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ORIGINAL ARTICLE

Risk of Congenital Heart Defects in Offspring of Affected Mothers and Fathers

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BACKGROUND: Smaller studies have reported a higher offspring risk of congenital heart defects (CHDs) for mothers with CHDs than for fathers with CHDs. In a large population-based study, we investigated whether offspring risk of CHD differed for mothers and fathers with CHDs.

METHODS: All people born in Denmark, 1977 to 2011, with at least 1 registered parent, were included in our cohort (n=2 341 061). Parent-child recurrence of CHDs was evaluated using risk ratios (RRs) comparing risks of CHDs in individuals with and without a parent with a CHD, estimated using log-linear binomial regression.

RESULTS: The RRs for any CHD in offspring were 5.39 (95% CI, 4.88–5.96) for mothers and 3.04 (95% CI, 2.59–3.57) for fathers affected with any CHD; the ratio of RRs for mothers versus fathers was 1.82 (P<0.0001). Recurrence RRs for the same cardiac phenotype in parent and offspring were significantly stronger for mothers than for fathers for conotruncal defects (ratio of RRs, 4.98), left ventricular outlet tract obstruction (ratio of RRs, 4.98), and ventricular septal defects (ratio of RRs, 2.51) but not for atrioventricular septal defects (ratio of RRs, 1.06). Birth rates among people with CHDs, relative to the general population, were 18% higher for women than for men, regardless of parental cardiac phenotype.

CONCLUSIONS: Recurrence risks of CHDs were significantly greater in the offspring of affected women than in the offspring of affected men. The excess maternal recurrence risks could not be explained by the slightly higher birth rates in women with CHDs.

Key Words: birth rate ■ cohort studies ■ epidemiology ■ genetics ■ heart defects, congenital ■ population ■ risk

See Editorial by Goldmuntz & Mitchell

Women with congenital heart defects (CHDs) are thought to have a considerably higher risk of having a child with a CHD than are men with such heart defects,[1,2] raising speculation that a woman with a CHD may affect her offspring's cardiac embryonic development both by passing her genes to the child and through an altered intrauterine milieu.[3] Alternatively, certain genes for cardiac embryonic development might be imprinted,[4] that is, one of the parental copy of allele of the genes might be more important in heart formation than the other parent allele. The observed excess of maternal recurrence risk of CHDs in offspring could in theory be explained by detrimental alleles of maternal origin, whereas a corresponding effect of paternal alleles would be less harmful to the developing embryonic heart. Few imprinted genes associated with cardiac embryonic development have to date been identified. The difference in recurrence risks associated with affected mothers and fathers[3,4] could also be due to sampling bias, reporting bias, and preferential selection of case series. In addition, heart defect recurrence risk studies published to date[3–5] have not had the power to examine whether recurrence risks for certain cardiac defects are more strongly associated with the sex of the affected parent.

Population-based recurrence figures are important in genetic counseling and prenatal investigation. Such

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Nonstandard Abbreviations and Acronyms

CHD	congenital heart defect
RR	risk ratio

figures will also add to our understanding of the extent to which CHDs cluster in families and further contribute to understanding the genetic architecture of cardiac malformations,[6] particularly with respect to studies of the epigenetic regulation of gene expression during cardiac embryonic development.

Denmark's large national health registers allowed us to conduct a large, well-powered study of the risks of CHDs in the offspring of mothers and fathers with CHDs, compared with the risks in the offspring of unaffected parents, to investigate the parent-of-origin hypothesis of CHDs. The aims of the study were (1) to investigate whether offspring CHD risk differed for mothers and fathers with CHDs, overall, and by heart defect type and (2) to evaluate the role of birth rate by estimating the ratio of birth rates for women and men with CHDs. We focused on the transgenerational recurrence of CHDs of the same embryological subtype (ie, where parent and offspring both had heart defects from the same phenotypic subgroup, eg, conotruncal defects), although we also present results for offspring risk of dissimilar heart defects (ie, where the heart defects in parent and offspring were of 2 different embryological subtypes) in the Supplemental Material.

METHODS

This study is based on Danish national register data. These data do not belong to the authors but to the Danish Ministry of Health, and the authors are not permitted to share them, except in aggregate (as, for example, in a publication). However, interested parties can obtain the data on which the study was based by submitting a research protocol to the Danish Data Protection Agency (Datatilsynet) and then once Data Protection Agency permission has been received, applying to the Danish Health Data Authority's Research Service (Forskerservice) at forskerservice@ssi.dk. This study was covered by Statens Serum Institut's umbrella approval from the Danish Data Protection Agency to conduct register-based studies (J.nr.2015-57-0102); no further consent from subjects was required. The Board of the Danish Cytogenetics Central Register also approved the study. The full Methods are provided in the Supplemental Material.

RESULTS

Our study cohort included 2 377 504 people without a chromosomal aberration born in Denmark in the period 1977 to 2011. Of these people, 21 596 had ≥1 CHDs; the overall prevalence of nonchromosomal CHDs was 90.8 per 10 000 live births. In Table S1, we report the prevalence of cardiac phenotypes by year of birth. In the analyses of recurrence of CHDs, we restricted the study cohort to those who were born as singletons, 2 341 061 people and among them, 20 868 people with CHD.

In the study cohort of 2 341 061 singleton births, their mothers were not identified in the Civil Registration System for 12 032 (0.51%) births, and likewise, their fathers were not identified for 69 367 (3.0%) births.

Parent-Child Recurrence of CHDs

Of 7793 people whose mother had a CHD, 373 had a CHD themselves (prevalence, 479 per 10 000 live births), while of 5430 people with an affected father, 147 also had a CHD themselves (prevalence, 271 per 10 000 live births). The offspring of mothers with CHDs had more than 5 times the risk of having a CHD themselves, compared with the offspring of mothers without CHDs (prevalence, 89.0 per 10 000 live births; risk ratio [RR], 5.39 [95% CI, 4.88–5.96]). The corresponding RR for fathers was 3.04 (95% CI, 2.59–3.57). Comparing the two RRs showed that the maternal effect estimate was significantly larger than the paternal effect estimate (ratio of RRs, 1.82 [95% CI, 1.50–2.21]; $P<0.0001$).

The overall RR for recurrence of the same cardiac phenotype was 9.45 (95% CI, 8.04–11.1) for mother-child recurrence and 4.61 (95% CI, 3.46–6.17) for father-child recurrence; in other words, the overall mother-child same-phenotype recurrence RR was more than twice as large as the father-child recurrence RR (ratio of RRs, 2.12 [95% CI, 1.51–2.97]; Table). RRs for parent-offspring recurrence of the same cardiac phenotypes, along with a comparison of the maternal and paternal effect magnitudes, are presented in Table and Figure 1. RRs for mother-child recurrence of defects of the same phenotype ranged from 5.90 to 336, while RRs for father-child recurrence ranged from 2.36 to 52 (Table; Figure 1). Comparison of maternal and paternal recurrence RRs revealed that the maternal RRs exceeded the paternal RRs for conotruncal defects (ratio of RRs, 4.98 [95% CI, 2.18–11.4]), left ventricular outlet tract obstruction (ratio of RRs, 4.98 [95% CI, 1.62–15.3]), and ventricular septum defects (ratio of RRs, 2.51 [95% CI, 0.94–6.69]), although the maternal excess was not statistically significant for ventricular septum defects ($P=0.06$).

Table S2 presents parent-child RRs for dissimilar CHDs (ie, parent and offspring had different cardiac phenotypes). Where cardiac phenotypes differed between parents and their offspring, maternal and paternal RRs did not differ significantly, except for other specified and unspecified heart defects.

In a sensitivity analysis, we assigned parents whose CHD was diagnosed within a year of the cohort member's birth as unaffected, since pregnant women with a previously unregistered diagnosis would be more likely

Table. Risk Ratios (RRs) for Congenital Heart Defects (CHDs), Any Type of Heart Defect, and Same Cardiac Phenotype, in the Offspring of Mothers and Fathers by Parental Cardiac Phenotype, Among 2 341 061 Singleton Births* in Denmark, 1977 to 2011

	Offspring of mothers with CHDs					Offspring of fathers with CHDs					Ratio of mother-offspring and father-offspring RRs		
Cardiac phenotype in the parent	Total number of off-spring	No. with heart defect	Heart defects per 10 000	RR†	95% CI	Total number of off-spring	No. with heart defect	Heart defects per 10 000	RR†	95% CI	Ratio of RRs‡	95% CI	*P* value
Any type of heart defect	7793	373	479	5.39	4.88–5.96	5430	147	271	3.04	2.59–3.57	1.82	1.50–2.21	<0.0001
Excl. PDA preterm§	7765	367	473	5.57	5.03–6.16	5414	142	262	3.08	2.61–3.62	1.86	1.52–2.27	<0.0001
Any, same cardiac phenotype‖	7793	144	185	9.45	8.04–11.1	5430	45	82.9	4.61	3.45–6.17	2.12	1.51–2.97	<0.0001
Heterotaxia	77	<5	390	336	110–1024	103	0						
Conotruncal defects	365	34	932	111	81–154	351	7	199	24.0	11.5–50	4.98	2.18–11.4	0.0001
AVSD	353	5	142	55.6	23.2–134	154	<5	130	52.4	13.2–208	1.06	0.20–5.50	0.95
APVR	51	0				29	0						
LVOTO	598	14	234	31.7	18.8–53.2	811	<5	49.3	6.59	2.48–17.5	4.98	1.62–15.3	0.005
RVOTO	305	5	164	30.4	12.7–72	173	0						
Septal defects¶	3286	54	164	4.48	3.43–5.84	2073	24	116	3.15	2.12–4.70	1.43	0.88–2.33	0.15
ASD	1550	15	96.8	8.83	5.33–14.6	1078	7	64.9	5.90	2.81–12.4	1.51	0.61–3.72	0.37
VSD	1516	21	139	5.90	3.85–9.03	904	5	55.3	2.36	0.98–5.65	2.51	0.94–6.69	0.06
Complex	<5	0				<5	0						
Valve defects	628	7	112	33.1	15.8–69	635	<5	47.2	13.0	4.20–40	2.57	0.66–9.98	0.17
Other specified	514	<5	77.8	19.3	7.26–51	320	<5	31.3	8.56	1.21–61	2.45	0.26–22.8	0.43
Unspecified	1131	12	106	9.50	5.41–16.7	652	<5	46.0	4.35	1.41–13.4	2.23	0.62–7.97	0.22
PDA	481	6	125	15.8	7.12–35.0	125	<5	80.0	10.2	1.45–72	1.53	0.18–12.8	0.70

Any, same cardiac phenotype indicates any concordant defect overall; APVR, anomalous pulmonary venous return; ASD, atrial septum defect; AVSD, atrioventricular septum defect; CHD, congenital heart defect; Excl., excluding; LVOTO, left ventricular outflow tract obstruction; PDA, persistent ductus arteriosus; RR, risk ratio; RVOTO, right ventricular outflow tract obstruction; and VSD, ventricular septum defect.

*Twins and births with chromosomal defects were excluded. Among 2 341 061 births, there were altogether 20 868 births with any CHD (birth prevalence, 89 per 10 000).

†RR with 95% CI adjusted for year of birth (5-y intervals) and heart defects in other family members (first-, second-, and third-degree relatives) in log-linear binomial regression analyses.

‡Approximate RR estimated as an odds ratio in logistic regression analyses adjusted for year of birth (5-y interval).

§PDA reported in preterm infant (<37 gestational age).

‖Same cardiac phenotype in parent and offspring. Common estimates for all same phenotypes' estimates in logistic regression analysis (PDA not included).

¶Including ASD+VSD, unspecified septal defects.

to be registered with CHD than men with an unregistered CHD. The resulting RR for recurrence of the same cardiac phenotype was 4.62 (95% CI, 4.10–5.21) for mother-child recurrence and 3.07 (95% CI, 2.60–3.63) for father-child recurrence, yielding a ratio of RRs of 1.51 (95% CI, 1.23–1.85).

Mother-Offspring Recurrence RRs After Adjustment for Cardiovascular Medication Use

In an external data set of 1 135 186 pregnancies with linked information on cardiovascular medication use from the National Prescription Register, and information on CHD in mothers and offspring (Supplemental Methods), the overall RR for mother-child recurrence of CHDs adjusted for maternal age and offspring year of birth was 5.24 (95% CI, 4.72–5.83), which matched the estimate of 5.39 obtained in the main study data set. When we further adjusted for cardiovascular medication use, the RR changed very little (RR, 5.15 [95% CI, 4.64–5.74]).

Effect of Sex-Specific Birth Rates in Women and Men With and Without CHDs

The observed maternal excess in parent-offspring recurrence of the same cardiac phenotype could occur if men with CHDs were less likely to have children than women with CHDs. To address this possibility, we analyzed first-birth rates in women and men born from 1970 onward (1 635 823 women and 1 692 165 men), among them 2085 women and 1226 men with CHDs and at least 1 child. For women with any CHD, the first-birth rate was 10.8 per 1000 person-years. In the general population of women without CHDs, the corresponding first-birth rate was 13.9 per 1000 person-years, yielding an age- and period-adjusted first-birth rate ratio of 0.98 (95% CI, 0.94–1.02) for women with any CHD, which is presented in the Forest plot in Figure 2. The corresponding age- and period-adjusted first-birth ratio for men with any CHD was 0.83 ([95% CI, 0.79–0.88] the ratio between first-birth rates among men with CHDs of 6.4 per 1000

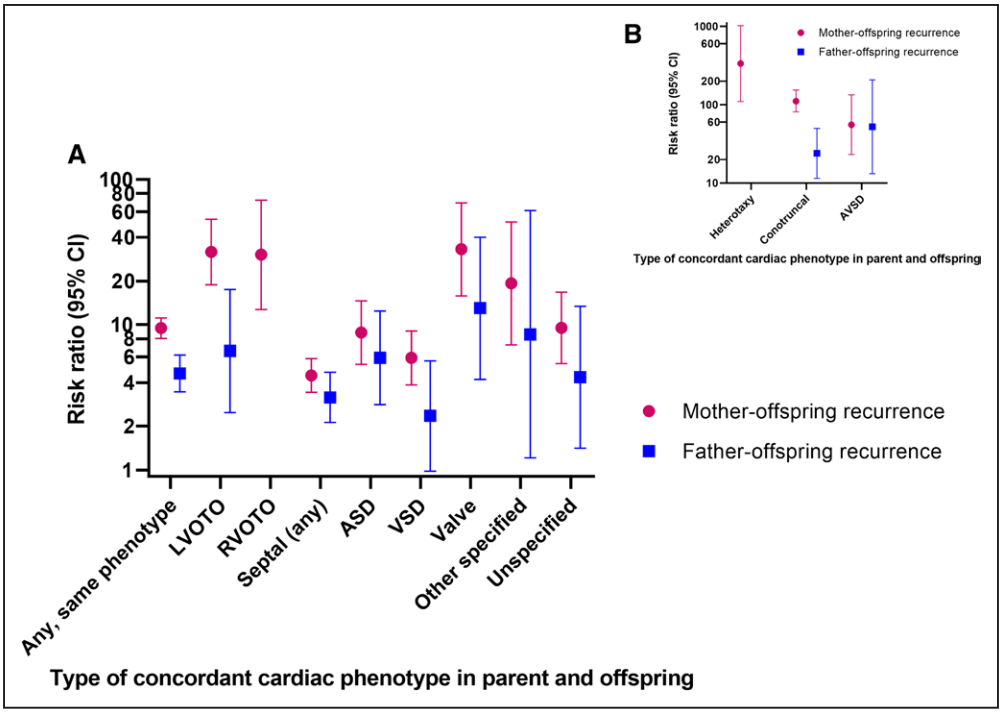

Figure 1. Concordant cardiac phenotype in parent and offspring.
Risk ratios (RRs) for congenital heart defects in offspring for concordant cardiac phenotypes for mother-offspring recurrence (red circles) and father-offspring recurrence (blue squares) among 2 341 061 singleton births in Denmark, 1977 to 2011. RRs with 95% CIs adjusted for year of birth and congenital heart defects in other family members (first-, second-, and third-degree relatives) in log-linear binomial regression analyses. **A**, Any concordant congenital cardiac defect overall (Any, same phenotype); left ventricular outflow tract obstruction (LVOTO); right ventricular outflow tract obstruction (RVOTO); any septal defect (Septal (any)); atrial septum defect (ASD); ventricular septum defect (VSD); valve defect (Valve); other specified cardiac defect (Other specified); and unspecified cardiac defect (Unspecified). **B**, Heterotaxy; conotruncal cardiac defect (Conotruncal); and atrioventricular septum defect (AVSD). There are no estimates for heterotaxia and RVOTO for father-offspring recurrence because there were no pairs where both father and child were affected.

person-years and the general [unaffected] male population of 10.2 per 1000 person-years). Figures for the cardiac phenotypes are also shown (Figure 2).

Comparing the birth rate ratios for women and men yielded a ratio of first-birth rate ratios of 1.18 (95% CI, 1.10–1.26), indicating that women with CHDs were indeed somewhat more likely to have at least 1 child than men with CHDs after adjusting for sex-specific first-birth rates in the general population (Figure S1).

The ratio of first-birth rate ratios differed by cardiac phenotype (Figure S1). Relative to first-birth rates in the background population, birth rates in women with CHDs exceeded birth rates in men with CHDs for the following phenotypes: atrioventricular septum defect (ratio of rate ratios, 1.71 [95% CI, 1.07–2.72]), Right ventricular outflow tract obstruction (ratio of rate ratios, 1.45 [95% CI, 1.01–2.07]), ventricular septum defect (ratio of rate ratios, 1.28 [95% CI, 1.10–1.49]), unspecified defects (ratio of rate ratios, 1.28 [95% CI, 1.08–1.51]), persistent ductus arteriosus (ratio of rate ratios, 1.55 [95% CI, 1.09–2.19]), and valve defects (ratio of rate ratios, 1.23 [95% CI, 0.96–1.59]). For all other cardiac phenotypes, there was no significant excess of births among affected women.

In Figure 3, we plot the cardiac phenotypes according to the relevant ratios of first-birth rate ratios for affected women and men (Figure S1) and the corresponding ratios of parent-child recurrence RR (Table). If the maternal excess in parent-offspring recurrence of the same cardiac phenotype was due to an excess of births among women with CHDs, relative to men with CHDs, we would expect the plotted values to lie along the diagonal from the lower left corner to the upper right corner. However, this was not the case. Conotruncal defects and left ventricular outflow tract obstruction, both of which showed an excess risk of recurrence for affected women compared with affected men, were not associated with more first births in affected women (upper left corner). Furthermore, atrioventricular septum defects and persistent ductus arteriosus had similar recurrence risks for affected women and men, but women with these defects were more likely to have children than affected men (lower right corner).

DISCUSSION

In our population-based study, the offspring of women with a CHD were 5× more likely than the offspring of unaffected women to have a CHD (RR, 5.39). In contrast, the magnitude of the recurrence RR for men and their offspring, while strong (RR, 3.04) and statistically significant, was smaller. There was a clear overall maternal excess in

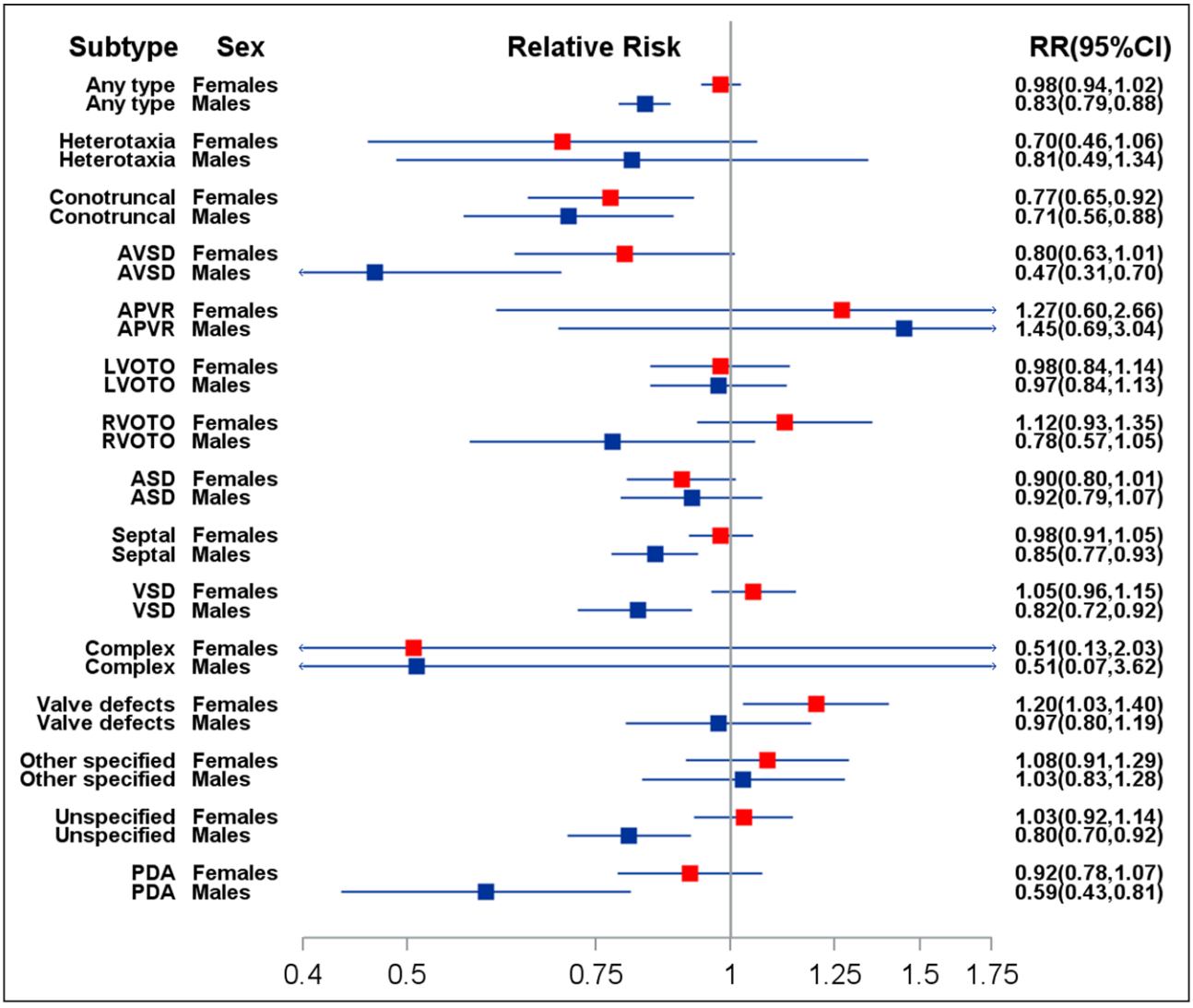

Figure 2. Forest plot with female birth rate ratios and male birth rate ratios among individuals with congenital heart defects relative to the general population* adjusted for age and period.

APVR indicates anomalous pulmonary venous return; ASD, atrial septum defect; AVSD, atrioventricular septum defect; LVOTO, left ventricular outflow tract obstruction; PDA, persistent ductus arteriosus; RR, risk ratio; RVOTO, right ventricular outflow tract obstruction; and VSD, ventricular septum defect. *Birth rate ratios for women with congenital heart defects (relative to the birth rate in the general female population) and men with congenital heart defects (relative to the birth rate in the general male population) among 1 635 823 women and 1 692 165 men born in Denmark in or after 1970.

parent-offspring recurrence risk (maternal:paternal ratio of recurrence RRs, 1.82), and this maternal excess was even more pronounced for same-phenotype recurrence and in particular for conotruncal defects and left ventricular outflow tract obstruction defects. The maternal excess in parent-offspring recurrence risk of CHD was unlikely to be related to differences in birth rates among women and men with CHDs.

The strong risks of CHD recurrence provide compelling evidence that there is a strong genetic contribution to many CHDs,[6–8] although most individuals with CHDs represent sporadic cases.[5] We previously estimated the contribution of a family history of CHDs to an individual's risk of CHDs; however, the previous study had insufficient power to investigate whether the recurrence risk differed for the offspring of affected mothers and fathers. The present study, updated with an additional 6 years of births, clearly showed an excess risk of recurrence associated with affected mothers, in line with findings from previous studies.[4]

In previous studies of selected families with ≥1 family members with CHDs, there was a higher percentage of affected mother-child pairs than affected father-child pairs, with "recurrence risks" being significantly greater in the offspring of affected women than in the offspring of affected men.[3,4] After finding that parent-offspring recurrence risks were 1.5 to 14× greater for women with heart defects than men with heart defects, Nora and Nora[3] suggested that a woman with a heart defect may influence embryonic development both by passing down her genes and by somehow providing a suboptimal fetal intrauterine

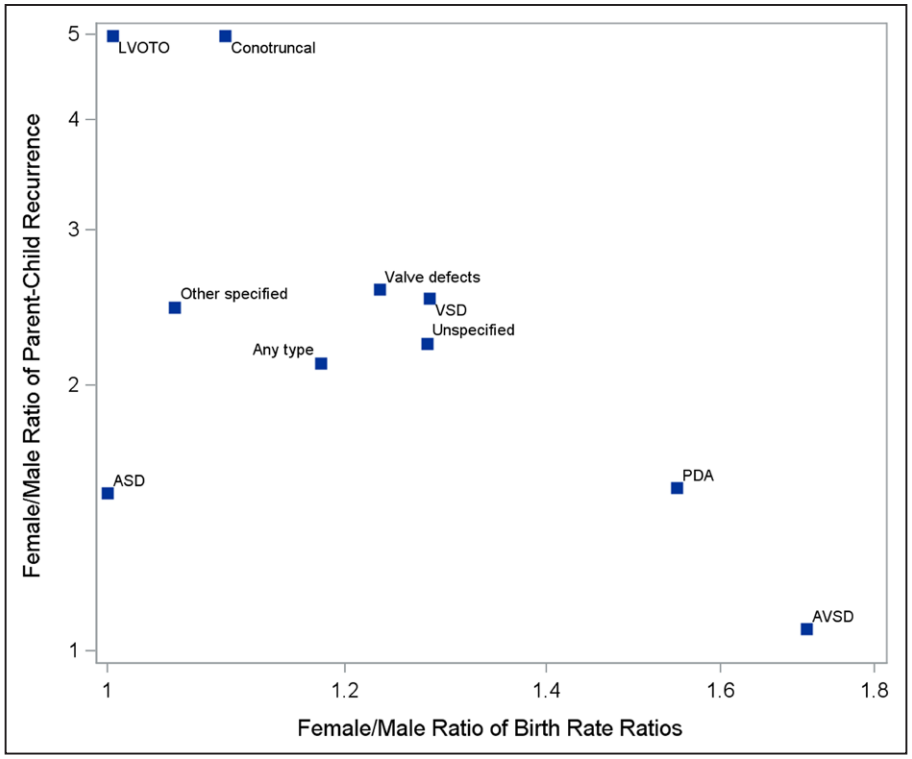

Figure 3. Congenital heart defects: mother/father ratio of recurrence risks in offspring (*y* axis) by female/male ratio of birth rate ratios (*x* axis).

Plot of the ratio of the female birth rate ratio and the male birth rate ratio among individuals with congenital heart defects relative to the general population* (*x* axis) and the ratio between the mother-offspring risk ratio and the father-offspring risk ratio for congenital heart defects† (*y* axis). ASD indicates atrial septum defect; AVSD, atrioventricular septum defect; LVOTO, left ventricular outflow tract obstruction; PDA, persistent ductus arteriosus; and VSD, ventricular septum defect. *The ratio compared birth rate ratios for women with congenital heart defects (relative to the birth rate in the general female population) and men with congenital heart defects (relative to the birth rate in the general male population) in 1 635 823 women and 1 692 165 men born in Denmark in or after 1970. †The ratio compared the offspring heart defect recurrence risk for women with congenital heart defects (relative to the offspring heart defect risk in unaffected mothers) and the offspring heart defect recurrence risk for men with congenital heart defects (relative to the offspring heart defect risk in unaffected fathers), in 2 341 061 singleton births in Denmark, 1977 to 2011.

milieu. Burn et al[4] explained their maternal:paternal ratio of recurrence RR of 2.6 by suggesting that imprinted maternal genes could explain the excess of cardiac defects in the offspring of women with CHDs. The previous reports were not sufficiently powered to examine parent-offspring recurrence of cardiac phenotypes, as our study did. When we looked at parent-offspring recurrence of same cardiac phenotypes, some phenotypes had even more dramatic maternal excesses.

The maternal excess in parent-offspring heart defect recurrence could be explained by true parent-of-origin effects, as suggested by both Nora and Nora[3] and Burn et al.[4] However, it could also be explained by sex-specific differences in birth rates, maternal comorbidity, or the potentially teratogenic influence of medication on cardiac embryonic development. We conducted multiple sensitivity analyses to address these possibilities.

In our study population, after adjusting for birth rates in the general population, women with CHDs had birth rates that were 18% higher than those in men with CHDs. The sex-specific differences in birth rates were similar across parental cardiac phenotypes. However, the differences in birth rates were insufficient to explain the dramatic maternal excess in parent-offspring recurrence risk observed for many cardiac phenotypes, the outflow defects in particular.

Maternal factors, such as diabetes,[9] obesity, or autoimmune diseases,[10] could conceivably modify the observed associations. Unfortunately, despite its large size, our study was insufficiently powered to investigate whether maternal comorbidity could partly explain the maternal excess in parent-offspring recurrence risks. Studies of effect modifications require tremendous power, especially when, as is the case with our study, both the exposure and the outcome are rare. In addition, maternal comorbidity must be a very strong risk factor for CHDs even for high prevalence of the risk factor, to observe no maternal excess in parent-offspring recurrence risks.

Cardiovascular drug use may have a teratogenic influence on cardiac embryonic development. In a 2015 systematic review and meta-analysis of 16 eligible studies of maternal hypertension and offspring CHDs, both treated and untreated maternal hypertension were associated with offspring CHDs overall (relative risks, 2.0 and 1.4, respectively).[11] Since women with CHDs may also develop heart failure and arrhythmia, in addition to

hypertension, and require medication to control the conditions, we examined the degree to which cardiovascular medication use might affect the mother-offspring recurrence of heart defects. Adjustment for maternal use of cardiovascular medications in the periconceptional period did not affect the mother-offspring recurrence RRs, suggesting that maternal cardiovascular complications such as hypertension, heart failure, arrhythmia, or the medications used to control these conditions do not explain the maternal excess in parent-offspring recurrence of CHDs.

Parent-of-origin effects or epigenetics may explain the excess heart defect risk in offspring of women with heart defects, compared with the risk in offspring of men with heart defects. Imprinting patterns whereby the phenotypic effect depends on the expression of the maternally inherited allele could theoretically contribute to an excess risk of CHDs in the offspring of women with heart defects. Changes in genes related to chromatin folding might be relevant for cardiac embryonic development with subsequent risk of heart defects,[8] but whether there are sex-specific differences in such epigenetic modifications is unknown. Interestingly, in a study of cardiac tissues from surgically repaired defects,[12] the authors reported silencing of expressed paternal imprinted genes. In theory, such imprinted paternal genes could be lethal if the embryo also inherited another pathological allele from the affected father. Alternatively, some of our findings may be explained by the threshold liability hypothesis originally proposed to explain the familial recurrence of pyloric stenosis,[13] in which the less affected sex is presumed to have a higher genetic burden, thus leading to a stronger relative risk of parent-offspring recurrence for parents of that sex. Left ventricular outflow tract obstruction showed a strong maternal excess recurrence in offspring, although it is more common in men.[14]

Study Limitations

Our estimates of mother-offspring recurrence RRs may underestimate the true magnitude, since women with severe CHDs and associated complications are advised against pregnancy, whereas the same recommendation does not apply to affected men. Pregnant women with CHDs are more likely to receive fetal echocardiography, although whether women with CHDs are more or less likely than unaffected women to terminate a pregnancy if the fetus is found to have a CHD is unknown. Knowledge of a paternal CHD should also prompt recommendations for fetal echocardiography, although whether this actually occurs in practice and how fathers with CHDs react to learning that their unborn children are also affected is also unclear. Consequently, it is difficult to determine how decisions to terminate pregnancies where the fetus is found to have a CHD might have affected our results.

Extra medical care and attention for pregnant women with known CHDs could give rise to surveillance bias, if the offspring of women with CHDs were examined more carefully than the offspring of fathers with such defects. However, according to guidelines,[15] prior knowledge of CHDs in either parent should trigger additional follow-up for similar defects in the offspring, both prenatally and after birth, minimizing the opportunity for a parent-specific difference in discovering offspring CHDs. Furthermore, regardless of parental CHD status, severe CHDs almost always come to medical attention shortly after birth (due to peri- or neonatal death, rapidly worsening conditions, or failure to thrive). Less severe CHDs will also usually eventually be discovered, which is why we did not limit the period after birth within which an offspring CHD could be identified. It is, therefore, difficult to see how surveillance bias could explain the large difference in parent-child recurrence risks observed for affected mothers and fathers.

We suspected that registration of cardiac defects differed for women and men, particularly early in the study period (before 1995) when outpatient diagnoses were not registered in the National Patient Register. Women might have been more likely to have previously unregistered diagnoses registered in the National Patient Register in connection with a pregnancy, whereas men diagnosed with a heart defect before 1995 lacked this opportunity for registration. However, when we performed sensitivity analyses in which we classified parents whose CHD was diagnosed within 1 year of a child's birth as unaffected, there were only slight changes in the maternal:paternal ratio of recurrence RRs, suggesting that overascertainment of maternal CHDs relative to paternal heart defects could not explain the maternal excess in parent-offspring recurrence risk.

Maternal comorbidity and subsequent medication use could explain part of the maternal excess in recurrence risk. However, when we examined an important potential explanatory factor, use of cardiovascular medication for treatment of hypertension, heart failure, or arrhythmia, we found little evidence that use of these medications could explain the observed maternal excess in recurrence risk. Maternal excess in parent-offspring same-phenotype recurrence could also have occurred if men with CHDs were less likely to have children than women with heart defects. However, we demonstrated that birth rates were only slightly higher for women than for men, regardless of parental cardiac defect phenotype.

Finally, men registered as fathers in the Civil Registration System have not been confirmed to be the genetic fathers. In genotypic analyses of >15 000 Icelanders, deCODE Genetics reported the proportion of nonpaternity to be 1.5%[16]; Denmark likely resembles Iceland on this point, suggesting that any effect of nonpaternity on our results would have been minimal, particularly since nonpaternity rates should not differ for registered fathers with and without CHDs. Therefore, nonpaternity is unlikely to explain the lower father-offspring recurrence relative to the mother-offspring recurrence of CHDs.

We report estimates of the parent-offspring recurrence of CHDs based on the entire Danish population

with negligible loss to follow-up, which minimized the possibility of selection bias. Previous studies have shown that registration of severe CHDs in particular is close to complete, with little misclassification of cardiac phenotypes; the *International Classification of Diseases* codes for severe CHDs have been validated against hospital records with very good agreement.[17]

In conclusion, CHDs are more common among the offspring of women with CHD than men with such heart defects, particularly for same cardiac outflow phenotypes. This might be due to epigenetics or parent-of-origin effects or excess loss very early in pregnancy of embryos with CHDs of paternal origin. Future research into the etiology of CHDs should be directed into epigenetic influences on embryonic cardiac development.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1 and S2
Figure S1
References [18–24]

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