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

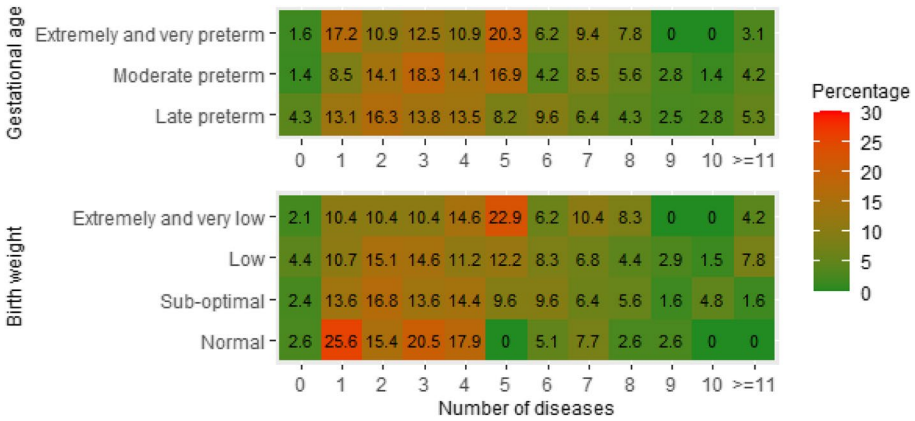

Fig. 1 The percentage of individuals diagnosed with varying numbers of certain separate diseases from birth to age 18, categorised by gestational age and birth weight (represented by heat maps)

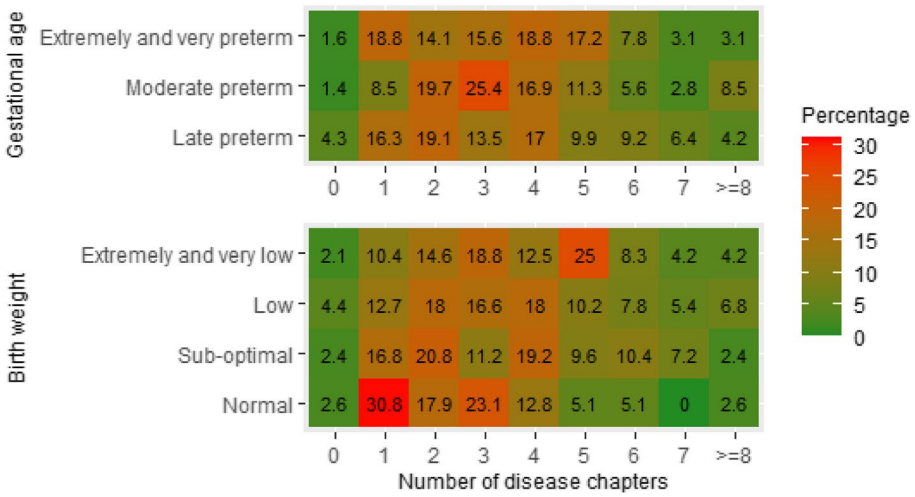

Fig. 2 The percentage of individuals diagnosed with varying numbers of ICD-10 disease chapters from birth to age 18, categorised by gestational age and birth weight and represented by heat maps

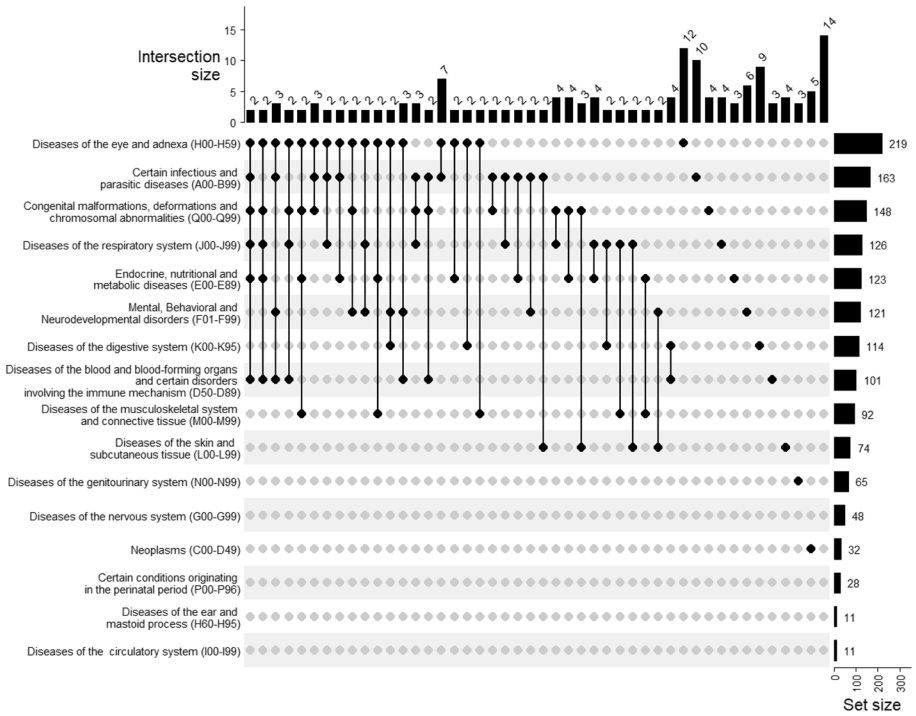

Fig. 3 Combination variants of different interrelated ICD-10 disease chapters provided by Upset graph. The horizontal bars on the right side represent the number of cases observed in each ICD-10 disease chapter, providing a quick overview of the distribution of diagnoses. The central matrix, marked by 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

Not applicable.

Competing interests

The authors declare no competing interests.

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