# Preterm birth and the risk of multimorbidity in adolescence: a multiregister-based cohort study

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## Summary

**Background** Multimorbidity affects people of all ages, but the risk factors of multimorbidity in adolescence are unclear. The aim of this study was to examine preterm birth (<37 weeks) as a shared risk factor for multiple health outcomes and the role of gestational age (degree of prematurity) in the development of increasingly complex multimorbidity (two, three, or four health outcomes) in adolescence (age 10–18 years).

**Methods** We used population-wide data from Finland (1 187 610 adolescents born 1987–2006) and Norway (555 431 adolescents born 1998–2007). Gestational age at birth was ascertained from medical birth registers and categorised as 23–27 weeks (extremely preterm), 28–31 weeks (very preterm), 32–33 weeks (moderately preterm), 34–36 weeks (late preterm), 37–38 weeks (early term), 39–41 weeks (term, reference category) and 42–44 weeks (post-term). Children who died or emigrated before their 10th birthday, and those with missing or implausible data on gestational age, birthweight, or covariates, were excluded. Health outcomes at age 10–18 years were ascertained from specialised health care and mortality registers. We calculated hazard ratios (HRs) and population attributable fractions (PAFs) with 95% CIs for multiple health outcomes during adolescence.

**Findings** Individuals were followed up from age 10 to 18 years (mean follow-up: 6 years, SD: 3 years). Preterm birth was associated with increased risks of 20 hospital-treated malignant, cardiovascular, endocrinological, neuropsychiatric, respiratory, genitourinary, and congenital health outcomes, after correcting for multiple testing and ignoring small effects (HR <1·2). Confounder-adjusted HRs comparing preterm with term-born adolescents were 2·29 (95% CI 2·19–2·39) for two health outcomes (PAF 9·0%; 8·3–9·6), and 4·22 (3·66–4·87) for four health outcomes (PAF 22·7%; 19·4–25·8) in the Finnish data. Results in the Norwegian data showed a similar pattern. We observed a consistent dose–response relationship between an earlier gestational age and elevated risks of increasingly complex multimorbidity in both datasets.

**Interpretation** Preterm birth is associated with increased risks of diverse multimorbidity patterns at age 10–18 years. Adolescents with a preterm-born background could benefit from diagnostic vigilance directed at multimorbidity and a multidisciplinary approach to health care.

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## Introduction

Worldwide, approximately 15 million babies (11%) each year are born preterm (ie, before 37 completed gestational weeks).[1] In high-income countries, most preterm-born babies, including those born very early (≤32 weeks) or with a very low birthweight (<1500 g) now survive infancy, and consequently, increasing numbers of children, young people, and adults have a preterm-born background.[2] Babies born prematurely miss the final weeks or months of development in the intrauterine environment and are often exposed to perinatal and postnatal complications or interventions, which can confer adverse effects on health during the early part of the life course and beyond.[3] Accordingly, respiratory, cardiovascular, and neuropsychiatric diseases are more common among preterm than term-born children, adolescents, and adults.[4–7] Compared with term-born individuals, preterm individuals have a 1·3–4·5 times increased risk of asthma,[7] a 1·1–3·1 times increased risk of depression,[8] and a 1·3–2·3 times increased chance of having autism spectrum disorder.[9]

Few studies have examined the link of premature birth with multimorbidity, that is, the co-occurrence of multiple physical or mental diseases or conditions of long duration in one individual.[10] Multimorbidity is an increasing concern worldwide, due to its effect on the individuals' health and quality of life, and the challenges it poses to the health-care systems and providers in caring for individuals with multiple, interlinked diseases and conditions.[11,12] Multimorbidity occurs across the life course and is estimated to affect 13–80% of adults (aged 18–60 years)[12] and 10–29% of children and adolescents (aged 2–17 years).[13,14] Important risk factors for adult multimorbidity include increasing

## Research in context

### Evidence before this study

Preterm birth (<37 gestational weeks) is a risk factor for many adverse health outcomes (including respiratory, cardiovascular, and neuropsychiatric diseases) in the early part of the life course. However, little is known about the clustering of multiple diseases among preterm-born people. We searched PubMed from database inception to Aug 17, 2022, using the search terms "preterm" OR "gestational age" AND "multimorbidity" OR "co-morbidity" OR "outcome-wide". Our search identified 2447 studies. No language restrictions were used. This literature suggests that preterm birth is associated with a wide range of diseases and conditions. Many studies reported that preterm-born people with an index disease (eg, asthma or a neuropsychiatric disease) were likely to have other, comorbid diseases. However, few studies have examined multimorbidity (the co-occurrence of multiple diseases or conditions, with none defined as an index disease) among preterm-born people, in comparison to their term-born counterparts. As far as we are aware, no study has yet ascertained multimorbidity from a wide range of health outcomes associated with preterm birth.

### Added value of this study

Our investigation, based on individual-level data from multiple, linked nationwide registers from Finland and Norway, quantified the associations of preterm birth and gestational age (degree of prematurity) with 68 predefined health outcomes and death in adolescence (age 10–18 years) and examined the role of gestational age at birth in subsequent multimorbidities (the number of health outcomes) in this age group. Focusing on multimorbidity reliably linked to preterm birth (with hazard ratios ≥1·2 and estimates robust to multiple testing), we found that preterm birth was associated with 20 hospital-treated health outcomes. Although the absolute risks were relatively low, they clustered strongly in the earliest born individuals. Earlier gestational age at birth had a consistent dose–response relationship, with elevated risks of increasingly complex multimorbidity. The risks of multimorbidity associated with preterm birth were also consistently higher than the risks of single diseases.

### Implications of all the available evidence

The associations between preterm birth and elevated risks of many individual chronic diseases are well recognised. Our investigation suggests that preterm birth, across the spectrum of gestational ages, is also strongly associated with the co-occurrence of multiple health outcomes at age 10–18 years. In combination, these findings suggest that a preterm-born background is a characteristic that should be considered to improve identification of multimorbidity in young people.

age, low socioeconomic position, smoking, and obesity,[12,15] but the risk factors of multimorbidity in younger age groups are largely unknown. Given the multifactorial nature of multimorbidity, the factors involved in the development of co-occurring diseases are likely to vary across the life course, and the exposures that play a role in the development of multimorbidity during the early part of the life course could stem not only from childhood but also from perinatal or prenatal periods.

We aimed to prospectively examine the risks of common adolescent health outcomes among individuals who were born preterm, across the spectrum of gestational ages, by comparison with those born at term, and characterise the association of preterm birth and gestational age with multimorbidity (two, three, or four health outcomes) in adolescence (age 10–18 years).

## Methods

### Study design and participants

We used longitudinal data from multiple, linked nationwide registers from Finland and Norway for this observational cohort study. The first study population, identified from the Finnish Medical Birth Register, comprised all individuals born alive in Finland during a baseline period extending from Jan 1, 1987, to Dec 31, 2006. Records were linked (using unique personal identity numbers) to the nationwide hospital care register, including inpatient care from Jan 1, 1987, to Dec 31, 2016, outpatient care from Jan 1, 1998, to Dec 31, 2016, and Statistics Finland population data from Jan 1, 1987, to Dec 31, 2016. To examine the robustness and generalisability of our findings, we repeated the analyses in multiregister data from Norway. The second study population, identified from the Norwegian Medical Birth Register, comprised all individuals born alive in Norway on or between Jan 1, 1998, and Dec 31, 2007. These individuals were followed up by record linkage (using unique identity numbers) to the nationwide hospital care register, causes of death register, and national statistics office's population data from Jan 1, 1988, to Dec 31, 2017. As data protection legislation precludes moving sensitive health register data between countries, we were unable to pool data and analysed each dataset separately.

All data were pseudonymised and linked by the register authorities. In Finland, research studies using only pseudonymised register data do not require national ethics committee approval or individual consent. The research described here was approved by the relevant register authorities, the institutional ethics review board of the Finnish Institute for Health and Welfare (THL/1984/6.02.01/2018) and the regional committee for Medical and Health Research in Norway (REK 2018/32/Midt), which granted an exemption from individual consent for the Norwegian data.

## Procedures

Sex, date of birth, and gestational age at birth for the individuals in the study were ascertained from medical birth registers in Finland and Norway. Gestational age at birth was estimated on the basis of ultrasound examination, information on the last menstrual period if ultrasound measure was unavailable, or the date of embryo transfer in cases of assisted reproduction. Gestational age, in completed weeks, was categorised as 23–27 weeks (extremely preterm), 28–31 weeks (very preterm), 32–33 weeks (moderately preterm), 34–36 weeks (late preterm), 37–38 weeks (early term), 39–41 weeks (term) and 42–44 weeks (post-term; appendix p 3).

Prenatal factors, which previous research has shown to be linked to preterm birth and a range of subsequent health outcomes (appendix p 3), were included as potential confounders in our analyses. Birthweight (kg), mother's age at the time of birth (years), and smoking during pregnancy (yes *vs* no) were ascertained from the medical birth registers in both countries. Mother's diabetes status (yes *vs* no) and hypertensive disorder (yes *vs* no) during pregnancy were ascertained from combined information from the medical birth registers and hospital care registers (appendix p 3). Diabetes status was defined as having a record of diabetes (any type) before or during pregnancy. Hypertensive disorder was defined as having a record of pre-eclampsia, eclampsia, gestational hypertension, or chronic hypertension. Birthweight *Z* score (the difference between the observed birthweight and the birthweight expected for the relevant gestational age) was calculated using Maršál estimated fetal weight reference.[16] Mother's socioeconomic position at the time of birth was determined from data on occupation, recorded in the birth register (Finland) and education, and from the national statistics office's population data (Norway; appendix p 4). Dates of death and emigration from Finland or Norway were obtained from the national statistics offices' population data and the Norwegian Institute of Public Health causes of death register.

Health outcomes during adolescence were ascertained from inpatient and outpatient care records in the Norwegian Patient Register and Finnish Care Register for Healthcare. Multimorbidity outcomes were identified from a pre-specified set of 68 health outcomes (representing International Classification of Diseases version 10 [ICD-10] chapters and diseases and death from any cause), which previous research has shown to represent key sources of disease and health-care burden among adolescents in high-income countries (appendix pp 4, 22).[17–19]

## Statistical analysis

Individuals with complete data on gestational age and birthweight were included in our analyses (figure 1). Full data on mother's age and pregnancy disorders were available and missing data on mother's smoking (2·2% in the Finnish dataset, none recorded in the Norwegian dataset) or other or unknown socioeconomic position during pregnancy (31·5% in Finland and 3·3% in Norway) were included in the analyses as a separate category (appendix p 4). Data from Finland and Norway were analysed separately. The proportional hazards assumption was examined visually from –log(–log(survival)) plots and by testing for interaction of Schoenfeld residuals with time (appendix pp 14–21). We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs for the 68 health outcomes, death, and multimorbidity (two, three, or four health outcomes) across categories of gestational age, with term-born individuals as the reference group. Each individual's time in the study began on their 10th birthday and was censored on the first of the following: date of the relevant health outcome, the day before their 19th birthday, date of emigration from their country of residence, date of death, or end of the register follow-up (Dec 31, 2016 in the Finnish data and Dec 31, 2017 in the Norwegian data; figure 1). Age was used as the timescale in the models.

See **Online** for appendix

First, we estimated HRs and 95% CIs for each of the a priori selected 68 health outcomes and death in separate models, comparing preterm-born individuals (born <37 gestational weeks) with term-born individuals (born at 39–41 weeks) and adjusting the estimates for sex, year of birth, and gestational age-specific birthweight *Z* scores. Second, we focused further analysis on the health outcomes that were associated with preterm birth to an extent that is meaningful in terms of public health and health care by selecting health outcomes that had HRs of 1·2 or more with 95% CIs excluding the null value, and that were significant at Bonferroni-adjusted α-level of 0·05/68, in either Finnish data or Norwegian data.[20,21] When health outcomes representing an ICD-10 chapter and specific diseases within the chapter both fulfilled these criteria, individual diseases were selected for further

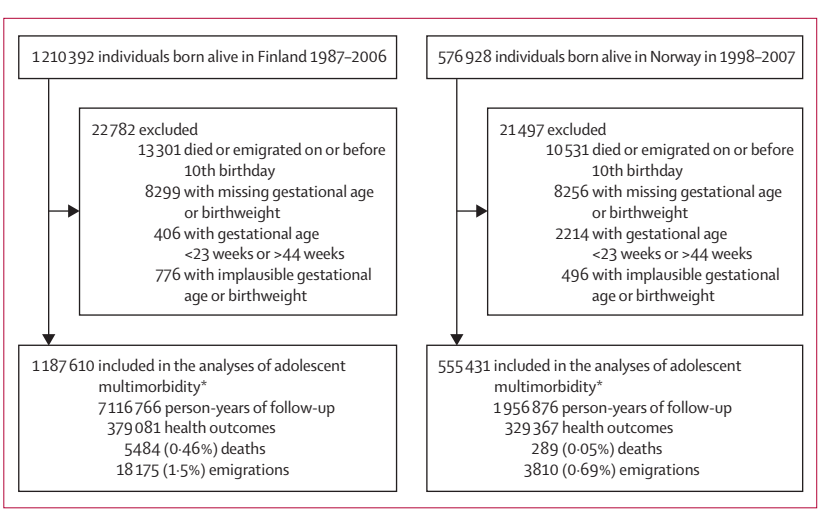


***Figure 1:*** **Overview of the study population**
*Alive and living in Finland or Norway on their 10th birthday.

analyses, to avoid overlap and facilitate interpretation. These health outcomes were used to construct the multimorbidity outcomes. Health outcomes with a HR indicating a 0·8-fold risk or smaller, 95% CIs excluding the null, and p<0·05/68 would have been included in a separate analysis; however, there was only one in our datasets, precluding the examination of combinations. A HR threshold of 1·2 was chosen because weaker associations are unlikely to represent differences that are meaningful in terms of public health or clinical practice.

| | Finland (n=1 187 610) | Norway (n=555 431) |
|---|---|---|
| **Year of birth** | | |
| 1987–97 | 683 086 (57·5%) | NA |
| 1998–2006 | 504 524 (42·5%) | 498 479 (89·8%) |
| 2007 | NA | 56 952 (10·3%) |
| **Sex** | | |
| Female | 581 087 (48·9%) | 270 668 (48·7%) |
| Male | 606 501 (51·1%) | 284 763 (51·3%) |
| Unknown | 22 (<0·1%) | 0 |
| **Gestational age at birth (completed weeks)** | | |
| 23–27 (extremely preterm) | 2840 (0·2%) | 1275 (0·2%) |
| 28–31 (very preterm) | 6313 (0·5%) | 3876 (0·7%) |
| 32–33 (moderately preterm) | 8339 (0·7%) | 5191 (0·9%) |
| 34–36 (late preterm) | 47 792 (4·0%) | 26 727 (4·8%) |
| 37–38 (early term) | 213 657 (18·0%) | 98 446 (17·7%) |
| 39–41 (term) | 855 554 (72·0%) | 375 646 (67·6%) |
| 42–44 (post-term) | 53 115 (4·5%) | 44 270 (8·0%) |
| **Gestational age-specific birthweight *Z* score*** | | |
| Mean (SD) | −0·45 (1·2) | −0·47 (1·2) |
| **Mother had diabetes during pregnancy** | | |
| No | 1 117 212 (94·1%) | 546 833 (98·5%) |
| Yes | 70 398 (5·9%) | 8598 (1·6%) |
| **Mother's hypertensive disorder during pregnancy** | | |
| No | 1 106 346 (93·2%) | 521 205 (93·8%) |
| Yes | 81 264 (6·8%) | 34 226 (6·2%) |
| **Multiple birth** | | |
| Singleton | 1 154 421 (97·2%) | 535 726 (96·5%) |
| Multiple | 33 189 (2·8%) | 19 705 (3·6%) |
| **Mother's age, years** | | |
| Mean (SD) | 29·1 (5·3%) | 29·4 (5·1%) |
| **Mother's smoking during pregnancy** | | |
| No | 981 437 (82·6%) | 423 323 (76·2%) |
| Yes | 179 720 (15·1%) | 132 108 (23·8%) |
| Missing | 26 453 (2·2%) | 0 |
| **Mother's socioeconomic position at time of birth** | | |
| Low | 255 571 (21·5%) | 105 402 (19·0%) |
| Intermediate | 397 742 (33·5%) | 201 499 (36·3%) |
| High | 159 615 (13·4%) | 230 493 (41·5%) |
| Other/unknown | 374 682 (31·5%) | 18 037 (3·3%) |

Data shown are n (%). NA=not applicable. *Maršál gestational growth reference standard.

***Table 1:*** **Baseline (at birth) characteristics**

We used Bonferroni correction because it provides strong control of the familywise error rate (ie, false positive findings), although the approach is conservative in the sense that is has low power to detect false negatives (appendix p 5).

To examine multimorbidity, we used Cox regression to model the associations of categories of gestational age (degree of prematurity), with the number of health outcomes (one, two, three, or four) indicating a single morbidity and the increasing complexity of multimorbidity, using term birth as the reference group. We ran three models: model 1 was adjusted for age only (as the timescale in the model), model 2 had adjustments for age, sex, year of birth, and birthweight *Z* score, and model 3 had adjustments for model 2 covariates and mother's diabetes status, hypertensive disorder, smoking during pregnancy, and mother's age and socioeconomic position at the time of birth. Multiplicative interactions were examined using likelihood ratio tests to compare models comprising preterm status and covariates with models including an additional preterm birth covariate interaction term and additive interactions, by calculating the relative excess risk due to interaction. We also ran models stratified by sex, year of birth, mother's smoking, diabetes status, and hypertensive disorder during pregnancy. In addition, we calculated absolute risks, cumulative incidence of multimorbidity, and population-attributable fractions (PAFs) to examine the contribution of preterm birth and gestational age to multimorbidity in adolescence (appendix p 5). To examine the extent to which our findings were driven by congenital anomalies and their consequences, we did a sensitivity analysis excluding extremely preterm (<27 weeks) born people and those with records of congenital anomalies at age 10–18 years. In addition, we examined temporal sequences of pairs of health outcomes. We also did post-hoc analyses of the association of gestational age with physical–mental multimorbidity (having a record of ≥1 mental disease or condition and ≥1 physical disease or condition at age 10–18 years) and the association of gestational age with an alternative composition of multimorbidity, on the basis of a less stringent method to multiple testing correction (appendix pp 6, 35). The Finnish data were analysed using Stata SE 17 and the Norwegian data using Stata MP 16.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

The target population for the analyses in the Finnish data comprised 1 210 392 individuals born alive in Finland from Jan 1, 1987, to Dec 31, 2006. We excluded 13 301 (1·1%) children who died or emigrated from Finland before their 10th birthday, and 9481 (0·8%)

children with missing or implausible data on gestational age or birthweight (probably representing data errors). A study population of 1 187 610 individuals was included, who remained alive and living in Finland at age 10 years (figure 1). Of these, 855 554 (72·0%) were born at term (39–41 completed weeks), 213 657 (18·0%) were born early term (37–38 weeks), and 65 284 (5·5%) were born preterm (23–36 weeks; table 1). During the 7 116 766 person-years of follow-up from age 10 to 18 years (median 6·9, IQR 3·2–9·0), there were hospital care records of 379 081 health outcomes and 5484 deaths. The target population for the analyses in the Norwegian data (ie, people born alive in Norway in 1998–2007) consisted of 576 928 individuals. Children who died or emigrated before their 10th birthday (10 531 [1·8%]) and those with missing or implausible data on gestational age or birthweight (10 966 [1·9%]) were excluded, and the study population consisted of 555 431 people. Of these, 375 646 (67·6%) individuals were born at term, 98 446 (17·7%) were born early term, and 37 069 (6·7%) were born preterm (table 1). During the 1 956 876 person-years of follow-up (median 3·1, IQR 1·2–5·5), there were records of 329 367 health outcomes and 289 deaths (figure 1).

Preterm birth was associated with increased risk of many of the 68 health outcomes we examined, whereas decreased risks or no association were observed for other health outcomes (table 2). Preterm birth was also associated with 1·29 times increased risk of death from any cause (95% CI 1·16–1·43) in the Finnish data and 1·20 times increased risk of death (95% CI 0·77–1·87) in the Norwegian data. We identified 20 health outcomes with HRs indicating at least 1·2 times increased risk and p values <0·05/68. These outcomes, used to construct the multimorbidity outcomes, comprised kidney cancer, thyroid disorders, diabetes, pituitary disorders, intellectual disability, disorders of psychological development, epilepsy, headaches, sleep disorders, cerebral palsy, hypertension, valve disorders, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, diseases of blood and blood forming organs, eye diseases, ear diseases, diseases of the genitourinary system, and congenital anomalies (table 2; appendix p 22).

Preterm-born individuals were more likely to have hospital care records of two, three, or four health outcomes (increasingly complex multimorbidity) at age 10–18 years (figure 2). As the Norwegian data contained a larger number of some health outcomes than the Finnish data (table 2), the absolute risks of multiple health outcomes were larger in the Norwegian study population. The cumulative incidence of having records of two health outcomes among preterm-born individuals was 4·6% in Finland and 17·1% in Norway, in comparison to 1·9% of term-born people in Finland and 9·5% of term-born individuals in Norway. The cumulative incidence of having records of four health outcomes was 0·6% among preterm-born people in the Finnish data and 2·5% in the Norwegian data, both estimates being higher than those in the term-born groups (0·1% in Finland and 0·7% in Norway). Although the numbers of individuals with four health outcomes were small, the elevated risk among preterm-born individuals, compared with those born at term, was consistent across adolescence in both datasets.

| | Finland | | Norway | |
|---|---|---|---|---|
| | Cases | HR (95% CI) | Cases | HR (95% CI) |
| Cancer | 888 | 1·28 (0·98–1·68) | 1147 | 1·14 (0·91–1·44) |
| Bone and articular cartilage | 51 | NA* | 53 | 0·75 (0·23–2·46) |
| Kidney† | 32 | 5·52 (2·15–14·14)‡ | 34 | NA* |
| Eye, brain, and other parts of the CNS | 168 | 1·02 (0·51–2·00) | 301 | 0·92 (0·58–1·48) |
| Neuroblastoma | 24 | 1·56 (0·35–6·89) | 8 | NA* |
| Thyroid and other endocrine glands | 46 | 1·48 (0·44–4·90) | 27 | 0·62 (0·08–4·76) |
| Lymphoma | 148 | 1·01 (0·49–2·08) | 123 | 1·83 (1·03–3·27) |
| Leukaemia | 319 | 1·41 (0·91–2·17) | 331 | 1·18 (0·77–1·80) |
| Diseases of blood and blood forming organs† | 2196 | 1·24 (1·04–1·47) | 2427 | 1·38 (1·19–1·59)‡ |
| Anaemia | 699 | 1·50 (1·13–1·99) | 1027 | 1·23 (0·97–1·54) |
| Endocrine diseases | 18 919 | 1·38 (1·30–1·46)‡ | 17 331 | 1·40 (1·33–1·48)‡ |
| Thyroid disorders† | 4257 | 1·32 (1·17–1·50)‡ | 1772 | 1·43 (1·21–1·70)‡ |
| Diabetes† | 10 664 | 1·21 (1·12–1·31)‡ | 3003 | 1·16 (1·01–1·33) |
| Pituitary disorders† | 676 | 2·03 (1·60–2·56)‡ | 1037 | 2·09 (1·75–2·50)‡ |
| Psychiatric and behavioural disorders | 107 695 | 1·21 (1·18–1·24)‡ | 70 918 | 1·30 (1·26–1·33)‡ |
| Substance abuse disorders | 286 | 0·88 (0·77–0·99) | 2156 | 1·07 (0·90–1·26) |
| Psychotic disorders | 3672 | 1·17 (1·02–1·33) | 656 | 1·40 (1·06–1·85) |
| Mood disorders | 33 895 | 1·00 (0·95–1·04) | 10 424 | 0·96 (0·89–1·04) |
| Anxiety disorders | 33 693 | 1·08 (1·03–1·13) | 23 170 | 1·12 (1·07–1·18)‡ |
| Intellectual disability† | 4190 | 2·53 (2·30–2·77)‡ | 3742 | 2·20 (1·99–2·42)‡ |
| Disorders of psychological development† | 22 734 | 1·54 (1·47–1·61)‡ | 17 509 | 1·50 (1·43–1·58)‡ |
| Diseases of the nervous system | 13 696 | 2·72 (2·58–2·86)‡ | 21 972 | 1·55 (1·48–1·62)‡ |
| Multiple sclerosis | 121 | 0·67 (0·25–1·83) | 57 | 0·71 (0·22–2·30) |
| Epilepsy† | 8703 | 1·72 (1·60–1·85)‡ | 5163 | 1·64 (1·50–1·80)‡ |
| Headaches† | 1715 | 1·48 (1·24–1·77)‡ | 8067 | 1·06 (0·97–1·16) |
| Sleep disorders† | 375 | 1·89 (1·33–2·69)‡ | 1861 | 1·49 (1·26–1·75)‡ |
| Cerebral palsy† | 2029 | 14·95 (13·53–16·51)‡ | 1536 | 7·85 (6·98–8·83)‡ |
| Diseases of the eye† | 11 368 | 1·53 (1·43–1·64)‡ | 45 445 | 1·49 (1·45–1·54)‡ |
| Diseases of the ear† | 11 849 | 1·47 (1·38–1·58)‡ | 21 408 | 1·40 (1·34–1·47)‡ |
| Diseases of the circulatory system | 7945 | 1·26 (1·16–1·37) | 8034 | 1·31 (1·21–1·42) |
| Hypertension† | 727 | 1·83 (1·42–2·36)‡ | 545 | 2·33 (1·82–2·99)‡ |
| Ischaemic heart disease | 119 | 1·57 (0·78–3·15) | 52 | 1·19 (0·42–3·36) |
| Thromboembolic disease | 401 | 1·50 (1·03–2·19) | 232 | 1·19 (0·73–1·92) |
| Arrhythmias | 2886 | 1·02 (0·87–1·20) | 2919 | 1·23 (1·07–1·41) |
| Congestive heart failure | 86 | 1·10 (0·47–2·57) | 86 | 0·92 (0·39–2·16) |
| Pericarditis | 94 | 1·55 (0·71–3·39) | 80 | 0·95 (0·38–2·42) |
| Other diseases of the pericardium | 31 | 0·98 (0·22–4·28) | 36 | 1·19 (0·36–3·95) |
| Valve disorders† | 1099 | 1·73 (1·40–2·14)‡ | 432 | 1·48 (1·06–2·05) |
| Cerebrovascular disease† | 394 | 1·18 (0·79–1·74) | 241 | 2·34 (1·58–3·46)‡ |
| Peripheral vascular disease | 570 | 0·73 (0·48–1·12) | 1210 | 1·05 (0·84–1·32) |

(Table 2 continues on next page)

| | Finland | | Norway | |
|---|---|---|---|---|
| | Cases | HR (95% CI) | Cases | HR (95% CI) |
| (Continued from previous page) | | | | |
| Diseases of the respiratory system | 87 996 | 1·17 (1·14–1·21)‡ | 58 501 | 1·17 (1·13–1·21)‡ |
| Chronic obstructive pulmonary disease† | 186 | 3·00 (1·98–4·55)‡ | 444 | 3·72 (2·91–4·75)‡ |
| Asthma† | 35 292 | 1·37 (1·31–1·42)‡ | 23 283 | 1·38 (1·32–1·45)‡ |
| Diseases of the digestive system | 23 158 | 1·13 (1·07–1·20)‡ | 37 709 | 1·08 (1·04–1·12)‡ |
| Ulcer disease | 23 | NA* | 129 | 1·26 (0·67–2·32) |
| Appendicitis | 7040 | 0·80 (0·72–0·90)‡ | 4976 | 0·95 (0·85–1·07) |
| Inflammatory gastric/bowel disease | 3291 | 1·12 (0·97–1·30) | 2221 | 1·00 (0·85–1·19) |
| Diseases of the liver | 329 | 1·90 (1·30–2·76) | 319 | 1·14 (0·75–1·72) |
| Cholelithiasis | 46 | 3·25 (1·32–8·03) | 225 | 1·35 (0·82–2·20) |
| Pancreatitis | 66 | 0·95 (0·29–3·06) | 27 | 1·54 (0·46–5·22) |
| Coeliac disease, dermatitis herpetiformis | 3738 | 0·96 (0·83–1·11) | 5890 | 0·84 (0·75–0·94) |
| Diseases of the skin | 18 851 | 0·95 (0·89–1·02) | 41 245 | 1·05 (1·01–1·10) |
| Diseases of the musculoskeletal system | 52 477 | 1·06 (1·03–1·11)‡ | 50 155 | 1·09 (1·05–1·13)‡ |
| Rheumatoid disease | 335 | 0·99 (0·89–1·10) | 3256 | 1·08 (0·94–1·24) |
| Osteoarthritis | 304 | 1·47 (0·93–2·31) | 329 | 1·15 (0·74–1·79) |
| Back pain | 5171 | 1·03 (0·91–1·16) | 3675 | 1·02 (0·89–1·16) |
| Soft tissue disorders | 9489 | 1·09 (1·00–1·19) | 18 835 | 0·99 (0·94–1·05) |
| Diseases of the genitourinary system† | 12 395 | 1·24 (1·16–1·34)‡ | 19 973 | 1·14 (1·08–1·20)‡ |
| Renal disease | 3819 | 1·22 (1·07–1·39) | 1742 | 1·26 (1·06–1·51) |
| Congenital anomalies† | 23 172 | 1·71 (1·64–1·80)‡ | 26 607 | 1·49 (1·42–1·55)‡ |
| Miscellaneous | | | | |
| Circulatory and respiratory symptoms | 3794 | 1·21 (1·06–1·38) | 24 456 | 1·06 (1·01–1·11) |
| Digestive and abdominal symptoms | 3 671 | 1·24 (1·09–1·42) | 24 712 | 0·96 (0·91–1·01) |
| Poisoning | 4 908 | 0·97 (0·85–1·10) | 2113 | 1·15 (0·97–1·37) |
| Road accidents | 63 | 0·67 (0·16–2·77) | 2 907 | 0·91 (0·78–1·06) |
| Falls | 91 | 1·10 (0·48–2·56) | 14 924 | 0·84 (0·78–0·90)‡ |
| Self-harm | 6 | NA* | 145 | 1·12 (0·62–2·05) |
| Injury | 12 406 | 0·94 (0·91–0·96)‡ | 166 230 | 0·96 (0·94–0·97)‡ |
| Bone fractures | 60 007 | 0·92 (0·89–0·96)‡ | 85 563 | 0·94 (0·92–0·97)‡ |
| Death | 5484 | 1·29 (1·16–1·43)‡ | 289 | 1·20 (0·77–1·87) |

All HRs and 95% CIs compare preterm-born individuals (<37 weeks) with term-born individuals (39–41 weeks) and are adjusted for age, sex, year of birth, and Maršál gestational age-specific birthweight *Z* score. HR=hazard ratio. NA=not applicable. *No cases in preterm-born individuals. †Included in the multimorbidity outcomes. ‡Significant at Bonferroni-corrected alpha-level of 0·05/68.

***Table 2:*** **Associations of preterm birth (<37 gestational weeks) with 68 health outcomes and death in adolescence (age 10–18 years)**

Compared with term-born individuals, preterm-born individuals had a 1·46-fold increased risk (95% CI 1·42–1·49) of having a record of one health outcome in the Finnish data and a 1·38 times increased risk (1·35–1·41) in the Norwegian data (table 3). The risks of a second health outcome were 2·29 times higher among preterm-born individuals in Finland (2·19–2·39) and 1·79 times higher among those born preterm in Norway (95% CI 1·73–1·86). The risks of a third and a fourth health outcome among preterm-born individuals increased in a graded manner in both datasets, when compared with term-born individuals. The risk of having a third health outcome was 3·40 times higher in Finland and 2·46 times higher in Norway, and the risk of having a fourth health outcome was 4·22 times higher in Finland and 3·21 times higher in Norway. Our analyses of categories of gestational age indicated a dose–response relationship between the degree of prematurity and an increased risk of two or more health outcomes (table 3). The risk estimates were similar in boys and girls (appendix p 24) and attenuated little with adjustment for pregnancy disorders (hypertensive disorder and diabetes) and mother's characteristics (age, smoking, and socioeconomic position; appendix pp 26–27). PAFs suggest that in the Finnish data, 9·0% (8·3–9·6) of adolescent multimorbidity consisting of two health outcomes, 16·6% (15·0–18·1) of multimorbidity consisting of three health outcomes, and 22·7% (19·4–25·8) of multimorbidity consisting of four health outcomes is attributable to preterm birth (table 3); the patterns were similar, although slightly less marked, in the Norwegian data. PAFs in both datasets point to late preterm birth (at 34–36 weeks) making a larger contribution to population risk than other categories of gestational age (table 3).

Analyses stratified by sex, year of birth, mother's smoking, or pregnancy disorders, and those excluding extremely preterm (<27 weeks) born people and those with records of congenital anomalies, had findings similar to those of our main analyses (appendix pp 28–32). Interaction tests indicated that the associations of preterm birth with multimorbidity in the Norwegian data were slightly more pronounced among individuals born in the later years of the study period (2005 and after), and that the associations of preterm birth with multimorbidity comprising two or three health outcomes were weaker among individuals whose mothers had records of hypertensive disorder during pregnancy. In post-hoc analyses, preterm-born adolescents had up to 3 times increased risk of physical–mental multimorbidity when compared with term-born adolescents (table 4). The results of the post-hoc analyses of an alternative composition of multimorbidity were similar to our main findings (appendix pp 35–36).

Multimorbidity among preterm-born individuals was heterogeneous. Multimorbidity consisting of four health outcomes among preterm-born individuals comprised 293 outcome combinations in the Finnish data and 461 combinations in the Norwegian data, each with a low prevalence. The most commonly occurring constituents of multimorbidity (in ≥20% of preterm-born individuals with four health outcomes) were congenital anomalies, intellectual disability, epilepsy, cerebral palsy, eye diseases, disorders of psychological development, ear diseases, asthma, and disorders of genitourinary system (appendix p 25). The temporal associations between pairs of health outcomes are shown in the appendix (pp 33–34).

Absolute risks of multimorbidity (≥2 health outcomes) were lower than the risks of just one health outcome, but were clearly elevated among preterm-born individuals (appendix pp 26–27). The risks of two-outcome multimorbidity ranged from 153·0 per 10 000 person-years in the extremely preterm group to 21·4 per 10 000 person-years among those born at term in the Finnish data, and 650·8 per 10 000 person-years among the extremely preterm group to 110·9 per 10 000 person-years among those born at term in the Norwegian data. Multimorbidity comprising four health outcomes was rarer (<300 per 10 000 person-years) in both countries' data.

## Discussion

Our findings show a robust and meaningful link (indicated by outcome-specific HRs ≥1·2 in a multiple-testing corrected analysis) between preterm birth and having specialised health-care records of 20 individual health outcomes between ages 10 and 18 years. These health outcomes affect numerous organs and organ systems, indicating heterogeneity of multimorbidity in adolescence, and a potentially long-reaching health effect of preterm birth. Compared with adolescents who were born at term, those who were born preterm had a 1·79 times increased risk (Norway) and a 2·29 times increased risk (Finland) of multimorbidity comprising two health outcomes, and a 3–4 times increased risk of multimorbidity comprising four health outcomes (both countries). We observed a dose–response relationship between an increasing degree of prematurity and increasing complexity of multimorbidity. The findings were similar in direction and magnitude in the Finnish and Norwegian datasets, similar for males and females, and similar irrespective of mother's smoking or diabetes status during pregnancy. Interaction tests provided some evidence that the associations of preterm birth with multimorbidity were more pronounced among later born individuals and less pronounced among those whose mothers had records of hypertensive disorder during pregnancy. However, these observations should be interpreted with caution as they might reflect varying quality of register data over time.

The associations between preterm birth and increased risks of many individual chronic diseases are well recognised, but our investigation is among the first to examine the link of preterm birth with a wide range of health outcomes and the co-occurrence of multiple diseases in the same set of analyses. This approach furthers a comprehensive understanding of the health effects of preterm birth in the early part of the life course. Our findings are in line with those of previous studies, which have reported that adolescents who were born prematurely have increased risks of asthma,[7] epilepsy,[22] psychiatric disorders,[23] and diabetes.[24] Our findings suggest that in relative terms, the excess risk for multimorbidity is higher than that observed for many single diseases. Furthermore, PAFs suggest that a considerable proportion of adolescent multimorbidity, particularly its complex manifestations comprising three or four health outcomes, is attributable to preterm birth. From the point of view of prevention, it is important to note that the PAFs represent the estimated proportion of multimorbidity attributable to being born preterm or at a gestational age other than at term, if age, sex, year of birth, and Maršál gestational age-specific birthweight *Z* score were the same as in the observed data. In a real-world setting, reducing the number of preterm births could also influence other risk factors and consequently, PAFs should not be interpreted as estimates of the burden of multimorbidity removed if preterm birth could be prevented.

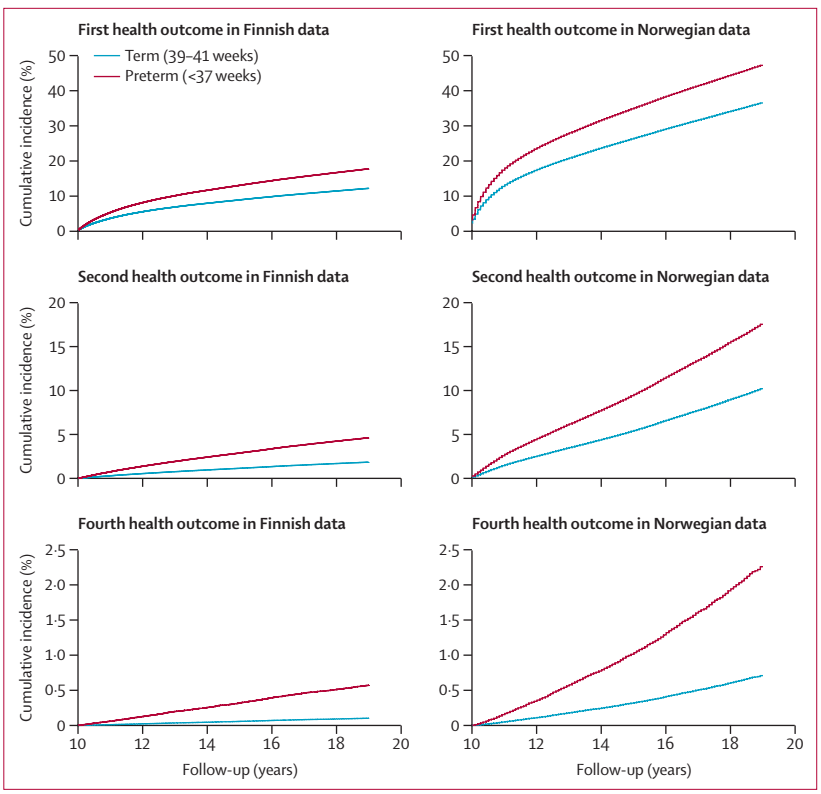


*Figure 2:* **Cumulative incidence of the number of health outcomes in the Finnish and Norwegian data**

Several mechanisms can potentially contribute to the strong association between preterm birth and an increased risk of multimorbidity. First, babies born prematurely miss the final weeks or months of intrauterine growth and development, and an early birth, if occurring at a critical developmental stage, can lead to disrupted organ development or function, thus increasing the risk of some diseases.[3,5,25] Second, it could be that adverse intrauterine environments are common causes of both preterm birth and the development of particular diseases in later life. For example, pregnancy complications (eg, pre-eclampsia) or fetal over-nutrition or undernutrition could introduce epigenetic

| | First health outcome | | | Second health outcome | | | Third health outcome | | | Fourth health outcome | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases, n (%) | HR (95% CI), p value | PAF (95% CI) | Cases | HR (95% CI), p value | PAF (95% CI) | Cases | HR (95% CI), p value | PAF | Cases | HR (95% CI), p value | PAF (95% CI) |
| **Finnish data** | | | | | | | | | | | | |
| Preterm (23–36 weeks) | 9688 (14·8%) | 1·46 (1·42 to 1·49), <0·0001 | 3·1% (2·9 to 3·3) | 2439 (3·7%) | 2·29 (2·19 to 2·39), <0·0001 | 9·0% (8·3 to 9·6) | 825 (1·3%) | 3·40 (3·14 to 3·69), <0·0001 | 16·6% (15·0 to 18·1) | 293 (0·5%) | 4·22 (3·66 to 4·87), <0·0001 | 22·7% (19·4 to 25·8) |
| Term (39–41 weeks) | 87 223 (10·2%) | 1 (ref) | 0% | 12 874 (1·5%) | 1 (ref) | 0% | 2682 (0·3%) | 1 (ref) | 0% | 693 (0·08%) | 1 (ref) | 0% |
| Extremely preterm (23–27 weeks) | 716 (25·2%) | 2·60 (2·42 to 2·80), <0·0001 | 0·5% (0·4 to 0·6) | 290 (10·2%) | 5·99 (5·32 to 6·74), <0·0001 | 1·8% (1·6 to 2·1) | 122 (4·3%) | 10·14 (8·42 to 12·22), <0·0001 | 4·0% (3·1 to 4·7) | 49 (1·7%) | 13·04 (9·65 to 17·63), <0·0001 | 6·0% (4·2 to 7·8) |
| Very preterm (28–31 weeks) | 1357 (21·5%) | 2·16 (2·05 to 2·28), <0·0001 | 0·8% (0·7 to 0·9) | 442 (7·0%) | 4·01 (3·64 to 4·42), <0·0001 | 2·5% (2·2 to 2·8) | 156 (2·5%) | 5·77 (4·88 to 6·82), <0·0001 | 4·5% (3·6 to 5·3) | 64 (1·0%) | 7·69 (5·88 to 10·05), <0·0001 | 7·2% (5·1 to 9·2) |
| Moderately preterm (32–33 weeks) | 1379 (16·5%) | 1·61 (1·53 to 1·70), <0·0001 | 0·6% (0·5 to 0·7) | 382 (4·6%) | 2·70 (2·43 to 2·99), <0·0001 | 1·8% (1·5 to 2·1) | 143 (1·7%) | 4·30 (3·63 to 5·11), <0·0001 | 3·8% (3·0 to 4·6) | 44 (0·5%) | 4·50 (3·30 to 6·13), <0·0001 | 4·5% (2·7 to 6·2) |
| Late preterm (34–36 weeks) | 6236 (13·1%) | 1·28 (1·25 to 1·31), <0·0001 | 1·4% (1·3 to 1·6) | 1325 (2·8%) | 1·76 (1·66 to 1·86), <0·0001 | 4·0% (3·5 to 4·5) | 404 (0·9%) | 2·45 (2·21 to 2·72), <0·0001 | 7·7% (6·4 to 8·9) | 136 (0·3%) | 3·01 (2·50 to 3·62), <0·0001 | 10·7% (8·0 to 13·4) |
| Early term (37–38 weeks) | 24 599 (11·5%) | 1·14 (1·12 to 1·15), <0·0001 | 1·9% (1·6 to 2·2) | 4239 (2·0%) | 1·32 (1·28 to 1·37), <0·0001 | 3·7% (3·0 to 4·4) | 1023 (0·5%) | 1·53 (1·42 to 1·64), <0·0001 | 4·9% (3·4 to 6·4) | 308 (0·1%) | 1·80 (1·55 to 2·02), <0·0001 | 6·4% (3·5 to 9·2) |
| Term (39–41 weeks) | 87 223 (10·2%) | 1 (ref) | 0% | 12 874 (1·5%) | 1 (ref) | 0% | 2682 (0·3%) | 1 (ref) | 0% | 693 (0·08%) | 1 (ref) | 0% |
| Post-term (42–44 weeks) | 5519 (10·4%) | 1·02 (0·99 to 1·04), 0·257 | 0·08% (0·08 to 0·2) | 877 (1·7%) | 1·07 (1·00 to 1·15), 0·049 | 0·4% (–0·02 to 0·8) | 175 (0·3%) | 1·00 (0·86 to 1·17), 0·972 | –0·06% (–1·0 to 0·9) | 43 (0·08%) | 0·93 (0·68 to 1·27), 0·652 | –0·6% (–2·4 to 1·2) |
| **Norwegian data** | | | | | | | | | | | | |
| Preterm (23–36 weeks) | 11 827 (31·9%) | 1·38 (1·35 to 1·41), <0·0001 | 3·1% (2·9 to 3·3) | 3508 (9·5%) | 1·79 (1·73 to 1·86), <0·0001 | 6·6% (6·1 to 7·1) | 1207 (3·3%) | 2·46 (2·30 to 2·62), <0·0001 | 12·3% (11·1 to 13·4) | 461 (1·2%) | 3·21 (2·88 to 3·59), <0·0001 | 18·3% (15·9 to 20·6) |
| Term (39–41 weeks) | 91 702 (24·4%) | 1 (ref) | 0% | 19 476 (5·3%) | 1 (ref) | 0% | 4590 (1·2%) | 1 (ref) | 0% | 1257 (0·3%) | 1 (ref) | 0% |
| Extremely preterm (23–27 weeks) | 699 (54·8%) | 3·07 (2·85 to 3·30), <0·0001 | 0·5% (0·5 to 0·6) | 318 (24·9%) | 5·25 (4·69 to 5·86), <0·0001 | 1·3% (1·1 to 1·5) | 162 (12·7%) | 9·49 (8·10 to 11·12), <0·0001 | 3·0% (2·5 to 3·6) | 75 (5·9%) | 13·82 (10·89 to 17·52), <0·0001 | 5·2% (3·9 to 6·4) |
| Very preterm (28–31 weeks) | 1497 (38·6%) | 1·73 (1·65 to 1·83), <0·0001 | 0·7% (0·6 to 0·8) | 530 (13·7%) | 2·50 (2·29 to 2·73), <0·0001 | 1·6% (1·4 to 1·8) | 198 (5·1%) | 3·41 (2·95 to 3·94), <0·0001 | 2·9% (2·3 to 3·5) | 78 (2·0%) | 4·32 (3·42 to 5·47), <0·0001 | 4·4% (3·1 to 5·6) |
| Moderately preterm (32–33 weeks) | 1704 (32·8%) | 1·42 (1·36 to 1·49), <0·0001 | 0·5% (0·5 to 0·6) | 526 (10·1%) | 1·90 (1·74 to 2·07), <0·0001 | 1·2% (1·0 to 1·5) | 177 (3·4%) | 2·48 (2·13 to 2·89), <0·0001 | 2·2% (1·7 to 2·8) | 64 (1·2%) | 3·01 (2·34 to 3·88), <0·0001 | 3·2% (2·0 to 4·4) |
| Late preterm (34–36 weeks) | 7927 (29·7%) | 1·27 (1·24 to 1·30), <0·0001 | 1·7% (1·5 to 1·8) | 2134 (8·0%) | 1·52 (1·46 to 1·59), <0·0001 | 3·4% (2·9 to 3·8) | 670 (2·5%) | 1·98 (1·82 to 2·14), <0·0001 | 6·3% (5·3 to 7·2) | 244 (0·9%) | 2·53 (2·20 to 2·90), <0·0001 | 9·7% (7·7 to 11·7) |
| Early term (37–38 weeks) | 25 824 (26·2%) | 1·11 (1·10 to 1·13), <0·0001 | 1·4% (1·2 to 1·79 | 6223 (6·3%) | 1·25 (1·21 to 1·28), <0·0001 | 3·0% (2·4 to 3·6) | 1649 (1·7%) | 1·42 (1·34 to 1·50), <0·0001 | 4·3% (3·2 to 5·5) | 551 (0·6%) | 1·73 (1·56 to 1·91), <0·0001 | 7·0% (4·8 to 9·2) |
| Term (39–41 weeks) | 91 702 (24·4%) | 1 (ref) | 0% | 19 746 (5·3%) | 1 (ref) | 0% | 4590 (1·2%) | 1 (ref) | 0% | 1257 (0·3%) | 1 (ref) | 0% |
| Post-term (42–44 weeks) | 11 455 (25·9%) | 1·01 (0·99 to 1·03), 0·284 | 0·1% (–0·1 to 0·3) | 2558 (5·8%) | 1·01 (0·97 to 1·05), 0·732 | 0·06% (–0·04 to 0·05) | 639 (1·4%) | 1·05 (0·96 to 1·14), 0·271 | 0·5% (–0·5 to 1·5) | 190 (0·4%) | 1·11 (0·95 to 1·29), 0·180 | 1·2% (–0·8 to 3·1) |

HRs are adjusted for age, sex, year of birth, and Maršál gestational age-specific birthweight *Z* score. HR=hazard ratio. PAF=population attributable fraction.

***Table 3:*** **Associations of gestational age at birth with the number of health outcomes in adolescence**

| | Cases, n (%) | Model 1* | | Model 2† | | Model 3‡ | |
|---|---|---|---|---|---|---|---|
| | | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| **Finnish data (n=1 187 610)** | | | | | | | |
| Extremely preterm (23–27 weeks) | 292 (10·3%) | 3·75 (3·34–4·21) | <0·0001 | 3·37 (3·00–3·79) | <0·0001 | 3·37 (3·00–3·79) | <0·0001 |
| Very preterm (28–31 weeks) | 445 (7·1%) | 2·59 (2·36–2·84) | <0·0001 | 2·29 (2·08–2·52) | <0·0001 | 2·28 (2·08–2·51) | <0·0001 |
| Moderately preterm (32–33 weeks) | 437 (5·2%) | 1·90 (1·72–2·08) | <0·0001 | 1·72 (1·57–1·89) | <0·0001 | 1·70 (1·55–1·87) | <0·0001 |
| Late preterm (34–36 weeks) | 1854 (3·9%) | 1·37 (1·31–1·44) | <0·0001 | 1·33 (1·27–1·40) | <0·0001 | 1·31 (1·25–1·37) | <0·0001 |
| Early term (37–38 weeks) | 7042 (3·3%) | 1·16 (1·13–1·19) | <0·0001 | 1·16 (1·13–1·19) | <0·0001 | 1·15 (1·12–1·18) | <0·0001 |
| Term (39–41 weeks) | 24 542 (2·9%) | 1 (ref) | NA | 1 (ref) | NA | 1 (ref) | NA |
| Post-term (42–44 weeks) | 1684 (3·2%) | 1·13 (1·07–1·18) | <0·0001 | 1·10 (1·05–1·16) | <0·0001 | 1·10 (1·04–1·15) | <0·0001 |
| **Norwegian data (n=555 431)** | | | | | | | |
| Extremely preterm (23–27 weeks) | 276 (21·7%) | 3·40 (3·02–3·82) | <0·0001 | 3·19 (2·83–3·60) | <0·0001 | 3·13 (2·78–3·53) | <0·0001 |
| Very preterm (28–31 weeks) | 524 (13·5%) | 1·92 (1·76–2·10) | <0·0001 | 1·80 (1·65–1·96) | <0·0001 | 1·72 (1·58–1·88) | <0·0001 |
| Moderately preterm (32–33 weeks) | 556 (10·7%) | 1·52 (1·40–1·65) | <0·0001 | 1·45 (1·34–1·58) | <0·0001 | 1·40 (1·28–1·52) | <0·0001 |
| Late preterm (34–36 weeks) | 2549 (9·5%) | 1·33 (1·28–1·38) | <0·0001 | 1·31 (1·25–1·36) | <0·0001 | 1·26 (1·21–1·31) | <0·0001 |
| Early term (37–38 weeks) | 7805 (7·9%) | 1·12 (1·09–1·14) | <0·0001 | 1·11 (1·09–1·14) | <0·0001 | 1·09 (1·06–1·12) | <0·0001 |
| Term (39–41 weeks) | 27 835 (7·4%) | 1 (ref) | NA | 1 (ref) | NA | 1 (ref) | NA |
| Post-term (42–44 weeks) | 3605 (8·1%) | 1·01 (0·97–1·04) | 0·724 | 1·00 (0·97–1·04) | 0·935 | 1·01 (0·97–1·05) | 0·596 |

Physical–mental multimorbidity was defined as having a record of at least one mental disease or condition (a disease or condition with an ICD-10 code F00-F99) and at least one physical disease or condition (a disease or condition with an ICD-10 code C00-C97, D50-D89, E00-E90, H00-H99, I00-I99, J00-J99, K00-K93, L00-L99, M00-M99, N00-N99 or Q00-Q99). NA=not applicable. *Adjusted for age only. †Adjusted for age, sex, year of birth, and Maršál gestational age-specific birthweight *Z* score. ‡Adjusted for age, sex, year of birth, Maršál gestational age-specific birthweight *Z* score, mother's diabetes status during pregnancy, mother's hypertensive disorder during pregnancy, mother's smoking during pregnancy, mother's age, and mother's socioeconomic position at the time of birth.

***Table 4:*** **Associations of gestational age at birth with physical–mental multimorbidity in adolescence**

adaptations that increase an individual's susceptibility to cardiometabolic diseases in later life.[26] In our analyses, adjustment for mother's diabetes status and hypertensive disorder during pregnancy did not markedly change the association estimates, but it is possible that these measures do not sufficiently capture the characteristics of the intrauterine environment to allow detailed examination of the mechanism for the link between intrauterine conditions and offspring morbidity. Pregnancy disorders (eg, placental insufficiency leading to fetal growth restriction) can be seen as a part of the preterm complex and, with such a viewpoint, adjustment for these would lead to underestimating the association of preterm birth with subsequent health outcomes. Again, in our analyses the adjustment had little effect on the estimates, suggesting that potential overadjustment was negligible. Third, it is possible that perinatal or postnatal complications or health-care interventions that aim to prevent or manage premature birth could predispose preterm-born individuals to later disease. For example, oxygen deprivation during birth, maternal corticosteroid treatment, neonatal nutrition, or extended mechanical ventilation as a part of neonatal intensive care could contribute to the development of immune function abnormalities, cerebral palsy, metabolic disturbances, or respiratory conditions among individuals born prematurely.[3,27] Further possibilities include characteristics of preterm-born individuals (eg, comparatively high prevalence of intellectual disability) increasing the risks of other adverse health outcomes in this group (eg, via biological or behavioural pathways).[5,28]

The strengths and limitations of our investigation are those shared by studies based on routinely collected data. Records from more than 1·7 million people in Finland and Norway, with follow-up periods from birth to the age of 18 years, provided analytical power to precisely estimate associations across the full spectrum of gestational ages, including extremely prematurely born individuals, who are often underrepresented in research studies. We used pre-defined criteria to select health outcomes with the highest disease burden and most convincing evidence for a link with preterm birth for the analyses of multimorbidity. The nationwide data from multiple, linked registers captured near-complete information on all births and hospital care episodes in Finland and Norway (appendix p 4), which reduced the opportunity for selection or recall biases influencing our findings and increased the generalisability of the findings to the Nordic countries and other high-income settings. The absolute risks of the multimorbidity outcomes were higher in the Norwegian data than the Finnish data, reflecting differences between the two countries in the organisation of adolescent health care and the recording of administrative health-care data. The sharing of responsibilities between primary and secondary health care differs in Finland and Norway, with some diseases treated in primary care in Finland being treated in specialised health care in Norway. The Norwegian data also include a larger share of information on private

sector care than the Finnish data, as a proportion of specialised outpatient care in Norway is done by private specialist practices contracted by the public sector health authorities.[29] As Norwegian data come from a later time period than the Finnish data, it is also possible that improvements in the quality of register data, along with increasing diagnostic vigilance, could also influence the numbers of health outcomes recorded in the Norwegian Patient Register. Despite these differences, the relative risks of multimorbidity across the categories of gestational age were similar in the two countries' data, suggesting that the differences in the numbers of health outcomes are unrelated to preterm birth or gestational age and, consequently, unlikely to bias the estimated associations of these exposures with the multimorbidity outcomes.

Health outcomes ascertained from hospital care data do not include all cases of diseases and conditions typically diagnosed and managed in primary health care (eg, asthma or depression), and for these health outcomes our analyses were limited to the severe end of the disease spectrum, necessitating specialised care. Consequently, our analyses might have underestimated the incidence of some health outcomes. Unfortunately, good quality nationwide primary care data were not available for the time period covered in our analyses and we were unable to explore this further. It is also possible that adolescents with a preterm-born background have a lower threshold for seeking or being referred to specialised health care than those born at term; however, we believe this is unlikely to have a major effect in adolescence, as routine follow-up programmes, even for the earliest and smallest born children, end before the age of 4–5 years.[30,31] Incomplete data on mother's smoking or socioeconomic position in the analyses could have introduced error to the estimates adjusted for these covariates. Unfortunately, our register data sources did not include sufficiently rich data on predictors of mother's characteristics and we were thus unable to use multiple imputation to improve estimation. Our application of a data-driven HR cutoff point to a set of pre-defined health outcomes focuses our definition of multimorbidity to health outcomes robustly associated with preterm birth and the overall disease burden among adolescents. The exclusion of health outcomes that were less strongly associated with preterm birth means that our results might underestimate the multimorbidity burden associated with premature birth. Based on observational data, our findings do not lend themselves to a causal interpretation of the association between gestational age and adolescent multimorbidity, and should be treated as hypothesis-generating, rather than confirmatory. Yet, as it would be unethical to randomise people to be born prematurely or at a set gestational age, longitudinal studies using comprehensive population-wide register data, such as ours, provide the best available evidence on the association of preterm birth and gestational age with the risk of multimorbidity. As the individuals in our study were followed up from age 10 years onwards, the association estimates from our analyses must be interpreted as the estimated risks of adolescent multimorbidity among those who survived to age 10 years, rather than estimates of risks pertaining to all individuals born preterm. Finally, our findings could have been influenced by residual confounding from unknown or unmeasured confounders—eg, some health outcomes included in our analyses have a heritable component and adjustment for parents' diagnoses of these (eg, psychotic disorders) would have helped to explore the role of familial risks on some disease combinations. Also, as Finland and Norway have relatively homogeneous, predominantly White populations, and register sources do not contain data on ethnicity, we were unable to explore ethnic differences in our analyses.

Our findings could have implications for risk stratification, the development of care guidelines, and the management of multimorbidity in younger age groups. Although multimorbidity has been estimated to affect 10–29% of children and adolescents,[13,14] the paucity of evidence of the determinants of childhood and adolescent multimorbidity is a major gap in the clinical and public health evidence. Preterm birth is not an easy interventional target, as it has a heterogeneous aetiology (with known causes including multiple pregnancy, infections, and pregnancy disorders) and in many cases the cause is unknown.[32] Our findings, pointing to preterm birth as a risk factor or a risk marker for having multiple diseases in adolescence, suggest that a preterm-born background, a characteristic affecting 5–10% of people worldwide,[33,34] would present useful clinical information to include in the assessment and could be more widely used in the assessment and characterisation of multiple disease risk in primary care as well as hospital, school, and student health-care settings.

#### Contributors

All authors participated in critically reviewing the analyses and the report and interpreting the findings. KH generated the hypotheses and designed the study, with input from MK and EK. KH, SMN, JM, and AP participated in data acquisition and generated analytical datasets. KR and EK led on data acquisition and secured funding. KH, SMN, JM, AP, KR, and EK have directly accessed and verified the data. All authors take final responsibility for the decision to submit the report for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

Data protection laws preclude us from sharing the data used in this study. Access to the Finnish data can be requested from Finnish Social and Health Data Permit Authority Findata (info@findata.fi) and Statistics Finland (info@stat.fi). Access to the Norwegian data can be requested from the Norwegian Health Data service (www.helsedata.no). Analytical syntax is provided in the online appendix.

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