Congenital Heart Defects and the Risk of Spontaneous Preterm Birth

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Objectives To estimate the association between major types of congenital heart defects (CHD) and spontaneous preterm birth, and to assess the potential underlying mechanisms.

Study design This nationwide, registry-based study included a cohort of all singleton pregnancies in Denmark from 1997 to 2013. The association between CHD and spontaneous preterm birth was estimated by multivariable Cox regression, adjusted for potential confounders. The following potential mechanisms were examined: maternal genetics (sibling analyses), polyhydramnios, preterm prelabor rupture of membranes, preeclampsia, and indicators of fetal and placental growth.

Results The study included 1 040 474 births. Compared with the general population, CHD was associated with an increased risk of spontaneous preterm birth, adjusted hazard ratio 2.1 (95% CI, 1.9-2.4). Several subtypes were associated with increased risks, including pulmonary stenosis combined with a septal defect, 5.2 (95% CI, 3.7-7.5); pulmonary stenosis or atresia, 3.1 (95% CI, 2.4-4.1); tetralogy of Fallot 2.5 (95% CI, 1.6-3.8); coarctation or interrupted aortic arch 2.2 (95% CI, 1.5-3.2); and hypoplastic left heart syndrome, 2.0 (95% CI, 1.0-4.1). Overall, preterm prelabor rupture of membranes mediated more than one-half of the association. Maternal genetics, polyhydramnios, or indicators of fetal or placental growth did not explain the reported associations.

Conclusions CHD, especially right ventricular outflow tract obstructions, were associated with an increased risk of spontaneous preterm birth. The risk was carried by the CHD and not by maternal genetics. Moreover, preterm prelabor rupture of membranes was identified as a potential underlying mechanism. *(J Pediatr 2021;229:168-74)*.

Moderate to severe congenital heart defects (CHD) are diagnosed in 0.6% of live births and represent the largest group of major congenital anomalies.[1] Despite significant clinical improvements over the last decades, CHD remains among the leading causes of childhood mortality and morbidity.[2-5] Worldwide 5%-18% of newborns are born preterm and preterm birth is considered the leading cause of childhood mortality and morbidity.[6-8] Both CHD and preterm birth are associated with an increased risk of neurodevelopmental disorders, currently considered to be the most common and distressful long-term morbidities associated with CHD.[8,9]

Moreover, the combination of CHD and preterm birth has been shown to result in even greater increases in mortality and morbidity. In children born with CHD, preterm birth has been associated with an increased mortality of 3- to 4-fold and an increased risk of neurodevelopmental disorders.[10-16] Newborns with some types of CHD exhibit signs of delayed brain maturation, potentially adding to the detrimental effects of preterm birth on the brain.[17,18]

Previous studies have shown associations between some subgroups of CHD and increased risks of preterm birth.[14,19,20] However, all previous population-based studies relied on external, noncontemporary references, were unable to account for important confounders, and limited numbers resulted in limited ability to address subgroups of CHD.[14,19,20] Only 1 study reported an estimate for the association between CHD and spontaneous preterm birth.[19]

CHD has also been associated with several other prenatal pathologies including polyhydramnios; preeclampsia; smaller placental, fetal, and newborn size; and various measures of smaller brain size.[21-27] However, the potential mechanisms underlying the association between CHD and spontaneous preterm birth, including preterm prelabor rupture of membranes (PPROM), have not been assessed.

We aimed to estimate the association between major types of CHD and spontaneous preterm birth in a large nationwide sample, accounting for a number of potential confounders. Moreover, we aimed to assess the influence of maternal factors and potential mediating effects of indicators of fetal and placental growth, polyhydramnios, PPROM, and preeclampsia.

aHR	Adjusted hazard ratio
BMI	Body mass index
CHD	Congenital heart defects
ICD-10	*International Classification of Diseases, 10th revision*
PPROM	Preterm prelabor rupture of membranes

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Methods

A cohort including all births in Denmark between January 1, 1997, and December 31, 2013, was identified in the Danish Medical Birth Registry. Nonsingleton births, registrations with implausible gestational ages at birth (<22 weeks), and mother-infant pairs without unique personal identifiers were excluded. By the use of the personal identification number assigned to all Danish citizens at birth, parents and newborns were linked to individual level data.[28] Variables from the following nationwide Danish registries were included: The Civil Registration System, The Danish National Patient Registry, The Danish Medical Birth Registry, The Danish Central Cytogenetic Registry, The Danish National Prescription Registry, and the educational registries of Statistics Denmark (**Table 1**; available at www.jpeds.com).[28-33]

In liveborn infants, CHD was identified in the Danish National Patient Registry. In stillbirths, CHD diagnosed prenatally has been registered to the mother since 2006.[34] For the whole period a number of malformations have been registered at birth in stillborn infants.[30] According to previous work we included the *International Classification of Diseases, the 10th revision* (ICD-10) codes Q20-26, excluding the following isolated codes: nonspecific codes of CHD, bicuspid aortic valve, patent ductus arteriosus, and codes not reflecting structural CHD (**Table II**; available at www.jpeds.com).[23,25] Preterm infants are likely to be subject to intense diagnostic investigations and more likely to be diagnosed with small atrial or ventricular septal defects of no clinical significance.[1] Consequently, isolated septal defects not requiring surgery were not considered in the present study. Similar to previous studies diagnoses were grouped into 3 hierarchies of descending diagnostic accuracy: (1) diagnoses from surgical contacts, (2) diagnoses from other contacts at a specialized center, and (3) less severe diagnoses from other university departments or severe diagnoses in individuals deceased before referral.[23,25,35] Only diagnoses from the highest level of accuracy were accepted in each child. CHD was grouped into 13 mutually exclusive groups (**Figure**) (for further details regarding the classification, see **Table II** and the **Appendix** [available at www.jpeds.com]).

Gestational age at birth was identified in the Danish Medical Birth Registry.[30] In 2000, more than 87% of the recordings were based on obstetric ultrasound measurements.[36] In 2004 universal ultrasound screening was implemented nationwide. Like in previous studies, implausible combinations of gestational age and birth weight were identified based on a recent US algorithm (in term births >5 SD or <–5 SD, in preterm births <–4 SD or >3 SD).[23,25,35,37] Gestational age at delivery of less than 37 weeks was defined as preterm birth.[6] In individuals with missing or implausible gestational ages preterm birth was determined on the basis of diagnostic codes in the National Patient Registry.[29] A birth was considered spontaneous when no code of labor induction or caesarean delivery before labor onset was registered (**Table III**; available at www.jpeds.com). As in previous studies placental weight, birth weight, and head circumference were standardized according to gestational age at birth.[23,25,35,38] Implausible values of birth weight were identified as stated above. Regarding the other measures, values more than 5 SDs from the mean were considered implausible and set to missing.

Additional covariates were recorded in accordance with previous studies[25,35,38,39]: maternal age (cubic spline), nulliparity (yes/no), smoking during pregnancy (yes/no), preterm onset preeclampsia (yes/no), prepregnancy hypertension (yes/no), prepregnancy diabetes (yes/no), asthma (yes/no), thyroid disease (yes/no), previous spontaneous preterm birth during the study period (yes/no), and from 2004 and onwards prepregnancy body mass index (BMI; cubic spline). In the child, sex, the presence of major extracardiac birth defects (yes/no), and 4 groups of congenital syndromes were identified: (1) Down syndrome, (2) the 22q11.2 deletion syndrome, (3) other genetic or chromosomal syndromes, and (4) teratogenic syndromes. Moreover, calendar year (cubic spline), parental education (low/medium/high), and non-Western origin (yes/no) were recorded (**Table III** and **Table IV** [available at www.jpeds.com] provide details regarding the definition of covariates).

In the primary analyses the association between subtypes of CHD and the risk of spontaneous preterm birth in liveborn infants was estimated using multivariable Cox proportional hazards regression. The comparison group comprised deliveries of children without CHD. Pregnancies entered the analyses at 22 completed weeks, and were followed until birth or 37 completed weeks, whichever occurred first. Deliveries were censored at the registration of a nonspontaneous delivery. The analyses were adjusted for the following potential confounders: maternal age, nulliparity, smoking, preterm onset preeclampsia, prepregnancy hypertension, prepregnancy diabetes, child sex, congenital syndromes, major extracardiac birth defects, calendar year, and parental education. Potential confounders were selected based on a priori knowledge and causal diagrams.[40] Clustering within mothers was accounted for using robust standard errors.

To investigate the influence of maternal genetics, maternal CHD, and other factors remaining constant within each mother between pregnancies, sibling analyses were conducted, comparing only pregnancies discordant on CHD status within the same mother. For this analysis a stratified Cox proportional regression model was applied (**Appendix**, Sibling Analyses).[38] To explore the potential mechanisms underlying the association between CHD and preterm birth, we assessed the potential mediating effect of prespecified potential mediators (mediation analyses).[41,42] This approach allows for the quantification of the overall proportion of the association (between CHD and preterm birth) eliminated, accounting for each mediator separately (**Appendix**, Mediation Analyses). Mediators considered were PPROM, polyhydramnios, and indicators of fetal and placental growth (head circumference z-score, birth weight z-score, and placental weight z-score). These analyses were

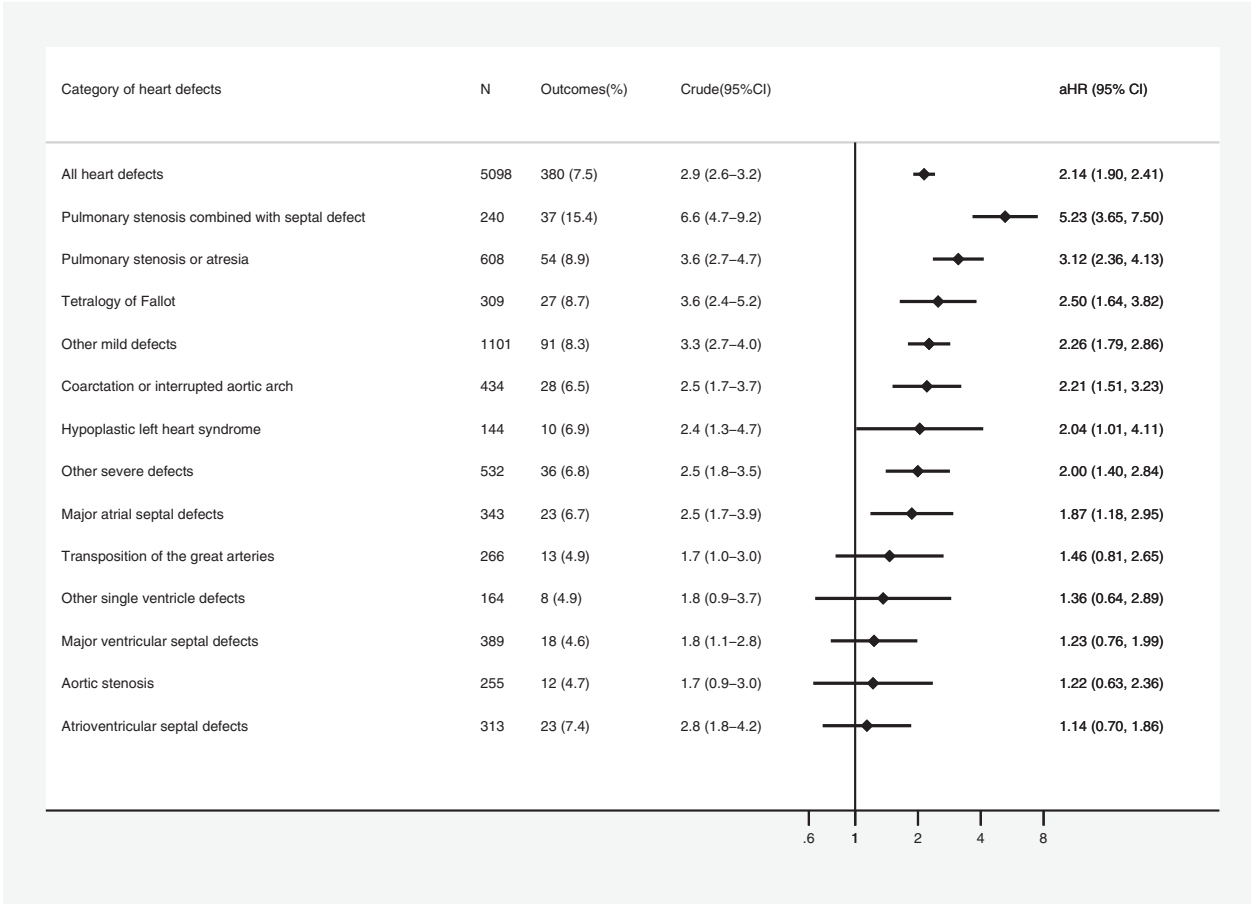

Figure. The associations between categories of heart defects and the risk of spontaneous preterm birth compared with pregnancies without heart defects in 1 040 474 singleton pregnancies, Denmark, 1997 to 2013. *N*, number of individual pregnancies within each category. *Outcomes,* report the number of spontaneous preterm births within each category. *Crude* shows the unadjusted hazard ratios for spontaneous preterm birth. aHR shows the aHRs for spontaneous preterm birth. The estimates were adjusted for maternal age, parity, smoking, prepregnancy hypertension, prepregnancy diabetes, preterm onset preeclampsia, parental education, newborn sex, extracardiac malformations, 4 groups of congenital syndromes, and calendar year. The comparison group consisted of 1 035 376 pregnancies with no heart defect.

carried out in 3 prespecified groups: (1) overall CHD; (2) right ventricular outflow tract obstructions—pulmonary stenosis with or without a septal defect, pulmonary atresia, or tetralogy of Fallot; and (3) left ventricular outflow tract obstructions—hypoplastic left heart syndrome, coarctation of the aorta, or aortic stenosis. All covariates included in the main analyses were also included in the mediation analyses as potential confounders.

Preplanned sensitivity analyses were conducted to test the robustness of the primary analysis. To address potential residual confounding from congenital syndromes we repeated the analyses excluding all infants with a known syndrome. To assess the influence of missing gestational ages (9411 observations [0.9%]) we repeated the primary analyses using logistic regression, identifying spontaneous preterm birth based on ICD-10 codes (**Table III**). To assess the potential influence of fetal death, we included stillbirths in the analyses, censoring stillborn infants. To test the influence of missing data, we omitted the variable with the largest fraction of missing values (maternal smoking, 37 006 observations [3.5%]). Because the relationship between CHD and preeclampsia remains incompletely understood, we repeated the analyses without this covariate. To assess the potential influence of other variables not consistently associated with CHD or preterm birth in previous studies, several variables were added separately to the primary analyses, including non-Western origin, maternal thyroid disease, asthma, and previous spontaneous preterm birth during the study period. Finally, we assessed whether additional adjustment for BMI changed the results in births with available BMI measurements. All sensitivity analyses, except additional adjustment for BMI, were carried out in all heart defects and in the different subgroups. Additional adjustment for BMI was only possible in all heart defects.

All analyses were conducted in Stata 15 (StataCorp LP, College Station, Texas). The study was approved by the Danish Data Protection Agency (reference 1-16-02-388-16).

Results

Overall, 1 092 740 births were registered during the time period and 71 707 (6.6%) were born preterm. After exclusions (nonsingletons, 47 646; no unique identifier, 359; implausible gestational age, 131; stillbirths, 4130) the primary analyses included 1 040 474 liveborn singletons, 5098 infants with CHD, and 1 035 376 infants without CHD. Summary statistics according to the presence of CHD are shown in **Table V**. Overall, 48 314 (4.7%) singletons in the general population and 702 (13.8%) singletons with CHD were born preterm. The number of spontaneous preterm births was 28 213 (2.7%) in the general population and 380 (7.5%) in children with CHD. Overall, 4130 (0.4%) of pregnancies ended in stillbirth. The number of infants in each subgroup of CHD and the number of spontaneous preterm birth is shown in the **Figure**.

The primary analyses included 107 784 425 gestational days at risk. Overall, CHD was associated with an increased risk of preterm birth compared with the general population, adjusted hazard ratio (aHR) 2.1 (95% CI, 1.9-2.4). Subtypes of CHD associated with an increased risk (aHR) were pulmonary stenosis combined with a septal defect, 5.2 (95% CI, 3.7-7.5); pulmonary stenosis or atresia, 3.1 (95% CI, 2.4-4.1); tetralogy of Fallot 2.5 (95% CI, 1.6-3.8); coarctation or interrupted aortic arch 2.2 (95% CI, 1.5-3.2); hypoplastic left heart syndrome 2.0 (95% CI, 1.0-4.1); large atrial septal defects 1.9 (95% CI, 1.2-3.0); other mild defects 2.3 (95% CI, 1.8-2.9); and other severe defects 2.0 (95% CI, 1.4-2.8) (**Figure**).

In the sibling analyses the results were similar to the results of the primary analysis (aHR): overall 2.8 (95% CI, 2.0-3.8) vs 2.1 (95% CI, 1.9-2.4); right ventricular outflow tract obstructions 3.0 (95% CI, 1.6-5.6) vs 3.3 (95% CI, 2.7-4.0); and left ventricular outflow tract obstructions 2.5 (95% CI, 1.1-5.8) vs 1.8 (95% CI, 1.4-2.5). The number of deliveries after PPROM was 11 884 (1.2%) in the general population and 157 (3.1%) in CHD deliveries. The number of pregnancies with polyhydramnios was 3794 (0.4%) in the general population and 122 (2.4%) in CHD pregnancies. As documented in previous studies CHD was associated with lower head circumference z-score, birth weight z-score, and placental weight z-score.[23,25] Considering the mediating effect of PPROM, the overall proportion eliminated in CHD was 53% (95% CI, 41-66) and 56% (95% CI, 39-73) in right ventricular outflow tract obstructions. No mediating effect of PPROM was found in left ventricular outflow tract obstructions. No evidence of a mediating effect of polyhydramnios or any indicator of fetal or placental growth was found.

The results of the primary analyses were similar when infants with known congenital syndromes were excluded, when diagnostic codes of preterm birth were used in cases of missing gestational age, and in the analysis including fetal deaths. Moreover, when smoking and preeclampsia were removed from the model, the results were virtually unchanged. Additional adjustment for non-Western origin, maternal thyroid disease, asthma, previous spontaneous preterm birth, or BMI resulted in estimates similar to the primary analysis (**Table VI** [available at www.jpeds.com] shows the results of the sensitivity analyses).

Table V. Characteristics of 1 040 474 singleton pregnancies according to the presence of CHD, Denmark, 1997 to 2013

Characteristics	Heart defects (n = 5098)	General population (n = 1 035 376)*
Maternal		
Age, years†	30.4 ± 5.1	30.4 ± 4.9
Nulliparity‡	2199 (43.1)	448132 (43.3)
BMI, kg/m²§	23.3 (21-27)	23.1 (21-26)
Smoking during pregnancy‡	833 (16.3)	152 000 (14.7)
Prepregnancy hypertension‡	146 (2.9)	20 613 (2.0)
Prepregnancy diabetes‡	198 (3.9)	23 646 (2.3)
Preterm onset preeclampsia‡	134 (2.6)	12 615 (1.2)
Thyroid disease‡	72 (1.4)	12 964 (1.3)
Asthma‡	278 (5.5)	51 610 (5.0)
Previous spontaneous preterm birth‡	96 (1.9)	16 802 (1.6)
Parental		
Lower education‡	587 (11.5)	94 148 (9.1)
Medium education‡	2430 (47.7)	468 027 (45.2)
Higher education‡	2081 (40.8)	473 201 (45.7)
Non-Western origin‡	806 (15.8)	149 841 (14.5)
Newborn		
Male sex‡	2675 (52.5)	530 960 (51.3)
Down syndrome‡	269 (5.3)	511 (0.1)
22q11.2 deletion‡	78 (1.5)	100 (0.0)
Teratogenic syndrome‡	20 (0.4)	408 (0.0)
Other genetic or chromosomal syndromes‡	504 (9.9)	4352 (0.4)
Major extracardiac malformations‡	900 (17.7)	29 981 (2.9)
Calendar year§	2004 (2000-2008)	2005 (2001-2009)

*Singleton pregnancies with no fetal heart defects according to the study definition.
†Values are mean ± SD.
‡number (%).
§median (IQR).

Discussion

CHD was associated with more than a 2-fold increased risk of spontaneous preterm birth. Right ventricular outflow tract obstructions were associated with an even greater risk. The severe left-sided defects were associated with a smaller increase in the risk of preterm birth. However, severe defects such as other single ventricle defects and transposition of the great arteries were not associated with a statistically significantly increased risk. The reported associations could not be explained by maternal genetics, maternal CHD, or other time stable maternal factors, indicating that the risk of preterm birth is likely carried by the fetal CHD rather than maternal factors. We found no indications that

polyhydramnios or any indicator of fetal or placental growth mediated the reported associations. However, accounting for PPROM revealed a large decrease in the estimated associations in CHD overall as well as in right ventricular outflow tract obstructions, but not in left ventricular outflow tract obstructions. Consequently, mechanisms acting through PPROM may explain part of the association.

Three population-based studies have investigated the association between subtypes of CHD and preterm birth.[14,19,20] Common to all studies is the lack of a contemporary comparison group with individual level information. Moreover, several comparisons are hampered by the application of more heterogeneous groups of CHD in some studies[19,20] and small numbers in the different subgroups.[20] Only 1 study provided an estimate of the association between CHD and spontaneous preterm birth.[19] Two studies dealt with congenital syndromes by exclusion, but several important common causes of CHD and preterm birth were not accounted for in one or more of the studies including multiple births, congenital syndromes, and extracardiac malformations, as well as the majority of potential confounders included in the present study.[14,19,20]

Nevertheless, our estimates are in line with previous studies reporting an association between any CHD and an approximately 2-fold increased risk of preterm birth (1.7-2.4).[14,19,20] The association between right ventricular outflow tract obstructions and a highly increased risk of preterm birth is in line with 1 previous study (the only study dealing with right ventricular outflow tract obstructions) and summary statistics of 2 other studies.[14,43,44] The association between coarctation of the aorta and the risk of spontaneous preterm birth, was also implied by 3 previous studies and summary statistics of another study.[14,19,20,43] A similar summary statistic has been published regarding hypoplastic left heart syndrome.[43] The association did not reach statistical significance in 2 previous studies.[14,20] In the present study, atrioventricular septal defects were associated with a high risk of spontaneous preterm birth in the unadjusted analysis that disappeared after adjustment for congenital syndromes. Studies not accounting for congenital syndromes indicated increased risks.[14,43] Finally, we found no clear indications of associations between other single ventricle defects or transposition of the great arteries and an increased risk of spontaneous preterm birth, which is also in accordance with 2 previous studies.[14,43]

In line with our results, 1 study reported no difference in estimates when growth restricted infants with CHD were excluded from the analyses.[19]

Disturbances of in utero circulation, decreased perfusion, and organ hypoxia have been suspected to underlie the association between some types of CHD and reduced fetal growth.[25,26,45] In the present study, indicators of fetal or placental growth did not mediate the reported associations with preterm birth. Moreover, transposition of the great arteries, believed to result in a pronounced decrease of cerebral oxygen delivery, and single ventricle defects believed to result in a large reduction in combined ventricular output, were not clearly associated with spontaneous preterm birth.[25,45] In contrast, right ventricular outflow tract obstructions were associated with a large increase in risk and left ventricular outflow tract obstructions with a smaller increase. It remains unclear whether CHD per se may result in circulatory disturbances triggering spontaneous preterm birth, but based on our results it may be speculated that outflow tract obstructions could be a potential trigger of spontaneous preterm birth.

PPROM potentially mediates about one-half of the increased risk associated with CHD and right ventricular outflow tract obstructions. Previous studies have associated PPROM with abnormal fetal cardiac function, also reported in right-sided fetal CHD, leaving the potential, but highly speculative, explanation that anomalies of fetal circulation might increase the risk of PPROM.[46-50] Moreover, in accordance with a previous study we speculate that CHD and PPROM, cervical insufficiency or disorders of connective tissue of the membranes may share a common cause, either genetic or environmental.[19] Several candidate genes underlying spontaneous preterm birth have been identified; however, no large studies have investigated the genetics underlying both preterm birth and CHD.[51] The present study does not support a major role for maternal genetics. In accordance with this finding, the fetal membranes originate solely from the fetus.[52] Several studies have associated CHD with abnormal placentation,[53] and it may also be speculated that the fetal placenta originating from the same blastocyst as the fetus could be involved in the pathophysiology of spontaneous preterm birth.

Several limitations apply. The study included several confounders, including detailed information on congenital syndromes from different sources. Nevertheless, unknown confounding factors cannot be ruled out.

Based on a previous validation study, and application of the current categorization in previous studies, misclassification of CHD is an unlikely explanation for the present results.[54] However, the inability to differentiate the different types of coarctation of the aorta based on ICD-10 codes is a limitation of the present study. The high validity of the registration of gestational age at birth has also been confirmed.[23,25] The validity of the remaining covariates has not been assessed in detail. Potential underdiagnosis of the 22q11.2 deletion syndrome (sometimes only associated with subtle dysmorphic features) is an unlikely explanation for the results, because the syndrome was not associated with an increased risk of spontaneous preterm birth in the present study (data not shown). In a nationwide study, selection bias owing to nonparticipation is not an issue. The number of missing values was low, and the results did not change after omitting the variable with the highest fraction of missing values, after considering diagnostic codes of preterm birth in infants with missing gestational ages, or accounting for stillbirths in the analyses.

The mediation analyses rely on strong assumptions of no confounding of both the CHD-mediator relationship and the mediator-preterm birth relationship.[41] We included

several known confounders, but unknown or unmeasured confounders may exist. Furthermore, longitudinal measures of fetal or placental growth were not available for these analyses and we had to rely on cross-sectional measures. Finally, it must be kept in mind that multiple comparisons are integral in studies examining multiple subgroups.

Future studies are warranted to investigate the association between prenatal changes in the fetal circulation and the risk of PPROM and spontaneous preterm birth in fetuses with CHD. Moreover, studies of fetal genetics underlying both CHD and PPROM would be of great interest. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890-900.
2. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. Circulation 2010;122:2254-63.
3. Jacobs JP, He X, Mayer JE Jr, Austin EH III, Quintessenza JA, Karl TR, et al. Mortality trends in pediatric and congenital heart surgery: an analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. Ann Thorac Surg 2016;102:1345-52.
4. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544.
5. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. J Am Coll Cardiol 2010;56:1149-57.
6. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.
7. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet 2016;388:3027-35.
8. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261-9.
9. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics 2015;135:816-25.
10. Attar MA, Dechert RE, Schumacher RE. The effect of late preterm birth on mortality of infants with hypoplastic left heart syndrome. Am J Perinatol 2012;29:593-7.
11. Atz AM, Travison TG, Williams IA, Pearson GD, Laussen PC, Mahle WT, et al. Prenatal diagnosis and risk factors for preoperative death in neonates with single right ventricle and systemic outflow obstruction: screening data from the Pediatric Heart Network Single Ventricle Reconstruction Trial. J Thorac Cardiovasc Surg 2010;140:1245-50.
12. Costello JM, Pasquali SK, Jacobs JP, He X, Hill KD, Cooper DS, et al. Gestational age at birth and outcomes after neonatal cardiac surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Circulation 2014;129:2511-7.
13. Laas E, Lelong N, Ancel PY, Bonnet D, Houyel L, Magny JF, et al. Impact of preterm birth on infant mortality for newborns with congenital heart defects: the EPICARD population-based cohort study. BMC Pediatr 2017;17:124.
14. Tanner K, Sabrine N, Wren C. Cardiovascular malformations among preterm infants. Pediatrics 2005;116:e833-8.
15. Goff DA, Luan X, Gerdes M, Bernbaum J, D'Agostino JA, Rychik J, et al. Younger gestational age is associated with worse neurodevelopmental outcomes after cardiac surgery in infancy. J Thorac Cardiovasc Surg 2012;143:535-42.
16. Newburger JW, Sleeper LA, Bellinger DC, Goldberg CS, Tabbutt S, Lu M, et al. Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the single ventricle reconstruction trial. Circulation 2012;125:2081-91.
17. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, et al. Brain maturation is delayed in infants with complex congenital heart defects. J Thorac Cardiovasc Surg 2009;137:529-36 [discussion: 36-7].
18. Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, et al. Abnormal brain development in newborns with congenital heart disease. N Engl J Med 2007;357:1928-38.
19. Laas E, Lelong N, Thieulin AC, Houyel L, Bonnet D, Ancel PY, et al. Preterm birth and congenital heart defects: a population-based study. Pediatrics 2012;130:e829-37.
20. van Velzen CL, Türkeri F, Pajkrt E, Clur SA, Rijlaarsdam MEB, Bax CJ, et al. Pregnancy complications in singleton pregnancies with isolated fetal heart defects. Acta Obstet Gynecol Scand 2016;95:1273-80.
21. Hara K, Kikuchi A, Miyachi K, Sunagawa S, Takagi K. Clinical features of polyhydramnios associated with fetal anomalies. Congenit Anom 2006;46:177-9.
22. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association between preeclampsia and congenital heart defects. JAMA 2015;314:1588-98.
23. Matthiesen NB, Henriksen TB, Agergaard P, Gaynor JW, Bach CC, Hjortdal VE, et al. Congenital heart defects and indices of placental and fetal growth in a nationwide study of 924 422 liveborn infants. Circulation 2016;134:1546-56.
24. Lauridsen MH, Uldbjerg N, Petersen OB, Vestergaard EM, Matthiesen NB, Henriksen TB, et al. Fetal heart defects and measures of cerebral size. J Pediatr 2019;210:146-53.
25. Matthiesen NB, Henriksen TB, Gaynor JW, Agergaard P, Bach CC, Hjortdal VE, et al. Congenital heart defects and indices of fetal cerebral growth in a nationwide cohort of 924 422 liveborn infants. Circulation 2016;133:566-75.
26. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL Jr, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. Circulation 2010;121:26-33.
27. Hansen T, Henriksen TB, Bach CC, Matthiesen NB. Congenital heart defects and measures of prenatal brain growth: a systematic review. Pediatr Neurol 2017;72:7-18.e1.
28. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541-9.
29. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39:30-3.
30. Bliddal M, Broe A, Pottegard A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. Eur J Epidemiol 2018;33:27-36.
31. Agergaard P, Olesen C, Ostergaard JR, Christiansen M, Sorensen KM. The prevalence of chromosome 22q11.2 deletions in 2,478 children with cardiovascular malformations. A population-based study. Am J Med Gen A 2012;158A:498-508.
32. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38-41.
33. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health 2011;39:91-4.

34. Svensson E, Ehrenstein V, Norgaard M, Bakketeig LS, Rothman KJ, Sorensen HT, et al. Estimating the proportion of all observed birth defects occurring in pregnancies terminated by a second-trimester abortion. Epidemiology 2014;25:866-71.
35. Matthiesen NB, Agergaard P, Henriksen TB, Bach CC, Gaynor JW, Hjortdal V, et al. Congenital heart defects and measures of fetal growth in newborns with Down syndrome or 22q11.2 deletion syndrome. J Pediatr 2016;175:116-22.e4.
36. Jørgensen FS. [Ultrasonography of pregnant women in Denmark 1999-2000. Description of the development since 1980-1990]. Ugeskr Laeger 2003;165:4409-15.
37. Talge NM, Mudd LM, Sikorskii A, Basso O. United States birth weight reference corrected for implausible gestational age estimates. Pediatrics 2014;133:844-53.
38. Aagaard K, Bach CC, Henriksen TB, Larsen RT, Matthiesen NB. Head circumference at birth and childhood developmental disorders in a nationwide cohort in Denmark. Paediatr Perinatol Epidemiol 2018;32:458-66.
39. Boyd HA, Basit S, Behrens I, Leirgul E, Bundgaard H, Wohlfahrt J, et al. Association between fetal congenital heart defects and maternal risk of hypertensive disorders of pregnancy in the same pregnancy and across pregnancies. Circulation 2017;136:39-48.
40. Williams TC, Bach CC, Matthiesen NB, Henriksen TB, Gagliardi L. Directed acyclic graphs: a tool for causal studies in paediatrics. Pediatr Res 2018;84:487-93.
41. Vanderweele TJ. A unification of mediation and interaction: a 4-way decomposition. Epidemiology 2014;25:749-61.
42. Discacciati A, Bellavia A, Lee JJ, Mazumdar M, Valeri L. Med4way: a Stata command to investigate mediating and interactive mechanisms using the four-way effect decomposition. Int J Epidemiol 2019;48:15-20.
43. Rosenthal GL, Wilson PD, Permutt T, Boughman JA, Ferencz C. Birth weight and cardiovascular malformations: a population-based study: the Baltimore-Washington infant study. AmJ Epidemiol 1991;133:1273-81.
44. Francannet C, Lancaster PAL, Pradat P, Cocchi G, Stoll C. The epidemiology of three serious cardiac defects. A joint study between five centres. Eur J Epidemiol 1993;9:607-16.
45. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation 2015;131:1313-23.
46. Müller ALL, De M, Barrios P, Kliemann LM, Valério EG, Gasnier R, et al. Tei index to assess fetal cardiac performance in fetuses at risk for fetal inflammatory response syndrome. Ultrasound Obstet Gynecol 2010;36:26-31.
47. Romero R, Espinoza J, Gonçalves LF, Gomez R, Medina L, Silva M, et al. Fetal cardiac dysfunction in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2004;16:146-57.
48. Chen Y, Lv G, Li B, Wang Z. Cerebral vascular resistance and left ventricular myocardial performance in fetuses with Ebstein's anomaly. Am J Perinatol 2009;26:253-8.
49. Inamura N, Kado Y, Nakajima T, Kayatani F. Left and right ventricular function in fetal tetralogy of Fallot with absent pulmonary valve. AmJ Perinatol 2005;22:199-204.
50. Inamura N, Taketazu M, Smallhorn JF, Hornberger LK. Left ventricular myocardial performance in the fetus with severe tricuspid valve disease and tricuspid insufficiency. Am J Perinatol 2005;22:91-7.
51. Hallman M, Haapalainen A, Huusko JM, Karjalainen MK, Zhang G, Muglia LJ, et al. Spontaneous premature birth as a target of genomic research. Pediatr Res 2019;85:422-31.
52. Bourne G. The foetal membranes: a review of the anatomy of normal amnion and chorion and some aspects of their function. Postgrad Med J 1962;38:193-201.
53. Courtney JA, Cnota JF, Jones HN. The role of abnormal placentation in congenital heart disease; cause, correlate, or consequence? Front Physiol 2018;9:1045.
54. Agergaard P, Hebert A, Bjerre J, Sorensen KM, Olesen C, Ostergaard JR. Children diagnosed with congenital cardiac malformations at the national university departments of pediatric cardiology: positive predictive values of data in the Danish National Patient Registry. Clin Epidemiol 2011;3:61-6.
55. World Health Organization (WHO). International classification of diseases. http://apps.who.int/classifications/icd10/browse/2015/en. Accessed July 18, 2019.
56. The Nordic Medico-Statistical Committee Classification of Surgical Procedures Version 1.16 (NOMESCO). www.nordclass.se/NCSP_1_16.pdf. Accessed July 18, 2019.
57. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.
58. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med 2013;369:830-9.
59. Kemppainen M, Lahesmaa-Korpinen AM, Kauppi P, Virtanen M, Virtanen SM, Karikoski R, et al. Maternal asthma is associated with increased risk of perinatal mortality. PloS One 2018;13:e0197593.
60. Garne E, Hansen AV, Morris J, Zaupper L, Addor M-C, Barisic I, et al. Use of asthma medication during pregnancy and risk of specific congenital anomalies: A European case-malformed control study. J Allergy Clin Immunol 2015;136:1496-502.e1497.

Table I. Danish registries and information used in the study

Registry	Established	General content	Information used in the study
The Civil Registration System[28,*]	1968	Administrative data on all persons living in Denmark	a) Unique personal identifiers of all newborns, mothers, and fathers b) Parental citizenship and place of birth
The Danish National Patient Registry[29,*]	1977	Individual-level data on all outpatient and inpatient admission to all Danish hospitals	a) Unique personal identifiers of all newborns and mothers b) Information on the specific hospital and hospital ward c) Physician assigned diagnoses[†] d) Surgeon assigned procedural and surgical codes[‡]
The Danish Medical Birth Registry[30,*]	1973	Individual-level data on all births in Denmark	a) Unique personal identifiers of all newborns, mothers, and fathers b) Data on multiple pregnancies c) Maternal: age, parity, smoking, prepregnancy BMI (since 2004), last menstrual period d) Child: birthdate and calendar year, sex, gestational age at birth, birth weight, head circumference (since 1997), placental weight (since 1997) e) Data on: cesarean deliveries, labor induction, PPROM, and polyhydramnios
The Danish Cytogenetic Central Registry[54,*]	1968	Individual level data on all cytogenetic tests performed in Denmark	a) Unique personal identifiers of all newborns b) Karyotypes of trisomy 21 c) Karyotypes of 22q11.2 deletions d) Other abnormal karyotypes
The Danish National Prescription Registry[32,*]	1994	Individual level information on all redeemed drug prescriptions in Denmark	a) Unique personal identifiers of all mothers b) Redeemed prescriptions of antihypertensive drugs c) Redeemed prescriptions of antidiabetic drugs d) Redeemed prescriptions of thyroid medication e) Redeemed prescriptions of asthma medication
Educational registries of Statistics Denmark[33]	1981	Individual level information on date and type of the highest completed or ongoing education	a) Unique personal identifiers of all mothers and fathers b) Highest completed or ongoing education of either parent

*The reporting to the registries is mandatory for all health care professionals in Denmark.
†All diagnoses throughout the study period were classified according to the ICD-10.[2,7] Before 1994, diagnoses were classified according to the ICD-8.[2]
‡Surgeries and procedures are classified according to the Nordic Classification of Procedures.[2,8] For a more in depth description of the registries please refer to the paper cited under each registry or to the supplemental material of previous studies.[9-11]

Table II. Diagnostic codes (ICD-10)[55] and surgical codes (NOMESCO)[56] used to identify subtypes of CHD

Severity	Subgroups	Codes (ICD-10)	Surgery
Highest	Hypoplastic left heart syndrome*	Q23.4	
	Other single ventricle defects*	Q20.4, Q22.6 or	Single ventricle surgery: KFAE, KFAF, KFBL40, KFDA, KFHH00
Intermediate	Transposition of the great arteries	Q20.3	
	Tetralogy of Fallot†	Q21.3	
	Atrioventricular septal defects	Q21.2, Q21.8B	
	Aortic stenosis	Q23.0, Q24.4, Q25.3	
	Coarctation of the aorta or Interrupted aortic arch‡	Q25.1, Q25.2	
	Pulmonary atresia§	Q22.0, Q25.5	
	Other severe defects¶	Q20.0, Q20.1, Q20.2, Q20.5, Q20.6, Q20.8, Q21.4, Q22.5, Q24.2, Q24.5, Q22.4, Q23.2, Q26.2, Q26.3, Q26.4	
Lowest	Major ventricular septal defects**	Q21.0 and	Isolated ventricular septal defect surgery: KFHB, KFHC
	Major atrial septal defects**	Q21.1 and	Isolated atrial septal defect surgery: KFFC excluding KFCC42, KFFD
	Pulmonary stenosis§	Q22.1, Q24.3, Q25.6,	
	Pulmonary stenosis combined with a septal defect††	Q21.0 /Q21.1, and Q22.1 /Q24.3 /Q25.6	
	Other mild defects‡‡	Q21.0 & Q21.1, Q21.8, Q22.2, Q22.3, Q22.8, Q23.1, Q23.4, Q23.8, Q24.0, Q24.1, Q24.8, Q25.4, Q25.8, Q26.8	

Severity: Highest, EUROCAT severity group I; intermediate, EUROCAT severity group II; lowest, EUROCAT severity group III. ICD-10: International Classification of Diseases, the tenth revision.[55] Surgeries: Surgical codes according to the Nordic Classification of Procedures.[56]

*Hypoplastic left heart syndrome omitted a diagnosis of other single ventricle defects. Other single ventricle defects required either a relevant diagnostic code or a code of single ventricle surgery.

†When both tetralogy of Fallot and pulmonary atresia were diagnosed in the same individual, the defect was categorized as tetralogy of Fallot.

‡Interrupted aortic arch was classified with coarctation of the aorta owing to low numbers.

§Pulmonary atresia with no other defects except minor were registered with pulmonary stenosis owing to low numbers.

¶Other severe defects included (1) isolated lesions with low numbers: common arterial trunk, double outlet right ventricle, double outlet left ventricle, ventricular inversion, isomerism of atrial appendages, other malformations of cardiac chambers and connections, aortopulmonary septal defects, tricuspid valve stenosis, Ebstein anomaly, mitral valve stenoses, cor triatriatum, malformations of the coronary vessels, and anomalous pulmonary venous return; and (2) combinations of at least 2 lesions of intermediate severity.

**Major ventricular septal defects and major atrial septal defects required both an isolated diagnostic code and an appropriate surgical code.

††Owing to the large size of the group, combinations of septal defects and pulmonary stenosis were categorized together. This group represents combinations of pulmonary stenosis and a septal defect not anatomically in accordance with a diagnosis of tetralogy of Fallot.

‡‡Other mild defects included (1) isolated lesions with low numbers: other malformations of the cardiac septa, pulmonary insufficiency, other congenital malformations of the pulmonary valve, other congenital malformations of the tricuspid valve, congenital aortic insufficiency, congenital mitral insufficiency, other congenital malformations of aortic and mitral valves, dextrocardia, levocardia, other specified congenital malformations of the heart, other congenital malformations of the aorta, other congenital malformations of the pulmonary artery, other congenital malformations of the great arteries, and other congenital malformations of the great veins. (2) Combinations of at least 2 lesions of the lowest severity including combinations of ventricular septal defects and atrial septal defects.

Table III. Definitions of variables included in the study

Variable	Definition
Maternal	
Age	Numerical value
Parity	Numerical value, categorized into: (0) parous; (1) nulliparous
Smoking during pregnancy	Numerical codes of maternal smoking, categorized into: (0) no smoking; (1) smoking
Preterm onset preeclampsia*	Any code (ICD-10*: O14.0 to O15.9)* of preeclampsia between 20 and 37 completed weeks of gestation, categorized into: (0) no preterm onset preeclampsia; (1) preterm onset preeclampsia
Prepregnancy hypertension†	Any code of chronic hypertension before the end of the first trimester (ICD-10: I1, O10-O11 and ICD-8: 40), or any code of pregnancy related hypertension during the first trimester (ICD-10: O13-O17), or a minimum of 2 prescriptions of separate classes of antihypertensive drugs within 90 days before the end of the first trimester (α adrenergic blockers, ATC: C02A, C02B, C02C, nonloop diuretics, ATC: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, vasodilators, ATC: C02DB, C02DD, C02DG, C04, C05, β blockers, ATC: C07, calcium channel blockers, ATC: C07F, C08, C09BB, C09DB, renin-angiotensin system inhibitors, ATC: C09), categorized into: (0) no prepregnancy hypertension; (1) prepregnancy hypertension
Prepregnancy diabetes‡	Any diagnosis of chronic or pregnancy related diabetes before the end of the first trimester (ICD10: E10-E14, O24 and ICD-8: 249-250, 63474, Y6449) or at least 2 redeemed prescriptions of anti-diabetic drugs before the end of the first trimester (ATC: *A10*), categorized into: (0) no prepregnancy diabetes; (1) prepregnancy diabetes
Thyroid disease	Any prescription of thyroid medication between 6 months before conception and the date of birth (ATC code H03), categorized into: (0) no thyroid disease; (1) thyroid disease
Asthma§	Any prescription of asthma medication between 3 months before conception and the date of birth (ATC code R03), categorized into: (0) no maternal asthma; (1) maternal asthma
Previous spontaneous preterm birth	Any registration of prior spontaneous preterm birth during the study period, categorized into: (0) No previous spontaneous preterm birth; (1) previous spontaneous preterm birth
Prepregnancy BMI	Numerical value
Child	
Sex	Gender, categorized into: (0) female; (1) male
Congenital syndromes	ICD-10 codes and karyotypes (for coding details see **Table IV**), categorized into: (0) no congenital syndrome registered; (1) Down syndrome; (2) The 22q11.2 deletion syndrome; (3) other genetic or chromosomal syndromes; (4) teratogenic syndromes
Major extracardiac malformations	ICD-10 codes categorized into (for coding details see **Table IV**): (0) no major extracardiac malformation registered; (1) major extracardiac malformation registered
Other variables	
Calendar year	Numerical value
Parental education	Educational codes of both parents' highest completed and ongoing education. The highest education (completed or ongoing) of either parent, categorized into: (0) low: lower secondary school or lower education, including no registered education; (1) medium: vocational, postcompulsory, or short-cycle higher education; (3) high: medium-cycle higher education, bachelor's degree, master's degree or higher
Parental non-Western origin¶	Either maternal or paternal origin or citizenship outside the following countries/regions: countries part of the European Union in 1997 (France, Belgium, Germany, Holland, Italy, Luxembourg, Ireland, Greece, Portugal, Great Britain, Spain, Finland, Austria, Denmark, Sweden), other countries in western Europe (Norway, Iceland, Andorra, Switzerland, Monaco, Liechtenstein, the Vatican, San Marino), countries in North America (the USA, Canada), and Australia (New Zealand, Australia), categorized into: (0) Western origin; (1) non-Western origin
PPROM	Any code of prelabor rupture of membranes (ICD-10: O42) and gestational age at birth before 37 completed weeks, categorized into: (0) no PPROM; (1) PPROM
Preterm birth	Any code (ICD-10: P07.2, P07.3, H35.1, P59.0, P61.2, Z87.6A, Z876.B) indicating preterm birth in newborns with missing information on gestational age at birth, categorized into: (0) no preterm birth registered; (1) preterm birth registered
Spontaneous birth	Any birth not registered with a diagnostic code of labor induction (ICD10: O80.2, O80.3, O83.8A), or cesarean section performed before labor onset (ICD10: O82.0, O82.1A, NOMESCO: KMCA10A, KMCA10B), categorized into: (0) nonspontaneous birth; (1) spontaneous birth
Polyhydramnios	Any code of polyhydramnios (ICD-10: O40), categorized into: (0) no polyhydramnios; (1) polyhydramnios

*Diagnostic codes were applied in accordance with a previous study.[39]
†Diagnostic and therapeutical codes in accordance with previous studies.[23,25,38,57]
‡Diagnostic and therapeutical codes in accordance with previous studies.[38,58]
§Therapeutic codes in accordance with previous studies.[59,60]
¶Coding in accordance with previous studies.[23,25]

Table IV. Diagnostic Codes (ICD-10) applied for the categorization of congenital birth defects and syndromes

Subgroups of birth defects and syndromes	ICD-10 codes and karyotypes
Isolated minor malformations*	Q101-Q103, Q105, Q135, Q170-Q175, Q179, 180-Q182, Q184-Q187, Q189, Q211C, Q250 (if gestational age <37), Q270, Q314, Q315, Q320, Q331, Q381, Q382, Q385, Q400, Q401, Q430, Q523 Q525 Q53, Q552F, Q610, Q627, Q633, Q662-Q669, Q670-Q678, Q680, Q682A, Q683-685, 740G, Q752, Q753, Q760, Q764L, Q765, Q766A, Q766C, Q767C, Q825, Q833, Q845, Q899.
Note: Not included in the study according to the European surveillance of congenital anomalies.[55]	*Examples: protuberant ears, stenosis or stricture of lacrimal duct, hallux varus etc.*
Major extracardiac defects†	Malformations of the nervous system: Q00-07
Note: Excluding all minor malformations, CHD, genetic, and chromosomal syndromes.	Malformations of eye, ear, face, neck: Q10-Q18
	Malformations of the circulatory system: Q20-Q28
	Malformations of the respiratory system: Q30-Q34
	Cleft lip and cleft palate: Q35-Q37
	Other malformations of the digestive system: Q38-Q45
	Malformations of genital organs: Q50-Q56
	Malformations of the urinary system: Q60-Q64
	Malformations of the musculoskeletal system: Q66-Q74, Q76-Q79
	Other congenital malformations Q80-Q84, Q89,
Teratogenic syndromes	Congenital rubella syndrome: P350
	Congenital cytomegalovirus infection: P351
	Congenital toxoplasmosis: P371
	Congenital malformation syndromes owing to known exogenous causes, not elsewhere classified (including fetal alcohol syndrome): Q86
Down syndrome	Q90 or a karyotype of trisomy 21
Deletion syndrome 22q11.2	D821 or a karyotype of 22q11.2 deletion
Other chromosomal or genetic syndromes‡	All other registered chromosomal anomalies: Q91-99 (excluding Q936, Q992) or A karyotype of any chromosomal anomaly.
Note: Excluding: Down syndrome and the 22q11.2 deletion syndrome	*Examples: trisomies, monosomies, deletions, duplications*
	All other registered genetic anomalies: Q447B, Q619A, Q740B, Q751, Q754, Q761, Q771, Q772, Q775, Q776, Q780, Q781, Q782, Q783, Q784A, Q796, Q798S, Q823, Q858A, Q858B, Q858C, Q858D, Q87, Q893F, Q936, Q992 (excluding Q870D, Q870G, Q870I, Q872E).
	Examples: Alagille syndrome, Noonan syndrome, VACTERL syndrome

All diagnostic ICD-10 codes were registered in the Danish National Patient Registry.[29] All karyotypes were registered in the Danish Cytogenetic Central Registry.[54]

*Some minor defects are not classified in the Danish version of ICD-10: Crocodile tears (Q0782), synophrys (Q1880), laryngomalacia (Q315), functional gastrointestinal disorders (Q4021, Q4320, Q4381 and Q4382), bifid scrotum (Q5521), and single/abnormal palmar crease (Q8280). These minor malformations are classified under other congenital malformations unspecified (Q899).

†In Denmark, cystic hygroma (D1810) is coded as Q898T4 and sacral teratoma (D215) is coded as Q898T1. As in previous studies hip dysplasia and dislocation (Q65) were not considered owing to poor validity in the Danish National Patient Registry.[23,25,58]

‡Genetic syndromes: some congenital syndromes are not registered in the Danish ICD-10 with specific codes: Larsen syndrome (Q7484), Frontonasal dysplasia (Q7581), Metatropic dysplasia (Q7780) Gardner's syndrome (Q8583). These syndromes are registered as other specified congenital malformation syndromes, not elsewhere classified (Q878).

Table VI. Results of the sensitivity analyses

Category of heart defects	Exclusion of congenital syndromes aHR (95%CI)	Logistic regression analyses aOR (95%CI)	Censoring of stillbirths aHR (95%CI)	Omitting maternal smoking aHR (95%CI)	Omitting Maternal preeclampsia aHR (95%CI)	Including non-Western origin aHR (95%CI)	Including maternal thyroid disease aHR (95%CI)	Including maternal asthma aHR (95%CI)	Including previous spontaneous preterm birth aHR (95%CI)	Including maternal BMI aHR (95%CI)
All heart defects	2.43 (2.15-2.74)	2.15 (1.90-2.43)	2.15 (1.90-2.42)	2.18 (1.94-2.45)	2.15 (1.91-2.43)	2.14 (1.90-2.41)	2.14 (1.90-2.41)	2.14 (1.90-2.41)	2.13 (1.89-2.40)	2.16 (1.82-2.56)
Pulmonary stenosis combined with septal defect	5.97 (4.13-8.63)	5.32 (3.64-7.79)	5.25 (3.66-7.52)	5.06 (3.56-7.19)	5.19 (3.62-7.45)	5.24 (3.65-7.51)	5.24 (3.65-7.51)	5.23 (3.65-7.50)	5.37 (3.75-7.68)	–
Pulmonary stenosis or atresia	3.32 (2.46-4.48)	2.99 (2.22-4.01)	3.12 (2.36-4.14)	3.06 (2.32-4.03)	3.17 (2.40-4.20)	3.12 (2.36-4.13)	3.12 (2.36-4.13)	3.12 (2.36-4.13)	3.07 (2.32-4.07)	–
Tetralogy of Fallot	2.18 (1.27-3.72)	2.41 (1.55-3.76)	2.50 (1.64-3.83)	2.52 (1.69-3.75)	2.49 (1.63-3.81)	2.49 (1.63-3.81)	2.50 (1.64-3.82)	2.50 (1.64-3.82)	2.58 (1.70-3.94)	–
Other mild defects	2.78 (2.17-3.57)	2.27 (1.78-2.89)	2.27 (1.80-2.87)	2.42 (1.94-3.01)	2.28 (1.80-2.88)	2.26 (1.79-2.86)	2.26 (1.79-2.85)	2.26 (1.79-2.86)	2.27 (1.79-2.88)	–
Coarctation or interrupted aortic arch	2.38 (1.56-3.63)	2.19 (1.47-3.26)	2.21 (1.51-3.23)	2.11 (1.45-3.06)	2.26 (1.55-3.30)	2.21 (1.51-3.23)	2.21 (1.51-3.22)	2.21 (1.51-3.23)	2.21 (1.52-3.23)	–
Hypoplastic left heart syndrome	2.34 (1.17-4.69)	2.30 (1.15-4.60)	2.05 (1.02-4.12)	2.00 (1.03-3.88)	2.01 (1.00-4.04)	2.04 (1.01-4.10)	2.04 (1.01-4.10)	2.04 (1.01-4.11)	2.09 (1.05-4.14)	–
Other severe defects	2.23 (1.53-3.26)	2.03 (1.41-2.94)	2.00 (1.40-2.84)	1.94 (1.37-2.75)	2.00 (1.40-2.85)	1.99 (1.40-2.84)	2.00 (1.40-2.85)	2.00 (1.40-2.84)	1.99 (1.39-2.84)	–
Major atrial septal defects	2.59 (1.64-4.09)	1.89 (1.17-3.05)	1.88 (1.19-2.96)	2.02 (1.31-3.12)	1.88 (1.19-2.97)	1.87 (1.18-2.95)	1.87 (1.18-2.95)	1.87 (1.18-2.95)	1.85 (1.16-2.93)	–
Transposition of the great arteries	1.57 (0.87-2.85)	1.62 (0.90-2.92)	1.46 (0.81-2.66)	1.51 (0.85-2.67)	1.49 (0.82-2.70)	1.46 (0.81-2.65)	1.46 (0.81-2.65)	1.46 (0.81-2.65)	1.48 (0.82-2.70)	–
Other single ventricle defects	1.38 (0.62-3.09)	1.37 (0.63-2.98)	1.36 (0.64-2.89)	1.43 (0.71-2.86)	1.34 (0.63-2.84)	1.36 (0.64-2.88)	1.36 (0.64-2.89)	1.36 (0.64-2.89)	1.31 (0.61-2.79)	–
Major ventricular septal defects	1.06 (0.57-1.99)	1.21 (0.74-1.97)	1.24 (0.77-1.99)	1.25 (0.78-1.98)	1.25 (0.77-2.01)	1.23 (0.76-1.99)	1.23 (0.76-1.99)	1.23 (0.76-1.98)	1.20 (0.74-1.94)	–
Aortic stenosis	1.18 (0.56-2.89)	1.35 (0.71-2.56)	1.22 (0.63-2.36)	1.39 (0.76-2.53)	1.24 (0.64-2.40)	1.22 (0.63-2.36)	1.22 (0.63-2.36)	1.22 (0.63-2.36)	1.19 (0.62-2.31)	–
Atrioventricular septal defects	1.53 (0.64-3.67)	1.10 (0.65-1.85)	1.15 (0.70-1.87)	1.26 (0.79-2.00)	1.12 (0.69-1.82)	1.14 (0.70-1.86)	1.14 (0.70-1.85)	1.14 (0.70-1.86)	1.11 (0.67-1.82)	–

Exclusion of congenital syndromes: the primary analyses were repeated with additional exclusion of all pregnancies with a congenital syndrome. Logistic regression analyses: the primary analyses were repeated using logistic regression. In infants with missing gestational age at birth, preterm birth was determined based on ICD-10 codes. Censoring of stillbirths: the primary analyses were repeated with additional inclusion of stillbirths. Stillbirths were censored. Omitting maternal smoking: the primary analyses were repeated omitting maternal smoking from the analyses. Omitting maternal preeclampsia: the primary analyses were repeated omitting maternal preeclampsia from the analyses. Including non-Western origin: the primary analyses were repeated with additional adjustment for parental non-Western origin. Including maternal thyroid disease: the primary analyses were repeated with additional adjustment for maternal thyroid disease. Including maternal asthma: the primary analyses were repeated with additional adjustment for maternal asthma. Including previous spontaneous preterm birth: the primary analyses were repeated with additional adjustment for maternal previous spontaneous preterm birth. Including maternal BMI: the primary analyses were repeated with additional adjustment for maternal BMI. This analysis was only conducted in all heart defects, because BMI was only available from 2004 and onward. Restriction to births after 2004 resulted in low numbers in the different subgroups.