Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study

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Summary

Background Breakthroughs in the treatment of preterm birth approximately 40 years ago have enabled a generation of preterm survivors to now reach mid-adulthood. Understanding their health sequelae is essential for guiding their long-term care. We did a study to examine preterm birth in relation to mortality into mid-adulthood.

Methods A national cohort study was done of all 4 296 814 singleton livebirths in Sweden between 1973 and 2015, who were followed up for mortality through Dec 31, 2017 (maximum age 45 years). Cox regression was used to examine gestational age at birth in relation to all-cause and cause-specific mortality, and cosibling analyses assessed for potential confounding by shared familial (genetic or environmental) factors.

Findings In 103·5 million person-years of follow-up, 43 916 (1·0%) deaths were reported. Gestational age at birth was inversely associated with mortality from infancy to mid-adulthood. Relative to full-term birth (39–41 weeks), the adjusted hazard ratios for mortality associated with gestational age at birth were: 66·14 (95% CI 63·09–69·34) for extremely preterm (22–27 weeks), 8·67 (8·32–9·03) for very preterm (28–33 weeks), 2·61 (2·52–2·71) for late preterm (34–36 weeks), and 1·34 (1·30–1·37) for early term (37–38 weeks), from birth to age 45 years; and 2·04 (0·92–4·55) for extremely preterm, 1·48 (1·17–1·87) for very preterm, 1·22 (1·07–1·39) for late preterm, and 1·16 (1·08–1·25) for early term, at ages 30–45 years. Preterm birth accounted for more deaths among males than females (additive interaction p<0·001). Multiple underlying causes were identified, including congenital anomalies; respiratory, endocrine, cardiovascular, and neurological diseases; cancer; and external causes. Cosibling analyses suggested that the observed associations were not due to shared genetic or environmental factors in families.

Interpretation Preterm and early term birth should be recognised as chronic conditions that require long-term follow-up for adverse health sequelae in adulthood.

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Introduction

Preterm birth (gestational age <37 completed weeks) has a prevalence of 11% worldwide[1] and 10% in the USA,[2] and most preterm infants now survive into adulthood.[3–5] The biggest breakthroughs in preterm birth survival occurred with treatment advances in the 1970s and 1980s, including antenatal corticosteroids, surfactant therapy, and high-frequency ventilation.[6] As a result, the earliest generation of preterm infants who survived because of those advances have now reached their mid-40s. Preterm birth has been linked with increased mortality in childhood and young adulthood (ages 18–36 years).[4] However, no studies have examined long-term mortality into mid-adulthood. Clinicians will increasingly encounter adults of all ages who were born preterm, and will need to understand the long-term health sequelae to enable better prevention, detection, and treatment.

We did a national cohort study of more than 4 million births in Sweden to examine gestational age at birth in relation to all-cause and cause-specific mortality from infancy to age 45 years. This study advances previous knowledge by extending follow-up by nearly a decade, enabling assessment of mortality in the mid-adulthood period for the first time; examining sex-specific differences in associations between gestational age at birth and mortality; and using cosibling analyses to assess for potential confounding effects of shared genetic and environmental factors in families. Our overarching goal is to understand the long-term outcomes of preterm birth and help to improve care for these patients across the life course.

Methods

Study population

We identified 4 305 460 singleton livebirths in Sweden from 1973 to 2015, using the Swedish Birth Registry. This registry contains prenatal and birth information for nearly all births nationwide since 1973. We excluded 8646 (0·2%) births that had missing information for gestational age, leaving 4 296 814 births (99·8%) for inclusion in the study. This study was approved by the ethics committee of Lund University, Sweden.

For the **Swedish Birth Registry** see https://www.socialstyrelsen.se/register/halsodataregister/medicinskafodelseregistret/inenglish

Ascertainment of gestational age at birth and mortality

Gestational age at birth was identified from the Swedish Birth Registry based on maternal report of last menstrual

Research in context

Evidence before this study

Advances in the treatment of preterm birth, made approximately 40 years ago, have enabled a generation of preterm survivors to reach mid-adulthood. Understanding their health sequelae is essential for guiding their long-term care. We did a PubMed search without date or language restrictions for studies in human beings from Jan 1, 1985, to Dec 31, 2018, using the terms ("preterm birth" or "gestational age") and "mortality" and "adulthood" (or related alternatives). Preterm birth has previously been linked to increased mortality in infancy and early childhood, and young adulthood (ages 18–36 years); however, so far, no studies have examined long-term mortality into mid-adulthood (ages ≥40 years). Clinicians will increasingly encounter adults of all ages who were born preterm, and will need to understand the long-term health sequelae to enable better prevention, detection, and treatment of these sequelae across the life course.

Added value of this study

This study, to our knowledge, is the first to examine gestational age at birth in relation to mortality into mid-adulthood. In a national cohort of more than 4 million people, preterm birth was associated with increased mortality at all attained ages up to 45 years—the longest follow-up currently possible. These associations affected both males and females, and were independent of other sociodemographic factors, fetal growth, and shared genetic and environmental factors within families that were controlled for through the use of cosibling analyses. Late preterm (34–36 weeks) and early term (37–38 weeks) births also were linked to significantly increased mortality in adulthood relative to full-term births (39–41 weeks). Multiple underlying causes were identified, including congenital anomalies; respiratory, endocrine, cardiovascular, and neurological diseases; cancer; and external causes.

Implications of all the available evidence

Preterm birth should be recognised as a chronic condition that requires long-term follow-up for prevention, screening, and treatment of potential health sequelae into mid-adulthood. Medical records and history should routinely include gestational age at birth and other perinatal history to provide essential early-life context for understanding patients' health. Such information can help trigger preventive actions and anticipatory screening to reduce the risks of cardiometabolic and other chronic disorders across the life course among people born preterm.

period in the 1970s and ultrasound estimation starting in the 1980s and later. Gestational age was analysed alternatively as a continuous variable or categorical variable with six groups: extremely preterm (22–27 weeks), very preterm (28–33 weeks), late preterm (34–36 weeks), early term (37–38 weeks), full term (39–41 weeks, used as the reference group), and post term (≥42 weeks). These categories were chosen to facilitate comparisons with previous studies and to examine mortality for specific gestational age groups with sufficient power. Early-term birth (37–38 weeks) was examined as a separate category because it has previously been associated with increased mortality in young adulthood relative to later term birth (39–41 weeks).[5] In addition, the first three groups were combined to provide summary estimates for preterm birth (<37 weeks).

The study cohort was followed up for all deaths through Dec 31, 2017 (maximum age 45 years), identified using the Swedish Death Registry. This registry began in 1960 and includes all deaths in Sweden with compulsory reporting nationwide. Cause of death is classified according to the International Classification of Diseases (ICD), revisions 8, 9, and 10 (appendix).

For the **Swedish Death Registry** see http://www.socialstyrelsen.se/statistics/statisticaldatabase/help/causeofdeath

See Online for appendix

Other study variables

Other perinatal and demographic characteristics that might be associated with gestational age at birth and mortality were identified using the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number. Adjustment variables included birth year (continuous variable), sex, birth order (first, second, or third or later), maternal age at delivery (<20, 20–24, 25–29, 30–34, 35–39, or ≥40 years), maternal education level (≤9 years, 10–12 years, or >12 years), and maternal smoking at the beginning of prenatal care (zero, one to nine, or ten or more cigarettes per day). Missing data were infrequent for birth order (<0·1%), maternal age (<0·1%), and maternal education (0·7%), whereas 25·6% of mothers lacked smoking data. Missing data for each covariate were imputed using a standard multiple imputation procedure based on the variable's relationship with all other covariates and mortality, to produce standard errors that account for the uncertainty in imputations and support valid inferences.[7]

Statistical analysis

Cox proportional hazards regression was used to determine hazard ratios (HRs) and 95% CIs for associations between gestational age at birth and all-cause or cause-specific mortality from birth to age 45 years, and in narrower age ranges (birth to younger than 1 year, 1–9 years, 10–19 years, 20–29 years, and 30–45 years) among people still alive at the beginning of the respective age range. These age intervals were chosen to examine these associations in different stages of life from childhood into mid-adulthood. Attained age was used as the Cox model time axis. Individuals were censored at the date of emigration (n=260 079; 6·1%), determined by absence of a Swedish residential address in census data. Emigrants and non-emigrants had a similar gestational duration

(median 40·1 weeks for both groups), and thus it was unlikely that emigration introduced any substantial bias.

Analyses were done both unadjusted and adjusted for covariates (as above). In secondary analyses, we further adjusted for fetal growth (birthweight standardised for gestational age and sex based on Swedish reference growth curves[8]) to explore the effects of gestational age at birth on mortality independent of fetal growth. Cause-specific mortality was examined for all ICD categories with 500 or more total deaths to enable sufficient statistical power for each outcome. The proportional hazards assumption was assessed by examining log-log plots, and was met in each model (appendix).

Potential interactions between preterm or early term birth and sex in relation to mortality were examined on the additive and multiplicative scale. Additive interactions were tested by use of the relative excess risk due to interaction (RERI), a measure of departure from additivity of effects on a relative risk scale.[9] Multiplicative interactions were tested by use of the ratio of the HR for the effect of both factors considered together to the product of HRs for their effects considered separately.[9]

Cosibling analyses were done to assess for potential confounding effects of unmeasured shared familial (genetic or environmental) factors. Shared environmental factors in families might potentially include lifestyle factors such as diet, or ambient exposures such as passive smoking or air pollution. These analyses used stratified Cox regression with a separate stratum for each family as identified by the mother's anonymous identification number, so that comparisons are made among siblings that control for their shared exposures. 3 562 267 individuals (82·9% of the cohort) had at least one sibling and were included in these analyses. In the stratified Cox model, each set of siblings has its own baseline hazard function that reflects the family's shared genetic and environmental factors, and thus comparisons of different gestational ages at birth are made within the family. In addition, these analyses were further adjusted for the same covariates as in the main analyses.

Sensitivity analyses were done by repeating the main analyses after excluding deaths due to congenital anomalies and other perinatal conditions, or deaths from external causes (ie, unnatural causes, including accidents, homicides, and suicides). All statistical tests were two-sided and used an α of 0·05. All analyses were done using Stata, version 15.1.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Extremely preterm (22–27 weeks; 0·2%)	Very preterm (28–33 weeks; 1%)	Late preterm (34–36 weeks; 4%)	Early term (37–38 weeks; 18%)	Full term (39–41 weeks; 69%)	Post term (≥42 weeks; 8%)
Total	8426	44 567	159 307	756 442	2 973 708	354 364
Sex						
Male	4615 (54·8%)	24 895 (55·9%)	86 744 (54·4%)	389 108 (51·4%)	1 511 124 (50·8%)	193 175 (54·5%)
Female	3811 (45·2%)	19 672 (44·1%)	72 563 (45·6%)	367 334 (48·6%)	1 462 584 (49·2%)	161 189 (45·5%)
Birth order						
First	4199 (49·8%)	22 904 (51·4%)	78 932 (49·6%)	304 260 (40·2%)	1 253 685 (42·2%)	176 327 (49·8%)
Second	2396 (28·4%)	12 623 (28·3%)	47 822 (30·0%)	276 917 (36·6%)	1 115 055 (37·5%)	114 202 (32·2%)
Third or later	1831 (21·7%)	9040 (20·3%)	32 553 (20·4%)	175 265 (23·2%)	604 968 (20·3%)	63 835 (18·0%)
Maternal age (years)						
<20	362 (4·3%)	2084 (4·7%)	6502 (4·1%)	22 257 (2·9%)	84 747 (2·8%)	13 046 (3·7%)
20–24	1602 (19·0%)	9018 (20·2%)	33 546 (21·1%)	141 176 (18·7%)	590 497 (19·9%)	77 240 (21·8%)
25–29	2466 (29·3%)	13 791 (30·9%)	51 927 (32·6%)	248 325 (32·8%)	1 043 905 (35·1%)	123 872 (35·0%)
30–34	2290 (27·2%)	11 892 (26·7%)	42 119 (26·4%)	216 965 (28·7%)	847 481 (28·5%)	95 651 (27·0%)
35–39	1337 (15·9%)	6175 (13·9%)	20 438 (12·8%)	103 813 (13·7%)	343 929 (11·6%)	38 363 (10·8%)
≥40	369 (4·4%)	1607 (3·6%)	4775 (3·0%)	23 906 (3·2%)	63 149 (2·1%)	6192 (1·7%)
Maternal education (years)						
≤9	1439 (17·1%)	7405 (16·6%)	24 783 (15·6%)	106 638 (14·1%)	378 085 (12·7%)	49 769 (14·0%)
10–12	3977 (47·2%)	21 197 (47·6%)	75 084 (47·1%)	344 694 (45·6%)	1 331 927 (44·8%)	159 696 (45·1%)
>12	3010 (35·7%)	15 965 (35·8%)	59 440 (37·3%)	305 110 (40·3%)	1 263 696 (42·5%)	144 899 (40·9%)
Maternal smoking (cigarettes per day)						
0	6176 (73·3%)	31 563 (70·8%)	116 493 (73·1%)	580 120 (76·7%)	2 290 045 (77·0%)	255 160 (72·0%)
1–9	1751 (20·8%)	10 245 (23·0%)	33 795 (21·2%)	139 123 (18·4%)	570 028 (19·2%)	88 190 (24·9%)
≥10	499 (5·9%)	2759 (6·1%)	9019 (5·7%)	37 199 (4·9%)	113 385 (3·8%)	11 014 (3·1%)

Data are n (%).

Table 1: **Characteristics of study participants by gestational age at birth, Sweden, 1973–2015**

Results

The overall prevalence of preterm birth among singletons in Sweden from 1973 to 2015 was 4·9% (4·6% in the 1970s, 5·4% in the 1980s, 5·0% in the 1990s and 2000s, and 4·6% in the 2010s). Prevalences were 0·2% for extremely preterm, 1·0% for very preterm, 3·7% for late preterm, 17·6% for early term, 69·2% for full-term, and 8·3% for post-term births. Preterm infants were more likely than full-term infants to be male or first born, and their mothers were more likely to be at the extremes of age (ie, age <20 years or ≥40 years), have low education level (ie, <10 years), or smoke (table 1).

43 916 (1·0%) deaths occurred in 103·5 million person-years of follow-up, yielding an overall mortality rate of 42·42 per 100 000 person-years across the entire age range (birth to age 45 years). The corresponding mortality rates

	All (n= 4 296 814)				Males (n=2 209 661)				Females (n=2 087 153)			
	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value
Attained ages 0–45 years												
Preterm‡	10 392	172·79	5·01 (4·88–5·15)	<0·001	6197	188·78	4·44 (4·30–4·60)	<0·001	4195	153·31	6·14 (5·89–6·40)	<0·001
Extremely preterm§	2937	2119·13	66·14 (63·09–69·34)	<0·001	1697	2363·28	60·68 (57·06–64·54)	<0·001	1240	1852·61	76·36 (70·95–82·18)	<0·001
Very preterm¶	3734	298·12	8·67 (8·32–9·03)	<0·001	2251	323·90	7·67 (7·27–8·08)	<0·001	1483	265·85	10·70 (10·02–11·42)	<0·001
Late preterm‖	3721	89·93	2·61 (2·52–2·71)	<0·001	2249	99·75	2·35 (2·24–2·46)	<0·001	1472	78·00	3·13 (2·95–3·33)	<0·001
Early term**	7502	44·14	1·34 (1·30–1·37)	<0·001	4747	53·69	1·30 (1·26–1·35)	<0·001	2755	33·73	1·39 (1·33–1·46)	<0·001
Full term††	22 429	33·45	Ref	..	14 161	41·79	Ref	..	8268	24·82	Ref	..
Post term‡‡	3593	39·76	1·09 (1·06–1·14)	<0·001	2255	47·48	1·06 (1·02–1·11)	0·009	1388	31·08	1·16 (1·09–1·23)	<0·001
Per additional week	..	..	0·78 (0·78–0·78)	<0·001	..	..	0·79 (0·78–0·79)	<0·001	..	..	0·76 (0·76–0·77)	<0·001
Attained ages 0 to <1 year												
Preterm‡	8545	2840·39	17·15 (16·50–17·82)	<0·001	4989	3028·49	16·99 (16·14–17·88)	<0·001	3556	2613·72	17·35 (16·37–18·40)	<0·001
Extremely preterm§	2884	34 437·6	236·32 (223·81–249·54)	<0·001	1668	37 585·0	241·14 (224·40–259·13)	<0·001	1216	30 831·4	230·09 (211·71–250·07)	<0·001
Very preterm¶	3284	5235·20	32·10 (30·49–33·79)	<0·001	1969	5639·36	32·27 (30·17–34·51)	<0·001	1315	4729·20	31·80 (29·37–34·43)	<0·001
Late preterm‖	2377	1118·07	6·75 (6·39–7·13)	<0·001	1352	1155·39	6·47 (6·01–6·96)	<0·001	1025	1073·58	7·14 (6·57–7·76)	<0·001
Early term**	2840	309·65	1·95 (1·86–2·05)	<0·001	1616	337·15	1·95 (1·83–2·09)	<0·001	1224	280·54	1·95 (1·81–2·10)	<0·001
Full term††	5715	162·87	Ref	..	3120	175·52	Ref	..	2595	149·81	Ref	..
Post term‡‡	1012	227·37	1·25 (1·16–1·35)	<0·001	549	224·49	1·19 (1·07–1·31)	0·001	463	230·83	1·34 (1·20–1·49)	<0·001
Per additional week	..	..	0·69 (0·69–0·69)	<0·001	..	..	0·69 (0·68–0·69)	<0·001	..	..	0·69 (0·69–0·69)	<0·001
Attained ages 1–9 years												
Preterm‡	547	33·93	2·22 (2·03–2·44)	<0·001	314	35·65	2·08 (1·85–2·34)	<0·001	233	31·86	2·44 (2·12–2·80)	<0·001
Extremely preterm§	24	60·81	4·52 (3·02–6·75)	<0·001	14	67·17	4·52 (2·67–7·65)	<0·001	10	53·70	4·52 (2·42–8·41)	<0·001
Very preterm¶	160	49·38	3·26 (2·78–3·82)	<0·001	91	50·61	2·99 (2·42–3·69)	<0·001	69	47·85	3·67 (2·88–4·67)	<0·001
Late preterm‖	363	29·08	1·90 (1·70–2·11)	<0·001	209	30·73	1·78 (1·54–2·06)	<0·001	154	27·09	2·06 (1·75–2·44)	<0·001
Early term**	1049	17·63	1·20 (1·12–1·28)	<0·001	582	18·97	1·14 (1·04–1·25)	0·006	467	16·20	1·27 (1·15–1·42)	<0·001
Full term††	3481	14·84	Ref	..	1995	16·75	Ref	..	1486	12·87	Ref	..
Post term‡‡	505	17·74	1·10 (1·01–1·21)	0·04	273	17·73	1·00 (0·88–1·13)	0·96	232	17·77	1·27 (1·10–1·46)	0·001
Per additional week	..	..	0·90 (0·89–0·91)	<0·001	..	..	0·90 (0·89–0·92)	<0·001	..	..	0·90 (0·88–0·92)	<0·001
Attained ages 10–19 years												
Preterm‡	390	29·40	1·48 (1·34–1·65)	<0·001	249	34·28	1·44 (1·26–1·64)	<0·001	141	23·50	1·57 (1·32–1·87)	<0·001
Extremely preterm§	9	33·35	1·89 (0·98–3·63)	0·06	5	35·52	1·68 (0·70–4·04)	0·25	4	30·99	2·25 (0·84–6·00)	0·11
Very preterm¶	99	37·64	1·91 (1·56–2·33)	<0·001	60	41·24	1·74 (1·35–2·25)	<0·001	39	33·19	2·23 (1·62–3·07)	<0·001
Late preterm‖	282	27·21	1·37 (1·21–1·55)	<0·001	184	32·46	1·35 (1·17–1·57)	<0·001	98	20·87	1·39 (1·14–1·71)	0·001
Early term**	1006	21·05	1·10 (1·03–1·18)	0·007	650	26·16	1·12 (1·03–1·22)	0·01	356	15·52	1·06 (0·95–1·19)	0·30
Full term††	3702	19·22	Ref	..	2296	23·49	Ref	..	1406	14·83	Ref	..
Post term‡‡	507	20·55	1·00 (0·91–1·10)	0·93	315	24·06	0·98 (0·87–1·10)	0·73	192	16·59	1·05 (0·90–1·22)	0·51
Per additional week	..	..	0·95 (0·94–0·96)	<0·001	..	..	0·95 (0·93–0·96)	<0·001	..	..	0·95 (0·93–0·97)	<0·001

(Table 2 continues on next page)

	All				Males				Females			
	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value
(Continued from previous page)												
Attained ages 20–29 years												
Preterm‡	591	69·08	1·38 (1·26–1·50)	<0·001	437	92·41	1·32 (1·20–1·46)	<0·001	154	40·25	1·54 (1·31–1·82)	<0·001
Extremely preterm§	14	102·40	2·12 (1·26–3·59)	0·005	7	101·48	1·45 (0·69–3·03)	0·33	7	103·34	4·00 (1·90–8·41)	<0·001
Very preterm¶	120	72·30	1·42 (1·19–1·70)	<0·001	91	98·52	1·40 (1·13–1·72)	0·002	29	39·41	1·50 (1·04–2·17)	0·03
Late preterm‖	457	67·62	1·35 (1·23–1·48)	<0·001	339	90·73	1·30 (1·17–1·46)	<0·001	118	39·05	1·50 (1·24–1·81)	<0·001
Early term**	1682	55·70	1·15 (1·09–1·22)	<0·001	1257	78·75	1·15 (1·08–1·22)	<0·001	425	29·82	1·16 (1·04–1·30)	0·006
Full term††	5873	47·15	Ref	..	4315	67·93	Ref	..	1558	25·53	Ref	..
Post term‡‡	881	50·76	1·06 (0·98–1·14)	0·12	651	72·21	1·06 (0·97–1·15)	0·19	230	27·58	1·06 (0·92–1·22)	0·40
Per additional week	..	..	0·96 (0·95–0·97)	<0·001	..	..	0·97 (0·96–0·98)	<0·001	..	..	0·95 (0·93–0·97)	<0·001
Attained ages 30–45 years												
Preterm‡	319	80·90	1·28 (1·14–1·43)	<0·001	208	94·22	1·17 (1·01–1·34)	0·03	111	63·96	1·55 (1·28–1·89)	<0·001
Extremely preterm§	6	128·59	2·04 (0·92–4·55)	0·08	3	127·40	1·53 (0·49–4·75)	0·46	3	129·81	3·11 (1·00–9·65)	0·05
Very preterm¶	71	95·17	1·48 (1·17–1·87)	0·001	40	94·97	1·15 (0·84–1·57)	0·38	31	95·44	2·31 (1·61–3·29)	<0·001
Late preterm‖	242	76·82	1·22 (1·07–1·39)	0·003	165	93·60	1·17 (1·00–1·36)	0·05	77	55·49	1·35 (1·07–1·70)	0·01
Early term**	925	70·39	1·16 (1·08–1·25)	<0·001	642	89·59	1·15 (1·06–1·26)	0·001	283	47·36	1·18 (1·04–1·35)	0·01
Full term††	3658	58·94	Ref	..	2435	76·81	Ref	..	1223	40·28	Ref	..
Post term‡‡	688	62·47	1·04 (0·96–1·13)	0·34	467	83·92	1·07 (0·97–1·19)	0·16	221	40·56	0·98 (0·85–1·13)	0·76
Per additional week	..	..	0·97 (0·96–0·98)	<0·001	..	..	0·98 (0·97–1·00)	0·049	..	..	0·94 (0·92–0·97)	<0·001

HR=hazard ratio. *Mortality per 100 000 person-years. †Adjusted for birth year, sex, birth order, maternal age, maternal education, and maternal smoking. ‡Less than 37 weeks. §Less than 28 weeks. ¶28–33 weeks. ‖34–36 weeks. **37–38 weeks. ††39–41 weeks. ‡‡42 weeks or more.

***Table 2*: Adjusted HRs for all-cause mortality by gestational age at birth, Sweden, 1973–2017**

were 172·79 among those born preterm, 44·14 among those born at early term, and 33·45 among those born at full term (table 2).

In analyses of the entire age range, a significant inverse association was observed between gestational age at birth and mortality (adjusted HR per additional week of gestation 0·78, 95% CI 0·78–0·78; p<0·001). People born preterm had 5-fold increased risk of mortality and those born early term 1·3-fold increased risk of mortality, relative to those born at full term (adjusted HR 5·01, 95% CI 4·88–5·15; p<0·001; and 1·34, 1·30–1·37; p<0·001). These associations were present among both males and females, although the HRs were slightly higher among females because of a lower baseline mortality rate among girls born at full term (table 2).

In analyses of narrower age intervals, both preterm and early term births were significantly associated with increased mortality during infancy (adjusted HRs 17·15 [95% CI 16·50–17·82] and 1·95 [1·86–2·05], respectively). The HRs weakened, but remained significantly elevated in each subsequent age interval (table 2). At ages 30–45 years, the adjusted HRs for mortality associated with preterm and early term birth were 1·28 (95% CI 1·14–1·43; p<0·001) and 1·16 (1·08–1·25, p<0·001), respectively, relative to full-term birth. These associations remained significant among both males and females. The adjusted HRs (fitted by cubic spline) for all-cause mortality by attained age for different gestational age groups are shown in the figure. Compared with all adjusted results, unadjusted HRs were an average of approximately 5% higher (appendix). Kaplan-Meier survival curves by gestational age group are shown in the appendix.

Interactions between preterm or early term birth and sex in relation to all-cause mortality across the entire age range are shown in table 3. Males born preterm had the highest overall mortality rate, which was significantly higher relative to females born preterm (adjusted HR 1·22, 95% CI 1·17–1·28; p<0·001). A significant positive additive interaction was found between preterm birth and male sex (ie, the combined effect of these factors on mortality exceeded the sum of their separate effects; p<0·001), indicating that preterm birth accounted for significantly more total deaths among males. In adulthood (ages 20–45 years), there was a positive additive interaction between early term (but not preterm) birth and male sex in relation to mortality (p=0·01; appendix).

Cosibling analyses were done to control for shared genetic and environmental factors within families. In these analyses, we would expect the HRs observed in the main analyses to be reduced to one if they were completely confounded by shared familial factors. Instead, they were attenuated by an average of approximately 3%,

suggesting that the associations observed in the main analyses were not because of unmeasured familial confounding (appendix). In analyses of the entire age range, the adjusted HRs were minimally changed. At ages 30–45 years, the risk estimates were no longer significant and CIs were considerably wider than in the main analyses, reflecting lower statistical power in the cosibling analyses.

In secondary analyses, further adjustment for fetal growth had a negligible effect on all risk estimates. A significant inverse association remained between gestational age at birth and all-cause mortality (eg, adjusted HR per additional week of gestation 0·77, 95% CI 0·77–0·78; p<0·001 from birth to age 45 years; 0·96, 0·95–0·98; p<0·001 at ages 30–45 years), and a significant association for preterm relative to full-term births (adjusted HR 5·04, 95% CI 4·91–5·17; p<0·001 from birth to age 45 years; 1·30, 1·15–1·45; p<0·001 at ages 30–45 years).

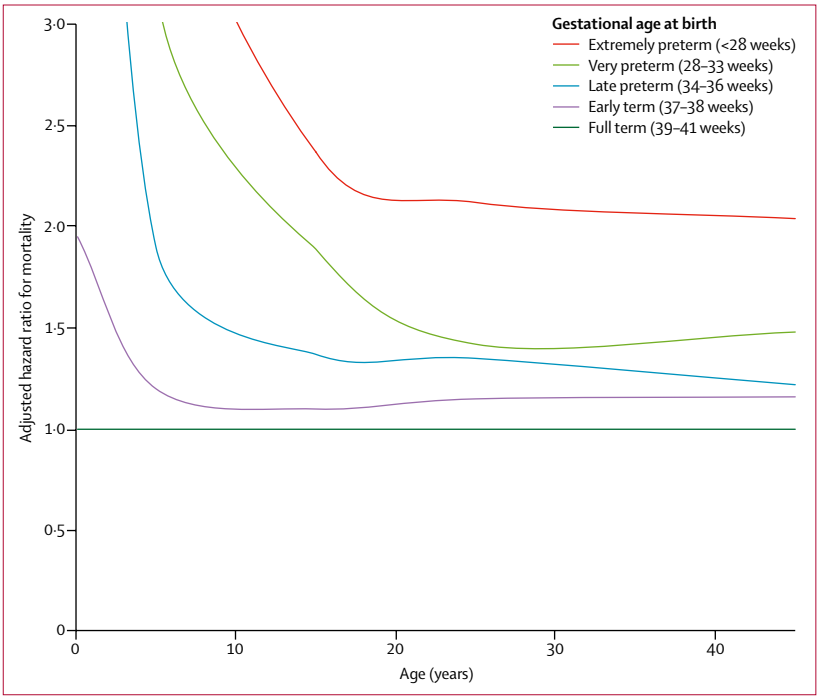

Figure: **Adjusted hazard ratios for all-cause mortality from birth to age 45 years by gestational age at birth relative to full-term births, Sweden, 1973–2017**

Associations between gestational age at birth (per additional week) and cause-specific mortality for ICD categories with 500 or more total deaths are shown in table 4. There were too few deaths attributed to kidney disease (n=59) to analyse this outcome separately with sufficient power. In analyses of the entire age range, gestational age at birth was inversely associated with all major causes of death examined in the entire cohort and among males or females. In infancy, the strongest associations were with mortality from respiratory disorders and other conditions specific to the perinatal period (eg, fetal haematological disorders or haemorrhage). However, associations with endocrine, cardiovascular, neurological, and cancer mortality also were present in infancy, childhood, and ages 20–29 years; and a significant association with endocrine mortality (mostly diabetes) extended further into adulthood (ages 30–45 years, both sexes adjusted HR per additional week of gestation 0·85, 95% CI 0·79–0·92; p<0·001).

In the main analyses (table 2), exclusion of deaths due to congenital anomalies or other perinatal conditions resulted in modest attenuation of the inverse association between gestational age at birth and mortality from birth to age 45 years (adjusted HR per additional week of gestation 0·86, 95% CI 0·85–0·86; p<0·001) and no change at ages 30–45 years (0·97, 0·96–0·98; p<0·001). Adjusted HRs comparing preterm to full-term births also remained significant (eg, 2·60, 2·51–2·70; p<0·001 from birth to age 45 years; 1·26, 1·12–1·41; p<0·001 at ages 30–45 years).

Exclusion of deaths due to external causes resulted in slightly stronger associations at all ages compared with the main analyses. Adjusted HRs per additional week of

	Full term (39–41 weeks)		Early term (37–38 weeks)		Preterm (<37 weeks)	
	Rate*	HR (95% CI)†	Rate*	HR (95% CI)†	Rate*	HR (95% CI)†
Sex						
Female	24·82	Ref	33·73	1·40 (1·34–1·46)‡	153·31	6·13 (5·88–6·40)‡
Early term *vs* full term	..	..	..	1·40 (1·34–1·46)‡	..	..
Preterm *vs* full term	..	..	..	..	..	6·13 (5·88–6·40)‡
Male	41·79	1·68 (1·64–1·73)‡	53·69	2·18 (2·10–2·27)‡	188·78	7·49 (7·22–7·77)‡
Early term *vs* full term	..	..	..	1·30 (1·25–1·34)‡	..	..
Preterm *vs* full term	..	..	..	..	..	4·45 (4·30–4·60)‡
Male *vs* female	..	1·68 (1·64–1·73)‡	..	1·56 (1·49–1·64)‡	..	1·22 (1·17–1·28)‡
Interaction on additive scale	..	..	..	0·10 (0·01–0·19)§¶	..	0·67 (0·36–0·98)§‡
Interaction on multiplicative scale	..	..	..	0·93 (0·88–0·98)‖	..	0·73 (0·69–0·76)‡

HR=hazard ratio. *Mortality per 100 000 person-years. †Adjusted for birth year, birth order, maternal age, maternal education, and maternal smoking. ‡p<0·001. §Data are relative excess risk due to interaction (95% CI). ¶p=0·03. ‖p=0·008.

Table 3: **Interactions between gestational age at birth and sex in relation to all-cause mortality at birth to age 45 years**

	All				Males				Females			
	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value
Attained ages 0–45 years												
Congenital anomalies	7922	6·75	0·75 (0·75–0·76)	<0·001	4298	7·01	0·75 (0·75–0·76)	<0·001	3624	6·47	0·76 (0·75–0·76)	<0·001
Other perinatal conditions	4886	3·22	0·60 (0·60–0·60)	<0·001	2850	3·68	0·60 (0·60–0·61)	<0·001	2036	2·74	0·60 (0·59–0·60)	<0·001
Respiratory diseases	2793	2·30	0·67 (0·66–0·67)	<0·001	1674	2·67	0·67 (0·66–0·68)	<0·001	1119	1·92	0·67 (0·66–0·68)	<0·001
Endocrine diseases	957	1·00	0·85 (0·83–0·87)	<0·001	555	1·14	0·85 (0·83–0·88)	<0·001	402	0·87	0·85 (0·81–0·88)	<0·001
Cardiovascular diseases	1571	1·65	0·86 (0·84–0·88)	<0·001	1014	2·08	0·86 (0·84–0·88)	<0·001	557	1·19	0·86 (0·83–0·89)	<0·001
Neurological diseases	1864	1·99	0·84 (0·83–0·86)	<0·001	1097	2·28	0·83 (0·82–0·85)	<0·001	767	1·68	0·86 (0·83–0·88)	<0·001
Cancer	4043	4·33	0·96 (0·94–0·97)	<0·001	2148	4·47	0·95 (0·93–0·97)	<0·001	1895	4·18	0·97 (0·95–0·99)	0·01
External causes	13 039	14·00	0·98 (0·97–0·98)	<0·001	9478	19·78	0·98 (0·97–0·99)	0·001	3561	7·88	0·96 (0·95–0·98)	<0·001
Other or unknown causes	6841	7·17	0·84 (0·83–0·84)	<0·001	4246	8·68	0·85 (0·84–0·86)	<0·001	2595	5·58	0·82 (0·81–0·83)	<0·001
Attained ages 0 to <1 year												
Congenital anomalies	6542	115·10	0·74 (0·74–0·75)	<0·001	3559	119·64	0·74 (0·73–0·75)	<0·001	2983	110·30	0·74 (0·73–0·75)	<0·001
Other perinatal conditions	4814	68·76	0·60 (0·59–0·60)	<0·001	2797	78·09	0·60 (0·59–0·60)	<0·001	2017	58·90	0·60 (0·59–0·60)	<0·001
Respiratory diseases	2198	36·35	0·64 (0·64–0·65)	<0·001	1316	42·01	0·64 (0·63–0·65)	<0·001	882	30·37	0·65 (0·64–0·65)	<0·001
Endocrine diseases	289	6·27	0·78 (0·76–0·81)	<0·001	166	7·09	0·79 (0·75–0·82)	<0·001	123	5·42	0·78 (0·74–0·82)	<0·001
Cardiovascular diseases	275	5·59	0·72 (0·70–0·74)	<0·001	149	5·94	0·71 (0·68–0·73)	<0·001	126	5·22	0·74 (0·71–0·77)	<0·001
Neurological diseases	544	12·55	0·77 (0·75–0·79)	<0·001	303	13·67	0·75 (0·73–0·77)	<0·001	241	11·36	0·80 (0·77–0·84)	<0·001
Cancer	198	4·25	0·77 (0·74–0·80)	<0·001	99	4·11	0·74 (0·70–0·77)	<0·001	99	4·40	0·82 (0·76–0·88)	<0·001
External causes	261	5·95	0·86 (0·82–0·90)	<0·001	137	6·03	0·89 (0·83–0·96)	0·002	124	5·85	0·82 (0·77–0·88)	<0·001
Other or unknown causes	2991	66·34	0·77 (0·76–0·78)	<0·001	1748	75·71	0·78 (0·77–0·79)	<0·001	1243	56·43	0·77 (0·75–0·78)	<0·001
Attained ages 1–9 years												
Congenital anomalies	912	2·69	0·83 (0·81–0·85)	<0·001	485	2·79	0·84 (0·81–0·87)	<0·001	427	2·59	0·82 (0·80–0·85)	<0·001
Other perinatal conditions	45	0·13	0·69 (0·65–0·73)	<0·001	29	0·17	0·69 (0·65–0·75)	<0·001	16	0·10	0·69 (0·63–0·76)	<0·001
Respiratory diseases	281	0·83	0·81 (0·78–0·85)	<0·001	155	0·89	0·83 (0·79–0·88)	<0·001	126	0·77	0·79 (0·75–0·84)	<0·001
Endocrine diseases	269	0·79	0·88 (0·84–0·92)	<0·001	135	0·78	0·88 (0·82–0·95)	<0·001	134	0·81	0·88 (0·81–0·94)	<0·001
Cardiovascular diseases	177	0·52	0·88 (0·83–0·94)	<0·001	94	0·54	0·85 (0·79–0·92)	<0·001	83	0·50	0·92 (0·83–1·02)	0·13
Neurological diseases	482	1·42	0·88 (0·85–0·92)	<0·001	267	1·53	0·87 (0·83–0·91)	<0·001	215	1·31	0·91 (0·85–0·97)	0·003
Cancer	1198	3·54	0·98 (0·95–1·01)	0·21	662	3·80	0·98 (0·94–1·02)	0·33	536	3·26	0·98 (0·94–1·03)	0·47
External causes	1509	4·46	0·99 (0·96–1·02)	0·47	943	5·42	0·99 (0·95–1·02)	0·46	566	3·44	1·00 (0·95–1·04)	0·87
Other or unknown causes	709	2·09	0·89 (0·86–0·92)	<0·001	394	2·26	0·89 (0·85–0·93)	<0·001	315	1·91	0·89 (0·84–0·93)	<0·001
Attained ages 10–19 years												
Congenital anomalies	255	0·92	0·84 (0·80–0·88)	<0·001	146	1·02	0·84 (0·79–0·90)	<0·001	109	0·80	0·84 (0·78–0·90)	<0·001
Other perinatal conditions	19	0·07	0·69 (0·62–0·76)	<0·001	18	0·13	0·68 (0·62–0·75)	<0·001	1	0·01	1·11 (0·32–3·91)	0·87
Respiratory diseases	108	0·39	0·86 (0·80–0·93)	<0·001	58	0·41	0·86 (0·78–0·96)	0·006	50	0·37	0·86 (0·76–0·96)	0·009
Endocrine diseases	128	0·46	0·98 (0·89–1·07)	0·59	77	0·54	0·95 (0·85–1·07)	0·39	51	0·38	1·01 (0·86–1·18)	0·89
Cardiovascular diseases	291	1·04	0·93 (0·88–0·98)	0·009	180	1·26	0·91 (0·85–0·98)	0·009	111	0·82	0·95 (0·87–1·05)	0·35
Neurological diseases	357	1·29	0·90 (0·85–0·94)	<0·001	209	1·46	0·91 (0·86–0·97)	0·003	148	1·10	0·87 (0·82–0·94)	<0·001
Cancer	834	2·99	0·98 (0·94–1·01)	0·18	496	3·47	0·95 (0·91–0·99)	0·02	338	2·50	1·03 (0·96–1·09)	0·43
External causes	3116	11·20	0·97 (0·96–0·99)	0·007	2057	14·40	0·98 (0·96–1·00)	0·05	1059	7·83	0·97 (0·94–1·00)	0·07
Other or unknown causes	497	1·78	0·93 (0·89–0·97)	0·001	269	1·88	0·94 (0·89–0·99)	0·04	228	1·68	0·92 (0·86–0·98)	0·01
Attained ages 20–29 years												
Congenital anomalies	143	0·79	0·86 (0·80–0·92)	<0·001	72	0·77	0·84 (0·77–0·92)	<0·001	71	0·81	0·88 (0·79–0·97)	0·01
Other perinatal conditions	5	0·03	0·75 (0·58–0·96)	0·02	4	0·04	0·69 (0·55–0·86)	0·001	1	0·01	3·54 (0·92–13·64)	0·07
Respiratory diseases	115	0·64	0·94 (0·86–1·03)	0·16	86	0·92	0·96 (0·86–1·07)	0·48	29	0·33	0·88 (0·75–1·03)	0·10
Endocrine diseases	158	0·88	0·92 (0·86–0·99)	0·04	97	1·04	0·94 (0·85–1·04)	0·24	61	0·70	0·89 (0·80–1·00)	0·06
Cardiovascular diseases	459	2·54	0·94 (0·90–0·98)	0·005	330	3·54	0·94 (0·89–0·99)	0·02	129	1·48	0·93 (0·86–1·02)	0·13
Neurological diseases	327	1·81	0·88 (0·84–0·93)	<0·001	228	2·45	0·89 (0·84–0·95)	<0·001	99	1·12	0·87 (0·79–0·94)	0·001
Cancer	814	4·51	0·96 (0·92–0·99)	0·02	448	4·81	0·96 (0·92–1·01)	0·11	366	4·19	0·95 (0·90–1·00)	0·07
External causes	5805	32·13	0·98 (0·97–0·99)	0·002	4538	48·67	0·98 (0·97–0·99)	0·01	1267	14·49	0·97 (0·94–1·00)	0·07
Other or unknown causes	1201	6·65	0·96 (0·93–0·99)	0·01	857	9·20	0·97 (0·94–1·01)	0·13	344	3·94	0·94 (0·89–0·99)	0·01

(Table 4 continues on next page)

	All				Males				Females			
	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value	Deaths	Rate*	HR (95% CI)†	p value
(Continued from previous page)												
Attained ages 30–45 years												
Congenital anomalies	70	0·78	0·86 (0·78–0·95)	0·003	36	0·77	0·89 (0·77–1·02)	0·10	34	0·78	0·84 (0·73–0·96)	0·01
Other perinatal conditions	3	0·03	0·57 (0·47–0·70)	<0·001	2	0·04	0·61 (0·47–0·79)	<0·001	1	0·02	0·57 (0·37–0·88)	0·01
Respiratory diseases	91	1·01	0·87 (0·80–0·95)	0·002	59	1·27	0·94 (0·83–1·06)	0·30	32	0·74	0·79 (0·70–0·89)	<0·001
Endocrine diseases	113	1·25	0·85 (0·79–0·92)	<0·001	80	1·72	0·84 (0·77–0·92)	<0·001	33	0·76	0·88 (0·75–1·02)	0·09
Cardiovascular diseases	369	4·09	0·97 (0·92–1·03)	0·33	261	5·60	0·99 (0·93–1·06)	0·77	108	2·48	0·94 (0·85–1·03)	0·18
Neurological diseases	154	1·71	1·02 (0·93–1·12)	0·63	90	1·93	1·05 (0·93–1·18)	0·43	64	1·47	0·98 (0·86–1·13)	0·82
Cancer	999	11·08	0·99 (0·95–1·02)	0·43	443	9·50	1·01 (0·96–1·06)	0·81	556	12·78	0·97 (0·93–1·01)	0·19
External causes	2348	26·04	0·99 (0·97–1·01)	0·29	1803	38·66	1·00 (0·98–1·03)	0·91	545	12·52	0·95 (0·91–0·99)	0·01
Other or unknown causes	1443	16·01	0·96 (0·93–0·98)	0·002	978	20·97	0·96 (0·93–0·99)	0·02	465	10·68	0·95 (0·90–0·99)	0·03

HR=hazard ratio. *Mortality per 100 000 person-years. †Adjusted for birth year, sex, birth order, maternal age, maternal education, and maternal smoking.

Table 4: **Associations between gestational age at birth (per additional week) and cause-specific mortality, Sweden, 1973–2017**

gestation were 0·74 (95% CI 0·74–0·74; p<0·001) from birth to age 45 years and 0·96 (0·94–0·97; p<0·001) at ages 30–45 years; and comparing preterm to full-term births were 7·69 (7·46–7·92; p<0·001) from birth to age 45 years and 1·34 (1·15–1·55; p<0·001) at ages 30–45 years.

Discussion

In this large national cohort study, low gestational age at birth was associated with increased mortality from infancy into mid-adulthood. This association appeared to be independent of sociodemographic factors, fetal growth, and shared genetic and environmental factors in families that were controlled for by use of cosibling analyses. Late preterm and early term births, which together composed more than 20% of all births, also were associated with significantly increased mortality in adulthood relative to full-term births.

To our knowledge, this is the first study to examine gestational age at birth in relation to mortality into mid-adulthood. In a smaller cohort, we previously found that preterm and early term births were associated with increased mortality in early childhood (up to age 5 years) and young adulthood (18–36 years), but by contrast with the present study, not in late childhood or adolescence (6–17 years).[3,5] This discrepancy in age-specific findings might have been because of insufficient statistical power in certain age intervals in the previous cohort. The present study extends those findings in a cohort that is more than six times larger, with nearly a decade of additional follow-up, and using cosibling analyses to search for potential confounding effects of shared familial factors. Another Swedish study[10] with a slightly smaller, overlapping cohort also reported associations between preterm birth and increased mortality up to age 36 years, and increased risks of psychiatric disorders. An Australian cohort study[11] of 722 399 births reported that low gestational ages were associated with non-significantly increased mortality at ages 6–30 years, but did not report mortality separately in adulthood. Because the earliest preterm survivors due to treatment advances in the 1970s and 1980s have now reached their mid-40s, the present study includes the longest follow-up currently possible in a large population-based cohort. We found that low gestational age at birth was linked with increased mortality at all attained ages up to 45 years, independent of both measured and unmeasured (familial) confounders. These associations affected both males and females, but accounted for significantly more deaths among males.

We found multiple underlying causes, including congenital anomalies; respiratory, endocrine, cardiovascular, and neurological diseases; cancer; and external causes. Although deaths from congenital anomalies and other perinatal conditions predominated in infancy and childhood, increased mortality from respiratory and endocrine disorders persisted into mid-adulthood. These findings are consistent with associations we previously reported between low gestational age at birth and various morbidities in a smaller cohort, including asthma,[12] diabetes,[13] thyroid disorders,[14] hypertension,[15] venous thromboembolism,[16] infections,[17] epilepsy,[18] and psychiatric disorders.[19] Other studies also have reported associations between preterm birth and increased risks of asthma and other pulmonary conditions,[20] type 2 diabetes,[21,22] hypertension,[23] metabolic syndrome,[24] and neurocognitive and psychiatric disorders[25] in adulthood. In the present study, gestational age at birth was inversely associated with mortality from cardiovascular disease or cancer at ages 20–29 years, but not 30–45 years. Additional follow-up will be needed to assess these outcomes at older ages in this or other large cohorts when such data become available.

Our findings provide further evidence for early-life origins of chronic disease. According to the developmental origins theory, alterations in the intrauterine and early postnatal environment might permanently alter

organ structure and metabolism, resulting in early-life programming for chronic disease later in life.[26] Developmental programming on the background of preterm birth might be particularly important. Preterm birth abruptly interrupts intrauterine growth and maturation of all fetal organs, with differential effects depending on the specific gestational age and critical growth periods for different organ systems, potentially leading to various chronic disorders and disabilities.[3] For example, preterm birth interrupts pulmonary alveolar development, which primarily occurs during the third trimester, resulting in morphologically immature lungs, reduced lung function, and increased respiratory symptoms that might persist into adulthood.[20] Prematurity might predispose to diabetes through multiple factors, including impaired function of pancreatic β cells, which are formed predominantly in the third trimester; exposure to antenatal corticosteroids; and rapid catch-up growth in infancy, which might contribute to visceral adiposity and insulin resistance.[21,22,24] Iatrogenic factors from intensive care, including suboptimal nutrition and adverse effects of medications or procedures, might further contribute to adverse long-term outcomes.[27]

Most adults who were born preterm remain healthy and report a high level of function and quality of life.[3,27,28] However, our findings show that increased long-term risks of various chronic disorders and mortality might also be expected. Preterm birth should be recognised as a chronic condition that requires long-term follow-up for prevention, screening, and treatment of potential health sequelae across the life course.[27,29,30] Physicians currently seldom seek birth histories from adult patients.[29,30] Medical records and initial history taking should routinely include gestational age at birth and other perinatal history to provide essential early-life context for understanding patients' health.[29,30] Such information can help trigger preventive actions and anticipatory screening to reduce the risks of cardiometabolic and other chronic disorders among people of all ages born preterm.[27,29,30]

A major strength of the present study was the ability to examine gestational age at birth in relation to mortality in a large national cohort with follow-up into mid-adulthood, using birth and death registry data that are nearly 100% complete. This study design minimises potential selection or ascertainment biases. The results were controlled for potential confounders, both measured and unmeasured using cosibling analyses.

Limitations included an absence of information on different types of preterm birth (eg, spontaneous or medically indicated), which was not systematically collected for earlier birth years and hence for individuals with sufficient follow-up into adulthood. Studies with more complete information on types of preterm birth are needed to further elucidate mechanisms and improve risk stratification for long-term outcomes. More detailed information on lifestyle risk factors (eg, smoking, poor diet, and obesity) or socioeconomic factors later in life would be useful to assess their potential modifying effects on mortality among people born prematurely. Because of ongoing changes in neonatal and paediatric care, it is unclear to what extent our findings will be generalisable to later cohorts. Studies of later birth cohorts and additional follow-up of existing cohorts to older ages will be needed when such data become available. Lastly, the present study was limited to Sweden. Studies in other geographical areas, including low-income and middle-income countries, are needed to assess long-term outcomes of preterm birth in other diverse populations.

In summary, we found that gestational age at birth is inversely associated with mortality from infancy to age 45 years in a large population-based cohort. Although mortality was highest for the earliest gestational ages, even late preterm and early term births were associated with significantly increased mortality into mid-adulthood. Preterm and early term birth should be recognised as chronic conditions that require long-term follow-up to facilitate prevention, timely detection, and treatment of adverse health sequelae in adulthood.

Contributors

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. CC drafted the Article. JS and KS acquired the data. CC, JS, and KS obtained funding. CC and JS did the statistical analysis. CC, JS, MAW, and KS contributed to study concept and design, analysed and interpreted data, and critically revised the Article.

Declaration of interests

We declare no competing interests.

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