings that premature dissociation from the maternal-placental-fetal unit predisposes preterm infants, especially those with extremely low BW, to endocrine, nutritional and metabolic bone diseases like rickets (186–188). Active rickets was notably prevalent in our study cohort (close to 22%) versus

less than 1% in the general population. Additionally, obesity was also more common in preterm children (about 4%) compared to their peers (close to 1%) (122,123)), consistent with the findings from other systematically reviewed studies (165).

Mental and behavioural disorders were significantly more prevalent in preterm infants compared to the general pediatric population (about 29% vs. almost 8% (122,123)). Meta-analyses and longitudinal studies reveal that preterm children are at a significantly higher risk of anxiety disorders (OR: 2.17 (189)), psychiatric conditions, and intellectual disabilities, particularly among the extremely preterm (190–192). Even late preterm children frequently experience milder neurodevelopmental challenges impacting academic performance (193,194). Specific developmental disorders of speech and language (F80) were the most common in our cohort, affecting almost 27% of preterm children compared to only just about 5% for the broader category of psychological development disorders in the general Lithuanian pediatric population (122,123). These findings align with prior studies that emphasise language delays in preterm survivors (195,196). While previous studies – ranging from meta-analyses to sibling-control designs (189,192–196) – provide insights into mental health outcomes, no other study matches the longitudinal scope and design of our study.

Notably, blood and immune disorders affected a quarter of the preterm population, more than ten times the prevalence in the general pediatric population. This disparity likely reflects the delayed hematopoietic maturation, leading to the conditions like anemia, thrombocytopenia, and leukopenia (197). Anemia (D64.9) was notably the fifth most common diagnosis among preterm infants with a significantly higher prevalence in those with lower birth weights, supporting this association.

Our findings conclusively demonstrate that lower BW (BW) significantly increases the number and diversity of diseases from birth to adolescence, as captured under various ICD-10 chapters. In contrast, gestational age (GA) showed weaker associations, likely due to its grouping into broader intervals necessitated by the limited number of cases for certain gestational weeks.

To better explore their respective contributions, BW and GA were analysed as independent variables rather than integrated into growth categories such as SGA, AGA, or LGA. This independent analysis allowed us to disentangle their distinct roles, with BW reflecting cumulative prenatal energy reserves and GA capturing developmental timing and intrauterine exposures. By avoiding combined classifications, our approach revealed that

BW has a stronger influence on long-term morbidity, emphasising its importance in shaping health trajectories, as shown in **Tables 14-15**.

These results align with earlier findings in this study, where BW consistently emerged as a critical determinant of growth and health outcomes, overshadowing the role of GA in many aspects. For instance, BW significantly influenced height and weight trajectories (SITAR analysis) and neonatal HC variability, reflecting its role as a direct measure of *in utero* energy reserves. In contrast, GA contributed more dynamically to BMI and certain growth patterns, demonstrating its importance in other developmental contexts.

The concept of developmental plasticity (112), previously discussed in the context of growth and anthropometric variability, provides a unifying framework. BW, as a marker of cumulative nutritional and environmental conditions, is central to metabolic programming and long-term energy allocation strategies. Adverse prenatal environments may permanently alter energy trade-offs, as highlighted in evolutionary medicine (111), leading to heightened susceptibility to chronic diseases such as cardiovascular conditions, diabetes, and mental health disorders. A recent study further supports these findings, associating low BW—even in non-preterm infants—with adverse health outcomes like prediabetes/diabetes, hypertension, and reduced educational attainment (198).

Moreover, individuals with lower BW exhibited more complex health conditions, characterised by highly individualised comorbidity patterns with few recurring combinations. This underscores the unique nature of multimorbidities in preterm-born patients. While most studies focus on the impact of prematurity on specific organ systems or individual diseases, few address the cumulative and complex health effects of preterm birth (83,85,86). Recent research (85) has shown that individuals born at earlier gestational ages, if compared to full-term individuals, are at a 29% higher risk of multimorbidity during adolescence (ages 10–17). Another study (86) found that preterm individuals were more likely to develop multimorbidity involving two, three, or even four health conditions, with late preterm birth (34–36 weeks) contributing more to this risk than other gestational categories. However, these studies relied on predefined diagnostic codes and analysed multimorbidity over specific periods, limiting their scope.

In contrast, our study recorded all diagnoses longitudinally, from birth to adolescence, providing a more comprehensive perspective on multimorbidity. This approach offers novel insights into the interconnected nature of health conditions in preterm individuals. Importantly, our findings highlight the uniqueness of comorbidity patterns, varying significantly from child to child—an aspect that has received limited attention in previous

research. This expanded understanding enhances the knowledge of health trajectories in preterm survivors, emphasizing the individualized challenges they face.

The heightened susceptibility to multimorbidity in preterm-born individuals may be attributed to *in utero* and perinatal disruptions during critical stages of organo- and histogenesis. Consequently, this could explain the intersections between the disease chapters involving organ systems derived from the same germ layer. Future investigations should focus on individual disease associations rather than broader ICD-10 chapter categorisations, as the ICD-10 framework often fails to accurately capture physiological health conditions and contains etiological inconsistencies. For instance, hernias (e.g., umbilical, inguinal) are classified as digestive system disorders (K00–K95), despite their basis in connective tissue weakness or incomplete fetal development. Reclassification under musculoskeletal and connective tissue disorders (M00–M99) would better reflect their pathophysiology. This is supported by our findings of umbilical hernias in about 18% of preterm-born individuals, compared to just 0.4% in the general pediatric population (122,123).

Limitations include a small number of extremely preterm survivors and fewer participants aged 12–18 years, potentially reducing statistical power. Unmeasured maternal, environmental, and genetic factors may have influenced the results. Multicenter studies with larger, more diverse cohorts are needed to strengthen these findings and improve generalizability.

Finally, our findings underscore the critical need for extended surveillance of preterm infants beyond infancy, particularly during the preschool years, where the disease burden is the highest. Prioritising medical interventions from birth to age 7 could significantly reduce long-term health risks associated with prematurity. Moreover, BW emerged as a key factor in assessing a chronic disease risk through adolescence, highlighting its importance in early health evaluations.

Furthermore, the unique comorbidity patterns observed emphasise the need for personalised medical care, tailoring treatment plans to each patient's specific health trajectory. This individualised approach can more effectively address immediate and long-term health challenges, advancing public health and patient-centered care.

6. CONCLUSIONS

1. Regional gestational age- and sex-adjusted population-based neonatal references reveal distinct differences in Lithuanian neonatal weight and length compared to the global standard Intergrowth-21st. Specifically, Intergrowth-21st substantially underestimates the prevalence of small for gestational age, and overestimates large for gestational age prevalence in Lithuanian newborns, particularly in term and post-term gestations. These regional references better capture the unique growth patterns of the Lithuanian population, highlighting the discrepancies in the classification of at-risk newborns.

2. Global standards such as Intergrowth-21st effectively evaluate neonatal head circumference in early gestations. However, in later gestations, the neonatal head circumference of Lithuanian newborns deviates from global standards, with gestational age and sex-adjusted population-based references demonstrating consistently larger head circumference values. These references better capture the specific characteristics of Lithuanian newborns, reflecting regional growth patterns not accounted for by global standards.

3. Birth weight strongly influences sustained growth deficits in preterm Lithuanian infants, while gestational age dynamically shapes BMI trajectories, increasing obesity risk in early preterm groups. Boys face greater long-term challenges in weight and BMI than girls.

4. Lithuanian preterm-born individuals exhibit a substantial burden of multimorbidity, with the highest prevalence of disease manifestations occurring before age 7. Lower birth weight is strongly associated with greater susceptibility to multimorbidity and a broader spectrum of conditions across multiple ICD-10 chapters. The unique and complex comorbidity patterns underscore the need for personalised, multidisciplinary care to address their intricate health trajectories.

7. PRACTICAL RECOMMENDATIONS

Adopting regional growth and health references tailored to population-specific factors can enhance the accuracy of neonatal and pediatric assessments. Population-based references developed in this study can now be used for assessing the physical condition of Lithuanian newborns, enabling precise identification of at-risk individuals and effective clinical decision-making.

Our findings emphasise the critical need to expand the current monitoring of preterm-born individuals in Lithuania, particularly up to the age of 7, when the disease burden is greatest. Early interventions addressing growth deficits, nutritional needs, and comorbidities can mitigate long-term health risks and support optimal developmental outcomes.

The complex and unique comorbidity patterns in preterm-born individuals highlight the importance of personalised, multidisciplinary care. Coordinated efforts among pediatric, endocrine, neurological, mental health and other specialists are essential to address the complex and diverse health trajectories of preterm-born individuals effectively.

Additionally, national healthcare strategies should advocate for regular follow-ups, timely vaccinations, and early screenings for chronic conditions. Raising awareness among families and healthcare providers of the risks associated with prematurity and the benefits of proactive, targeted care must be among top priorities in initiating public health.

8. FUTURE PERSPECTIVES

Developing methodological guidelines for regional growth standards in clinical settings could enhance the consistency and quality of neonatal and pediatric care. This approach will help integrate research findings into practice, ensuring that the specific needs of preterm-born individuals are met effectively.

In addition, further research should focus on exploring the intricate relationships and interconnections among various health conditions in preterm-born individuals. Special attention should be given to understanding the influence of early-life factors, such as BW and GA, on developmental plasticity and long-term health trajectories. To validate these findings and uncover disease-specific associations beyond ICD-10 classifications, it is essential to deploy multicenter longitudinal studies involving diverse cohorts coupled with advanced analytical models.

SANTRAUKA LIETUVIŲ KALBA

SANTRUMPOS

AGA	Atitinkantis gestacijos amžių
BCT	*Box-Cox t* (BCT) pasiskirstymas
DGA	Didelis pagal gestacijos amžių
GA	Gestacijos amžius
GAMLSS	Postūmio, mastelio ir formos parametrų (angl. *Generalized Additive Models for Location, Scale and Shape*) apibendrintieji adityvieji modeliai
GAp	Galvos apimtis
GS	Gimimo svoris
IG-21 T	Tarptautinis vaisiaus ir naujagimio augimo konsorciumas XXI amžiuje (angl. „*International Foetal and Newborn Growth Consortium for the 21st Century*“, INTERGROWTH-21st)
IUAA	Intrauterininis augimo apribojimas
YMGS	Ypač mažas gimimo svoris
KMI	Kūno masės indeksas
LMGS	Labai mažas gimimo svoris
LMS	*Lambda-Mu-Sigma* metodas
LMST	*Lambda-Mu-Sigma-Tau* metodas
M	Vidurkis
MGA	Mažas pagal gestacijos amžių
N	Imtis
PI	Pasikliautinis intervalas
PK	Paplitimo koeficientas
PSO	Pasaulio sveikatos organizacija
SITAR	SITAR modelis (angl. *SuperImposition by Translation and Rotation*)
SN	Standartinis nuokrypis
SP	Standartinė paklaida
TG	Tuklumo grąža
TKI	Tarpkvartilinis intervalas
TLK-10	Tarptautinės statistinės ligų ir sveikatos sutrikimų klasifikacijos 10-asis pataisytas ir papildytas leidimas
VK	Variacijos koeficientas

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Ši daktaro disertacija parengta pagal keturias mokslines publikacijas. Mokslinės publikacijos tolesniame tekste žymimos nurodytais romėniškais skaitmenimis:

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II. **Morkuniene R**, Tutkuviene J, Cole TJ, Jakimaviciene EM, Isakova J, Bankauskiene A, Drazdiene N, Basys V. *Neonatal Head Circumference by Gestation Reflects Adaptation to Maternal Body Size: Comparison of Different Standards*. Sci Rep 12, 11057 (2022). Published 2022 June 30.
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III. **Morkuniene R**, Cole TJ, Levuliene R, Suchomlinov A, Tutkuviene J. *The Associations of Preterm Birth and Low Birth Weight with Childhood Growth Curves between Birth and 12 Years: A Sitar-Based Longitudinal Analysis.* Ann. Hum. Biol.
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PREAMBULĖ

Ši daktaro disertacija teikiama gynimui kaip mokslinių straipsnių rinkinys. Kai kurios jos dalys pažodžiui cituojamos iš anksčiau publikuotų straipsnių, išvardytų knygos pabaigoje.

Disertacija susideda iš tarpusavyje susijusių dalių, kurių kiekviena prisideda prie išsamios Lietuvos neišnešiotų naujagimių augimo ir sveikatos būklės analizės, atsižvelgiant į skirtingą gestacijos amžių ir gimimo svorį.

Pirmiausia buvo ištirtas Lietuvos naujagimių gimimo svorio ir ilgio pasiskirstymas bei variacija pagal gestacijos amžių ir lytį, parengtos populiacinės Lietuvos naujagimių gimimo svorio ir ilgio ribinės vertės ir kreivės, kurios buvo lyginamos su tarptautiniais standartais. Vėliau atitinkamai buvo analizuotas Lietuvos naujagimių galvos apimties pasiskirstymas ir variacija pagal gestacijos amžių ir lytį, sudarytos Lietuvos naujagimių populiacinės galvos apimties ribinės vertės ir kreivės, kurios taip pat buvo lyginamos su tarptautiniais standartais. Tada buvo įvertinti ilgalaikiai neišnešiotų naujagimių augimo rezultatai, analizuojant augimo (svorio, ūgio, KMI) dėsningumus skirtingose gimimo svorio ir gestacijos amžiaus grupėse nuo gimimo iki 12 metų. Galiausiai disertacijoje buvo nagrinėjami daugiasistemiai prieš laiką gimusių vaikų sveikatos padariniai nuo kūdikystės iki paauglystės, daugiausia dėmesio skiriant gimimo veiksnių įtakai sveikatos būklės sudėtingumui ir įvairių sutrikimų tarpusavio ryšiams.

1. ĮVADAS

1.1. Tiriamoji problema ir jos aktualumas

Priešlaikinis gimdymas išlieka reikšmingu pasaulinės sveikatos iššūkiu: 2020 m. užfiksuota apie 13,4 milijono priešlaikinio gimdymo (<37 gestacijos savaitės) atvejų (1). Nepaisant medicinos pažangos, priešlaikinio gimdymo rodikliai per pastarąjį dešimtmetį beveik nepakito, dėl to kasmet miršta beveik 1 milijonas naujagimių, o milijonams kitų lieka ilgalaikių sveikatos sutrikimų (2, 3). Be to, nepalankios naujagimystės laikotarpio būklės išlieka pagrindine prarasto žmogiškojo kapitalo priežastimi visame pasaulyje: ši tendencija nepakito nuo 1990 m. (3).

Prieš laiką gimusių naujagimių augimo ir sveikatos būklės vertinimas remiasi įvairiomis augimo normomis ir ribinių verčių diagramomis, kurios yra būtinos klinikinėje praktikoje užtikrinant tikslią diagnozę ir pagrįstus sprendimus. Tačiau iki šiol nėra pasaulinio lygio sutarimo dėl tinkamiausių neišnešiotų naujagimių augimo kriterijų. Diskusijų kyla dėl intrauterinių (4–6) ir postnatalinių (7, 8) augimo kreivių, individualizuotų ir populiacijos pagrindu sudarytų (9–12) diagramų, taip pat regioninių ir pasaulinių standartų (6, 13–19) pasirinkimo. Pavyzdžiui, *Intergrowth-21st* (IG-21) konsorciumas pasiūlė taikyti vieną bendrą tarptautinį augimo standartą, tačiau, vis daugėjant įrodymų apie fiziologinius skirtingų šalių ir etninių grupių naujagimių skirtumus, kyla abejonių dėl tokio „vieno standarto visiems“ taikymo tinkamumo (13–15).

Lietuvos naujagimių gimimo svorio ir ilgio rodikliai vertinami remiantis daugiau kaip dvidešimties metų senumo (1998–2002 m.) matematiškai neišlygintomis, empirinėmis ir ne visai išsamiais populiaciniais duomenimis pagrįstomis gimimo svorio ir ilgio procentilėmis (20). Lietuvoje iki šiol nebuvo sukurta regioninių populiacijos pagrindu sudarytų Lietuvos naujagimių galvos apimties ribinių verčių pagal gestacijos amžių ir lytį. Šie trūkumai pabrėžia poreikį atnaujinti ir pritaikyti augimo normogramas regioniniam kontekstui, siekiant pagerinti klinikinių vertinimų tikslumą ir aktualumą.

Šis poreikis ypač svarbus atsižvelgiant į tai, kad neišnešioti naujagimiai susiduria su didesne pogimdyminio augimo sulėtėjimo rizika, kurią dažnai lydi kompensacinis augimo „atsigriebimo“ fenomenas (angl. *catch-up growth*) per pirmuosius 2–3 metus. Vis dėlto jie dažniausiai pasiekia mažesnį galutinį ūgį nei laiku gimę bendraamžiai (21–23). Mažesnis gimimo svoris (GS) pailgina „atsigriebimo“ laikotarpį (21), o mažo pagal

gestacijos amžių (MGA) naujagimio būklė dar labiau padidina neigiamų perinatalinių padarinių riziką (24–26). Pažymėtina, kad užaugę ypač neišnešioti naujagimiai (<26 gestacijos savaičių) dažnai išlieka žemesni ir smulkesni, bet pasižymi didesniu kūno masės indeksu (KMI) (27). Nors mažesnis galutinis ūgis siejamas su mažesniu gestacijos amžiumi (GA) (28), kai kurie tyrimai rodo, kad suaugusieji, gimę ypač, labai ir vėlyvai neišnešioti, gali būti panašaus ūgio, brendimo laiko ir maksimalaus augimo greičio kaip laiku gimę bendraamžiai (29, 30).

Taigi, tyrimų rezultatai reikšmingai skiriasi vertinant amžių, kada neišnešioti vaikai „pasiveja“ savo bendraamžius, augimo tempą ir greitį, brendimo laiką bei su lytimi susijusius skirtumus (22, 31, 32). Neatitikimus lemia skirtingi neišnešiotų naujagimių klasifikavimo metodai (pvz., pagal GA ir (arba) GS), nevienoda tyrimų trukmė ir diskusijos dėl optimalių augimo kriterijų (33, 34). Dauguma atliktų tyrimų yra skerspjūvio pobūdžio, dažnai išskiria tik GA arba tik GS, todėl trūksta žinių apie jų bendrą poveikį augimui ir sveikatos būklei; ypač trūksta longitudinių tyrimų, apimančių visą augimo laikotarpį (35).

Vystymosi nulemtų sveikatos problemų priežasčių ir padarinių (angl. *developmental origins of health and disease*) koncepcija pabrėžia reikšmingą vaisiaus periodo poveikį sveikatai viso gyvenimo laikotarpiu (36). Gimę neišnešioti vaikai susiduria su didesne neurologinės raidos sutrikimų rizika, įskaitant cerebrinį paralyžių (37–41), autizmo spektro sutrikimus ir kognityvinius ar mokymosi sutrikimus (40–50), kurių sunkumas labai priklauso nuo GA (51). Jie yra jautresni ir kvėpavimo sutrikimams, tokiems kaip bronchopulmoninė displazija ir astma (52–63), taip pat virškinimo sutrikimams (59). Gimę neišnešioti suaugę asmenys dažniau serga širdies ir kraujagyslių ligomis, tokiomis kaip hipertenzija ir išeminė širdies liga (64, 65), taip pat endokrininės sistemos ir medžiagų apykaitos sutrikimais, tokiais kaip metabolinis sindromas ir hipotirozė (64, 66–71), patiria inkstų funkcijos sutrikimų (72–74). Nors sukaupta daug duomenų apie atskirų organų sistemų sutrikimus, ligų sąveika ir bendra neišnešiotų asmenų sergamumo našta nepakankamai ištirta. Be to, dauguma tyrėjų daugiausia dėmesio skiria ypač neišnešiotiems kūdikiams, o vėlyvai neišnešiotų ir suboptimalaus GS naujagimių grupės lieka nepakankamai ištirtos (75–81). Atliekant longitudinius tyrimus dažnai akcentuojami trumpalaikiai rezultatai (iki 7 metų) (40, 52, 56, 69, 70), dėl to trūksta žinių apie sveikatą paauglystėje ir suaugus (48, 82–86).

Siekiant užpildyti minėtas spragas, pagrindinis šio tyrimo tikslas buvo įvertinti Lietuvos naujagimių kūno dydį gimimo metu atsižvelgiant į GA ir lytį bei atlikti longitudinę Lietuvos neišnešiotų naujagimių fizinės būklės, augimo

dinamikos ir sveikatos rezultatų analizę. Ši daktaro disertacija parengta remiantis keturiais išspausdintais moksliniais straipsniais. **I straipsnyje** ištirtas Lietuvos naujagimių gimimo svorio ir ilgio pasiskirstymas bei variacija pagal gestacijos amžių ir lytį, sudarytos ir su tarptautiniais standartais palygintos populiacinės Lietuvos naujagimių gimimo svorio ir ilgio ribinės vertės bei kreivės. **II straipsnyje** analizuotas Lietuvos naujagimių galvos apimties pasiskirstymas ir variacija pagal gestacijos amžių ir lytį, sukurtos ir su pasauliniais standartais palygintos populiacinės Lietuvos naujagimių galvos apimties ribinės vertės ir kreivės. **III straipsnyje** vertinami Lietuvos neišnešiotų naujagimių longitudiniai augimo rezultatai, analizuojami augimo dėsningumai pagal GA ir GS. **IV straipsnyje** nagrinėjami daugiasistemiai Lietuvoje gimusių neišnešiotų asmenų sveikatos padariniai nuo kūdikystės iki paauglystės, daugiausia dėmesio skiriant gimimo veiksnių įtakai sveikatos būklės sudėtingumui ir įvairių sutrikimų tarpusavio ryšiams.

1.2. Tyrimo tikslas

Šio tyrimo tikslas – įvertinti Lietuvos naujagimių kūno dydį gimimo metu pagal gestacijos amžių ir lytį bei atlikti longitudinę prieš laiką gimusių vaikų fizinės būklės, augimo dinamikos ir sveikatos padarinių analizę, atsižvelgiant į gestacijos amžių ir gimimo svorį.

1.3. Tyrimo uždaviniai

1. Išanalizuoti Lietuvos naujagimių gimimo svorio ir ilgio pasiskirstymą ir variaciją pagal gestacijos amžių ir lytį, gautus duomenis palyginti su tarptautiniais standartais (**I straipsnis**).
2. Išanalizuoti Lietuvos naujagimių galvos apimties pasiskirstymą ir variaciją pagal gestacijos amžių ir lytį, gautus duomenis palyginti su tarptautiniais standartais (**II straipsnis**).
3. Įvertinti Lietuvos neišnešiotų naujagimių longitudinius augimo rezultatus nuo kūdikystės iki paauglystės, analizuojant augimo (svorio, ūgio, KMI) dėsningumus pagal gestacijos amžiaus ir gimimo svorio grupes (**III straipsnis**).
4. Ištirti daugiasistemes prieš laiką gimusių Lietuvos vaikų sveikatos pasekmes nuo kūdikystės iki paauglystės analizuojant gimimo veiksnių įtaką sveikatos būklės sudėtingumui ir įvairių sutrikimų tarpusavio ryšius (**IV straipsnis**).

1.4. Mokslinis naujumas

Iki šiol Lietuvos naujagimių gimimo svorio ir ilgio rodikliai buvo vertinami remiantis gestacijos amžiui ir lyčiai pritaikytomis procentilėmis, parengtomis pagal 164 662 naujagimių, gimusių 1998–2002 m. laikotarpiu, duomenis (20). Šiame tyrime minėti rodikliai buvo atnaujinti taikant pasaulyje pripažintus statistinius metodus (LMS), skirtus šiuolaikinėms, išlygintoms gimimo rodiklių procentilėms sudaryti (87).

Be to, tai yra pirmasis tyrimas, kuriame išsamiai įvertinta Lietuvos naujagimių galvos apimtis, atsižvelgiant į gestacijos amžių ir lytį, parengtos regioninės populiacijos pagrindu sudarytos Lietuvos naujagimių galvos apimties ribinės vertės.

Šiuo tyrimu pirmą kartą Lietuvoje apžvelgta neišnešiotų asmenų augimo ir sveikatos dinamika nuo kūdikystės iki paauglystės taikant pažangiausius longitudinio augimo tyrimo metodus (SITAR) (88). Tyrimas suteikia išsamią apžvalgą apie skirtingo gestacijos amžiaus ir gimimo svorio neišnešiotų vaikų augimo iššūkius ir išeitis bei užpildo mokslinių darbų, apsiribojančių trumpalaikiais efektais sveikatai, spragas.

Tyrimo rezultatai atskleidžia naujus gimimo veiksnių ir ilgalaikių daugiasistemių padarinių sveikatai tarpusavio ryšius, padedančius geriau suprasti bendrąją neišnešiotumo naštą ir suteikiančius vertingų įžvalgų klinikinei praktikai ir visuomenės sveikatos strategijų formavimui.

1.5. Praktinė tyrimo vertė

Šiame tyrime pristatomos atnaujintos gimimo svorio ir ilgio bei naujai sukurtos populiacinės Lietuvos naujagimių galvos apimties ribinės vertės ir kreivės, atsižvelgiant į gestacijos amžių ir lytį. Šios priemonės, geriau atspindėdamos vietinės populiacijos ypatumus, padeda tiksliau vertinti Lietuvos naujagimių kūno dydį, yra ypač svarbios diagnozuojant augimo sutrikimus ir priimant pagrįstus klinikinius sprendimus.

Išplėtus analizę nuo kūdikystės iki paauglystės, tyrimo rezultatai suteikia vertingų įžvalgų apie ilgalaikę prieš laiką gimusių asmenų augimo dinamiką ir daugiasistemius padarinius sveikatai. Tyrimas pabrėžia ankstyvo rizikos grupėms priklausančių asmenų nustatymo svarbą ir gimimo veiksnių įtaką augimo ir sveikatos būklės dinamikai. Šie rezultatai išryškina individualiai pritaikytos, daugiadalykės priežiūros svarbą ir siūlo praktines rekomendacijas, padedančias užtikrinti efektyvesnę ilgalaikę prieš laiką gimusių asmenų sveikatos priežiūrą.

1.6. Ginamieji teiginiai

1. Gestacijos amžiui ir lyčiai pritaikytos populiacijos pagrindu sudarytos gimimo svorio ir ilgio ribinės vertės tiksliau nei pasauliniai standartai atspindi Lietuvos naujagimių kūno dydį ir sveikatos būklę (**I straipsnis**).
2. Gestacijos amžiui ir lyčiai pritaikytos populiacijos pagrindu sudarytos naujagimių galvos apimties ribinės vertės tiksliau negu pasauliniai standartai atspindi Lietuvos naujagimių specifines galvos apimties ypatybes (**II straipsnis**).
3. Gimimo veiksniai daro reikšmingą poveikį Lietuvos neišnešiotų naujagimių augimo dinamikai (**III straipsnis**).
4. Lietuvoje gimusieji prieš laiką susiduria su sudėtingomis ilgalaikėmis sveikatos problemomis, kurios turi įtakos įvairioms organų sistemoms ir priklauso nuo gimimo veiksnių (**IV straipsnis**).

2. TYRIMO PLANAS IR METODAI

2.1. Leidimas atlikti mokslinį darbą

Tyrimui pritarė Lietuvos bioetikos komitetas (leidimas Nr. 57, paskutinis leidimo papildymas 2017 02 06). Tyrimas atliktas remiantis Helsinkio deklaracijos nuostatomis.

2.2. Tyrimo plano apžvalga

Šis tyrimas susideda iš dviejų viena kitą papildančių dalių: (1) Lietuvos naujagimių antropometrinių rodiklių populiacinio skerspjūvio tyrimo ir (2) retrospektyvinio longitudinio prieš laiką gimusių asmenų augimo bei sveikatos būklės tyrimo nuo kūdikystės iki paauglystės. Tiriant skerspjūvį ištirtas Lietuvos naujagimių gimimo svorio, ilgio ir galvos apimties pasiskirstymas ir kitimas pagal gestacijos amžių ir lytį, sudarytos ir su tarptautiniais standartais palygintos populiacinės Lietuvos naujagimių gimimo svorio, ilgio ir galvos apimties ribinės vertės ir kreivės. Retrospektyvinio longitudinio tyrimo metu stebėtas ir analizuotas prieš laiką gimusių asmenų augimas ir sveikatos būklė nuo gimimo iki paauglystės siekiant įvertinti ilgalaikę gimimo veiksnių įtaką.

2.3. Lietuvos naujagimių galvos apimties, svorio ir ilgio pagal gestacijos amžių ir lytį populiacinis skerspjūvio tyrimas

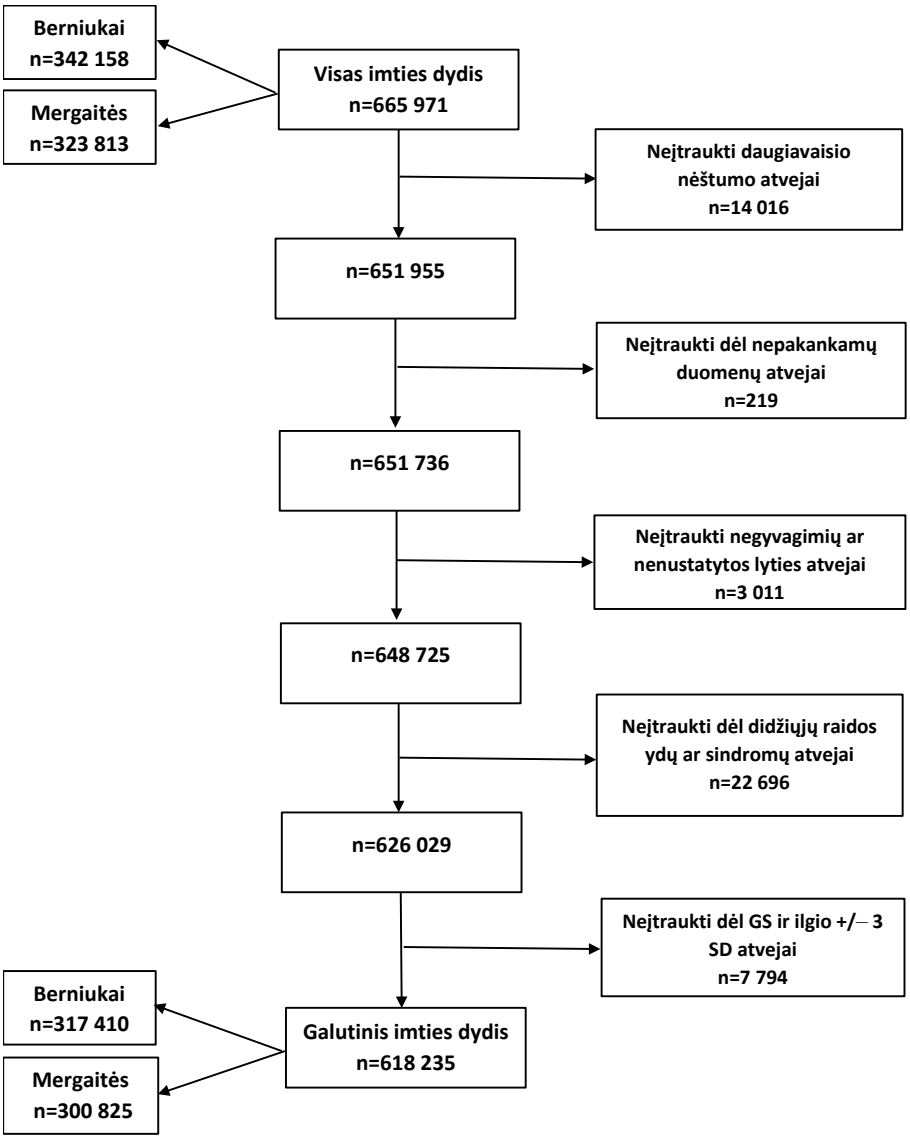
2.3.1. Tyrimo planas ir kohortos atranka

Šioje tyrimo dalyje buvo nagrinėjami anoniminiai Lietuvos gimimų medicininių duomenų registro duomenys, pateikti Higienos instituto Sveikatos informacijos centro Vilniuje, Lietuvoje.

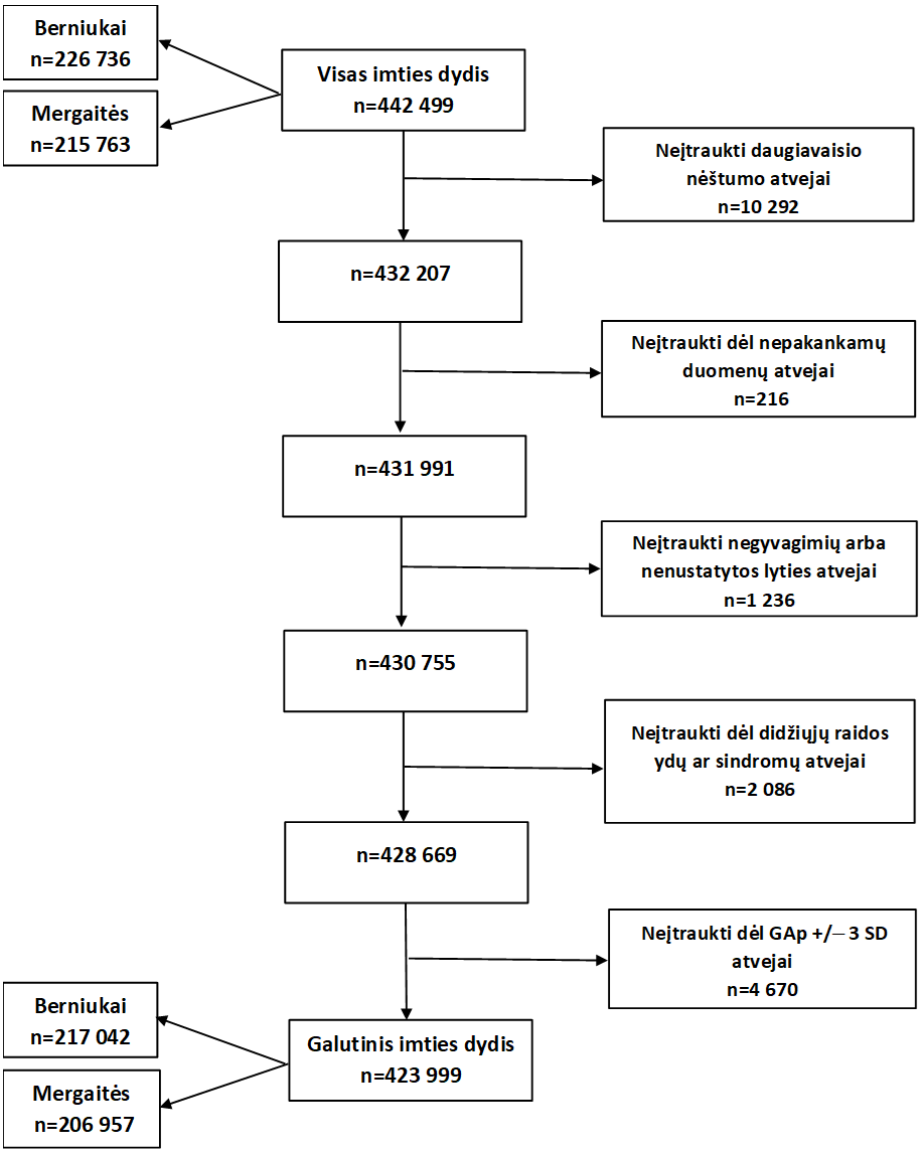
Gimimo svorio (GS) ir ilgio duomenys analizuoti remiantis 1995–2015 m. laikotarpio įrašais, apimančiais gyvus vienvaisius naujagimius nuo 22 iki 42 pilnų gestacijos savaičių. Naujagimių galvos apimties (GAp) analizė pagrįsta duomenimis, registruotais 2001–2015 m., nes GAp matavimai į Lietuvos gimimų įrašus buvo įtraukti tik nuo 2001 m. Į šį duomenų rinkinį buvo įtraukti visi gyvi vienvaisiai naujagimiai nuo 24 iki 42 pilnų gestacijos savaičių. Gestacijos amžiaus (GA) intervalai buvo parinkti taip, kad atitiktų IG-21 pasauliniuose standartuose taikomus intervalus tolesnei lyginamajai analizei atlikti.

Į abu duomenų rinkinius nebuvo įtraukti daugiavaisių gimimų duomenys, negyvagimiai, nenustatytos lyties naujagimiai, turintys didžiųjų raidos ydų, sindromų ar neišsamius duomenis (dėl lyties, GA, GS, ilgio arba GAp) atvejai. Iš analizuotų duomenų taip pat pašalinti atvejai, kai pagrindiniai antropometriniai rodikliai (svoris, ilgis arba GAp) buvo didesni nei ±3 standartiniai nuokrypiai (SN) nuo vidurkio (M), remiantis PSO standartais (113).

Galutinę GS ir ilgio analizės imtį sudarė 618 235 naujagimiai ir 423 999 GAp analizei atlikti atrinkti naujagimiai. Išsamios imčių atrankos procedūros ir atmetimo kriterijai GS ir ilgio bei GAp tyrimams pavaizduoti srauto diagramose **1–2 paveiksluose**.



1 pav. Imties sudarymo procedūrą ir neįtraukimo į tyrimą kriterijus atspindinti srauto diagrama. GS – gimimo svoris, n – skaičius, SD – standartinis nuokrypis



2 pav. Imties sudarymo procedūrą ir neįtraukimo į tyrimą kriterijus atspindinti srauto diagrama. GAp – galvos apimtis, n – skaičius, SD – standartinis nuokrypis

2.3.2. Augimo rodiklių procentilių apskaičiavimas LMST metodu

LMS (*Lambda-Mu-Sigma*) metodas leidžia apskaičiuoti augimo rodiklių procentiles koreguojant duomenų pasiskirstymo asimetriją ir taikant laipsninę transformaciją (87). Išplėstinis LMST (*Lambda-Mu-Sigma-Tau*)

metodas (114) sprendžia ir asimetrijos, ir didesnio eksceso problemą per *Box-Cox t* (BCT) pasiskirstymą. Taikant standartinį LMS metodą neatsižvelgiama į didesnį eksceso koeficientą nei yra normaliojo skirstinio atveju. BCT pasiskirstymui taikoma laipsninė transformacija Y^{ν} siekiant normalizuoti duomenis, o transformuotos vertės atitinka nupjautąjį t pasiskirstymą, apibrėžtą laisvės laipsniais (τ). Šį pasiskirstymą apibūdina keturi parametrai: μ (mediana), σ (skalė, arba kintamumas), ν (asimetrija) ir τ (ekscesas). Jie visi kartu nusako duomenų centro padėtį, sklaidą, simetriškumą ir skirstinio uodegų sunkumą.

Statistinė analizė atlikta naudojant SPSS 22.0, EXCEL ir R programinę įrangą. Siekiant apskaičiuoti išlygintas gimimo svorio (GS), ilgio ir galvos apimties (GAp) ribinių verčių procentiles ir kreives buvo taikomi postūmio, mastelio ir formos parametrų apibendrintieji adityvieji modeliai (angl. *Generalized Additive Models for Location, Scale and Shape*, GAMLSS). Šiems skaičiavimams atlikti taikytas LMST metodas (BCT pasiskirstymas) siekiant modeliuoti asimetriją ir kurtozę (87, 114). Kiekvienam matavimo rodikliui ir lyčiai buvo pritaikyti atskiri modeliai. Aprašomoji statistika ir procentilės (3-ioji, 10-oji, 25-oji, 50-oji, 75-oji, 90-oji ir 97-oji) buvo apskaičiuotos pagal GA ir lytį. Duomenų analizė atlikta R programa (4.0.3 versija) naudojant GAMLSS paketą (4.3–3 versija) (www.r-project.org) (115).

Lyginamajai analizei IG-21 procentilės pateiktos abiem lytims atskirai kiekvienai gestacijos savaitei ir dienai (pvz., 30+0, 30+1), o šiame tyrime GA buvo užfiksuotas kaip visos gestacijos savaitės (pvz., 30, 31). Siekiant suderinti su IG-21 standartų duomenimis, vidutinės GAp, GS ir ilgio vertės kiekvienai visai gestacijos savaitei šiame tyrime buvo palygintos su IG-21 atitinkamos savaitės vidurio diena (pvz., 30+3). Šios suderinimo procedūros patikimumas buvo patikrintas matematiškai. Vidurkių skirtumai buvo įvertinti naudojant t testą, o skirtumai laikyti statistiškai reikšmingais, kai p reikšmė buvo <0,05.

Pagrindinės GS ir ilgio (3-ioji, 10-oji, 50-oji, 90-oji ir 97-oji) ir GAp (3-ioji, 50-oji ir 97-oji) procentilės buvo lyginamos su atitinkamomis IG-21 standartų reikšmėmis (16, 18). Buvo apskaičiuotas GAp variacijos koeficientas (VK), kuris buvo taikomas lyginamojoje analizėje kartu su užsienio tyrimais (116). Taip pat, remiantis IG-21 standartais, buvo apskaičiuoti GS, ilgio ir GAp standartiniai įverčiai (angl. *Z-score*) (16, 18). Pagal GS buvo nustatyta ir palyginta naujagimių, priskiriamų mažiems pagal gestacijos amžių (MGA, GS <10-osios procentilės), ir dideliems pagal gestacijos amžių (DGA, GS >90-osios procentilės), dažnis ir procentinė dalis naudojant tiek šio tyrimo, tiek IG-21 standartų ribines reikšmes.

2.4. Retrospektyvinis longitudinis prieš laiką gimusių asmenų Lietuvoje tyrimas

2.4.1. Tyrimo planas ir kohortos atranka

Disertacijos longitudinės dalies duomenys buvo retrospektyviai renkami iš popierinių medicininių sveikatos kortelių dviejuose didžiuosiuose Vilniaus pirminės sveikatos priežiūros centruose ir jų filialuose. Į tyrimą buvo įtraukti 467 prieš laiką gimę asmenys (GA: 22–36 savaitės; 238 mergaitės, 229 berniukai; 384 vienvaisiai, 86 dvyniai), neturintys didžiųjų raidos ydų ar sindromų, gimę 2000–2015 m. Išsamūs sveikatos duomenys, apimantys su gimimu susijusius kintamuosius, tokius kaip GA, GS ir lytis, buvo fiksuojami nuo gimimo iki paauglystės.

Kaip kontrolinė grupė longitudiniam augimo modeliui palyginti buvo naudojami laiku gimusių asmenų (GA 37–42 savaitės) duomenys, sukaupti Vilniaus universiteto Medicinos fakulteto Anatomijos, histologijos ir antropologijos katedroje. Šie asmenys gimė 1996 m. Ir nors neišnešiotų (2000–2015 m.) ir išnešiotų (1996 m.) vaikų kohortos gimė skirtingais metais, abi paauglystę pasiekė panašiomis aplinkos, socialinėmis ir mitybos sąlygomis. Augimo duomenys buvo renkami toje pačioje geografinėje vietovėje ir sveikatos priežiūros sistemoje, taip sumažinant sisteminių veiksnių įtaką. Antropometriniai matavimai, tokie kaip ūgis (arba ilgis iki 2 metų) ir svoris, buvo renkami ilguoju laikotarpiu, leidžiant apskaičiuoti kūno masės indeksą (KMI). Į tyrimo analizę buvo įtraukti visi asmenys, turintys bent vieną matavimo įrašą.

Duomenys apie GS ir ūgį (arba ilgį iki 2 metų) buvo renkami nuo gimimo iki 18 metų, tačiau tolesnei analizei pasirinktas laikotarpis iki 12 metų dėl nepakankamo matavimų skaičiaus vyresnio amžiaus grupėse. Pirmaisiais metais duomenys buvo renkami kas mėnesį, antraisiais ir trečiaisiais – tris kartus per metus, vėliau – du kartus per metus. Iš viso buvo užregistruoti 16 159 matavimai, kurių mediana – 17 matavimų vienam vaikui, o tarpkvartilinis intervalas (TKI) buvo 13–21.

Svorio, ūgio ir KMI augimo modeliai buvo analizuojami trijose GS grupėse (mažo, mažo–normalaus, normalaus GS) ir trijose GA grupėse (ypač ir labai neišnešiotų (NN), vėlyvai neišnešiotų (NN), išnešiotų naujagimių). Asmenų pasiskirstymas šiose grupėse pagal lytį pateikiamas **1 lentelėje**.

1 lentelė. Vaikų pasiskirstymas pagal gestacijos amžiaus ir gimimo svorio grupes bei lytį

Lytis	**Gimimo svoris** / **Gestacijos amžius**	**Mažas** (<2 500 g)	**Mažas–normalus** (2 500 – <3 000 g)	**Normalus** (3000 – <4 000 g)	**Iš viso**
Berniukai	Ypač ir labai neišnešioti (<34 savaičių)	67	1	0	**68**
	Vėlyvojo neišnešiotumo (34 –<37 savaitės)	67	70	24	**161**
	Išnešioti (37–<42 savaitės)	2	12	226	**240**
	Iš viso (berniukai)	**136**	**83**	**250**	**469**
Mergaitės	Ypač ir labai neišnešioti (<34 savaičių)	75	3	0	**78**
	Vėlyvojo neišnešiotumo (34–<37 savaitės)	71	68	21	**160**
	Išnešioti (37–<42 savaitės)	5	33	205	**243**
	Iš viso (mergaitės)	**151**	**104**	**226**	**481**
Iš viso	Ypač ir labai neišnešioti (<34 savaičių)	142	4	0	**146**
	Vėlyvojo neišnešiotumo (34–<37 savaitės)	138	138	45	**321**
	Išnešioti (37–<42 savaitės)	7	45	431	**483**
	Iš viso	**287**	**187**	**476**	**950**

Siekiant išanalizuoti daugiasistemius padarinius sveikatai, buvo įtraukta 1818 pirmą kartą dokumentuotų diagnozių, nustatytų prieš laiką gimusiems asmenims pagal Tarptautinės statistinės ligų ir sveikatos sutrikimų klasifikacijos 10-ąjį pataisytą ir papildytą leidimą (TLK-10) (117) nuo gimimo iki tyrimo atlikimo momento. Siekiant pabrėžti ligos atsiradimo laiką kiekviename TLK-10 ligų skyriuje, atsinaujinusios ar pakartotinai diagnozuotos ligos nebuvo įtrauktos. Į analizę įtraukti ligų skyriai išsamiai aprašyti **IV straipsnio** 1 papildomoje lentelėje.

Longitudinė prieš laiką gimusių asmenų sveikatos būklės sudėtingumo analizė buvo atlikta pagal šias gimimo svorio (GS) grupes: ypač ir labai mažas (<1 000–1 500 g), mažas [1 500–2 500 g), suboptimalus [2 500–3 000 g), normalus [3 000–4 000 g). Gestacijos amžiaus (GA) grupės buvo apibrėžtos taip: ypač ir labai neišnešiotas – (22–32) savaitės, vidutinio neišnešiotumo – [32–34) savaitės ir vėlyvojo neišnešiotumo – [34–37) savaitės.

Statistinei analizei atlikti ligos suskirstytos pagal TLK-10 ligų skyrius, o amžiaus intervalai buvo suskirstyti į [0–3], (3–7], (7–12], (12–18]

ir [0–18] metų. Lenkti skliaustai nurodo, kad intervalo krašto taškas nėra įtrauktas, o laužtiniai skliaustai reiškia, kad taškas yra įtrauktas į intervalą.

2.4.2. SITAR modelis prieš laiką Lietuvoje gimusių vaikų longitudinei augimo (svorio, ūgio, KMI) analizei atlikti

SITAR modelis (angl. *SuperImposition by Translation And Rotation*) (88) buvo taikytas modeliuoti vidutines ūgio, svorio ir KMI kreives nuo gimimo iki 12-os metų gestacijos amžiaus ir gimimo svorio grupėms atskirai berniukams ir mergaitėms. SITAR yra mišriųjų efektų modelis, kuris apibūdinamas kubinio splaino vidurkio kreive ir trimis individualiaisiais atsitiktiniais efektais (dydžiu (angl. *size*), laiku (angl. *timing*), intensyvumu (angl. *intensity*), kurie koreguoja vidurkio kreivę aprašant individų charakteristikų kreives (88, 118, 119). Tai formos nekeičiantis modelis, todėl šiuo modelio atveju tariama, kad individų augimo kreivės yra tos pačios formos trijų transformacijų atžvilgiu: 1) kreivės pastūmimas aukštyn / žemyn (dydžio parametras), 2) kreivės paslinkimas į kairę / dešinę (laiko arba tempo parametras), 3) ištempimas / suspaudimas laiko atžvilgiu (intensyvumo parametras). Kovariančių įtaka SITAR modelyje aprašoma įtraukiant fiksuotuosius efektus, t. y. į modelį galima įtraukti fiksuotuosius efektus kiekvienam SITAR parametrui (119, 120).

Analizėje naudotas koreguotas postnatalinis amžius, apskaičiuotas pagal formulę: koreguotas postnatalinis amžius = chronologinis amžius (metais) + (gestacijos savaitės – 40) * 7 / 365,25. Korekcija buvo taikoma visų gestacijų vaikams, taip pat ir gimusiems laiku, visame amžiaus intervale. Toks sprendimas padeda išvengti modeliavimo sunkumų, atsirandančių, kai korekcija taikoma tik iki vienerių ar dvejų metų. Siekiant išvengti neigiamų amžiaus reikšmių, devyni mėnesiai (t. y. 3/4 metų) buvo pridėti prie koreguoto postnatalinio amžiaus gaunant postkoncepcinio amžiaus skalę.

Stebėjimai, kurių standartizuotos paklaidos absoliutiniu didumu viršijo 4, buvo laikyti išskirtimis ir pašalinti iš analizės. Laisvės laipsnių skaičius, apibūdinantis kubinio splaino glodumą, buvo parenkamas atsižvelgiant į Bajeso informacijos kriterijaus (angl. *Bayesian Information Criterion*, BIC) reikšmę. Nagrinėti modeliai su pradinėmis ir logaritmuotomis kintamųjų reikšmėmis. Nustatyta, kad logaritminė amžiaus transformacija pagerino modelį. Jeigu modelis nekonvergavo, buvo parenkamas redukuotas modelis, atsisakant dalies fiksuotųjų ir (arba) atsitiktinių efektų. Nustatyta, kad geriausiai tiko modeliai be laiko atsitiktinio efekto.

Dėl lytinių skirtumų augimo modeliuose, ypač brendimo laikotarpiu, berniukams ir mergaitėms buvo parenkami atskiri SITAR modeliai. Iš pradžių

į modelius buvo įtrauktos dvi kovariantės (gestacijos grupė ir gimimo amžiaus grupė), tačiau, siekiant išvengti kolinearumo ir įvertinti jų savarankišką etiologinį poveikį, buvo parenkami modeliai atskirai berniukams ir mergaitėms įtraukiant tik vieną kovariantę. Tuklumo grąžos laikas buvo nustatytas kaip amžius, kai KMI pasiekė mažiausią tašką modeliuotose vidutinio KMI kreivėse.

Analizė atlikta R programa (versija 4.4.1), taikant SITAR paketą (versija 1.4.0) (121). Paketas ggplot2 (3.5.1 versija) buvo taikomas duomenims vizualizuoti.

2.4.3. Prieš laiką Lietuvoje gimusių vaikų longitudinių sveikatos padarinių statistinė analizė

Šios statistinės analizės tikslas buvo ištirti sergamumo dažnį ir pasiskirstymą tarp skirtingų prieš laiką gimusių vaikų pogrupių nuo gimimo iki paauglystės, įvertinti gimimo veiksnių poveikį vieno vaiko vidutiniam ligų ir TLK-10 ligų skyrių skaičiui ir išanalizuoti sveikatos būklės sudėtingumą ir sąsajas tarp TLK-10 ligų skyrių.

Apibūdinant vaikų pasiskirstymą GA ir GS grupėse, duomenys buvo susisteminti taikant dažnius ir procentus (2 papildoma lentelė, **IV straipsnis**). Visų ligų dažniai ir procentai buvo apskaičiuoti amžiaus intervalams atskirose GA ir GS grupėse. Be to, diagnozės buvo suskirstytos į kategorijas pagal TLK-10 ligų skyrius, kad būtų galima analizuoti sergamumo struktūrą ir pasiskirstymą skirtingose prieš laiką gimusių vaikų grupėse. GA ir GS grupių lyginamoji analizė atlikta taikant Fišerio tikslųjį testą, o bendrosios Lietuvos vaikų populiacijos sergamumo rodikliai apskaičiuoti remiantis oficialiomis sveikatos statistikos duomenų bazėmis (122, 123).

Vidutiniam vieno vaiko ligų ir TLK-10 ligų skyrių skaičiui modeliuoti buvo taikomi Puasono ir neigiamos binominės regresijos modeliai su logaritmine ryšio funkcija (124). Dėl mažo vieno vaiko ligų skaičiaus trumpesniuose amžiaus intervaluose modeliavimas atliktas visu [0, 18] metų amžiaus laikotarpiu. Lytis, GA ir GS grupės regresijos modeliuose buvo įtrauktos kaip kovariantės, atsižvelgiant į trukdančius veiksnius, kad būtų nustatyti reikšmingi sergamumo prognozės veiksniai. Dėl didesnės negu vidurkis dispersijos nebuvo tenkinama Puasono regresijos prielaida, todėl galutiniu modeliu pasirinkta neigiama binominė regresija.

Rezultatai pateikti kaip paplitimo koeficientai (PK) (angl. *Incidence Rate Ratios*, IRRs), apskaičiuoti iš į eksponentę pakeltų regresijos koeficientų. PK rodo, kiek kartų (arba procentinių punktų) pakinta vidutinis ligų skaičius, kai vienetu padidėja skaitinio kintamojo reikšmė, o kategorinių kintamųjų

atveju lyginant konkrečią kintamojo reikšmę su lyginamąja reikšme (125). Pavyzdžiui, PK lyties atžvilgiu (lyginamoji kategorija – mergaitės) rodo vidutinį berniukų ligų skaičiaus padidėjimą kartais, palyginti su mergaitėmis.

Šilumos žemėlapiai (angl. *heat map*) buvo naudojami pavaizduoti skirtingų ligų ir TLK-10 ligų skyrių skaičių turinčių asmenų procentines dalis pagal GA ir GS grupes. Fišerio tikslusis testas taikytas grupėms palyginti, o vizualizacijos sukurtos naudojant R programos paketą „ggplot2“.

Analizuojant TLK-10 ligų skyrių sąsajas taikytas *UpSet* grafikas, išryškinantis komorbidiškumo dėsningumus. Šiuo vizualizavimo metodu analizuojamos duomenų reikšmių aibės ir jų sankirtos (126). Vizualizacija sukurta naudojant R programos paketą „UpSetR“ (127), į kurį dėl aiškumo įtrauktos tik tos sankirtos, kurių dažniai didesni už vienetą.

3. REZULTATAI

3.1. Gestacijos amžiui ir lyčiai pritaikytos populiacijos pagrindu sudarytos Lietuvos naujagimių gimimo svorio ir ilgio ribinės vertės

3.1.1. Gimimo svoris ir ilgis pagal gestacijos amžių ir lytį

Tyrimo imties dydis (**2 lentelė**) reikšmingai augo kartu su GA, svyruodamas nuo mažiau nei 50 naujagimių 22–24 savaičių laikotarpiu iki daugiau kaip 140 000 laiku gimusių abiejų lyčių kūdikių. Neišnešiotų berniukų vidutinis gimimo svoris (GS) buvo maždaug 50–100 g didesnis nei mergaičių ir 100–180 g didesnis už laiku gimusių bei po termino gimusių naujagimių grupėse. Panašiai vidutinio gimimo ilgio skirtumas tarp lyčių svyravo nuo 0,1 iki 0,6 cm neišnešiotumo laikotarpiu ir padidėjo iki 0,6–0,8 cm vėlesnėmis gestacijos savaitėmis (**2 lentelė**).

2 lentelė. Lietuvos naujagimių gimimo svoris (GS) (g) ir ilgis (cm) pagal lytį ir gestacijos amžių (GA) savaitėmis. n – stebėtųjų skaičius, M – vidurkis, SN – standartinis nuokrypis

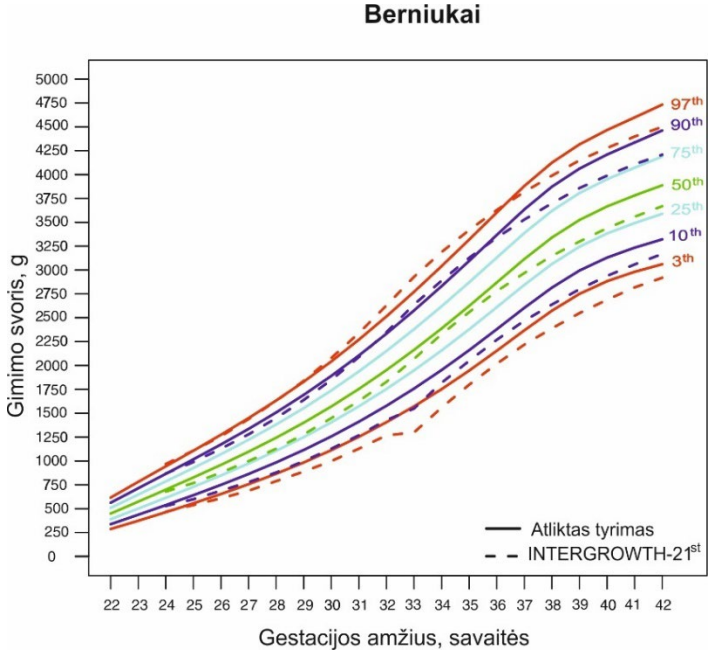
BERNIUKAI (n = 317 410)					**GA (sav.)**	**MERGAITĖS (n = 300 825)**				
Stebėtų skaičius (n)	**Svoris (g)**		**Ilgis (cm)**			**Stebėtų skaičius (n)**	**Svoris (g)**		**Ilgis (cm)**	
	M	**SD**	**M**	**SD**			**M**	**SD**	**M**	**SD**
1*	915,0	-	37,0	-	**22**	8	635,3	111,0	29,0	3,2
12	706,9	115,0	31,8	2,2	**23**	13	649,9	83,2	30,9	1,9
38	773,0	109,0	33,2	3,0	**24**	46	71,.0	96,3	33,0	2,6
93	849,3	121,6	33,7	2,8	**25**	82	798,0	105,5	33,6	2,2
136	966,9	144,7	35,4	2,4	**26**	139	892,4	157,3	34,7	2,8
196	1 106,9	181,0	37,0	2,8	**27**	174	1 028,6	187,9	36,3	3,3
304	1 229,3	193,9	38,1	2,9	**28**	239	1 181,3	237,4	37,9	3,0
291	1 375,5	235,2	39,8	2,9	**29**	255	1 314,2	236,0	39,2	3,1
445	1 542,7	243,4	41,4	2,8	**30**	405	1 485,8	253,2	40,9	3,1
488	1 756,5	263,3	42,9	2,9	**31**	431	1 662,7	298,7	42,3	3,0
849	1 946,9	288,2	44,3	2,6	**32**	720	1 886,5	309,4	44,0	2,8
1 116	2 152,2	326,1	45,6	2,6	**33**	909	2 061,3	325,4	45,0	2,7
1 877	2 381,1	351,6	46,8	2,5	**34**	1 609	2 289,8	355,2	46,3	2,5
2 858	2 585,0	354,1	47,8	2,3	**35**	2 421	2 482,8	355,9	47,4	2,3
5 592	2 772,3	368,8	48,9	2,3	**36**	4 967	2 679,1	360,8	48,5	2,2
13 141	3 124,5	404,4	50,7	2,2	**37**	11 219	3 009,5	393,0	50,1	2,1

BERNIUKAI (n = 317 410)					GA (sav.)	MERGAITĖS (n = 300 825)				
Stebėtų skaičius (n)	Svoris (g)		Ilgis (cm)			Stebėtų skaičius (n)	Svoris (g)		Ilgis (cm)	
	M	SD	M	SD			M	SD	M	SD
33 850	3 363,7	417,5	51,7	2,1	**38**	29 873	3 224,0	407,3	51,1	2,1
68 016	3 540,8	413,1	52,5	2,1	**39**	63 919	3 397,1	405,0	51,8	2,1
144 625	3 670,0	421,4	53,0	2,1	**40**	141 902	3 519,9	405,9	52,3	2,1
40 947	3 773,0	425,0	53,5	2,2	**41**	39 209	3 609,1	415,1	52,7	2,1
2 535	3 774,2	492,0	53,4	2,4	**42**	2 285	3 594,3	449,3	52,6	2,3

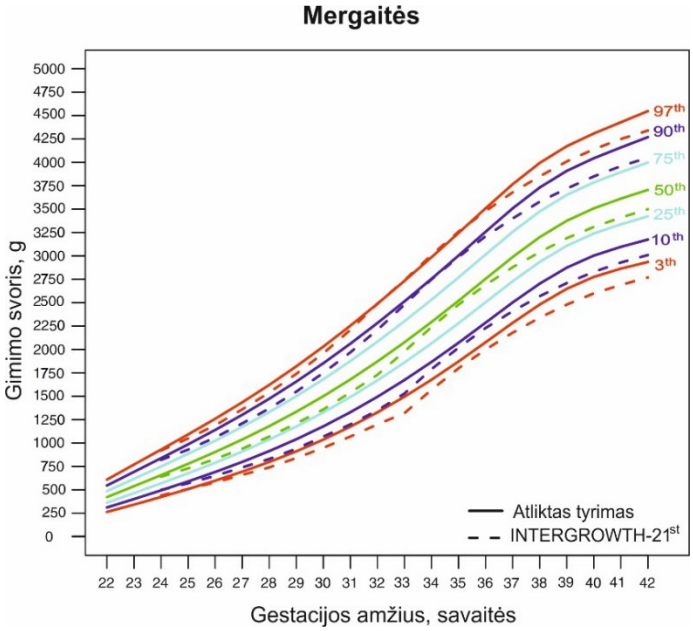
* Tikras atvejis, kuris neviršija kritinio gimimo svorio / ilgio nuokrypio

4.1.2. Išlygintos gestacijos amžiui ir lyčiai pritaikytos Lietuvos naujagimių GS ir ilgio procentilių kreivės

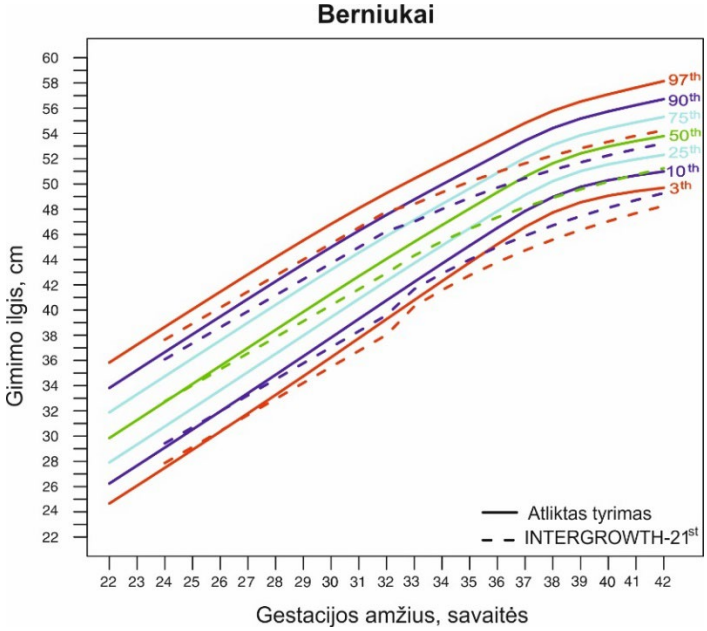
Išlygintos 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios gestacijos amžiui ir lyčiai pritaikytos Lietuvos naujagimių GS ir ilgio procentilių kreivės pateiktos **3–6 paveiksluose**. GS variacija didėjo didėjant gestacijos amžiui abiejų lyčių grupėse. Priešingai, gimimo ilgio variacija mažėjo kartu su augančiu gestacijos amžiumi, išryškėjo neigiama pasiskirstymo asimetrija (**3-6 pav.**).



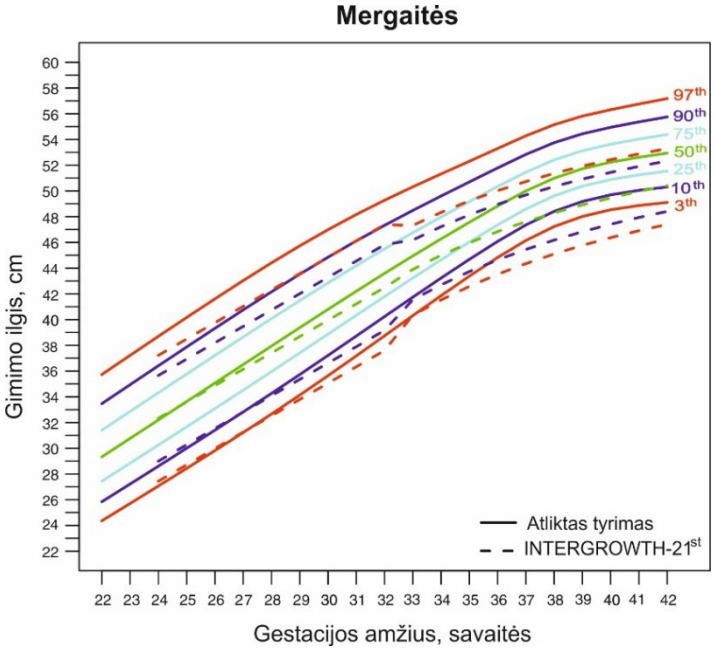
3 pav. Lietuvos berniukų gimimo svorio (g) 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios išlygintos procentilių kreivės ir 3-ioji, 10-oji, 50-oji, 90-oji ir 97-oji INTERGROWTH-21 standarto procentilės



4 pav. Lietuvos mergaičių gimimo svorio (g) 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios išlygintos procentilių kreivės ir 3-ioji, 10-oji, 50-oji, 90-oji ir 97-oji INTERGROWTH-21 standarto procentilės



5 pav. Lietuvos berniukų gimimo ilgio (cm) 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios išlygintos procentilių kreivės ir 3-ioji, 10-oji, 50-oji, 90-oji ir 97-oji INTERGROWTH-21 standarto procentilės



6 pav. Lietuvos mergaičių gimimo ilgio (cm) 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios išlygintos procentilių kreivės ir 3-ioji, 10-oji, 50-oji, 90-oji ir 97-oji INTERGROWTH-21 standarto procentilės

3 ir 4 lentelėse pateikiamos išlygintos gestacijos amžiui ir lyčiai pritaikytų procentilių reikšmės (3–97-oji procentilės) Lietuvos naujagimių GS ir ilgiui. GS ir ilgio LMS parametrai pagal gestacijos amžių ir lytį pateikti atitinkamai **I straipsnio** 1 ir 2 papildomose lentelėse.

3 lentelė. Lietuvos naujagimių gimimo svorio (g) išlygintos procentilės pagal lytį ir gestacijos amžių (GA)

BERNIUKAI							GA (savaitės)	MERGAITĖS						
Gimimo svorio procentilės								Gimimo svorio procentilės						
3	10	25	50	75	90	97		3	10	25	50	75	90	97
288	339	391	450	510	564	618	**22**	264	312	363	422	486	546	610
375	438	503	575	649	716	783	**23**	342	402	465	539	618	693	770
465	539	615	701	788	867	946	**24**	424	494	569	657	750	838	930
558	643	730	829	928	1 019	1 109	**25**	509	590	677	778	885	987	1 092
655	751	850	960	1 073	1 174	1 276	**26**	598	691	789	904	1 025	1 140	1 259
758	865	975	1 098	1 223	1 337	1 450	**27**	694	798	909	1 038	1 173	1 302	1 435
867	986	1 108	1 245	1 383	1 509	1 634	**28**	798	914	1 038	1 181	1 331	1 474	1 622
985	1 117	1 251	1 402	1 555	1 694	1 832	**29**	912	1 041	1 177	1 335	1 501	1 657	1 820
1 114	1 258	1 406	1 572	1 740	1 892	2 044	**30**	1 037	1 179	1 328	1 501	1 682	1 854	2 031
1 254	1 412	1 574	1 756	1 939	2 106	2 272	**31**	1 176	1 330	1 492	1 680	1 877	2 062	2 254
1 407	1 579	1 755	1 953	2 153	2 335	2 515	**32**	1 328	1 495	1 670	1 872	2 084	2 283	2 489
1 573	1 759	1 950	2 165	2 381	2 578	2 773	**33**	1 496	1 674	1 861	2 077	2 303	2 515	2 733
1 753	1 954	2 159	2 389	2 621	2 832	3 042	**34**	1 677	1 867	2 066	2 294	2 532	2 756	2 986
1 948	2 162	2 380	2 625	2 873	3 097	3 320	**35**	1 872	2 072	2 281	2 521	2 771	3 005	3 246
2 156	2 381	2 612	2 871	3 132	3 369	3 604	**36**	2 077	2 287	2 505	2 756	3 016	3 259	3 509
2 370	2 605	2 846	3 116	3 389	3 636	3 882	**37**	2 285	2 503	2 729	2 989	3 257	3 509	3 766
2 575	2 817	3 064	3 341	3 621	3 874	4 126	**38**	2 481	2 704	2 936	3 201	3 476	3 732	3 994
2 752	2 996	3 246	3 526	3 808	4 064	4 318	**39**	2 649	2 875	3 109	3 376	3 652	3 909	4 173
2 884	3 132	3 385	3 668	3 953	4 211	4 468	**40**	2 776	3 004	3 240	3 509	3 786	4 044	4 309
2 983	3 236	3 494	3 783	4 074	4 338	4 600	**41**	2 865	3 097	3 338	3 612	3 896	4 159	4 429
3 062	3 323	3 590	3 889	4 190	4 463	4 734	**42**	2 935	3 175	3 423	3 706	3 998	4 270	4 548

4 lentelė. Lietuvos naujagimių gimimo ilgio (cm) išlygintos procentilės pagal lytį ir gestacijos amžių (GA)

BERNIUKAI							GA (savaitės)	MERGAITĖS						
Gimimo ilgio procentilės								Gimimo ilgio procentilės						
3	10	25	50	75	90	97		3	10	25	50	75	90	97
24,7	26,2	27,9	29,8	31,9	33,8	35,8	**22**	24,4	25,8	27,4	29,3	31,4	33,5	35,7
26,1	27,7	29,3	31,3	33,3	35,2	37,3	**23**	25,7	27,2	28,8	30,8	32,9	34,9	37,2
27,5	29,1	30,8	32,7	34,7	36,7	38,7	**24**	27,1	28,6	30,2	32,2	34,3	36,4	38,7
28,9	30,5	32,2	34,1	36,2	38,1	40,1	**25**	28,4	30,0	31,7	33,6	35,8	37,9	40,2
30,4	32,0	33,6	35,6	37,6	39,5	41,4	**26**	29,8	31,4	33,1	35,1	37,2	39,3	41,6
31,8	33,4	35,1	37,0	39,0	40,9	42,8	**27**	31,2	32,8	34,5	36,5	38,7	40,8	43,0
33,3	34,9	36,5	38,4	40,4	42,3	44,2	**28**	32,7	34,3	36,0	37,9	40,1	42,2	44,4
34,8	36,3	38,0	39,9	41,8	43,6	45,5	**29**	34,1	35,7	37,4	39,4	41,5	43,5	45,7
36,3	37,8	39,4	41,3	43,2	45,0	46,8	**30**	35,6	37,2	38,9	40,8	42,9	44,8	47,0
37,8	39,3	40,9	42,7	44,5	46,3	48,1	**31**	37,2	38,7	40,3	42,2	44,2	46,1	48,2
39,3	40,8	42,3	44,1	45,9	47,5	49,3	**32**	38,7	40,2	41,8	43,6	45,5	47,3	49,3
40,8	42,2	43,7	45,4	47,1	48,8	50,4	**33**	40,3	41,7	43,2	44,9	46,8	48,5	50,3
42,3	43,7	45,1	46,7	48,4	50,0	51,5	**34**	41,9	43,2	44,6	46,3	48,0	49,6	51,3
43,8	45,1	46,5	48,0	49,6	51,1	52,6	**35**	43,4	44,7	46,0	47,6	49,2	50,7	52,3
45,2	46,5	47,8	49,3	50,9	52,3	53,7	**36**	44,8	46,1	47,4	48,8	50,3	51,8	53,3
46,6	47,8	49,1	50,6	52,1	53,4	54,8	**37**	46,1	47,4	48,6	50,0	51,5	52,8	54,3
47,7	49,0	50,2	51,6	53,1	54,4	55,8	**38**	47,2	48,4	49,6	51,0	52,4	53,8	55,1
48,5	49,8	51,0	52,4	53,9	55,2	56,5	**39**	48,0	49,2	50,4	51,7	53,1	54,4	55,8
49,1	50,3	51,5	53,0	54,4	55,7	57,1	**40**	48,5	49,7	50,9	52,2	53,6	54,9	56,3
49,4	50,7	52,0	53,4	54,9	56,2	57,6	**41**	48,9	50,0	51,3	52,6	54,0	55,4	56,8
49,7	51,0	52,3	53,8	55,3	56,7	58,1	**42**	49,1	50,3	51,5	52,9	54,4	55,8	57,2

3.1.3. Lietuvos ir IG-21 standarto gimimo svorio ir ilgio procentilių palyginimas pagal GA

Lietuvos gimimo svorio 3-ioji, 50-oji ir 97-oji procentilės pagal lytį ir GA labai artimai atitiko IG-21 standartus ankstyvuoju gestacijos laikotarpiu (24–27 savaitės), ypač berniukų ir 97-ojoje procentilėje (**3 ir 4 pav.**). Tačiau, didėjant GA, ypač po 37 gestacijos savaitės, atotrūkis tarp Lietuvos ir IG-21 procentilių išsiplėtė beveik iki vieno procentilių kanalo, arba dviejų trečdalių SN (**3 ir 4 pav.**). Laiku gimusių naujagimių IG-21 mediana atitiko Lietuvos 25-ąją procentilę (skirtumas ~200 g), o 97-oji IG-21 procentilė sutapo su Lietuvos 90-ąja procentile (skirtumas ~350 g). 3-iojoje procentilėje skirtumai buvo ryškesni tarp laiku gimusių naujagimių (37–40 gestacijos savaitės) – 200 g, palyginti su 100 g po gimdymo termino laikotarpiu (**3 ir 4 pav.**).

Gimimo ilgiui IG-21 mediana ir žemesnės procentilės buvo artimos Lietuvos procentilėms ankstyvuoju gestacijos laikotarpiu, tačiau aukštesnės procentilės skyrėsi beveik visu procentilių kanalu, t. y. 1,0–1,5 cm (**5 ir 6 pav.**). Vėlyvojo neišnešiotumo laikotarpiu (34–36 savaitės) skirtumai tapo ryškesni visose procentilėse, jie padidėjo iki beveik dviejų procentilių kanalų. 97-oji IG-21 procentilė atitiko Lietuvos 50-ąją procentilę, o IG-21 mediana sutapo su Lietuvos 10-ąja procentile. Laiku gimusių naujagimių skirtumai 50-ojoje ir 97-ojoje procentilėse pasiekė 3–4 cm, o 3-iojoje procentilėje skirtumai buvo mažesni – maždaug 2 cm (**5 ir 6 pav.**).

3.1.4. Mažų pagal gestacijos amžių (MGA) ir didelių pagal gestacijos amžių (DGA) naujagimių paplitimo palyginimas pagal Lietuvos ir IG-21 standartus

Iš viso 9,7 proc. (30 859) berniukų buvo klasifikuoti kaip MGA, remiantis Lietuvos 10-ąja procentile, palyginti su 4,1 proc., remiantis IG-21 10-ąja procentile, t. y. mažiau nei per pusę mažesnis paplitimas (**5 lentelė**). Panašiai ir mergaičių MGA paplitimas pagal Lietuvos procentilę siekė 10,1 proc. (30 439), o pagal IG-21 – 4,4 proc. Abu metodai rodė esant didžiausią MGA paplitimą tarp labai ir vėlyvai neišnešiotų bei po gimimo termino gimusių abiejų lyčių naujagimių grupėse. Be to, didėjant gestacijos amžiui, tyrimų duomenys vis labiau skyrėsi. Itin ankstyvose gestacijos stadijose (24–27 savaitės) IG-21 standartas nepakankamai įvertino kaip MGA iki 3,1 proc. berniukų ir 6,9 proc. mergaičių. Didžiausi skirtumai buvo pastebėti laiku ir po gimdymo termino gimusių naujagimių grupėse, jie siekė 6,9 proc. berniukų ir 8,1 proc. mergaičių (**5 lentelė**). Šiuos neatitikimus iliustruoja 10-osios procentilės kreivės (**3 ir 4 pav.**), čia IG-21 10-oji

procentilė beveik sutapo su Lietuvos 3-iąja procentile iki 32 savaitės ir išliko šiek tiek aukštesnė vėlesnėse gestacijos stadijose.

Priešingi buvo DGA rezultatai: DGA berniukų paplitimas pagal Lietuvos 90-ąją procentilę buvo 10,1 proc. (31 972), o pagal IG-21 90-ąją procentilę – 20,7 proc., t. y. daugiau kaip du kartus didesnis (**5 lentelė**). Mergaičių DGA paplitimas pagal Lietuvos procentilę siekė 9,9 proc. (29 810), palyginti su 19,1 proc. pagal IG-21. Šie skirtumai itin būdingi ypač ankstyvuose (4,4–8 proc.) ir laiku ar gestacijos perioduose po termino gimusiems naujagimiams; čia berniukų skirtumai siekė 4,8–12,4 proc. 90-osios procentilės kreivės (**3 ir 4 pav.**) akivaizdžiai parodo šiuos skirtumus, čia 90-oji IG-21 procentilė buvo arti Lietuvos 75-osios procentilės ankstyvose gestacijos stadijose ir gimdymo termino laikotarpiu, o po gimdymo termino skirtumas pasiekė beveik vieną procentilių kanalą.

5 lentelė. Šio tyrimo metu nustatyto mažų pagal gestacijos amžių (MGA, gimimo svoris < 10-osios procentilės) ir didelių pagal gestacijos amžių (DGA, gimimo svoris > 90-osios procentilės) naujagimių paplitimo pagal lytį ir gestacijos amžių (GA) palyginimas taikant Lietuvos ir INTERGROWTH-21 (IG-21) standartus

BERNIUKAI								GA (savaitės)	MERGAITĖS							
Dabartinis tyrimas				IG-21					Dabartinis tyrimas				IG-21			
MGA		DGA		MGA		DGA			MGA		DGA		MGA		DGA	
0	0,0 %	9	23,7 %	0	0,0 %	9	23,7 %	**24**	1	2,2 %	7	15,2 %	1	2,2 %	7	15,2 %
3	3,2 %	10	10,8 %	1	1,1 %	10	10,8 %	**25**	1	1,2 %	3	3,7 %	0	0,0 %	7	8,5 %
5	3,7 %	11	8,1 %	3	2,2 %	17	12,5 %	**26**	11	7,9 %	8	5,8 %	7	5,0 %	15	10,8 %
13	6,6 %	17	8,7 %	7	3,6 %	32	16,3 %	**27**	21	12,1 %	9	5,2 %	9	5,2 %	23	13,2 %
31	10,2 %	16	5,3 %	10	3,3 %	33	10,9 %	**28**	24	10,0 %	31	13,0 %	14	5,9 %	44	18,4 %
36	12,4 %	23	7,9 %	19	6,5 %	36	12,4 %	**29**	31	12,2 %	21	8,2 %	15	5,9 %	39	15,3 %
55	12,4 %	31	7,0 %	23	5,2 %	37	8,3 %	**30**	44	10,9 %	27	6,7 %	22	5,4 %	56	13,8 %
46	9,4 %	38	7,8 %	18	3,7 %	47	9,6 %	**31**	58	13,5 %	30	7,0 %	36	8,4 %	51	11,8 %
85	10,0 %	71	8,4 %	35	4,1 %	62	7,3 %	**32**	73	10,1 %	77	10,7 %	28	3,9 %	102	14,2 %
123	11,0 %	107	9,6 %	42	3,8 %	71	6,4 %	**33**	97	10,7 %	75	8,3 %	49	5,4 %	89	9,8 %
188	10,0 %	164	8,7 %	102	5,4 %	129	6,9 %	**34**	166	10,3 %	135	8,4 %	112	7,0 %	135	8,4 %
321	11,2 %	200	7,0 %	199	7,0 %	164	5,7 %	**35**	285	11,8 %	141	5,8 %	233	9,6 %	161	6,7 %
762	13,6 %	315	5,6 %	443	7,9 %	349	6,2 %	**36**	633	12,7 %	277	5,6 %	496	10,0 %	338	6,8 %
1 293	9,8 %	1 366	10,4 %	653	5,0 %	2 001	15,2 %	**37**	1 094	9,8 %	1 090	9,7 %	647	5,8 %	1 630	14,5 %
3 195	9,4 %	3 761	11,1 %	1 370	4,0 %	6 719	19,8 %	**38**	2 946	9,9 %	3 164	10,6 %	1 472	4,9 %	5 562	18,6 %
5 928	8,7 %	7 130	10,5 %	2 248	3,3 %	14 617	21,5 %	**39**	5 976	9,3 %	6 622	10,4 %	2 619	4,1 %	12 983	20,3 %
14 231	9,8 %	14 527	10,0 %	5 482	3,8 %	32 460	22,4 %	**40**	14 561	10,3 %	14 179	10,0 %	5 594	3,9 %	28 251	19,9 %
4 085	10,0 %	3 964	9,7 %	1 811	4,4 %	8 561	20,9 %	**41**	4 026	10,3 %	3 734	9,5 %	1 798	4,6 %	7 582	19,3 %
459	18,1 %	207	8,2 %	283	11,2 %	461	18,2 %	**42**	391	17,1 %	170	7,4 %	207	9,1 %	352	15,4 %
30 859	9,7 %	31 967	10,1 %	12 749	4,1 %	65 815	20,7 %	**Iš viso**	30 439	10,1 %	29 800	9,9 %	13 359	4,4 %	57 427	19,1 %

3.2. Gestacijos amžiui ir lyčiai pritaikytos populiacijos pagrindu sudarytos Lietuvos naujagimių galvos apimties ribinės vertės

3.2.1. Galvos apimtis pagal gestacijos amžių ir lytį

Tyrimo imties dydis (**6 lentelė**) reikšmingai didėjo kartu su gestacijos amžiumi – nuo mažiau nei 50 naujagimių 24 savaitę iki beveik 100 000 kiekvienos lyties laiku gimusių naujagimių kūdikių grupėje. Berniukų vidutinė galvos apimtis (GAp) visose gestacijos savaitėse buvo 0,5–0,8 cm didesnė nei mergaičių. Priešingai, standartinis nuokrypis (SN) ir galvos apimties variacijos koeficientas (VK) pastebimai mažėjo didėjant gestacijos amžiui (**2 lentelė**).

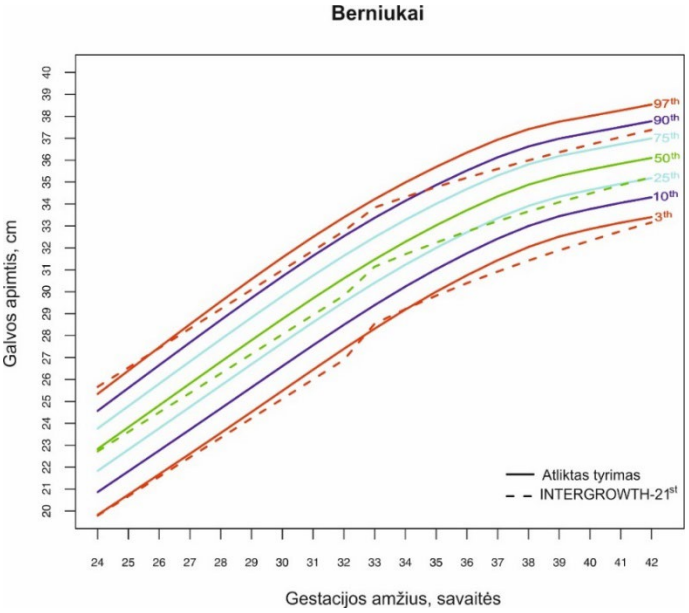
6 lentelė. Lietuvos naujagimių galvos apimties (GAp) palyginimas pagal lytį ir gestacijos amžių (GA) su IG-21 standartu (16,18). n – stebėtųjų skaičius, M – vidurkis, SN – standartinis nuokrypis, VK – variacijos koeficientas, apibrėžtas kaip standartinis nuokrypis / vidurkis

GA (savaitė-mis)	DABARTINIS TYRIMAS				INTERGROWTH – 21st				VIDURKIO SKIRTU-MAS LT – IG-21
	n	M	SN	VK	n	M	SN	VK	
BERNIUKAI									
24	28	23,0	1,0	0,043	3	22,7	1,6	0,070	0,3
25	71	23,6	1,4	0,059	10	23,6	1,6	0,068	0,0
26	89	24,5	1,4	0,057	13	24,5	1,6	0,065	0,0
27	124	25,5	1,5	0,059	12	25,4	1,6	0,063	0,1
28	211	26,6	1,7	0,064	19	26,3	1,6	0,061	0,3
29	190	27,5	1,7	0,062	19	27,2	1,6	0,059	0,3
30	303	28,5	1,7	0,060	25	28,1	1,6	0,057	0,4
31	306	29,7	1,7	0,057	37	28,9	1,6	0055	0,8
32	533	30,6	1,6	0,052	52	29,8	1,6	0,054	0,8
33	744	31,5	1,6	0,051	33	31,1	1,3	0,042	0,4
34	1 305	32,3	1,5	0,046	48	31,7	1,3	0,041	0,6
35	1 977	33,0	1,5	0,045	127	32,2	1,3	0,040	0,8
36	3 682	33,5	1,5	0,045	322	32,7	1,2	0,037	0,8
37	9 651	34,3	1,5	0,044	848	33,2	1,2	0,036	1,1
38	24 745	34,9	1,4	0,040	2 032	33,7	1,2	0,036	1,2
39	51 027	35,3	1,4	0,040	2 985	34,1	1,1	0,032	1,2
40	93 843	35,5	1,4	0,039	2 532	34,5	1,1	0,032	1,0
41	27 226	35,8	1,4	0,039	1 147	34,9	1,1	0,032	0,9
42	987	35,8	1,5	0,042	204	35,2	1,1	0,031	0,6

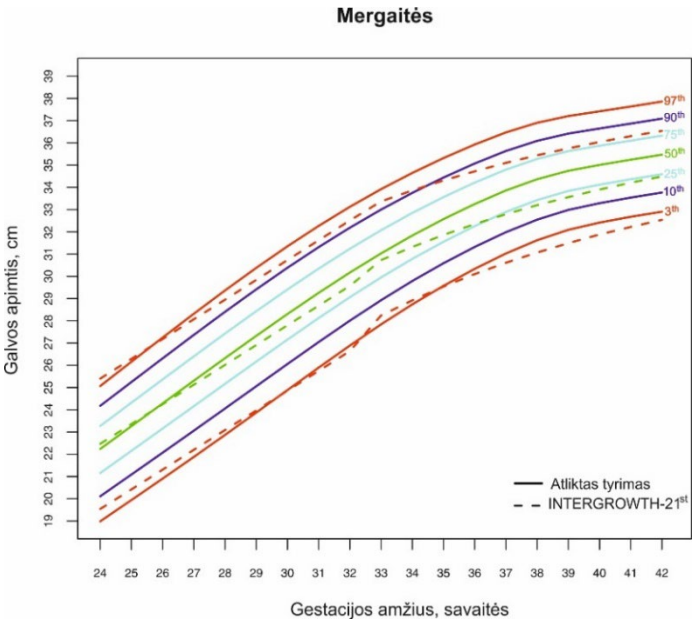
GA (savaitė-mis)	DABARTINIS TYRIMAS				INTERGROWTH – 21st				VIDURKIO SKIRTU-MAS LT – IG-21
	n	M	SN	VK	n	M	SN	VK	
MERGAITĖS									
24	40	22,2	1,3	0,059	3	22,5	1,6	0,071	-0,3
25	65	23,1	1,3	0,056	7	23,4	1,6	0,068	-0,3
26	98	23,7	1,6	0,068	7	24,3	1,6	0,066	-0,6
27	122	25,0	1,7	0,068	11	25,1	1,6	0,064	-0,1
28	153	26,2	1,9	0,073	16	26,0	1,6	0,062	0,2
29	168	27,0	1,7	0,063	22	26,9	1,6	0,059	0,1
30	248	28,2	1,8	0,064	24	27,8	1,6	0,058	0,4
31	274	29,0	1,7	0,059	33	28,7	1,6	0,056	0,3
32	454	30,4	1,7	0,056	43	29,6	1,6	0,054	0,8
33	610	31,1	1,6	0,051	17	30,7	1,3	0,042	0,4
34	1 066	31,9	1,5	0,047	65	31,3	1,2	0,038	0,6
35	1 635	32,5	1,5	0,046	111	31,9	1,2	0,038	0,6
36	3 183	33,1	1,5	0,045	293	32,3	1,2	0,037	0,8
37	8 078	33,8	1,4	0,041	798	32,8	1,1	0,034	1,0
38	21 708	34,3	1,4	0,041	1 783	33,2	1,1	0,033	1,1
39	48 487	34,8	1,4	0,040	2 849	33,6	1,1	0,033	1,2
40	93 307	35,0	1,3	0,037	2 486	33,9	1,1	0,032	1,1
41	26 354	35,2	1,3	0,037	1 180	34,2	1,0	0,029	1,0
42	907	35,3	1,4	0,040	218	34,5	1,0	0,029	0,8

3.2.2. Išlygintos gestacijos amžiui ir lyčiai pritaikytos Lietuvos naujagimių GAp procentilės

Išlygintos 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios gestacijos amžiui ir lyčiai pritaikytos Lietuvos naujagimių GAp procentilių kreivės pateikiamos **7 ir 8 paveiksluose**. Didėjant GA, GAp variacija pastebimai mažėja. Taip pat matyti neigiama pasiskirstymo asimetrija, kuri atsispindi platesniu tarpu tarp žemesnių procentilių, palyginti su viršutinėmis procentilėmis.



7 pav. Išlygintos Lietuvos naujagimių berniukų GAp 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios procentilių kreivės (cm) ir 3-ioji, 50-oji bei 97-oji procentilės pagal IG-21 standartus (16, 18)



8 pav. Išlygintos Lietuvos naujagimių mergaičių GAp 3-iosios, 10-osios, 25-osios, 50-osios, 75-osios, 90-osios ir 97-osios procentilių kreivės (cm) ir 3-ioji, 50-oji bei 97-oji procentilės pagal IG-21 standartus (16, 18)

4.2.3. Lietuvos ir IG-21 GAp procentilių palyginimas pagal gestacijos amžių

Lietuvos neišnešiotų ir išnešiotų naujagimių GAp vidurkis buvo nuosekliai didesnis už atitinkamas IG-21 standartų vertes (16, 18), pradedant nuo 31 savaitės (berniukų) ir 32 savaitės (mergaičių), o skirtumas didėjo didėjant gestacijos amžiui (**6 lentelė**). Šis dėsningumas taip pat atsispindėjo GA ir lyčiai pritaikytuose GAp standartiniuose įverčiuose, apskaičiuotuose pagal IG-21 standartus, kurie parodė panašią tendenciją (2 papildomas paveikslas, **II straipsnis**).

Lietuvos GAp 3-iąją, 50-ąją ir 97-ąją procentiles lyginant pagal GA ir lytį su IG-21 standartų procentilėmis, buvo patvirtintas **6 lentelėje** pastebėtas dėsningumas. Ankstyvosiose gestacijose procentilių skirtumai buvo nedideli, tačiau didėjant gestacijai tarpas ryškėjo, ypač aukštesnėse procentilėse (**7 ir 8 pav.**). 3-iojoje procentilėje laiku gimusių naujagimių (37–40 savaitės) skirtumai svyravo nuo 0,5 iki 0,75 cm, o po termino gimusiųjų sumažėjo iki mažiau nei 0,5 cm. 50-ojoje ir 97-ojoje procentilėse skirtumai buvo didesni – nuo 1 iki 1,5 cm (**7 ir 8 pav.**).

3.3. Prieš laiką Lietuvoje gimusių vaikų longitudiniai augimo rezultatai pagal GA ir GS nuo kūdikystės iki paauglystės

3.3.1. Prieš laiką gimusių vaikų augimo kreivės (SITAR modelio veiksmingumas)

Siekiant išanalizuoti prieš laiką gimusių vaikų augimo dinamiką, SITAR modelis buvo taikytas modeliuoti atskirai berniukų ir mergaičių vidutines ūgio, svorio ir KMI kreives gestacijos amžiaus ir gimimo svorio grupėse nuo gimimo iki 12-os metų (2 lentelė, **III straipsnis**). Modeliai, kuriuose buvo taikyta logaritminė amžiaus transformacija, tiko geriau, laisvės laipsniai svyravo nuo 6 iki 8. SITAR modeliai gerai aprašė duomenis, paaiškino nuo 72 proc. iki 92 proc. augimo modelių variacijos, o didžiausias tikslumas buvo užfiksuotas svorio analizėje (92 proc. mergaičių, 90 proc. berniukų).

3.3.2. Ūgio augimo modeliai pagal GA ir GS

Reikšmingi SITAR vidutinio ūgio modelių skirtumai nuo gimimo iki 12-os metų tarp GA ir GS grupių, suskirstytų pagal lytį, pateikti **7 lentelėje**. Ypač ir labai neišnešioti berniukai ir mergaitės buvo vidutiniškai 0,9 cm žemesni nei laiku gimę jų bendraamžiai. Be to, mažo GS mergaitės ir

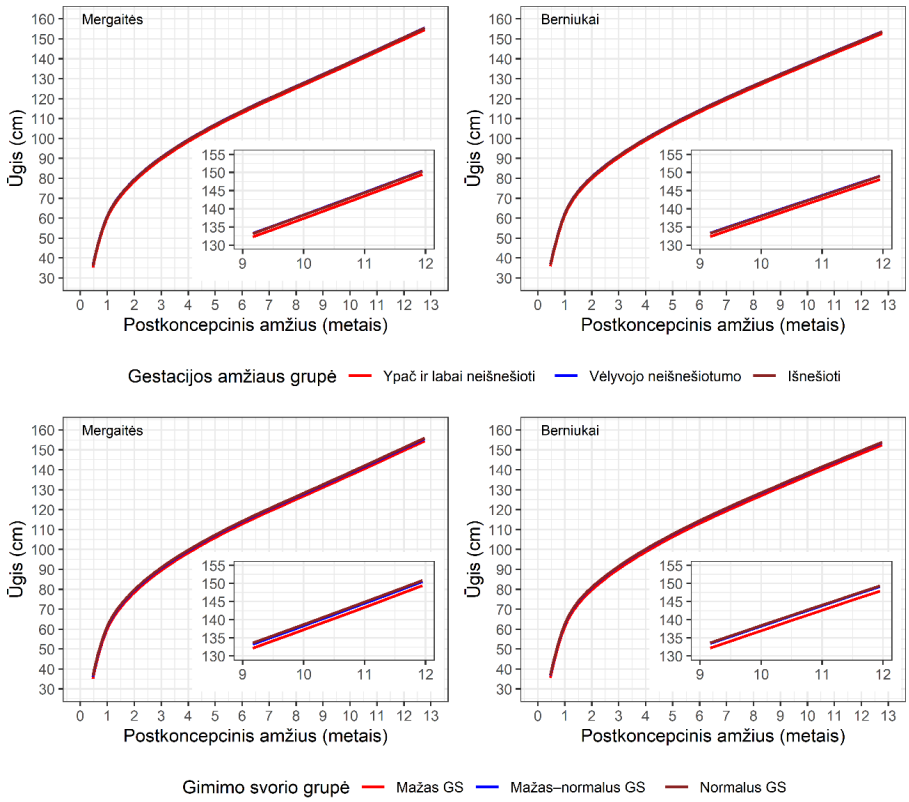
berniukai buvo reikšmingai žemesni už jų normalaus GS bendraamžius: skirtumas siekė 1,4 cm.

Nepaisant šių skirtumų, vidutinės ūgio kreivės tarp grupių (**9 pav.**) išliko glaudžiai suderintos visą vaikystę. Skirtumai tapo ryškesni 9–12 metų amžiaus laikotarpiu, kai grupių atotrūkiai išliko, tačiau augimo kreivės išliko lygiagrečios, be divergencijos požymių.

7 lentelė. Reikšmingi gestacijos amžiaus (GA) ir gimimo svorio (GS) grupių vidutiniai ūgio skirtumai SITAR ūgio modelyje nuo gimimo iki 12-os metų. PI – pasikliautinasis intervalas, SP – standartinė paklaida

Kovariantė	Lytis	Efektas	SITAR parametras	Koeficientas (95 % PI) (cm)	SP (cm)	P reikšmė
GA grupė	Mergaitės	Ypač ir labai neišnešioti	a	–0,92 (–1,49; –0,34)	0,29	0,002
		Vėlyvojo neišnešiotumo	(dydis)	0,08 (–0,37; 0,53)	0,23	0,7
	Berniukai	Ypač ir labai neišnešioti	a	–0,89 (–1,48; –0,29)	0,30	0,003
		Vėlyvojo neišnešiotumo	(dydis)	0,09 (–0,34; 0,53)	0,22	0,7
GS grupė	Mergaitės	Mažas GS	a	–1,45 (–1,90; –0,99)	0,23	<0,001
		Mažas–normalus GS	(dydis)	–0,35 (–0,86; 0,15)	0,26	0,2
	Berniukai	Mažas GS	a	–1,43 (–1,88; –0,99)	0,23	<0,001
		Mažas–normalus GS	(dydis)	–0,18 (–0,71; 0,34)	0,27	0,5

Lyginamosios grupės: išnešiotų naujagimių GA grupė; normalaus GS grupė



9 pav. GA ir GS grupių vidutinės SITAR modelio ūgio kreivės

3.3.3. Svorio augimo modeliai pagal GA ir GS

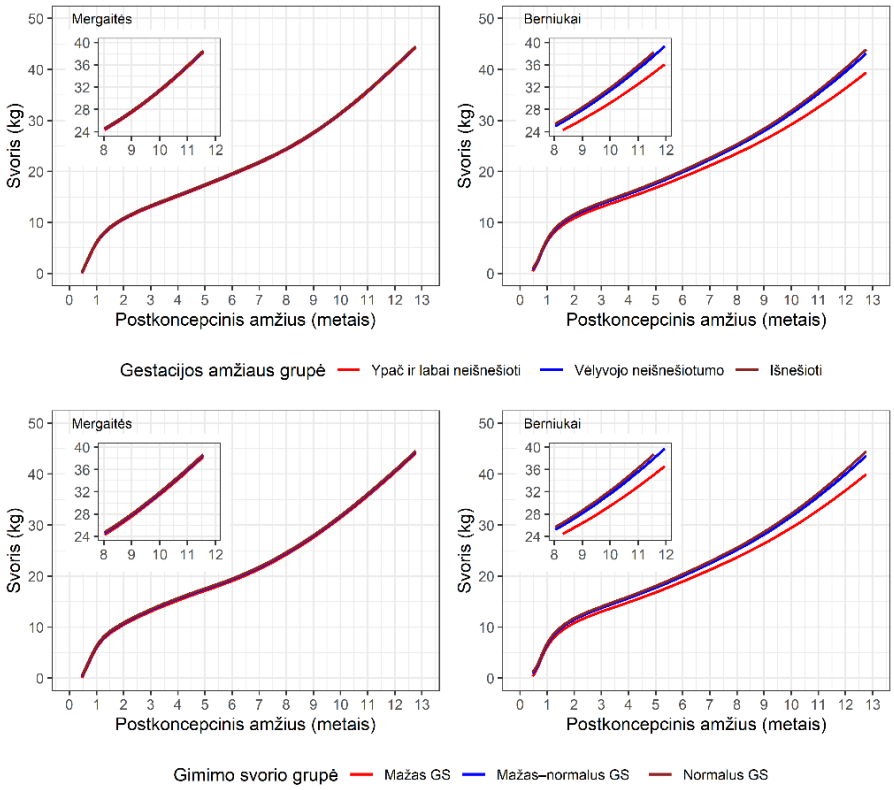
Reikšmingas GA ir GS poveikis svorio dydžiui ir augimo intensyvumui per visą tyrimo laikotarpį (0–12 metų) buvo mažiau ryškus mergaitėms nei berniukams (**8 lentelė**). Ypač ir labai neišnešiotų naujagimių grupėje mergaitės / berniukai svėrė atitinkamai 0,3/0,8 kg vidutiniškai mažiau nei jų laiku gimę bendraamžiai. Ypač ir labai neišnešiotų naujagimių grupės berniukai svėrė vidutiniškai 0,8 kg mažiau nei jų išnešioti bendraamžiai (95 proc. PI: –1,19; –0,48), o mergaitės – 0,3 kg mažiau (95 proc. PI: –0,50; –0,07). Panašiai ir mažo GS grupėje berniukai buvo 1,0 kg lengvesni nei jų normalaus GS bendraamžiai (95 proc. PI: –1,26; –0,73), o mergaitės – 0,5 kg lengvesnės (95 proc. PI: –0,62; –0,29), pabrėžiant reikšmingą lyčių skirtumą. GA ir GS taip pat reikšmingai paveikė berniukų augimo intensyvumą: ypač ir labai neišnešiotų naujagimių grupėje augimo šuoliai buvo 4 proc. mažesni, o mažo GS grupėje – 3,7 proc. mažesni, palyginti su laiku gimusių ir normalaus GS bendraamžiais.

Vidutinės mergaičių ir berniukų svorio kreivės (**10 pav.**) rodo, kad GA ir GS grupių skirtumai buvo akivaizdesni nei ūgio atveju (**9 pav.**). Mergaičių kreivės grupėse išliko gana artimos visos vaikystės metu, ir tai rodo mažesnį GA ir GS poveikį mergaičių svorio augimui. Berniukų kreivės – priešingai, tarp grupių skyrėsi labiau, ypač sulaukusiųjų 9-erių metų, nes ypač ir labai neišnešiotų ir mažo GS berniukų augimas buvo lėtesnis nei jų laiku gimusių ir normalaus GS bendraamžių. Įterpti grafikai išryškina šiuos dėsningumus ir rodo daug didesnius berniukų nei mergaičių skirtumus, ypač ankstyvojo neišnešiotumo ir mažo GS grupėse, palyginti su kitomis grupėmis.

8 lentelė. Reikšmingi gestacijos amžiaus (GA) ir gimimo svorio (GS) grupių vidutiniai svorio skirtumai SITAR svorio modelyje nuo gimimo iki 12-os metų. PI – pasikliautinasis intervalas, SP – standartinė paklaida

Kovariantė	Lytis	Efektas	SITAR parametras	Koeficientas (95 proc. PI)	SP	P reikšmė
GA grupė	Mergaitės	Ypač ir labai neišnešioti	a	–0,29 (–0,50; –0,07)	0,11	0,009
		Vėlyvojo neišnešiotumo	(dydis)	–0,07 (–0,24; 0,09)	0,09	0,4
	Berniukai	Ypač ir labai neišnešioti	a	–0,83 (–1,19; –0,48)	0,18	<0,001
		Vėlyvojo neišnešiotumo	(dydis)	–0,26 (–0,53; –0,01)	0,13	0,05
		Ypač ir labai neišnešioti	c (intensyvumas)	–0,040 (–0,068; –0,012)	0,01	0,005
		Vėlyvojo neišnešiotumo		–0,005 (–0,025; 0,015)	0,01	0,6
GS grupė	Mergaitės	Mažas GS	a	–0,46 (–0,62; –0,29)	0,09	<0,001
		Mažas–normalus GS	(dydis)	–0,15 (–0,34; 0,04)	0,10	0,1
	Berniukai	Mažas GS	a	–1,00 (–1,26; –0,73)	0,14	<0,001
		Mažas–normalus GS	(dydis)	–0,30 (–0,61; 0,02)	0,160	0,07
		Mažas GS	c (intensyvumas)	–0,037 (–0,058; –0,016)	0,011	0,001
		Mažas–normalus GS		–0,006 (–0,030; –0,019)	0,013	0,7

Lyginamosios grupės: išnešiotų naujagimių GA grupė; normalaus GS grupė. Koeficientai: dydis – kg, intensyvumas – dalis



10 pav. GA ir GS grupių vidutinės SITAR modelio svorio kreivės

3.3.4. Kūno masės indekso (KMI) augimo modeliai pagal GA ir GS

Nustatyti reikšmingi GA ir GS poveikio KMI dydžiui ir laikui skirtumai per visą 12-os metų tyrimo laikotarpį (**9 lentelė**). Vidutinis KMI buvo mažesnis ypač ir labai / vėlyvojo neišnešiotumo naujagimių GA ir mažo / mažo–normalaus GS grupėse: mergaičių atitinkamai 0,8/0,3 kg/m^2, berniukų atitinkamai 0,9/0,6 kg/m^2. Panašiai ir augimo laikas buvo ankstesnis abiejose neišnešiotų grupėse – 0,11/0,08 vieneto abiejų lyčių grupėse, o mažesnė įtaka pastebėta GS grupėse – 0,08/0,05 vieneto. Neigiamas laiko koeficientas rodo ankstyvesnį augimo šuolį; dalinis koeficientas gali būti padaugintas iš 100 ir vertinamas kaip procentinis skirtumas. Didesnis GA poveikis, palyginti su GS, paaiškinamas tuo, kad laiko poveikis tiesiogiai atspindi poslinkį amžiaus skalėje ir todėl atitinka GA.

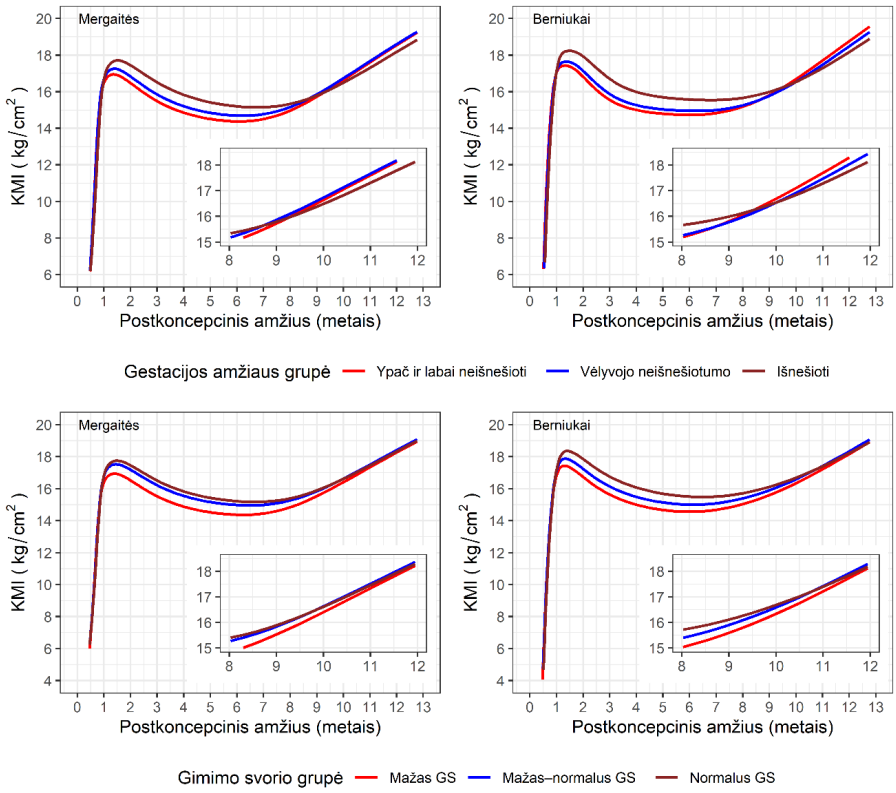
Vidutinės mergaičių ir berniukų KMI kreivės pagal GA ir GS grupes išryškina skirtingas KMI kitimo tendencijas tarp grupių (**11 pav.**). Ypač ir labai neišnešioti vaikai pradžioje turėjo mažesnį KMI nei vėlyvojo neišnešiotumo ir laiku gimę vaikai, tačiau jiems buvo būdinga ankstyvesnė ir staigesnė tuklumo

grąža (TG) (angl. *adiposity rebound*). TG prasidėjo anksčiau ypač ir labai / vėlyvojo neišnešiotumo naujagimių GA grupėse, palyginti su laiku gimusių vaikų grupėmis, atitinkamai 10,2/5,3 mėnesiais anksčiau berniukams ir 7,8/7,8 mėnesiais anksčiau mergaitėms (**III straipsnio** 1 papildoma lentelė). Tačiau sulaukus 9–10 metų GA kreivės susikerta ir ypač ir labai neišnešiotų KMI tampa santykinai didesnis; būtent tai ir prognozuoja ankstyvesnė TG. Panašiai ir TG laikas buvo ankstyvesnis mažo / mažo–normalaus GS grupėse, palyginti su normalaus GS grupe, atitinkamai 7,6/5,2 mėnesiais anksčiau berniukų ir 5,2/0,0 mėnesiais anksčiau mergaičių (**III straipsnio** 1 papildoma lentelė). Kalbant apie GS grupių kreives, mažo GS grupės KMI kreivė yra nuosekliai žemesnė už kitas dvi grupes, kol kreivės susilieja ties maždaug 12 metų amžiumi.

9 lentelė. Reikšmingi gestacijos amžiaus (GA) ir gimimo svorio (GS) grupių vidutiniai KMI skirtumai SITAR KMI modelyje nuo gimimo iki 12-os metų. PI – pasikliautinasis intervalas, SP – standartinė paklaida

Kovariantė	Lytis	Efektas	SITAR parametras	Koeficientas (95 proc. PI)	SP	P reikšmė
GA Grupė	Mergaitės	Ypač ir labai neišnešioti	a (dydis)	–0,77 (–1,05; –0,48)	0,14	<0,001
		Vėlyvojo neišnešiotumo		–0,46 (–0,68; –0,24)	0,11	<0,001
		Ypač ir labai neišnešioti	b (laikas)	–0,110 (–0,123; –0.089)	0,007	<0,001
		Vėlyvojo neišnešiotumo		–0,080 (–0,095; –0,070)	0,009	<0,001
	Berniukai	Ypač ir labai neišnešioti	a (dydis)	–0,81 (–1,13; –0,49)	0,16	<0,001
		Vėlyvojo neišnešiotumo		–0,60 (–0,83; –0,36)	0,11	<0,001
		Ypač ir labai neišnešioti	b (laikas)	–0,120 (–0,136; –0,098)	0,010	<0,001
		Vėlyvojo neišnešiotumo		–0,078 (–0,091; –0,065)	0,007	<0,001
GS grupė	Mergaitės	Mažas GS	a (dydis)	–0,81 (–1,03; –0,58)	0,11	<0,001
		Mažas–normalus GS		–0,22 (–0,47; 0,03)	0,13	0,09
		Mažas GS	b (laikas)	–0,069 (–0,085; –0,054)	0,009	<0,001
		Mažas–normalus GS		–0,028 (–0,046; –0,011)	0,008	0,001
	Berniukai	Mažas GS	a (dydis)	–0,92 (–1,17; –0,68)	0,13	<0,001
		Mažas–normalus GS		–0,48 (–0,77; –0,19)	0,15	0,001
		Mažas GS	b (laikas)	–0,078 (–0,094; –0,062)	0,008	<0,001
		Mažas–normalus GS		–0,054 (–0,073; –0,036)	0,010	<0,001

Lyginamosios grupės: išnešiotų naujagimių GA grupė; normalaus GS grupė. Koeficientai: dydis – kg, intensyvumas, laikas – dalis



11 pav. GA ir GS grupių vidutinės SITAR modelio KMI kreivės

3.4. Daugiasistemiai prieš laiką Lietuvoje gimusių vaikų sveikatos padariniai nuo kūdikystės iki paauglystės

3.4.1. Sergamumo dažnis ir ligų pasiskirstymas skirtingose prieš laiką gimusių vaikų grupėse nuo gimimo iki paauglystės

Vidutinis ligų skaičius, nustatytas nuo gimimo iki 18 metų pagal gimimo svorio (GS) ir gestacijos amžiaus (GA) kategorijas, atskleidė aiškią tendenciją: mažesnis GS nuolat buvo susijęs su didesne ligų našta. Ypač ir labai mažo bei mažo GS grupėse vidutinis ligų skaičius buvo didžiausias (4,6 ± 2,6/3,2 atitinkamai). Suboptimalaus GS grupės asmenų rodikliai buvo mažesni (4,24 ± 2,8), o normalaus GS grupė pasižymėjo mažiausiu vidutiniu ligų skaičiumi (3,2 ± 2,2).

GA grupėse vidutinio neišnešiotumo vaikams buvo nustatytas didžiausias vidutinis ligų skaičius (4,55 ± 2,82), po jų sekė vėlyvojo neišnešiotumo (4,33 ± 3,08) ir ypač ir labai ankstyvo neišnešiotumo

(4,28 ± 2,73) grupės. Mažesnis GS rodė stipresnį ryšį su didesniu ligų skaičiumi, GA grupių ryšys buvo ne toks ryškus, ir tai leidžia manyti, kad GS yra stipresnis bendro sergamumo rodiklis nei GA.

Ligų pasiskirstymas pagal GS ir GA kategorijas skirtingais amžiaus tarpsniais apibendrintas **10 ir 11 lentelėse**. Daugiausia diagnozių nustatyta per pirmuosius trejus metus (47,5 proc.) ir ikimokykliniame amžiuje (32,7 proc.), o 80,2 proc. visų 1 818 diagnozių diagnozuotos iki 7 metų.

Mažesnis GS koreliavo su didesniu sergamumu (**10 lentelė**): mažo GS grupei teko 51,8 proc. diagnozių, o suboptimalaus ir normalaus GS grupėms – atitinkamai 29,2 proc. ir 6,8 proc. Ypač ir labai mažo GS grupėje buvo nustatyta didžiausia diagnozių dalis, tačiau ją ribojo nedidelis imties dydis.

GA grupėse daugiausia diagnozių buvo nustatyta vėlyvojo neišnešiotumo asmenims. Tačiau ypač ir labai neišnešiotų ir vidutinio neišnešiotumo naujagimių grupės turėjo didesnę proporcinę ligų naštą ankstyvuoju gyvenimo laikotarpiu, pabrėžiant didesnę jų sergamumo riziką (**11 lentelė**).

10 lentelė. Skirtingais amžiaus tarpsniais (nuo gimimo iki paauglystės) diagnozuotų ligų pasiskirstymas pagal gimimo svorio grupes. Pirmoje eilutėje ligų dažnis nurodytas skaičiais, o antroje – eilutės procentais

Gimimo svorio (GS) grupė	**Pagal TLK-10 diagnozuotų ligų skaičius**				
	[0–3]	**(3–7]**	**(7–12]**	**(12–18]**	**Iš viso**
Ypač ir labai mažo GS naujagimiai	126 56,8	73 32,9	21 9,5	2 0,9	**222**
Mažo GS naujagimiai	451 47,9	298 31,6	149 15,8	44 4,7	**942**
Suboptimalaus GS naujagimiai	223 42,1	183 34,5	84 15.8	40 7,5	**530**
Normalaus GS naujagimiai	63 50,8	40 32,3	14 11,3	7 5,6	**124**
Iš viso	**863** **47,5**	**594** **32,7**	**268** **14,7**	**93** **5,1**	**1 818** **100**

Lenktinis ir laužtinis skliaustai atitinkamai rodo neįtrauktą arba įtrauktą laiko intervalo krašto tašką

11 lentelė. Skirtingais amžiaus tarpsniais (nuo gimimo iki paauglystės) diagnozuotų ligų pasiskirstymas pagal gestacijos amžiaus grupes. Pirmoje eilutėje ligų dažnis nurodytas skaičiais, o antroje – eilutės procentais

Gestacijos amžiaus (GA) grupė	**Pagal TLK-10 diagnozuotų ligų skaičius**				
	[0–3]	**(3–7]**	**(7–12]**	**(12–18]**	**Iš viso**
Ypač ir labai neišnešioti naujagimiai	153 55,8	80 29,2	33 12,0	8 2,9	**274**
Vidutinio neišnešiotumo naujagimiai	173 53,6	99 30,7	41 12,7	10 3,1	**323**
Vėlyvojo neišnešiotumo naujagimiai	537 44,0	415 34,0	194 15,9	75 6,1	**1 221**
Iš viso	**863** **47,5**	**594** **32,7**	**268** **14,7**	**93** **5,1**	**1 818** **100**

Lenktinis ir laužtinis skliaustai atitinkamai rodo neįtrauktą arba įtrauktą laiko intervalo krašto tašką

TLK-10 ligų skyrių struktūra (N=1818) nuo gimimo iki paauglystės atskleidė, kad dažniausia kategorija buvo akių ir priedinių organų ligos, sudarančios beveik 17 proc. atvejų (3–4 lentelės, **IV straipsnis**). Po jų – įgimtos anomalijos ir tam tikros infekcinės ligos, kurių paplitimas siekė apie 10–11 proc. Trečioji pagal dažnumą grupė – kvėpavimo takų, endokrininės, mitybos ir medžiagų apykaitos ligos bei psichikos ir elgesio sutrikimai (8–9 proc.). Vis dėlto kai kurie dideli paplitimo rodikliai gali būti klaidinantys, nes šios ligos taip pat dažnai pasireiškia bendrojoje vaikų populiacijoje (**12 lentelė**).

Skirtingų ligų kategorijų pasiskirstymas laiko atžvilgiu buvo analizuojamas keturiais amžiaus tarpsniais (3–4 lentelės, **IV straipsnis**), daugiausia dėmesio skiriant dažniausiems TLK-10 skyriams. Kraujo ir imuninės sistemos ligos beveik išimtinai buvo diagnozuotos 0–3 metų amžiaus laikotarpiu (iki 90 proc. atvejų). Panaši tendencija buvo pastebėta įgimtų anomalijų atveju (nuo 55 proc. didesnio GS ir GA grupėse iki 80 proc. mažesnio GS ir GA grupėse) bei virškinimo sistemos ligų atveju, kai daugiau kaip pusė atvejų pasireiškė šiuo laikotarpiu (vienodai visose GS ir GA grupėse). Akių ir priedinių organų ligos buvo dažnos visos vaikystės laikotarpiu, o jų paplitimas buvo panašus 0–3 ir 3–7 metų amžiaus grupėse. Kvėpavimo takų ligos ir tam tikros infekcijos pasiekė piką 3–7 metų amžiaus

grupėje, kai reikšminga dalis atvejų buvo diagnozuota šiuo laikotarpiu (nuo 45 proc. iki 80 proc.).

Kai kurios būklės pasiekė piką vėlesniu laikotarpiu (3–4 lentelės, **IV straipsnis**). Endokrininės ir medžiagų apykaitos ligos dažniausiai buvo diagnozuojamos 0–3 metų amžiaus laikotarpiu, tačiau antras reikšmingas jų skaičiaus padidėjimas buvo pastebėtas mokykliniame amžiuje (7–12 metų). Psichikos ir elgesio sutrikimai taip pat dažniausiai buvo diagnozuojami 3–7 metų amžiuje, tačiau aukštesnio GS ir GA grupėse pasireiškė antras pikas mokykliniais metais (7–12 metų). Paauglystė (12–18 metų) pasižymėjo palyginti mažesniu naujų diagnozių skaičiumi, tačiau įtraukė kai kurias vėlyvojo pasireiškimo būkles, tokias kaip nervų sistemos ligos, odos ligos ir raumenų bei kaulų sistemos sutrikimai.

Ši TLK-10 klasifikacija paremta ligų atsiradimo perspektyva atskleidžia nevienodą įvairių susirgimų laiką, daugumai ligų pasireiškiant ankstyvoje vaikystėje. Išsamus naujai diagnozuotų atvejų pasiskirstymas pagal TLK-10 ligų skyrius GA grupėse pateikiamas 3 lentelėje, **IV straipsnyje**, pagal GS kategorijas – 4 lentelėje, **IV straipsnyje**.

Be to, nustatyti tiriamųjų sergamumo paplitimo skirtumai pagal TLK-10 ligų skyrius bei GA ir GS grupes (**12 lentelė**) ir apskaičiuotas dažniausių konkrečių ligų ar sveikatos būklių paplitimas šiuose skyriuose (**13 lentelė**).

12 lentelė. Tiriamųjų sergamumo pasiskirstymas pagal TLK-10 ligų skyrius ir pagal gestacijos amžiaus (GA) ir gimimo svorio (GM) grupes (pirmoje eilutėje nurodytas vaikų skaičius, o antroje – procentinė dalis pagal gestacijos amžiaus ir gimimo svorio kategorijas), ir Lietuvos vaikų populiacijos sergamumas (šis rodiklis įtrauktas palyginimo tikslais, sudarytas nuo 0–18 metų amžiaus tarpsniui pagal šaltinius (122, 123)

Ligų skyrius	Gestacijos amžiaus grupės			Gimimo svorio grupės				Iš viso tiriamųjų (pagal ligų skyrius) (n=417)	Iš viso Lietuvos vaikų populiacijoje (pagal ligų skyrius) (n=556 620
	Ypač ir labai neišnešioti naujagimiai (n=64)	Vidutinio neišnešiotumo naujagimiai (n=71)	Vėlyvojo neišnešiotumo naujagimiai (n=282)	Ypač ir labai mažo GS naujagimiai (n=48)	Mažo GS naujagimiai (n=205)	Suboptimalaus GS naujagimiai (n=125)	Normalaus GS naujagimiai (n=39)		
A00-B99 - Tam tikros infekcinės ir parazitų sukeliamos ligos	21 32,8	23 32,4	119 42,2	20 41,7	74 36,1	57 45,6	12 30,8	**163** **39,1*****	**81 107** **14,6**
C00-D49 - Navikai	5 7,8	8 11,3	19 6,7	6 12,5	18 8,8	7 5,6	1 2,6	**32** **7,7*****	**10 015** **1,8**
D50-D89 - Kraujo ir kraujodaros organų ligos bei tam tikri sutrikimai, susiję su imuniniais mechanizmais (° GS*)	13 20,3	20 28,2	68 24,1	12 25,0	55 26,8	31 24,8	3 7,7	**101** **24,2*****	**12 555** **2,3**
E00-E89 - Endokrininės, mitybos ir medžiagų apykaitos ligos	16 25,0	25 35,2	82 29,1	14 29,2	64 31,2	35 28,0	10 25,6	**123** **29,5*****	**62 505** **11,2**
F01-F99 - Psichikos ir elgesio sutrikimai	16 25,0	25 35,2	80 28,4	13 27,1	63 30,7	34 27,2	11 28,2	**121** **29,1*****	**43 720** **7,8**
G00-G99 - Nervų sistemos ligos	9 14,1	6 8,5	33 11,7	7 14,6	22 10,7	16 12,8	3 7,7	**48** **11,5*****	**15 881** **2,8**
H00-H59 - Akies ir jos priedinių organų ligos	36 56,3	41 57,4	142 50,4	29 60,4	110 53,7	64 51,2	16 41,0	**219** **52,5*****	**171 310** **30,8**
H60-H95 - Ausies ir speninės ataugos ligos	4 6,3	3 4,2	4 1,4	3 6,3	4 2,0	4 3,2	0 0,0	**11** **2,6*****	**46 349** **8,3**
I00-I99 - Kraujotakos sistemos ligos	0 0,0	1 1,4	10 3,5	0 0,0	5 2,5	5 4,0	1 2,6	**11** **2,6**	**18 801** **3,4**
J00-J99 - Kvėpavimo sistemos ligos	23 35,9	23 32,4	80 28,4	20 41,7	61 29,8	38 30,4	7 17,9	**126** **30,2*****	**322 052** **57,9**

Ligų skyrius	Gestacijos amžiaus grupės			Gimimo svorio grupės				Iš viso tiriamųjų (pagal ligų skyrius) (n=417)	Iš viso Lietuvos vaikų populiacijoje (pagal ligų skyrius) (n=556 620
	Ypač ir labai neišnešioti naujagimiai (n=64)	Vidutinio neišnešiotumo naujagimiai (n=71)	Vėlyvojo neišnešiotumo naujagimiai (n=282)	Ypač ir labai mažo GS naujagimiai (n=48)	Mažo GS naujagimiai (n=205)	Suboptimalaus GS naujagimiai (n=125)	Normalaus GS naujagimiai (n=39)		
K00-K95 - Virškinimo sistemos ligos	21 32,8	17 23,9	76 27,0	17 35,4	51 24,9	35 28,0	11 28,2	**114** **27,3***	**183 997** **33,1**
L00-L99 - Odos ir poodžio ligos	9 14,1	14 19,7	51 18,1	5 10,4	39 19,0	25 20,0	5 12,8	**74** **17,7***	**74 953** **13,5**
M00-M99 - Jungiamojo audinio ir raumenų bei skeleto ligos (° GS, GA*)	9 14,1	12 16,9	71 25,2	8 16,7	48 23,4	27 21,6	9 23,1	**92** **22,1*****	**60 376** **10,8**
N00-N99 - Lyties ir šlapimo sistemos ligos	9 14,1	13 18,3	43 15,2	6 12,5	35 17,1	19 15,2	5 12,8	**65** **15,6*****	**25 428** **4,6**
P00-P96 - Tam tikros perinatalinio laikotarpio būklės	5 7,8	5 7,0	18 6,4	4 8,3	15 7,3	7 5,6	2 5,1	**28** **6,7*****	**10 693** **1,9**
Q00-Q99 - Įgimtos formavimosi ydos, deformacijos ir chromosomų anomalijos (* GS)	29 45,3	27 38,0	92 32,6	22 45,8	82 40,0	37 29,6	7 17,9	**148** **35,5*****	**55 649** **10**
Iš viso (atvejų skaičius visuose ligų skyriuose)	225	263	988	186	746	441	103	**1 476**	-

p reikšmė ° <0,1, * <0,05, ** <0,01, *** <0,00; GS ir GA skliausteliuose rodo, kurie palyginimai buvo reikšmingi. Žvaigždutės skiltyje „Iš viso (pagal skyrių) mūsų tyrime“ nurodo statistiškai reikšmingus sergamumo paplitimo skirtumus tarp mūsų tyrimo kohortos ir bendrosios Lietuvos vaikų populiacijos

13 lentelė. Tiriamosios populiacijos (nuo gimimo iki 18 metų) sergamumas labiausiai paplitusiomis specifinėmis ligomis ir sveikatos sutrikimais pagal TLK-10 ligų klasifikaciją

Nr.	Diagnozė	TLK-10 kodas	Vaikų skaičius	Procentais proc.	Ligų skyrius
1.	**Hipermetropija**	H52.0	158	**37,9**	H00-H59 – Akies ir jos priedinių organų ligos
2.	**Vėjaraupiai**	B01	137	**32,9**	A00-B99 – Tam tikros infekcinės ir parazitų sukeliamos ligos
3.	**Specifinis tarimo ir kalbos raidos sutrikimas**	F80	112	**26,9**	F01-F99 – Psichikos ir elgesio sutrikimai
4.	**Rachitas (aktyvus)**	E55.0	90	**21,6**	E00-E89 – Endokrininės, mitybos ir medžiagų apykaitos ligos
5.	**Anemija (nepatikslinta)**	D64.9	82	**19,7**	D50-D89 – Kraujo ir kraujodaros organų ligos bei tam tikri sutrikimai, susiję su imuniniais mechanizmais
6.	**Bambos išvarža**	K42	74	**17,7**	K00-K95 – Virškinimo sistemos ligos
7.	**Laikysenos kifozė**	M40.0	67	**16,1**	M00-M99 – Jungiamojo audinio ir raumenų bei skeleto ligos
8.	**Įgimtos pėdos deformacijos**	Q66	63	**15,1**	Q00-Q99 – Įgimtos formavimosi ydos, deformacijos ir chromosomų anomalijos
9.	**Astigmatizmas**	H52.2	61	**14,6**	H00-H59 – Akies ir jos priedinių organų ligos
10.	**Adenoidų hipertrofija**	J35.2	61	**14,6**	J00-J99 – Kvėpavimo sistemos ligos
11.	**Įgimtos širdies pertvaros formavimosi ydos**	Q21	61	**14,6**	Q00-Q99 – Įgimtos formavimosi ydos, deformacijos ir chromosomų anomalijos
12.	**Astma**	J45	57	**13,7**	J00-J99 – Kvėpavimo sistemos ligos
13.	**Atopinis dermatitas**	L20	56	**13,4**	L00-L99 – Lyties ir šlapimo sistemos ligos
14.	**Trumparegystė**	H52.1	48	**11,5**	H00-H59 – Akies ir jos priedinių organų ligos
15.	**Hemangioma**	D18.0	26	**6,2**	C00-D49 **–** Navikai
16.	**Alerginis rinitas**	J30	24	**5,8**	J00-J99 – Kvėpavimo sistemos ligos
17.	**Šlapimo takų infekcija, kurios lokalizacija nepatikslinta**	N39.0	22	**5,3**	N00-N99 – Urogenitalinės sistemos ligos
18.	**Neorganinė enurezė**	F98.0	19	**4,6**	F01-F99 – Psichikos ir elgesio sutrikimai
19.	**Skarlatina**	A38	18	**4,3**	A00-B99 – Tam tikros infekcinės ir parazitų sukeliamos ligos
20.	**Nutukimas**	E66	18	**4,3**	E00-E89 – Endokrininės, mitybos ir medžiagų apykaitos ligos

Dažniausios buvo akių ir priedinių organų ligos, paveikusios daugiau kaip pusę tiriamosios populiacijos, o jų paplitimas ypač ir labai mažo GS grupėje buvo 1,5 karto didesnis nei normalaus GS grupėje (**12 lentelė**). Dažniausiai pasitaikančios būklės buvo hipermetropija (beveik 38 proc.), astigmatizmas (apie 15 proc.) ir trumparegystė (apie 12 proc.) (**13 lentelė**).

Tam tikros infekcinės ligos paveikė 39 proc. neišnešiotų vaikų populiacijos, be reikšmingų skirtumų tarp neišnešiotumo subkategorijų; iš jų vėjaraupiai sudarė apie 33 proc. atvejų (**12** ir **13 lentelės**). Įgimtos anomalijos buvo diagnozuotos beveik 36 proc. neišnešiotų vaikų, dažniausios būklės – įgimtos pėdų deformacijos (apie 15 proc.) ir įgimtos širdies pertvaros anomalijos (apie 15 proc.). Šios būklės buvo reikšmingai dažnesnės ypač ir labai mažo (apie 46 proc.) ir mažo (maždaug 40 proc.) GS grupėse nei suboptimalaus (apie 30 proc.) ir normalaus (beveik 18 proc.) GS grupėse ($p<0,05$) (**12** ir **13 lentelės**).

Aukštas sergamumas (beveik 30 proc.) pasireiškė kvėpavimo takų ligų skyriuje, čia didesnio GS grupėse sergamumas buvo mažesnis (**12 lentelė**). Dažniausios šios kategorijos ligos buvo adenoidų hipertrofija (apie 15 proc.), astma (beveik 14 proc.) ir alerginis rinitas (maždaug 6 proc.) (**13 lentelė**). Endokrininės, mitybos ir medžiagų apykaitos ligos sudarė beveik 30 proc., o jų pasiskirstymas tarp analizuotų grupių buvo panašus; dažniausiai pasitaikė aktyvus rachitas (apie 22 proc.) ir nutukimas (maždaug 4 proc.) (**12** ir **13 lentelės**).

Psichikos ir elgesio sutrikimai buvo pastebėti beveik 30 proc. neišnešiotų vaikų populiacijos ir buvo tolygiai pasiskirstę tarp subkategorijų, o specifiniai tarimo ir kalbos raidos sutrikimai sudarė beveik 27 proc. ir užėmė trečiąją vietą pagal paplitimą (**12** ir **13 lentelės**). Be to, anemija paveikė beveik penktadalį tiriamosios populiacijos, o normalaus GS grupėje sergamumas kraujo ir imuninės sistemos ligomis buvo reikšmingai mažesnis nei žemesnio GS grupėse ($p<0,1$) (**12 lentelė**).

Nors statistiškai reikšmingų sergamumo analizės rezultatų tarp grupių buvo nedaug, giliau neišnešiotų vaikų grupėse diagnozės buvo dažnesnės daugumoje TLK-10 ligų skyrių. Šis dėsningumas analizuojant ligų procentinį pasiskirstymą pagal GS buvo ryškesnis nei pagal GA, išskyrus raumenų ir skeleto bei jungiamojo audinio ligas; čia vėlyvojo neišnešiotumo grupės kūdikių sergamumas buvo didesnis ($p<0,1$) (**12 lentelė**). Be to, didesnis kumuliacinis tiriamosios populiacijos sergamumas buvo ypač ryškus lyginant su bendrosios Lietuvos vaikų populiacijos sergamumu (**12 lentelė**).

3.4.2. Individualių vaiko gimimo veiksnių įtaka vidutiniam ligų skaičiui ir TLK-10 ligų skyriams

Pagrindinis neigiamos binominės regresijos analizės tikslas buvo nustatyti individualių vaiko gimimo veiksnių įtaką vidutiniam ligų skaičiui

nuo gimimo iki 18 metų. Rezultatai parodė, kad vidutinis ligų skaičius yra 34 proc. didesnis suboptimalaus GS grupėje, 50 proc. didesnis mažo GS grupėje, net 77 proc. didesnis ypač ir labai mažo GS grupėje, palyginti su normalaus GS grupės vaikais (**14 lentelė**). Šie rezultatai leidžia daryti išvadą, kad mažesnis GS yra reikšmingas rizikos veiksnys, lemiantis didesnį ligų skaičių nuo gimimo iki paauglystės.

Priešingai nustatyta, kad GA ir lytis neturėjo reikšmingos įtakos vidutiniam ligų skaičiui. Šis rezultatas pateisina lyčiai neutralaus požiūrio taikymą analizėje. Nereikšmingas GA grupės poveikis gali būti paaiškinamas grupavimu į tris kategorijas, tai buvo būtina dėl mažo atvejų skaičiaus tam tikromis gestacijos savaitėmis.

Modeliuojant vidutinį vieno vaiko TLK-10 ligų skyrių skaičių tame pačiame amžiaus tarpsnyje (**15 lentelė**) paaiškėjo, kad mažesnis GS susijęs su didesne sveikatos problemų įvairove tarp TLK-10 skyrių, pabrėžiant jo, kaip lemiamo ilgalaikio sergamumo veiksnio, svarbą.

14 lentelė. Tiriamosios populiacijos (nuo gimimo iki 18 metų) lyties, gimimo svorio ir gestacijos amžiaus grupių įtaka tam tikrų skirtingų ligų paplitimui, remiantis neigiamos binominės regresijos rezultatais. PK – paplitimo koeficientas (angl. *Incidence rate ratio*). PI – pasikliautinasis intervalas

Faktorius	**Koeficientas**	**P reikšmė**	**PK ir 95 % PI**	
			PK	**95 % PI**
Lytis (mergaitė)	–0,0192	0,7715	0,9810	(0,8615; 1,1170)
Gimimo svorio grupė (suboptimalaus GS naujagimiai)	0,2899	0,0279 *	1,3363	(1,0331; 1,7326)
Gimimo svorio grupė (mažo GS naujagimiai)	0,4061	0,0020 **	1,5009	(1,1619; 1,9437)
Gimimo svorio grupė (ypač ir labai mažo GS naujagimiai)	0,5726	0,0039 **	1,7728	(1,2042; 2,6150)
Gestacijos amžiaus grupė (vidutinio neišnešiotumo naujagimiai)	–0,0527	0,5890	0,9487	(0,7839; 1,1479)
Ypač ir labai neišnešioti naujagimiai	–0,2195	0,1257	0,8029	(0,6065; 1,0612)

p reikšmė * <0,05, ** <0,01, *** <0,001

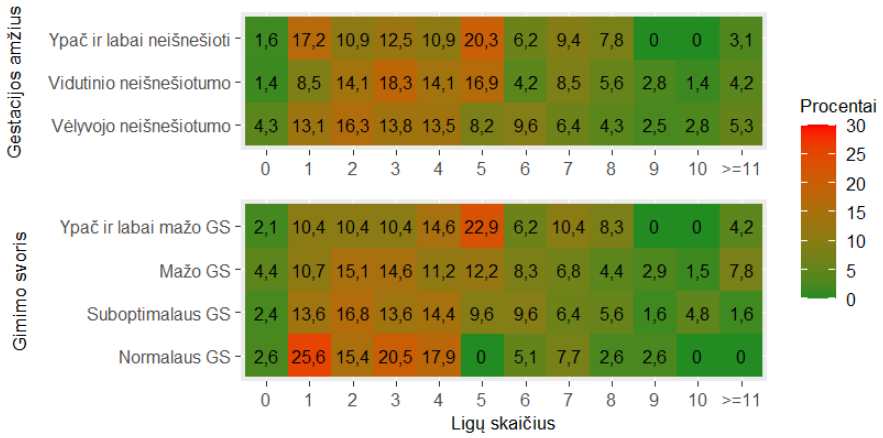
15 lentelė. Tiriamosios populiacijos (nuo gimimo iki 18 metų) lyties, gimimo svorio ir gestacijos amžiaus grupių įtaka skirtingų TLK-10 ligų skyrių paplitimui, remiantis neigiamos binominės regresijos rezultatais. PK – paplitimo koeficientas (angl. *Incidence rate ratio*). PI – pasikliautinasis intervalas

Faktorius	Koeficientas	p reikšmė	PK ir 95 proc. PI	
			PK	95 % PI
Lytis (mergaitė)	–0,0036	0,95136	0,9964	(0,8875; 1,1188)
Gimimo svorio grupė (suboptimalaus GS naujagimiai)	0,2904	0,0161 *	1,3369	(1,0591; 1,7005)
Gimimo svorio grupė (mažo GS naujagimiai)	0,3496	0,0037 **	1,4185	(1,1248; 1,8028)
Gimimo svorio grupė (ypač ir labai mažo GS naujagimiai)	0,5730	0,0014 **	1,7735	(1,2512; 2,5231)
Gestacijos amžiaus grupė (vidutinio neišnešiotumo naujagimiai)	–0,0025	0,7701	0,9749	(0,8219; 1,1545)
Ypač ir labai neišnešioti naujagimiai	–0,2155	0,0961	0,8062	(0,6236; 1,0361)

p reikšmė * <0,05, ** <0,01, *** <0,00

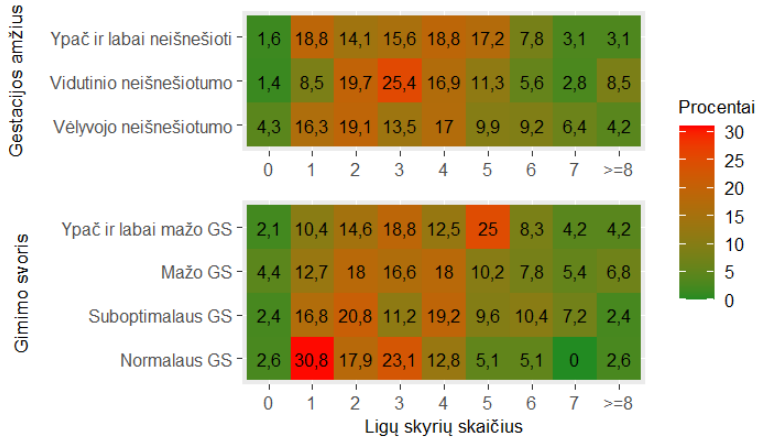
3.4.3. Sveikatos būklės sudėtingumas ir skirtingų TLK-10 ligų skyrių sutrikimų tarpusavio ryšiai

Mažesnis GS ir gilesnis neišnešiotumo laipsnis buvo susiję su didesniu vienam vaikui diagnozuotų ligų skaičiumi nuo gimimo iki 18 metų. Šį dėsningumą aiškiai iliustruoja ligų skaičiaus pasiskirstymas pagal GA ir GS kategorijas (**12 pav.**)



12 pav. Asmenų, kuriems nuo gimimo iki 18 metų diagnozuotas skirtingas tam tikrų atskirų ligų skaičius, procentinė dalis, suskirstyta pagal GA ir GS grupes (vaizduojama šilumos žemėlapiais)

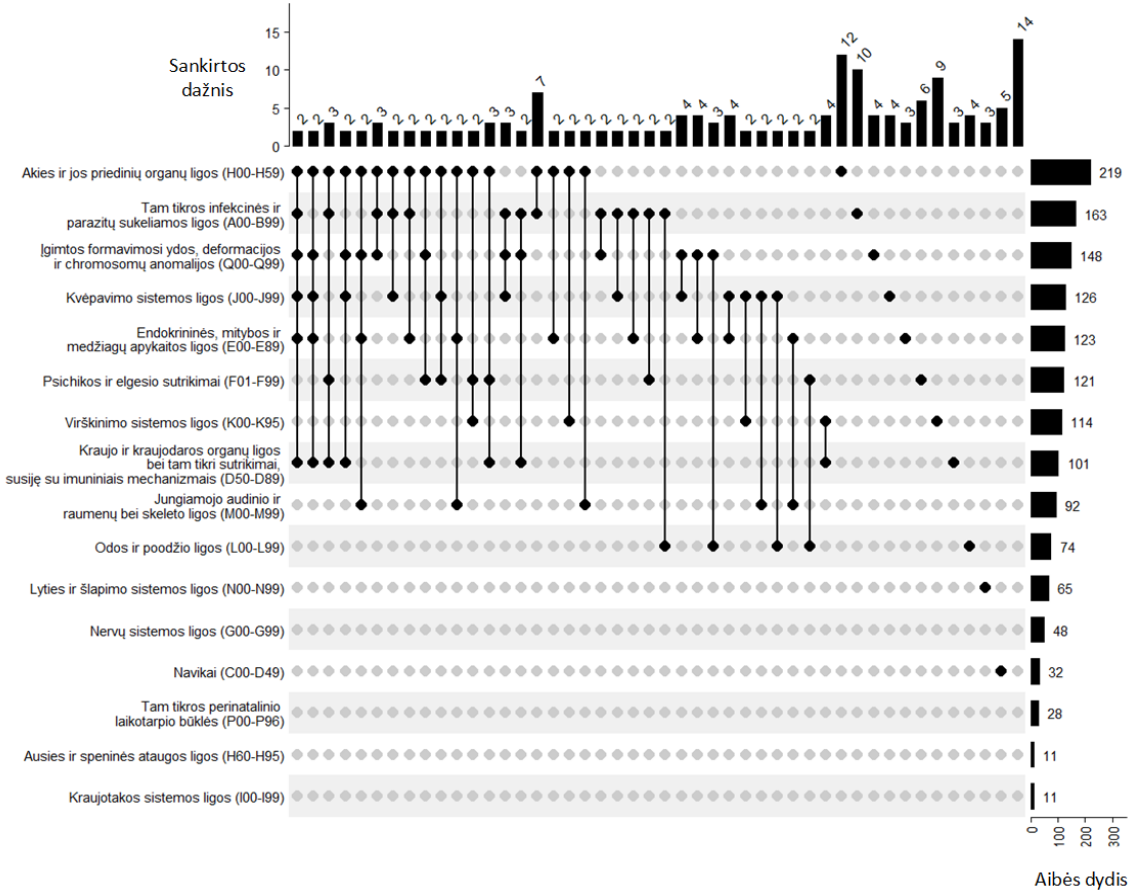
Asmenims, gimusiems su mažesniu GS ir didesniu neišnešiotumo laipsniu, dažniau buvo diagnozuoti sutrikimai, apimantys kelis TLK-10 ligų skyrius nuo gimimo iki 18 metų. Ši tendencija atsispindi vieno vaiko TLK-10 ligų skyrių skaičiaus pasiskirstymo dažnyje (**13 pav.**). Taigi, šilumos žemėlapiai parodė, kad ir mažesnis GS, ir mažesnis GA buvo susiję su didesne tikimybe turėti kelias ligas ir ligų skyrius, tačiau ryškesnė tendencija pastebėta GS kategorijose.



13 pav. Asmenų, kuriems nuo gimimo iki 18 metų diagnozuotas skirtingas TLK-10 ligų skyrių skaičius, procentinė dalis, suskirstyta pagal GA ir GS grupes (vaizduojama šilumos žemėlapiais)

Vis dėlto, atlikus Fišerio tikslųjį testą, reikšmingų ligų skaičiaus skirtumų tarp GA grupių nenustatyta. Reikšmingi skirtumai nustatyti tarp ypač ir labai mažo ir normalaus GS grupių ($p<0,05$) bei tarp mažo ir normalaus GS grupių ($p<0,05$). Ypač ir labai mažo GS grupės asmenys, turintys penkias ar daugiau ligų, sudarė 52 proc., mažo GS grupės – 44 proc., o normalaus GS grupėje tik 18 proc. (**12 pav.**). Atsižvelgiant į TLK-10 ligų skyrius, reikšmingi skirtumai buvo pastebėti tik tarp ypač ir labai mažo ir normalaus GS grupių ($p<0,05$) bei tarp mažo ir normalaus GS grupių ($p<0,05$). Ypač ir labai mažo GS grupės asmenys, turintys diagnozes iš penkių ar daugiau TLK-10 ligų skyrių, sudarė 41,7 proc., mažo GS grupėje – 30,2 proc., o normalaus GS grupėje tik 12,8 proc. (**13 pav.**).

Be to, sudėtingų ryšių ir sankirtų tarp skirtingų TLK-10 ligų skyrių ištyrimui ir analizei buvo naudojama *UpSet* diagrama (**14 pav.).** Ši diagrama rodo visas pagal TLK-10 ligų skyrius diagnozuotų ligų sankirtas, leidžiančias įžvelgti unikalius ligų sankibų modelius. Iš viso buvo gauta 300 skirtingų tarpusavyje susijusių TLK-10 ligų skyrių derinių variantų. Į diagramą buvo įtraukti tik tie atvejai, kurių dažnis viršijo vieną. Horizontaliose juostose parodytas atvejų dažnis pagal skyrius, o centrinėje matricoje, pažymėtoje užpildytais taškais ir sujungtoje vertikaliomis linijomis, nurodyti kiekvienoje sankibos variacijoje dalyvaujantys skyriai. Pavyzdžiui, septyniems asmenims diagnozės buvo nustatytos ir H00-H59 (Akių ir pridėtinių organų ligos), ir A00-B99 (infekcinės ligos) skyriuose, o į kitus skyrius įtrauktų ligų nebuvo. Dažnai pasikartojančių ligų skyrių sankibų variacijų buvo nedaug, todėl dauguma (84,7 proc.) ligų skyrių tarpusavio sąveikų variacijų atvejų neišnešiotų vaikų populiacijoje buvo labai individualūs ir unikalūs, kurie dažniausiai pasireiškė pavieniais dažniais ir neatsispindi šioje diagramoje.



14 pav. Įvairių tarpusavyje susijusių TLK-10 ligų skyrių derinių variantai, pateikti *UpSet* grafike. Dešinėje grafiko pusėje esantys horizontalūs stulpeliai rodo kiekviename TLK-10 ligų skyriuje pasitaikiusių atvejų skaičių. Centrinėje matricoje, pažymėtoje užpildytais taškais ir sujungtoje vertikaliomis linijomis, nurodyti kiekvienoje sankibos variacijoje dalyvaujantys skyriai. Vertikalūs stulpeliai grafiko viršuje kiekybiškai nurodo atvejus kiekviename derinyje, pavyzdžiui, dvylika asmenų, kuriems diagnozės nustatytos tik H00-H59 (Akių ir priedinių organų ligų) skyriuje

4. IŠVADOS

1. Gestacijos amžiui ir lyčiai pritaikytos populiacijos pagrindu sudarytos Lietuvos naujagimių svorio ir ilgio ribinės vertės atskleidžia reikšmingus Lietuvos naujagimių kūno dydžio ir pasaulinio *Intergrowth-21st* standarto skirtumus. *Intergrowth-21st* standartas statistiškai reikšmingai nepakankamai įvertina mažo pagal gestacijos amžių naujagimių paplitimą ir pervertina didelio pagal gestacijos amžių naujagimių paplitimą, ypač išnešiotų ir užsitęsusių nėštumų atvejais. Regioninės normogramos tiksliau atspindi unikalius Lietuvos naujagimių augimo dėsningumus, išryškina rizikos grupių naujagimių klasifikavimo skirtumus.
2. Pasauliniai standartai, tokie kaip *Intergrowth-21st*, yra tinkami vertinti naujagimių galvos apimtį ankstyvose gestacijos savaitėse, tačiau vėlesnėse gestacijos savaitėse Lietuvos naujagimių galvos apimtis sistemingai viršija pasaulinius standartus. Regioninės gestacijos amžiui ir lyčiai pritaikytos populiacijos pagrindu sudarytos naujagimių galvos apimties ribinės vertės geriau atspindi specifinius Lietuvos naujagimių galvos apimties ypatumus ir taip pabrėžia regioninių ribinių verčių svarbą.
3. Gimimo svoris daro reikšmingą poveikį ilgalaikiams Lietuvos neišnešiotų naujagimių augimo sutrikimams, o gestacijos amžius dinamiškai formuoja kūno masės indekso (KMI) trajektorijas ir didina nutukimo riziką ypač ir labai neišnešiotų naujagimių grupėse. Berniukai patiria didesnius ilgalaikius svorio ir KMI iššūkius nei mergaitės.
4. Prieš laiką Lietuvoje gimę asmenys susiduria su didele daugiasistemio sergamumo našta, nes didžiausias ligų paplitimas pasireiškia iki 7 metų. Mažas gimimo svoris reikšmingai susijęs su didesniu polinkiu į daugiasistemį sergamumą ir didesne ligų įvairove pagal TLK-10 skyrius. Unikalūs ir sudėtingi gretutinių ligų dėsningumai pabrėžia personalizuotos, daugiadalykės priežiūros poreikį, siekiant veiksmingai valdyti sudėtingą prieš laiką gimusių asmenų sveikatos dinamiką.

5. PRAKTINĖS REKOMENDACIJOS

Adaptuojant regionines konkrečios populiacijos specifiniams veiksniams pritaikytas kūno dydžio vertinimo ribines vertes, galima pagerinti naujagimių ir vaikų sveikatos vertinimo tikslumą. Šiame tyrime populiacijos pagrindu sudarytos ribinės vertės ir kreivės jau dabar gali būti naudojamos Lietuvos naujagimių fizinei būklei vertinti, padėtų tiksliau nustatyti rizikos grupėms priklausančius asmenis ir priimti pagrįstus klinikinius sprendimus.

Šio tyrimo rezultatai pabrėžia būtinybę išplėsti šiuo metu Lietuvoje vykdomą prieš laiką gimusių vaikų stebėseną, ypač iki 7-erių metų, nes tuo laikotarpiu susergama daugiausia ligų. Ankstyvosios intervencijos, skirtos augimo sutrikimams, mitybos poreikiams ir gretutinėms ligoms koreguoti, gali sumažinti ilgalaikes sveikatos rizikas ir užtikrinti optimalų vystymąsi.

Sudėtingi ir unikalūs prieš laiką gimusių asmenų gretutinių ligų dėsningumai pabrėžia personalizuotos, daugiadalykės priežiūros svarbą. Koordinuotas pediatrų, endokrinologų, neurologų, psichikos sveikatos ir kitų specialistų bendradarbiavimas yra būtinas, siekiant veiksmingai valdyti sudėtingą ir daugialypę prieš laiką gimusių asmenų sveikatos dinamiką.

Be to, nacionalinės sveikatos priežiūros strategijos turėtų skatinti reguliarias prieš laiką gimusių asmenų sveikatos patikras, laiku atliekamą vakcinaciją ir ankstyvą lėtinių ligų diagnostiką. Visuomenės sveikatos iniciatyvos taip pat turėtų būti orientuotos į šeimų ir sveikatos priežiūros specialistų informuotumo didinimą apie neišnešiotumo keliamas rizikas ir aktyvios, tikslinės sveikatos priežiūros naudą.

6. ATEITIES PERSPEKTYVOS

Parengus regioninių populiacijos pagrindu sudarytų normogramų taikymo klinikinėje praktikoje metodines rekomendacijas, būtų galima pagerinti naujagimių ir vaikų sveikatos priežiūros nuoseklumą ir kokybę. Tai padėtų integruoti mokslinių tyrimų rezultatus į praktiką ir užtikrinti, kad būtų veiksmingai patenkinti specifiniai prieš laiką gimusių asmenų poreikiai.

Be to, tolesni tyrimai turėtų būti skirti sudėtingų tarpusavio ryšių tarp įvairių prieš laiką gimusių asmenų sveikatos būklių nagrinėjimui. Ypač daug dėmesio reikėtų skirti gimimo veiksnių, tokių kaip gimimo svoris ir gestacijos amžius, poveikiui siekiant suprasti vystymosi plastiškumą ir ilgalaikę sveikatos dinamiką. Siekiant patvirtinti tyrimo išvadas ir nustatyti specifinius ligų ryšius, kurie neapsiribotų TLK-10 klasifikacija, būtina atlikti daugiacentrius longitudinius tyrimus, kuriuose dalyvautų įvairios kohortos, ir taikyti pažangius analitinius modelius.

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Regional references vs. international standards for assessing weight and length by gestational age in Lithuanian neonates

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Introduction: There is no global consensus as to which standards are the most appropriate for the assessment of birth weight and length. The study aimed to compare the applicability of regional and global standards to the Lithuanian newborn population by sex and gestational age, based on the prevalence of small or large for gestational age (SGA/LGA).
Materials and Methods: Analysis was performed on neonatal length and weight data obtained from the Lithuanian Medical Birth Register from 1995 to 2015 (618,235 newborns of 24–42 gestational weeks). Their distributions by gestation and sex were estimated using generalized additive models for location, scale, and shape (GAMLSS), and the results were compared with the INTERGROWTH-21st (IG-21) standard to evaluate the prevalence of SGA/LGA (10th/90th centile) at different gestational ages.
Results: The difference in median length at term between the local reference and IG-21 was 3 cm–4 cm, while median weight at term differed by 200 g. The Lithuanian median weight at term was higher than in IG-21 by a full centile channel width, while the median length at term was higher by two channel widths. Based on the regional reference, the prevalence rates of SGA/LGA were 9.7%/10.1% for boys and 10.1%/9.9% for girls, close to the nominal 10%. Conversely, based on IG-21, the prevalence of SGA in boys/girls was less than half (4.1%/4.4%), while the prevalence of LGA was double (20.7%/19.1%).
Discussion: Regional population-based neonatal references represent Lithuanian neonatal weight and length much more accurately than the global standard IG-21 which provides the prevalence rates for SGA/LGA that differ from the true values by a factor of two.

KEYWORDS

birth, growth charts, newborns, preterm (birth), SGA (small for gestational age), LGA (large for gestational age), global, regional

Introduction

The health status of a newborn is reflected by its body size at birth. Therefore, the assessment of birth weight and length by applying appropriate standards not only plays an essential role in good clinical care but is also sustainable with an increasing evidence of preventable adverse growth-related outcomes (1).

When considering neonatal body size, two groups with an increased risk for negative perinatal outcomes and future cardio-metabolic changes have been identified (2): infants born Small for Gestational Age (SGA) and infants born Large for Gestational Age (LGA). The WHO expert committee defined SGA as infants born below the 10th centile of birth weight for gestational age and sex specific reference population (3). Accordingly, LGA is defined as birth weight above the 90th centile. Importantly, SGA refers to both, infants who are constitutionally small and fall within the lower tail of the distribution and those with intra-uterine growth restriction (IUGR) due to various adverse factors (4).

Moreover, a range of recent publications established the relationship between the preterm newborn body's parameters at birth, postnatal growth restriction and later growth failure with short- and long-term health consequences (5–7).

Thus, from a clinical perspective, the priority would be to reduce health effects related to size at birth by providing a preventive and promotive care, and monitoring for complications (8). Adequate early nutrition is extremely important in clinical practice to foster optimal neurodevelopmental outcomes to avoid negative consequences of aggressive nutritional approaches in the future. However, to provide the mentioned nutrition, doctors must properly evaluate the newborn size according to their gestational age (small, large, and appropriate) at birth. This classification is difficult to achieve, especially for preterm infants who are a unique and highly heterogeneous group. Currently, neonatal standards and references are the most widely used tools for categorizing newborns into sub-groups.

At present, several types of charts for growth assessment of premature newborns are available. One of the commonly used types is intrauterine growth charts based on cross-sectional anthropometric measurements taken from infants of varying gestational ages at birth presented as the gold standard for premature infant growth (9). However, the application of intrauterine growth rates to VLBW infants in an extra-uterine environment is considered controversial (10, 11). Instead, a separate set of postnatal growth curves is promoted. This group of charts reflects the longitudinal growth of preterm infants experiencing various clinical conditions which might be treated with different nutritional management plans (12). And while postnatal growth curves increase our understanding of postnatal preterm born child growth, they also have their drawbacks, such as being too highly influenced by medical and nutritional support practices applied to the sample size (13).

Another point of debate is the choice between customized and population-based references. Proponents of customized charts claim that they improve the prediction of adverse perinatal outcomes and differentiate better between "small-but-healthy" infants and growth-restricted ones (14, 15). Opponents argue that the existing customization models may be confusing pathological and physiological causes of "smallness" and that customizing birthweight centiles for maternal characteristics has little justification (16, 17). Instead, the best estimate of a given infant's birthweight is claimed to be the one that is close to the population average (16).

A similar discussion arises when choosing between the regional or global references (9, 18–21). Recently, the Intergrowth-21st (IG-21) consortium proposed to adopt their single set of international standards for assessment of newborn size and physical status but found little support (22–24). With the rising evidence that there is a normal physiological variation between different countries and ethnic groups, the "one-size-fits-all" standard seems to fit less than expected.

Considering all the above, in this study, we have set several objectives: (a) to construct the national birth weight/length reference values and curves for Lithuanian newborns from 22 to 42 GA weeks; (b) to compare the results with the recently adopted global IG-21 (18, 20) standards; (c) to assess the diagnostic accuracy of clinical practice in identifying and classifying newborns of various gestational age as SGA and LGA infants, by using different tools.

Materials and methods

Study design and sample selection

Birth data from the Lithuanian Medical Data of Births for the period of 1995–2015 were retrieved from the Health Information Center of the Institute of Hygiene in Vilnius, Lithuania, including liveborn singletons of between 22 and 42 completed weeks of gestational age (GA). We excluded multiple births, stillbirths, infants with undetermined sex or major congenital malformations and syndromes, and those with incomplete data. Also, the cases where weight or length were more than 3 standard deviations (SD) from the mean, following WHO standards (25), were excluded. In total, 618,235 newborns were included. **Figure 1** shows the flow diagram.

LMST method

The LMS method estimates growth reference centiles by modelling any skewness present in the measurement distribution (26). It assumes that a power transformation can normalize the data by adjusting for skewness. LMST method (27) is an extension of the LMS method that models both skewness and leptokurtosis using the Box-Cox t (BCT) distribution. It can be used to model excess kurtosis over the normal distribution (leptokurtic data) when the Box-Cox transformation fails to transform the data close to normality due to the presence of kurtosis. The BCT distribution is defined by a power transformation, Y^{ν}, which follows a truncated t distribution that is shifted and scaled. The truncated t distribution has a degrees

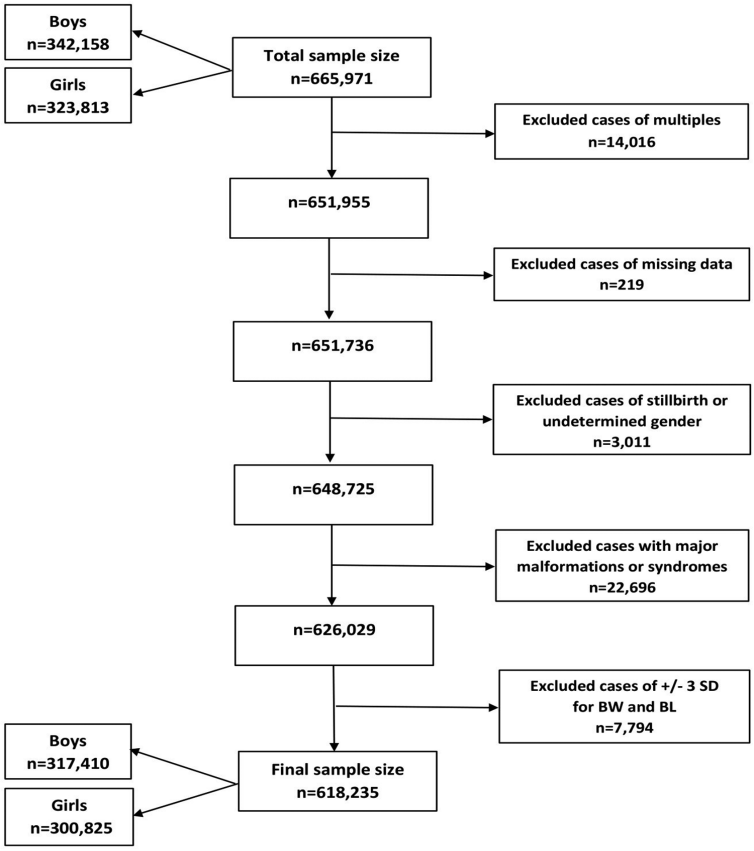

FIGURE 1
Flow diagram of the sampling procedure and exclusion criteria in this study. BW, birth weight; BL, birth length; *n*, number; SD, standard deviation.

of freedom parameter, τ. The BCT distribution is characterized by four parameters and is denoted as BCT (μ, σ, ν, τ). The parameters μ, σ, ν and τ may be interpreted as relating to location (median), scale (centile-based coefficient of variation), skewness (power transformation to symmetry) and kurtosis (degrees of freedom), respectively.

Statistical analysis

Generalized additive models for location, scale, and shape (GAMLSS) were fitted to obtain the centile (3rd, 10th, 25th, 50th, 75th, 90th and 97th) reference values and curves of birth weight/length by GA and sex separately (26). The LMST method (BCT distribution) was applied to the data obtained on each sex and each measurement. The resulting main centiles (3rd, 10th, 50th, 90th and 97th) from 24 gestational weeks were compared with their counterparts in IG-21 (18, 20). The analysis was carried out using the GAMLSS package (version 4.3-3) of R 4.0.3 (28).

Two published standards of the IG-21 project (18, 20) were presented for both sexes for every gestational week and day separately (e.g., 30 + 0, 30 + 1), while GA of the present study was recorded as complete gestational weeks (e.g., 30, 31). Therefore, the comparison of present study with IG-21 project by GA was made comparing the middle day of gestational week of IG-21 (i.e., 30 + 3) which referred to the mean of birth weight/length of the certain gestational week. The validity of this procedure was checked and proved mathematically. The

frequency and percentage of neonates meeting the criteria for SGA defined as birth weight below the 10th centile and LGA defined as birth weight above the 90th centile were determined and compared using the cut-off values based on our reference and the IG-21.

Results

The sample size of our study (Table 1) increased steeply with gestational age from less than 50 neonates at 22–24 gestational weeks to more than 140,000 at term for each sex. The mean birth weight of boys was ∼50–100 g larger than for girls at preterm gestations, and larger by ∼100–180 g at term and post-term periods. The difference in mean birth length between sexes varied mainly from 0.1 to 0.6 cm at preterm period, and from 0.6 to 0.8 cm at later gestations (Table 1).

Our study constructed the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th smoothed centile curves according to gestational age and sex for birth weight and length of Lithuanian newborns (Figures 2–5). The variability of birth weight rose with gestational age for both sexes. In contrast, the variability of birth length fell with increasing gestation, and negative skewness in the distribution was evident (Figures 2–5). Tables 2, 3 demonstrate the values of smoothed gestational age- and sex-adjusted centiles (3rd–97th) for birth weight/length of Lithuanian newborns. The LMS parameters for birth weight/length by sex and gestational age are presented in Supplementary Tables S1, S2.

The 3rd, 50th and 97th Lithuanian birth weight centiles by sex and gestation were similar to those of IG-21 at extremely early gestations (24–27 weeks), especially for boys and the 97th centile (Figures 2, 3). With increasing gestation, and particularly after 37 weeks, the gap between the Lithuanian and IG-21 centiles widened to almost one centile channel or two-thirds of an SD (Figures 2, 3). The IG-21 median was close to the Lithuanian 25th centile (difference of ∼200 g), while the 97th IG-21 centile was near the Lithuanian 90th (difference of ∼350 g). At the 3rd centile, the differences among term newborns (37–40 gestational weeks) were more pronounced (200 g) than post-term (100 g) (Figures 2, 3).

For birth length, the median and lower IG-21 centiles were close to the Lithuanian centiles at early gestations, while the higher centiles differed by almost a full centile channel, i.e., 1.0–1.5 cm (Figures 4, 5). In late preterm (34–36 weeks) the differences became more pronounced and extended across all centiles, the gap widening to nearly two centile channels. The 97th IG-21 centile fell to near the Lithuanian 50th, while the 50th IG-21 centile fell to the Lithuanian 10th. At the 50th and 97th centiles, the differences at term amounted to 3 cm–4 cm, while at the 3rd centile, the difference was less at 2 cm (Figures 4, 5).

A total of 9.7% (30,859) boys were SGA based on the Lithuanian 10th centile, compared to 4.1% based on the IG-21 10th centile, less than half the prevalence (Table 4). Similarly for girls, the prevalence of SGA was 10.1% Lithuanian (30,439) vs. 4.4% IG-21. Both instruments showed the highest prevalence of

TABLE 1 Birth weight (g) and length (cm) of Lithuanian newborns by sex and gestational age (GA).

Boys ($n = 317,410$)					GA (in weeks)	Girls ($n = 300,825$)				
Count (n)	Weight (g)		Length (cm)			Count (n)	Weight (g)		Length (cm)	
	Mean	SD	Mean	SD			Mean	SD	Mean	SD
1*	915.0	–	37.0	–	**22**	8	635.3	111.0	29.0	3.2
12	706.9	115.0	31.8	2.2	**23**	13	649.9	83.2	30.9	1.9
38	773.0	109.0	33.2	3.0	**24**	46	715.0	96.3	33.0	2.6
93	849.3	121.6	33.7	2.8	**25**	82	798.0	105.5	33.6	2.2
136	966.9	144.7	35.4	2.4	**26**	139	892.4	157.3	34.7	2.8
196	1,106.9	181.0	37.0	2.8	**27**	174	1,028.6	187.9	36.3	3.3
304	1,229.3	193.9	38.1	2.9	**28**	239	1,181.3	237.4	37.9	3.0
291	1,375.5	235.2	39.8	2.9	**29**	255	1,314.2	236.0	39.2	3.1
445	1,542.7	243.4	41.4	2.8	**30**	405	1,485.8	253.2	40.9	3.1
488	1,756.5	263.3	42.9	2.9	**31**	431	1,662.7	298.7	42.3	3.0
849	1,946.9	288.2	44.3	2.6	**32**	720	1,886.5	309.4	44.0	2.8
1,116	2,152.2	326.1	45.6	2.6	**33**	909	2,061.3	325.4	45.0	2.7
1,877	2,381.1	351.6	46.8	2.5	**34**	1,609	2,289.8	355.2	46.3	2.5
2,858	2,585.0	354.1	47.8	2.3	**35**	2,421	2,482.8	355.9	47.4	2.3
5,592	2,772.3	368.8	48.9	2.3	**36**	4,967	2,679.1	360.8	48.5	2.2
13,141	3,124.5	404.4	50.7	2.2	**37**	11,219	3,009.5	393.0	50.1	2.1
33,850	3,363.7	417.5	51.7	2.1	**38**	29,873	3,224.0	407.3	51.1	2.1
68,016	3,540.8	413.1	52.5	2.1	**39**	63,919	3,397.1	405.0	51.8	2.1
144,625	3,670.0	421.4	53.0	2.1	**40**	141,902	3,519.9	405.9	52.3	2.1
40,947	3,773.0	425.0	53.5	2.2	**41**	39,209	3,609.1	415.1	52.7	2.1
2,535	3,774.2	492.0	53.4	2.4	**42**	2,285	3,594.3	449.3	52.6	2.3

n, count; Mean, mean; SD, standard deviation.
*An actual case that does not exceed the critical deviation from birth weight/length.

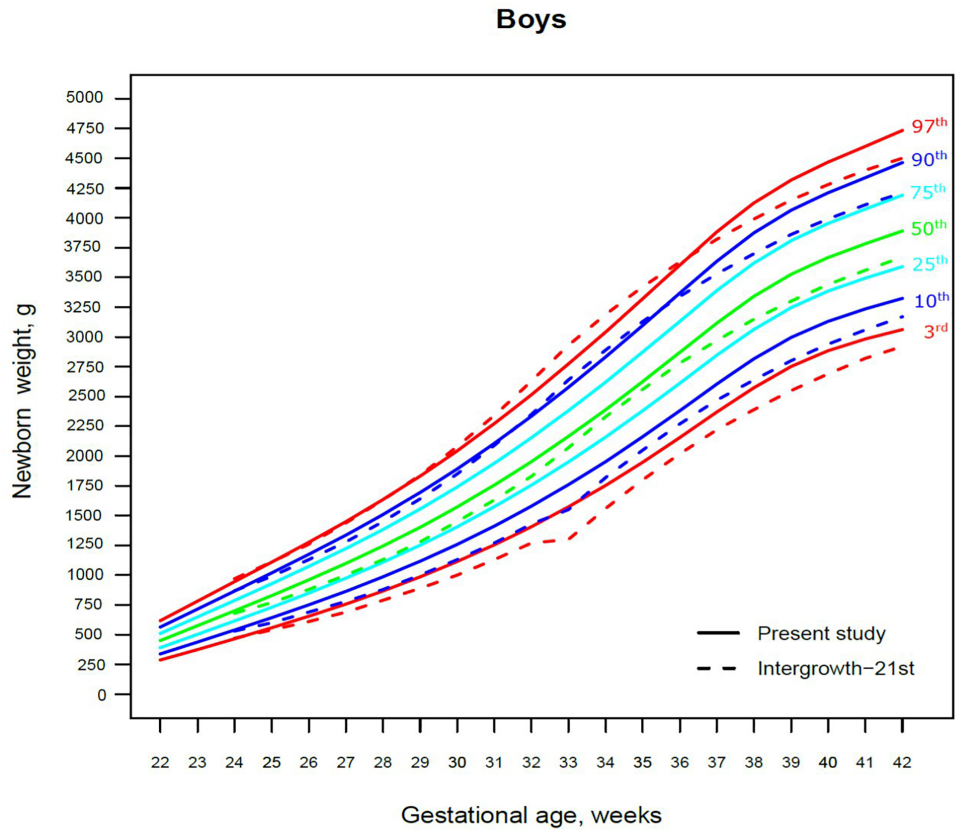

FIGURE 2
The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for birth weight (g) in Lithuanian boys and the 3rd, 10th, 50th, 90th and 97th centiles for INTERGROWTH-21st.

SGA in very and late preterm and post-term gestations of both sexes. What is more, the older the gestational age, the larger the discrepancy between the studies. At extremely preterm gestations (24–27 weeks), IG-21 underestimated SGA in boys by up to 3.1%, and in girls up to 6.9%. The largest SGA discrepancies at term and post-term were 6.9% for boys and 8.1% for girls (Table 4). The 10th centile curves in Figures 2, 3 illustrate the discrepancies in SGA. The IG-21 10th centile is close to the Lithuanian 3rd centile until 32 weeks, and only slightly higher at later gestations (Figures 2, 3).

In contrast, the incidence of LGA was 10.1% (31,972) for boys based on the Lithuanian 90th centile as against 20.7% using the IG-21 90th centile, i.e., more than double (Table 4). Similarly in girls, LGA prevalence was 9.9% (29,810) vs. 19.1%. The differences in prevalence were particularly marked in extremely preterm (4.4%–8%) and term, post-term periods (the difference of 4.8%–12.4% more expressed for boys). The 90th centile curves in Figures 2, 3 illustrate the discrepancies in LGA between the studies. The IG-21 90th centile is near the Lithuanian 75th centile at extremely preterm and term, with a gap of almost one centile channel post-term (Figures 2, 3).

Discussion

Growth centiles as clinical tools for assessing the infant's physical status have gained much importance in recent years. The choices between global or regional, and between customized and population-based growth references or growth standards for different populations are under debate (29, 30).

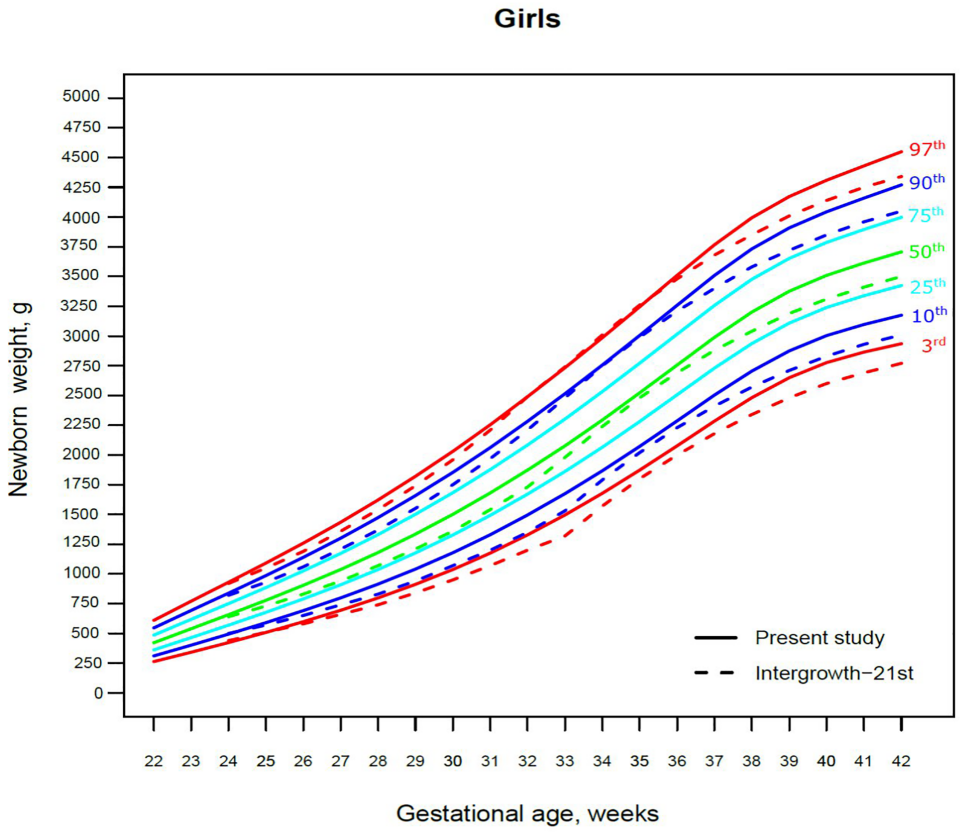

FIGURE 3
The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for birth weight (g) in Lithuanian girls and the 3rd, 10th, 50th, 90th and 97th centiles for INTERGROWTH-21st.

The findings of our study advocate the use of regional population-based growth curves that more precisely represent the neonatal body size of Lithuanian population than the global standard IG-21 which provides the prevalence rates for SGA/LGA that differ from the true values by a factor of two in term neonates.

Our study revealed slightly better agreement in the main centiles of extremely preterm newborns (**Figures 2–5**). However, considering the way too modest sample size for <37 gestational weeks of the IG-21 (18), the parallels observed between the studies in the extreme centiles at early gestations should be evaluated with caution. A low sample size may explain the "waves" observed at 33 gestational weeks in the centile curves of the IG-21 (**Figures 2–5**).

Moreover, a larger discrepancy was observed starting from the late preterm period (34–36 gestational weeks) with certain disparities evident in mean newborn weight and length data at term (**Figures 2–5**). Noteworthy, our previous study comparing the Lithuanian neonatal head circumference reference with the IG-21 showed similar concerning results for term newborns (31). Likewise, other studies from different continents also found their regional neonatal reference charts to be significantly different from the neonatal standards provided by the IG-21 (24, 29, 32–35). In spite of the fact that the IG-21 found some support (36, 37), an increasing number of studies consider the IG-21 with caution including the findings of our study that support this position.

In addition, the insights drawn from the comparison of centiles between the studies when supplemented with the categorization of

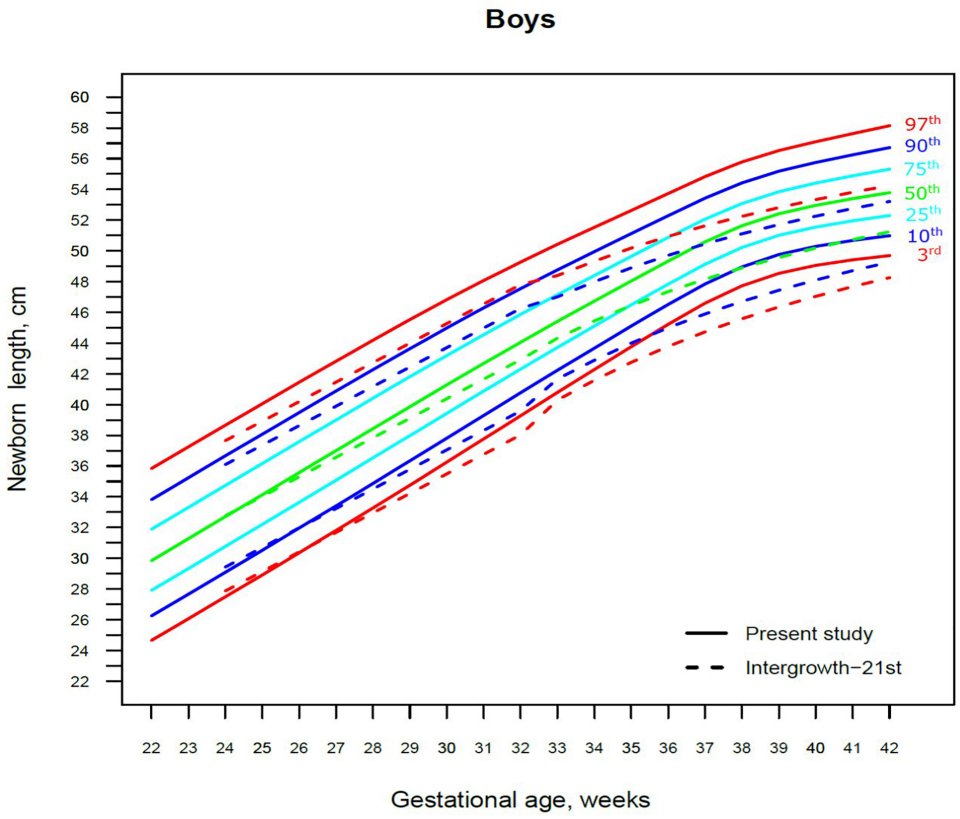

FIGURE 4
The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for birth length (cm) in Lithuanian boys and the 3rd, 10th, 50th, 90th and 97th centiles for INTERGROWTH-21st.

newborns as SGA/LGA (**Table 4**) demonstrate a particular relevance of the application of these standards in clinical practice. The SGA/LGA outliers were derived from the same sample of Lithuanian newborns as the regional neonatal reference curves. As shown in the results, both tails of the birth weight distribution would be strongly affected if evaluated by international standard. The possibility to evaluate the prevalence of SGA/LGA newborns at all gestational weeks may be considered a major strength of our study. While there are studies examining the newborn size categorization at term period depending on the tools used (2, 33, 38), less of them are focused on the SGA/LGA prevalence in different gestations (39). This is of a particular interest in terms of a deeper understanding of biological processes during the fetal development. Fetal growth is characterized by rapid cellular hyperplasia during the first 16 weeks, cellular hyperplasia combined with hypertrophy extending up to 32 gestational week, and cellular hypertrophy dominating afterwards till term (40). This explains the different outcomes and prognosis of being categorized as SGA at different gestational age. When the phase of cellular hyperplasia is affected (early type or symmetric hypertrophy), irreversible neurological and other sequelae of the bodily systems take place. Thus, SGA newborns born less than 32 gestational weeks experience a higher risk of death and major morbidities (41). When the phase of cellular hypertrophy is affected (late type or asymmetric hypertrophy), the processes are reversible if hypoxic ischemic encephalopathy is avoided, and the prognosis for such neonates is much more optimistic. Indeed, while newborns with birth weight of <10th centile (mild hypotrophy) may be intrinsically small because of normal biological, ethnic and other factors, it

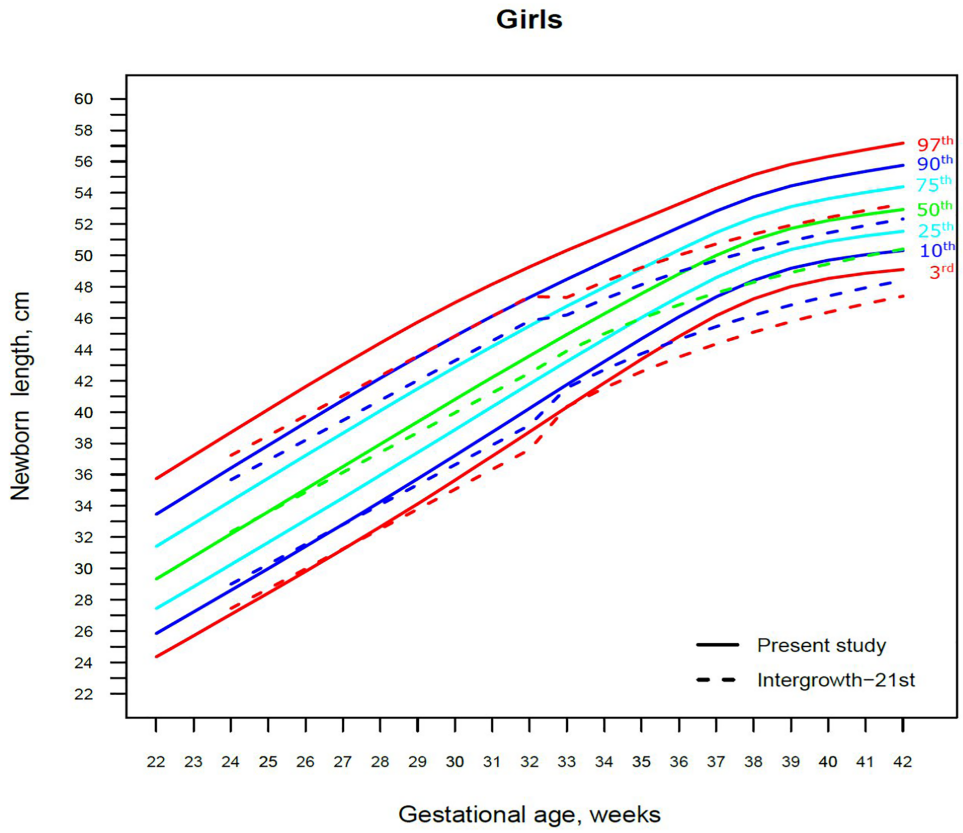

FIGURE 5
The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed centile curves for birth length (cm) in Lithuanian girls and the 3rd, 10th, 50th, 90th and 97th centiles for INTERGROWTH-21st.

would be clinically meaningful to pay great attention to the newborns born of less than 3rd centile (severe hypotrophy) as the ones having most adverse outcomes. In this context, emphasis should be laid that adapting suitable neonatal charts is highly important for clinical practice, as failure to do so may lead to misclassification of newborns in need of timely interventions to avoid adverse consequences to their future health. Indeed, clinical decisions should be based on careful evaluation of the individual clinical case, and suitable neonatal charts are one of the tools in the decision-making algorithm.

In addition to the strengths mentioned above, our study has some limitations. Using these growth centiles for monitoring postnatal growth of preterm infants may not be realistic or ideal, because they do not reflect the initial water and weight loss that occurs in infants during the first 2–3 weeks (11, 42). Understanding this, we have set ourselves a goal of creating growth curves based on longitudinal growth data in the future.

It should also be noted that IG-21 was designed to become an international standard and included only low-risk pregnancies with women whose health and nutritional needs were met and who received adequate antenatal care in 8 socioeconomically stable developing or developed countries such as Lithuania. The data of our study included all births regardless of maternal socioeconomic status. Therefore, we believe that the main findings of our study would be even more pronounced if we had only applied the same inclusion criteria as IG-21. There are around 15% of ethnic minorities in Lithuania and Lithuanian newborns were found to be the

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TABLE 2 Smoothed centiles for Lithuanian birth weight (g) by sex and gestational age (GA).

Boys							GA (in weeks)	Girls						
Birth weight centiles								Birth weight centiles						
3	10	25	50	75	90	97		3	10	25	50	75	90	97
288	339	391	450	510	564	618	**22**	264	312	363	422	486	546	610
375	438	503	575	649	716	783	**23**	342	402	465	539	618	693	770
465	539	615	701	788	867	946	**24**	424	494	569	657	750	838	930
558	643	730	829	928	1,019	1,109	**25**	509	590	677	778	885	987	1,092
655	751	850	960	1,073	1,174	1,276	**26**	598	691	789	904	1,025	1,140	1,259
758	865	975	1,098	1,223	1,337	1,450	**27**	694	798	909	1,038	1,173	1,302	1,435
867	986	1,108	1,245	1,383	1,509	1,634	**28**	798	914	1,038	1,181	1,331	1,474	1,622
985	1,117	1,251	1,402	1,555	1,694	1,832	**29**	912	1,041	1,177	1,335	1,501	1,657	1,820
1,114	1,258	1,406	1,572	1,740	1,892	2,044	**30**	1,037	1,179	1,328	1,501	1,682	1,854	2,031
1,254	1,412	1,574	1,756	1,939	2,106	2,272	**31**	1,176	1,330	1,492	1,680	1,877	2,062	2,254
1,407	1,579	1,755	1,953	2,153	2,335	2,515	**32**	1,328	1,495	1,670	1,872	2,084	2,283	2,489
1,573	1,759	1,950	2,165	2,381	2,578	2,773	**33**	1,496	1,674	1,861	2,077	2,303	2,515	2,733
1,753	1,954	2,159	2,389	2,621	2,832	3,042	**34**	1,677	1,867	2,066	2,294	2,532	2,756	2,986
1,948	2,162	2,380	2,625	2,873	3,097	3,320	**35**	1,872	2,072	2,281	2,521	2,771	3,005	3,246
2,156	2,381	2,612	2,871	3,132	3,369	3,604	**36**	2,077	2,287	2,505	2,756	3,016	3,259	3,509
2,370	2,605	2,846	3,116	3,389	3,636	3,882	**37**	2,285	2,503	2,729	2,989	3,257	3,509	3,766
2,575	2,817	3,064	3,341	3,621	3,874	4,126	**38**	2,481	2,704	2,936	3,201	3,476	3,732	3,994
2,752	2,996	3,246	3,526	3,808	4,064	4,318	**39**	2,649	2,875	3,109	3,376	3,652	3,909	4,173
2,884	3,132	3,385	3,668	3,953	4,211	4,468	**40**	2,776	3,004	3,240	3,509	3,786	4,044	4,309
2,983	3,236	3,494	3,783	4,074	4,338	4,600	**41**	2,865	3,097	3,338	3,612	3,896	4,159	4,429
3,062	3,323	3,590	3,889	4,190	4,463	4,734	**42**	2,935	3,175	3,423	3,706	3,998	4,270	4,548

TABLE 3 Smoothed centiles for Lithuanian birth length (cm) by sex and gestational age (GA).

Boys							GA (in weeks)	Girls						
Birth length centiles								Birth length centiles						
3	10	25	50	75	90	97		3	10	25	50	75	90	97
24.7	26.2	27.9	29.8	31.9	33.8	35.8	**22**	24.4	25.8	27.4	29.3	31.4	33.5	35.7
26.1	27.7	29.3	31.3	33.3	35.2	37.3	**23**	25.7	27.2	28.8	30.8	32.9	34.9	37.2
27.5	29.1	30.8	32.7	34.7	36.7	38.7	**24**	27.1	28.6	30.2	32.2	34.3	36.4	38.7
28.9	30.5	32.2	34.1	36.2	38.1	40.1	**25**	28.4	30.0	31.7	33.6	35.8	37.9	40.2
30.4	32.0	33.6	35.6	37.6	39.5	41.4	**26**	29.8	31.4	33.1	35.1	37.2	39.3	41.6
31.8	33.4	35.1	37.0	39.0	40.9	42.8	**27**	31.2	32.8	34.5	36.5	38.7	40.8	43.0
33.3	34.9	36.5	38.4	40.4	42.3	44.2	**28**	32.7	34.3	36.0	37.9	40.1	42.2	44.4
34.8	36.3	38.0	39.9	41.8	43.6	45.5	**29**	34.1	35.7	37.4	39.4	41.5	43.5	45.7
36.3	37.8	39.4	41.3	43.2	45.0	46.8	**30**	35.6	37.2	38.9	40.8	42.9	44.8	47.0
37.8	39.3	40.9	42.7	44.5	46.3	48.1	**31**	37.2	38.7	40.3	42.2	44.2	46.1	48.2
39.3	40.8	42.3	44.1	45.9	47.5	49.3	**32**	38.7	40.2	41.8	43.6	45.5	47.3	49.3
40.8	42.2	43.7	45.4	47.1	48.8	50.4	**33**	40.3	41.7	43.2	44.9	46.8	48.5	50.3
42.3	43.7	45.1	46.7	48.4	50.0	51.5	**34**	41.9	43.2	44.6	46.3	48.0	49.6	51.3
43.8	45.1	46.5	48.0	49.6	51.1	52.6	**35**	43.4	44.7	46.0	47.6	49.2	50.7	52.3
45.2	46.5	47.8	49.3	50.9	52.3	53.7	**36**	44.8	46.1	47.4	48.8	50.3	51.8	53.3
46.6	47.8	49.1	50.6	52.1	53.4	54.8	**37**	46.1	47.4	48.6	50.0	51.5	52.8	54.3
47.7	49.0	50.2	51.6	53.1	54.4	55.8	**38**	47.2	48.4	49.6	51.0	52.4	53.8	55.1
48.5	49.8	51.0	52.4	53.9	55.2	56.5	**39**	48.0	49.2	50.4	51.7	53.1	54.4	55.8
49.1	50.3	51.5	53.0	54.4	55.7	57.1	**40**	48.5	49.7	50.9	52.2	53.6	54.9	56.3
49.4	50.7	52.0	53.4	54.9	56.2	57.6	**41**	48.9	50.0	51.3	52.6	54.0	55.4	56.8
49.7	51.0	52.3	53.8	55.3	56.7	58.1	**42**	49.1	50.3	51.5	52.9	54.4	55.8	57.2

biggest in size in comparison to newborns of other ethnic groups (43). What is more, our previous comparison (43) of newborns' weight by mother's ethnicity in relation to education level revealed nearly no discrepancies between size of newborns from mothers with the same education level at different ethnic groups. Thus, even if ethnic differences may have influenced the discrepancies of this study, socioeconomic factors probably would be determining.

TABLE 4 Prevalence of small for gestational age (SGA, birth weight <10th centile) and large for gestational age (LGA, birth weight >90th centile) according to the present study's Lithuanian reference and INTERGROWTH-21st (IG-21) by sex and gestational age (GA).

Boys								GA (in weeks)	Girls							
Present study				IG-21					Present study				IG-21			
SGA		LGA		SGA		LGA			SGA		LGA		SGA		LGA	
0	0.0%	9	23.7%	0	0.0%	9	23.7%	**24**	1	2.2%	7	15.2%	1	2.2%	7	15.2%
3	3.2%	10	10.8%	1	1.1%	10	10.8%	**25**	1	1.2%	3	3.7%	0	0.0%	7	8.5%
5	3.7%	11	8.1%	3	2.2%	17	12.5%	**26**	11	7.9%	8	5.8%	7	5.0%	15	10.8%
13	6.6%	17	8.7%	7	3.6%	32	16.3%	**27**	21	12.1%	9	5.2%	9	5.2%	23	13.2%
31	10.2%	16	5.3%	10	3.3%	33	10.9%	**28**	24	10.0%	31	13.0%	14	5.9%	44	18.4%
36	12.4%	23	7.9%	19	6.5%	36	12.4%	**29**	31	12.2%	21	8.2%	15	5.9%	39	15.3%
55	12.4%	31	7.0%	23	5.2%	37	8.3%	**30**	44	10.9%	27	6.7%	22	5.4%	56	13.8%
46	9.4%	38	7.8%	18	3.7%	47	9.6%	**31**	58	13.5%	30	7.0%	36	8.4%	51	11.8%
85	10.0%	71	8.4%	35	4.1%	62	7.3%	**32**	73	10.1%	77	10.7%	28	3.9%	102	14.2%
123	11.0%	107	9.6%	42	3.8%	71	6.4%	**33**	97	10.7%	75	8.3%	49	5.4%	89	9.8%
188	10.0%	164	8.7%	102	5.4%	129	6.9%	**34**	166	10.3%	135	8.4%	112	7.0%	135	8.4%
321	11.2%	200	7.0%	199	7.0%	164	5.7%	**35**	285	11.8%	141	5.8%	233	9.6%	161	6.7%
762	13.6%	315	5.6%	443	7.9%	349	6.2%	**36**	633	12.7%	277	5.6%	496	10.0%	338	6.8%
1,293	9.8%	1,366	10.4%	653	5.0%	2,001	15.2%	**37**	1,094	9.8%	1,090	9.7%	647	5.8%	1,630	14.5%
3,195	9.4%	3,761	11.1%	1,370	4.0%	6,719	19.8%	**38**	2,946	9.9%	3,164	10.6%	1,472	4.9%	5,562	18.6%
5,928	8.7%	7,130	10.5%	2,248	3.3%	14,617	21.5%	**39**	5,976	9.3%	6,622	10.4%	2,619	4.1%	12,983	20.3%
14,231	9.8%	14,527	10.0%	5,482	3.8%	32,460	22.4%	**40**	14,561	10.3%	14,179	10.0%	5,594	3.9%	28,251	19.9%
4,085	10.0%	3,964	9.7%	1,811	4.4%	8,561	20.9%	**41**	4,026	10.3%	3,734	9.5%	1,798	4.6%	7,582	19.3%
459	18.1%	207	8.2%	283	11.2%	461	18.2%	**42**	391	17.1%	170	7.4%	207	9.1%	352	15.4%
30,859	9.7%	31,967	10.1%	12,749	4.1%	65,815	20.7%	**Total**	30,439	10.1%	29,800	9.9%	13,359	4.4%	57,427	19.1%

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In conclusion, the global standard IG-21 should be considered with caution, as requiring validation before implementation. Instead, the findings of our study advocate the use of regional population-based neonatal centiles that more accurately represent the size of the Lithuanian newborn population. Furthermore, the prevalence of SGA/LGA at different gestations depending on the instrument used reveals the clinical importance of using local standards to benefit the most vulnerable infant populations.

Data availability statement

The data are available from the authors upon a reasonable request and with the permission of the Health Information Center of the Institute of Hygiene of Lithuania.

Ethics statement

The studies involving human participants were reviewed and approved by the Lithuanian Bioethics Committee (Permission No. 57, last update of February 6, 2017) and was performed in accordance with the relevant ethical guidelines and regulations. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

RM analysed the data, performed the calculations, and took the lead in writing the manuscript with input from other authors. JT raised the main conceptual idea, designed and supervised the study, helped in data interpretation and manuscript writing, and revised the final version. TJC contributed to revising the manuscript and advising on the valuable improvements to the quality and the conceptual idea of the study. EJ, ND, and VB contributed to the interpretation of the results and the final version of the manuscript. JI collected the database according to the required inclusion criteria. AB performed the statistical analysis and provided suggestions for data interpretation. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1173685/full#supplementary-material.

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Supplementary Table 1. Parameters of the LMST model (BCT distribution) for birth weight by sex and gestational age (GA).

BOYS				GA (in weeks)	GIRLS			
μ	σ	υ	τ		μ	σ	υ	τ
0.450	0.195			**22**	0.422	0.216		
0.575	0.189			**23**	0.539	0.209		
0.701	0.183			**24**	0.657	0.203		
0.829	0.177			**25**	0.778	0.198		
0.960	0.172			**26**	0.904	0.193		
1.098	0.168			**27**	1.038	0.188		
1.245	0.164			**28**	1.181	0.184		
1.402	0.161			**29**	1.335	0.179		
1.572	0.157			**30**	1.501	0.174		
1.756	0.154			**31**	1.680	0.169		
1.953	0.151	0.900	95695.480	**32**	1.872	0.163	0.597	113.139
2.165	0.148			**33**	2.077	0.157		
2.389	0.144			**34**	2.294	0.150		
2.625	0.139			**35**	2.521	0.144		
2.871	0.134			**36**	2.756	0.137		
3.116	0.129			**37**	2.989	0.131		
3.341	0.124			**38**	3.201	0.125		
3.526	0.118			**39**	3.376	0.119		
3.668	0.115			**40**	3.509	0.115		
3.783	0.114			**41**	3.612	0.114		
3.889	0.114			**42**	3.706	0.115		

Supplementary Table 2. Parameters of the LMST model (BCT distribution) for birth length by sex and gestational age (GA).

BOYS				GA (in weeks)	GIRLS			
μ	σ	υ	τ		μ	σ	υ	τ
29.846	0.098			**22**	29.330	0.099		
31.276	0.094			**23**	30.765	0.096		
32.706	0.090			**24**	32.199	0.093		
34.136	0.086			**25**	33.634	0.090		
35.568	0.082			**26**	35.069	0.087		
37.000	0.078			**27**	36.505	0.083		
38.432	0.075			**28**	37.941	0.080		
39.860	0.071			**29**	39.373	0.076		
41.278	0.067			**30**	40.797	0.072		
42.679	0.064			**31**	42.206	0.067		
44.057	0.060	0.229	114.1754	**32**	43.592	0.062	-0.318	51.148
45.407	0.056			**33**	44.947	0.058		
46.733	0.052			**34**	46.272	0.053		
48.042	0.049			**35**	47.565	0.049		
49.339	0.045			**36**	48.821	0.045		
50.582	0.043			**37**	49.999	0.042		
51.638	0.041			**38**	50.989	0.040		
52.418	0.040			**39**	51.724	0.039		
52.965	0.040			**40**	52.234	0.039		
53.406	0.040			**41**	52.617	0.039		
53.793	0.041			**42**	52.940	0.040		

2nd publication/ 2 publikacija

Neonatal Head Circumference by Gestation Reflects Adaptation to Maternal Body Size: Comparison of Different Standards

Morkuniene R, Tutkuviene J, Cole TJ, Jakimaviciene EM, Isakova J, Bankauskiene A, Drazdiene N, Basys V

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Neonatal head circumference by gestation reflects adaptation to maternal body size: comparison of different standards

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Neonatal head circumference (HC) not only represents the brain size of *Homo sapiens*, but is also an important health risk indicator. Addressing a lack of comparative studies on head size and its variability in term and preterm neonates from different populations, we aimed to examine neonatal HC by gestation according to a regional reference and a global standard. Retrospective analysis of data on neonatal HC obtained from the Lithuanian Medical Birth Register from 2001 to 2015 (423 999 newborns of 24–42 gestational weeks). The varying distribution by gestation and sex was estimated using GAMLSS, and the results were compared with the INTERGROWTH-21st standard. Mean HC increased with gestation in both sexes, while its fractional variability fell. The 3rd percentile matched that for INTERGROWTH-21st at all gestations, while the 50th and 97th percentiles were similar up to 27 weeks, but a full channel width higher than INTERGROWTH-21st at term. INTERGROWTH-21st facilitates the evaluation of neonatal HC in early gestations, while in later gestations, the specific features of neonatal HC of a particular population tend to be more precisely represented by regional references.

Head circumference (HC) is a routine paediatric measurement that "acts as a proxy for brain size"[1]. Hence, HC at birth is an indirect measure of brain growth in utero that helps, in general, to evaluate foetal growth. Although at birth the human brain is 25% of its adult weight and continues growing until the age of approximately 10 years, HC is usually of interest primarily in infancy when the head growth velocity rate is maximal[1].

Moreover, newborn HC, especially in those born preterm, is a significant health indicator. HC at birth and its postnatal growth dynamics are correlated with short-term and long-term health outcomes[2–8]. Greater HC at birth and faster postnatal head growth are associated with better neurocognitive and intellectual abilities in adolescence and young adulthood rather than birth weight per se[3–5]. In contrast, small HC at birth is related to the increased male risk of low intellectual performance[6], emotional and behavioral disorders[8], and higher arterial, especially systolic, blood pressure[9]. Considering neonatal HC an important health risk indicator for various periods of human development, an adequate HC growth assessment can facilitate not only the identification of infants at highest risk for long-term growth impairments, but also the choice of timely preventive health measures[10].

Head size with its huge encephalisation ratio is the main characteristic of *Homo sapiens*. Thus it is likely to be more constant and less variable than other body size traits in a given population. On the other hand, postnatal growth is widely variable, and body size indices differ across geographic regions, populations[11,12], or due to socio-economic circumstances[13–15].

Thus tools for growth monitoring should be age- and sex-specific growth references or growth standards. Growth references describe how children from a particular region are growing, while growth standards present how children should grow under almost optimal conditions. The choice of growth reference for clinical practice is important for the evaluation of individual growth pattern. V. Neubauer et al.[16] found that the interpretation

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of the postnatal growth of very preterm infants differed considerably depending on the four different references that were used: the proportion of microcephaly in very preterm infants varied from 3 to 25%. These distinct interpretations may lead to misdiagnosis and affect treatment and health monitoring strategies in clinical practice.

In 2006, the World Health Organization (WHO) published its child growth standards for children under five years. Subsequently the use of the WHO charts for particular countries or regions has been widely discussed[14,17]. In 2008, the International Foetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st, IG-21) launched a multi-country project to develop similar prescriptive standards for foetal growth, neonatal size and postnatal growth of preterm infants[18,19].

Many recent studies[11–13] have considered the evaluation of postnatal growth in newborns. So far, there is a lack of studies comparing head size and its variability in term and preterm neonates from different populations and geographic regions. There is no clear evidence on whether global standards for newborn HC apply to neonates from all geographical areas. Moreover, the increasing prevalence of caesarean section in clinical practice, with fewer neonates born vaginally, described by M. Odent[20] as a phenomenon of a sudden disappearance of the "evolutionary bottleneck", may lead to increased variability in HC at birth.

In this context, the aim of the present study was to analyse HC in Lithuanian newborns according to their gestational age and sex and to compare the results with those provided by the IG-21 study and other countries with evolutionary insights on variability.

Methods

Study design and cohort selection. Our study examined the anonymized database from the Health Information Center of the Institute of Hygiene in Vilnius, Lithuania. The study was based on the Lithuanian Medical Data of Births registered from the year 2001 to 2015 and included all data on singleton liveborn newborns between 24 and 42 completed weeks of gestational age (GA), retrieved from medical records with the total duration of pregnancy in weeks. We excluded all cases of multiple births, stillbirth, undetermined gender, incomplete data (for sex, gestational age, birth weight, birth length, head circumference) or newborns with major congenital malformations and syndromes. The cases with the main newborn anthropometric indices (weight, length, head circumference) incompatible with gestational age (more or less than Mean (M) ± 3 Standard Deviations (SD) following the WHO standards[21]) were removed from the analysis. In total, the cohort sample size of 423 999 newborns was derived. The sampling procedure and exclusion criteria are presented in a flow diagram (Supplementary Fig. 1).

Statistical analysis. The statistical analysis of data was performed using the standard statistical programs (SPSS 22.0, EXCEL, and R). The major parameters of descriptive statistics and percentiles of HC by GA and sex for Lithuanian newborns were calculated. The coefficient of variation (CV) was calculated and used in the comparative analysis with the foreign studies[22].

GAMLSS was used to estimate the distribution applied to smooth the 3rd, 10th, 25th, 50th, 75th, 90th and 97th HC percentiles by GA and sex separately[23]. The LMST method (BCT distribution) were applied to the data obtained on each sex and each measurement, respectively. The resulting main percentiles (3rd, 50th and 97th) were compared with IG-21 from 24 weeks. The analysis was carried out using the GAMLSS package (version 4.3–3) of R 4.0.3 software (www.r-project.org).

The comparison of the present data on HC of Lithuanian neonates with the data provided by the IG-21 project was conducted. Both the published standards of IG-21 project[19,24] were presented for both sexes for every gestational week and day separately (i.e. 30 + 0, 30 + 1), while GA of the present study was recorded as complete gestational weeks (i.e. 30, 31). Therefore, the comparative analysis of the present study with the IG-21 project by GA was made by comparing the mean of HC at the specific gestational week of IG-21. The differences between the means were calculated using *t*-test. A *p-value* of < 0.05 was considered to indicate a statistically significant difference.

The data were also expressed as sex and gestation specific Z-scores using IG-21 as reference.

Ethics approval. The study was granted the approval of the governmental institution the Lithuanian Bioethics Committee (Permission No. 57, last addition—2017–02-06) and was performed in accordance with the relevant ethical guidelines and regulations.

Results

The sample size of our study (Table 1) increased dramatically with gestational age from less than 50 neonates at 24 gestational weeks to nearly 100 000 at term for each sex. The mean HC of boys was 0.5–0.8 cm greater than for girls at every gestational week. Conversely the standard deviation (SD) and the coefficient of variation (CV) of HC fell steeply with gestational age (Table 1).

The mean HC of Lithuanian preterm and term newborns was greater than for IG-21[18,19] from 31 weeks for boys and 32 weeks for girls, the difference increasing with gestational age (Table 1). The gestational age- and sex-adjusted Z-scores of HC based on IG-21[19,24] showed the same pattern (Supplementary Fig. 2).

The 3rd, 10th, 25th, 50th, 75th, 90th, and 97th smoothed gestational age- and sex-adjusted percentile curves for HC of Lithuanian newborns are shown in Fig. 1 and 2. The variability of HC declines with increasing gestational age, and the negative skewness in the distribution is visible as wider gaps between the lower than the upper percentiles.

Comparing the 3rd, 50th and 97th Lithuanian HC percentiles by sex and gestation with those for IG-21 confirmed the pattern seen in Table 1, of close agreement at early gestations but a widening gap with increasing gestation, though restricted to the higher percentiles (Fig. 1 and 2). On the 3rd percentile, the differences in term

	Present study				Intergrowth – 21st				
GA (in weeks)	n	M	SD	CV	n	M	SD	CV	Mean difference LT – IG-21
Boys									
24	28	23.0	1.0	0.043	3	22.7	1.6	0.070	0.3
25	71	23.6	1.4	0.059	10	23.6	1.6	0.068	0.0
26	89	24.5	1.4	0.057	13	24.5	1.6	0.065	0.0
27	124	25.5	1.5	0.059	12	25.4	1.6	0.063	0.1
28	211	26.6	1.7	0.064	19	26.3	1.6	0.061	0.3
29	190	27.5	1.7	0.062	19	27.2	1.6	0.059	0.3
30	303	28.5	1.7	0.060	25	28.1	1.6	0.057	0.4
31	306	29.7	1.7	0.057	37	28.9	1.6	0.055	0.8
32	533	30.6	1.6	0.052	52	29.8	1.6	0.054	0.8
33	744	31.5	1.6	0.051	33	31.1	1.3	0.042	0.4
34	1305	32.3	1.5	0.046	48	31.7	1.3	0.041	0.6
35	1977	33.0	1.5	0.045	127	32.2	1.3	0.040	0.8
36	3682	33.5	1.5	0.045	322	32.7	1.2	0.037	0.8
37	9651	34.3	1.5	0.044	848	33.2	1.2	0.036	1.1
38	24,745	34.9	1.4	0.040	2032	33.7	1.2	0.036	1.2
39	51,027	35.3	1.4	0.040	2985	34.1	1.1	0.032	1.2
40	93,843	35.5	1.4	0.039	2532	34.5	1.1	0.032	1.0
41	27,226	35.8	1.4	0.039	1147	34.9	1.1	0.032	0.9
42	987	35.8	1.5	0.042	204	35.2	1.1	0.031	0.6
Girls									
24	40	22.2	1.3	0.059	3	22.5	1.6	0.071	-0.3
25	65	23.1	1.3	0.056	7	23.4	1.6	0.068	-0.3
26	98	23.7	1.6	0.068	7	24.3	1.6	0.066	-0.6
27	122	25.0	1.7	0.068	11	25.1	1.6	0.064	-0.1
28	153	26.2	1.9	0.073	16	26.0	1.6	0.062	0.2
29	168	27.0	1.7	0.063	22	26.9	1.6	0.059	0.1
30	248	28.2	1.8	0.064	24	27.8	1.6	0.058	0.4
31	274	29.0	1.7	0.059	33	28.7	1.6	0.056	0.3
32	454	30.4	1.7	0.056	43	29.6	1.6	0.054	0.8
33	610	31.1	1.6	0.051	17	30.7	1.3	0.042	0.4
34	1066	31.9	1.5	0.047	65	31.3	1.2	0.038	0.6
35	1635	32.5	1.5	0.046	111	31.9	1.2	0.038	0.6
36	3183	33.1	1.5	0.045	293	32.3	1.2	0.037	0.8
37	8078	33.8	1.4	0.041	798	32.8	1.1	0.034	1.0
38	21,708	34.3	1.4	0.041	1783	33.2	1.1	0.033	1.1
39	48,487	34.8	1.4	0.040	2849	33.6	1.1	0.033	1.2
40	93,307	35.0	1.3	0.037	2486	33.9	1.1	0.032	1.1
41	26,354	35.2	1.3	0.037	1180	34.2	1.0	0.029	1.0
42	907	35.3	1.4	0.040	218	34.5	1.0	0.029	0.8

Table 1. Comparison of head circumference (HC) of Lithuanian newborns by sex and gestational age (GA) and the INTERGROWTH-21st (IG-21) reference[19,24]. n—count, M—mean, SD—standard deviation, CV—coefficient of variation, defined as standard deviation / mean.

newborns (gestation 37–40 weeks) amounted to 0.5–0.75 cm, falling to less than 0.5 cm in the post-term period. On the 50th and 97th percentiles, the differences varied from 1–1.5 cm (Fig. 1 and 2).

Discussion

When monitoring the growth and development of neonatal HC, the primary concern is to use the best tools[10]. There is a lot of discussion recently concerning the choice of whether regional or global, age and sex-specific growth references or growth standards should be used for different populations[11–13]. Our study revealed that in late preterm and term periods, with a typically smallest neonatal head circumference (HC) variability within a population, the differences between populations are the most pronounced (Table 2). The differences between the findings of the studies examined increase with the increasing GA, and particularly starting from the late preterm period, and especially, in the term newborns. In the present Lithuanian study, the variation of the mean HC in extremely, moderate to late preterm newborns HC was < 1 cm, in term newborns—> 1 cm compared to IG-21

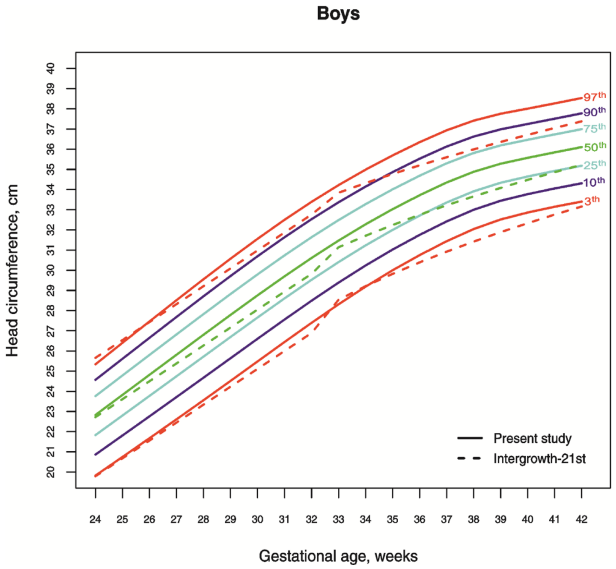

Figure 1. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed percentile curves for head circumference (cm) in Lithuanian neonate boys and the 3rd, 50th and 97th percentiles for INTERGROWTH-21st[20,25].

(Table 1). In extremely preterm gestations, the means of HC varies within most studies[25–28] less than 0.5 cm compared to Lithuanian. However, according to some studies, in later gestations and in term newborns, the differences between populations in HC increase to more than 1 cm. Most of the similarities were found between Lithuanian and Finnish neonatal HC, the biggest differences – between Lithuania and Indonesia (Table 2).

Analysing the variability of HC with regard to gestational age within and between populations, the coefficient of variation (CV) was examined. According to different studies[25–28], the CV of HC in every population varies within a very narrow range, but is the highest in extremely preterm gestations, however, within the population, it decreases together with the increasing gestational age, same as the standard deviation (SD) (Tables 1 and 2). Hence, the closer to term, the narrower was the variability of the population's neonatal HC. The CV of HC is higher in extremely preterm periods, but HC means and extremes appear to be very similar in different populations. We presume that in early gestation there is no need to strictly set head parameters according to the mother's pelvis size, hence, greater biological variation is allowed, which is similar in most populations. On the other hand, the CV decreases with the increasing gestational age, but the means and marginal HC variants move according to a population-specific direction which is highly dependent on maternal size, particularly height and pelvic size[29]. Here, the size of the neonatal head seems to be maximally adapted to maternal pelvic size. These considerations support the idea that head circumference is strongly anthropometrically limited by the maternal bony pelvis—"evolutionary bottleneck", as named by M. Odent[20].

As the shape of the human pelvis is often interpreted as an evolutionary compromise between bipedal locomotion and childbirth of a highly encephalized neonate[30], HC is expected to be more strongly genetically determined and anthropometrically limited by the indices of the bony birth canal. Even though the newborn HC should be less influenced by internal or external factors than birth weight or length, many studies have raised the discussion on the complex interaction between the intrinsic and extrinsic factors in the development of neonatal HC[31,32]. Furthermore, females with a large head, who are likely to give birth to neonates with a large head, were found to possess birth canals that are shaped to better accommodate large-headed neonates[29]. Moreover, it is already known that variation in the shape of the female pelvis is significantly geographically structured[33].

What is more, the pelvis shape was found to be significantly associated with the stature for taller women having a more oval pelvic inlet and better accommodating a larger foetal head[29]. In the study of R. G. Tague[34] femoral length/stature in females showed a significant, positive partial correlation with the anteroposterior diameter and shape of the pelvic inlet. A recent Swedish study[35] proved this relationship from the clinical point of view reporting decreasing risk of caesarean section (CS) with increasing maternal height after adjustment for maternal age, BMI, gestational age, parity, high birth weight and country of birth. With average Swedish women's height of 166.1 cm, maternal height of 178–179 cm was associated with the lowest risk of CS (OR = 0.76, 95%

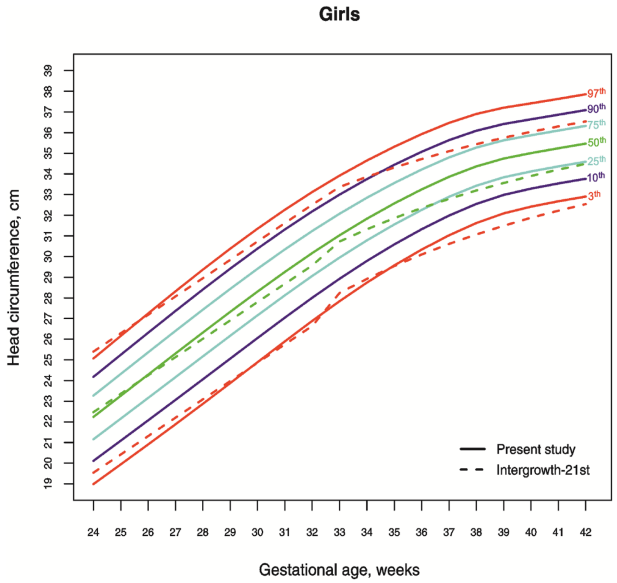

Figure 2. The 3rd, 10th, 25th, 50th, 75th, 90th and 97th smoothed percentile curves for head circumference (cm) in Lithuanian neonate girls and the 3rd, 50th and 97th percentiles for INTERGROWTH-21st[20,25].

GA (in weeks)	U. Sankilampi et al., FINLAND						Barbier et al., CANADA						Haksari et al., INDONESIA						Fok et al., CHINA					
	BOYS			GIRLS			BOYS			GIRLS			BOYS			GIRLS			BOYS			GIRLS		
	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV
24	22.08	1.43	0.06	21.64	1.43	0.07	22.4	2.6	0.12	22.1	2.4	0.11	N/A	N/A	N/A	N/A	N/A	N/A	22.6	0.5	0.02	23.4	1.7	0.07
25	23.13	1.45	0.06	22.73	1.44	0.06	23.6	1.9	0.08	22.9	1.6	0.07	N/A	N/A	N/A	N/A	N/A	N/A	23.7	0.8	0.03	24.1	1.6	0.07
26	24.19	1.47	0.06	23.81	1.46	0.06	24.6	1.8	0.07	23.8	1.4	0.06	26.7	2.79	0.10	26.6	2.81	0.11	24.8	1	0.04	23.8	0.8	0.03
27	25.26	1.49	0.06	24.88	1.47	0.06	25.5	1.8	0.07	24.8	1.5	0.06	25.9	2.48	0.10	27	2.53	0.09	25.3	1.5	0.06	25	0.8	0.03
28	26.32	1.5	0.06	25.93	1.48	0.06	26.3	1.5	0.06	25.7	1.4	0.05	27.8	3.19	0.11	27.4	3.16	0.12	26.2	1.4	0.05	25.7	1.2	0.05
29	27.37	1.5	0.05	26.96	1.49	0.06	27.3	1.7	0.06	26.8	1.5	0.06	29	2.83	0.10	29.5	2.36	0.08	27.1	1.6	0.06	26.8	1.3	0.05
30	28.4	1.5	0.05	27.96	1.48	0.05	28.3	1.6	0.06	27.7	1.5	0.05	28.6	1.89	0.07	28.4	2.3	0.08	28.1	1.4	0.05	28.1	1.6	0.06
31	29.41	1.5	0.05	28.95	1.48	0.05	29.1	1.7	0.06	28.6	1.5	0.05	29.2	1.8	0.06	29.3	1.75	0.06	29	1.5	0.05	28.4	2	0.07
32	30.38	1.49	0.05	29.89	1.46	0.05	30.1	1.6	0.05	29.6	1.6	0.05	31.3	1.4	0.04	31.1	1.53	0.05	30	2	0.07	29.3	1.4	0.05
33	31.3	1.48	0.05	30.81	1.45	0.05	31.1	1.6	0.05	30.4	1.6	0.05	30.4	1.86	0.06	30.3	1.75	0.06	30.7	1.6	0.05	30.4	1.3	0.04
34	32.17	1.46	0.05	31.69	1.43	0.05	31.9	1.6	0.05	31.5	1.6	0.05	31	1.42	0.05	30.8	1.32	0.04	31.2	1.3	0.04	31.1	1.3	0.04
35	32.98	1.44	0.04	32.52	1.41	0.04	32.8	1.4	0.04	32.4	1.4	0.04	31.2	1.19	0.04	31.2	1.32	0.04	32.1	1.5	0.05	32.1	1.4	0.04
36	33.71	1.41	0.04	33.24	1.39	0.04	33.5	1.3	0.04	33.1	1.4	0.04	32.6	1.09	0.03	32.4	1.23	0.04	33.1	1.4	0.04	32.8	1.1	0.03
37	34.35	1.38	0.04	33.85	1.35	0.04	34.1	1.3	0.04	33.6	1.3	0.04	32.7	1.18	0.04	32.7	1.26	0.04	33.6	1.1	0.03	33.2	1.1	0.03
38	34.88	1.34	0.04	34.31	1.31	0.04	34.6	1.3	0.04	34	1.2	0.04	33.3	0.871	0.03	33.2	0.85	0.03	34.1	1.2	0.04	33.5	1.1	0.03
39	35.24	1.3	0.04	34.61	1.26	0.04	34.9	1.2	0.03	34.3	1.2	0.03	33.7	0.778	0.02	33.6	0.77	0.02	34.3	1.1	0.03	33.8	1.1	0.03
40	35.51	1.27	0.04	34.86	1.22	0.03	35.2	1.2	0.03	34.6	1.2	0.03	33.9	0.751	0.02	33.8	0.75	0.02	34.7	1.2	0.03	34	1.1	0.03
41	35.86	1.26	0.04	35.19	1.21	0.03	35.6	1.2	0.03	34.9	1.1	0.03	34.2	0.763	0.02	34.1	0.78	0.02	35	1.2	0.03	34.3	1.1	0.03
42	36.25	1.26	0.03	35.56	1.23	0.03	N/A	N/A	N/A	N/A	N/A	N/A	34.1	0.809	0.02	34	0.84	0.02	34.9	1.2	0.03	34.5	1.3	0.04

Table 2. The comparison of neonatal head circumference (HC) of Lithuanian newborns by sex and gestational age (GA) and its coefficient of variation (CV) and the data provided by other studies[19,24–28]. SD—standard deviation, CV—coefficient of variation, defined as standard deviation/mean, N/A – not available.

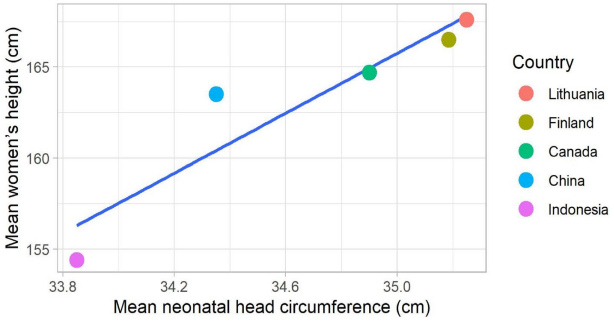

Figure 3. Neonatal head circumference (cm) at term (40 weeks gestation) in relation to average women's height across countries[26–29,37].

CI 0.71–0.81), whereas height below 160 cm explained 7% of CS cases[35]. It is worth mentioning that according to the NCD Risk Factor Collaboration[36], Lithuanian women are among the tallest women in the world with an average height of 167.6 cm. The comparative results of the female average height reflect the differences found between the mean neonatal HC from different populations, as shown in Table 2. Finnish women with an average height of 166.5 cm are closest to Lithuanians, followed by Canadians (164.7 cm), Chinese (163.5 cm), and finally Indonesians (154.4 cm)[36]. This supports the previous study's findings[29] that perhaps maternal height is linked to pelvic size, particularly the size of the birth canal, and through that to the neonatal HC. This possible relationship between neonatal HC (cm) at term (40 weeks of gestation) and average women's height across compared countries is presented in Fig. 3 and compiled after[26–29,35].

With regard to these findings, scientists debate the appropriateness of growth standards vs. references, regional vs. global for proper evaluation of growth and development of neonatal HC. In our study, most of similarities with global study of IG-21 were disclosed in cut-off points for the lowest percentiles in extremely preterm newborns, apart from that, extremely preterm newborns (especially girls) had more similarities not only in the third, but also in the 50th and 97th percentiles of HC. The Brazilian study[37] revealed a similar pattern and found the trajectory of the third percentile parallel with the IG-21 study until the term period. The sample size of the IG-21[19] reference was only modest for < 37 weeks gestation, and the later study on very preterm neonates 'should be interpreted with caution given the small sample size'[24]. This may explain a "wave" at 33 gestational weeks observed in the percentile curves of IG-21 (Figs. 1 and 2). Thus, although IG-21 facilitates the evaluation of the main HC percentiles for extremely preterm newborns and might serve as cut-off points for the pathological microcephaly in preterm newborns of different populations, it should be considered with caution to be confidently used as a global standard at early gestations.

As for the other extreme, the 97th percentile, above which infants would be diagnosed with macrocephaly, a large gap between the curves of both studies of more than 1 cm from late preterm to post-term was detected which could lead to an overestimation of macrocephaly in our cohort. If we compared our results with the HC curves provided by the Centers for Disease Control and Prevention (CDC)[38], the gap would be smaller. In line with other studies[39] evaluating the influence of growth curves used for the distribution of HC, our study also claims that the important consequences could have been triggered by the percentile misclassification. Therefore, from the standpoint of clinical practice, to predict the course of HC higher percentiles in moderate or late preterm periods and, especially, in Lithuanian term newborns, regional standards should be used.

Accordingly, the question has been raised by scientists whether children's growth references should be global, or specific to different populations: 'it has become apparent that a single "global" reference fails adequately to mirror the diversity in human growth'[17]. Human growth is determined by inherited factors, and the significant variability of foetal growth in utero between ethnic groups supports this statement[31]. Therefore, the IG-21 project charts based on the idea that foetuses, infants, and children grow similarly all over the world under ideal nutritional, environmental, psychological living conditions have been widely discussed. A number of studies[32,37,40–46] recently have compared their foetal and neonatal national growth references with the IG-21 study that was recently published, and obtained diverse results. Some studies did not find appreciable differences with IG-21 for newborn HC[40] or a statistically significant difference was observed only of female HC in the 97th percentile[32]. While others determined that IG-21 standards for foetuses[47] were found to be unrepresentative for regional populations leading to considerable overdiagnosis of foetal microcephaly or misclassification of infant birth size[37,41–46] and a conclusion that regional validation was needed prior to the implementation of IG-21. We found that global standards like INTERGROWTH-21st might facilitate the evaluation of neonatal head circumference in early gestations, while in later gestations, the specific features of neonatal head circumference of a particular population tend to be more precisely represented by regional standards.

Therefore, we suggest taking into consideration the regional standards for neonatal head circumference in order to better evaluate a possible clinical pathology. It is important to stress that over the process of evolution,

neonatal body size and head circumference have adapted to the mother's body size, especially her pelvis, as a result of diverse adaptation mechanisms common to different populations in different geographical areas and under different living conditions.

Conclusions

The closer to the late preterm—term period, the greater the differences between neonatal head circumferences in different populations. This threshold is slight, but it marks the inevitable influence of the evolutionary mechanisms that operate to first concentrate on vital biological capacities for neurodevelopment and only then allow genetics, ethnicity and other complex factors to influence the variability of neonatal head circumference.

Consequently, the global standards as IG-21 may serve for the evaluation of HC in early gestations, taking into account that most countries do not have a possibility to construct their own references due to small numbers of neonates born extremely preterm. In later gestations, regional standards more precisely represent the specific features of the neonatal HC of a particular population.

Data availability

The data that support the findings of this study are available at the Health Information Center of the Institute of Hygiene of Lithuania, however restrictions apply to the availability of these data, used under a license for the current study, therefore they are not publicly available. The data are available from the corresponding author upon a reasonable request and with the permission of the Health Information Center of the Institute of Hygiene of Lithuania.

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Author contributions

R.M. analysed the data, performed the calculations, and took the lead in writing the manuscript with the input from other authors. J.T. raised the main conceptual idea, designed and supervised the study, helped in data interpretation and manuscript writing, revised the final version. T.J.C. contributed in revising the manuscript, and advising on the valuable improvements to the quality and the conceptual idea of the study. E.M.J., N.D., V.B. contributed to the interpretation of the results and the final version of the manuscript. J.I. collected the database according to the required inclusion criteria. A.B. performed the statistical analysis and provided suggestions for data interpretation.

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Competing interests

The authors declare no competing interests.

Additional information

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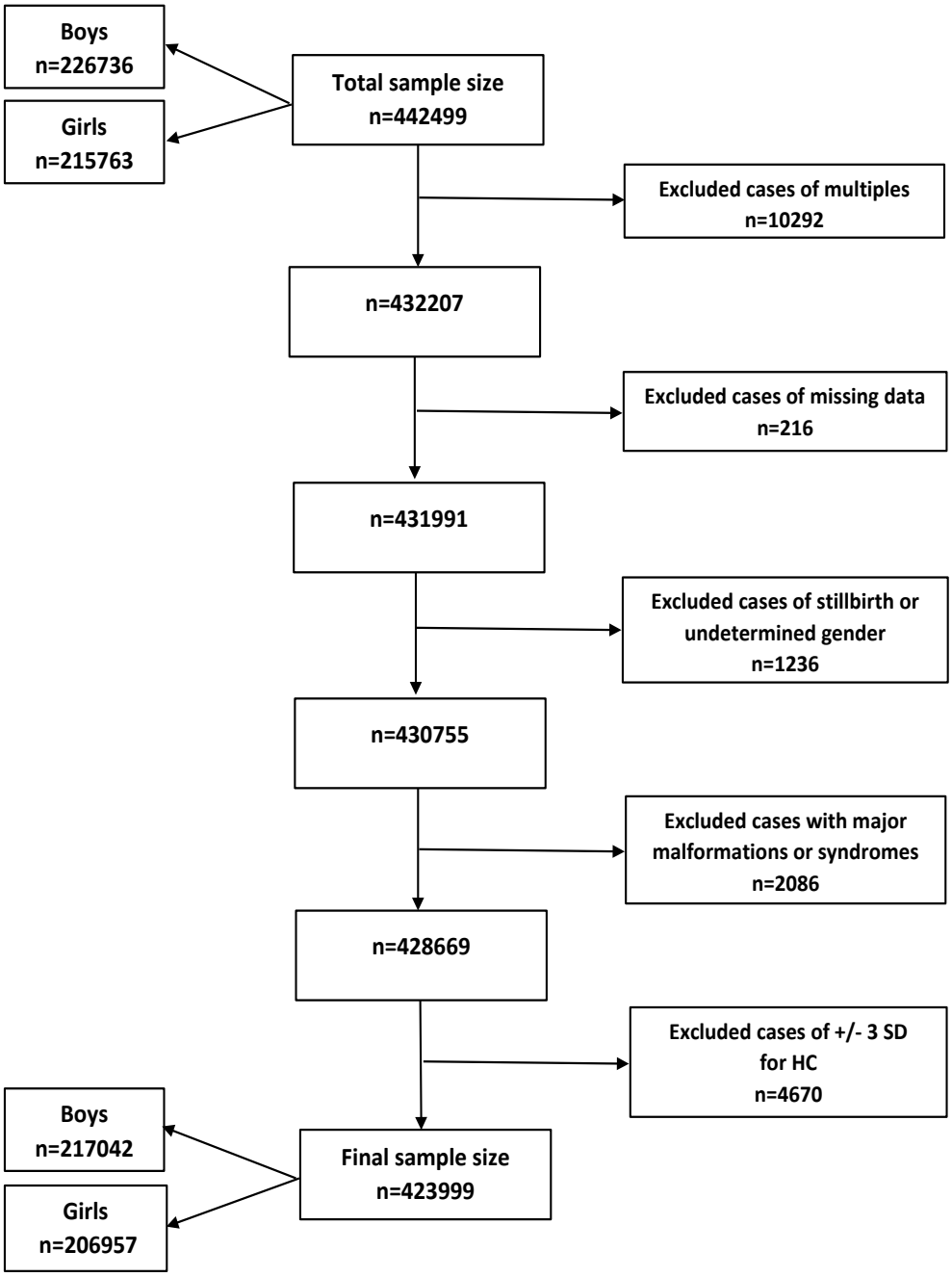
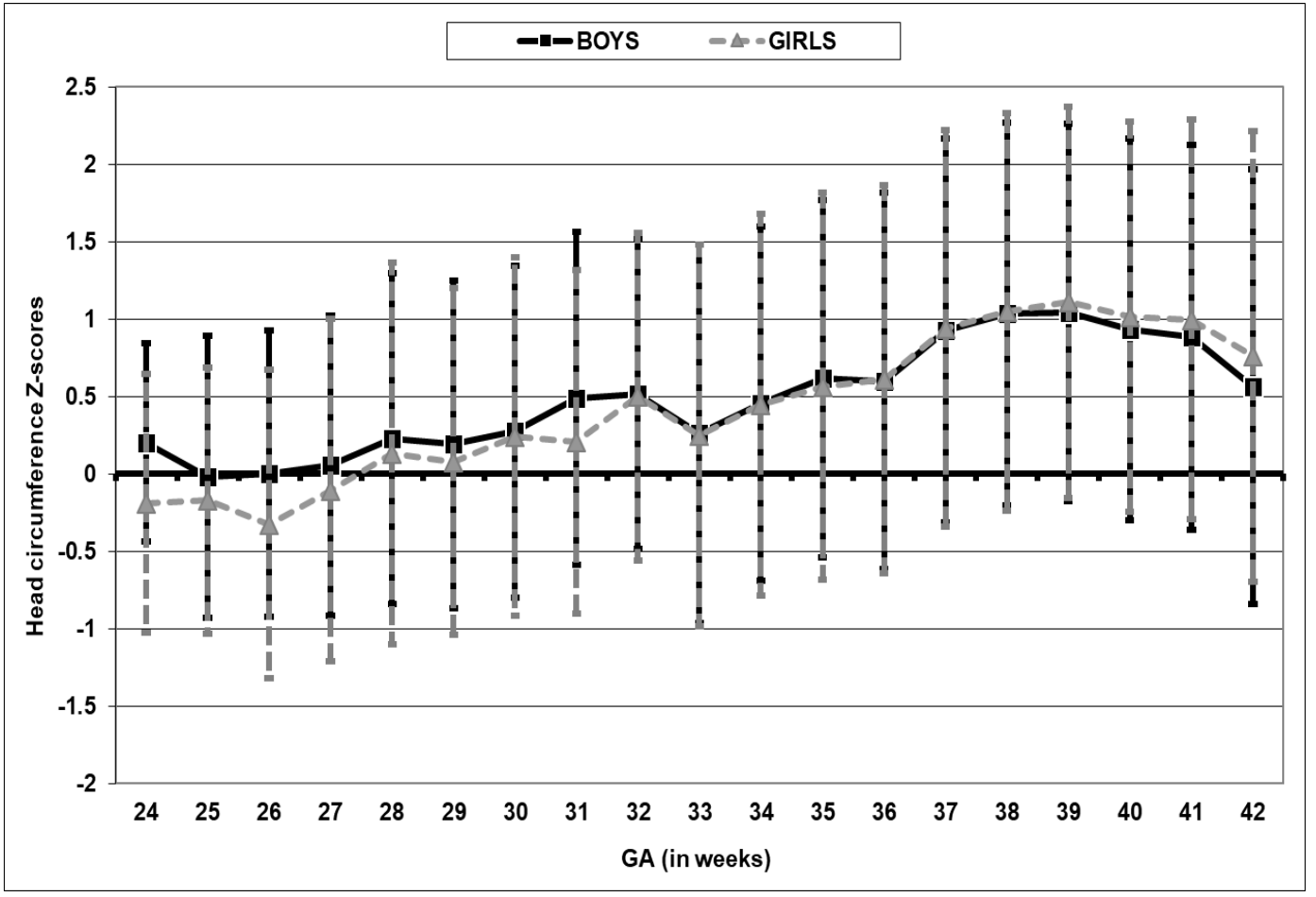


Supplementary Figure 1 Flow diagram representing the sampling procedure and the exclusion criteria of the study. HC - head circumference, n – number, SD – standard deviation.



Supplementary Figure 2 Z-scores for head circumference in Lithuanian boys and girls of 24 – 42 gestational weeks in relation to the INTERGROWTH-21st study[20,25]. GA – gestational age.

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THE ASSOCIATIONS OF PRETERM BIRTH AND LOW BIRTH WEIGHT WITH CHILDHOOD GROWTH CURVES BETWEEN BIRTH AND 12 YEARS: A SITAR-BASED LONGITUDINAL ANALYSIS

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ABSTRACT

Background: Children born preterm grow differently from those born at term.

Aim: To compare growth in length/height, weight, and BMI of preterm- and term-born children, grouped by birth weight (BW) and gestational age (GA).

Subjects and Methods: Longitudinal data of 950 children (birth to 12 years) were collected retrospectively. Growth trajectories were modelled using SITAR (Superimposition by Translation and Rotation) by sex, with three groups each for GA and BW.

Results: SITAR summarized growth patterns from birth to 12 years and explained 76-79% of height variance, 90-92% for weight, and 72-75% for BMI. Early preterm and low BW groups were shorter, lighter and thinner on average than their term or normal BW peers, with late preterm and low-normal BW groups intermediate. Effects were larger for BW than GA, e. g. early preterm girls/boys were 0.3/0.8 kg lighter, 0.9/0.9 cm shorter and 0.8/0.8 kg/m^2 thinner, while low BW girls/boys were 0.5/1.0 kg lighter, 1.5/1.4 cm shorter and 0.8/0.9 kg/m^2 thinner. Moreover, faster growth rates were associated with lower BW.

Conclusion: Both BW and GA significantly impacted growth, but low BW more so than early preterm birth. This underscores the need for targeted interventions for low BW children to address potential long-term growth challenges.

Keywords: preterm infants, growth, longitudinal study, SITAR

INTRODUCTION

Preterm infants, particularly those born very preterm (before 32 weeks) or with very low birth weight (VLBW), are at high risk for medical and developmental challenges, including growth restriction with long-lasting effects into adulthood. Numerous studies have established clear links between birth parameters, postnatal growth restriction, and subsequent growth failure, with significant short- and long-term health consequences (1–3). Specifically, preterm infants often experience substantial growth failure early in the postnatal period, typically followed by incomplete catch-up growth over the first 2-3 years, leading to lower average adult height than term-born peers (2). Moreover, the smaller the birth weight, the longer the compensatory growth period (1). This is particularly true for small-for-gestational-age infants born before 32 weeks, who demonstrate slower catch-up growth during early childhood and face poorer neurodevelopmental outcomes if they fail to catch up (4,5).

In addition to these challenges, VLBW infants, especially those who are SGA, are also at considerable risk for later growth failure and adverse health outcomes in adulthood, including obesity, type 2 diabetes, cardiovascular diseases, and stroke (3,6–8). Notably, extremely preterm survivors (born before 26 weeks) tend to remain shorter and lighter into adulthood, however, often having elevated BMI (9). Furthermore, shorter final height is associated with decreasing gestational age, a particularly pronounced trend in women born very preterm (10).

This pattern of growth challenges is also evident among moderately preterm-born children, who consistently remain shorter and weigh less than their term-born peers during the early years of life (11,12). This disparity often persists into adolescence; moderately preterm-born children also face growth challenges, consistently being shorter and weighing less than their term-born peers during the early years of life (13,14). However, findings vary significantly across studies regarding the age at which preterm-born children catch up with their peers, the pace and rate of their growth, the onset of puberty, or differences observed between sexes (2,4,5). Additionally, by adulthood, some studies suggest that very, moderately, and late preterm-born men and women may achieve similar adult size, age at peak height velocity, and pubertal timing as term-born peers (15,16). Different classification methods (e.g., gestational age vs. birth weight) and study parameters may influence these varying findings, significantly impacting observed growth patterns (17).

Moreover, while traditional classifications such as small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA) offer valuable clinical insights, they integrate birth weight (BW) and gestational age (GA) into a single measure. This integration, while clinically useful, may obscure the independent influences of BW and GA on later health outcomes. As highlighted by VanderWeele et al. (18), directly adjusting for an intermediate variable (such as BW) when assessing the impact of an exposure can lead to biased results. Therefore, in this study, we adopt a stratification approach, examining BW and GA as separate variables to disentangle their respective impacts on long-term growth and health outcomes.

This allows us to investigate the effects of different GA strata and BW strata independently, offering new perspectives on the interplay between prenatal growth and developmental trajectories. Specifically, BW reflects cumulative energy reserves and trade-offs during fetal development (19), while GA captures the timing of developmental processes and the duration of exposure to intrauterine environment. By analysing these factors independently, we aim to provide a nuanced understanding of prematurity-related health challenges, framed within the contexts of developmental biology (20) and evolutionary medicine (21). Analysing these factors separately is essential for etiological research, as including both in the same model can lead to multicollinearity and paradoxical interpretations. This approach allows for a clearer understanding of the distinct roles of GA and BW in shaping growth trajectories while avoiding confounding in causal analyses.The aforementioned inconsistent findings on growth, influenced by classification methods, study duration, and ongoing debates about the optimal growth rate for preterm infants (22,23), underscore the need for further research into the growth characteristics of different sub-groups of preterm infants. Until now, the growth of such infants has predominantly been examined through cross-sectional studies, leaving a gap in longitudinal research (24). Furthermore, analysing largely variable human growth (25) requires expertise in longitudinal statistical methods, which can be analytically challenging (26–28). This large variability, especially in growth outcomes among preterm infants, calls for robust growth models to accurately capture and understand these patterns over time. Growth models (29–32) are essential for analysing longitudinal data, as they capture overall growth patterns in the population while including and accounting for individual characteristics of growth trajectories.

However, traditional growth models, such as linear or nonlinear regression, often struggle to accommodate the unique growth trajectories observed in preterm infants. In contrast, the SITAR (SuperImposition by Translation And Rotation) model has proven to be a valuable tool in this context (32). By aligning individual growth curves with a population-average curve and adjusting for differences in growth timing and intensity, SITAR provides a more nuanced understanding of growth dynamics. This makes it particularly effective for studying preterm infants, whose growth patterns can significantly deviate from the norm.

Considering all the above the aim of this study is to examine growth outcomes in preterm infants, focusing on both GA and BW, using SITAR-based longitudinal analysis. To achieve this, the study has the following objectives: 1) evaluate children's growth patterns (height, weight, BMI) in relation to BW groups using SITAR modelling; 2) assess growth trajectories across GA groups for the same measures; and 3) perform a comparative analysis of the resulting growth curves and derive practical insights for clinical or developmental applications.

MATERIALS AND METHODS

Study design and cohort selection

The retrospective longitudinal study analysed medical records from two primary health care centers and their affiliates in Vilnius, Lithuania, involving 950 children (469 boys, 481 girls). It included preterm infants (GA 22–36 weeks) born between 2000–2015 and term infants (GA 37–42 weeks) born in 1996. Although the preterm cohort (2000–2015) and the term cohort (1996) were born several years apart, both grew into adolescence during a similar timeframe, experiencing comparable environmental, socioeconomic, and nutritional conditions (33). All growth data were collected within the same geographical region and healthcare system, minimizing variability from systemic differences. The birth variables were sex, birth weight (BW), and gestational age (GA). Height (or length up to age 2) and weight were subsequently measured longitudinally, with BMI calculated from these measurements. The three birth weight (BW) groups (Low, Low-normal, Normal) and three gestational age (GA) groups (Early preterm, Late preterm, Term) were considered (see Table 1). The distributions of birth-related variables, expressed in frequencies, are given in Table 1.

All individuals with at least one measurement were included in the analysis. Height (length up to 2 years) and weight were collected from birth to 12 years, monthly for the first year, three times for the second and third years, and twice a year after that. There were 16 159 measurements. The median numbers of measurements per child was 17, interquartile range was 13-21.

SITAR model

The SITAR model (SuperImposition by Translation And Rotation) (32) was applied to obtain mean curves for the period from birth to 12 years for height, weight, and BMI in GA and BW groups of boys and girls. SITAR is a mixed effects model featuring a cubic spline mean curve and three subject-specific random effects (size, timing, intensity) that adjust the mean curve to best match the subjects' data (32,34,35). It is a shape-invariant model such that individuals are assumed to have the same shape of the growth curve, subject to three transformations: 1) shift the curve up/down (size parameter), 2) shift it left/right (timing or tempo), 3) stretch/shrink the age scale (intensity or velocity). The effect of covariates can be included in the SITAR model as fixed effects, i.e. the model can include separate fixed effects for each SITAR parameter (35,36).

The corrected postnatal age was used in the analysis: Corrected postnatal age = chronological age (years) + (gestation weeks - 40) * 7 / 365.25. The correction was applied to children of all gestations, including term, and at all ages. This avoided a disjunction between term and preterm, and at 1 and 2 years of age. To avoid negative ages, nine months (i.e. 3/4 years) were added to corrected postnatal age giving postconceptual age, also known as postmenstrual age, which is equivalent to gestational age at birth plus chronological age.

The number of degrees of freedom (d.f.), which controls the smoothness of the natural cubic spline, was chosen to minimise the Bayesian Information Criterion (BIC). Models without and with logarithmic transformation were considered. The analysis showed that log transforming age improved model fit. Outliers with standardised residuals exceeding 4 in absolute value were excluded. If the model failed to converge, we fitted reduced models, omitting some fixed and/or random effects, and models omitting the timing random effect fitted best. There were sex differences in the mean growth curve approaching early adolescence, so separate models were fitted for boys and girls. Initially, we explored models that included both GA group and BW group

as covariates; however, to avoid collinearity and to independently assess their etiological effects, we analysed these variables separately. So separate models for BW group and GA group were fitted, by sex. The timing of AR was derived as the age at the lowest BMI point on the modelled mean BMI curves.

The analysis was done in R version 4.4.1 using the SITAR package version 1.4.0 (37). The ggplot2 package version 3.5.1 was employed to visualise the results.

Ethics approval

The study was approved by the Lithuanian Bioethics Committee (Permission No. 57, last updated 2017-02-06) and was performed according to the relevant ethical guidelines and regulations.

RESULTS

SITAR models were fitted to height, weight, and BMI from birth to 12 years (Table 2), each adjusted separately for GA group and BW group in boys and girls. Models with log-transformed age fitted better, with degrees of freedom ranging from 6 to 8. The variance explained ranged from 72% to 92%, with the best fit for weight (92% for girls, 90% for boys).

Table 3 shows significant mean differences for the period from birth to 12 years between the GA and BW groups in the SITAR height models by sex. Girls and boys in the early preterm GA group were on average 0.9 cm shorter than those in the term group. Furthermore, low BW girls and boys were 1.4 cm significantly shorter than their normal BW peers. Figure 1 shows mean curves by BW and GA group and sex, where despite the significant ~1 cm differences in size between groups in Table 3 the group curves were closely aligned. The inset graphs focus on ages 9-12, where the group differences were more evident, with a constant offset between groups but no sign of the curves diverging.

Table 4 shows significant effects of GA and BW on weight size and intensity across the entire study period (0–12 years), with these effects being more pronounced in boys than girls. On average, boys in the early preterm group were 0.8 kg lighter than their term peers (95% CI: -

1.19 to -0.48), compared to 0.3 kg for girls (95% CI: -0.50 to -0.07). Similarly, in the low BW group, boys were 1.0 kg lighter than their normal BW counterparts (95% CI: -1.26 to -0.73), compared to 0.5 kg for girls (95% CI: -0.62 to -0.29), showing a significant sex difference. GA and BW also significantly impacted growth intensity in boys, with the early preterm group showing 4% and the low BW group showing 3.7% less intense growth spurts compared to their term and normal BW counterparts.

Figure 2 shows the mean weight curves for girls and boys, where the differences between the GA and BW groups were more obvious than for height (Figure 1). The girls' curves were closely aligned across groups throughout childhood, indicating a smaller effect of GA and BW on weight development in girls. In contrast, for boys, the curves diverged more noticeably across groups, particularly after age 9, with preterm and lower BW boys growing more slowly than their term and normal BW peers. The insets highlight these patterns, showing much larger differences for boys than girls, particularly for early preterm and low BW compared to the other groups.

Table 5 shows significant effects of GA and BW on BMI size and timing over the entire 12-year period modelled. Mean BMI was smaller for the early/late preterm GA and low/low-normal BW groups, by 0.8/0.3 kg/m^2 in girls and 0.9/0.6 kg/m^2 in boys. Similarly, timing was earlier in the two preterm groups, by 0.11/0.08 units in both sexes, and to a lesser extent with the BW groups, by 0.08/0.05 units. A negative timing coefficient indicates an earlier growth spurt, where the fractional coefficient can be multiplied by 100 and viewed as a percentage difference. The larger effect for GA than BW is because the timing effect is a shift on the age scale and hence corresponds directly to GA.

Figure 3 shows the mean BMI curves for the GA and BW groups in girls and boys, highlighting distinct trends in BMI development across the groups. The early preterm children are initially lower than the late preterm and term children, and with an earlier adiposity peak and earlier adiposity rebound (AR). But after age 9-10 the GA curves cross and the early preterm becomes relatively higher, which is what the earlier AR predicts. For the BW curves the low BW group is consistently lower than the other two groups until the curves merge at around age 12. However, the age at AR is very similar in all three BW groups, and the low BW curve does not cross the others in the same way as the early preterm group.

AR occurred earlier in the early/late preterm GA groups compared to term, by 10.2/5.3 months in boys and 7.8/7.8 months in girls (Table 6). Similarly, AR timing was earlier in the low/low-normal BW groups than normal BW, by 7.6/5.2 months in boys and 5.2/0.0 months in girls (Supplementary Table 1).

DISCUSSION

This study analyses growth in children born preterm using the SITAR model to assess height, weight, and BMI trajectories up to 12 years of age. Our findings demonstrate significant disparities in growth patterns between children grouped by birth weight (BW) and gestational age (GA). Importantly, low BW emerged as a more robust etiological determinant of adverse growth outcomes than early preterm birth, as children in the low BW group exhibited notably smaller size effects than in the early preterm group, with growth deficits persisting into later years. Low BW girls/boys showed greater growth deficits, being 1.4 cm shorter and 0.5/1.0 kg lighter than their normal BW peers, compared to early preterm girls/boys, who were 0.9 cm shorter and 0.3/0.8 kg lighter than term peers. Low BW children were 1.4 cm shorter than their normal BW peers, compared to early preterm, who were 0.9 cm shorter, resulting in an additional deficit of 0.5 cm for the low BW group relative to the early preterm group. Similarly, low BW girls/boys were 0.5/1.0 kg lighter than their normal BW peers, compared to early preterm girls/boys, who were 0.3/0.8 kg lighter, reflecting a further deficit of 0.2/0.2 kg for the low BW group relative to the early preterm group.

While our findings suggest the bigger role of BW than GA in determining long-term growth outcomes, this influence is particularly evident in height and weight. Low BW children exhibit significant and persistent deficits in height and weight compared to their peers, with some studies reporting that extremely low BW (ELBW) infants remain smaller and lighter throughout childhood and adolescence (24). Even with catch-up growth during adolescence, ELBW children often fail to reach the same height as term-born peers, with deficits persisting into adulthood (38–40). Although height and weight are critical growth indicators, BMI trajectories also highlight important differences. For example, some research suggests that normalising BMI does not imply

a full resolution of growth challenges, as height may continue to lag behind, emphasising the need for targeted interventions in low BW children (24,41). This contrasts with findings that GA is a crucial factor, with each additional week of gestation contributing to improved growth outcomes, including height, weight, and BMI, after discharge (42). However, in our cohort, extremely preterm (EP) infants remained shorter and lighter compared to term-born controls throughout childhood, with girls and boys being 0.9 cm shorter and 0.8 kg lighter, respectively. Additionally, EP infants exhibited an elevated BMI by adulthood, consistent with other findings in the literature (9).

In general, BMI rapidly increases in the first year, declines to a nadir at around age 6, and then rises again in a phase known as the adiposity rebound (AR) (43). Studies have shown that early AR (before age 5) occurs in a significant proportion of preterm infants, with rates as high as 54% in some cohorts (44). This earlier timing is associated with increased BMI and a higher risk of developing obesity or worse cardiometabolic health later in life (45–47). In our study, AR timing appears later in term-born children compared to preterm groups, indicating that preterm children may experience an earlier AR. Moreover, the magnitude of AR differs significantly between the groups. In the GA groups, early preterm children experience a stronger AR, with their BMI rising sharply after AR and surpassing term-born children by age 9-9.5, indicating a higher risk of overweight and future obesity (43). However, for BW groups, while the timing of AR remains more consistent, the magnitude varies. These groups show a more gradual and stable BMI increase after AR, with no curve crossing, suggesting they may follow a healthier BMI trajectory. According to the literature (43,48), a later AR (at or after 7 years of age) is associated with a lower risk of overweight, decreased likelihood of developing obesity, and an increased chance of reversing obesity in young children, highlighting its protective role against long-term obesity and metabolic risks. Moreover, within the GA groups, early and late preterm children follow more similar growth trajectories, with the term group being more distinct until the crossing occurs. The BW groups are more evenly spaced in BMI throughout childhood, particularly among boys, indicating a more stable difference between groups. This could imply that BW has a more linear relationship with BMI, while GA may affect growth more dynamically, especially in the preterm vs. term-born distinction. As BW reflects in-utero energy reserves more directly than gestational age (GA), our findings support the hypothesis of energy trade-offs

impacting long-term growth and may contribute to understanding developmental plasticity, emphasising how in-utero nutritional and environmental conditions shape energy allocation for optimal growth (20,21). However, both perspectives (20,21) agree that preterm infants, regardless of GA or BW, are a heterogeneous group with physiological and developmental immaturity, leading to varying growth outcomes.

Moreover, our study identified that boys are more vulnerable to long-term growth deficits than girls. Specifically, low BW boys weighed 1.0 kg less than normal BW boys, whereas low BW girls weighed only 0.5 kg less than normal BW girls. The confidence intervals confirm a statistically significant difference between sexes in the low BW group. This suggests that girls may have greater resilience in terms of weight outcomes, though they still experience significant growth deficits, especially in height. Boys also experience less intense growth spurts (3.7% less intense growth spurt than their normal BW peers), indicating they may have difficulty catching up in growth. This vulnerability in boys was also noted in their more pronounced long-term growth challenges compared to girls (3). However, other studies (15) reported no increased risk for early puberty in preterm boys or girls, suggesting that while sex-based differences in growth trajectories exist, they may not extend to pubertal timing. These conflicting findings indicate that while boys may be more prone to growth challenges, further research is needed to explore how these vulnerabilities manifest across different stages of development.

Notably, children in the low BW group exhibited faster weight gain but less intense BMI increases during the observed period, indicating a distinct growth trajectory that may contribute to long-term growth challenges. This aligns with findings by Jones-Smith et al. (41,49), who found that accelerated growth during infancy, especially among small or normal-sized infants, is associated with an increased risk of childhood overweight. Their research highlights the complexity of growth patterns, noting that infants born larger do not experience the same risks, suggesting that early life growth velocity plays a role in later overweight risk, particularly in smaller infants. Our findings suggest that faster early growth spurts in early preterm children may predispose them to future health risks, including obesity, underscoring the potential protective role of delayed adiposity rebound (AR) against long-term obesity and metabolic risks, as mentioned previously.

One of the strengths of this study is the application of the SITAR model, which provides a refined understanding of growth trajectories by accounting for individual differences in size, timing, and intensity. Moreover, our large sample size and extended follow-up period enhance the generalizability of our findings. Furthermore, although the preterm cohort (2000–2015) and the term cohort (1996) were born several years apart, they grew into adolescence during a similar timeframe, ensuring similar environmental, socioeconomic, and nutritional conditions (33). All growth data were collected from the same geographical region and healthcare system, reducing variability due to systemic differences. This overlap minimises the potential influence of secular trends on our findings. Additionally, advances in neonatal care in Lithuania were implemented from 1995 onward, ensuring that the care provided during the study period was relatively consistent for the preterm cohort.

Nonetheless, the study's retrospective nature introduces certain limitations. Although we could not directly account for the pubertal stage in this study, the SITAR model is designed to adjust for pubertal timing and intensity through its random effects. These effects capture individual differences in the age of peak growth velocity (timing) and the magnitude of the growth spurt (intensity), key components of pubertal growth. For example, in our data, girls exhibited smaller timing variance in SITAR compared to boys, suggesting more consistent growth patterns during the observed age range, which could indicate earlier growth dynamics in girls relative to boys below age 13. Demonstrating how these random effects alter the mean growth curve could provide additional insight, particularly as boys may be underrepresented in terms of pubertal growth in this dataset. Since some studies suggest that very, moderately, and late preterm individuals may reach similar adult size, peak height velocity, and pubertal timing as term-born peers (15,16), extending the data collection into adolescence could better capture these dynamics and their impact on long-term growth outcomes.

Additionally, this study focused on infant sex, GA, and BW as primary variables for growth modeling due to their well-established relevance in determining growth trajectories. While other potential covariates, such as maternal age and maternal education attainment, may influence growth outcomes, their adjustment would likely have minimal impact in this analysis, as the same infants are being compared for both BW and GA. The study's primary focus on preterm-specific and birth-related variables aligns with its objectives. However, future research could incorporate

a broader range of covariates in studies with more heterogeneous populations to provide additional insights into growth determinants. In conclusion, our study highlights the significant role of BW in shaping growth trajectories, with low BW often exerting a stronger influence than GA, but not uniformly affecting all parameters. Specifically, GA appears to be more prominent in shaping BMI trajectories, as evidenced by the sharper velocity in BMI post-adiposity rebound in early preterm children. This divergence suggests that while low BW is linked to sustained growth deficits, GA influences BMI patterns more dynamically, potentially elevating the risk of overweight and obesity in early preterm groups. In our data, boys in the low BW group exhibited larger weight deficits compared to girls in the same group during the growth period studied.

Clinically, these findings underscore the need for targeted growth interventions in children with low BW, as their growth deficits persist longer than those associated with preterm birth alone. These findings suggest that clinical interventions should prioritise children born with low BW (including their preterm status) to address their unique growth challenges and optimise developmental outcomes. Further research is needed to investigate the growth characteristics of low birth weight and preterm infants, particularly in relation to different metabolic factors and environmental exposures.

DATA AVAILABILITY

The datasets collected and analysed during the current study are available upon reasonable request from the corresponding author.

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This research received no external funding.

AUTHOR CONTRIBUTIONS

R.M. collected, analysed, interpreted the data, and took the lead in writing the manuscript with the input from other authors. J.T. raised the main conceptual idea, designed and supervised

the study, helped in data interpretation and manuscript writing, and revised the final version. T.J.C. advised on the fitting of the SITAR models, commented on the study design and contributed to revising the manuscript. R.L. performed the statistical analysis, provided suggestions for data interpretation, and contributed to revising the manuscript. A.S. contributed to the interpretation of the results and the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

CONSENT STATEMENT

All data used in this research were retrospective, anonymised and handled in accordance with relevant data protection regulations. As such, individual consent was not required for this study.

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Table 1. Number of children in the gestational and birth weight groups by sex.

Sex	**Birth weight** / **Gestational age**	**Low** (<2500 g)	**Low-normal** (2500 to <3000 g)	**Normal** (3000 to <4000 g)	**Total**
Boy	Early preterm (<34 weeks)	67	1	0	**68**
	Late preterm (34 to <37 weeks)	67	70	24	**161**
	Term (37 to <42 weeks)	2	12	226	**240**
	Total (boys)	**136**	**83**	**250**	**469**
Girl	Early preterm (<34 weeks)	75	3	0	78
	Late preterm (34 to <37 weeks)	71	68	21	160
	Term (37 to <42 weeks)	5	33	205	243
	Total (girls)	**151**	**104**	**226**	**481**
Total	Early preterm (<34 weeks)	142	4	0	**146**
	Late preterm (34 to <37 weeks)	138	138	45	**321**
	Term (37 to <42 weeks)	7	45	431	**483**
	Total	**287**	**187**	**476**	**950**

Table 2. Summary of SITAR models fitted to height, weight and BMI by sex, adjusted separately for GA group and BW group.

Sex	Fixed effects	Response variable	Points	d.f.	Random effects*	Variance explained (%)	Residual SD
Girls (n=481)	GA	Height (cm)	7939	7	a c	78.5	2.1
		Weight (kg)	7914	7	a c	91.7	1.2
		BMI (kg/cm^2)	7949	8	a b c	75.2	1.0
	BW	Height (cm)	7939	7	a c	78.5	2.1
		Weight (kg)	7915	6	a c	91.6	1.2
		BMI (kg/cm^2)	7951	8	a b c	75.3	1.0
Boys (n=469)	GA	Height (cm)	7897	8	a c	76.6	2.1
		Weight (kg)	7869	7	a c	90.4	1.2
		BMI (kg/cm^2)	7894	7	a b c	72.2	1.0
	BW	Height (cm)	7896	6	a c	76.4	2.1
		Weight (kg)	7869	7	a c	90.4	1.2
		BMI (kg/cm^2)	7894	8	a b c	72.3	1.0

* Random effects: a = size, b = timing, c = intensity

Table 3. Significant GA and BW group mean differences in the SITAR height model for the period from birth to 12 years.

Covariate	Sex	Effect	SITAR parameter	Coefficient (95% CI) (cm)	Standard Error (cm)	p-value
GA	Girls	Early preterm	a (size)	-0.92 (-1.49; -0.34)	0.29	0.002
		Late preterm		0.08 (-0.37; 0.53)	0.23	0.7
	Boys	Early preterm	a (size)	-0.89 (-1.48; -0.29)	0.30	0.003
		Late preterm		0.09 (-0.34; 0.53)	0.22	0.7
BW	Girls	Low	a (size)	-1.45 (-1.90; -0.99)	0.23	<0.001
		Low-normal		-0.35 (-0.86; 0.15)	0.26	0.2
	Boys	Low	a (size)	-1.43 (-1.88; -0.99)	0.23	<0.001
		Low-normal		-0.18 (-0.71; 0.34)	0.27	0.5

References: Term GA group; Normal BW group.

Table 4. Significant GA and BW group mean differences in the SITAR weight model for the period from birth to 12 years.

Covariate	Sex	Effect	SITAR parameter	Coefficient (95% CI)	Standard Error	p-value
GA group	Girls	Early preterm	a (size)	-0.29 (-0.50; -0.07)	0.11	0.009
		Late preterm		-0.07 (-0.24; 0.09)	0.09	0.4
	Boys	Early preterm	a (size)	-0.83 (-1.19; -0.48)	0.18	<0.001
		Late preterm		-0.26 (-0.53; -0.01)	0.13	0.05
		Early preterm	c	-0.040 (-0.068; -0.012)	0.01	0.005
		Late preterm	(intensity)	-0.005 (-0.025; 0.015)	0.01	0.6
BW group	Girls	Low	a (size)	-0.46 (-0.62; -0.29)	0.09	<0.001
		Low-normal		-0.15 (-0.34; 0.04)	0.10	0.1
	Boys	Low	a (size)	-1.00 (-1.26; -0.73)	0.14	<0.001
		Low-normal		-0.30 (-0.61; 0.02)	0.160	0.07
		Low	c	-0.037 (-0.058; -0.016)	0.011	0.001
		Low-normal	(intensity)	-0.006 (-0.030; -0.019)	0.013	0.7

References: Term GA group; Normal BW group. Coefficients: size – kg, intensity – fractional.

Table 5. Significant GA and BW group mean differences in the SITAR BMI model for the period from birth to 12 years.

Covariate	Sex	Effect	SITAR parameter	Coefficient (95% CI)	Standard Error	p-value
GA Group	Girls	Early preterm	a (size)	-0.77 (-1.05; -0.48)	0.14	<0.001
		Late preterm		-0.46 (-0.68; -0.24)	0.11	<0.001
		Early preterm	b (timing)	-0.110 (-0.123; -0.089)	0.007	<0.001
		Late preterm		-0.080 (-0.095; -0.070)	0.009	<0.001
	Boys	Early preterm	a (size)	-0.81 (-1.13; -0.49)	0.16	<0.001
		Late preterm		-0.60 (-0.83; -0.36)	0.11	<0.001
		Early preterm	b (timing)	-0.120 (-0.136; -0.098)	0.010	<0.001
		Late preterm		-0.078 (-0.091; -0.065)	0.007	<0.001
BW Group	Girls	Low	a (size)	-0.81 (-1.03; -0.58)	0.11	<0.001
		Low-normal		-0.22 (-0.47; 0.03)	0.13	0.09
		Low	b (timing)	-0.069 (-0.085; -0.054)	0.009	<0.001
		Low-normal		-0.028 (-0.046; -0.011)	0.008	0.001
	Boys	Low	a (size)	-0.92 (-1.17; -0.68)	0.13	<0.001
		Low-normal		-0.48 (-0.77; -0.19)	0.15	0.001
		Low	b (timing)	-0.078 (-0.094; -0.062)	0.008	<0.001
		Low-normal		-0.054 (-0.073; -0.036)	0.010	<0.001

References: Term GA group; Normal BW group. Coefficients: size – kg, intensity, timing – fractional.

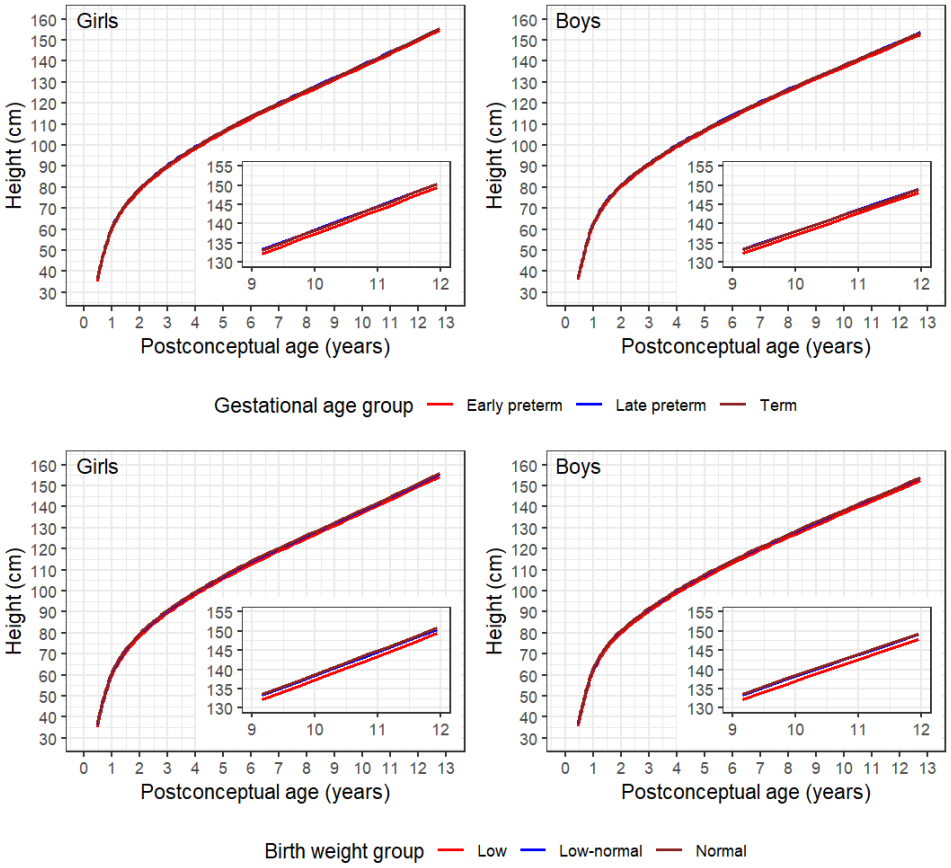
Girls
Boys
Height (cm)
Postconceptual age (years)
Gestational age group
Early preterm
Late preterm
Term
Girls
Boys
Height (cm)
Postconceptual age (years)
Birth weight group
Low
Low-normal
Normal

Figure 1.

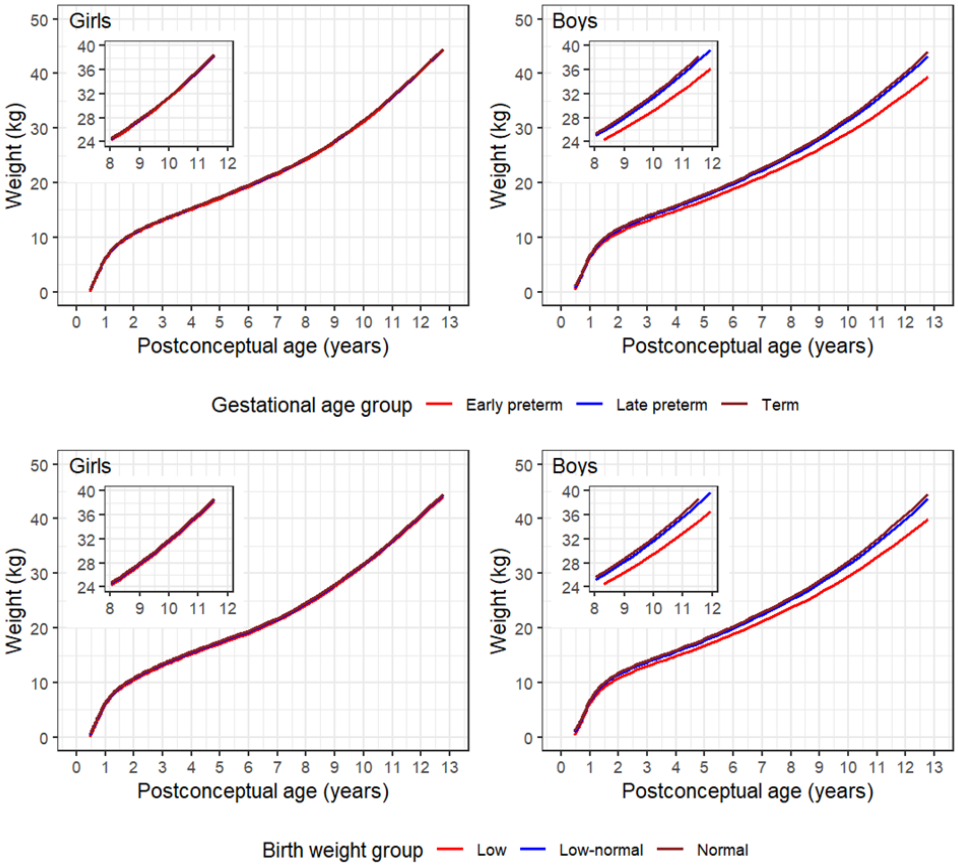
Girls
Boys
Weight (kg)
Postconceptual age (years)
Gestational age group
Early preterm
Late preterm
Term
Birth weight group
Low
Low-normal
Normal

Figure 2.

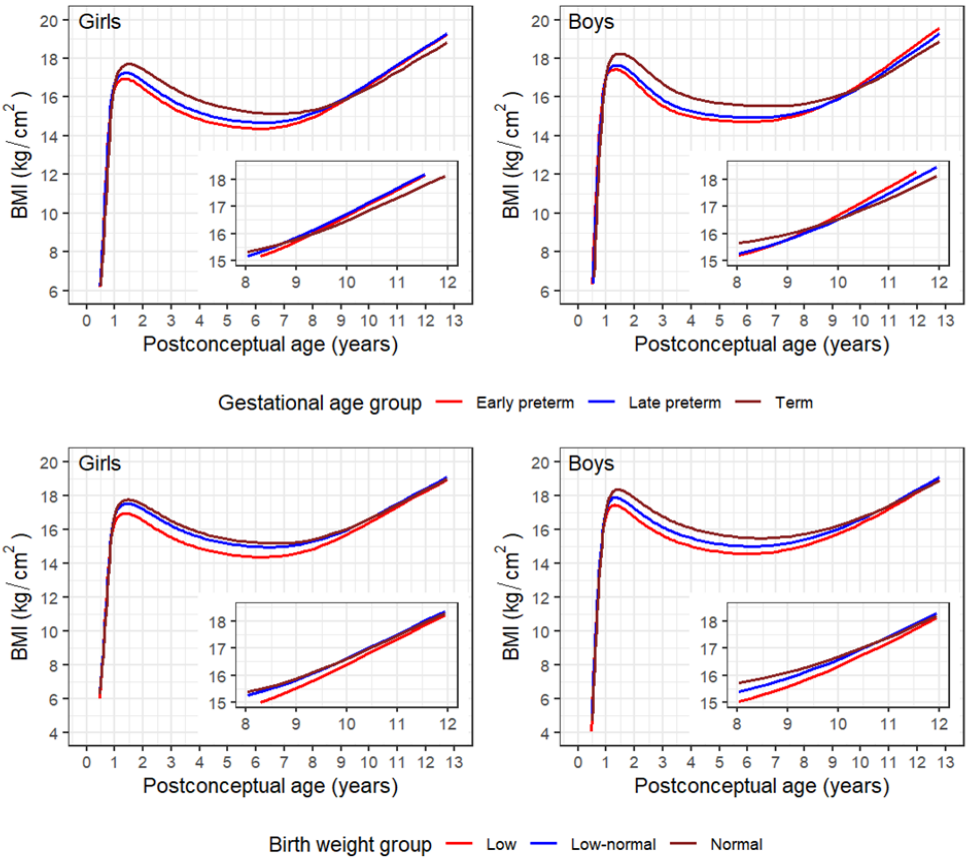
Girls
Boys
BMI (kg/cm^2)
Postconceptual age (years)
Gestational age group
Early preterm
Late preterm
Term
Girls
Boys
BMI (kg/cm^2)
Postconceptual age (years)
Birth weight group
Low
Low-normal
Normal

Figure 3.

FIGURE CAPTIONS:

Figure 1. Mean SITAR height curves for the GA and BW groups.
Figure 2. Mean SITAR weight curves for the GA and BW groups.
Figure 3. Mean SITAR BMI curves for the GA and BW groups.

4th publication/ 4 publikacija

Surviving Prematurity: Retrospective Longitudinal Study of Multisystem Consequences in Preterm-Born Individuals from Infancy to Adolescence

Morkuniene R, Levuliene R, Gegzna V, Jakimaviciene EM, Tutkuviene J

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Surviving prematurity: retrospective longitudinal study of multisystem consequences in preterm-born individuals from infancy to adolescence

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Abstract

Background Prematurity is linked to diverse and significant health outcomes, but a comprehensive understanding of its long-term multisystem impacts remains limited.

Methods Retrospective longitudinal cohort study on 417 preterm children born between 2000 and 2015 explores the incidence, dynamics, and interrelationships of health conditions from infancy to adolescence. Data on 1818 diagnoses, categorised by birth weight (BW) and gestational age (GA) and documented according to ICD-10, were analysed using non-parametric tests and negative binomial regression models.

Results Most diagnoses occurred by age 7, with eye diseases, congenital malformations, and infections most prevalent, but the greatest disparities with the general population were in blood, nervous system, mental, and neoplastic diseases. Lower BW significantly correlated with higher mean disease counts and greater diversity of health conditions across various ICD-10 chapters, while GA showed less pronounced associations. Children in "Extremely and very low," "Low," and "Sub-optimal" BW categories exhibited 1.77, 1.50, and 1.34 times more diseases, respectively, than those in the "Normal" BW category. Unique and highly individual patterns of disease co-occurrence were observed, increasing in complexity as BW decreased.

Conclusions The highest disease burden for preterm-born individuals occurred by age 7, with lower BW linked to greater health complexity and unique comorbidities.

Keywords Prematurity, Multimorbidity, Longitudinal study, ICD-10, Diseases

Background

The concept of the developmental origins of health and disease [1] highlights the critical impact of fetal life on adult health, identifying the brain, cardiovascular, liver, and kidney systems as particularly vulnerable to adverse fetal programming. Premature newborns are unique because they miss part of the natural developmental changes of the fetal period in the womb. Instead, they are born early and immediately exposed to environmental factors despite their immature physiology. Studies focusing on individual organ systems have revealed a range of

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health issues tied to premature birth, from cardiovascular diseases such as arterial hypertension and ischemic heart disease [2, 3] to endocrine and metabolic disorders [4, 5], including congenital hypothyroidism [6], and metabolic syndrome-like symptoms [2, 7–9]. Additionally, research has documented various respiratory diseases linked to preterm birth, like bronchopulmonary dysplasia and pulmonary hypertension [10–12], as well as complications from respiratory syncytial virus infections [13–15], viral-induced wheezing [16–18] and school-age asthma [19–21]. Moreover, digestive and renal dysfunctions, such as necrotising enterocolitis [11] and renal impairment [22–24], have been observed following preterm birth.

Furthermore, neurodevelopmental impairments are among the most extensively researched as significant consequences of prematurity. Diseases of the nervous system and mental and behavioural disorders, including cerebral palsy [25–29], autism spectrum disorders, and a range of cognitive, language, and academic challenges [28–38], are highly related to preterm birth. The severity of these neurodevelopmental disorders often correlates with the degree of prematurity, underlining that even late preterm infants, despite being born with no immediate major health issues, face an elevated risk of neurodevelopmental impairments [39].

While extensive research has been conducted on individual organ system outcomes or diseases associated with preterm birth, this singular focus inadequately addresses the complex health landscape of preterm survivors. The prevalence of multimorbidity—where two or more chronic conditions coexist in an individual [40]—and the shared embryological and histological origins of these organ systems [41, 42] suggest a more intricate interplay of health issues than currently understood. Microvascular dysfunction has also been suggested as a potential mechanism underlying many of these outcomes, as impaired angiogenesis and vascular development during critical periods may contribute to systemic consequences [2, 43]. These microvascular impairments may underlie the increased risk of cardiovascular diseases [24], neurodevelopmental disorders [44], and other health issues observed in preterm-born individuals [45]. Additionally, while research on extremely or very low birth weight preterm children is more emphasised [43, 46], there are fewer studies on the long-term health effects of those born with sub-optimal birth weight or late prematurity [47, 48], with a lack of studies comparing morbidity patterns and the timing of disease onset across different sub-categories of prematurity. Longitudinal studies on morbidity also vary widely in duration, with most focusing on short-term outcomes (up to 2 or 5–7 years) [4, 5, 17, 19, 28], and only a few recent studies extending into adolescence or adulthood [36, 49–53]. This gap in research leaves a fragmented understanding of the health challenges that preterm survivors from all sub-categories of prematurity face, overlooking the potential interconnectedness and cumulative burden of multiple health conditions.

Moreover, while traditional classifications such as small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA) provide valuable clinical insights, they integrate birth weight (BW) and gestational age (GA) into a single measure, potentially obscuring the independent effects of these variables. Our study adopts a distinct approach, examining BW and GA as separate variables. This methodological choice allows us to disentangle their respective impacts on long-term health outcomes, offering new insights into the interplay between prenatal growth and developmental timing. Specifically, BW reflects cumulative energy reserves and trade-offs during fetal development [50], while GA captures the timing of developmental processes and exposure to intrauterine conditions. By separating these factors, we aim to provide a nuanced understanding of prematurity-related health challenges from an evolutionary [54] and developmental perspective [55].

Therefore, recognising these limitations, we hypothesise that diseases affecting different organ systems in premature individuals may be interrelated (by positive or negative correlations) and occur over a certain period of time, indicating a common or individual nature of development and efforts of the organism to allocate the energetical resources in order to ensure the most important functions first. Therefore, this study proposes a retrospective longitudinal approach aiming to: 1) examine the incidence and distribution of morbidity across prematurity sub-categories from birth to adolescence; 2) investigate the impact of birth-related factors for the mean number of diseases and ICD-10 disease chapters per child; 3) explore health condition complexity and interrelationships among disorders across different ICD-10 disease chapters.

Methods

Study design and cohort selection

A retrospective longitudinal cohort study was conducted on 417 prematurely born children (201 boys, 216 girls; 331 singletons, 86 twins) from 2000 to 2015. Data were retrospectively collected from paper medical records in two of the largest primary health care centres in Vilnius, Lithuania, and their affiliates. These centres represent major providers of care for children's health in the Vilnius region, one of only two cities in Lithuania (along with Kaunas) that house third-level centers for neonatal care. The medical records included detailed health histories from birth and all diagnoses documented according

to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [56] from birth up to the time of the study (in total – 1818 diagnoses). Recurrent or subsequently re-diagnosed conditions were excluded, focusing solely on first-time diagnoses to emphasise the timing and onset of new conditions. Clinical terms and conditions within ICD-10 are coded in 22 systemic disease chapters with varying numbers of disease groups and subgroups within the chapters. Disease chapters selected for analysis are detailed in Supplementary Table 1 and include all possible newly diagnosed diseases, highlighting the time of onset of new disease cases within the chapter.

To explore the distinct contributions of birth weight (BW) and gestational age (GA) on long-term health outcomes, these variables were analysed independently rather than combined into categories such as SGA/AGA/LGA. This approach aligns with our aim to uncover nuanced associations that might otherwise be masked in traditional classifications, reflecting BW as a marker of prenatal energy reserves and GA as a measure of developmental timing. Observed variables included sex, birth weight categories defined by birth weight in grams: "Extremely and very low" (< 1000 – 1500) g, "Low" [1500 – 2500) g, "Sub-optimal" [2500 – 3000) g, "Normal" [3000 – 4000) g), and gestational age categories defined by gestational weeks: "Extremely and very preterm" (22 – 32), "Moderate preterm" [32 – 34), "Late preterm" [34 – 37). Diseases were categorised by ICD-10 disease chapters for statistical analysis, with age intervals set at [0–3], (3–7], (7–12], (12–18], and [0–18] years. A round and square bracket denotes that an endpoint of a time interval is excluded or included, respectively.

Table 1 Distribution of diseases diagnosed at different age intervals from birth to adulthood across various birth weight categories. The first row shows the frequency in numbers and the second presents the row percentages

Birth weight category	Number of ICD-10 diseases diagnosed				
	[0–3]	(3–7]	(7–12]	(12–18]	Total
Extremely and very low	126 56.8	73 32.9	21 9.5	2 0.9	**222**
Low	451 47.9	298 31.6	149 15.8	44 4.7	**942**
Sub-optimal	223 42.1	183 34.5	84 15.8	40 7.5	**530**
Normal	63 50.8	40 32.3	14 11.3	7 5.6	**124**
Total	**863** **47.5**	**594** **32.7**	**268** **14.7**	**93** **5.1**	**1818** **100**

A round and square bracket denotes that an endpoint of a time interval is excluded or included, respectively

Table 2 Distribution of diseases diagnosed at different age intervals from birth to adulthood across various gestational age categories. The first row shows the frequency in numbers and the second presents the row percentages

Gestational age category	Number of ICD-10 diseases diagnosed				
	[0–3]	(3–7]	(7–12]	(12–18]	Total
Extremely and very preterm	153 55.8	80 29.2	33 12.0	8 2.9	**274**
Moderate preterm	173 53.6	99 30.7	41 12.7	10 3.1	**323**
Late preterm	537 44.0	415 34.0	194 15.9	75 6.1	**1221**
Total	**863** **47.5**	**594** **32.7**	**268** **14.7**	**93** **5.1**	**1818** **100**

A round and square bracket denotes that an endpoint of a time interval is excluded or included, respectively

Statistical analysis

Data visualisation, non-parametric tests, and regression models were employed to achieve the study's main goals. The R (version 4.3.2) software was used to perform the computations.

Firstly, the data were summarised by counts and percentages to show the number of children in the GA and BW groups (Supplementary Table 2). Then, the counts and percentages of all diseases in age intervals by GA and BW groups were obtained (Tables 1 and 2). Moreover, the same characteristics were computed by the ICD-10 disease chapters for the structure of diagnoses (Tables 3 and 4) and morbidity within the analysed groups (Tables 5 and 6). Furthermore, the GA groups were compared using the Fisher exact test, and the same analysis was performed for the BW groups (Table 5). Morbidity was expressed as a percentage of children affected from the total study population or sub-category analysed. The morbidity rates for the general Lithuanian pediatric population were similarly calculated using data from official health statistics databases [57, 58].

The Poisson and negative binomial regression with the logarithmic link function [59] were considered for modelling the mean number of diseases and ICD-10 disease chapters per individual (Tables 7 and 8). Due to the small number of diseases and disease chapters per child in age intervals, the modelling was done only for the whole age interval [0, 18]. At first, the number of diseases for each child was obtained from the data set. Then, the mean number of diseases per child was modelled by regression, taking sex, BW and GA groups as covariates. The regression approach was used to identify significant factors by adjusting for the other considered variables. The analysis

Table 3 Distribution of newly diagnosed cases in different ICD-10 disease chapters according to gestational age categories during subsequent age intervals (the first row shows the number of cases, and the second and third rows– the row and column percentages, respectively). The last column represents the total number of cases and column percentages

Disease Chapter	Gestational age categories															Total (for the chapter in [0–18]) ($n=417$)
	Extremely and very preterm ($n=64$)					Moderate preterm ($n=71$)					Late preterm ($n=282$)					
	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	
A00-B99—Certain infectious and parasitic diseases	8	10	4	0	**22**	3	22	2	0	**27**	27	88	15	3	**133**	**182**
	36.4	45.5	18.2	0.0	**100**	11.1	81.5	7.4	0.0	**100**	20.3	66.2	11.3	2.3	**100**	-
	5.2	12.5	12.1	0.0	**8.0**	1.7	22.2	4.9	0.0	**8.4**	5.0	21.2	7.7	4.0	**10.9**	**10.0**
C00-D49—Neoplasms	5	0	0	0	**5**	8	0	0	0	**8**	15	2	2	1	**20**	**33**
	100	0.0	0.0	0.0	**100**	100	0.0	0.0	0.0	**100**	75.0	10.0	10.0	5.0	**100**	-
	3.3	0.0	0.0	0.0	**1.8**	4.6	0.0	0.0	0.0	**2.5**	2.8	0.5	1.0	1.3	**1.6**	**1.8**
D50-D89—Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	12	1	0	0	**13**	20	0	0	0	**20**	63	4	0	1	**68**	**101**
	92.3	7.7	0.0	0.0	**100**	100	0.0	0.0	0.0	**100**	92.7	5.9	0.0	1.5	**100**	-
	7.8	1.3	0.0	0.0	**4.7**	11.6	0.0	0.0	0.0	**6.2**	11.7	1.0	0.0	1.3	**5.6**	**5.6**
E00-E89—Endocrine, nutritional and metabolic diseases	15	1	1	0	**17**	23	5	5	2	**35**	69	4	23	10	**106**	**158**
	88.2	5.9	5.9	0.0	**100**	65.7	14.3	14.3	5.7	**100**	65.1	3.8	21.7	9.4	**100**	-
	9.8	1.3	3.0	0.0	**6.2**	13.3	5.1	12.2	20	**10.8**	12.8	1.0	11.9	13.3	**8.7**	**8.7**
F01-F99—Mental, Behavioral and Neurodevelopmental disorders	7	8	1	0	**16**	8	14	5	1	**28**	18	68	23	2	**111**	**155**
	43.8	50.0	6.3	0.0	**100**	28.6	50.0	17.9	3.6	**100**	16.2	61.3	20.7	1.8	**100**	-
	4.6	10	3.0	0.0	**5.8**	4.6	14.1	12.2	10	**8.7**	3.4	16.4	11.9	2.7	**9.1**	**8.5**
G00-G99—Diseases of the nervous system	10	0	0	1	**11**	4	0	2	1	**7**	25	3	4	6	**38**	**56**
	90.9	0.0	0.0	9.1	**100**	57.1	0.0	28.6	14.3	**100**	65.8	7.9	10.5	15.8	**100**	-
	6.5	0.0	0.0	12.5	**4.0**	2.3	0.0	4.9	10	**2.2**	4.7	0.7	2.1	8.0	**3.21**	**3.1**
H00-H59—Diseases of the eye and adnexa	21	20	12	4	**57**	25	15	13	2	**55**	54	81	36	23	**194**	**306**
	36.8	35.1	21.1	7.0	**100**	45.5	27.3	23.6	3.6	**100**	27.8	41.8	18.6	11.9	**100**	-
	13.7	25.0	36.4	50.0	**20.8**	14.5	15.2	31.7	20	**17.0**	10.1	19.5	18.6	30.7	**15.9**	**16.8**
H60-H95—Diseases of the ear and mastoid process	3	1	2	0	**6**	2	1	0	0	**3**	0	1	1	2	**4**	**13**
	50.0	16.7	33.3	0.0	**100**	66.7	33.3	0.0	0.0	**100**	0.0	25.0	25.0	50.0	**100**	-
	2.0	1.3	6.1	0.0	**2.2**	1.2	1.0	0.0	0.0	**0.9**	0.0	0.2	0.5	2.7	**0.3**	**0.7**
I00-I99—Diseases of the circulatory system	0	0	0	0	**0**	0	1	0	0	**1**	3	2	2	4	**11**	**12**
	0.0	0.0	0.0	0.0	**-**	0.0	100	0.0	0.0	**100**	27.3	18.2	18.2	36.4	**100**	-
	0.0	0.0	0.0	0.0	**0.0**	0.0	1.0	0.0	0.0	**0.3**	0.6	0.5	1.0	5.3	**0.9**	**0.7**
J00-J99—Diseases of the respiratory system	12	18	2	0	**32**	12	14	5	0	**31**	32	66	13	4	**115**	**178**
	37.5	56.3	6.3	0.0	**100**	38.7	45.2	16.1	0.0	**100**	27.8	57.4	11.3	3.5	**100**	-
	7.8	22.5	6.1	0.0	**11.7**	6.9	14.1	12.2	0.0	**9.6**	6.0	15.9	6.7	5.3	**9.4**	**9.8**
K00-K95—Diseases of the digestive system	16	5	2	0	**23**	15	7	3	1	**26**	64	15	12	4	**95**	**144**
	69.6	21.7	8.7	0.0	**100**	57.7	26.9	11.5	3.9	**100**	67.4	15.8	12.6	4.2	**100**	-
	10.5	6.3	6.1	0.0	**8.4**	8.7	7.1	7.3	10	**8.0**	11.9	3.6	6.2	5.3	**7.8**	**7.9**
L00-L99—Diseases of the skin and subcutaneous tissue	5	1	1	3	**10**	12	3	0	0	**15**	41	10	2	1	**54**	**79**
	50.0	10.0	10.0	30.0	**100**	80.0	20.0	0.0	0.0	**100**	75.9	18.5	3.7	1.9	**100**	-
	3.3	1.3	3.0	37.5	**3.6**	6.9	3.0	0.0	0.0	**4.6**	7.6	2.4	1.0	1.3	**4.4**	**4.3**

Table 3 (continued)

Disease Chapter	Gestational age categories															Total (for the chapter in [0–18]) (*n* = 417)
	Extremely and very preterm (*n* = 64)					Moderate preterm (*n* = 71)					Late preterm (*n* = 282)					
	[0–3]	[3–7]	[7–12]	[12–18]	[0–18]	[0–3]	[3–7]	[7–12]	[12–18]	[0–18]	[0–3]	[3–7]	[7–12]	[12–18]	[0–18]	
M00-M99—Diseases of the musculoskeletal system and connective tissue	1	3	5	0	**9**	1	7	4	0	**12**	9	23	37	9	**78**	**99**
	11.1	33.3	55.6	0.0	**100**	8.3	58.3	33.3	0.0	**100**	11.5	29.5	47.4	11.5	**100**	-
	0.7	3.8	15.2	0.0	**3.3**	0.6	7.1	9.8	0.0	**3.7**	1.7	5.5	19.1	12.0	**6.4**	**5.4**
N00-N99—Diseases of the genitourinary system	5	6	0	0	**11**	11	3	0	1	**15**	32	14	6	2	**54**	**80**
	45.5	54.6	0.0	0.0	**100**	73.3	20.0	0.0	6.7	**100**	59.3	25.9	11.1	3.7	**100**	-
	3.3	7.5	0.0	0.0	**4.0**	6.4	3.0	0.0	10	**4.6**	6.0	3.4	3.1	2.7	**4.4**	**4.4**
P00-P96—Certain conditions originating in the perinatal period	6	0	0	0	**6**	6	0	0	0	**6**	17	1	0	0	**18**	**30**
	100	0.0	0.0	0.0	**100**	100	0.0	0.0	0.0	**100**	94.4	5.6	0.0	0.0	**100**	-
	3.9	0.0	0.0	0.0	**2.2**	3.5	0.0	0.0	0.0	**1.9**	3.2	0.2	0.0		**1.5**	**1.7**
Q00-Q99—Congenital malformations, deformations and chromosomal abnormalities	27	6	3	0	**36**	23	7	2	2	**34**	68	33	18	3	**122**	**192**
	75.0	16.7	8.3	0.0	**100**	67.7	20.6	5.9	5.9	**100**	55.7	27.1	14.8	2.5	**100**	-
	17.6	7.5	9.1	0.0	**13.1**	13.3	7.1	4.9	20	**10.5**	12.7	8.0	9.3	4.0	**10.0**	**10.6**
Total (the number of cases in all disease chapters)	**153**	**80**	**33**	**8**	**274**	**173**	**99**	**41**	**10**	**323**	**537**	**415**	**194**	**75**	**1221**	**1818**
	55.8	**29.2**	**12.0**	**2.9**	**100**	**53.6**	**30.7**	**12.7**	**3.1**	**100**	**44.0**	**34.0**	**15.9**	**6.1**	**100**	-
	100	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 4 Distribution of newly diagnosed cases in different ICD-10 disease chapters according to birth weight categories during subsequent age intervals (the first row shows the number of cases, and the second and third rows– the row and column percentages, respectively)

Disease Chapter	Birth weight categories																				Total (for the chapter in [0, 18]) ($n=417$)
	Extremely and very low ($n=48$)					Low ($n=205$)					Sub-optimal ($n=125$)					Normal ($n=39$)					
	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	
A00-B99—Certain infectious and parasitic diseases	7 31.8 5.6	12 54.6 16.4	3 13.6 14.3	0 0.0 0.0	**22** **100** **9.9**	12 14.5 2.7	59 71.1 19.8	11 13.3 7.4	1 1.2 2.3	**83** **100** **8.8**	14 21.5 6.3	44 67.7 24.0	6 9.2 7.1	1 1.5 2.5	**65** **100** **12.3**	5 41.7 7.9	5 41.7 12.5	1 8.3 7.1	1 8.3 14.3	**12** **100** **9.7**	**182** - **10.0**
C00-D49—Neoplasms	6 100 4.8	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**6** **100** **2.7**	17 89.5 3.8	0 0.0 0.0	1 5.3 0.7	1 5.3 2.3	**19** **100** **2.0**	4 57.1 1.8	2 28.6 1.1	1 14.3 1.2	0 0.0 0.0	**7** **100** **1.3**	1 100 1.6	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**1** **100** **0.8**	**33** - **1.8**
D50-D89—Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	11 91.7 8.7	1 8.3 1.4	0 0.0 0.0	0 0.0 0.0	**12** **100** **5.4**	54 98.2 12.0	1 1.8 0.3	0 0.0 0.0	0 0.0 0.0	**55** **100** **5.8**	27 87.1 12.1	3 9.7 1.6	0 0.0 0.0	1 3.2 2.5	**31** **100** **5.8**	3 100 4.8	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**3** **100** **2.4**	**101** - **5.6**
E00-E89—Endocrine, nutritional and metabolic diseases	13 86.7 10.3	1 6.7 1.4	1 6.7 4.8	0 0.0 0.0	**15** **100** **6.8**	58 64.4 12.9	6 6.7 2.0	19 21.1 12.8	7 7.8 15.9	**90** **100** **9.6**	25 61.0 11.2	3 7.3 1.6	8 19.5 9.5	5 12.2 12.5	**41** **100** **7.7**	11 91.7 17.5	0 0.0 0.0	1 8.3 7.1	0 0.0 0.0	**12** **100** **9.7**	**158** - **8.7**
F01-F99—Mental, Behavioral and Neurodevelopmental disorders	4 28.6 3.2	9 64.3 12.3	1 7.1 4.8	0 0.0 0.0	**14** **100** **6.3**	22 27.2 4.9	42 51.9 14.1	15 18.5 10.1	2 2.5 4.5	**81** **100** **8.6**	5 11.1 2.2	28 62.2 15.3	11 24.4 13.1	1 2.22 2.5	**45** **100** **8.5**	2 13.3 3.2	11 73.3 27.5	2 13.3 14.3	0 0.0 0.0	**15** **100** **12.1**	**155** - **8.5**
G00-G99—Diseases of the nervous system	6 75.0 4.8	0 0.0 0.0	1 12.5 4.8	1 12.5 50.0	**8** **100** **3.6**	20 76.9 4.4	0 0.0 0.0	2 7.7 1.3	4 15.4 9.1	**26** **100** **2.8**	11 57.9 4.9	2 10.5 1.1	3 15.8 3.6	3 15.8 7.5	**19** **100** **3.6**	2 66.7 3.2	1 33.3 2.5	0 0.0 0.0	0 0.0 0.0	**3** **100** **2.4**	**56** - **3.1**

Table 4 (continued)

Disease Chapter	Birth weight categories																				Total (for the chapter in [0, 18]) ($n=417$)
	Extremely and very low ($n=48$)					Low ($n=205$)					Sub-optimal ($n=125$)					Normal ($n=39$)					
	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	
H00-H59—Diseases of the eye and adnexa	18 40.9 14.3	19 43.2 26.0	6 13.6 28.6	1 2.3 50.0	**44** **100** **19.8**	48 30.6 10.6	60 38.2 20.0	35 22.3 23.5	14 8.9 31.8	**157** **100** **16.7**	25 29.8 11.2	30 35.7 16.4	18 21.4 21.4	11 13.1 27.5	**84** **100** **15.8**	9 42.9 14.3	7 33.3 17.5	2 9.5 14.3	3 14.3 42.9	**21** **100** **16.9**	**306** - **16.8**
H60-H95—Diseases of the ear and mastoid process	2 66.7 1.6	0 0.0 0.0	1 33.3 4.8	0 0.0 0.0	**3** **100** **1.4**	2 33.3 0.4	2 33.3 0.7	1 16.7 0.7	1 16.7 2.3	**6** **100** **0.6**	1 0.25 0.4	1 0.25 0.5	1 0.25 1.2	1 0.25 2.5	**4** **100** **0.8**	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**0** - **0.0**	**13** - **0.7**
I00-I99—Diseases of the circulatory system	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**0** - **0.0**	2 33.3 0.4	1 16.7 0.3	1 16.7 0.7	2 33.3 4.5	**6** **100** **0.6**	1 20.0 0.4	2 40.0 1.1	0 0.0 0.0	2 40.0 5.0	**5** **100** **0.9**	0 0.0 0.0	0 0.0 0.0	1 100 7.1	0 0.0 0.0	**1** **100** **0.8**	**12** - **0.7**
J00-J99—Diseases of the respiratory system	11 37.9 8.7	17 58.6 23.3	1 3.5 4.8	0 0.0 0.0	**29** **100** **13.1**	25 29.4 5.5	44 51.8 14.8	16 18.8 10.7	0 0.0 0.0	**85** **100** **9.0**	16 29.1 7.2	33 60.0 18.0	3 5.5 3.6	3 5.5 7.5	**55** **100** **10.4**	4 44.4 6.3	4 44.4 10.0	0 0.0 0.0	1 11.1 14.3	**9** **100** **7.3**	**178** - **9.8**
K00-K95—Diseases of the digestive system	12 63.2 9.5	5 26.3 6.8	2 10.5 9.5	0 0.0 0.0	**19** **100** **8.6**	47 67.1 10.4	10 14.3 3.3	11 15.7 7.4	2 2.9 4.5	**70** **100** **7.4**	28 66.7 12.6	7 16.7 3.8	4 9.5 4.8	3 7.1 7.5	**42** **100** **7.9**	8 61.5 12.7	5 38.5 12.5	0 0.0 0.0	0 0.0 0.0	**13** **100** **10.5**	**144** - **7.9**
L00-L99—Diseases of the skin and subcutaneous tissue	4 80.0 3.2	1 20.0 1.4	0 0.0 0.0	0 0.0 0.0	**5** **100** **2.3**	29 69.1 6.4	8 19.1 2.7	2 4.8 1.3	3 7.1 6.8	**42** **100** **4.5**	19 73.1 8.5	5 19.2 2.7	1 3.9 1.2	1 3.9 2.5	**26** **100** **4.9**	6 100 9.5	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**6** **100** **4.8**	**79** - **4.3**
M00-M99—Diseases of the musculoskeletal system and connective tissue	1 12.5 0.8	3 37.5 4.1	4 50.0 19.0	0 0.0 0.0	**8** **100** **3.6**	8 15.4 1.8	22 42.3 7.4	19 36.5 12.8	3 5.8 6.8	**52** **100** **5.5**	1 3.33 0.4	6 20.0 3.3	18 60.0 21.4	5 16.7 12.5	**30** **100** **5.7**	1 11.1 1.6	2 22.2 5.0	5 55.6 35.7	1 11.1 14.3	**9** **100** **7.3**	**99** - **5.4**
N00-N99—Diseases of the genitourinary system	5 83.3 4.0	1 16.7 1.4	0 0.0 0.0	0 0.0 0.0	**6** **100** **2.7**	26 59.1 5.8	14 31.8 4.7	2 4.6 1.3	2 4.6 4.5	**44** **100** **4.7**	14 60.9 6.3	6 26.1 3.3	2 8.7 2.4	1 4.4 2.5	**23** **100** **4.3**	3 42.9 4.8	2 28.6 5.0	2 28.6 14.3	0 0.0 0.0	**7** **100** **5.6**	**80** - **4.4**

Table 4 (continued)

Disease Chapter	Birth weight categories																				Total (for the chapter in [0, 18]) ($n=417$)
	Extremely and very low ($n=48$)					Low ($n=205$)					Sub-optimal ($n=125$)					Normal ($n=39$)					
	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	[0–3]	(3–7]	(7–12]	(12–18]	[0–18]	
P00-P96—Certain conditions originating in the perinatal period	5 100 4.0	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**5** **100** **2.3**	15 93.8 3.3	1 6.3 0.3	0 0.0 0.0	0 0.0 0.0	**16** **100** **1.7**	7 100 3.1	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**7** **100** **1.3**	2 100 3.2	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0	**2** **100** **1.6**	**30** - **1.7**
Q00-Q99—Congenital malformations, deformations and chromosomal abnormalities	21 80.8 16.7	4 15.4 5.5	1 3.9 4.8	0 0.0	**26** **100** **11.7**	66 60.0 14.6	28 25.5 9.4	14 12.7 9.4	2 1.8 4.5	**110** **100** **11.7**	25 54.4 11.2	11 23.9 6.0	8 17.4 9.5	2 4.4 5.0	**46** **100** **8.7**	6 60.0 9.5	3 30.0 7.5	0 0.0 0.0	1 10.0 14.3	**10** **100** **8.1**	**192** - **10.6**
Total (the number of cases in all disease chapters)	**126** **56.8** **100**	**73** **32.9** **100**	**21** **9.5** **100**	**2** **0.9** **100**	**222** **100** **100**	**451** **47.9** **100**	**298** **31.6** **100**	**149** **15.8** **100**	**44** **4.7** **100**	**942** **100** **100**	**223** **42.1** **100**	**183** **34.5** **100**	**84** **15.8** **100**	**40** **7.5** **100**	**530** **100** **100**	**63** **50.8** **100**	**40** **32.3** **100**	**14** **11.3** **100**	**7** **5.6** **100**	**124** **100** **100**	**1818** - **100**

Table 5 Morbidity of different ICD-10 disease chapters distributed according to gestational age (GA) and birth weight (BW) categories of our study (the first row shows the number of children, and the second row – shows the percentage in the gestational age and birth weight category), and morbidity in the Lithuanian pediatric population (included for comparison, compiled according to [57, 58]) from 0 to 18 years

Disease Chapter	Gestational age categories			Birth weight categories				Total (for the chapter) in our study ($n=417$)	Total (for the chapter) in the Lithuanian pediatric population ($n=556\,620$)
	Extremely and very preterm ($n=64$)	Moderate preterm ($n=71$)	Late preterm ($n=282$)	Extremely and very low ($n=48$)	Low ($n=205$)	Sub-optimal ($n=125$)	Normal ($n=39$)		
A00-B99—Certain infectious and parasitic diseases	21 32.8	23 32.4	119 42.2	20 41.7	74 36.1	57 45.6	12 30.8	**163** **39.1*****	**81 107** **14.6**
C00-D49—Neoplasms	5 7.8	8 11.3	19 6.7	6 12.5	18 8.8	7 5.6	1 2.6	**32** **7.7*****	**10 015** **1.8**
D50-D89—Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (° BW)	13 20.3	20 28.2	68 24.1	12 25.0	55 26.8	31 24.8	3 7.7	**101** **24.2*****	**12 555** **2.3**
E00-E89—Endocrine, nutritional and metabolic diseases	16 25.0	25 35.2	82 29.1	14 29.2	64 31.2	35 28.0	10 25.6	**123** **29.5*****	**62 505** **11.2**
F01-F99—Mental, Behavioral and Neurodevelopmental disorders	16 25.0	25 35.2	80 28.4	13 27.1	63 30.7	34 27.2	11 28.2	**121** **29.1*****	**43 720** **7.8**
G00-G99—Diseases of the nervous system	9 14.1	6 8.5	33 11.7	7 14.6	22 10.7	16 12.8	3 7.7	**48** **11.5*****	**15 881** **2.8**
H00-H59—Diseases of the eye and adnexa	36 56.3	41 57.4	142 50.4	29 60.4	110 53.7	64 51.2	16 41.0	**219** **52.5*****	**171 310** **30.8**
H60-H95—Diseases of the ear and mastoid process	4 6.3	3 4.2	4 1.4	3 6.3	4 2.0	4 3.2	0 0.0	**11** **2.6*****	**46 349** **8.3**
I00-I99—Diseases of the circulatory system	0 0.0	1 1.4	10 3.5	0 0.0	5 2.5	5 4.0	1 2.6	**11** **2.6**	**18 801** **3.4**

Table 5 (continued)

Disease Chapter	Gestational age categories			Birth weight categories				Total (for the chapter) in our study ($n=417$)	Total (for the chapter) in the Lithuanian pediatric population ($n=556\,620$)
	Extremely and very preterm ($n=64$)	Moderate preterm ($n=71$)	Late preterm ($n=282$)	Extremely and very low ($n=48$)	Low ($n=205$)	Sub-optimal ($n=125$)	Normal ($n=39$)		
J00-J99—Diseases of the respiratory system	23 35.9	23 32.4	80 28.4	20 41.7	61 29.8	38 30.4	7 17.9	**126** **30.2*****	**322 052** **57.9**
K00-K95—Diseases of the digestive system	21 32.8	17 23.9	76 27.0	17 35.4	51 24.9	35 28.0	11 28.2	**114** **27.3***	**183 997** **33.1**
L00-L99—Diseases of the skin and subcutaneous tissue	9 14.1	14 19.7	51 18.1	5 10.4	39 19.0	25 20.0	5 12.8	**74** **17.7***	**74 953** **13.5**
M00-M99—Diseases of the musculoskeletal system and connective tissue (° BW, GA)	9 14.1	12 16.9	71 25.2	8 16.7	48 23.4	27 21.6	9 23.1	**92** **22.1*****	**60 376** **10.8**
N00-N99—Diseases of the genitourinary system	9 14.1	13 18.3	43 15.2	6 12.5	35 17.1	19 15.2	5 12.8	**65** **15.6*****	**25 428** **4.6**
P00-P96—Certain conditions originating in the perinatal period	5 7.8	5 7.0	18 6.4	4 8.3	15 7.3	7 5.6	2 5.1	**28** **6.7*****	**10 693** **1.9**
Q00-Q99—Congenital malformations, deformations and chromosomal abnormalities (* BW)	29 45.3	27 38.0	92 32.6	22 45.8	82 40.0	37 29.6	7 17.9	**148** **35.5*****	**55 649** **10**
Total (the number of cases in all disease chapters)	225	263	988	186	746	441	103	**1476**	-

p-value ° < 0.1, * < 0.05, ** < 0.01, *** < 0.00; BW and GA in the brackets shows which comparisons were significant.The asterisks in the "Total (for the chapter) in our study" column indicate statistically significant differences in morbidity prevalence between our study cohort and the general pediatric population in Lithuania

showed that the problem of overdispersion exists, therefore, the negative binomial regression was chosen as the final model.

Computations were performed by the R function glm.nb from the R package MASS. The results were presented using the incidence rate ratios (IRRs), i.e. exponentiated slope regression coefficients. The IRR describes the estimated multiplicative change in the mean count for each one-unit increase in a continuous covariate, or versus a reference category

Table 6 Morbidity of the most common specific diseases or health conditions classified under ICD-10 in the study population from birth to 18 years

No	Diagnosis	ICD-10 code	Number of children	Percentage, %	Disease Chapter
1	**Hypermetropia**	H52.0	158	**37.9**	H00-H59—Diseases of the eye and adnexa
2	**Varicella (chickenpox)**	B01	137	**32.9**	A00-B99—Certain infectious and parasitic diseases
3	**Specific developmental disorders of speech and language**	F80	112	**26.9**	F01-F99—Mental, Behavioral and Neurodevelopmental disorders
4	**Rickets, active**	E55.0	90	**21.6**	E00-E89—Endocrine, nutritional and metabolic diseases
5	**Anemia, unspecified**	D64.9	82	**19.7**	D50-D89—Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
6	**Umbilical hernia**	K42	74	**17.7**	K00-K95—Diseases of the digestive system
7	**Postural kyphosis**	M40.0	67	**16.1**	M00-M99—Diseases of the musculoskeletal system and connective tissue
8	**Congenital deformities of feet**	Q66	63	**15.1**	Q00-Q99—Congenital malformations, deformations and chromosomal abnormalities
9	**Astigmatism**	H52.2	61	**14.6**	H00-H59—Diseases of the eye and adnexa
10	**Hypertrophy of adenoids**	J35.2	61	**14.6**	J00-J99—Diseases of the respiratory system
11	**Congenital malformations of cardiac septa**	Q21	61	**14.6**	Q00-Q99—Congenital malformations, deformations and chromosomal abnormalities
12	**Asthma**	J45	57	**13.7**	J00-J99—Diseases of the respiratory system
13	**Atopic dermatitis**	L20	56	**13.4**	L00-L99—Diseases of the skin and subcutaneous tissue
14	**Myopia**	H52.1	48	**11.5**	H00-H59—Diseases of the eye and adnexa
15	**Hemangioma, any site**	D18.0	26	**6.2**	C00-D49—Neoplasms
16	**Allergic rhinitis**	J30	24	**5.8**	J00-J99—Diseases of the respiratory system
17	**Urinary tract infection, site not specified**	N39.0	22	**5.3**	N00-N99—Diseases of the genitourinary system
18	**Nonorganic enuresis**	F98.0	19	**4.6**	F01-F99—Mental, Behavioral and Neurodevelopmental disorders
19	**Scarlatina**	A38	18	**4.3**	A00-B99—Certain infectious and parasitic diseases
20	**Obesity**	E66	18	**4.3**	E00-E89—Endocrine, nutritional and metabolic diseases

Table 7 The influence of sex, birth weight and gestational age categories on certain separate disease incidence from birth to 18 years by negative binomial regression outcomes. CI – confidence interval

Factor	Coef	*p*-value	IRR and 95% CI	
			IRR	95% CI
Sex (girl)	−0.0192	0.7715	0.9810	(0.8615, 1.1170)
Birth weight group (Sub-optimal)	0.2899	0.0279 *	1.3363	(1.0331, 1.7326)
Birth weight group (Low)	0.4061	0.0020 **	1.5009	(1.1619, 1.9437)
Birth weight group (Extremely and very low)	0.5726	0.0039 **	1.7728	(1.2042, 2.6150)
Gestational age group (Moderate pre-term)	−0.0527	0.5890	0.9487	(0.7839, 1.1479)
Extremely and very preterm	−0.2195	0.1257	0.8029	(0.6065, 1.0612)

p-value * < 0.05, ** < 0.01, *** < 0.001

Table 8 The influence of sex, birth weight and gestational age categories on the incidence of different ICD-10 disease chapters from birth to 18 years by negative binomial regression outcomes. CI – confidence interval

Factor	Coef	*p*-value	IRR	
			IRR	95% CI
Sex (girl)	−0.0036	0.95136	0.9964	(0.8875, 1.1188)
Birth weight group (Sub-optimal)	0.2904	0.0161 *	1.3369	(1.0591, 1.7005)
Birth weight group (Low)	0.3496	0.0037 **	1.4185	(1.1248, 1.8028)
Birth weight group (Extremely and very low)	0.5730	0.0014 **	1.7735	(1.2512, 2.5231)
Gestational age group (Moderate pre-term)	−0.0025	0.7701	0.9749	(0.8219, 1.1545)
Extremely and very preterm	−0.2155	0.0961	0.8062	(0.6236, 1.0361)

p-value * < 0.05, ** < 0.01, *** < 0.00

for a categorical covariate [60]. For example, having IRR = exp(β) for sex covariate with the reference category girl, it could be concluded that the mean number of diseases (ICD-10 disease chapters) per child is exp(β) times (or 100*(exp(β)−1)%) larger than for boys. IRR has the same purpose as the odds ratio in the logistic regression.

The heat maps (Figs. 1 and 2) were used to visualise the percentages of individuals diagnosed with varying numbers of diseases from birth to age 18, categorised by GA and BW (the number of individuals in the GA and BW groups is given in Supplementary Table 2. Moreover, the Fisher exact test was employed to compare these percentages. The same analysis was done for the ICD-10 disease chapters. The R package ggplot2 was employed to create heat maps and the package stats was used for the Fisher test.

The UpSet graph (Fig. 3) was used to investigate the intersections of ICD-10 disease chapters. This visualisation technique is designed to analyse sets and their intersections [61]. The R package UpSetR [62] was used to create the UpSet graph. First, all possible combinations were included in the graph; however, the frequency of the large majority of cases was equal to one. Thus, only intersections with a frequency larger than one were included in the final graph.

Ethics approval

The study was approved by the Lithuanian Bioethics Committee (Permission No. 57, last updated

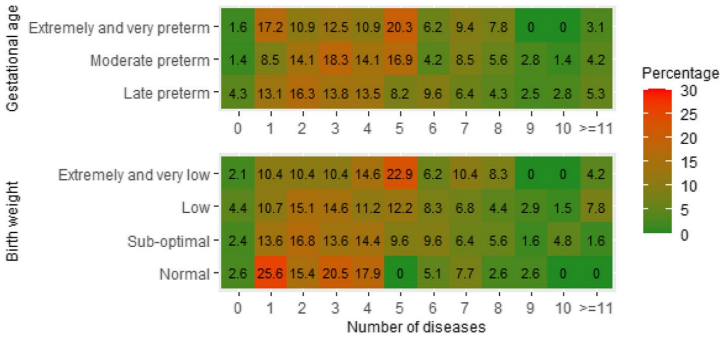

Fig. 1 The percentage of individuals diagnosed with varying numbers of certain separate diseases from birth to age 18, categorised by gestational age and birth weight (represented by heat maps)

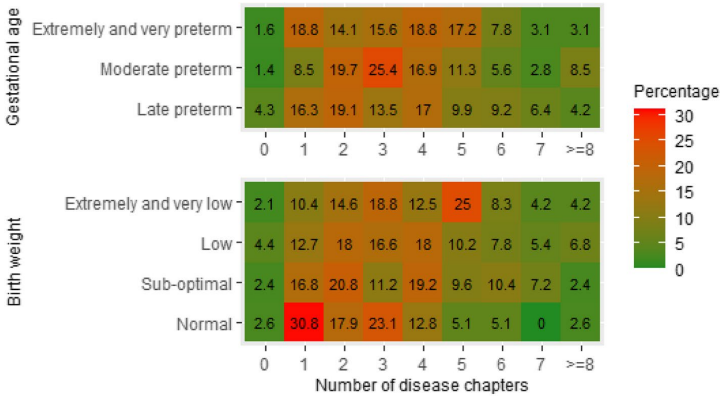

Fig. 2 The percentage of individuals diagnosed with varying numbers of ICD-10 disease chapters from birth to age 18, categorised by gestational age and birth weight and represented by heat maps

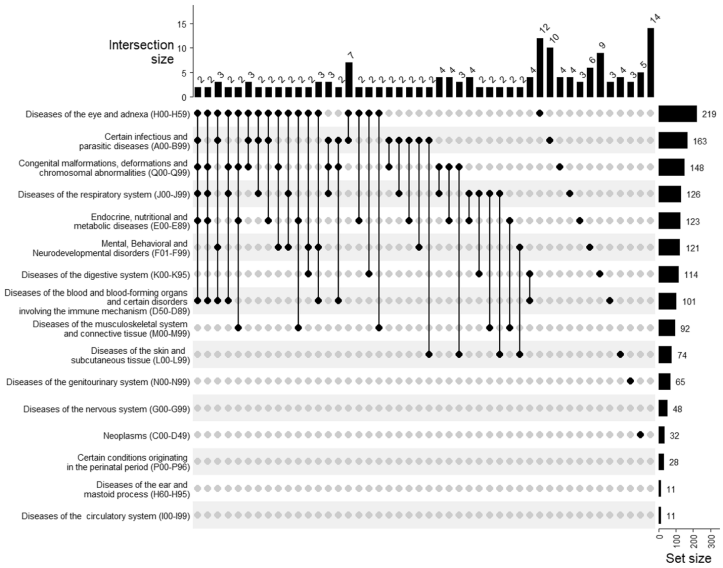

Fig. 3 Combination variants of different interrelated ICD-10 disease chapters provided by Upset graph. The horizontal bars on the right side represent the number of cases observed in each ICD-10 disease chapter, providing a quick overview of the distribution of diagnoses. The central matrix, marked by filled and empty dots, denotes the involvement of each disease chapter in the intersections; filled dots indicate participation in a given intersection, linked by vertical lines within the respective column. This matrix reveals, for instance, that seven individuals have diagnoses in both the H00-H59 (Diseases of the eye and adnexa) and A00-B99 (Certain infectious and parasitic diseases) chapters without overlapping with other ICD-10 chapters

2017–02–06) and was performed according to the relevant ethical guidelines and regulations.

Results

Incidence and distribution of morbidity across prematurity sub-categories from birth to adolescence

General description of birth-related variables in the study cohort

The distribution of birth-related variables, expressed in frequencies, is given in Supplementary Table 2. Boys accounted for 48% of newborns in the considered data set. The distribution across GA categories revealed that "Late preterm" births were the most common ($n=282$), followed by "Moderate preterm" ($n=71$) and "Extremely and very preterm" ($n=64$) births. A significant proportion of these preterm births fell into the "Low" and "Sub-optimal" BW categories. "Extremely and very low" weights were notably prevalent among the "Extremely and very preterm" GA group, indicating a close relationship between GA and BW. The data indicate a higher occurrence of extremely low BW in girls [24] compared to boys [18].

Trends in overall morbidity among sub-categories of birth weight and gestational age

The overall morbidity, expressed as the mean number of diseases acquired from birth to age 18, categorised by gestational age and birth weight, revealed a tendency that lower BW is associated with a higher mean number of diseases from 4.6 in "Extremely and very low" and "Low" BW categories to 3.2 in “Normal” BW category. The differences in mean disease numbers were less pronounced among GA groups: "Moderate preterm" children had the highest mean number of diseases (4.55), followed by "Late preterm" (4.33) and "Extremely and very preterm" (4.28). Results presume that birth weight (BW) has a greater impact on the mean number of diseases acquired up to adulthood.

Diseases distribution during the study period by birth weight and gestational age sub-categories

An overview of the distribution of diseases, stratified by BW and GA categories across different age intervals from birth to adulthood, is provided in Tables 1 and 2. Regardless of analysed categories, almost half of the diagnoses

occurred from birth to 3 years and more than one-third – in preschool years, indicating that the critical period for disease burden in all study groups extends from birth to 7 years – 80.2% in total of all 1818 new diagnoses from birth to adulthood. Moreover, disease incidence is inversely related to BW (Table 1). Due to the small sample size, the "Extremely and very low" BW group is considered an outlier. However, the "Low" BW group accounts for more than half of all diagnoses up to age 18, while the "Sub-optimal" and "Normal" BW groups comprise almost 30% and 7% of the total, respectively. In the GA groups, while "Late preterm" individuals have a higher absolute number of diagnosed diseases, the relative burden is more evenly distributed across the age intervals for the "Extremely and very preterm" and "Moderate preterm" groups (Table 2). This suggests that although "Late preterm" individuals might experience more diagnoses overall, "Extremely and very preterm" individuals and "Moderate preterm" face a higher proportional burden of morbidity, particularly in the earlier years of life.

The structure of diagnoses ($N=1818$) among the ICD-10 disease chapters from birth to adulthood revealed that the most prevalent category was eye and adnexa conditions (almost 17%) (Tables 3 and 4). However, this high prevalence is somewhat misleading, as these diseases are also prevalent in the general pediatric population (see Table 5 and further discussion below). Following this, congenital malformations and certain infectious diseases were the following most frequent categories (around 10–11%). A third group, comprising respiratory, endocrine, nutritional, metabolic, mental, behavioural, and neurodevelopmental disorders (8–9%), accounted for similar proportions in the overall structure of diagnoses.

Timing and distribution of diagnoses across ICD-10 disease chapters

The timing of different condition categories was analysed across four age periods (Tables 3 and 4), focusing on the most frequent ICD-10 chapters. Blood and immune system disorders were almost exclusively diagnosed in the 0–3 age period (up to 90%). A similar pattern was observed for congenital malformations (ranging from 55% in higher BW and GA groups to 80% in lower BW and GA groups) and digestive system diseases, with over half of the cases manifesting during this period (equally to all GA and BW groups). Eye and adnexa diseases were common throughout childhood, with similar prevalence in the 0–3 and 3–7 age groups. Respiratory diseases and certain infections peaked in the 3–7 age group, with a significant portion of cases occurring during this interval (from 45 to 80%).

Some conditions showed later peaks. Endocrine and metabolic disorders were primarily diagnosed in the 0–3 age group but exhibited a second notable increase during school-age years [7–12]. Similarly, mental and behavioural disorders were most commonly diagnosed in the 3–7 age group, but higher BW and GA groups saw a secondary peak during school years [7–12]. Adolescence (12–18 years) contributed relatively fewer diagnoses but included some late-onset cases in the categories of nervous system diseases, skin conditions, and musculoskeletal system.

This disease chapter-based perspective highlights the variability in timing across conditions, with most diagnoses concentrated in early childhood. Detailed distributions are provided in Tables 3 and 4.

Morbidity prevalence across ICD-10 chapters by birth weight and gestational age sub-categories

Further, differences in morbidity prevalence from 0 to 18 years across ICD-10 disease chapters among prematurity sub-categories were identified (Table 5), and the incidence of the most common specific diseases or health conditions within these chapters was calculated (Table 6). The following sections highlight the most common conditions in the study population, focusing on those mostly exceeding 30% prevalence. It is important to note that some of these conditions, such as refractive errors and some other diseases, are also prevalent in the general population, as discussed further below.

Eye and adnexa conditions were the most prevalent, affecting more than half of the study population (Table 5), with 1.5 times higher prevalence in the "Extremely and very low" BW group compared to the "Normal" group. The most common cases were hypermetropia at almost 38%, astigmatism at close to 15%, and myopia at about 12% (Table 6).

Certain infectious diseases affected 39% of the preterm population without significant differences between prematurity sub-categories – here, varicella was about 33% (Tables 5 and 6). Congenital malformations were diagnosed in almost 36% of preterm children, with the most common being congenital deformities of feet at around 15% and congenital malformations of cardiac septa at nearly 15%. These conditions were significantly more prevalent in the "Extremely and very low" (almost 46%) and "Low" (40%) BW categories than in the "Sub-optimal" (almost 30%) and "Normal" (nearly 18%) groups ($p<0.05$) (Tables 5 and 6).

High incidences (almost 30%) were also observed in respiratory diseases, with lower morbidity in higher BW groups (Table 5). The most common cases in this chapter were hypertrophy of adenoids at almost 15%, asthma at nearly 14%, and allergic rhinitis at 6% (Table 6). Endocrine, nutritional, and metabolic diseases accounted for almost 30% and were similarly distributed across the

analysed groups, with active rickets at nearly 22% and obesity at 4% being the most prevalent (Tables 5 and 6).

Moreover, mental, behavioural, and neurodevelopmental disorders were observed in almost 30% of the preterm population and were relatively evenly distributed across sub-categories, with specific developmental disorders of speech and language accounting for nearly 27%, making it the third most common diagnosis (Tables 5 and 6). Notably, anaemia affected almost one-fifth of the study population (Table 6), and the "Normal" BW category exhibited a significantly lower incidence of blood and immune disorders compared to lower BW groups ($p < 0.1$) (Table 5).

Although statistically significant results of morbidity analysis were modest, the more severely premature groups exhibited a higher prevalence of diagnoses across the majority of ICD-10 disease chapters. This pattern was more distinct when analysing disease percentage distribution by BW rather than GA, except for musculoskeletal and connective tissue diseases, where "Late preterm" infants showed a higher incidence ($p < 0.1$) (Table 5). Moreover, total cumulative morbidity was particularly pronounced when comparing our results with the overall prevalence of certain diagnoses and ICD-10 disease chapters in the general Lithuanian pediatric population, which is further explored in the discussion.

Impact of birth-related factors for the mean number of diseases and ICD-10 disease chapters per child

The primary goal of the negative binomial regression analysis was to determine the effect of birth-related variables on the mean number of diseases per child between the ages of 0 and 18. Results showed that the mean number of diseases per child (Table 7) is 34% greater for individuals from the "Sub-optimal" BW group, 50% greater for the "Low" BW group and 77% greater for the "Extremely and very low" BW group comparing to "Normal" BW individuals. This results in the conclusion that lower BW is a significant risk factor for a larger number of diseases acquired from birth till adulthood.

In contrast, the analysis found that the other two factors considered (sex and GA category) were not significant. This outcome justified a sex-neutral approach in the analysis. The non-significance of the GA group may be attributed to the grouping into three intervals, which was necessary due to the limited number of cases for certain gestational weeks.

Similarly, when modelling the mean number of ICD-10 disease chapters per child within the same age range (Table 8), the results indicated that lower BW is a significant factor for a higher number of different disease classification categories. This reinforces the conclusion that lower BW predisposes children to a broader range of different health issues.

Health condition complexity and interrelationships among disorders across different ICD-10 disease chapters

Health condition complexity depending on birth weight and gestational age

Lower birth weights (BW) and greater prematurity were associated with a higher number of diagnosed diseases per child from birth to age 18. This pattern is clearly illustrated in the distribution of disease counts across GA and BW categories (Fig. 1).

Individuals with lower birth weights and greater prematurity were more likely to have diagnoses involving multiple ICD-10 disease chapters from birth to age 18. This trend is highlighted in the frequency distribution of disease chapters per child (Fig. 2). Overall, the heatmaps revealed that both lower GA and lower BW were associated with an increased likelihood of having multiple diseases and disease chapters, with a more pronounced trend observed in BW categories.

However, the Fisher exact test showed that there was no significant difference in the proportions of various numbers of diseases in the GA groups. Nevertheless, the differences were significant between “Extremely and very low” and “Normal” BW groups ($p < 0.05$) and between “Low” and “Normal” BW groups ($p < 0.05$). Figure 1 shows that in the “Extremely and very low” BW group, individuals with five or more diseases make up 52%, in the “Low” BW group 44%, while in the “Normal” BW group only 18%. By considering the ICD-10 disease chapters, the only significant differences were between “Extremely and very low” and “Normal” BW groups ($p < 0.05$) and between “Low” and “Normal” ($p < 0.05$) BW groups. Figure 2 shows that in the “Extremely and very low” BW group, individuals with five or more ICD-10 disease chapters make up 41.7%, in the “Low” group 30.2%, while in the “Normal” BW group only 12.8%.

Individual interrelationships among disorders across different ICD-10 disease chapters

To explore the intricate relationships and overlaps among different ICD-10 disease chapters, the UpSet graph in Fig. 3 was utilised. This graph effectively visualises the individual intersections of diagnosed ICD-10 disease chapters, providing insights into the mostly unique patterns of comorbidities with 300 combinations detected in total. Only cases with a frequency greater than one were included in the graph. The UpSet graph provides an overview of the distribution and intersections of ICD-10 disease chapters, with horizontal bars showing the number of cases in each chapter. Using filled and empty dots, the central matrix highlights chapter involvement in comorbidities. For example, it reveals that seven individuals have diagnoses in both the H00-H59 (eye and adnexa

diseases) and A00-B99 (infectious diseases) chapters without overlapping with other chapters.

However, there were few frequently recurring variations of the co-morbid disease chapters. Thus, the vast majority of cases (84.7%) in the preterm population were highly individual and unique variations of disease chapters' interrelations, which have been found to occur at single frequencies and are not reflected in this graph.

Discussion

Incidence and distribution of morbidity across prematurity sub-categories from birth to adolescence: comparison with general pediatric populations

Our study revealed a complex pattern of multimorbidity in preterm-born survivors from infancy through adolescence, with the highest disease burden occurring from birth to preschool age. Lower BW was strongly associated with a higher mean number of diseases from birth to age 18 (4.6 vs. 3.2 for "Extremely and very low" and "Normal" BW groups, respectively) and a broader range of health issues across ICD-10 chapters. In contrast, GA differences were less pronounced. While many studies focus on morbidity risks without examining cumulative burdens [52, 53], our longitudinal approach provides detailed insights into the progression and timing of health conditions, addressing key gaps in understanding the long-term challenges faced by preterm-born individuals.

Morbidity in preterm children was markedly higher compared to the general Lithuanian pediatric population aged 0–18 in 2019, with statistically significant differences observed in the prevalence of many ICD-10 disease chapters (Table 5, compiled according to [57, 58]). Although the most common conditions in preterm children included eye and adnexa diseases, respiratory conditions, and certain infectious diseases, the greatest disparities compared to the general pediatric population were noted in blood and immune disorders, which were over ten times more prevalent. Neoplasms, nervous system diseases, mental disorders, congenital malformations, and genitourinary diseases were 3–4 times more prevalent in the preterm population. Certain infectious diseases and endocrine and metabolic disorders were 2.5 times more frequent, and musculoskeletal and eye conditions were nearly twice as common. The prevalence of skin and subcutaneous tissue diseases was comparable between the groups. In contrast, respiratory and digestive diseases were less prevalent, and ear and mastoid disorders were three times less frequent. The detailed structure of diagnoses within these categories is discussed below.

Eye and adnexa diseases affected over half of preterm-born individuals, compared to almost 31% in the general population [57, 58]. In the general population, eye disorders ranked third after respiratory and digestive diseases. Hypermetropia was over three times more common in premature children (almost 38%) than in the general population (about 13% [57, 58]), and eight times higher than global prevalence (4.6% [63]). This high rate may reflect either physiological hyperopia in children aged 5–7 years [64], or pathological refractive error, as the ICD-10 classification does not distinguish between the two. Notably, myopia, which is never physiological in children, was nearly twice as high in preterm infants (almost 12%) compared to the general population (about 7%), consistent with other longitudinal research [65]. Similarly, astigmatism in preterm infants (almost 15%) was comparable to other studies (nearly 14% [66]) and supports its higher prevalence in preterm-born children versus term-born peers [65, 67]. In Lithuania, national guidelines [68, 69] recommend regular ophthalmological follow-ups for preterm infants to detect conditions like retinopathy of prematurity (ROP). This proactive monitoring likely contributes to higher detection rates in preterm children, whereas undiagnosed issues in term-born peers may underestimate their prevalence.

Certain infectious diseases were the second most prevalent in the preterm population, occurring almost three times as frequently as in the general pediatric population (about 40% vs. 15%). A similar longitudinal study found that preterm birth, particularly before 32 weeks, increases the risk of long-term infectious morbidity, with each additional week of gestation reducing this risk [70]. This susceptibility may stem from immature immune systems [45], inadequate passive immunity [71], or delayed vaccinations [72]. Varicella (B01) was the second most common disease in our study's population. In Lithuania, varicella vaccination is not part of the national immunisation program but is recommended for at-risk groups or optionally offered [73]. Higher varicella rates in preterm-born children may reflect actual incidence and proactive follow-up, potentially amplifying diagnosis rates compared to term-born peers.

Congenital malformations affected almost 36% of the preterm population, over three times higher than the 10% prevalence in the general pediatric population [57, 58]. A prospective study similarly reported congenital anomalies in 33% of preterm infants compared to only about 5% in full-term infants [74], though it focused only on malformations diagnosed within the first month of life. Consistent with follow-up study up to 5 years [75], cardiac septal malformations (Q21) were among the most common, occurring in almost 15% preterm children—more than four times the prevalence of congenital circulatory system malformations (Q20-Q28) in the general pediatric population (about 3%) [57, 58].

Respiratory diseases were less prevalent in preterm children (30.2%) compared to the general Lithuanian child population (close to 58% [57, 58]), where they are the leading disease chapter. Though Lithuania has no specific national policies mandating delayed child care or school entry for preterm-born children, this may be related to delayed kindergarten and school entry for preterm-born children [76] and fewer opportunities for peer interaction and socialisation [77], resulting in reduced exposure to communicable respiratory diseases. However, chronic respiratory conditions, such as bronchial asthma, were significantly more common in preterm children (almost 14%) compared to the overall prevalence in Lithuanian children (close to 5%) [57, 58]. Longitudinal studies similarly report an increased risk of asthma in preterm-born children up to age 10 [78] and a high prevalence of severe asthma among adolescents born prematurely [79].

Endocrine, nutritional, and metabolic diseases were nearly three times more prevalent in preterm children (almost 30%) compared to the general pediatric population (about 11% [57, 58]). This aligns with studies highlighting the impact of premature dissociation from the maternal-placental-fetal unit on endocrine and nutritional health [80]. Metabolic bone disease, particularly rickets, was notably higher in preterm children (close to 22%) than in the general population (less than 1% [81, 82]). Additionally, obesity was also more common in preterm children (about 4%) compared to their peers (close to 1%) [57, 58], consistent with findings from other systematically reviewed studies [83].

Mental and behavioural disorders were significantly more prevalent in preterm infants compared to the general pediatric population (about 29% vs. almost 8% [57, 58]). A recent meta-analysis found that preterm children aged 3–19 have higher odds of anxiety disorders (OR: 2.17) than their term-born peers [84], while extremely preterm children are over three times more likely to have psychiatric disorders by age 11 [85]. Intellectual challenges, including comorbid intellectual and learning disabilities, are common in extremely preterm children [86, 87], with even late preterm children showing mild neurodevelopmental issues affecting academic performance [88, 89]. In our study, developmental speech and language disorders (F80) were the most prevalent, affecting almost 27% of preterm-born children, compared to only just about 5% for broader psychological development disorders (F80-F89) in the general Lithuanian pediatric population. [57, 58]. This aligns with research emphasising language delays in preterm survivors [90, 91]. While previous studies – ranging from meta-analyses to sibling-control designs [84, 85, 88–91] – provide insights into mental health outcomes, no study matches the longitudinal scope and design of ours.

Notably, blood and immune disorders (D50-D89) affected a quarter of the preterm population, more than ten times the prevalence in the general pediatric population. This may be linked to delayed maturation of hematopoietic processes, leading to conditions like anaemia, thrombocytopenia, and leukopenia [92]. Anaemia (D64.9) was notably the fifth most common diagnosis among preterm infants, with a significantly higher prevalence in those with lower birth weights, supporting this association.

Impact of birth-related factors for the mean number of diseases and ICD-10 disease chapters per child: importance of birth weight

The findings of our study conclusively demonstrate that lower birth weight (BW) is a significant risk factor for an increased number of diseases from birth through adolescence, as well as a greater diversity of health conditions classified under various ICD-10 chapters. In contrast, gestational age (GA) showed weaker associations, likely due to its grouping into broader intervals necessitated by the limited number of cases for certain gestational weeks.

To better explore their respective contributions, BW and GA were analysed as independent variables rather than integrated into growth categories such as SGA, AGA, or LGA. This independent analysis allowed us to disentangle their distinct roles, with BW reflecting cumulative prenatal energy reserves and GA capturing developmental timing and intrauterine exposures. By avoiding combined classifications, our approach revealed that BW has a stronger influence on long-term morbidity, emphasising its importance in shaping health trajectories, as shown in Tables 7 and 8.

While other studies [52, 53] observed a consistent dose–response relationship between an earlier GA and elevated risks of complex multimorbidity in adolescence and early adulthood, our findings highlight the critical role of BW in developmental plasticity [55], where the body adjusts its energy allocation strategies in response to environmental conditions. BW serves as a direct measure of the energy reserves available at birth, which are more closely tied to metabolic programming and developmental adaptations than GA alone [50]. In the context of evolutionary medicine [54], adverse conditions can lead to permanent changes in energy allocation strategies, reflecting how organisms prioritise and distribute energy resources to maximise survival, on the other hand, influencing an individual's susceptibility to diseases like cardiovascular conditions, diabetes, and mental health disorders in the future. A recent study supports this view, low BW to adverse health conditions, including

prediabetes/diabetes, high blood pressure and lack of tertiary education [93], reinforcing the importance of BW as a determinant of long-term health.

Health condition complexity and interrelationships among disorders across different ICD-10 disease chapters: unique comorbidity patterns

Moreover, health conditions were more complex in individuals with lower BW, with most cases exhibiting unique comorbidity patterns, underscoring the individualised nature of preterm comorbidities. While most studies focus on single organ systems or specific diseases, few examine the cumulative health effects of preterm birth [50, 52, 53]. Recent studies found that preterm individuals have a 29% higher risk of multimorbidity in adolescence [52] and a greater likelihood of developing multiple chronic conditions, with late preterm birth (34–36 weeks) contributing significantly to this risk [53]. However, these studies [52, 53] relied on predefined diagnostic codes over limited periods, restricting the scope of multimorbidity identified. In contrast, our study recorded all diagnoses from birth to adulthood, offering a comprehensive longitudinal perspective of the full extent of multimorbidity. This approach reveals the interconnected and highly individualised nature of multimorbidity in preterm individuals, providing new insights into their health trajectories that were previously unexplored.

This heightened susceptibility to multimorbidity in preterm-born individuals may stem from in utero and perinatal factors disrupting critical stages of organo- and histogenesis. Consequently, this could explain intersections between disease chapters involving organ systems derived from the same germ layer. To explore this theory further in the future, it would be more beneficial to examine individual disease association trends rather than ICD-10 disease chapter associations. We suggest this not only because the ICD-10 classification does not accurately reflect physiological health conditions but also contains some etiological allogisms. For example, hernias (umbilical, inguinal), though classified as digestive system disorders (K00-K95), are pathophysiologically linked to connective tissue weakness or incomplete fetal development [94] and may align better with musculoskeletal system diseases (M00-M99). This is supported by the high prevalence of umbilical hernias in our preterm group (17.7%) compared to 0.4% of hernias (K41-K46) in the general Lithuanian pediatric population [57, 58].

Future research should continue to investigate individualised comorbidity patterns in preterm-born individuals, focusing on unique links between specific diseases and their developmental origins. Our study's insights highlight the need for proactive, personalised, and multidisciplinary healthcare strategies, integrating principles of developmental biology and neonatal pathology. Such an approach could better address long-term health issues in this vulnerable population, improving their quality of life and health outcomes.

Strengths and limitations

A key strength of our study is its longitudinal design, tracing comorbidities over 18 years and analysing disease patterns across prematurity sub-categories. Furthermore, it provides a comprehensive ICD-10 chapter-wise overview of their health trajectories. This holistic perspective on health outcomes is rare in prematurity research, contributing to a broader understanding and informing further investigation and hypothesis generation.

The small number of extremely preterm survivors likely contributed to the non-significance of the GA group in negative binomial regression analysis. Additionally, the limited number of individuals aged 12–18 affected the scarce results in this age interval, where a larger cohort may yield more statistically significant findings. Furthermore, the study reflects outcomes from two primary health care centers in Vilnius and may not represent the entire Lithuanian population. While adjusted for several potential confounders, the lack of consistent data on maternal, environmental, inherited factors, or specific neonatal conditions may have influenced our estimates. A multicentered study with a larger, more diverse sample size could address these limitations and improve the robustness and generalizability of the findings.

Implications in clinical practice

Our findings highlight the need for expanded surveillance of preterm infants beyond infancy, particularly during the preschool years when the disease burden is greatest. Focused medical intervention from birth to age 7 could mitigate long-term health risks associated with prematurity. Moreover, the study emphasises the importance of BW in assessing chronic disease risk through adolescence and the need to address the potential for multiple organ system involvement. Moreover, personalised medical care is essential, as the unique comorbidity patterns require customised treatment plans to effectively address their complex, long-term health needs.

Conclusions

This study highlights the long-term health challenges faced by preterm-born individuals, with nearly half of diagnoses occurring before age three and another third during the preschool years. Notably, the "Low" BW group accounted for over half of all diagnoses up to age 18, with the "Sub-optimal" and "Normal" BW groups comprising one-third. Among preterm-born children, the most common conditions were eye and

adnexa diseases, also respiratory and certain infectious diseases, less frequent – endocrine and metabolic disorders, congenital malformations, neoplasms, mental disorders and nervous system diseases. However, when compared to the general population, the greatest disparities were in blood and immune disorders (tenfold), followed by nervous system diseases, mental disorders, neoplasms, and congenital malformations (3.5–fourfold). Moreover, lower BW was strongly associated with a higher mean number of diseases and a greater diversity of health conditions across various ICD-10 chapters from birth to age 18. The "Sub-optimal" BW group showed a higher disease burden than the "Normal" BW group, with an even greater increase in the "Low" and "Extremely and very low" BW groups. The integral role of BW (more than GA) in shaping long-term health outcomes underscores the importance of incorporating this variable into early health assessments. Furthermore, unique patterns of disease co-occurrence were observed, increasing in complexity as BW decreased, with few recurring combinations. These findings suggest that in every case, the organism possibly reallocates its resources in a highly individual way to navigate complex health situations with minimal life-threatening disruptions, though not without losses. This underscores the highly individualised nature of comorbidities in preterm patients and the importance of personalised medical care.

Abbreviations

BW	Birth weight
GA	Gestational age
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IRR	Incidence rate ratios
OR	Odds ratio
SD	Standard deviation

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
R.M. collected, analysed, and interpreted the data and took the lead in writing the manuscript with input from other authors. J.T. raised the main conceptual idea, designed and supervised the study, helped in data interpretation and manuscript writing, and revised the final version. R.L. performed the statistical analysis, provided suggestions for data interpretation, and contributed to revising the manuscript. V.G. prepared raw data for the calculations and provided suggestions for data interpretation. E.M.J. contributed to the interpretation of the results and the final version of the manuscript.

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Data availability
The datasets collected and analysed during the current study are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Lithuanian Bioethics Committee (Permission No. 57, last updated 2017–02-06) and was conducted in accordance with the relevant ethical guidelines and regulations, including the principles of the Declaration of Helsinki. All data used in this research were retrospective, anonymised, and handled in compliance with applicable data protection regulations. In accordance with local regulations, individual consent was not required for this study as the data were anonymised and retrospective in nature.

Consent for publication
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Competing interests
The authors declare no competing interests.

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Publisher's Note

Supplementary Table 1. Disease chapters according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).

Chapter	Description	Chapter	Description
A00-B99	Certain infectious and parasitic diseases	C00-D49	Neoplasms
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	E00-E89	Endocrine, nutritional and metabolic diseases
F01-F99	Mental, Behavioural and Neurodevelopmental disorders	G00-G99	Diseases of the nervous system
H00-H59	Diseases of the eye and adnexa	H60-H95	Diseases of the ear and mastoid process
I00-I99	Diseases of the circulatory system	J00-J99	Diseases of the respiratory system
K00-K95	Diseases of the digestive system	L00-L99	Diseases of the skin and subcutaneous tissue
M00-M99	Diseases of the musculoskeletal system and connective tissue	N00-N99	Diseases of the genitourinary system
P00-P96	Certain conditions originating in the perinatal period	Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities

Supplementary Table 2. Number of observations.

Sex	Birth weight / Gestational age	Extremely and very low	Low	Sub-optimal	Normal	Total
Boy	Extremely and very preterm	18	12	0	0	**30**
	Moderate preterm	1	31	1	0	**33**
	Late preterm	0	56	61	21	**138**
	Total (boys)	**19**	**99**	**62**	**21**	**201**
Girl	Extremely and very preterm	24	10	0	0	34
	Moderate preterm	4	32	2	0	38
	Late preterm	1	64	61	18	144
	Total (girls)	**29**	**106**	**63**	**18**	**216**
Total	Extremely and very preterm	42	22	0	0	**64**
	Moderate preterm	5	63	3	0	**71**
	Late preterm	1	120	122	39	**282**
	Total	**48**	**205**	**125**	**39**	**417**

LIST OF PRESENTATIONS

1. "*Intrauterine head growth, and head circumference as the health risk indicator*" Oral presentation. 24th International Conference of Auxological Society. Jurata, Poland, November 5, 2016.
   Conference thesis printed in Ped. Endocrinol. Rev. 2017;14(3):326-334.
2. „*Naujagimių galvos apimtis – svarbus augimo ir sveikatos rizikos rodiklis*". Oral presentation. „BIOATEITIS: gamtos ir gyvybės mokslų perspektyvos", conference of Lithuanian Academy of Sciences. Vilnius, Lithuania, December 7, 2016.
3. "*The Distribution of Newborns' Head Circumference: An Example for The Evolutionary Fixed Developmental Mechanisms?* ". Oral presentation. International Conference of Evolutionary Medicine („Evoliucinė medicina: sveikata ir ligos besikeičiančioje aplinkoje"). Vilnius, Lithuania, June 5-8, 2018.
   Conference thesis printed in Acta Medica Lituanica, supp. Vol. 25, 2018:37.
4. „*Prevalence of Prematurity in Lithuania During the 1995-2015 Period in Relation to Maternal Age, Antenatal and Perinatal Pathologies*". Oral presentation. "Baltic Morphology", 10th International Scientific Conference. Kaunas, Lithuania, October 24-25, 2019,
   Conference thesis printed in "Medicina„(Kaunas) 2019; 55(supplement 2), p.239.
5. "*The Incidence and Timing of Different Diseases in Relation to Sub-Categories of Prematurity till The Adolescence (Retrospective Longitudinal Study)*". Best PhD student's oral presentation. Joint International Meeting: 22nd EAA Congress, 15th ISGA Congress, 5th International Conference of Evolutionary Medicine. Vilnius, Lithuania, August 24-27, 2022.
6. "*Growth of Preterm Children in Early Childhood: The Relationship Between Gestational Age, Body Size, General Health Status, and Timing of Diseases*". Oral presentation. Joint International Meeting: 22nd EAA Congress, 15th ISGA Congress, 5th International Conference of Evolutionary Medicine. Vilnius, Lithuania, August 24-27, 2022.
7. "*The Onset and Timing of Mental, Behavioural and Neurodevelopmental Disorders, and Diseases of the Nervous System in Relation to Sub-Categories of Prematurity from Birth till the Adolescence (Retrospective Longitudinal Study)*". Poster

presentation. Congress of Joint European Neonatal Societies (jENS 2023). Rome, Italy, September 19-23, 2023.

8. „*Metas atsinaujinti: Lietuvos naujagimių antropometrinių rodiklių diagramos ir ribinės vertės pagal gestacinį amžių ir lytį*". Invited oral presentation. „Visada kartu, kad ir kas nutiktų...“, conference of Lithuanian Neonatology Association („Lietuvos Neonatologijos Asociacija“), Kaunas, Lithuania, December 4, 2023.
9. "*Preterm Birth and Health Outcomes: A Longitudinal Study from Birth to Adolescence*". Best PhD student‘s oral presentation. 6th International Conference of Evolutionary Medicine: How Evolutionary Thinking Can Contribute to The Medical and Health Sciences. Vilnius, Lithuania, June 18-21, 2024.
10. "*Health Outcomes and Their Associations in Preterm Survivors from Birth to Adolescence: A Longitudinal Cohort Study*". Oral Presentation. 23rd EAA Congress -16th ISGA Congress - SSHB Congress. Zagreb, Croatia, September 5-8, 2024."

OTHER ACHIEVEMENTS:

- **1st Place**: Doctoral Students Competition *"3 Minutes Thesis/3MT"* (*"3 Minučių Disertacija"*), Vilnius, Lithuania, March 23, 2022.
- **2nd Place**: Early-Stage Researchers Competition *"Tyrėjų Grand Prix 2023"*, Vilnius, Lithuania, October 18, 2023.

CURRICULUM VITAE

Rūta Morkūnienė qualified as a medical doctor at the Faculty of Medicine of Vilnius University in 2012. From 2012 to 2015, she studied a residency in pediatrics and neonatology while working as a junior researcher at the Clinic of Children's Diseases of the Faculty of Medicine of Vilnius University. Since 2015, she has worked as a junior assistant at the Department of Anatomy, Histology and Anthropology, Faculty of Medicine, Vilnius University. In 2024, she was awarded for excellence as the best lecturer in the English language programme of Studies in Medicine.

From 2016 to 2023, R. Morkūnienė was a PhD student at Vilnius University. She has published extensively, including in high-impact journals, and she actively enhances her expertise through participation in local and international conferences, congresses, and research projects, contributing to the development of interdisciplinary research. Rūta is an active participant and an award-winning competitor in science communication contests. Between 2021 and 2024, Rūta was a member of the Steering Committee and a junior research assistant in the international project Horizon 2020 MotherNet, where she focused on contemporary European motherhood through the lens of medical humanities.

Rūta Morkūnienė is a member of the Lithuanian Morphology Association, the International Society for the Study of Human Growth and Clinical Auxology (ISGA), and the European Anthropological Association (EAA), where she has been elected as a Board Member for the 2024–2026 term.

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ANNEX

LIETUVOS BIOETIKOS KOMITETAS

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DĖL TYRĖJŲ DALYVAVIMO BIOMEDICININIAME TYRIME NR. 1

Susipažinę su Jūsų gautu prašymu dėl papildomų tyrėjų dalyvavimo biomedicininiame tyrime „Lietuvių populiacijos fizinė būklė, jos veiksniai ir epochiniai pokyčiai“ (protokolo Nr. 1), informuojame, kad Lietuvos bioetikos komitetas neprieštarauja doc. Lauros Nedzinskienės, dokt. Rūtos Morkūnienės, dokt. Andrės Amšiejienės, dokt. Violetos Bartuškienės ir doc. Ramunės Čepulienės dalyvavimui minėtame tyrime.

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