ORIGINAL RESEARCH

Neonatal Risk in Children of Women With Congenital Heart Disease: A Cohort Study With Focus on Socioeconomic Status

Stine Kloster, Msc; Janne S. Tolstrup, PhD, DMSci; Morten Smærup Olsen, MD, PhD; Søren Paaske Johnsen, MD, PhD; Lars Søndergaard, MD, DMSc; Dorte Guldbrand Nielsen, MD, PhD; Annette Kjær Ersbøll, PhD

***Background*—**We hypothesized that women with congenital heart disease (CHD) are at increased risk of giving birth preterm, including very and moderately preterm and giving birth to infants small for gestational age (SGA). We aimed to investigate this in a nation-wide study with focus on the potential modifying effect of socioeconomic status.

***Methods and Results*—**We performed a cohort study using Danish nation-wide registers between 1997 and 2014. The exposure, maternal CHD, was subdivided into simple, moderate and complex based on severity of defects. Outcomes were preterm birth and SGA. Cox regression was used to estimate hazard ratios (HR). A total of 933 149 births including 3745 births among women with CHD were studied. The risk of giving birth preterm and SGA were higher among women with CHD as compared with women without CHD; for example, adjusted hazard ratios of preterm birth according to severity: simple 1.33 (95% CI, 1.11–1.59), moderate 1.45 (95% CI, 1.14–1.83) and complex 3.26 (95% CI, 2.41–4.40). Same pattern was seen for very and moderately preterm births and SGA. Education was a strong predictor of both preterm birth and SGA but did not modify the association between maternal congenital heart disease and preterm birth (P=0.38) or SGA (P=0.99).

***Conclusions*—**Women with CHD were at increased risk of preterm birth both, moderately and very preterm, as well as giving birth to infants SGA. Education was a strong predictor of both preterm birth and SGA but the association between CHD and risk of preterm birth and SGA was independent of educational level. **(*J Am Heart Assoc*. 2019;8:e013491. DOI: 10.1161/JAHA.119.013491.)**

Key Words: congenital heart disease • pregnancy • preterm birth • small for gestational age • socioeconomic position

Because of advances in diagnosis and treatment, more women with congenital heart disease (CHD) are reaching childbearing age compared with earlier.[1,2] Some CHDs increase risk of obstetric and cardiac complications during pregnancy and childbirth.[3–11] Likewise, studies indicate an increased risk of adverse neonatal outcomes such as premature birth and small for gestational age (SGA),[3,9,12–15] which are predictors of neonatal morbidity and mortality,[16,17] and morbidity in adult life.[18] The adverse effect of being born preterm is associated with the degree of prematurity. However, the association between maternal CHD and preterm birth primarily focus on preterm birth, and only a few studies examine degree of prematurity.[19,20] These studies are limited by the small sample sizes and selected study populations. Hence, evidence of the risk of very premature birth in the general population of women with CHD is still lacking.

Preterm birth and giving birth to an SGA infant in general occur more commonly among disadvantaged socioeconomic groups,[21] thereby contributing to inequalities in health. However, whether this inequality also exists among women with CHD is unknown. A study showed no association between countries with different Human Development Index and the rate of SGA among women with CHD; however, individual socioeconomic status was not accounted for.[22]

We hypothesized that women with CHD, who have entered 22 completed weeks of pregnancy (ie, gestational age is 154 days), are at increased risk of giving birth preterm, including very (22–31 completed weeks) and moderately (32–36 completed weeks) preterm and giving birth to SGA infants.

From National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark (S.K., J.S.T., A.K.E.); Departments of Radiology (M.S.O.) and Cardiology (D.G.N.), Aarhus University Hospital, Aarhus, Denmark; Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (S.P.J.); Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (L.S.); University Hospital of Copenhagen, Copenhagen, Denmark (L.S.); Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (D.G.N.).

Accompanying Data S1 and Tables S1 through S7 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013491

Correspondence to: Stine Kloster, Msc, National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 Copenhagen K, Denmark. E-mail: stkl@sdu.dk

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Clinical Perspective

What Is New?

- We showed that the risk of preterm birth, both moderately and very preterm, was higher among women with congenital heart disease in an unselected population.
- Socioeconomic status was a strong predictor of preterm birth and small for gestational age also among women with congenital heart disease, however, the association between congenital heart disease and risk of preterm birth and small for gestational age apparently seemed to be independent of socioeconomic status in a population with free and equal access to health care.

What Are the Clinical Implications?

- In particular, the increased risk of very preterm birth may potentially be used during counselling regarding risk in pregnancy among women with a congenital heart disease.
- The difference in risk between different socioeconomic groups for both preterm birth and small for gestational age in a country with free and equal access to health care need awareness and mechanisms behind this inequality among women with congenital heart disease need to be addressed.

We aimed to investigate this in a nation-wide study with particular focus on the potential modifying effect of socioeconomic status at an individual level.

Methods

Study Design

In Denmark, all citizens have free access to health care and are assigned a unique identification number, which enables individual-level linkage across national registers.[23] The study was a national cohort study with prospectively collected data from the Danish Medical Birth Register[24,25] and the Danish National Patient Register.[26] Data will not be made available to other researchers for the purpose of reproducing the results because this would be a violation of the Danish General Data Protection Regulation and data Privacy Regulation by Statistic Denmark.

Study Population

All births registered in the Danish Medical Birth Register between 1997 and 2014 constituted the study population. All singleton births among women born in Denmark were included (n=952 882). The register holds information on all live and stillbirths, including information of both mother and child related to the pregnancy and delivery.[24,25] Women were included in the cohort at day 154 of gestation (22 completed weeks) and followed until birth.

Maternal Congenital Heart Disease

Information about maternal CHD was obtained from the Danish National Patient Register, which is a population-based administrative register holding information on all hospital admissions since 1977.[26] All women with a diagnosis of CHD (*International Classification of Diseases, Tenth Revision* [*ICD-10*]; Q20–Q26, *International Classification of Diseases, Eighth Revision* [*ICD-8*]; 746–747) between 1977 and 2016 were included except *ICD-10* Q26.5 to Q26.6 and *ICD-8* 746.7 and 747.5 to 747.9, which are not specific for CHD. To increase the positive predictive value of the diagnosis of CHD, we excluded individuals with, for example, unspecific diagnoses using an algorithm previously described.[27] For example, diagnosis of ASD was excluded if given at ages <2 months without an associated operation code; diagnosis of congenital stenosis of aortic valve was excluded if given at ages >40 years, etc (see appendix in Olsen et al for more details[27]). Based on guidelines from the European Society of Cardiology, CHD was categorized into no, simple, moderate, and complex.[28] Women with >1 diagnosis were categorized according to the more-severe diagnosis. We included women diagnosed before, during, and after pregnancy under the hypothesis that underlying CHD affected the pregnancy and its outcome irrespective of whether the disease was diagnosed at the time of delivery.

Outcomes

Information on preterm birth and SGA was obtained from the Danish Medical Birth Register.[24,25] During the study period, gestational age was primarily determined based on ultrasonography. Preterm birth was defined as birth between 22 and 36 weeks of completed gestation (154–258 days). Preterm birth was further categorized into very preterm (22–31 completed weeks) and moderately preterm (32–36 completed weeks).[29,30] Births with implausible birthweights according to gestational age were excluded.[31] SGA was defined as birthweight falling below the 10th percentile of birthweight according to standard references[32] and calculated for males and females, separately.

Covariates

Ethnicity, maternal age, parity, educational level, and calendar year were identified as confounders a priori using Directed Acyclic Graphs (available from the authors).[33] Information about ethnicity was obtained from the Danish Civil Registration System and grouped into Europeans/North Americans,

Asians, and Africans/others. This was done because CHD is more prevalent among Asians and Europeans[34] and preterm birth is more prevalent among Africans.[35] Maternal age and calendar year were assessed at inclusion. Age was categorized into: <20, 20 to 24, 25 to 29, 30 to 34, and ≥35 years. Year of inclusion was grouped into 5-year bands, except the last interval which contained 4 years. Information about parity was obtained from the Danish Medical Birth Register and grouped into nulli-, primi-, and multiparous. Parity was corrected based on the available information in the Danish Medical Birth Register (Data S1).

Socioeconomic status was assessed by educational level, which has shown to be a strong socioeconomic predictor of the risk of both preterm birth and SGA in Denmark.[29] Information about the highest level of completed education October 1 the year preceding each birth was obtained from the Danish Education Register.[36] Education was classified according to the International Standard Classification of Education System (ISCED 2011)[37] and categorized into 3 groups: low education (preprimary, primary, and lower secondary; ISCED level 1–2); medium (upper secondary and postsecondary; ISCED level 3–4); and high (tertiary education ISCED level 5–8).

For descriptive purposes information on smoking, prepregnancy body mass index, number of hospital contacts 1 year before start of the index pregnancy, stillbirths, and induction was included.

Statistical Analysis

For the descriptive analyses, median and interquartile range was used for continuous variables, and counts with proportions was used for categorical variables.

A Cox proportional hazard model was used to investigate the association between maternal CHD and preterm birth and SGA. Gestational age in days was used as the underlying time scale. Women entered the cohort at day 154 of gestation. For preterm birth, the follow-up time was terminated at birth or after 258 days of gestation, whichever came first. Pregnancies ending with stillbirth were censored at the time of stillbirth or after 258 days. When analyzing the risk of very preterm birth, the follow-up time was terminated at birth or after 223 days (cut point for very preterm birth, <32 completed weeks), and all ongoing pregnancies were censored. When analyzing the risk of moderately preterm birth, all pregnancies not ending in a very preterm birth were included and follow-up time was terminated at birth or after 258 days. When analyzing the association with SGA, the pregnancies were followed until birth. Adjustment was made for maternal age, calendar year, ethnicity, parity, and educational level. Some women contributed with >1 birth to the cohort. To account for the clustered structure of the data, a cluster-robust standard error estimator was used. Results were presented as hazard ratios (HRs) with 95% CIs. The overall effect of CHD and educational level was derived using Wald's test.

The possible effect modification of educational level on the association between CHD and the outcomes was tested on a multiplicative scale by including the main effects and the interaction term in the fully adjusted model. Wald's test was used to test whether the interaction was significant. The joint effect was examined by combining CHD and educational level into a single variable with 12 categories with a common reference group (women with high education without CHD). Differences in HRs between complex CHD and no CHD were compared at the different educational levels using Wald's test: low versus medium, low versus high, and medium versus high. Likewise, this was done for simple and moderate CHD.

The proportional hazard assumption was evaluated visually using log-log plots.

Births with missing information on gestational age and birthweight were excluded.

Sensitivity Analysis

The assumption of proportional hazards was violated for the age category <20 years for preterm birth. To examine whether this affected the estimates of the main exposure (CHD), all analyses were conducted in strata of age and by including an interaction term between age and gestational age. To further examine the potential influence of nonproportional hazards, all analyses were also conducted using a Poisson regression of incidence rates.

Several sensitivity analyses were conducted. First, the risk of preterm birth was modeled with stillbirth as a competing risk. Second, analyses of preterm birth and SGA were restricted to women diagnosed with CHD before delivery to examine the effect of knowing the disease beforehand. Third, the analysis was restricted to nulliparous women in order to eliminate the effect of any similar previous pregnancy outcome (eg, preterm birth). Fourth, induced births were modeled as a competing risk to spontaneous preterm births. Last, an analysis was conducted where SGA was defined as birthweight below 2 SDs of the mean birthweight according to standard references[32] and calculated for males and females, separately. This was done because both <10th percentile and 2 SDs below the mean are used in the literature. The definition with 2 SDs only captures the most extreme SGA infants.

Data management done in order to derive the CHD cohort was done using SAS software (version 9.4; SAS Institute Inc, Cary, NC. All analyses were performed using Stata/IC software (version 15.0; StataCorp LP, College Station, TX).

Ethical Considerations

The study was approved by the Danish Data Protection Agency (2015-57-0008, no. 16/48885). In Denmark, written informed consent or ethical approval is not required for register-based studies. All data were provided by Statistics Denmark, and because of their data privacy regulation, data with <5 individuals per cell were not reported.

Results

Participants

We identified 952 882 singleton births in the study period. Of these, 218 births were excluded because pregnancy ended before 22 (n=159) or after 44 (n=59) weeks of completed gestation, 577 births because of implausible birthweights, and 18 938 (≈2%) births because of missing information on gestational age resulting in a study population of 933 149 births among 548 714 women (Figure 1). Birthweight was missing for another 7024 (0.75%) births, and the analysis sample for SGA therefore consisted of 926 125 births among 546 903 women. A total of 3745 births were among 2212 women with CHD.

Maternal and Birth Characteristics

The most common CHDs were the simple defects, atrial septal defect and ventricular septal defect. Within complex CHDs, transposition of the great arteries constituted the majority of diagnosis. The distribution of each CHD, stratified by complexity, is reported in Table S1. Compared with women without CHD, women with CHD were slightly younger, less educated, and more were nulliparous (Table). Furthermore, there were a larger proportion of stillbirths and inductions among women with CHD, and they had, on average, more hospital contacts the year before pregnancy as compared with women without CHD.

The overall proportion of preterm birth was 5.0% (n=46 601) and SGA 10.5% (n=96 802). The median gestational age was 280 days (interquartile range, 273–287). Median follow-up time (ie, time from 154 days of gestation to censoring or birth) was 105 days (range, 1–105) in the analysis of preterm births and 127 days (range, 1–161) in the analysis of SGA.

Main Results

Women with CHD had a higher risk of any preterm birth as compared with women without CHD (Figure 2A). The risk of preterm birth increased with increasing severity of the maternal CHD, with an HR of 1.33 (95% CI, 1.11–1.59) for simple, 1.45 (95% CI,1.14–1.83) for moderate, and 3.26 (95% CI, 2.41–4.40) for complex defects. The same pattern was found when analyzing subgroups of preterm birth with even higher HR of very preterm birth with an HR at 1.62 (95% CI, 1.09–2.39) for simple, 1.37 (95% CI, 0.70–2.70) for moderate, and 5.02 (95% CI, 2.84–8.90) for complex defects. Adjustment for confounders did not affect the HRs substantially, for example, 3% for any preterm birth (crude estimates in Table S2).

Likewise, the risk of giving birth to an infant born SGA was higher among women with CHD as compared with women without. As for preterm birth, the risk increased with increasing severity of the heart disease; adjusted HRs of simple 1.27 (95% CI, 1.11–1.45), moderate 1.56 (95% CI, 1.29–1.87), and complex 2.32 (95% CI, 1.69–3.18) defects.

A lower educational level was strongly associated with higher risk of any preterm birth (Figure 2B). The adjusted HRs of low and medium education as compared with high education was 1.76 (95% CI, 1.71–1.82) and 1.25 (95% CI, 1.22–1.28), respectively. The association between maternal CHD and any preterm birth was independent of educational level (*P* value for interaction=0.38). HRs of preterm birth and SGA within strata of education are given in Figure 3.

Differences in HR between each group of CHD and women without were similar between educational levels. The only exception was among women with a complex CHD, where differences in HR were significantly higher for women with a low education as compared with women with a medium education (Figure 3).

Likewise, education was strongly associated with SGA (Figure 2B). The adjusted HRs of low and medium education as compared with high education was 1.96 (95% CI, 1.92–2.00) and 1.26 (95% CI, 1.24–1.28), respectively. As for preterm births, the association between CHD and SGA was independent of educational level (*P* value for interaction=0.99). Differences in HR among women with CHD and women without were similar at all educational levels.

Sensitivity Analyses

Cox regressions conducted in strata of age or by including an interaction term between age and gestational age showed that HRs for simple, moderate, and complex defects were essentially the same. Likewise, estimates of CHD were similar when analyses were run as Poisson regression of incidence rates. However, for very preterm birth, the analysis did not converge.

Modelling stillbirth as a competing risk to preterm birth essentially gave the same estimates (Table S3). Restricting the analysis to women diagnosed with CHD before the index pregnancy showed the same pattern, but resulted in slightly higher adjusted HR, for example, simple 1.39 (95% CI, 1.14–1.69) and complex 3.40 (95% CI, 2.49–4.65) for preterm birth (Table S4). Restricting the analysis to nulliparous women

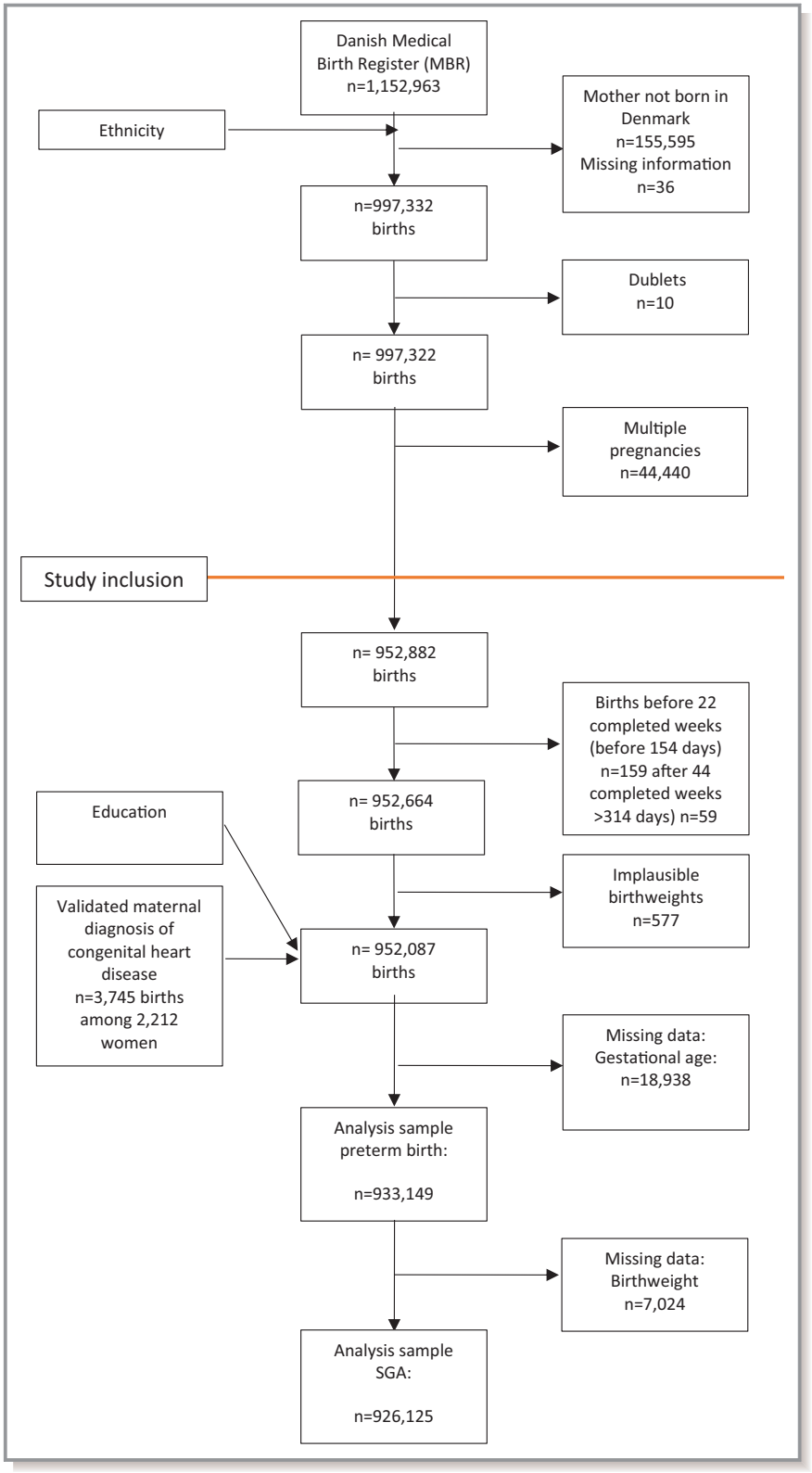

Figure 1. Flow diagram of data from the Danish Medical Birth Register.

resulted in the same pattern as for the full cohort (Table S5). However, the differences for simple and moderate were only borderline significant.

Modeling induced births as a competing risk to spontaneous preterm birth, the pattern and size of estimates were almost similar (Table S6).

Table. Baseline Characteristics by Congenital Disease Status in 548 714 Women and 933 149 Births

	Maternal Congenital Heart Disease							
	No (n=929 462)		Simple (n=2224)		Moderate (n=1082)		Complex (n=381)	
	N	(%)	N	(%)	N	(%)	N	(%)
	929 462		2224		1082		381	
Age, y								
Median (IQR)		30.1 (26.9–33.4)		29.3 (25.6–32.6)		29.5 (26.4–32.8)		29.0 (25.7–32.4)
<20		1.8		3.8		2.9		2.4
20 to 24		12.3		18.1		14.0		19.4
25 to 29		35.2		34.2		38.3		34.9
30 to 34		34.9		31.6		31.9		32.8
≥35		15.8		12.3		12.9		10.5
Ethnicity	929 455		2224		1082		381	
Europeans/North Americans		99.4		98.5		99.7		98.2
Asians		0.5	<30*	NA†	<5*	NA†	<5*	NA†
Africans/others		0.1	<30*	NA†	<5*	NA†	<5*	NA†
Parity	917 499		2198		1069		380	
Nulliparous		43.8		48.4		48.4		45.3
Primiparous		38.7		36.3		37.0		35.0
Multiparous		17.5		15.3		14.6		19.7
Education	917 427		2219		1067		372	
Low		19.1		27.1		22.6		27.2
Medium		43.7		40.3		41.4		46.8
High		37.2		32.6		36.0		26.1
Smoking	845 078		2068		972		341	
Yes		17.6		19.7		15.4		17.3
Prepregnancy BMI	531 049		1462		682		246	
Underweight (<18.5)		4.1		4.9		5.7		5.7
Normal (18.5–<25)		62.4		62.3		62.2		65.8
Overweight (≥25)		33.5		32.8		32.1		28.5
No. of hospital contacts 1 year before start of pregnancy‡	929 462		2224		1082		381	
Median (IQR)		0 (0–1)		0 (0–1)		0 (0–1)		0 (0–2)
Mean±SD		0.63±1.35		0.91±1.65		0.88±1.63		1.05±1.75
Stillbirth	2942	0.3	16	0.7	9	0.8	6	1.6
Induction overall	136 845	14.7	401	18.0	196	18.1	72	18.9
Induction among preterm births	5533	12.0	15	10.0	13	16.7	<5*	NA†

N indicates number of births; BMI indicates body mass index; IQR, interquartile range; NA, not applicable.
*Exact n is not given because of data privacy policy. The exact number is known by the researchers and used in calculations.
†Not applicable because of low n.
‡Number of contacts the year before the start of the index pregnancy. Contacts with primary reason of congenital heart disease or pregnancy were excluded.

When defining SGA as infants falling below 2 SDs of the mean birthweight, the same pattern was noted. However, the HR of SGA was higher for complex CHD when the definition of 2 SDs was used (Table S7).

Discussion

We found that women with CHD had a higher risk of preterm birth, both moderately and very preterm, and SGA. Furthermore, the risk

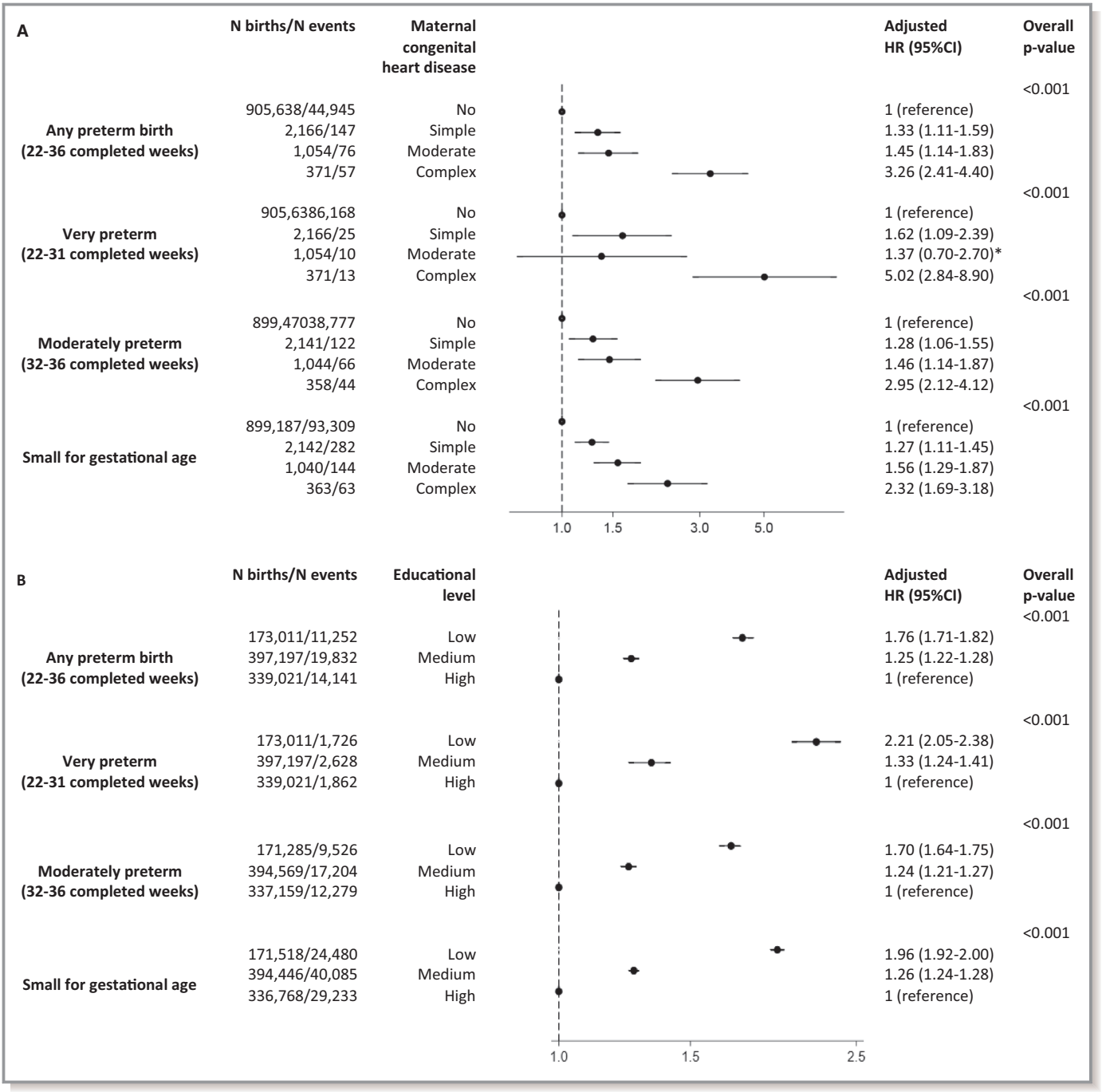

Figure 2. **A**, Hazard ratios (HRs) of the association between severity of maternal congenital heart disease and preterm birth and small for gestational age. HRs are adjusted for maternal age and calendar year at inclusion, ethnicity, parity, and level of education. Women without congenital heart disease are used as a reference. *Not significantly different from simple congenital heart disease. **B**, HRs of the association between educational level and preterm birth and small for gestational age. HRs are adjusted for congenital heart disease, maternal age, and calendar year at inclusion, ethnicity, and parity. Women with a high level of education are used as a reference.

of both outcomes increased with severity of the CHD. Socioeconomic status, as determined by maternal educational level, was a strong predictor of preterm birth and SGA. The association between CHD and risk of preterm birth and SGA apparently seems to be independent of educational level; however, this could be attributable to low power because of few events.

Our results add to the literature showing that maternal CHD is associated with preterm birth and SGA.[3,9,12–15] Although some studies found no association between preterm birth or SGA and CHD,[8,38] this may be attributable to small sample sizes. By including the total population of pregnant women with and without CHD in Denmark during

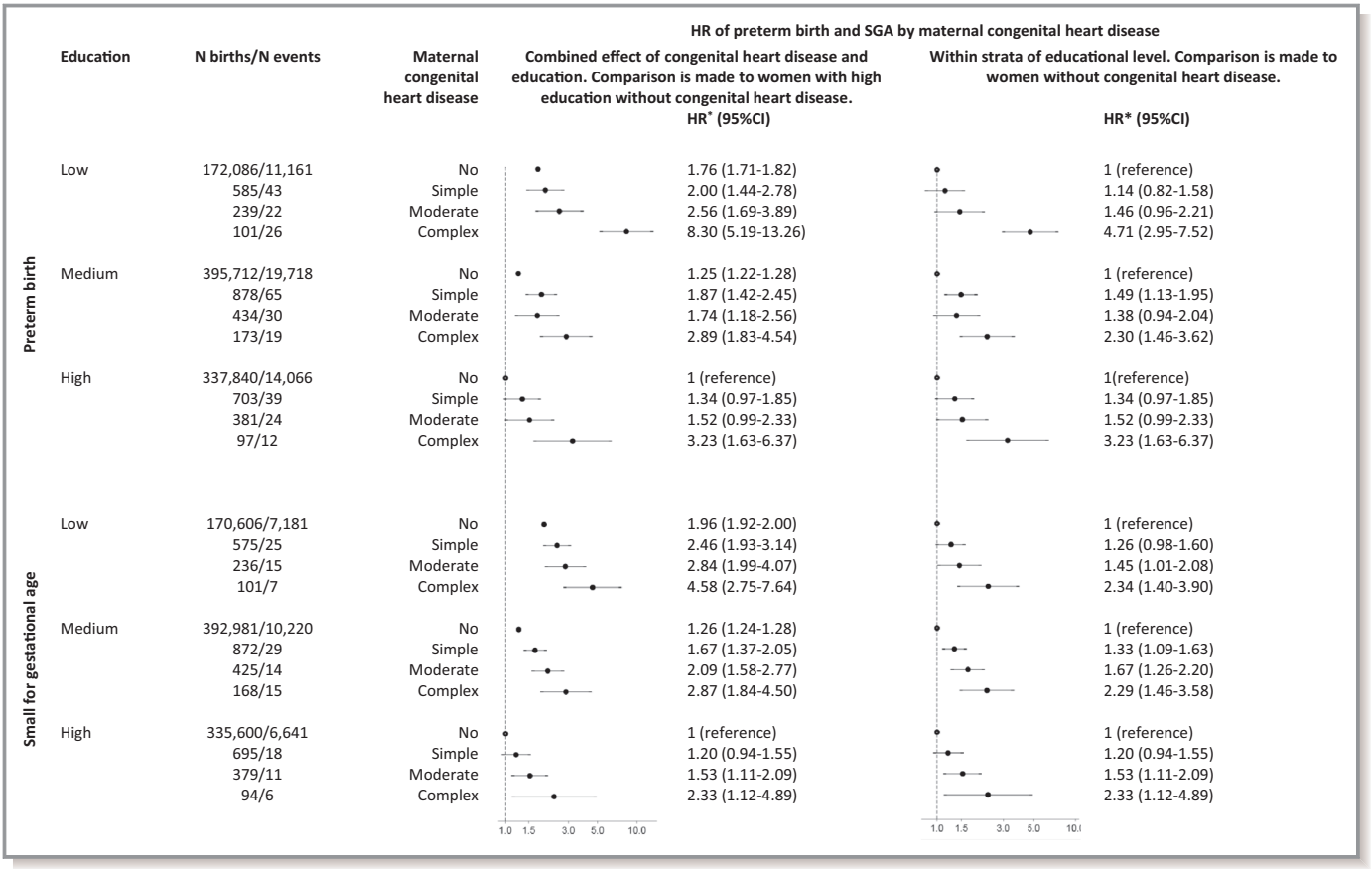

Figure 3. To the left, hazard ratios (HRs) of preterm birth (upper) and small for gestational age (SGA; lower) for the joint effect of educational level and maternal congenital heart disease are given. To the right, HRs of preterm birth (upper) and SGA (lower) by maternal congenital heart disease within strata of educational level are given. *Adjusted for maternal age and calendar year at inclusion, ethnicity, and parity. †Differences in HR between women without congenital heart disease and women with a complex congenital heart disease were significantly higher for women with a low education as compared with women with a medium education (P=0.03). P value of interaction; preterm birth, P=0.38; SGA, P=0.99.

18 years, we obtained a large sample size to estimate the association between CHD and preterm birth and SGA, thereby contributing with solid evidence from a nation-wide register in a country with universal and free healthcare coverage.

Our estimates are similar to the findings of Hayward et al, who report an odds ratio of 1.6 for noncomplex and 3.0 for complex CHD.[13] The definition of severity differs because they categorized CHD into complex and noncomplex; however, the definition of complex CHD is similar with the primary exception of tetralogy of Fallot, which, in our study, is categorized as a moderate defect. Thompson et al[5] evaluated women with CHD as 1 group and found an odds ratio of 1.66. This is a lower estimate compared with ours when considered that women with complex CHD are included in the estimate. In both studies, the researchers adjusted for comorbidities that might be mediators of the association between CHD and preterm birth.

To our knowledge, the degree of prematurity has not previously been determined in the general population of women with CHD. Only a few small studies report event frequencies of degree of prematurity.[19,20] We report a higher risk of both very preterm and moderately preterm births among women with CHD.

Births among women with CHD are more often induced[20,39] which is also the case in our study. However, among preterm births, there was no difference in frequency of induction among women with CHD and women without (data not shown). Furthermore, when induction was modeled as a competing risk to spontaneous preterm births, the results were similar as in the main analysis, indicating that the association is not attributable to difference in induction among women with and without CHD.

Our results add to the evidence that maternal CHD predisposes to a lower fetal growth rate. As recently shown, women with CHD have smaller babies compared with healthy

women.[12] Similar findings have been reported by others.[5,8,15,19] However, the size of effect differs between studies and might partly be explained by differences in the definition of SGA. When SGA was defined as infants falling below 2 SDs of the mean birthweight, we found the same pattern. However, the HR of SGA was higher among women with a complex CHD. Given that defining SGA as falling below 2 SDs of the mean birthweight only captures the most extreme SGA infants, this might indicate that women with a complex CHD tend to give birth to smaller infants and this effect is then attenuated when the definition of SGA is broader. Regardless of the definition of SGA, the restriction in fetal growth among women with CHD could be attributable to a reduced cardiac output that causes a disturbed uteroplacental blood flow.[40,41]

Influence of Socioeconomic Status

Little is known about if and how socioeconomic status affects birth outcome among women with CHD. Our results indicate that inequality in adverse birth outcomes does exist among women with CHD even in a country with free and equal access to health care. The educationally patterned risk of preterm birth and SGA is worrying because this might be the first sign of health inequality in health in later life.[21] This might be even more pronounced among children of women with CHD given that more of these children will have CHD and other malformations themselves,[15] which are also known to cluster in more socially disadvantaged groups,[21] thereby placing children of women with CHD as a particularly vulnerable group with higher concentration of risk factors for inequality in health in later life. Children with CHD will furthermore tend to achieve a lower educational level,[42] and thereby social inequality is passed across generations. Additionally, it has been well documented that the inequality in health does exist in the risk of disease, as shown in this study, but also in the consequence of disease.[43]

Research and Clinical Implications

We showed a 5-fold increased risk of very preterm birth among women with a complex CHD. Therefore, the risk of preterm birth is not just a question of giving birth close to term. This is of clinical importance given that the adverse effects of being born preterm differ by degree of prematurity. This information might be used in future counseling regarding risk in pregnancy among women with CHD. Furthermore, children born to women with CHD will be at increased risk of being born SGA, making these children even more vulnerable.

In Denmark, all citizens have free and equal access to health care; however, we found a socioeconomic patterned risk of preterm birth and SGA. The mechanism behind this association is complex and not completely understood,[44] but might partly be explained by differences in health behavior and differences in the experience of social advantages or disadvantages across the life course.[45] However, the mechanisms behind this might differ for women with and without CHD and need further investigation.

Factors such as preeclampsia and gestational hypertension might be important to consider when predicting the risk of preterm birth and SGA among women with CHD. However, we consider these conditions as mediators on the causal path from maternal CHD to preterm birth or SGA. Therefore, these conditions were not included in the statistical analysis.[46] Higher prevalence of preeclampsia/eclampsia or other gestational hypertensive disorders have been reported among women with heart disease.[9,13] To investigate the mediating factors between CHD and adverse perinatal outcomes was beyond the scope of this article. However, in order to reduce adverse neonatal outcomes among women with CHD, future studies should focus on the mediating factors between CHD and adverse neonatal outcomes. Neonatal complications tend to follow a pattern similar to maternal and obstetric outcomes among women with heart disease in general,[9] indicating that the association between CHD and these different outcomes might be mediated through shared factors.

Strengths and Limitations

Inclusion of all women diagnosed with a CHD in Denmark, as opposed to including from specialized clinics, limits the risk of selection bias. Additionally, this increases power to analyze subgroups of preterm births. Given that data are based on a nation-wide sample, we were able to include women with simple CHD, who constitute the biggest part of women with CHD and, as shown in this study, also have a higher risk of preterm birth and SGA than women without CHD. Furthermore, this improves the ability to transfer the results to a real-world setting.

When analyses were restricted to nulliparous women findings were similar, which strengthen the main findings in the study, ruling out that risks are attributable to previous similar birth outcomes such as preterm birth.

A further strength of our study is the validation of CHD diagnosis. As recently described, the use of diagnosis of CHD from administrative databases is associated with some inaccuracy.[47] In general, diagnosis of CHD has a high positive predictive value in the Danish National Patient Register,[48,49] and to further increase the validity of the included diagnoses, we used an algorithm previously described[27] to exclude invalid diagnosis of CHD or inaccurate coding in the Danish National Patient Register.

The Danish universal healthcare system with free and equitable access to care regardless of economic resources offers unique possibilities for studying the socioeconomic

gradient in risk of preterm birth and SGA among women with CHD. We were able to include information about socioeconomic status at an individual level, which, to our knowledge, has not previously been done among women with CHD.

A drawback of the study is the inability to account for the variability in severity within both the CHD category, but also within a given diagnosis of CHD.

In conclusion, our study showed that women with CHD were at increased risk of preterm birth, both moderately and very preterm, and giving birth to an SGA infant. The risk was higher in complex CHD. Education was a strong predictor of both preterm birth and SGA, with higher risk among lower-educated women. However, the association between CHD and risk of preterm birth and SGA apparently seems to be independent of educational level in a country with universal healthcare coverage.

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Kloster, Ersbøll, and Tolstrup participated in the conception of the study design and acquisition and interpretation of the data. Kloster and Ersbøll had full access to the data and conducted the analysis, and Kloster drafted the first manuscript, which was critically revised for important intellectual content by all authors. All authors have approved the submitted manuscript.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Parity:

Information about parity was corrected based on the available information in the Danish Medical Birth Register during the study period. In case a woman was noted as e.g. nulliparous and was registered with more than one birth during the study period, parity was corrected based on the available number of births in the study period. Based on the available information it was only possible to increase the parity of women. Information about parity was corrected for 1.5% of the births.

Maternal age:

Maternal date of birth registered in the Danish Civil Registration System was used to calculate maternal age at inclusion. For women with missing information on maternal date of birth maternal age registered in the Danish Medical Birth Register was used (n=74).

Table S1. Distribution of congenital heart disease.

	Disease	ICD-10 code	ICD-8 code	n*
Complex/high risk	Univentricular heart (Complex, mWHO III-IV)	Q201, Q202, Q234, Q226, Q204		154
	Eisenmenger syndrome (Complex, mWHO IV)	Q218A		<5†
	Pulmonary arterial hypertension (Complex, mWHO IV)	Q256, Q257		74
	Pulmonary atresia (Complex, mWHO II-IV)	Q255	74739	178
	Transposition of great ateries* (Complex, mWHO III)	Q203	74619	286
	Truncus arteriosus (Complex, mWHO II)	Q200	74609	54
	Other disconnections (ccTGA, isomerisme etc.) (Complex, mWHO III)	Q205, Q208, Q209, Q241		62
Moderate/moderate risk	Atrio-ventricular septal defect (Moderate to complex, mWHO II-III)	Q212	74659, 74641	319
	Ebstein's anomalia (Moderate to complex, mWHO II)	Q225, Q224, Q228, Q229	74661	97
	Pulmonary valve stenosis (Simple to complex, mWHO I-III)	Q220, Q221	74663	321
	Tetralogy of Fallot (Moderate to complex, mWHO II)	Q213	74629	439
	Partly or totally abnormal pulmonary venous connection (Complex, mWHO I)	Q262, Q263, Q242		29
	Coarctatio of the aorta (Moderate to complex, mWHO II)	Q251	74719, 74729	622
	Infundibular right ventricle outflow tract obstruction (Moderate, mWHO II)	Q243		16
	Pulmonary valve regurgitate (Simple to complex, mWHO I-III)	Q222		33
	Subvalvular/supravalvular aortic stenosis (Moderate, mWHO II-III)	Q244, Q252, Q253		86
	Malformation of coronary vessels (ALCAPA, ARCAPA) (Moderate, mWHO II)	Q245		20
	Aortic valve disease (Simple to complex mWHO II-III)	Q230, Q231	74662, 74669	598
	Mitral valve disease (Simple to complex, mWHO II-III	Q232, Q233, Q238, Q239	74660	181
Simple/low risk	Atrial septal defect (Simple, mWHO I-II)	Q211	74649, 74640	1,611
	Ventricular septal defect (Simple, mWHO I-II)	Q210, Q214, Q218, Q219	74639	2,073
	Mild pulmonary stenosis (Simple, mWHO I)	Q223		9

Ductus arteriosus (Simple, mWHO I-II)	Q250	74709	697
Other malformations in aorta (Right aortic arch, vascular ring) (Simple, mWHO I)	Q254		26
Malformations in large veins without hemodynamic Importance (Simple, mWHO I)	Q260, Q264 , Q268		30
Other specified congenital malformations of heart	Q248	74689, 74699	57

*****Women might have more than one diagnosis.

† Exact n is not given due to data privacy policy. The exact number is known by the researchers and used in calculations.

Modified from[1]

Table S2. Crude Hazard ratios of preterm birth and small for gestational age among women with congenital heart disease.

		Crude		
	N events	**HR**	**95% CI**	**Overall p-value**
Any preterm birth (22-36 completed weeks)	46,601			<0.001
No CHD		1		
Simple		1.37	1.5-164	
Moderate		1.47	1.17-1.86	
Complex		3.39	2.52-4.55	
Very preterm (22-31 completed weeks)	6,405			<0.001
No CHD		1		
Simple		1.72	1.17-2.52	
Moderate		1.50	0.79-2.85*	
Complex		5.12	2.88-9.08	
Moderately preterm (32-36 completed weeks)	40,196			<0.001
No CHD		1.32	1.09-1.59	
Simple		1.47	1.15-1.88	
Moderate		3.09	2.24-4.28	
Complex				
Small for gestational age	96,802			<0.001
No CHD		1		
Simple		1.38	1.21-1.58	
Moderate		1.61	1.34-1.93	
Complex		2.40	1.76-3.27	

* not significantly different from simple congenital heart disease

Table S3. Hazard ratios of preterm among women with congenital heart disease – stillbirth as competing risk.

	Crude				Adjusted*			
	N events	**HR**	**95% CI**	**Overall p-value**	**N events**	**HR**	**95% CI**	**Overall p-value**
Any preterm birth (22-36 completed weeks)	46,601			<0.001	45,225			<0.001
No CHD		1				1		
Simple		1.37	1.15-1.63			1.32	1.11-1.58	
Moderate		1.47	1.16-1.85			1.44	1.14-1.82	
Complex		3.34	2.48-4.48			3.22	2.39-4.35	
Very preterm (22-31 completed weeks)	6,405			<0.001	6,216			<0.001
No CHD		1				1		
Simple		1.71	1.17-2.51			1.61	1.09-2.38	
Moderate		1.49	0.78-2.84			1.36	0.69-2.68	
Complex		5.06	2.85-8.97			4.98	2.81-8.83	
Moderately preterm (32-36 completed weeks)	40,196			<0.001	39,009			<0.001
No CHD		1				1		
Simple		1.31	1.09-1.59			1.28	1.06-1.55	
Moderate		1.47	1.15-1.88			1.46	1.14-1.87	
Complex		3.10	2.24-4.28			2.95	2.12-4.12	

*Adjusted for maternal age and calendar year at inclusion, ethnicity, parity and level of education

Table S4. Hazard ratio of preterm birth and small for gestational age among women diagnosed with congenital heart disease before delivery.

	Crude				Adjusted*			
	N events	**HR**	**95% CI**	**Overall p-value**	**N events**	**HR**	**95% CI**	**Overall p-value**
Any preterm birth (22-36 completed weeks)	46,564			<0.001	45,189			<0.001
No CHD		1				1		
Simple		1.43	1.18-1.74			1.39	1.14-1.69	
Moderate		1.58	1.23-2.02			1.54	1.20-1.98	
Complex		3.51	2.58-4.76			3.40	2.49-4.65	
Small for gestational age	96,723			<0.001	93,722			<0.001
No CHD		1				1		
Simple		1.39	1.20-1.61			1.26	1.08-1.46	
Moderate		1.76	1.45-2.13			1.71	1.41-2.08	
Complex		2.49	1.80-3.44			2.42	1.75-3.36	

*Adjusted for maternal age and calendar year at inclusion, ethnicity, parity and level of education

Table S5. Hazard ratio of preterm birth restricted to nulliparous women.

	Crude				Adjusted*			
	N events	**HR**	**95% CI**	**Overall p-value**	**N events**	**HR**	**95% CI**	**Overall p-value**
Any preterm birth (22-36 completed weeks)	25,309			<0.001	24,938			<0.001
No CHD		1				1		
Simple		1.20	0.96-1.49			1.20	0.96-1.50	
Moderate		1.35	1.00-1.82			1.35	0.99-1.82	
Complex		2.98	2.08-4.27			2.93	2.03-4.22	
Small for gestational age	55,790			<0.001	54,906			<0.001
No CHD		1				1		
Simple		1.27	1.09-1.47			1.23	1.06-1.43	
Moderate		1.60	1.31-1.97			1.56	1.27-1.93	
Complex		2.21	1.56-3.13			2.29	1.62-3.24	

*Adjusted for maternal age and calendar year at inclusion, ethnicity, and level of education

Table S6. Hazard ratio of spontaneous preterm birth – stillbirth and induction as competing risk.

	Crude				Adjusted*			
	N events	**HR**	**95% CI**	**Overall p-value**	**N events**	**HR**	**95% CI**	**Overall p-value**
Any preterm birth (22-36 completed weeks)	41,036			<0.001	39,806			<0.001
No CHD		1				1		
Simple		1.40	1.16-1.68			1.36	1.13-1.64	
Moderate		1.38	1.07-1.79			1.37	1.01-1.78	
Complex		3.51	2.60-4.74			3.40	2.50-4.63	

*Adjusted for maternal age and calendar year at inclusion, parity, ethnicity, and level of education

Table S7. Hazard ratio of SGA (SGA defines as falling below two standard deviations of the mean birth weight).

	Crude				Adjusted*			
	N events	**HR**	**95% CI**	**Overall p-value**	**N events**	**HR**	**95% CI**	**Overall p-value**
Small for gestational age	25,056			<0.001	24,182			<0.001
No CHD		1.37	1.09-1.74			1.25	0.98-1.59	
Simple		1.67	1.20-2.31			1.63	1.17-2.27	
Moderate		3.81	2.52-5.75			3.72	2.46-5.64	
Complex								

*Adjusted for maternal age and calendar year at inclusion, parity, ethnicity, and level of education

Supplemental Reference:

1. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2018;39:3165-241.