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RESEARCH ARTICLE

Maternal age and the prevalence of congenital heart defects in Europe, 1995–2015: A register-based study

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Abstract

Background: Evidence on the direction and strength of association between maternal age and the prevalence of congenital heart defects (CHD) in different age group categories is conflicting. Some studies have illustrated different trends with an increase in prevalence in younger and older age groups while other studies have reported a linear relationship. Given the increase in maternal age over recent years, it is important to study the CHD prevalence by maternal age.

Objectives: To examine the association between maternal age and the prevalence of CHD in Europe between 1995 and 2015 using population-based data from 24 registries belonging to the European Surveillance of Congenital Anomalies (EUROCAT) network.

Methods: Associations over time of all nonsyndromic CHD according to maternal age category and for three CHD severity groupings (severity group I: very severe; severity group II: severe; severity group III: less severe) were examined using Bayesian multilevel Poisson regression modeling. Further subgroup analyses were undertaken within four maternal age-bands: ≤24, 25–29, 30–34 and 35–44 years. Descriptive summaries are also presented.

Results: There were 51,608 nonsyndromic CHD cases in Europe over the 20-year study period. Total prevalence for all CHD combined was increased for younger mothers (≤24 years) and for mothers 35–44 years of age when compared with mothers aged 25–29 years (reference group) (IRR: 1.05, 95% CI: 1.02, 1.07). The total prevalence was increased for severity group I (very severe) only for younger mothers compared to those aged 25–29 years (IRR: 1.14, 95% CI: 1.04, 1.23). We found an increased prevalence of the following CHD subtypes: double outlet right ventricle (IRR:1.33, 95% CI: 1.09, 1.60), hypoplastic left heart syndrome (IRR: 1.18, 95% CI: 1.05, 1.32), hypoplastic right heart syndrome (IRR: 1.41, 95% CI: 1.05, 1.84), atrioventricular septal defect (IRR: 1.15, 95% CI: 1.01, 1.32), coarctation of aorta (IRR: 1.15, 95% CI: 1.03, 1.28) and atrial septal defect (IRR: 1.08, 95% CI: 1.02, 1.13). For older mothers (35–44 years) compared to the reference category, we observed an increased risk in the prevalence for severity group II (IRR: 1.09, 95% CI: 1.03, 1.14), severity group III (IRR: 1.05, 95% CI: 1.01, 1.08) and an increased prevalence of the CHD subtypes: Pulmonary valve stenosis (IRR: 1.22, 95% CI: 1.09, 1.34), ASD (IRR: 1.07, 95% CI: 1.02, 1.13), CoA (IRR: 1.18, 95% CI: 1.06, 1.32) and

Tetralogy of Fallot (IRR: 1.14, 95% CI: 1.01, 1.28). Finally, for all age categories compared to the reference category, different associations of ASD and an increased prevalence of CoA was also observed.

Conclusions: Based on data for cases of CHD from 24 European population-based registries, evidence of a positive association between maternal age and the total prevalence of CHD for younger (≤24 years old) and older (35–44 years old) mothers was observed. The results suggest that young maternal age (≤24 years old) is a factor associated with severe CHD phenotypes while a positive association between advanced maternal age (35–44 years old) and mild CHD phenotypes was observed.

KEYWORDS

congenital Heart Defects, European Surveillance of Congenital Anomalies, maternal age, prevalence, register-based study

1 | BACKGROUND

Congenital heart defects (CHD) are the most common type of congenital anomalies, occurring in approximately 3–9 of every 1,000 live births and are the leading cause of infant mortality and morbidity (Jenkins et al., 2007). The etiology of CHD has been widely discussed and studies have suggested that genetic and environmental causes can be identified in ∼30% of CHD cases (Pradat, Francannet, Harris, & Robert, 2003).

Apart from these influences, previous research has implicated that epigenetic factors and maternal inherent characteristics such as biological age might also be responsible for specific phenotypes of CHD (Markunas et al., 2016). Average maternal age at the time of delivery, for instance in England the average age at first pregnancy has increased steadily since the mid-1970 s from 26.4 to 29.5 in 2010. Therefore, it is important to understand the impact that advanced maternal age has on the prevalence of CHD (Hamilton & Ventura, 2006).

Previous studies have investigated the association between older maternal age (35–44 years) and CHD, but there have been conflicting results overall and for specific CHD phenotypes (Luo et al., 2013; Miller, Riehle-Colarusso, Siffel, Frias, & Correa, 2011; Reller, Strickland, Riehle-Colarusso, Mahle, & Correa, 2008). For example, a significant association between advanced maternal age (35–44) and atrial septal defect (ASD) has been found (Forrester & Merz, 2008; Miller et al., 2011; Pradat et al., 2003), while other investigators have not reported any association (Hashim et al., 2020; Luo et al., 2013). However, those differences might be due to differences in definition of ASD between the studies. On the other hand, few epidemiological studies have investigated the risk of CHD among the offspring of younger mothers.

The aim of this study was to examine the association between maternal age and the prevalence of CHD in Europe from 1995 to 2015 using population-based data.

2 | METHODS

The European Surveillance of Congenital Anomalies (EUROCAT) is a collaborative network of population-based congenital anomaly registries (EUROCAT, 2021a). Forty-two registries in 22 countries use multiple sources to collect data on anomalies occurring in live births, spontaneous fetal deaths from 20 weeks gestation and terminations of pregnancy for a congenital anomaly at any gestation following prenatal diagnosis. All registries use the WHO International Statistical Classification of Diseases and Related Health Problems version 9 or 10 (ICD-9 or ICD-10). For this study, 21 of 42 registries agreed to participate, all of which provided maternal age data. We included cases born between January 1, 1995 and December 31, 2015 from 21 regional registries in 12 European countries.

Denominator data were provided by EUROCAT (EUROCAT, 2021b) and aggregated according to the year of birth and maternal age at delivery. Maternal age was categorized into four age-bands: ≤24, 25–29, 30–34 and 35–44. The second group (age 25–29) was chosen as the reference because women aged 25–29 years represent the largest proportion of women giving birth (National Center for Health Statistics, 2022). We do not provide estimates for mothers aged ≥45 years due to small numbers which would lead to wide standard errors.

For the present study, cases with a final diagnosis of CHD were included. Minor cases, as listed in the EUROCAT list of minor anomalies, were excluded as they have

lesser medical, functional or cosmetic consequences for the child and their definitions and diagnosis vary considerably (EUROCAT, 2013). Cases with patent ductus arteriosus (PDA) associated with preterm birth only, were also excluded in line with the EUROCAT exclusion list (EUROCAT, 2013). Advanced maternal age increases the risk of chromosomal anomalies (Richards & Garg, 2010). Therefore, cases with CHD and a chromosomal anomaly were not included as chromosomal anomalies increase the risk of CHD (Richards & Garg, 2010). Cases occurring in multiple pregnancies were removed from the analysis because multiple births are more common as maternal age increases (Richards & Garg, 2010) and identical twins that share a placenta have almost twice the increased risk of being born with CHD compared to single births (Best & Rankin, 2015). We also excluded anomalies that related to maternal infections and teratogenic syndromes due to under ascertainment of these conditions (Ardinger et al., 1988; Jones, 1986). Finally, cases of CHD with amniotic band syndrome were excluded because of the evidence of the pathogenetic mechanism underlying the amniotic band (Cignini et al., 2012). All other CHD cases were eligible and coded as nonsyndromic where these CHD occurred without the presence of any other noncardiac major congenital anomaly (Figure 1).

We investigated the association between maternal age and the prevalence of all nonsyndromic CHD in Europe between the years 1995 to 2015. We also examined the association according to three CHD severity groupings based on the EUROCAT classification of the severity of CHD (EUROCAT, 2000) as follows:

1. Very severe (severity group I) (single ventricle, hypoplastic left heart syndrome [HLHS], hypoplastic right heart syndrome [HRHS], Ebstein anomaly, tricuspid atresia); accounted for approximately 8% of all cases.
2. Severe (severity group II) (pulmonary valve atresia [PVS], common arterial truncus, atrioventricular septal defects) (AVSD, aortic valve atresia/stenosis [AVA], transposition of great vessels [TGA], tetralogy of Fallot [TOF], total anomalous pulmonary venous return, Coarctation of the aorta [CoA]); accounted for approximately 21% excluding cases with coexisting severity I CHD anomalies;
3. Less severe (severity group III) (ventricular septal defect (VSD), ASD, pulmonary valve stenosis [PVS]); accounted for approximately 65% excluding cases with coexisting severity I or severity II CHD anomalies.

Altogether these groups accounted for almost 94% of all cases of CHDs. The other ~6% included those with PDA in term infants and others (double outlet right ventricle [DORV], Mitral valve anomalies, aortic atresia/interrupted aortic arch) which were not included in the initial EUROCAT severity groups.

Descriptive statistics including incidence rate ratio (IIR) and 95% CIs were produced for maternal characteristics. We could not adjust for other demographic

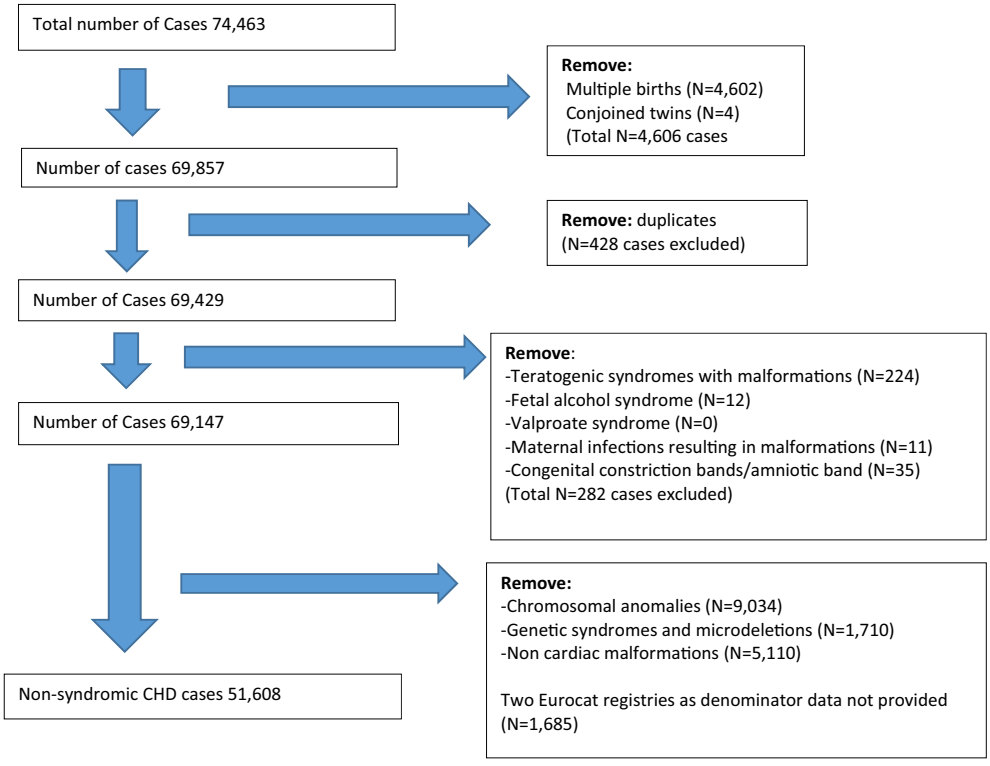


FIGURE 1 Derivation of the study sample.

variables as denominator data for these variables were not available. We applied a Bayesian approach as the credible intervals presented may be interpreted as probability intervals, meaning that there is the specified probability of the true value lying within this interval. This is not technically the case for a frequentist confidence interval. Noninformative priors were used to reflect a position of prior ignorance (McNeish, 2016). Bayesian multilevel Poisson regression modeling (with levels defined by different registers) was used to estimate the IRR of CHD according to maternal age at delivery, adjusted for year of delivery (as a continuous variable) and imposed a linear trend over the 20 years. We also performed a subgroup analysis of each CHD subtype separately for further investigation among the different age group categories using Bayesian Poisson regression models of individual CHD subtypes without any adjustment of multiple testing.

All analyses were performed using Stata software (version 15; StataCorp, College Station, Texas) for both descriptive and multilevel analysis (Table 1).

3 | RESULTS

There were 51,608 nonsyndromic CHD cases in Europe over the 20-year study period (Figure 1). The results from the Bayesian Poisson regression models in the total prevalence of CHD and for the three mutually exclusive CHD severity groups are presented in Table 2. Note that some cases had CHD subtypes from different severity groups but we coded by the most severe. Estimates showed an increased risk and a credible range (IRR: 1.05, 95% CI: 1.02, 1.07) both for younger mothers (aged ≤24) and older mothers (35–44 years) respectively compared with the reference group (25–29 years). For CHD severity group I, the total prevalence was 0.33 per 1,000 and we found an increased risk (IRR: 1.14, 95% CI: 1.04, 1.23) for the younger mothers (≤ 24 years). For severity groups II and III, we found an increased risk in the prevalence of CHD for mothers aged 35–44 years. Specifically, the total prevalence of CHD for severity group II for mothers 35–44 was 0.99 per 1,000 (IRR: 1.09, 95% CI: 1.03, 1.14) while for severity group III, the most prevalent group, the total prevalence of CHD was 2.86 per 1,000 (IRR: 1.05, 95% CI: 1.01, 1.08). Figure 2a,b present the total prevalence for each CHD subtype separately.

We also performed a subgroup analysis for each CHD subtype using Bayesian Poisson regression models. Based on this subgroup analysis among the different age group categories, we found an indication of an association between maternal age and the prevalence of CHD in younger mothers (≤24 years) compared with the reference group (25–29 years) for the following subtypes (acronyms in Table 1): HRHS (IRR: 1.41, 95% CI: 1.05, 1.84), DORV (IRR:1.33, 95% CI: 1.09, 1.60), AVSD (IRR: 1.15, 95% CI: 1.01, 1.32), CoA (IRR:1.15, 95% CI: 1.03, 1.28), HLHS (IRR: 1.18, 95% CI: 1.05, 1.32), ASD (IRR:1.08, 95% CI: 1.02, 1.13).

We also found evidence of association among mothers aged 35–44 years for PVS (IRR: 1.22, 95% CI: 1.09, 1.34), ASD (IRR: 1.07, 95% CI: 1.02, 1.13), CoA (IRR: 1.18, 95% CI: 1.06, 1.32), ToF (IRR: 1.14, 95% CI: 1.01, 1.28).

We found different associations of ASD for all age categories compared to the reference category (25–29 years) while an increased prevalence of CoA for all age categories was also observed (Table 1).

4 | DISCUSSION

This study aimed to examine the association between maternal age and the prevalence of CHD in Europe between 1995 and 2015 using high-quality population-based congenital anomaly registry data. Based on our analysis, the findings suggest a positive association between maternal age and the total prevalence of CHD for mothers 35–44 years of age compared to the reference category (25–29 years of age). This finding is consistent with previous studies, which reported an increased risk of CHD associated with advanced maternal age (35–44 years of age) (Agha, Glazier, Moineddin, Moore, & Guttmann, 2011; Forrester & Merz, 2008; Miller et al., 2011). However, one study suggested little evidence of an association between advanced maternal age and the incidence of CHD (Best & Rankin, 2015), while two smaller studies did not find any association, perhaps due to low study power (Chaudhary et al., 2017; Liu et al., 2009).

Interestingly, even though previous studies did not report an association between total CHD and maternal age, some did report an association of maternal age and specific CHD subtypes (Hashim et al., 2020; Miller et al., 2011). Specifically, based on our subgroup analysis, we found a positive association of ASD, PVS, CoA, ToF phenotypes with advanced maternal age. Our finding of an association of ASD, VSD, PVS and CoA is consistent with the study Miller et al (Miller et al., 2011) which suggested that the birth prevalence of those specific CHD phenotypes might be associated with maternal age, especially among children of mothers 35 years or older. Additionally, Best et al (Best & Rankin, 2015) reported a marginally greater prevalence of PVS among mothers ≥35 years of age, while previous studies reported an increased risk of VSD and ASD (Forrester & Merz, 2008; Pradat et al., 2003). However, some discrepancies

TABLE 1 Prevalence per 1,000 live and stillbirths IRR (95% Cred. Interval) of specific subtypes CHD by maternal age in Europe between 1995 and 2015

	Maternal age: ≤24 years			Maternal age: 30–34 years			Maternal age: 35–44 years		
Subtypes of CHD	***N***	**Prevalence**	**IRR (95% Cred. Interval)**	***N***	**Prevalence**	**IRR (95% Cred. Interval)**	***N***	**Prevalence**	**IRR (95% Cred. Interval)**
Patent ductus arteriosus only in term (PDA)	520	0.19	1.04 (0.93 1.16)	852	0.21	1.01 (0.91 1.12)	547	0.23	1.06 (0.94 1.18)
Double outlet right ventricle (DORV)	214	0.08	1.33 (1.09 1.60)	255	0.06	1.07 (0.88 1.28)	169	0.07	1.14 (0.91 1.39)
Mitral valve anomalies	208	0.08	1.02 (0.85 1.20)	315	0.08	0.99 (0.84 1.16)	171	0.07	0.85 (0.71 1.01)
Aortic atresia with interrupted aortic arch	39	0.01	0.72 (0.47 1.04)	97	0.02	1.14 (0.84 1.57)	63	0.03	1.13 (0.77 1.56)
Single ventricle defect	121	0.04	1.06 (0.85 1.33)	174	0.04	0.87 (0.70 1.07)	141	0.06	0.95 (0.84 1.08)
Hypoplastic left heart syndrome(HLHS)	492	0.18	1.18(1.05 1.32)	642	0.16	0.93 (0.83 1.04)	416	0.17	0.99 (0.89 1.13)
Hypoplastic right heart syndrome(HRHS)	92	0.03	1.41(1.05 1.84)	93	0.02	0.98 (0.73 1.28)	69	0.03	1.18 (0.83 1.63)
Ebstein anomaly	84	0.03	1.00 (0.74 1.30)	135	0.03	1.00 (0.78 1.28)	88	0.04	0.97 (0.72 1.27)
Tricuspid atresia(TA)	136	0.05	1.16 (0.93 1.44)	181	0.04	0.88 (0.72 1.08)	135	0.06	1.02 (0.81 1.23)
Pulmonary valve atresia (PVA)	179	0.07	1.14 (0.93 1.39)	255	0.06	0.91(0.76 1.07)	185	0.08	1.01 (0.83 1.23)
Common arterial trunk (CAT)	91	0.03	0.95 (0.72 1.23)	143	0.04	1.06 (0.84 1.33)	110	0.05	1.28 (1.00 1.63)
Atrioventricularseptal (AVSD)	383	0.14	1.15 (1.01 1.32)	479	0.12	0.90 (0.79 1.01)	332	0.14	0.94 (0.80 1.09)
Aortic valve atresia (AVA)	240	0.09	1.01 (0.86 1.20)	378	0.09	1.04 (0.89 1.20)	241	0.10	1.07 (0.90 1.29)
Transposition of the great arteries(TGA)	542	0.20	0.93 (0.83 1.03)	972	0.24	1.03 (0.93 1.13)	647	0.27	1.05 (0.94 1.16)
Tetralogy of Fallot (ToF)	446	0.17	1.05(0.94 1.19)	724	0.18	1.04 (0.94 1.717)	524	0.22	1.14 (1.01 1.28)
Total anomalous pulmonary venous (TAPVR)	129	0.05	1.24 (0.96 1.56)	155	0.04	0.90 (0.71 1.13)	108	0.05	0.97 (0.75 1.26)
Coartation of aorta (CoA)	603	0.22	1.15 (1.03 1.28)	972	0.24	1.12 (1.02 1.23)	662	0.28	1.18 (1.06 1.32)
Ventricular septal defect (VSD)	5,376	2.00	1.02(0.99 1.05)	8,927	2.18	1.02 (0.99 1.05)	5,685	2.37	1.01 (0.98 1.05)
Atrial septal defect (ASD)	2,690	1.00	1.08(1.02 1.13)	3,810	0.93	1.01 (0.96 1.05)	2,478	1.03	1.07 (1.02 1.13)
Pulmonary valve stenosis (PVS)	718	0.27	1.06 (0.95 1.16)	1,022	0.25	1.00 (0.92 1.10)	776	0.32	1.22 (1.09 1.34)

TABLE 2 Prevalence per 1,000 live and stillbirths and IRR (95% Cred Interval) of CHD by maternal age in Europe between 1995 and 2015

CHD severity	≤24 years	25–29 years (reference category)	30–34 years	35–44 years
Total CHD subtype[a] ($N = 53,293$)				
Prevalence	3.84	3.60	3.94	4.45
IRR (95% CI)	1.05(1.02, 1.07)	1	1.01(0.99, 1.03)	1.05(1.02,1.07)
Severity I ($N = 4,088$)				
Prevalence	0.33	0.28	0.29	0.34
IRR (95% CI)	1.14 (1.04, 1.23)	1	0.92 (0.85, 1.00)	0.98 (0.90, 1.07)
Severity II ($N = 11,286$)				
Prevalence	0.80	0.74	0.85	0.99
IRR (95% CI)	1.05(1.00, 1.11)	1	1.04(0.99, 1.09)	1.09(1.03, 1.14)
Severity III ($N = 34,605$)				
Prevalence	2.47	2.35	2.55	2.86
IRR (95% CI)	1.03(1.00,1.07)	1	1.01(0.98,1.04)	1.05(1.01,1.08)

[a]Total number of nonsyndromic CHD cases (Including PDA in term infants and others).

between our analysis and previous studies regarding the above CHD subtypes may be partly due to differences in methodology, inclusion and exclusion criteria, sample size, and time period.

Several maternal co-morbidities such as smoking, obesity and diabetes could partly explain or modify the association between advanced maternal age and CHD subtypes (Caton et al., 2009; Correa et al., 2008; Garne et al., 2012; Gilboa et al., 2010). For example, the Baltimore-Washington infant study reported that women with advanced maternal age who smoked >1 pack of cigarettes per day, were more likely to have a child with PVS compared to nonsmoking younger mothers. Unfortunately, we did not have data on these potential risk factors so it was not possible to account for these co-morbidities in our analyses.

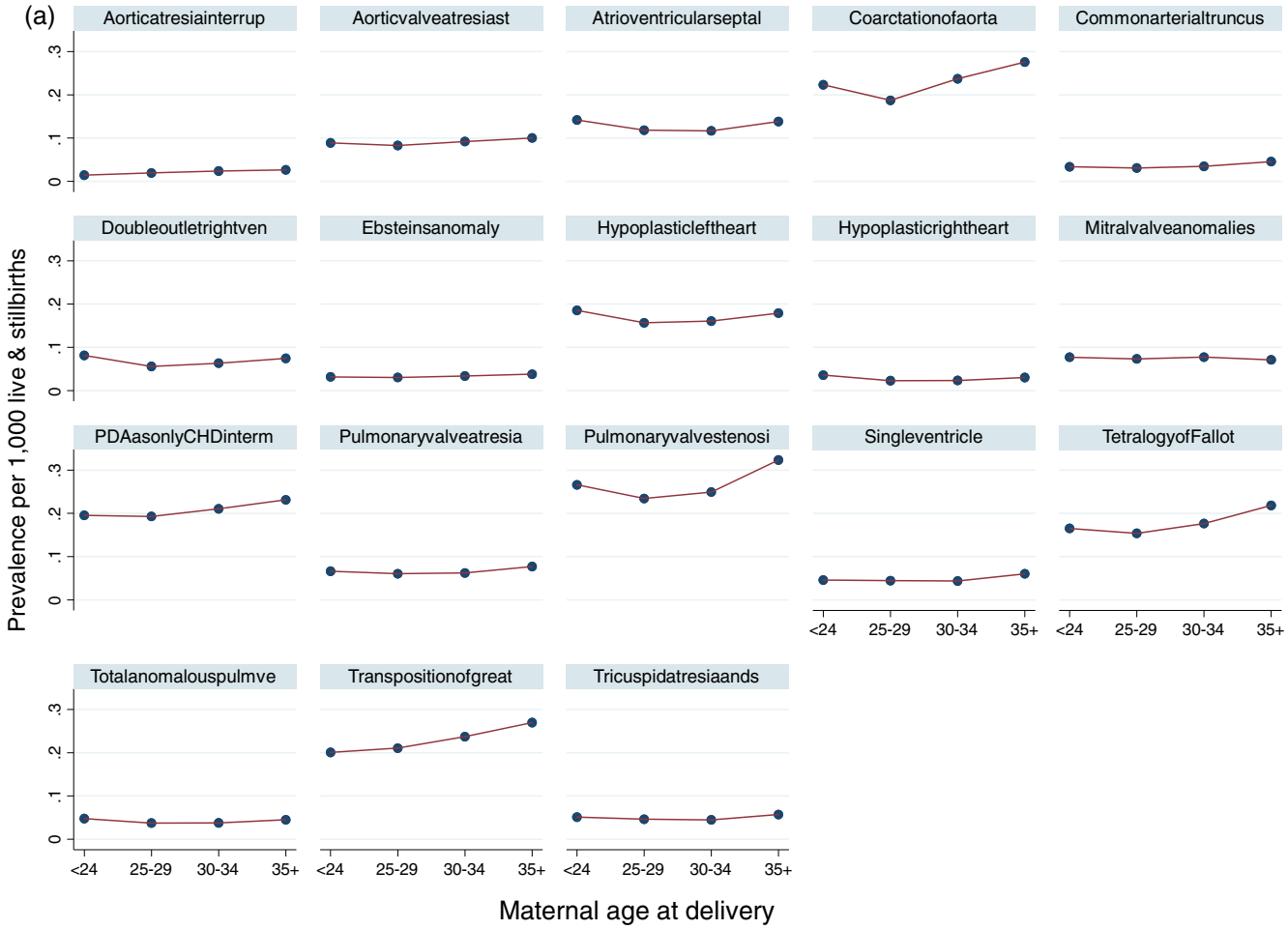
Our positive association of ToF with advanced maternal age is in line with previous USA studies which found that the prevalence of nonsyndromic ToF was significantly higher among children of mothers >35 years compared to mothers aged between 25 and 29 (Long, Ramadhani, & Mitchell, 2010; Reller et al., 2008). Interestingly, a European study also found an association (with a 2.6-fold higher odds) between ToF and ART and not for the other specific CHD: CoA, TGA and HLHS (Tararbit et al., 2014).

Another study (Markunas et al., 2016) reported that maternal age possibly affects the health of the offspring through epigenetic modification such as DNA methylation. Aging is strongly correlated with changes in DNA methylation (Sedivy, Banumathy, & Adams, 2008). Genomic patterns of methylation in the cardiac genome of newborn mouse are correlated with variables that influence the maternal-age associated risk of CHD and suggest that a maternal factor might affect CHD risk through epigenetic modification of cardiac genes in the embryo (Siegel, 2018).

Interestingly, Cordell et al. in a Genome-wide Association study (GWAS) found regions on chromosomes 12 and 13 to be associated with ToF (Cordell et al., 2013). Further modeling indicated that the most significant results on chromosome 13 could be well modeled by a maternally inherited imprinting effect (Howey et al., 2015).

We also reported different associations of ASD and an increase in prevalence of CoA for all age categories compared to the reference category (25–29 years); however, a significant association between mothers aged <35 and CoA has not been reported previously in the literature.

Finally, we investigated the association of advanced maternal age and CHD according to the CHD severity group. We found for both severity II and III groups, a positive association between maternal age and CHD among mothers 35–44 years of age. This is consistent with previous studies, which found that the association between older mothers and CHD is restricted to milder CHD subtypes such as ASD, VSD and CoA (Agha et al., 2011; Forrester & Merz, 2008; Miller et al., 2011). However, it is in contrast to a UK study which reported no significant association between maternal age and severity II and III groups (Best & Rankin, 2015). That previous absence of association may be related to low-statistical power or differences in the maternal age distributions (there are a greater proportion of younger mothers and lower proportion of older mothers in the North East of England, where this UK study took place [Best & Rankin, 2016]).



Footnote: *The graphs presented separately to allow easily interpretation because of the need of different scale.*

FIGURE 2 (a) Prevalence of congenital heart disease (CHD) according to maternal age at delivery and CHD subtype. (b) Prevalence of Atrial septal defect, Ventricular septal defect according to maternal age. The graphs presented separately to allow easily interpretation because of the need of different scale.

On the other side of the maternal age spectrum, few epidemiological studies have investigated the association between young maternal age and congenital anomalies despite the high proportion of teenage pregnancies being unplanned, which might lead to poorer pregnancy outcomes overall (Ranatunga & Jayaratne, 2020).

The limited number of published studies investigated the association between younger mothers and CHD may be due to small sample sizes, differences in methodological approaches or because the investigation of older mothers is of particular interest due to the increasing maternal age distribution worldwide. Furthermore, very few studies have been population-based and have mainly been conducted in the USA and Asia (Hashim et al., 2020; Long et al., 2010; Luo et al., 2013; Miller et al., 2011; Reller et al., 2008).

A study based on data from 15 European countries reported significant associations between younger mothers and gastrointestinal anomalies, nervous system anomalies, gastroschisis and anencephaly (Loane, Dolk, & Morris, 2009). In our study, we found evidence of an association between maternal age and the total prevalence of CHD in younger mothers (≤24 years of age). This result is consistent with a Spanish study (Benavides, Faerron, Umana, & Romero, 2011) which suggested that maternal age < 20 years of age is a factor associated with CHD but is in contrast with a Chinese study which reported that maternal age < 25 years reduced the risk of CHD (Luo et al., 2013). However, as there was not adequate power to detect an association in the Chinese study, the results should be treated with caution.

The maternal age distribution of pregnant women affected by a congenital anomaly varies among European countries, suggesting that genetic, lifestyle factors and so forth, might contribute to the etiology of CHD in younger mothers (Loane et al., 2009). For example, the mean age of women at birth is slightly higher in countries such as Spain, Switzerland, Italy and slightly lower in Croatia and the UK (Eurostat, 2021). However, by using denominator data, this effect was minimized.

As for the association between young maternal age and CHD severity, we found an increased risk of CHD in the age group ≤24 years compared to the reference category of the most severe group (severity I) which has not been found in previous studies. With regard to young maternal age and specific phenotype categories, we found a positive association between some severe forms of CHD. Specifically, we report a positive association between HLHS, HRHS phenotypes and CHD. According to published work, many congenital anomalies including HLHS, HRHS etiology remains unknown, with one study finding no significant association between the age of mothers of HLHS children and the age of the mothers of non-HLHS children (Gładki, Składzień, & Skalski, 2015). However, the sample size in this study was small (100 cases compared to 501 cases in our study).

We also found a positive association between maternal age and the risk of DORV, AVSD, ASD CHD phenotypes. Based on previous literature, most cases of DORV are apparently not the result of genetic anomalies (Obler, Juraszek, Smoot, & Natowicz, 2008) and factors suspected of playing a role in the etiology such as poor diet, smoking, alcohol consumption and drug use might be more common during pregnancies of young mothers compared to older mothers (Jones, Smith, Ulleland, & Streissguth, 1973). For instance, previous studies found that prenatal exposure to ethanol was reported in humans with DORV (Lammer et al., 1985; Park, Schmer, & Myers, 1990). Thus, taking into consideration that alcohol consumption during pregnancy can cause congenital anomalies (Jones et al., 1973) and that there is an increase in binge drinking among young people across Europe (Quigley & Marlatt, 1996; Reefhuis, Honein, Schieve, Correa, & Hobbs, 2009) some of the association between young maternal age and CHD could be confounded by alcohol consumption. A previous analysis of a small case group also identified associations between maternal smoking and AVSDs suggesting that smoking might also be a confounding factor (EUROCAT, 2013).

We found evidence of an association between younger mothers and AVSD. Although an association between pregestational diabetes and AVSD has been reported previously using data from the EUROCAT network (Garne et al., 2012), there are no current evidence for an association between pregestational diabetes and younger mothers. Therefore, additional studies are warranted in order to further investigate these associations.

The primary strength of this study is the inclusion of a large sample of cases of CHD and high-quality population-based data derived from established congenital anomaly registries. We had an adequate sample size to investigate possible associations of specific CHD phenotypes across the maternal age spectrum. This is one of only a few epidemiological studies that has examined the association of maternal age for CHD using a Bayesian approach. Using Bayesian methods allows the analysis of a wide range of statistical models which apply to multilevel modeling. A Bayesian approach has advantages over the frequentist approach in the case of low sample size in specific subgroups and seems more intuitive in the interpretation of credible intervals (McNeish, 2016). However, despite the statistical advantages, few epidemiological studies have managed to use this useful tool to investigate exposure-disease relationships (Greenland, 2006).

Our study also has some limitations. Firstly, even though it is a large study, there is not sufficient power due to the small sample size to investigate whether maternal age of specific CHD subtypes differs between registries. Secondly, we were not able to investigate the impact of potential exposures on the interaction between maternal age and CHD prevalence. For instance, previous studies reported an association between maternal age

and CHD prevalence in White and non-Whites (Miller et al., 2011) but we were not able to investigate whether the association with maternal age was influenced by maternal ethnicity. Thirdly, mothers aged ≥45 years were not included in the analysis as these numbers were small and there was insufficient power to explore the similarity in results from their age group with groups of younger mothers.

The results suggest that maternal age, under 24 and 35–44 years, is a factor associated with the occurrence of CHD. We reported a positive association between younger mothers and severe CHD phenotypes. This finding warrants further research to confirm and to investigate the impact of behavioral or genetic factors (Nees & Chung, 2020) while the positive association between advanced maternal age and offspring CHD is of importance from a public health perspective since age at childbirth is continuing to increase in many European countries.

Differences in exposure to assisted reproductive technology (ART) between study populations might also explain some of the variations in findings. Advanced maternal age has been associated with the use of ART, which in turn has been associated with septal heart defects (Reefhuis et al., 2009; Tararbit et al., 2011). Parents who have had children with CHD have a higher rate of infertility treatment than the general European population (EIM, 2022). Also, if part of the relation between advanced maternal age and CHD was mediated by higher use of ART, it would be interesting to investigate the possible underlying mechanisms between maternal age and CHD by using a path analysis approach.

Finally, prenatal cardiac screening and early management can reduce the risk of complications and neonatal mortality in selected types of CHD (Sharland, 2010). Ultrasound investigations for the detection of congenital anomalies are part of antenatal care in most European countries. Specifically, major cardiac anomalies can be prenatally diagnosed by sonographic assessment of the four-chamber view (Garne, Stoll, & Clementi, 2001). However, pregnant women in Europe are not offered detailed echocardiography screening based on age (Prenatal Screening Policies in Europe, 2021). Thus, further work is needed to understand whether both younger and older pregnant women would benefit from having extra prenatal cardiac scanning according to their age.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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