

Pre-eclampsia is associated with increased neurodevelopmental disorders in children with congenital heart disease

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Aims

Our primary aim was to examine whether exposure to pre-eclampsia increases the risk of neurodevelopmental disorders in children born with congenital heart disease (CHD). Our secondary aim was to evaluate whether CHD and pre-eclampsia may act in synergy and potentiate this risk.

Method and results

Using population-based registries, we included all Danish children born with CHD between 1994 and 2017. Non-singletons and children born with a syndrome were excluded. Neurodevelopmental disorders including attention-deficit/hyperactivity disorder, autism spectrum disorders, and tic disorders were identified with the use of the 10th edition of International Classification of Disease (ICD-10) codes DF80–DF98. Using Cox proportional hazard regression, we estimated the risk of neurodevelopmental disorders in children with CHD exposed to pre-eclampsia compared with those with CHD not exposed to pre-eclampsia. The population consisted of 11 449 children born with CHD. Children exposed to pre-eclampsia had an increased risk of neurodevelopmental disorders, hazard ratio: 1.84 (95% confidence interval: 1.39–2.42). Furthermore, a comparison cohort of 113 713 children with no CHD diagnoses were included. Using cumulative incidence analyses with death as competing risk, we compared the risk of neurodevelopmental disorders if exposed to pre-eclampsia among children with CHD and children without CHD. Exposure to pre-eclampsia drastically increased the cumulative incidence of neurodevelopmental disorders in children born with CHD.

Conclusion

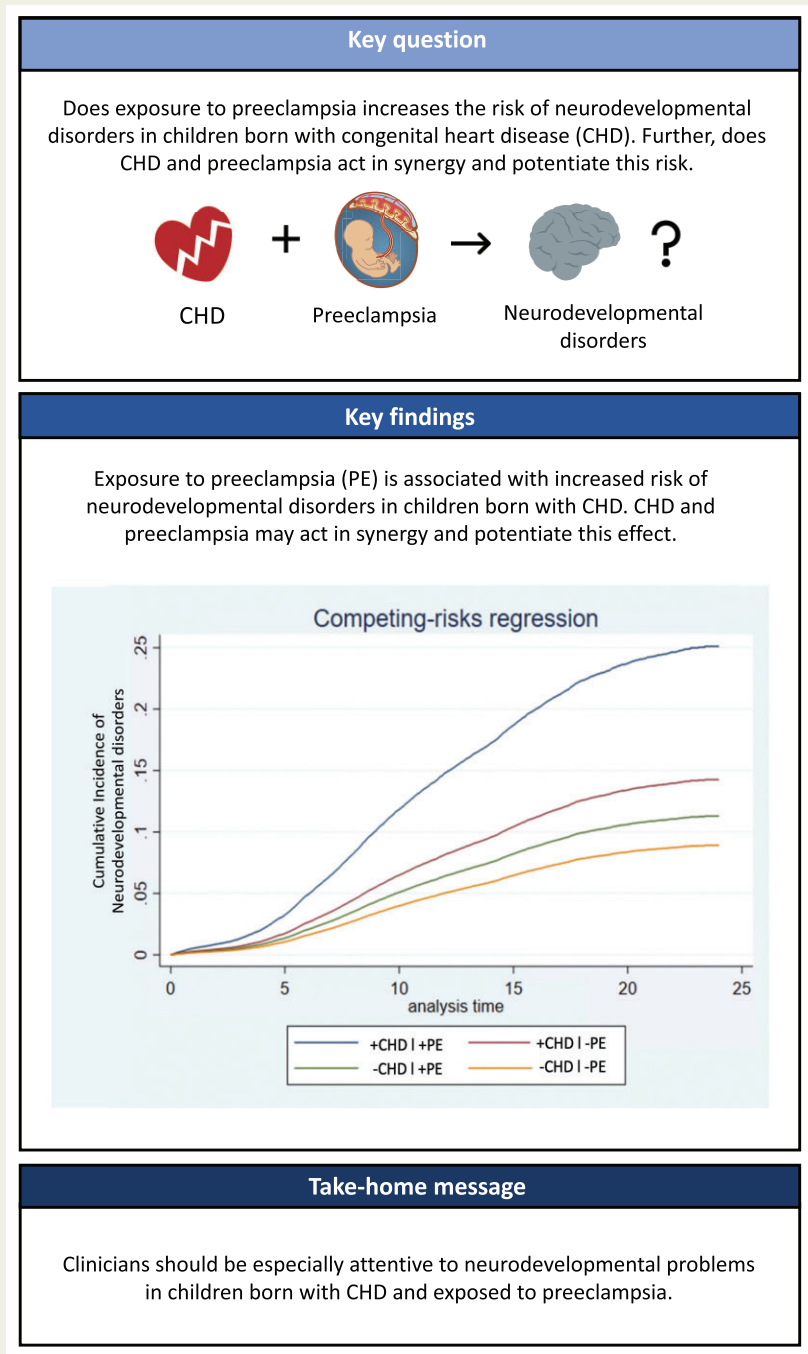
Exposure to pre-eclampsia is associated with increased risk of neurodevelopmental disorders in children born with CHD. CHD and pre-eclampsia may act in synergy and potentiate this effect. Clinicians should therefore be especially attentive to neurodevelopmental problems in this vulnerable subgroup.

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Graphical Abstract



Keywords

Congenital heart disease • Pre-eclampsia • Neurodevelopment • Psychiatry • Foetus

Introduction

Over the past four decades, mortality in children born with a congenital heart disease (CHD) has dramatically decreased due to both

improved pre-natal diagnostics and post-natal treatment. There is a growing population of adult survivors with CHD. With improved survival, there has been increasing recognition of the considerable risk of neurodevelopmental problems in children and adults with CHD.¹⁻⁵

Studies have observed an association between being born with CHD and an increased risk of psychiatric morbidity later in life, including neurodevelopmental disorders like autism spectrum disorders, attention-deficit/hyperactive disorders (ADHD), and tic disorder.⁶ These findings apply to both major and minor heart defects.^{6,7}

The association between CHD and neurodevelopmental disorders is not easily explained, but a main determinant appears to be impaired cerebral development *in utero*.^{1,4,8} The underlying aetiological mechanisms are likely multifactorial with hypoxia as a proposed leading cause.^{9–11}

Inducing additional hypoxia in an already oxygen-deprived brain, as seen in children with CHD, could therefore worsen the potential risk of neurodevelopmental problems. In the case of pre-eclampsia and an impaired placental function, the foetus may be exposed to additional hypoxia. Pre-eclampsia is an independent risk factor for neurodevelopmental disorders^{12–14} and pre-eclampsia and placental abnormalities have been shown to be overrepresented in pregnancies with foetuses with CHD.^{15–17} However, we do not know if the exposure to pre-eclampsia further increases the risk of neurodevelopmental disorders when born with CHD.

Our primary aim was to evaluate whether exposure to pre-eclampsia in foetal life increased the risk of neurodevelopmental disorders in all Danish children born with CHD between 1994 and 2017. Our secondary aim was to examine whether CHD and pre-eclampsia may act in synergy. We hypothesized that pre-eclampsia potentiates the risk of neurodevelopmental disorders in children with CHD.

Methods

Data source

We conducted a nationwide population-based registry study. The Danish health care system is free of charge and equally accessible to all citizens. Each Danish citizen has since 1968 received a unique personal identification number. Several national registries can be linked using this unique number as this unique identifying number is included as a variable in most registries.¹⁸ Data included in this study were obtained from numerous national registries, including the following: The Danish National Patient Registry (DNPR), The Danish Cytogenetic Central Registry (DCCR), The Danish Medical Birth Registry, The Danish National Patient Register on Psychiatric Admissions, and The Family Sociogroup Registry.

Study population

The study population consisted of children diagnosed with CHD and born between 1 January 1994 and 31 December 2017 in Denmark.

Considering our secondary aim of examining whether CHD and pre-eclampsia may act in synergy, we created a comparison cohort of 10 randomly drawn age- and gender-matched individuals without CHD for each CHD patient. This comparison cohort was drawn based on the same exclusion criteria as applied to the CHD population.

CHD diagnosis

We used the DNPR to identify all Danish children diagnosed with CHD between 1994 and 2017. The DNPR contains information from the outpatient setting and on all hospital admissions including date of admission and discharge, surgical procedures, hospital of admission, and discharge diagnoses coded according to the International Classification of Disease (ICD). The 10th edition of the ICD has been used since 1994, hence, the cut-off at 1994 for our study period of interest. The following ICD-10 codes, including sub-codes, were used to identify CHD diagnosis:

DQ20–DQ26. The CHD diagnoses were grouped into two hierarchical categories, major and minor, according to severity of the CHD based on definitions described in previous studies.¹⁹ If a child had more than one CHD diagnosis, the most severe CHD diagnosis given at the earliest point in time was included. Similar to earlier studies, only children with a CHD diagnosis issued at a University Hospital were included in order to increase the diagnostic validity.¹⁴

Exclusion criteria

Children born with one of the following syndromes were identified and excluded based on information obtained from the DCCR: Trisomy 13, Trisomy 18, Trisomy 21, Turner Syndrome(45, X), Klinefelter Syndrome(47, XXY), DiGeorge Syndrome (22q11 deletion), and Williams-Beuren Syndrome. The DCCR is a nationwide register to which all chromosome analyses performed in Denmark since 1960 are reported.

Non-singletons were excluded with the use of The Danish Medical Birth Registry. This registry links mother and child and contains information on a large number of variables regarding maternal characteristics, pregnancy, and childbirth. Individuals who were not included in the Danish Medical Birth Registry, for example, due to adoption from another country or immigration, were likewise excluded.

Exposure

Exposure was defined as being born by a mother diagnosed with pre-eclampsia, eclampsia, or HELLP syndrome in the index pregnancy. The diagnostic criteria for pre-eclampsia is the presence of gestational hypertension (blood pressure ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic after Gestational Week 20 in women, who were normotensive pre-pregnancy) with associated newly emerged proteinuria and/or signs of organ dysfunction.²⁰ Using the Danish Medical Birth Registry, we identified all mothers of children born with CHD and not excluded due to the criteria mentioned above. With the use of the DNPR, the following ICD-10 codes were used to identify pre-eclampsia including HELLP syndrome in the mother: DO11, DO14, DO140, DO141, DO142, DO149, DO15, DO151, DO152, and DO159. Both primary and secondary diagnoses were included. To ensure correct linkage of the mother and child the diagnosis of pre-eclampsia, eclampsia or HELLP syndrome had to be given between 200 days before and 60 days after birth of the index child, and by definition the foetus had to be 20 weeks of gestation or more at the time of diagnosis. Early-onset pre-eclampsia was defined as pre-eclampsia diagnosed between 20 and 33 weeks of gestation. Late-onset pre-eclampsia was defined as pre-eclampsia diagnosed during or after 34 weeks of gestation.

Exposure limited to exclusively gestational hypertension was considered in a sub-analysis comparing children exposed exclusively to gestational hypertension to children not exposed to any type of hypertension. Gestational hypertension was identified with the use of the following ICD-10 codes: DO13, DO139, DO16, and DO169.

Outcomes: neurodevelopmental disorders

The outcome was defined as being diagnosed with a neurodevelopmental disorder including attention disorder, autism spectrum disorders, and tic disorders within the available follow-up period. If a child had one or more of these included diagnoses during this time period, only the first given diagnosis was included as an event.

These neurodevelopmental disorders were identified with the use of the DNPR and the Danish National Patient Register on Psychiatric Admissions using the following ICD-10 codes: DF80–DF98.

DF80–DF89 covers Disorders of Psychological Development, of which DF84 including sub-diagnoses accounted for autism. DF90–DF98 covers Behavioural and Emotional Disorders with onset usually occurring in

childhood and adolescence of which DF90 including sub-diagnosis and DF98.8 covers attention disorders and DF95 accounted for tic disorders.

Additional variables

Using a directed acyclic graph, the socioeconomic status (SES) was considered a confounder in the association between CHD and neurodevelopmental disorders, whereas pre-term birth may act as intermediate factor.

The SES was obtained based on the family SES as most children included in the study did not yet have their own individual status in the registers. This was done with the use of The Family Sociogroup Registry. In this registry, the parent with the highest income in the family determines the total family SES. The highest achieved family SES over time was used. All children and parents of a family unit were assigned the same unique family ID. This allowed for us to identify the family unit of each included child. We categorised the family SES into four groups (Groups 1–4) of hierarchical descending SES. Group 1 included business owners and employees with a high income, Group 2 accounted for employees with middle or low income, Group 3 included students and unemployed, and Group 4 accounted for others.

Gestational age (GA) at birth was identified using The Danish Medical Birth Registry. We categorised pre-term birth into two groups. Group 1 contained all pre-term births, defined as being born with a GA at delivery of <37 weeks. Group 2 contained only early pre-term births, defined as being born with a GA at delivery of <34 weeks.

Data analysis

Direct comparison between groups were done using students *t*-test if data were continuous. For binomial data, the chi-square test was used. When comparing exposed children to unexposed children in the population of children born with CHD, we used Cox proportional regression analysis to compute hazard ratio (HR). This was done for the first hospital contact (inpatient or outpatient contacts in the hospital) with a diagnosis for neurodevelopmental disorders registered, with follow-up beginning at the time of birth using age as the underlying scale. This statistical method was chosen in order to account for the lack of complete follow-up in all children. All analyses were adjusted for SES.

All statistical tests presumed a significance level of 5%. Furthermore, we compared the potential effect of exposure to pre-eclampsia between a population of children born with CHD and a population of children born with no CHD in order to examine whether CHD and pre-eclampsia may act in synergy. To account for the great difference in the risk of death among the two populations,²¹ Fine and Gray competing risk regression was used to estimate the cumulative incidence of neurodevelopmental disorders among exposed and unexposed children born with and without CHD.

Data cleaning and analysis was conducted by the use of Statistics Denmark's encrypted online data service (Forskertjeneste). For statistical analyses, Stata Statistical Software, release 15 (StataCorp LP, TX, USA) was used.

Results

Primary aim: examine whether exposure to pre-eclampsia increases the risk of neurodevelopmental disorders in children born with CHD

We identified 16 799 children born with CHD between 1 January 1994 and 31 December 2017 in the DNPR (Figure 1). Of these, 773 children had a syndrome and were excluded. Furthermore, 615 children were missing in the Danish Medical Birth Registry and

1247 non-singletons were excluded. After exclusion of children, who did not receive their CHD diagnosis at a university hospital, a total of 11 449 children with CHD were included in the study. Median follow-up time was 11.0 years (range 0.02–23.9 years).

Baseline characteristic of children with CHD included in the study are shown in Table 1. No overall differences were observed between children exposed to pre-eclampsia, eclampsia or HELLP syndrome compared with unexposed children regarding distribution of sex, year of birth, or SES. More children exposed to pre-eclampsia were born pre-term.

No differences were found between the distribution of the individual subtypes of CHD between exposed and unexposed children (Table 2). In total, 57 children born with CHD and exposed to pre-eclampsia were diagnosed with a neurodevelopmental disorder, whereas 929 unexposed CHD children had a neurodevelopmental disorder. The distribution of the individual neurodevelopmental disorders can be found in Supplementary material online, supplementary material 1. The distribution of neurodevelopmental disorders based on CHD status can be found in Supplementary material online, supplementary material 2.

In the population of children born with CHD, children exposed to pre-eclampsia had a higher risk of neurodevelopmental disorders compared with unexposed children, HR: 1.84 [95% confidence interval (CI): 1.23–2.42] (Table 3). Children exposed to exclusively gestational hypertension did not have a higher risk of neurodevelopmental disorders compared with unexposed children, HR: 1.05 (95% CI: 0.77–1.43).

When adjusting for all pre-term births (GA at delivery of <37 weeks), the HR decreased to 1.65 (95% CI: 1.24–2.18) suggesting that some effect, however not all, could have been mediated through pre-term birth. No additional effect was observed when adjusting for early pre-term (GA at delivery of <34 weeks), HR: 1.63 (95% CI: 1.22–2.16).

When excluding CHD children diagnosed with only a patent ductus arteriosus, the risk of neurodevelopmental disorders between exposed and unexposed CHD children was HR: 1.67 (95% CI: 1.25–2.25).

Furthermore, we found in this population of children born with CHD, that if exposed to early-onset pre-eclampsia the risk of neurodevelopmental disorders was higher than if exposed to late-onset pre-eclampsia (Table 4).

The HR of neurodevelopmental disorders was higher in male children born with CHD than in female children born with CHD and exposed to pre-eclampsia (Table 3). When considering the type of CHD, we found that the HR of neurodevelopmental disorders was higher between exposed and unexposed children born with a minor CHD than between exposed and unexposed children born with a major CHD (Table 3).

Mortality rates during the follow-up period between children born with a minor CHD and children born with a major CHD can be found in Supplementary material online, supplementary material 3. We found that 82.8% of the children born with a major CHD were alive at the end of follow-up compared with 98.3% in the group of children born with a minor CHD.

Secondary aim: examine whether CHD and pre-eclampsia may act in synergy

A comparison cohort of 113 713 children with no CHD diagnoses were included. No overall differences were found in baseline characteristics between the population of children born with CHD

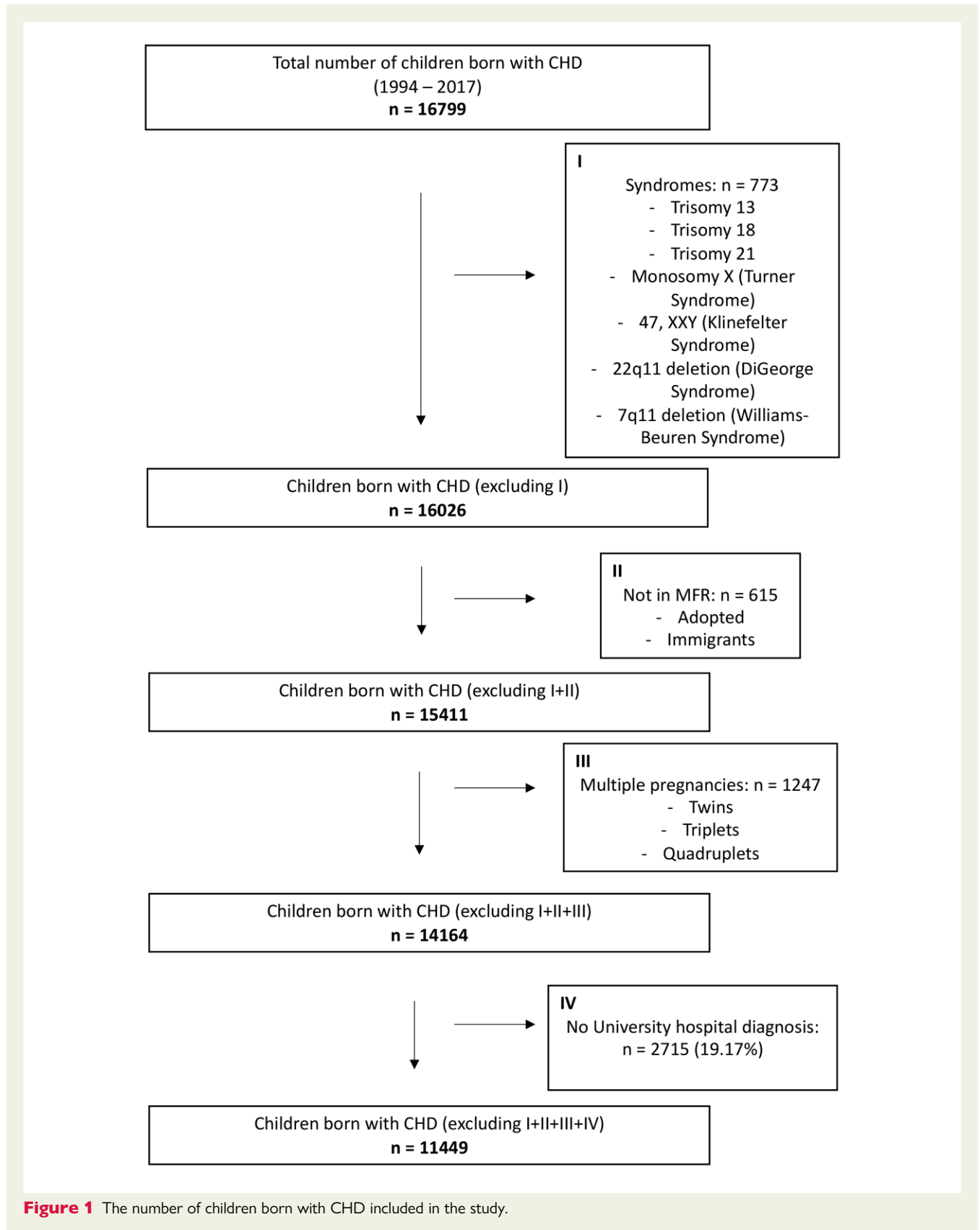


Figure 1 The number of children born with CHD included in the study.

Table 1 Baseline characteristics of children born with CHD

	Pre-eclampsia n = 502 (4.4%)	No pre-eclampsia n = 10 947 (95.6%)	P-value
Male sex, n (%)	271 (54.0)	5581 (51.0)	0.19
Surgery for CHD, n (%)	156 (31.1)	3503 (32.0)	0.66
Small for GA, n (%)	52 (10.4)	1226 (11.2)	0.56
Pre-term birth, n (%)			
Term: GA \geq 37 weeks	273 (54.4)	9142 (83.5)	<0.001
Group 1: GA <37 weeks	223 (44.4)	1590 (14.5)	<0.001
Group 2: GA <34 weeks	149 (33.3)	776 (7.1)	<0.001
Missing	6 (1.2)	215 (2.0)	<0.001
Maternal age, mean (95% CI)	29.7 (29.2–30.2)	29.5 (29.8–29.9)	0.57
Year of birth, n (%)			
1994–2001	152 (30.3)	3506 (32.0)	0.02
2002–2009	156 (31.1)	3841 (35.1)	
2010–2017	194 (38.6)	3600 (32.9)	
Socioeconomic status, n (%)			
Group 1: Low	119 (23.7)	2650 (24.2)	0.92
Group 2: Lower middle	257 (51.2)	5440 (49.7)	0.03
Group 3: Higher middle	87 (17.3)	1887 (17.2)	
Group 4: High	9 (2.0)	212 (1.9)	
Missing	30 (6.5)	758 (6.9)	
Length of follow-up, median (interquartile range)	11.0 (5.4–17.2)	9.3 (4.6–16.8)	

compared with the population of children born with no CHD. Baseline characteristic of this population stratified on exposure to pre-eclampsia can be found in [Supplementary material online, supplementary material 4](#).

From [Figure 2](#), we see that children with CHD and exposed to pre-eclampsia had a drastically higher cumulative incidence of neurodevelopmental disorders over time compared with unexposed CHD children but also compared with both exposed and unexposed children with no CHD.

Discussion

In this large nationwide population-based registry study, the overall risk of neurodevelopmental disorders was higher in children with

Table 2 Distribution of the individual types of CHD stratified by exposure status

	CHD		P-value
	Pre-eclampsia, n (%)	No pre-eclampsia, n (%)	
Minor CHD	372 (82.9)	8810 (80.1)	0.19
VSD	109 (24.3)	3024 (27.5)	
CoA	16 (3.6)	389 (3.5)	
Aortic valve disease	17 (3.8)	466 (4.2)	
Pulmonary valve disease	35 (7.8)	934 (8.5)	
MV disease	11 (2.4)	392 (3.6)	
PAPVD	< 5	29 (0.3)	
ASD	104 (23.2)	2272 (20.7)	
PDA	76 (16.9)	1055 (9.6)	
Simple miscellaneous	< 5	46 (0.4)	
Major CHD	77 (17.1)	2190 (19.9)	0.19
UVH	< 5	92 (0.8)	
TAC	< 5	56 (0.5)	
I/HAA	< 5	114 (1.0)	
TGA	19 (4.2)	525 (4.8)	
AVSD	19 (4.2)	486 (4.4)	
TAPVD	< 5	162 (1.5)	
PA	< 5	63 (0.6)	
TOF	< 5	69 (0.6)	
Ebsteins anomaly	15 (3.3)	341 (3.1)	
Tricuspid valve disease	< 5	51 (0.5)	
Eisenmenger syndrome	< 5	49 (0.4)	
Complex miscellaneous	< 5	232 (2.1)	

VSD, ventricular septal defect; CoA, coarctatio aortae; MV disease, mitral valve disease; PAPVD, partial anomalous pulmonary venous drainage; ASD, arterial septal defect; PDA, patent ductus arteriosus; UVH, univentricular heart; TAC, truncus arteriosus communis; I/HAA, interrupted/hypoplastic aortic arch; TGA, transposition of the great arteries; AVSD, artrioventricular septal defect; TAPVD, total anomalous pulmonary venous drainage; PA, pulmonary atresia; TOF, Tetralogy of Fallot.

CHD exposed to pre-eclampsia compared with children unexposed to pre-eclampsia. The risk of neurodevelopmental disorders among children born with CHD of mothers with pre-eclampsia appeared to depend on the onset of pre-eclampsia, as CHD children exposed to early-onset pre-eclampsia had a higher risk of neurodevelopmental disorders than CHD children exposed to late-onset pre-eclampsia. We also found a higher risk of neurodevelopmental disorders in males born with CHD and exposed to pre-eclampsia than female with the same exposure, suggesting effect modification by sex.

Table 3 Risk of neurodevelopmental disorders in children with CHD according to sex and type of CHD.

	CHD children exposed to PE vs. CHD children unexposed to PE	
	HR (95% CI)	P-value
Risk of neurodevelopmental disorders		
Overall	1.84 (1.39–2.42)	<0.001
Female	1.29 (0.77–2.17)	0.33
Male	2.19 (1.59–3.04)	<0.001
Major CHD	1.44 (0.70–2.94)	0.32
Minor CHD	1.90 (1.41–2.57)	<0.001

Adjusted for socioeconomic status.
PE, pre-eclampsia.

Table 4 Risk of neurodevelopmental disorders among children with CHD according to the onset of pre-eclampsia

	No pre-eclampsia	Onset of pre-eclampsia	
		Early onset	Late onset
Total (N)	11 001	179	264
Risk of neurodevelopmental disorders	1.0 (reference)	2.3 (1.58–3.35)	1.54 (0.105–2.26)
HR (95% CI)			

Adjusted for socioeconomic status.

Furthermore, the severity of the heart disease was found to inversely modify the risk of neurodevelopmental disorders as the risk of neurodevelopmental disorders was higher between exposed and unexposed children born with a minor CHD than between exposed and unexposed children born with a major CHD.

To our knowledge, no studies have yet investigated how a pregnancy complicated by pre-eclampsia affects the neurodevelopment in a population of children born with CHD. The relationship between the CHD, pre-eclampsia, and neurodevelopmental outcomes is complex. CHD causes abnormal brain development, in part due to decreased cerebral oxygen delivery. Placental dysfunction expressed as pre-eclampsia may exacerbate this. The association between maternal pre-eclampsia and offspring CHD is well documented,^{15,22,23} and particularly early-onset pre-eclampsia is associated with CHD.¹⁵ There may be shared genetic mechanisms between pre-eclampsia and CHD, especially in angiogenic genes,^{24,25} however this remains uncertain. It is therefore difficult to disentangle the potential causal pathways between CHD, pre-eclampsia, and neurodevelopmental disorders.

In this study, exposure to pre-eclampsia was associated with a further increase in the risk of neurodevelopmental disorders in children born with CHD. Exposure to pre-eclampsia drastically increased the cumulative incidence of neurodevelopmental disorders in children born with CHD compared with the cumulative incidence of neurodevelopmental disorders among exposed and unexposed children born with no CHD. This could potentially indicate that CHD and pre-eclampsia may act in synergy and thereby potentiate the risk of neurodevelopmental disorders in children born with CHD.

Furthermore, we saw that children born with CHD but not exposed to pre-eclampsia had a higher incidence of neurodevelopmental disorders compared with children born with no CHD yet exposed to pre-eclampsia. As previously mentioned, the underlying aetiological mechanisms are likely multifactorial. Hypoxia in foetal life is likely a leading cause, but other factors including genetics could be of importance.

We saw that exposure to early-onset pre-eclampsia increased the risk of neurodevelopmental disorders when compared with exposure to late-onset pre-eclampsia. Considering this impact of the timing of the onset of pre-eclampsia on neurodevelopmental it is therefore important to distinguish between early and late-onset pre-eclampsia in this population of children born with CHD.

Exposure to pre-eclampsia heightens the risk of being born pre-mature. Being born pre-term increases the risk of neurodevelopmental problems and could potentially be the underlying cause for neurodevelopmental disorders in this population. However, we find that only a very limited effect is mediated through pre-term birth, indicating that pre-eclampsia acts independently as a risk factor for neurodevelopmental disorders in children born with CHD.

It is well-known that major CHD is associated with neurodevelopmental complications in children.^{9,26} However, recent studies from our group also demonstrate an association between being born with a minor CHD and an increased risk of lifetime psychiatric morbidity.^{5,7} Our data support the importance of not neglecting those with a minor CHD, as they also seem to be vulnerable to the exposure of pre-eclampsia in terms of neurodevelopmental disorders. Children born with a minor CHD in this study seem to be relatively more vulnerable pre-eclampsia compared with children born with a major CHD. This paradox may occur because major CHDs are already severely compromised in circulation and oxygenation, and pre-eclampsia contributes with little or no extra measurable effect on this. Another important factor is live birth bias where the higher survival rate among minor CHD generate a larger group of patients who can live to experience neurodevelopmental problems. Furthermore, children born with a major CHD have a higher mortality than children born with a minor CHD. Therefore, it could potentially be the case, that children born with a major CHD does not live long enough to get a diagnosis of neurodevelopmental disorders.

The higher psychiatric morbidity in males vs. females has previously been observed in the general population as well as in a population of children with CHD.⁶ We also observed that neurodevelopment in males with CHD was more vulnerable to the exposure of pre-eclampsia. If a male with CHD was exposed to pre-eclampsia he had a higher risk of neurodevelopmental disorders compared with males with CHD who were not exposed to pre-eclampsia. We did not find the same important difference in females with CHD.

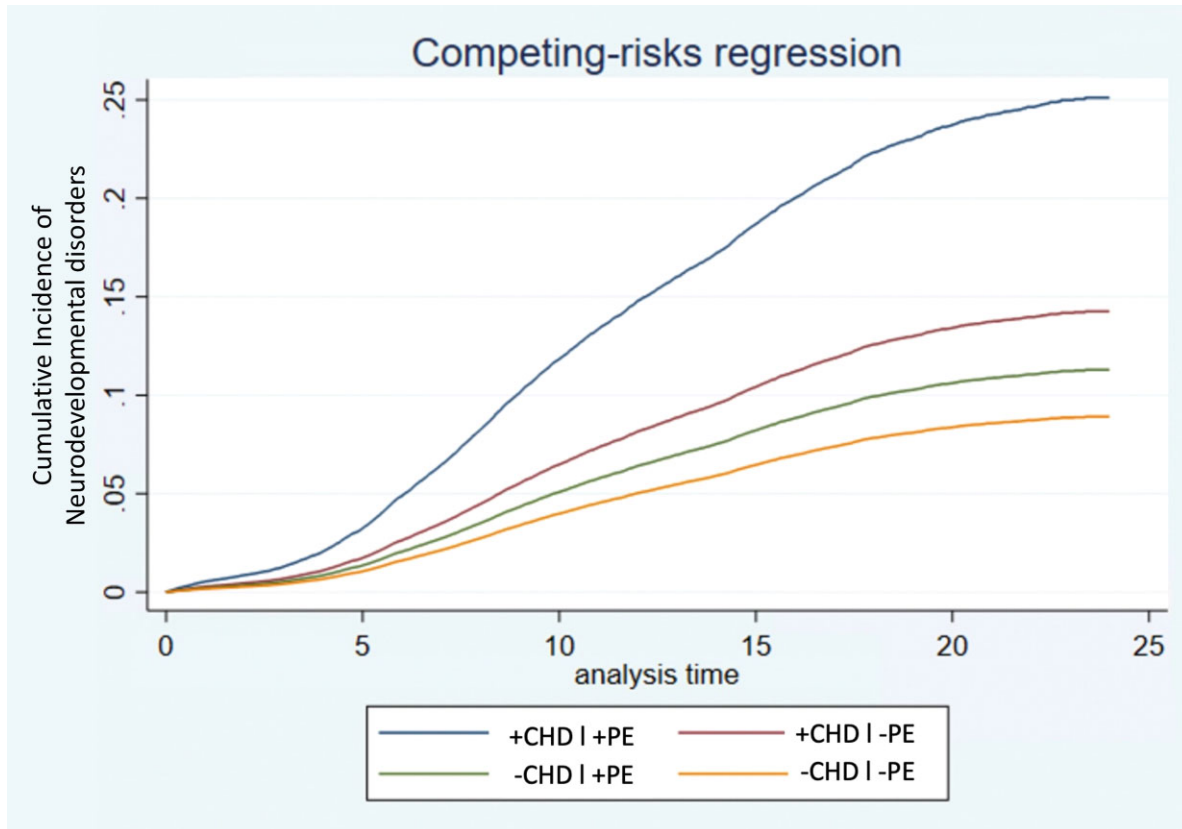


Figure 2 Cumulative incidence of neurodevelopmental disorders with death as competing risk between four groups: (i) children born with CHD and exposed to pre-eclampsia, (ii) children born with CHD but not exposed to pre-eclampsia, (iii) children with no CHD but exposed to pre-eclampsia, and (iv) children with no CHD and not exposed to pre-eclampsia.

It is well-known that autism spectrum disorders and ADHD in general are more frequent in men albeit it is discussed whether females are potentially underdiagnosed. This may be caused by the symptoms of autism and ADHD being expressed different and in more hidden ways among girls than boys.²⁷ It is therefore important to be cautious when interpreting these gender-specific findings.

Limitations

The Danish registries provides us a great opportunity to include large populations with long follow-up times. However, registry-based studies are limited by the accuracy of the diagnostic coding. In order to account for inaccurate diagnoses, we only included CHD diagnoses issued at a University Hospital. Agergaard et al.²⁸ found that diagnoses obtained from the four University Hospitals matched the discharge diagnoses in the patient's clinical records in 98% of the cases and that the DNPR diagnosis was a true reflection of the patient's actual malformation in 90% of the cases. The diagnosis for pre-eclampsia has a positive predictive value 74.4%.²⁹ In the Danish Psychiatric Central Research Registry, 86.8% of hyperkinetic disorders fulfilled the diagnostic criteria³⁰

and 94% of the cases with autism could be confirmed.³¹ Another limitation is the fact that, as previously mentioned, it is difficult to disentangle the causal pathways between CHD, pre-eclampsia and neurodevelopmental disorders. To lower the risk of introducing colliders stratification bias we have kept adjustments to a minimum and thereby reduced the risk of adjusting for covariates that open biasing pathways.

Conclusion

Due to improvements in surgical and medical techniques, children born with CHD are highly likely to survive and thereby grow into adults with CHD. However, it has become clear that even though the heart disease may not be lethal these children potentially face a life with considerable neurodevelopmental problems. In this study, we demonstrated that exposure to pre-eclampsia increased the already existing risk of neurodevelopmental disorders in children born with a CHD. We urge clinicians to be particularly attentive to these vulnerable children for timely diagnosis and treatment of neurodevelopmental problems in order to improve their prognosis and quality of life.

Lead author biography



Camilla Omann, MD, is a PhD fellow at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark. She specializes in maternal–fetal interactions in congenital heart disease, investigating the complex relationship between the maternal–fetal environment and neurodevelopmental outcomes. She has used her great experience with

more methods to examine this field of research. Camilla has both national and international research collaborations, and she has with great success presented her previous work at numerous conferences.

Data availability

The data underlying this article were provided by Statistics Denmark under licence. Data will be shared on request to the corresponding author with permission of Statistics Denmark.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: None declared.

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