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Association of Preterm Birth With Risk of Ischemic Heart Disease in Adulthood

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IMPORTANCE Preterm birth has previously been associated with increased risks of hypertension and diabetes, but not ischemic heart disease (IHD), in adulthood. The reasons for this lack of association with IHD despite associations with its risk factors have been elusive, but may be associated with methodologic issues, such as survivor bias, in prior studies.

OBJECTIVE To determine whether preterm birth is associated with an increased risk of IHD in adulthood in a large population-based cohort.

DESIGN, SETTING, AND PARTICIPANTS This national, population-based cohort study included all 2 141 709 persons who were born as singleton live births in Sweden during 1973 to 1994. The data were analyzed in September 2018.

EXPOSURES Gestational age at birth, identified from nationwide birth records in the Swedish Birth Registry.

MAIN OUTCOMES AND MEASURES Ischemic heart disease that was identified from nationwide inpatient and outpatient diagnoses through 2015 (maximum age, 43 years). A Cox regression was used to examine gestational age at birth in association with IHD in adulthood while adjusting for other perinatal and maternal factors. Cosibling analyses assessed for potential confounding by unmeasured shared familial factors.

RESULTS Of 2 141 709 participants, 1 041 906 (48.6%) were female and there were 1921 persons (0.09%) who received a diagnosis of IHD in 30.9 million person-years of follow-up. Gestational age at birth was inversely associated with IHD risk in adulthood. At ages 30 to 43 years, adjusted hazard ratios for IHD associated with preterm (gestational age <37 weeks) and early-term birth (37-38 weeks) were 1.53 (95% CI, 1.20-1.94) and 1.19 (1.01-1.40), respectively, compared with full-term birth (39-41 weeks). Preterm-born women had lower IHD incidence than preterm-born men (15.16 vs 22.00 per 100 000 person-years) but had a higher adjusted hazard ratio (1.93; 95% CI, 1.28-2.90 vs 1.37; 95% CI, 1.01-1.84). These associations did not appear to be explained by shared genetic or environmental factors in families.

CONCLUSIONS AND RELEVANCE In this large national cohort, preterm and early-term birth were associated with an increased IHD risk in adulthood. Persons born prematurely need early evaluation and preventive actions to reduce the risk of IHD.

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Supplemental content

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Preterm birth (gestational age, <37 completed weeks) has been linked with increased risks of cardiometabolic disorders in adulthood, including hypertension,[1,2] diabetes,[3-6] and metabolic syndrome,[7] which are major risk factors for ischemic heart disease (IHD).[8,9] However, most studies have failed to show an association between preterm birth and the risk of IHD.[10-13] Prior null findings may potentially be due to survivor bias in earlier birth cohorts or insufficient follow-up into adulthood when IHD is more likely to manifest.[14] Further elucidation of IHD risks in preterm survivors is important for informing the long-term care of these patients. Clinicians will increasingly encounter adult patients who were born preterm and thus will need to understand their long-term health risks.

We hypothesized that preterm birth is associated with an increased risk of IHD in adulthood. To test this hypothesis, we conducted a large national cohort study of more than 2 million persons in Sweden. The goals of this study were to examine associations between gestational age at birth and IHD risk up to age 43 years, the maximum follow-up currently possible in this large cohort, to assess whether these associations differ according to sex or fetal growth and explore for potential confounding by shared familial (genetic and/or environmental) factors using cosibling analyses. Because the most substantial breakthroughs in neonatal care occurred approximately 40 years ago,[15] this study has the longest follow-up currently possible for a population-based cohort that would have received such care.

Key Points

Question Is preterm birth associated with an increased risk of ischemic heart disease (IHD) in adulthood?

Findings In this population-based cohort study of 2.1 million persons, preterm birth (gestational age <37 weeks) and early-term birth (37-38 weeks) were associated with 53% and 19% increased relative risks of IHD at ages 30 to 43 years, respectively, compared with full-term birth (39-41 weeks); these were significant increases.

Meaning Persons born prematurely need long-term follow-up and early preventive actions to reduce the risk of IHD in adulthood.

Methods

Study Population

The Swedish Birth Registry contains prenatal and birth information for nearly all births nationwide since 1973.[16] Using this registry, we identified all 2 242 967 singleton live births in Sweden during 1973 to 1994. These birth years were chosen to allow sufficient follow-up into adulthood. Of this total, 2 148 356 persons (95.8%) were still living in Sweden without a prior diagnosis of IHD at age 18 years. We excluded 6647 (0.3%) who had missing information for gestational age, leaving 2 141 709 persons (95.5% of the original cohort) for inclusion in the study. This study was approved by the ethics committee of Lund University in Sweden, and informed consent was waived because the study included only deidentified secondary data.

Ascertainment of Gestational Age at Birth and IHD

Gestational age at birth was identified from the Swedish Birth Registry based on maternal report of last menstrual period in the 1970s and ultrasonography estimation from the 1980s onward. This was analyzed alternatively as a continuous variable or categorical variable with 5 groups: early preterm (<34 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). In addition, the first 2 groups were combined to provide summary estimates for preterm birth (<37 weeks). Early-term birth (37-38 weeks) was examined as a separate category because it has previously been associated with increased cardiovascular mortality in young adulthood compared with later-term birth.[17] There were too few adults born extremely preterm (<28 weeks) and an insufficient number of IHD cases to allow for a separate analysis of this group.

The study cohort was followed up for the earliest diagnosis of IHD through 2015 (maximum age 43 years). Ischemic heart disease was identified using *International Classification of Diseases* (*ICD*) codes from all primary and secondary diagnoses in the Swedish Hospital and Outpatient Registries and all deaths attributed to IHD in the Swedish Death Registry (codes 410-414 in *ICD-8/9*, and I20-I25 in *ICD-10*). The Swedish Hospital Registry contains all primary and secondary hospital discharge diagnoses from 6 populous counties in southern Sweden starting in 1964 and with nationwide coverage starting in 1987; these diagnoses are currently more than 99% complete and their positive predictive value for IHD has been reported to be 98%.[18,19] The Swedish Outpatient Registry contains all outpatient diagnoses from specialty clinics nationwide starting in 2001. The Swedish Death Registry includes all deaths and causes of death for all persons registered in Sweden since 1960, with compulsory reporting nationwide.

Other Study Variables

Other perinatal and maternal characteristics that may be associated with gestational age at birth and IHD were identified using the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number. The following were included as adjustment variables: birth year (continuous), sex, fetal growth (continuous, defined as number of SD from the mean birth weight for gestational age and sex based on Swedish reference intrauterine growth curves[20]), birth order (1, 2, and ≥3; included because extremes of birth order have been associated with preterm birth and potentially with IHD risk[21,22]), congenital anomalies (yes/no, identified using codes 740-759 in *ICD-8/9* and Q00-Q99 in *ICD-10*; included because of prior associations with preterm birth and IHD risk[22,23]), maternal age at delivery (continuous; included because extremes of maternal age have been associated with preterm birth and potentially with IHD risk[21,22]), maternal education level (≤9, 10-12, and >12 years), maternal birth country or region (Sweden, other Europe/United States/Canada, Asia/Oceania, Africa, Latin America, and Other/unknown), maternal body mass index (calculated as weight in kilograms divided by height in meters squared; continuous), maternal smoking (0, 1-9, and ≥10 cigarettes/d),

preeclampsia (codes 637 in *ICD-8*; 624.4-624.7 in *ICD-9*; and O14-O15 in *ICD-10*), other hypertensive disorders during pregnancy (ie, chronic or gestational hypertension without preeclampsia: codes 400-404 in *ICD-8*; 401-405, 642.0-642.3, 642.9 in *ICD-9*; and I10-I15, O10-O11, O13, and O16 in *ICD-10*), and diabetes during pregnancy (ie, pregestational type 1 or type 2 or gestational diabetes: codes 250 in *ICD-8*; 250, 648.0 in *ICD-9*; and E10-E14 and O24 in *ICD-10*). A summary of the *ICD* codes and diagnoses included in the analyses is provided in eTable 1 in the Supplement.

Maternal body mass index and smoking were assessed at the beginning of prenatal care starting in 1982 and were available for 786 007 (36.7%) and 1 188 649 (55.5%) women, respectively. Data were more than 99% complete for all other variables. Missing data for each covariate were imputed using a standard multiple imputation procedure based on the variable's association with all other covariates and IHD.[24]

Statistical Analysis

Cox proportional hazards regressions were used to compute hazard ratios (HRs) and 95% confidence intervals for associations between gestational age at birth and incident IHD at ages 18 to 43 years and in narrower age ranges (18-29 years and 30-43 years) among persons still alive and without a prior diagnosis of IHD at the beginning of the respective age range. These age intervals were chosen to examine these associations in different stages of early to mid adulthood. The attained age was used as the Cox model time axis. Individuals were censored at death as identified in the Swedish Death Registry (16 263 [0.8%]) or emigration as determined by the absence of a Swedish residential address in census data (131 702 [6.1%]). Analyses were conducted with and without adjustment for covariates (as previously described). The proportional hazards assumption was assessed by examining log-log plots[25] and was met in each model.

Cosibling analyses were performed to assess for potential confounding effects of unmeasured shared familial (genetic and/or environmental) factors. These analyses used a stratified Cox regression with a separate stratum for each family as identified by the mother's anonymous identification number. A total of 1 797 058 individuals (83.9%) had at least 1 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.

The potential interactions between preterm or early-term birth and sex, fetal growth, or mode of delivery (vaginal or Cesarean delivery) were examined in association with IHD risk on the additive and multiplicative scale.[26,27] All statistical tests were 2-sided and used an α level of .05. All analyses were conducted using Stata, version 15.1 (StataCorp).

Results

Table 1 shows perinatal and maternal characteristics by gestational age at birth. Preterm infants were more likely than full-term infants to be male or first born or have congenital anomalies; their mothers were more likely to be at the extremes of age, have a low education level, smoke, or have preeclampsia, other hypertensive disorders, or diabetes during their pregnancy.

Associations Between Gestational Age at Birth and IHD

At ages 18 to 43 years, 1921 persons (0.09%) received a diagnosis of IHD in 30.9 million person-years of follow-up, yielding an overall IHD incidence rate of 6.21 per 100 000 person-years. The corresponding incidence rates were 8.79 among those born preterm, 6.48 among those born at early term, and 5.85 among those born full term (**Table 2**).

Across the entire age range examined (18-43 years), gestational age at birth was inversely associated with IHD risk (adjusted HR per additional week of gestation, 0.96; 95% CI, 0.93-0.98; Table 2). Adjusted HRs for those born preterm or early-term were 1.44 (95% CI, 1.19-1.73) and 1.16 (95% CI, 1.02-1.31), respectively, compared with those born full term. The association between preterm birth and IHD was driven by an increased risk among persons born late preterm (34-36 weeks). No association was detected among those born at gestational ages earlier than 34 weeks, but this was based on only 17 IHD cases in 21 748 persons (1.0%), resulting in a wide confidence interval (Table 2). Unadjusted HRs were approximately 5% higher compared with adjusted HRs (Table 2; eTable 2 in the Supplement).

Preterm birth and male sex had a negative multiplicative interaction in association with IHD risk (ie, their combined effect was less than the product of their separate effects; eTable 3 in the Supplement). However, there was no additive interaction (eTable 3 in the Supplement), suggesting that preterm birth accounted for a similar number of IHD cases among men and women.

In sex-stratified analyses, preterm birth was associated with a significantly increased relative risk of IHD among women but not men (Table 2). The background IHD incidence rate among persons born full term was nearly twice as high among men than women. Although preterm-born men had the highest IHD incidence (9.69 per 100 000 person-years), the relative hazards were higher among preterm-born women.

In analyses of narrower age intervals, there was no significant linear association between gestational age at birth and IHD risk at ages 18 to 29 years. Preterm birth was associated with increased risk among women (adjusted HR, 1.78; 95% CI, 1.15-2.76) but not men (1.10; 95% CI, 0.75-1.61). At ages 30 to 43 years, low gestational age at birth was more strongly associated with IHD risk compared with earlier adulthood, including a strong inverse linear trend (adjusted HR per additional week, 0.95; 95% CI, 0.92-0.98). Preterm and early-term birth were associated with 53% and 19% increased risks of IHD, respectively, compared with full-term birth (adjusted HRs, 1.53; 95% CI 1.20-1.94 and 1.19; 95% CI, 1.01-1.40).

Sex-stratified results at ages 30 to 43 years showed higher HRs among women than men, similar to findings for the entire age range (Table 2). Men who were born preterm had the highest IHD incidence rate (22.00 per 100 000 person-years vs 15.16 for women). However, they had lower adjusted HRs

Table 1. Characteristics of Study Participants by Gestational Age at Birth in Sweden From 1973 to 1994

Characteristic	No. (%)				
	Early Preterm (<34 wk) (n = 21 748)	Late Preterm (34-36 wk) (n = 80 240)	Early-Term (37-38 wk) (n = 361 132)	Full-Term (39-41 wk) (n = 1 479 457)	Postterm (≥42 wk) (n = 199 132)
Child Characteristics					
Sex					
Male	11 937 (54.9)	44 065 (54.9)	189 368 (52.4)	750 754 (50.7)	103 679 (52.1)
Female	9811 (45.1)	36 175 (45.1)	171 764 (47.6)	728 703 (49.3)	95 453 (47.9)
Fetal growth[a]					
>1 SD below mean	3322 (15.3)	10 976 (13.7)	40 470 (11.2)	221 399 (15.0)	57 636 (28.9)
−1 to 1 SD from mean	16 825 (77.4)	58 828 (73.3)	260 689 (72.2)	1 042 526 (70.5)	123 005 (61.8)
>1 SD more than mean	1601 (7.4)	10 436 (13.0)	59 973 (16.6)	215 532 (14.6)	18 491 (9.3)
Birth order					
1	10 896 (50.1)	38 762 (48.3)	143 759 (39.8)	606 062 (41.0)	95 725 (48.1)
2	6150 (28.3)	24 060 (30.0)	131 049 (36.3)	557 077 (37.6)	66 378 (33.3)
≥3	4702 (21.6)	17 418 (21.7)	86 324 (23.9)	316 318 (21.4)	37 029 (18.6)
Congenital anomalies	80 (0.4)	297 (0.4)	805 (0.2)	1721 (0.1)	303 (0.2)
Death during follow-up	234 (1.1)	787 (1.0)	2895 (0.8)	10 629 (0.7)	1718 (0.9)
Emigration during follow-up	1003 (4.6)	4460 (5.6)	20 842 (5.8)	92 082 (6.2)	13 315 (6.7)
Maternal Characteristics					
Age, y					
<20	1396 (6.4)	4518 (5.6)	14 674 (4.1)	58 011 (3.9)	10 345 (5.2)
20-24	5535 (25.5)	20 867 (26.0)	86 225 (23.9)	376 336 (25.4)	56 203 (28.2)
25-29	6861 (31.6)	27 281 (34.0)	128 656 (35.6)	563 933 (38.1)	75 307 (37.8)
30-34	4989 (22.9)	17 853 (22.3)	87 648 (24.3)	345 432 (23.4)	42 222 (21.2)
35-39	2393 (11.0)	7952 (9.9)	36 043 (10.0)	116 842 (7.9)	13 088 (6.6)
≥40	574 (2.6)	1769 (2.2)	7886 (2.2)	18 903 (1.3)	1967 (1.0)
Education, y					
≤9	4221 (19.4)	14 654 (18.3)	59 650 (16.5)	220 756 (14.9)	32 723 (16.4)
10-12	11 310 (52.0)	41 120 (51.2)	181 009 (50.1)	737 256 (49.8)	98 740 (49.6)
>12	6217 (28.6)	24 466 (30.5)	120 473 (33.4)	521 445 (35.3)	67 669 (34.0)
Birth country or region					
Sweden	18 862 (86.7)	70 494 (87.8)	316 289 (87.6)	1 323 231 (89.4)	179 612 (90.2)
Other Europe/United States/Canada	1964 (9.0)	6626 (8.3)	28 917 (8.0)	108 667 (7.4)	14 311 (7.2)
Asia/Oceania	601 (2.8)	2122 (2.6)	11 100 (3.1)	31 913 (2.2)	3193 (1.6)
Africa	122 (0.6)	382 (0.5)	1726 (0.5)	6219 (0.4)	988 (0.5)
Latin America	112 (0.5)	438 (0.6)	2478 (0.7)	7258 (0.5)	718 (0.4)
Other/unknown	87 (0.4)	178 (0.2)	622 (0.2)	2169 (0.1)	310 (0.2)
Body mass index[b]					
<18.5	501 (2.3)	2564 (3.2)	11 434 (3.2)	34 620 (2.3)	2625 (1.3)
18.5-24.9	19 922 (91.6)	72 157 (89.9)	322 770 (89.4)	1 342 188 (90.7)	183 958 (92.4)
25.0-29.9	994 (4.6)	4267 (5.3)	21 497 (5.9)	83 058 (5.6)	9909 (5.0)
≥30.0	331 (1.5)	1252 (1.6)	5431 (1.5)	19 591 (1.3)	2640 (1.3)
Smoking, cigarettes/d					
0	12 683 (58.3)	48 168 (60.0)	229 370 (63.5)	940 845 (63.6)	116 006 (58.3)
1-9	7163 (32.9)	25 978 (32.4)	106 921 (29.6)	460 344 (31.1)	75 440 (37.9)
≥10	1902 (8.8)	6094 (7.6)	24 841 (6.9)	78 268 (5.3)	7686 (3.9)
Preeclampsia	3123 (14.4)	7978 (9.9)	22 988 (6.4)	66 241 (4.5)	9491 (4.8)
Other hypertensive disorders	297 (1.4)	824 (1.0)	3032 (0.8)	8295 (0.6)	806 (0.4)
Diabetes	198 (0.9)	933 (1.2)	2585 (0.7)	2874 (0.2)	141 (0.1)

[a] Fetal growth was defined as number of SDs from mean birth weight for gestational age and sex based on Swedish reference intrauterine growth curves.

[b] Calculated as weight in kilograms divided by height in meters squared.

than women (1.37; 95% CI 1.01-1.84 vs 1.93; 95% CI, 1.28-2.90). The background IHD incidence in men born full term was more than twice that for women born full term (15.91 vs 7.64 per 100 000 person-years). The **Figure** shows adjusted HRs and 95% confidence intervals (fitted by cubic spline) for IHD risk by attained age for different gestational age groups. Nelson-

Table 2. Associations Between Gestational Age at Birth and Risk of IHD in Sweden From 1973 to 2015

Characteristic	All				Men[a]			Women[a]		
	No. of Cases	Rate[b]	HR (95% CI) Unadjusted	Adjusted[c]	No. of Cases	Rate[b]	Adjusted,[c] HR (95% CI)	No. of Cases	Rate[b]	Adjusted,[c] HR (95% CI)
Attained ages 18-43 y										
Preterm (<37 wk)	126	8.79	1.55 (1.29-1.87)	1.44 (1.19-1.73)	77	9.69	1.25 (0.99-1.58)	49	7.67	1.86 (1.38-2.51)
Early preterm (<34 wk)	17	5.71	1.02 (0.63-1.65)	0.93 (0.58-1.51)	9	5.45	0.70 (0.36-1.36)	8	6.03	1.47 (0.73-2.97)
Late preterm (34-36 wk)	109	9.60	1.69 (1.39-2.06)	1.57 (1.29-1.91)	68	10.80	1.40 (1.09-1.79)	41	8.10	1.96 (1.42-2.71)
Early term (37-38 wk)	323	6.48	1.17 (1.04-1.33)	1.16 (1.02-1.31)	221	8.32	1.15 (0.99-1.33)	102	4.38	1.17 (0.94-1.46)
Full term (39-41 wk)	1247	5.85	1 [Reference]	1 [Reference]	830	7.64	1 [Reference]	417	3.99	1 [Reference]
Postterm (≥42 wk)	225	7.04	1.09 (0.94-1.26)	0.98 (0.85-1.13)	157	9.55	1.02 (0.86-1.22)	68	4.38	0.90 (0.70-1.17)
Per additional week (trend)			0.96 (0.94-0.98)	0.96 (0.93-0.98)			0.97 (0.94-1.00)			0.93 (0.90-0.97)
Attained ages 18-29 y										
Preterm (<37 wk)	52	4.98	1.46 (1.09-1.94)	1.32 (0.99-1.76)	29	5.03	1.10 (0.75-1.61)	23	4.92	1.78 (1.15-2.76)
Early preterm (<34 wk)	5	2.28	0.67 (0.28-1.61)	0.59 (0.25-1.43)	3	2.48	0.53 (0.17-1.65)	2	2.04	0.72 (0.18-2.91)
Late preterm (34-36 wk)	47	5.70	1.66 (1.23-2.24)	1.52 (1.13-2.05)	26	5.71	1.25 (0.84-1.87)	21	5.69	2.07 (1.31-3.26)
Early term (37-38 wk)	142	3.85	1.13 (0.94-1.35)	1.12 (0.93-1.35)	100	5.14	1.20 (0.96-1.51)	42	2.42	0.95 (0.68-1.33)
Full term (39-41 wk)	520	3.42	1 [Reference]	1 [Reference]	332	4.29	1 [Reference]	188	2.52	1 [Reference]
Postterm (≥42 wk)	79	3.74	1.08 (0.85-1.37)	0.96 (0.75-1.22)	54	4.92	1.00 (0.75-1.34)	25	2.46	0.88 (0.58-1.34)
Per additional week (trend)			0.97 (0.94-1.01)	0.97 (0.93-1.01)			0.97 (0.93-1.02)			0.96 (0.90-1.03)
Attained ages 30-43 y										
Preterm (<37 wk)	74	18.99	1.63 (1.28-2.07)	1.53 (1.20-1.94)	48	22.00	1.37 (1.01-1.84)	26	15.16	1.93 (1.28-2.90)
Early preterm (<34 wk)	12	15.31	1.31 (0.74-2.33)	1.22 (0.69-2.16)	6	13.64	0.84 (0.37-1.89)	6	17.44	2.23 (0.99-5.01)
Late preterm (34-36 wk)	62	19.92	1.71 (1.32-2.22)	1.60 (1.24-2.08)	42	24.12	1.50 (1.09-2.06)	20	14.59	1.85 (1.17-2.93)
Early term (37-38 wk)	181	13.92	1.21 (1.03-1.42)	1.19 (1.01-1.40)	121	17.08	1.11 (0.91-1.36)	60	10.15	1.39 (1.05-1.85)
Full term (39-41 wk)	727	11.86	1 [Reference]	1 [Reference]	498	15.91	1 [Reference]	229	7.64	1 [Reference]
Postterm (≥42 wk)	146	13.46	1.10 (0.92-1.31)	1.00 (0.83-1.20)	103	18.79	1.04 (0.83-1.29)	43	8.01	0.92 (0.67-1.29)
Per additional week (trend)			0.95 (0.92-0.98)	0.95 (0.92-0.98)			0.97 (0.93-1.00)			0.91 (0.86-0.96)

Abbreviations: HR, hazard ratio; IHD, ischemic heart disease.

[a] Wald tests for interaction between preterm birth and sex in association with IHD risk: additive scale, $P = .30$; multiplicative scale, $P = .008$ (see eTable 3 in the Supplement for more complete interaction results).

[b] Ischemic heart disease incidence rate per 100 000 person-years.

[c] Adjusted for child characteristics (birth year, sex, fetal growth, birth order, and congenital anomalies) and maternal characteristics (age, education, birth country or region, body mass index [calculated as weight in kilograms divided by height in meters squared], smoking, preeclampsia, other hypertensive disorders, and diabetes).

Aalen cumulative hazard functions by gestational age group are shown in the eFigure in the Supplement.

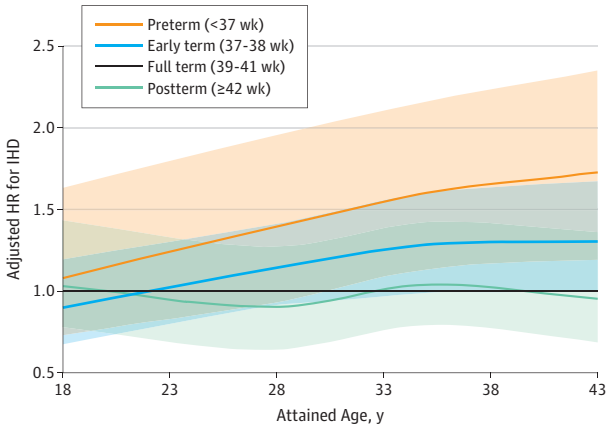
Cosibling Analyses

Cosibling analyses were performed to control for unmeasured shared familial factors among individuals who had at least 1 sibling (1 797 058 [83.9%]). These analyses can help elucidate whether the associations observed in the main analyses were due to direct effects of preterm birth as opposed to shared genetic and/or environmental factors that may predispose to preterm birth and IHD. These analyses resulted in only a modest attenuation of most risk estimates (**Table 3**). For example, in the entire age range examined (18-43 years), the adjusted HR for IHD associated with preterm birth was 1.44 in the main analysis and 1.35 in the cosibling analysis. When modeled as a continuous variable, gestational age at birth was slightly more strongly inversely associated with IHD risk in the cosibling analysis and remained statistically significant (HR per additional week, 0.94; 95% CI, 0.88-0.99) compared with the main analysis (0.96; 95% CI, 0.93-0.98). All confidence intervals were wider in the cosibling analyses, reflecting lower statistical power than in the main analyses. These findings suggest that the associations between preterm birth and IHD were only partly due to shared genetic or environmental factors in families.

Other Interactions

There was no significant interaction between preterm birth and fetal growth on the additive or multiplicative scale (eTable 4 in the Supplement). At ages 18 to 43 years, the highest risk of IHD was observed among persons born preterm who also had low fetal growth (>1 SD less than the mean birth weight for gestational age and sex; adjusted HR, 1.85; 95% CI, 1.22-2.81; compared with those born full term with moderate fetal growth

Figure. Adjusted Hazard Ratios (HRs) for Ischemic Heart Disease (IHD)



At ages 18 to 43 years by gestational age at birth (solid lines) compared with full-term birth. The shaded areas represent 95% confidence intervals.

Table 3. Cosibling Analyses for Gestational Age at Birth in Association With IHD Risk in Sweden From 1973 to 2015

Characteristic	No. of Cases	HR (95% CI)[a]
Attained ages 18-43 y		
Preterm (<37 wk)	82	1.35 (0.87-2.09)
Early term (37-38 wk)	228	1.12 (0.87-1.44)
Full term (39-41 wk)	902	1 [Reference]
Per additional week (trend)		0.94 (0.88-0.99)
Attained ages 18-29 y		
Preterm (<37 wk)	40	1.46 (0.82-2.61)
Early term (37-38 wk)	108	0.97 (0.69-1.36)
Full term (39-41 wk)	433	1 [Reference]
Per additional week (trend)		0.93 (0.86-1.00)
Attained ages 30-43 y		
Preterm (<37 wk)	42	1.23 (0.69-2.31)
Early term (37-38 wk)	120	1.30 (0.87-1.94)
Full term (39-41 wk)	469	1 [Reference]
Per additional week (trend)		0.95 (0.87-1.04)

Abbreviations: HR, hazard ratio, IHD, ischemic heart disease.

[a] Adjusted for shared familial (genetic and/or environmental) factors in addition to specific child characteristics (birth year, fetal growth, birth order, and congenital anomalies) and maternal characteristics (age, education, birth country or region, body mass index [calculated as weight in kilograms divided by height in meters squared], smoking, preeclampsia, other hypertensive disorders, and diabetes).

[within 1 SD of the mean]). However, the association between preterm birth and IHD risk did not vary significantly by fetal growth. For example, the adjusted HR for IHD comparing preterm vs full term was 1.52 (95% CI, 1.22-1.90) among persons with moderate fetal growth and 1.47 (95% CI, 0.87-2.07) among those with low fetal growth. The association between preterm birth and IHD risk was also similar among persons born by cesarean delivery (215 034 [10.0%]; adjusted HR, 1.27; 95% CI, 0.81-2.00) as those delivered vaginally (1 926 456 [90.0%]; adjusted HR, 1.32; 95% CI, 1.03-1.68; tests for interaction: additive, P = .98; multiplicative, P = .89).

Discussion

In this large national cohort study, gestational age at birth was inversely associated with the risk of IHD in adulthood. Adjusting for other factors, preterm and early-term birth were associated with a 53% (95% CI, 20% to 94%) and 19% (95% CI, 1% to 40%) increased relative risk of new-onset IHD, respectively, at ages 30 to 43 years. Preterm-born men had the highest IHD incidence. However, preterm-born women had the highest relative risk, possibly because of lower baseline incidence among women born full term. These findings were statistically significant after adjusting for fetal growth and other perinatal and maternal factors, and cosibling analyses suggested that they were not explained by unmeasured shared familial factors.

To our knowledge, this is the largest study to date of preterm birth in association with IHD risk and one of the first to include a population-based cohort that was born late enough to receive modern neonatal care starting in the 1970s to 1980s.[15] Our findings contradict the null results reported by most earlier studies. For example, a Finnish study of 19 015 persons born during 1924 to 1944 reported no association between preterm birth and IHD risk (adjusted HR, 1.03; 95% CI, 0.89-1.18).[13] Two Swedish studies of 6425 persons born during 1925 to 1949 and 14 193 persons born during 1915 to 1929 also reported null findings for IHD incidence and mortality, respectively.[10,11] Another Swedish study of a more recent birth cohort of 1.3 million persons born during 1983 to 1995 also found no association between preterm birth and IHD risk but included follow-up only to age 15 to 27 years (adjusted HR for gestational ages 32-36 compared with 37-41 weeks, 1.44; 95% CI, 0.81-2.56).[12] Lastly, a Swedish study of 1.9 million persons who overlapped with the present cohort and were followed up to age 38 years reported a borderline-significant association between preterm birth and IHD risk adjusted for age and sex (HR, 1.36; 95% CI, 1.00-1.85) and no association when further adjusted for other perinatal, familial, and comorbidity factors.[22]

These discrepant findings may be due to several factors. Some of the prior null findings for IHD may potentially be due to survivor bias. Before neonatal care advances in the 1970s to 1980s, survival rates for preterm infants were much lower and the strongest and healthiest infants who survived may be less susceptible to IHD later in life than more recent preterm survivors.[14] On the other hand, prior null findings may possibly be associated with protective factors in preterm survivors, such as conscientiousness[28] and risk aversion,[29] which may lead to healthier lifestyles, including lower smoking rates and alcohol use.[29] In addition, the few prior studies of later birth cohorts (ie, born during the 1970s to 1990s) may have had insufficient follow-up into adulthood for IHD risks to manifest. This study extends follow-up to age 43 years compared with ages in the 20s and 30s in prior studies of birth cohorts that received modern neonatal care.[12,22] Prior discrepant findings may also have been influenced by differences in how the reference group was defined. Early-term birth (37-38 weeks) has increasingly been linked with adverse health outcomes into

adulthood compared with later-term birth.[17] Such findings have supported a redefinition of term pregnancy.[30] Combining early and later-term births as the reference group may partially obscure an association between preterm birth and IHD. However, large cohorts are needed to examine more narrowly defined gestational age groups with sufficient power.

This study's findings are consistent with previously reported associations between preterm birth and cardiometabolic disorders that are risk factors for IHD, including hypertension,[1,2] diabetes,[3-6] and metabolic syndrome,[7] and cardiovascular mortality in adulthood.[31] Moreover, we found that the association between preterm birth and IHD did not vary by fetal growth. Preterm birth was associated with increased IHD risk among persons with either normal or low fetal growth, and conversely, low fetal growth was associated with increased IHD risk even among those born full term. These findings suggest that there are multiple different mechanisms in the perinatal period that affect long-term IHD risks. Preterm birth interrupts intrauterine growth and the maturation of all fetal organs and may permanently compromise cardiovascular system structure and function, leading to hypertension, endothelial dysfunction, and atherosclerosis.[2,32,33] Preterm birth also has been associated with impaired glucose metabolism, leading to insulin resistance, diabetes, and metabolic syndrome.[4-7] The combined effects of these cardiometabolic changes may predispose to the development of IHD later in life. Iatrogenic effects of medication treatment in preterm infants may also contribute to these long-term health risks.[34]

The prevalence of preterm birth is currently 10% in the United States,[35,36] 5% to 8% in most European countries,[37] and an estimated 11% worldwide.[38] Even a modestly increased risk of IHD among preterm-born adults has major public health implications. Although the underlying mechanisms need further elucidation, our findings suggest that persons born prematurely need long-term follow-up for health surveillance and preventive actions to reduce the risk of IHD. More aggressive treatment of other risk factors, including obesity, hypertension, and diabetes, and anticipatory screening for IHD may be warranted in preterm-born adults. Medical records and history taking should routinely include gestational age at birth to help facilitate interventions, including patient counseling, to promote lifestyle prevention of IHD.[39-41]

Strengths and Limitations

A strength of this study was the ability to examine preterm birth in association with IHD in a large national cohort born during the 1970s and later, with follow-up into the fifth decade of life, using birth and medical registry data that are highly complete. This study design minimizes potential selection or ascertainment biases. The results were controlled for other perinatal and maternal factors as well as unmeasured shared familial factors using cosibling analyses.

Its limitations include the lack of more detailed clinical data to verify IHD diagnoses, although a positive predictive value of 98% has been reported.[19] The large size of this cohort provided high statistical power for examining most gestational age groups, including those born at early term or late preterm. However, there were too few IHD diagnoses among adults born extremely preterm (<28 weeks) to examine this group separately, and power was still limited for those born earlier than 34 weeks. We also lacked information on spontaneous vs medically indicated preterm birth, which were not systematically recorded during most years of this birth cohort. Additional follow-up will be needed to examine longer-term outcomes in older adulthood. We found that IHD risks associated with preterm birth were higher at ages 30 to 43 years than earlier in adulthood, but longer-term risks are still unclear. Lastly, this study was limited to Sweden and will need replication in other diverse populations.

Conclusions

We found that preterm (including late preterm) and early-term birth are associated with an increased risk of IHD at ages up to 43 years in a large population-based cohort. These findings suggest that preterm and early-term birth are risk factors for the development of IHD in adulthood. Persons born prematurely need long-term follow-up and early preventive actions to reduce the risk of IHD.

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