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Advanced maternal age and risk of adverse perinatal outcome among women with congenital heart disease: A nationwide register-based cohort study

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Running head: Advanced maternal age and maternal congenital heart disease

Social media quote

Women with congenital heart disease have a higher risk of preterm birth as well as giving birth to a small for gestational age infant at all maternal ages. These two risk factors do not, however, seem to potentiate each other.

Link to figure 2.

Synopsis

Study question

Is the effect of age on the risk of preterm birth (PTB) and small for gestational age (SGA) higher among women with congenital heart disease?

What´s already known?

Women with congenital heart disease have a higher risk of PTB and SGA. Advanced maternal age (≥35 years) likewise increases the risk of PTB and SGA, probably explained by poorer cardiovascular status. However, knowledge about whether these two risk factors potentiate each other is not well described.

What this study adds

Women with congenital heart disease have a higher risk of PTB and giving birth to a SGA infant at all maternal ages. These two risk factors did not, however, seem to potentiate each other.

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Abstract

Background: Women with maternal congenital heart disease have a higher risk of preterm birth (PTB) and giving birth to a small for gestational age (SGA) infant. Advanced maternal age (≥35 years) likewise increases the risk of PTB and SGA, probably explained by poorer cardiovascular status. It is likely that advanced maternal age is particularly detrimental in women with congenital heart disease.

Objectives: We aimed to determine whether the pattern of higher risk of PTB and SGA with higher maternal age varied among women with and without congenital heart disease. We hypothesized that the effect of age is higher among women with congenital heart disease.

Methods: We did a cohort study using Danish nation-wide registers Births from 1997-2014 were included. Cox regressions were used to estimate hazard ratios (HR) for PTB and SGA. Universal and congenital heart disease specific references was used for comparison.

Results: We included 932,772 births among 548,314 women. HRs of PTB and SGA were 1.55 (95% confidence interval [CI] 1.37, 1.77) and 1.43 (95% CI 1.29, 1.58) in women with congenital heart disease as compared to women without. For both PTB and SGA, HRs were higher for women 35 years as compared to women aged 25-29 years. HRs of PTB and SGA were higher among women with congenital heart within all strata of maternal age as compared to women without (e.g. 2.46, 95% CI 1.18, 5.14 vs. 1.63, 95% CI 1.56, 1.70) for SGA for women aged 40-44 years). The pattern of higher risk of PTB and SGA with higher maternal age was, however, similar among women with and without congenital heart disease.

Conclusions: Women with congenital heart disease had a higher risk of PTB and giving birth to an SGA infant at all maternal ages. These two risk factors did not, however, seem to potentiate each other.

Keywords

Congenital heart disease; maternal age; preterm birth; small for gestational age

Word count: 3320

BACKGROUND

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Due to advances in diagnosis and treatment more people with congenital heart disease now survive into adulthood and more women are reaching the childbearing age.[1] In the United States, e.g., the rate of deliveries among women with congenital heart disease increased from 6.4 per 10,000 deliveries in 2000 to 9.0 per 10,000 in 2010.[2] These women will in general experience more cardiac, obstetric and neonatal complications.[2-6]

Women in the Western world tend to delay motherhood and give birth at more advanced ages.[7, 8] Advanced maternal age (≥35 years) has been associated with higher risk of fetal death, preterm birth (PTB) and giving birth to infants born small for gestational age (SGA).[9] The mechanism behind this increase is poorly understood but has partly been explained by poorer cardiovascular status among older women which impacts placental function.[10]

Due to poorer cardiovascular status among women with congenital heart disease, it is likely that advanced maternal age is particularly detrimental in these women and they therefore experience a greater effect of age with higher maternal age as compared to women without congenital heart disease. However, the consequence of the combination of congenital heart disease and advanced maternal age in relation to adverse neonatal outcomes has not been well described.

To provide the best advice for women with congenital heart disease more knowledge about the combined effects of congenital heart disease and advanced maternal age is needed. Therefore, we aimed to determine whether the pattern of higher risk of PTB and SGA with higher maternal age varied among women with and without congenital heart disease. Due to poorer cardiovascular status among women with congenital heart disease we hypothesised that the effect of age is higher among women with congenital heart disease as compared to women without congenital heart disease.

METHODS

The study is a cohort study with nation-wide prospectively collected register data. Data from the Danish National Birth Register,[11, 12] the Danish National Patient Register,[13, 14] and the Danish Civil Registration System[15] were linked at an individual level, using the unique personal identification number carried by all residents in Denmark.[15, 16]

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Study population

The study population consisted of women born in Denmark giving birth to a single child in Denmark between 1997 and 2014 (n=952,882). Information about maternal age was obtained from the Danish Civil Registration System.[15] Maternal age was assessed at inclusion and estimated based on date of delivery, gestational age and maternal date of birth. We restricted the study population to births among women aged 15 to 44 years. All women carrying a pregnancy to 22 weeks of completed gestation (154 days) were included in the cohort.[12] The final study population consisted of 932,772 births. Figure 1 shows the study inclusion and exclusions.

Maternal congenital heart disease

Information about maternal congenital heart disease was obtained from the Danish National Patient Register, which is a population-based administrative register holding information on all hospital admissions since 1977.[13, 14] All women with a diagnosis of congenital heart disease (ICD-10; Q20-Q26, ICD-8; 746-747) between 1977 and 2015 were included except ICD-10 Q26.5-Q26.6 and ICD-8 746.7 and 747.5-747.9, which are not specific for congenital heart disease. To increase the positive predictive value of the diagnoses of congenital heart disease we excluded individuals with e.g. unspecific diagnoses using an algorithm previously described.[17] We included women diagnosed before, during, and after pregnancy under the hypothesis that underlying congenital heart disease affected the pregnancy and its outcome irrespective of whether the disease was diagnosed at the time of delivery. Based on guidelines from the European Society of Cardiology, congenital heart disease was categorized into simple, moderate and complex.[18] Women with more than one diagnosis were categorised according to the more severe diagnosis.

Preterm birth and small for gestational age

Information about birthweight and gestational age was obtained from the Danish Medical Birth Register.[11, 12] PTB was defined as giving birth to a liveborn child before 37 weeks of completed gestation. Births with implausible combinations of birthweights and gestational age according to standards from Alexander et al.[19] were excluded (n=602). SGA was calculated for males and females separately and defined as birthweight below the 10th

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percentile of standard references given by Marsál et al.[20] During the study period, the estimation of gestational age was based on best clinical estimates based on ultrasound, last menstrual period and judgment of the child.

Covariates

Ethnicity, parity, socio-economic position and calendar year were identified as potential confounders *a priori* using Directed Acyclic Graphs (eFigure 1). Information about ethnicity was obtained from the Danish Civil Registration System and grouped into Western and non-Western according to Statistic Denmark.[21] Information on parity was obtained from the Danish Medical Birth Register and after logical cleaning grouped into nulli-, primi- and multiparous.

Socioeconomic position was assessed by level of education, which has shown to be a strong socioeconomic predictor of the risk of both PTB and SGA in Denmark.[22, 23] Level of education was assessed as the highest ongoing or attained education. Information about educational level 1st of October the year preceding each birth was obtained from the Danish Education Register.[24] Education was classified according to the International Standard Classification of Education System (ISCED 2011) and categorised into four groups; low education (pre-primary, primary and lower secondary; levels 1-2), medium (upper secondary and postsecondary; levels 3-4) short and medium cycle higher education (short-cycle tertiary and Bachelor´s; levels 5-6) and long-cycle higher education (Master´s or higher; levels 7-8). Age was categorized into five groups; 15-24, 25-29, 30-34, 35-40 and 40-44 years. Calendar year was grouped into 5-year bands.

Statistical analysis

For the descriptive analysis, median and interquartile range (IQR) was used for continuous variables and counts with proportions was used for categorial variables. The association between congenital heart disease and, respectively, PTB and SGA was estimated using a Cox proportional hazard models with gestational age as underlying time scale. For PTB, the follow-up ended at birth or after 258 days of gestation whichever came first. Pregnancies resulting in stillbirth were censored at the time of stillbirth or after 258 days. When analysing the association with SGA, the pregnancies were followed until birth. Likewise,

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stillbirths were censored at the time of births. Adjustment was made for calendar year, ethnicity, parity and educational level. Some women contributed with more than one birth to the cohort. To account for the clustered structure of data, a cluster-robust standard error estimator was used. Results were presented as hazard ratio (HR) with 95% confidence interval (CI).

We hypothesised that the effect of age on the risk of PTB and SGA was higher among women with congenital heart disease as compared to women without congenital heart disease. Therefore, we tested the possible multiplicative interaction between maternal age and congenital heart disease on the risk of PTB and SGA, respectively. The joint effect of maternal age and congenital heart disease was tested by including the interaction term in the model without the main effects using a universal reference group (women without congenital heart disease aged 25-29 years). The relative excess risk due to interaction (RERI) and 95% CI was calculated to assess effect modification on an additive scale.[25] Lastly, analyses were conducted within strata of congenital heart disease. Linear trends were tested by treating age categories as a continuous variable. The proportional hazard assumption was evaluated visually using log-log plots with no violations detected.

Missing data

The amount of missing data was low (<2.0 %) and observations with missing data on the observed variables were excluded from the analyses (Figure 1).

Sensitivity analysis

To examine the robustness of our results several sensitivity analyses were conducted. Firstly, the analysis was restricted to nulliparous women to account for selected fertility based on outcomes from the first pregnancy. Secondly, we conducted an analysis where preterm stillbirths and SGA stillbirths were included as events instead of getting censored. Lastly, we conducted an analysis where women diagnosed with a complex congenital heart disease were excluded to examine whether the association was driven by the more severely affected women.

Ethics approval

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The study was approved by the Danish Data Protection Agency (2015-57-0008, no.16/48885). According to Danish law, register-based studies do not need ethical approval. All data were provided by Statistic Denmark.

RESULTS

Birth and maternal characteristics

A total of 3,688 single births were observed among 2,193 women with congenital heart disease. The proportion of births of women with congenital heart disease increased from 0.31% in the start of the study period to 0.52% at the end. Most of the women diagnosed with congenital heart disease were diagnosed with a simple defect (60.3%) of which atrial septal defect and ventricular septal defect constituted the main defects. Complex diagnoses constituted 10.4 % of the diagnoses. Women with congenital heart disease were younger when giving birth and more were nulliparous as compared to women without congenital heart disease (Table 1).

The median gestational age was 280 days (IQR 273-287). Mean follow-up time, from inclusion at 154 days of gestation to censoring or birth, was 104 days (range 1-105) for PTB and 126 days (range 1-161) for SGA. The overall proportion of PTB was 5.0% (n=46,540) and SGA 10.4% (n=93,723).

Main effects of congenital heart disease and maternal age

Women with congenital heart disease had a higher risk of both PTB and SGA as compared to women without congenital heart disease with adjusted HRs (HR) of 1.55 (95% CI 1.37, 1.77) and 1.43 (95% CI 1.29, 1.58).

There was a higher risk of PTB with higher maternal age. In comparison to women aged 25-29 years, the HRs of PTB were 0.90 (95% CI 0.88, 0.93), 1.07 (95% CI 1.05, 1.10), 1.28 (95% CI 1.24, 1.32) and 1.56 (95% CI 1.47, 1.66) for women aged <25, 30-34, 35-39 and 40-44, respectively. Likewise, the risk of giving birth to a child born SGA was higher with higher maternal age. In comparison to women aged 25-29 years, the HRs of SGA were 0.93 (95% CI 0.91, 0.95), 1.11 (95% CI 1.09, 1.12), 1.31 (95% CI 1.28, 1.34), and 1.63 (95% CI 1.56, 1.71) for women aged <25, 30-34, 35-39 and 40-44 years, respectively.

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Combined effect of congenital heart disease and maternal age

Women with congenital heart disease had a higher risk of PTB at all maternal ages. The pattern of higher risk from maternal age 25-29 years and above did not diverge between women with and without congenital heart disease (p of multiplicative interaction=0.71, p of additive interaction=0.62). In comparison to women aged 25-29 years without congenital heart disease, women with congenital heart disease aged 35-39 years and 40-44 years had an HR of 1.72 (95% CI 1.18, 2.51) and 3.38 (95% CI 1.44, 7.90), respectively (Figure 2, eFigure 2 and eTable1). Crude estimates for women ≥30 years were somewhat lower. Adjustment for confounders increased HRs among older women, e.g. 18% for women with congenital heart disease aged 35-39 years. Adjustment for educational level and parity increased estimates the most.

Women with congenital heart disease had a higher risk of giving birth to a child born SGA at all maternal ages. As for PTB the pattern of higher risk of SGA from maternal age of 30-34 years was similar among women with and without congenital heart disease (P of multiplicative interaction=0.55, P of additive interaction=0.63). In comparison to women aged 25-29 years without congenital heart disease, women with congenital heart disease aged 35-39 and 40-44 years had HRs of 1.68 (95% CI 1.23, 2.28) and 3.71 (95% CI 1.80, 7.63), respectively (Figure 2, eFigure2 and eTable1).

Sensitivity analysis

The risk of PTB among women 35-44 years with congenital heart disease was less clear with an HR of 0.68 (95% CI 0.25, 1.82) when restricting the analyses to nulliparous women (eFigure 3), whereas the HR of SGA was essentially the same as for the whole population of women with congenital heart disease (eFigure 3). When a preterm stillbirth or an SGA stillbirth was included as events instead of getting censored results were essentially similar (eFigure 4). When women diagnosed with complex congenital heart disease were excluded from the analyses the same pattern was seen with a higher risk of both PTB and SGA with higher maternal age. Likewise, the pattern of higher risk was similar between women with and without congenital heart disease (eFigure 5).

COMMENT

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Principal findings

In this nation-wide register-based study we found that women with congenital heart disease had a higher risk of PTB and giving birth to an SGA infant at all maternal ages. However, these two risk factors did not seem to potentiate each other.

Strengths of the study

Using national population-based registries based on prospectively collected data enables inclusion of all deliveries as well as all women diagnosed with congenital heart disease in Denmark which limits the risk of selection bias related to both deliveries and congenital heart disease. To limit the risk of information bias, all diagnoses of congenital heart disease were validated using an algorithm previously described.[6, 17]

A further strength of the study is the adjustment for socioeconomic position by educational level. Inability to adjust for socioeconomic position may give a spuriously high risk among younger women and a spuriously low risk among older women.[26] We assessed educational level as expected level of education in case it was higher than the attained level of education to overcome a dependency between age and education among younger women.

We find the results to be robust since similar findings were found in the sensitivity analyses. The HR for PTB among nulliparous women, however, was lower. We find it plausible that this finding is due to chance since the sample is very small; however, we cannot rule out, that the lower HR is due to a natural selection - that women with congenital heart disease who have their first child at the age ≥35 years are healthier, have a better cardiovascular status etc. and therefore have a lower risk.

Limitations of the study

Even though we have conducted a nation-wide study with a large study sample the number of women of more advanced age among women with congenital heart disease is still small. However, despite the small number of women we found a higher risk of giving birth to a SGA infant among women with congenital heart disease of more advanced age and a clear tendency for PTB.

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Women who are foreseen to be at high risk during pregnancy and delivery may due to counselling decide not to become pregnant. Thus, the group of women with congenital heart disease may only include the women with best cardiovascular conditions. Furthermore, the amount of induced abortion is lower among women with congenital heart disease[27, 28] as compared to the general population, which is suggested to reflect a different psychological or social situation for women with congenital heart disease.[28] This could further support the fact that women with congenital heart disease who end up pregnant in general are a more selected group than the general population of pregnant women and despite a poorer cardiovascular status might be more selected on other parameters of importance for PTB and SGA.

Congenital heart disease is a heterogeneous group and risk might differ between different subgroups of congenital heart disease. However, due to the low amounts of women with congenital heart disease who have had children at advanced maternal age we are not able to divide into further subgroups. However, excluding the most complex diagnoses from the analyses essentially gave the same findings indicating that the associations are not purely driven by the most severely affected women.

Lastly, we cannot rule out that we have missed some women diagnosed with a congenital heart disease before 1977. However, for those women not to be included in our sample they should have been diagnosed before 1977 without having a single contact to the hospital with a diagnosis of congenital heart disease after 1977 even during pregnancy and delivery. We do not consider this to be very likely; however, not impossible. We would expect such bias to lead towards null.

Interpretation

In the general population women of advanced maternal age have a higher risk of both PTB and SGA.[9] Only a single study has investigated the association between maternal age, congenital heart disease and neonatal outcomes[28] while other studies have included maternal age as a predictor of neonatal outcomes.[3, 29] Furenäs et al.[28] did not find a higher risk among women >35 years as compared to women ≤35 years. The study however was limited by the fact that age was dichotomized at 35 years. Within the comparison group the

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age ranged from 15-35 years in which the risk is known to increase and therefore might attenuate the contrast between women with the lowest risk and women above 35 years, especially when socioeconomic position is not accounted for.

To some extend it is questioned whether the effect of maternal age on adverse neonatal outcome is due to biology or due to selection.[30] Advanced maternal age has been associated with a range of adverse pregnancy outcomes showing the same shape of increase in risk across different outcomes[9, 26, 31, 32] which might indicate a biologic explanation. In our study we likewise demonstrate a similar higher risk of both PTB and SGA with increasing age. Furthermore, the association is similar between women with and without congenital heart disease indicating that the biological explanation is the same in both groups. Whereas the selection into motherhood at more advanced ages, as touched upon previously, might be different between the general population and among women with congenital heart disease.

The underlying biologic mechanism proposed to modify the association between advanced maternal age and adverse neonatal outcomes is an abnormal placental function due to accelerated placental aging among older women.[10] Women with congenital heart disease have a disturbed uteroplacental blood flow which has been suggested to cause the increased risk of giving birth to an SGA infant among women with congenital heart disease.[33, 34] Our results indicate that these processes, however, might act independent and do not work in synergy.

In our study population women with congenital heart disease were on average younger when giving birth as compared to women without congenital heart disease. This is similar to what was found in a Swedish population based study[35], whereas others have reported similar mean age across women with and without congenital heart disease.[2, 4, 28, 36] The lower age may be due to counselling by medical staff or because young people living with a congenital heart disease feel more mature and appreciate life in another way than peers.[37] This could cause them not extend their youth to the same extend as seen in the general population where readiness to become a parent is also highly associated with fulfilling other life goals[8] economic stability among others factors.[8, 38]

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While we in consistency with other studies show an increased risk of common pregnancy complications in women with congenital heart disease, this study also demonstrates that the risk is not higher than 10 years older women without congenital heart disease. The study indicates that women with congenital heart disease can 'normalise' their risk for PTB and SGA by having children at younger age.

Conclusions

Women with congenital heart disease had a higher risk of PTB and giving birth to a SGA infant at all maternal ages. The pattern of higher risk with increasing maternal age apparently seemed to be similar among women with and without congenital heart disease. Since even some of the young women with congenital heart disease had a higher risk of neonatal complications as compared to women without congenital heart disease, it might be of importance to advice these women to have children at a younger age to minimize the risk of adverse neonatal outcomes.

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DISCLOSURES

None

FIGURE LEGENDS

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

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Figure 2. HRs of preterm birth (upper) and small for gestational age (lower) among women with and without congenital heart disease (CHD) at different maternal ages. To the left the combined effect of CHD and maternal age is shown using a universal reference group (women without CHD aged 25-29 years). To the right comparison is made within women with and without CHD. Comparison is made to women aged 25-29 years. Adjusted for parity, ethnicity, level of education, and year of inclusion

Table 1. Baseline characteristics by congenital heart disease status of 932,722 births in 548,314 women

	No congenital heart disease		Congenital heart disease	
	N	%	N	%
Age	929,084		3,688	
Median (IQR)	30 (26-33)		29 (25-32)	
15-24	130,747	14.1	752	20.4
25-29	327,656	35.3	1,308	35.5
30-34	324,464	34.9	1,172	31.8
35-39	127,675	13.7	397	10.7
40-44	18,542	2.0	59	1.6
Missing	0		0	
Parity	916,892		3,645	
0	401,787	43.8	1,752	48.1
1	354,954	38.7	1,326	36.4
≥2	160,151	17.5	567	15.5
Missing	12,192	1.3	43	1.2
Ethnicity	929,084		3,688	

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Western	916,852	98.7	3,613	98.0
Non-western	12,232	1.3	75	2.0
Missing	0		0	
Education	918,200		3,643	
Low (Primary/secondary)	143,320	15.7	758	20.8
Medium (Upper secondary/postsecondary)	360,896	39.3	1,373	37.7
Short/medium cycle higher education	304,507	33.1	1,131	31.0
Long cycle higher education	109,477	11.9	381	10.5
Missing	10,884	1.2	45	1.2
Year	929,084		3,688	
1996-2000	260,058	28.0	812	22.0
2001-2005	265,390	28.6	945	25.6
2006-2010	258,442	27.8	1,166	31.6
2011-2014	145,194	15.6	765	20.8
Missing	0		0	

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

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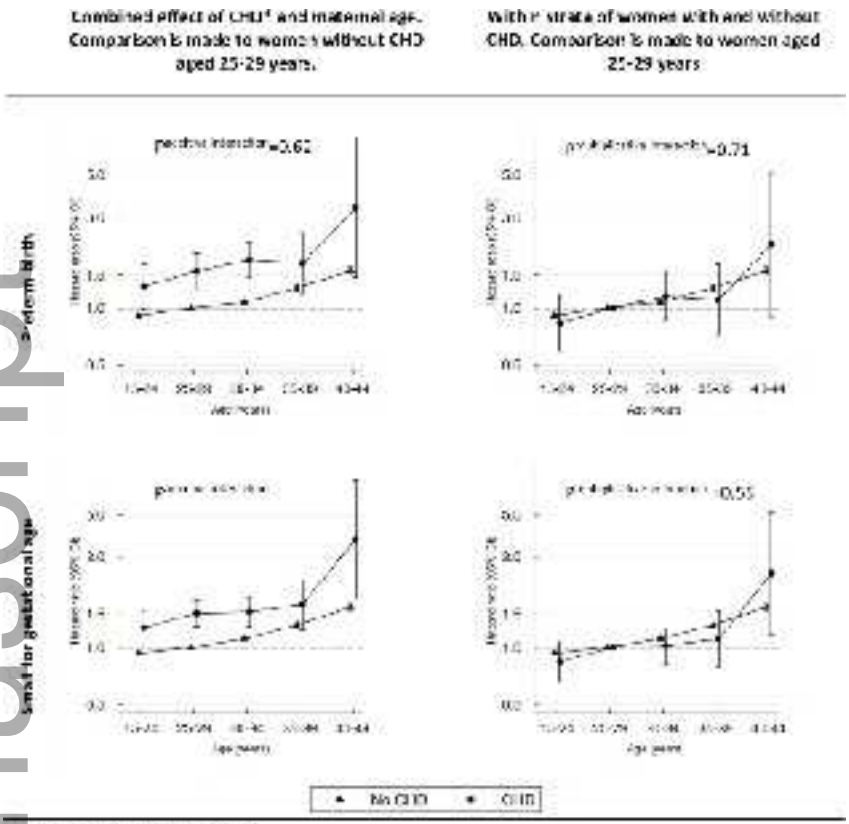

*CHD: Congenital heart disease

Figure 2. RRs of preterm birth (upper) and small for gestational age (lower) among women with and without congenital heart disease (CHD), in different maternal ages. To the left the combined effect of CHD and maternal age is shown as age-specific relative risks (women without CHD aged 25-29 years) and to the right comparisons are made within women with and without CHD. Comparison is made to women aged 25-29 years. Adjusted for parity, ethnicity, level of education, and year of birth.

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