News in October 2024

1. Age at menopause and risk of ischaemic stroke: a systematic review and meta-analysis

Aims

Despite ischaemic stroke having much importance as one of the top 10 causes of death in older women, there are limited data on age at menopause and ischaemic stroke. We performed a systematic review and meta-analysis to estimate the effect of age at menopause on ischaemic stroke.

Methods and results

We screened four databases (PubMed, Cochrane, Web of Science, and EMBASE databases) up to 17 July 2023. This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and was registered with PROSPERO (CRD42023444245). Data extraction and quality assessment were independently undertaken by two reviewers. A random-effects model was used for meta-analysis using Revman5.4 to calculate the risk ratio of the incidence of ischaemic stroke. Heterogeneity was assessed using *I*2. Meta-regression and assessment for bias were performed. Out of 725 records identified, 10 studies were included in the qualitative synthesis and the quantitative meta-analysis. The pooled incidence rate for ischaemic strokes which age at menopause before 43 years old was 1.22 [95% confidence interval (CI): 1.02–1.46]. The pooled incidence rate of early menopause was 1.26 (95% CI: 1.07–1.48) for ischaemic stroke. The incidence rate of ischaemic stroke for women with early menopause may be in an environment with a high incidence for a long time.

Conclusion

This meta-analysis suggests that early menopause is associated with an increased risk of ischaemic stroke. Age at onset of menopause before 43 years old may be the cut-off value of increased risk of ischaemic stroke.

2.AI-Measured Breast Artery Calcification Tied to CV Outcomes in Women

Breast artery calcification (BAC) seen on a mammogram is associated with worse cardiovascular outcomes in women, according to a study that quantified the incidental finding using artificial intelligence (AI).

Even after accounting for traditional CV risk factors, BAC was tied to greater risks of all-cause mortality and a composite of acute MI, heart failure, stroke, or mortality, with particularly strong relationships observed in younger women.

This could have implications for personalized CVD risk stratification, researchers led by Tara Shrout Allen, MD, and Quan Bui, MD (both from UC San Diego, La Jolla, CA), suggest in their paper published online recently in JACC: Advances.

BAC being more predictive of adverse outcomes in younger versus older women is a welcome finding, senior author Lori Daniels, MD (UC San Diego), told TCTMD, because “many older women already are at risk or know they're at risk for heart disease merely because of their age or comorbidities. It's the younger women who may not know that they're at risk yet.”

A lot of women start getting mammograms at age 40, so incident BAC is “a good way to pick up risk early on when there's still something we can do about it,” Daniels said, adding, however, that the appropriate response to the finding—whether that’s lifestyle modification, medications, or something else—remains to be determined in future studies.

But in the meantime, she and her colleagues say “the presence of BAC should at the minimum stimulate patient-provider conversations on

lifestyle changes to mitigate cardiovascular risk, especially among younger women aged 40 to 59 years."

Commenting for TCTMD, Ana Barac, MD, PhD (Inova Schar Cancer and Inova Schar Heart and Vascular, Falls Church, VA), who wrote an accompanying editorial with Rupinder Bahniwal, MD (Inova Schar Heart and Vascular), said the presence of BAC "should not convey a signal of panic."

But she, too, suggested this might be a reason for patients to take a look at their CV risk factors. "BAC is a good reminder for us all to ask a question: whether we know our CV risk factors and whether they are being well controlled," she said. "So, if you are already seeing the cardiologist or internist, or other physician, and you happen to learn that you have BAC, you should mention it as a reason to review your CV risk factor control and individual goals."

Incidental BAC on Mammograms

BAC is often seen as an incidental finding on mammograms, and it has been shown to be a marker of increased risk of atherosclerotic cardiovascular disease (ASCVD). "BAC has tremendous appeal for cardiovascular risk stratification because it is noninvasive, comes at no additional cost or radiation, and the majority of women over the age of 40 years already undergo annual screening mammography for breast cancer," the investigators note.

They add, however, that there is a lack of tools for quantifying BAC and linking that with CV outcomes, and little consensus on how the finding should be detailed on radiology reports.

In the current study, researchers used an automated, AI-based assessment of BAC (cmAngio; CureMetrix) that generates a score of 0 to 100 to indicate the severity of BAC—calcification is considered present when the score is 5 or greater.

The analysis included 18,092 women ages 40 to 90 (mean age 56.8 years) who underwent a screening mammogram at UC San Diego Health between 2007 and 2016. Overall, 40% had hyperlipidemia, 36% hypertension, and 13% diabetes, and 5% were smokers.

BAC was present in 23% of women, with a median score of 15 among those with calcifications. Those with higher BAC scores tended to be older; to have diabetes, hypertension, CVD, chronic kidney disease, or hyperlipidemia; and to be taking statins or antihypertensive medications.

> **BAC is a good reminder for us all to ask a question: whether we know our CV risk factors and whether they are being well controlled.**Ana Barac

The presence of BAC was associated with a higher rate of all-cause death over a median follow-up of 4.8 years (7.8% vs 2.3%) and of the composite outcome over a median follow-up of 4.3 years (12.4% vs 4.3%). After adjustment for potential confounders, differences were significant for both mortality (adjusted HR 1.49; 95% CI 1.33-1.68) and the composite outcome (adjusted HR 1.57; 95% CI 1.42-1.74).

Risks also were increased when BAC score was evaluated as a continuous variable or in quartiles and when patients who were prescribed statins or who had ASCVD at baseline were excluded.

The relationships between BAC and adverse outcomes varied significantly by age, systolic blood pressure, total and LDL cholesterol, smoking, and diabetes ($P < 0.001$ for all interactions).

Of note, the associations were strongest in the youngest age group (40 to 59 years). After accounting for traditional CV risk factors, BAC correlated with greater risks of mortality (adjusted HR 1.51; 95% CI 1.22-1.87) and the composite outcome (adjusted HR 1.52; 95% CI 1.25-1.85) in this age group. The relationships were weaker but still significant among women ages 60 to 74 years, losing statistical significance among women ages 75 and older.

“Results from this study and others suggest that BAC may develop at an earlier age than other traditional cardiovascular risk factors, and thus could serve as an early biomarker of underlying ASCVD risk,” the researchers say. “These findings are important since they suggest that early risk stratification with BAC in younger women may help identify

new candidates for lifestyle modification and preventative therapies and may ultimately help improve their outcomes."

Questions Remain

Though the presence of BAC may aid in risk stratification, many questions remain, Barac indicated, noting that the link between outcomes and breast calcification hasn't been as systematically studied as for coronary artery calcifications, for instance.

One piece of information that is missing from the current study is the association of BAC with cause-specific mortality, Barac said. She commended the researchers, however, on their scientific approach to studying the impact of BAC, which should be considered, for now, as a "finding," not a "disease."

"The emerging evidence, including the evidence from this study, is that they are associated with cardiovascular risk factors and events such as stroke, heart failure, and cardiovascular disease," Barac said.

But BAC is a finding for which there is no proven course of action. "We do not have evidence that treating something is going to improve the outcomes," Barac said. "We are just finding these patients may be at increased risk. We don't fully understand what that risk is."

Another major question, she indicated, is how incidental BAC should be reported. "I think it's a big deal that we do not have standards for reporting BACs because this will result in a huge discrepancy. This is something that the American College of Radiology should have for physicians interpreting and reporting mammograms."

When BAC is reported, it should spark some thought about CV risk factor control, she reiterated. "You should be seen and be treated for, for example, blood pressure," Barac said.

> **So many women get mammograms every year, and there's information there that can help them assess their risk essentially for free.**Lori Daniels

What's not clear is whether BAC might one day achieve the status of a risk enhancer. Other unrelated research has identified factors like

family history, genetics, or pregnancy complications that elevate future ASCVD risk, warranting more aggressive risk factor control.

“Right now on the basis of these findings, I don't have data to say that we should treat a person's blood pressure or cholesterol to a different goal compared to somebody who doesn't have calcifications,” said Barac.

Moving forward, Daniels said, it would be reasonable for radiologists to start reporting incidental BAC when it’s seen on mammograms, so that research can continue into the significance of the finding and how the associated cardiovascular risk might be modified, similar to the process that occurred with the systematic evaluation of coronary artery calcification as a risk factor.

“The main reason I'm excited about this is because this data is sitting there and so many women get mammograms every year and there's information there that can help them assess their risk essentially for free,” she said. “If it were me and I had that risk factor sitting there, I would want to know it probably even before it's 100% proved that early intervention could improve outcomes.”

3.Automated Breast Arterial Calcification Score Is Associated With Cardiovascular Outcomes and Mortality

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in women despite significant advances in cardiovascular diagnostics and treatments.**1** Delays in diagnosis and treatment, as well as undertreatment, contribute to morbidity and mortality.**2** This is further exacerbated by under-representation of women in cardiovascular clinical trials and lack of sex-specific screening tools.**3** Efficient and effective methods to broadly screen women for CVD risk are sorely needed.

Breast arterial calcification (BAC), an incidental finding on mammograms, has emerged as a sex-specific biomarker for atherosclerotic cardiovascular disease (ASCVD) that offers the potential for personalized risk stratification.**4** The prevalence of mammographic BAC increases with age, occurring in 10% of women at age 40 but in up to 50% by age 80 years.**5-7** In semiquantitative analysis using radiologist assessments, high-grade or severe BAC was rare in younger women, but approached 14% by age 70 years.**8**

Gleaning information from an imaging study beyond its original intent is not new; analogous to BAC on mammography is coronary artery calcifications (CACs) seen on chest computed tomography obtained for noncardiac purposes.**9** BAC has tremendous appeal for cardiovascular risk stratification because it is noninvasive, comes at no additional cost or radiation, and the majority of women over the age of 40 years already undergo annual screening mammography for breast cancer.**10**

Multiple studies have found significant associations between the presence of BAC and prevalent CVD.**4** It is postulated that BAC represents lifetime exposure to risk factors related to arterial stiffening, which increases the risk of CVD through both coronary and noncoronary mechanisms (ie, heart failure [HF] and stroke).**11** However, routine clinical use of BAC has not been adopted due to a lack of outcomes studies as well as technological challenges in measuring and reporting BAC.**4** Currently, there is no consensus recommendation on the inclusion or standardized reporting of BAC, and American College of Radiology guidelines on breast imaging classifies reporting of vascular calcifications as optional.**12**,**13** However, in 2023, the Canadian Society of Breast Imaging took a progressive stance, advocating for standardized reporting of BAC in mammogram reports.**14**

Moreover, most BAC studies are limited to the binary presence or absence of BAC, and thus are blind to the severity or burden of BAC. Few studies measure or categorize BAC by severity and there is

significant heterogeneity in classification.**7** The purpose of this study was to evaluate not only the association of BAC presence with CVD risk factors and hard clinical outcomes in a large population but also to validate the utility of a novel automated, artificial intelligence (AI) algorithm for personalized BAC quantification.

Methods

Study population

This single-center retrospective study included women between the ages of 40 and 90 years who underwent screening digital mammography between 2007 and 2016 at the University of California-San Diego Health. For each subject, only the index mammogram was analyzed. All protocols were approved by the Institutional Review Board (IRB #170154).

Evaluation of BAC

BAC was quantified using a validated, proprietary investigational software (cmAngio, CureMetrix) based on a deep neural, AI network, and previously trained with an 80:20 split using over 34,000 2D full-field digital mammograms and digital breast tomosynthesis mammograms obtained from multiple sites across 13 health care facilities in Australia, Brazil, and the United States (not including University of California San Diego Health).

As a standard, 4 full-field digital mammograms or digital breast tomosynthesis images from each participant were used. The software cmAngio assesses screening mammography images and feeds them through the deep learning model to identify regions of interest within the breast. These regions correspond to areas that the algorithm suspects to have a high probability of BAC. From these identified regions, local and global imaging features such as density, contrast, and other physical dimensions are combined to determine the presence and severity of BAC. This process is applied to each of the 4

standard screening mammography images. Following these calculations, each image is assigned a score between 0 and 100 corresponding to the severity of the BAC finding(s), with 0 representing no BAC and 100 representing the highest percentile of BAC. To balance the algorithm's false positive and false negative rate, all image-level scores less than 5 are floored to 0. The patient-level score (or BAC score) is the mean of the threshold image-level scores across all 4 views. As such, BAC presence was defined as a mean BAC score ≥5. BAC was evaluated as a binary variable (presence vs absence), continuous variable (BAC score 0-100), and quartile groups (first-fourth). Scores were distributed by severity into the following groups: first quartile [score 1-25], second quartile [score 26-50], third quartile [score 51-75], and fourth quartile [score 76-100].

During development, each case was reviewed by 2 of 11 Mammography Quality Standards Act-certified radiologists. The performance of the software for detecting BAC, as assessed by area under the receiver operating characteristic curve was 0.98, with a sensitivity of 94% and a specificity of 96%. The software is cleared for BAC detection by the Food and Drug Administration and has been deployed in investigational clinical settings with Institutional Review Board approval.

Clinical data and outcomes

All clinical data including baseline characteristics and outcomes were collected using electronic health records (EHRs) and International Classification of Diseases (ICD)-10 codes, which are provided in **Supplemental Table 1**. All incident diagnoses occurred at least 6 months after the index mammogram and until death or the censoring date of December 31, 2020. The primary outcome was all-cause mortality. Secondary outcomes included acute myocardial infarction (MI), HF, stroke, and a cardiovascular composite outcome (MI, HF, stroke, and mortality). Stroke (cerebrovascular disease) included ischemic and hemorrhagic stroke. Those with baseline MI, HF, or

stroke were excluded from the relevant outcome analyses, including the composite outcome. Additionally, in a sensitivity analysis, all participants with baseline ASCVD were excluded to reassess the associations. ASCVD was defined by the following ICD-10 diagnoses: ASCVD, coronary artery disease (CAD), peripheral arterial disease (PAD), HF, and/or cerebrovascular disease.

Analyses and statistical methods

Continuous variables were reported either as mean with standard deviation or as median with interquartile range as appropriate based on normality of distribution assessed by Shapiro-Wilk test. Categorical variables were expressed as counts with percentages. Variables were compared using the unpaired Student *t*-test, Mann-Whitney test, and Fisher's exact test, as appropriate. Proportional hazards assumptions were tested for all outcomes to verify modeling assumption. Furthermore, Schoenfeld residual plots were generated for confirmation. Kaplan-Meier survival curves (plotted with 95% CIs), cumulative incidence plots (as appropriate), and Cox proportional hazards regression analyses were used to determine associations between BAC (as a binary and continuous variable) and clinical outcomes, while adjusting for variables at the time of mammogram (age, race/ethnicity, smoking status, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein [LDL] cholesterol, diabetes mellitus, and a history of CVD or chronic kidney disease [CKD]).

Age was continuous and measured in years. Smoking status was categorical and defined as current, former, never, or unknown. Systolic and diastolic blood pressures were continuous and measured in mm Hg. Total cholesterol and LDL cholesterol were continuous and measured in mg/dL. For other covariates, diabetes mellitus and CKD were defined by the associated ICD-10 code (**Supplemental Table 1**). CVD was defined as an ICD-10 code for any of the following: ASCVD, MI, CAD, HF, and/or stroke (cerebrovascular disease). For those

without covariate data from the time of the index mammogram, imputation was performed to account for these missing data. Data were imputed by training a nearest neighbor multiple-imputation model in Python to predict missing variables using the 10 nearest neighbors based on the collected diagnosis codes, age, ethnicity, smoking status, blood pressure (systolic and diastolic), and cholesterol (total and LDL).

Forest plots were created to assess the association between BAC and outcomes, stratified by subgroups of baseline characteristics. Tails represent 95% CIs. All reported *P* values were 2-sided with a value of <0.05 considered statistically significant. Statistical analyses and figures were completed using Python 3.11.5 with packages including Pandas 2.1.0 and SciPy 1.11.2.

Results

Study population

There were 21,438 screening mammograms obtained between 2007 and 2016. Of these, 1,546 were excluded for age and 1,800 were excluded for not being the index study. Therefore, 18,092 women with index mammograms were included in the study (**Figure 1**). Among the 18,092 women included, the mean age was 56.8 ± 11.0 years with prevalent CVD risk factors of diabetes (13%), hypertension (36%), and hyperlipidemia (40%) (**Table 1**). BAC was present in 4,223 (23%). BAC was more prevalent among women who were older, Black or Hispanic, diabetic, hypertensive, with a history of ASCVD or CKD, and taking statins and/or antihypertensive medications. BAC was less prevalent in current smokers. Among those with BAC, the median score was 15 (IQR: 4, 50). Scores were distributed by severity into the following quartile groups: first quartile [score 1-25], n = 2,552 (60.4%); second quartile [score 26-50], n = 643 (15.2%); third quartile [score 51-75], n = 509 (12.1%); and fourth quartile [score 76-100], n = 519 (12.3%). Correspondingly, those with a higher BAC score were more likely to be

older, diabetic, hypertensive, having a history of CVD, CKD or hyperlipidemia, and taking statin and antihypertensive medications. (**Supplemental Table 2**). Additionally, details on imputation and missing covariate data are presented in **Supplemental Table 3**.

Figure 1

Participant Flow Diagram

After exclusions for age and non-index mammograms, there were 18,092 unique women with index mammograms included in this study.

Table 1Baseline Participant Characteristics by Presence of Breast Arterial Calcification	**Total (n = 18,092)**	**BAC Present (n = 4,223; 23%)**	**BAC Absent (n = 13,869; 77%)**	***P* Value**
Age, y	56.8 ± 11.4	65.2 ± 11.6	54.2 ± 10.0	<0.001
Race/ethnicity				
Caucasian	11,319 (62.6)	2,617 (62.0)	8,702 (62.7)	0.38
Black/African American	907 (5.0)	241 (5.7)	666 (4.8)	0.02
Hispanic/Latino	1,694 (9.4)	455 (10.8)	1,239 (8.9)	<0.001
Asian/Pacific Islander	2,321 (12.8)	496 (11.8)	1,825 (13.2)	0.02
Other	1,851 (10.2)	414 (9.8)	1,437 (10.4)	0.31
Diabetes	2,267 (12.5)	730 (17.3)	1,537 (11.1)	<0.001
Hypertension	6,529 (36.1)	2,179 (51.6)	4,350 (31.4)	<0.001
Hyperlipidemia	7,256 (40.1)	2,071 (49.0)	5,185 (37.4)	<0.001
History of CVD	874 (4.8)	424 (10.0)	450 (3.2)	<0.001
History of CKD	802 (4.4)	358 (8.48)	444 (3.2)	<0.001
Current smoking	834 (4.6)	134 (3.17)	700 (5.1)	<0.001
Never smokers	9,245 (51.1)	2,046 (48.5)	7,199 (52.6)	<0.001
Systolic blood pressure, mm	123 (21)	128 (20)	122 (20)	<0.001

Table 1Baseline Participant Characteristics by Presence of Breast Arterial Calcification	**Total (n = 18,092)**	**BAC Present (n = 4,223; 23%)**	**BAC Absent (n = 13,869; 77%)**	***P* Value**
Hg				
Total cholesterol, mg/dL	198 (52)	194 (53)	199 (51)	<0.001
Statin use	3,947 (21.8)	1,430 (33.9)	2,517 (18.1)	<0.001
Antihypertensive use	3,498 (19.3)	1,313 (31.1)	2,185 (15.8)	<0.001

Values are mean ± SD, n (%), or median (IQR).

BAC = breast arterial calcification; CKD = chronic kidney disease; CVD = cardiovascular disease.

Clinical outcomes

Over a median follow-up for mortality of 4.8 years (IQR: 4.2 years), there were 329 deaths in those with BAC (7.8%) and 313 deaths in those without BAC (2.3%) ($P < 0.001$) (**Table 2**). Over a median follow-up for the composite outcome of 4.3 years (IQR: 4.3 years), there were 500 events in those with BAC (12.4%) and 582 events in those without BAC (4.3%) ($P < 0.001$). Stroke, MI, and HF were more frequently observed in those with BAC present, although the competing risk of death precludes statistical comparison. Kaplan-Meier Plots for mortality and the composite outcome are shown in **Figure 2**, which demonstrate a significantly increased risk of outcomes in those with BAC ($P < 0.001$ for each). Additionally, for HF, over a median follow-up of 3.0 years (IQR: 4.6 years), there were 154 events in those with BAC (3.7%) and 144 events in those without BAC (1.0%) ($P < 0.001$). For MI, over a median follow-up of 3.3 years (IQR: 3.9 years), there were 36 events in those with BAC (0.9%) and 47 events in those without BAC (0.3%) ($P < 0.001$). Lastly, for stroke, over a median follow-up of 3.0 years (IQR: 4.7 years), there were 110 events in those with BAC (2.7%) and 149 events in those without BAC (1.1%) ($P < 0.001$). Cumulative

incidence plots for individual outcomes of stroke, MI, and HF are shown in **Supplemental Figure 1**, which also demonstrate significantly increased risk in those with BAC (P < 0.001 for each outcome).

Table 2Clinical Outcomes by Breast Arterial Calcification Presence	**Total (N = 18,092)**		**BAC Present (n = 4,223)**		**BAC Absent (n = 13,869)**		***P* Value**
Myocardial infarction	18,051	83 (0.5%)	4,204	36 (0.9%)	13,847	47 (0.3%)	
Heart failure	17,911	298 (1.7%)	4,119	154 (3.7%)	13,792	144 (1.0%)	
Stroke	17,914	259 (1.5%)	4,138	110 (2.7%)	13,776	149 (1.1%)	
Mortality	18,092	642 (3.6%)	4,223	329 (7.8%)	13,869	313 (2.3%)	<0.001
Composite outcomea	17,720	1,082 (6.1%)	4,031	500 (12.4%)	13,689	582 (4.3%)	<0.001

Values are N or n (%).

Abbreviations as in **Table 1**.

a The cardiovascular composite outcome included acute myocardial infarction, heart failure, stroke, and mortality.

Kaplan-Meier Plots for Mortality and Composite Outcome by Breast Arterial Calcification Presence

Risk for (A) mortality, and (B) the cardiovascular composite outcome significantly varied by the presence of breast arterial calcification (P < 0.001 for each). The composite outcome included acute myocardial infarction, heart failure, stroke, and mortality. Time points of 208 weeks and 468 weeks are indicative of approximately 4 years and 9 years, respectively. BAC = breast arterial calcification; BAC+ = presence of BAC; BAC− = absence of BAC.

In multivariable analysis, women with BAC present had a significantly higher risk of mortality (adjusted HR [aHR]: 1.49 [95% CI: 1.33-1.68], *P* < 0.001) and the composite outcome (aHR: 1.57 [95% CI: 1.42-1.74], *P* < 0.001), compared to those without BAC (**Table 3**). Exclusion of those prescribed statin therapy (n = 3,947) did not materially affect the results: mortality aHR 1.45 (95% CI: 1.29-1.63), *P* < 0.001 and the composite outcome aHR 1.53 (95% CI: 1.38-1.69), *P* < 0.001 (**Table 3**). After excluding those with any baseline ASCVD, results were essentially unchanged (**Table 3**). For example, for the morality outcome, exclusion of 758 participants with baseline ASCVD still led to a significant difference (aHR: 1.44 [95% CI: 1.28-1.62]; *P* < 0.001). For the composite outcome, exclusion of those with baseline ASCVD, CAD, and PAD (n = 399) did not significantly alter the results (aHR: 1.50 [95% CI: 1.35-1.66]; *P* < 0.001) (**Table 3**).

Table 3Association of Breast Arterial Calcification Presence and Clinical Outcomes	**Mortality HR (95% CI)**	***P* Value**	**Composite Outcomea HR (95% CI)**	***P* Value**
Among all participants	(n = 642/18,092)		(n = 1,082/17,720)	
Model 1	1.70 (1.52-1.90)	<0.001	1.92 (1.74-2.11)	<0.001
Model 2	1.58 (1.41-1.77)	<0.001	1.67 (1.51-1.84)	<0.001
Model 3	1.49 (1.33-1.68)	<0.001	1.57 (1.42-1.74)	<0.001
Excluding those prescribed statins	(n = 400/14,145)		(n = 739/14,145)	
Model 3	1.45 (1.29-1.63)	<0.001	1.53 (1.38-1.69)	<0.001
Excluding those with baseline ASCVDb	(n = 565/17,334)		(n = 1,025/17,321)	
Model 3	1.44 (1.28-1.62)	<0.001	1.50 (1.35-1.66)	<0.001

ASCVD = atherosclerotic cardiovascular disease.

a Composite outcome: acute myocardial infarction, heart failure, stroke, and mortality.

b An additional 758 participants with any baseline ASCVD were excluded for the mortality outcome and an additional 399 participants

with specific baseline conditions not already accounted for were excluded for the composite outcome. Model 1: unadjusted. Model 2: adjusted for age and race/ethnicity. Model 3: adjusted for age, race/ethnicity, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol, low-density lipoprotein cholesterol, history of cardiovascular disease, history of chronic kidney disease, and smoking status.

When BAC was quantified and analyzed as a continuous score, each 10-point increase in the BAC score was significantly and independently associated with higher risk for adverse outcomes: mortality (aHR: 1.08 [95% CI: 1.06-1.11]; *P* < 0.001)and composite outcome (aHR: 1.08 [95% CI: 1.06-1.10]; *P* < 0.001) (**Table 4**). After excluding those on statin therapy, results again were unchanged: mortality (aHR: 1.01 [95% CI: 1.007-1.013]; *P* < 0.001) and the composite outcome (aHR: 1.01 [95% CI: 1.008-1.013]; *P* < 0.001). After excluding those with baseline ASCVD, results again remained significant for both mortality (aHR: 1.01 [95% CI: 1.006-1.011]; *P* < 0.001) and the composite outcome (aHR: 1.01 [95% CI: 1.007-1.011]; *P* < 0.001) (**Table 4**).

Table 4Association of the Breast Arterial Calcification Score and Clinical Outcomes	**Mortality aHR (95% CI)**	***P* Value**	**Composite Outcomea aHR (95% CI)**	***P* Value**
Among all participants	(n = 642/18,092)		(n = 1,082/17,720)	
BAC negative, n = 13,869	Referent	–	Referent	–
Per 10-point BAC score increase	1.08 (1.06-1.11)	**<0.001**	1.08 (1.06-1.10)	**<0.001**
First quartile [score 1-25], n = 2,552	1.22 (1.06-1.41)	**0.006**	1.26 (1.11-1.43)	**<0.001**
Second quartile [score 26-50], n = 643	1.44 (1.13-1.85)	**0.004**	1.74 (1.42-2.13)	**<0.001**
Third quartile [score 51-75],	1.69 (1.33-2.14)	**<0.001**	1.83 (1.49-2.25)	**<0.001**

Table 4Association of the Breast Arterial Calcification Score and Clinical Outcomes	**Mortality aHR (95% CI)**	***P* Value**	**Composite Outcomea aHR (95% CI)**	***P* Value**
n = 509				
Fourth quartile [score 76-100], n = 519	2.27 (1.81-2.85)	**<0.001**	2.30 (1.88-2.82)	**<0.001**
Excluding those prescribed statins	(n = 400/14,145)		(n = 739/14,145)	
BAC negative, n = 11,352	Referent	–	Referent	–
Per 10-point BAC score increase	1.01 (1.007-1.013)	**<0.001**	1.01 (1.008-1.013)	**<0.001**
First quartile [score 1-25], n = 1,838	1.27 (1.07-1.51)	**0.007**	1.25 (1.07-1.46)	**0.006**
Second quartile [score 26-50], n = 390	1.48 (1.07-2.06)	**0.018**	1.72 (1.31-2.27)	**<0.001**
Third quartile [score 51-75], n = 295	1.58 (1.13-2.19)	**0.007**	1.69 (1.26-2.25)	**<0.001**
Fourth quartile [score 76-100], n = 270	2.53 (1.81-3.53)	**<0.001**	2.61 (1.97-3.47)	**<0.001**
Excluding those with baseline ASCVDb	(n = 565/17,428)		(n = 1,025/17,428)	
BAC negative, n = 13,540	Referent	–	Referent	–
Per 10-point BAC score increase	1.01 (1.006-1.011)	**<0.001**	1.01 (1.007-1.011)	**<0.001**
First quartile [score 1-25], n = 2,414	1.21 (1.05-1.40)	**0.007**	1.15 (0.97-1.36)	0.111
Second quartile [score 26-50], n = 593	1.39 (1.09-1.78)	**0.008**	1.34 (0.98-1.83)	0.071
Third quartile [score 51-75], n = 459	1.59 (1.26-2.01)	**<0.001**	1.62 (1.15-2.29)	**0.006**
Fourth quartile [score 76-	2.20 (1.75-2.75)	**<0.001**	2.14 (1.53-3.00)	**<0.001**

Table 4Association of the Breast Arterial Calcification Score and Clinical Outcomes	Mortality aHR (95% CI)	*P* Value	Composite Outcomea	aHR	*P* Value
100], n = 422					

aHR = adjusted HR; other abbreviation as in **Table 3**.

a Composite outcome: acute myocardial infarction, heart failure, stroke, and mortality.

b An additional 758 participants with any baseline ASCVD were excluded for the mortality outcome and an additional 399 participants with specific baseline conditions not already accounted for were excluded for the composite outcome. All data from the multivariable-adjusted model (Model 3), which adjusted for age, race/ethnicity, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol, low-density lipoprotein cholesterol, history of CVD, history of chronic kidney disease, and smoking status.

When assessed by BAC score quartiles, there was a significantly higher risk in a consistently graded manner for both mortality and the composite outcome (**Figure 3**), even after adjustment for cardiovascular risk factors (**Table 4**). After excluding those on statin therapy, there were no significant differences (**Table 4**). After excluding those with baseline ASCVD, similar results were seen for mortality, though for the composite outcome, the graded association only reached statistical significance starting with the third quartile (**Table 4**).

Figure 3

Kaplan-Meier Plots for Mortality and Composite Outcome by Breast Arterial Calcification Score Quartiles

Risk for (A) mortality, and (B) the cardiovascular composite outcome significantly varied by the quantified breast arterial calcification score quartile (log-rank $P < 0.001$ for each). The composite outcome included acute myocardial infarction, heart failure, stroke, and

mortality. Time points of 208 weeks and 468 weeks are indicative of approximately 4 years and 9 years, respectively. BAC = breast arterial calcification; BAC+ = presence of BAC; BAC− = absence of BAC.

Similar associations were also seen for HF and stroke, though results for MI (only 83 incident events) did not reach statistical significance (**Supplemental Figure 2**, **Supplemental Tables 4** and **5**) of BAC. Time points of 208 weeks and 468 weeks are indicative of approximately 4 years and 9 years, respectively.

Breast arterial calcification and clinical outcomes among subgroup

BAC prediction for mortality and the composite cardiovascular outcome significantly varied by age, systolic blood pressure, total cholesterol, LDL cholesterol, smoking, and diabetes (*P* interaction terms <0.001 for each). Additionally, prediction significantly varied by history of CVD for mortality (*P* interaction term <0.001) and the composite outcome (*P* interaction term 0.009). While prediction also significantly varied by history of CKD for mortality (*P* interaction term 0.004), it did not for the composite outcome (*P* interaction term 0.16). Kaplan-Meier plots for mortality and the composite outcome stratified by age groups (**Figure 4**) demonstrate a significant separation of curves for women aged 40 to 59 and 60 to 74 years of age ($P < 0.001$) but not for those aged 75 to 90 years (morality, $P = 0.10$; composite, $P = 0.05$).

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Figure 4

Association of Breast Arterial Calcification and Mortality and Cardiovascular Composite Outcome Stratified by Age Groups

Risk for mortality (A to C) and the cardiovascular composite outcome (D to F) by breast arterial calcification (BAC) presence/absence. Risk

for both outcomes significantly varied by BAC status among women aged 40 to 59 years (A and D) and those aged 60 to 74 years (B and E) ($P < 0.001$ for each); however, among women aged 75 to 90 years (C and F), there was no significant difference in risk for either outcome by BAC status. The composite outcome included acute myocardial infarction, heart failure, stroke, and mortality. Time points of 208 weeks and 468 weeks are indicative of approximately 4 years and 9 years, respectively. BAC = breast arterial calcification; BAC+ = presence of BAC; BAC− = absence of BAC.

Forest plots demonstrating aHRs for outcomes by stratification of baseline characteristics are shown in **Figure 5**. When stratified by age groups, and after accounting for traditional risk factors, those in the youngest age group of 40 to 59 years had the highest residual risk associated with BAC (mortality: aHR: 1.51; 95% CI: 1.22-1.87; composite outcome: aHR: 1.52; 95% CI: 1.25-1.85). There remained significantly increased risk associated with BAC beyond traditional risk factors for women aged 60 to 74 years (mortality: aHR: 1.26; 95% CI: 1.06-1.50; composite outcome: aHR: 1.36; 95% CI: 1.18-1.58) but not among those aged 75 to 90 years (mortality: aHR: 1.19; 95% CI: 0.91-1.54; composite outcome: aHR: 1.23; 95% CI: 0.98-1.55). When stratified by other baseline characteristics, including systolic blood pressure and diabetes, the association between BAC and future cardiovascular events remained robust, even after accounting for traditional risk factors (**Figure 5**).

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Figure 5

Association of Breast Arterial Calcification and Mortality and Cardiovascular Composite Stratified by Baseline Characteristics

Adjusted HRs for (A) mortality and (B) the cardiovascular composite outcome by breast arterial calcification (BAC) presence vs absence are

presented. The composite outcome included acute myocardial infarction, heart failure, stroke, and mortality. HRs presented were adjusted for age, race/ethnicity, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol, low-density lipoprotein cholesterol, smoking status, and history of cardiovascular disease, history of chronic kidney disease. BAC = breast arterial calcification; BAC+ = presence of BAC; BAC− = absence of BAC.

Discussion

In this large, retrospective study, both the presence and quantity of BAC were significantly associated with all-cause mortality and the CVD composite outcome, even after adjusting for established cardiovascular risk factors. The prevalence of BAC was 23%, which constitutes a substantial proportion of women (mean age of 56.8 years) undergoing routine screening mammography. To our knowledge, this is the first study to demonstrate a significant, independent relationship between a quantitative BAC score and all-cause mortality or a CVD composite outcome. Indeed, each 10-point increase as well as sequential quartiles of the BAC score were significantly associated with higher risk of mortality and adverse cardiovascular outcomes, highlighting the potential utility of BAC quantification for personalized risk assessment (**Central Illustration**).

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Central Illustration

Association of Automated Breast Arterial Calcification Scores With Cardiovascular Outcomes and Mortality

Prior studies have evaluated the association of BAC using a binary or a semiquantitative approach (such as absence, slight, moderate, and severe intensity) with CVD outcomes.**4**,**15** In the present study, BAC was quantified using an automated method driven by a trained deep neural AI network, recently validated with high diagnostic

performance.**16** Other machine learning techniques have been developed for BAC quantification, including a densitometry method, and have been validated prospectively.**17** Such studies have assessed methods of BAC quantification, though await association with clinical outcomes.**18-20** The findings in our study support the efficacy of assessing both BAC presence and a quantitative BAC score to improve risk assessment for mortality and CVD outcomes in women undergoing screening mammography. With the advent of AI in medical imaging, automated, quantitative BAC assessment may facilitate seamless integration into clinical workflow and allow personalized risk assessment.

Importantly, this study also demonstrates the association of BAC with CVD outcomes and mortality even among subgroups not already known to be "high risk," including younger women, nonsmokers, and those without diabetes, hypertension, hyperlipidemia, CKD, or known CVD. We found that BAC was most predictive of future events among those in the youngest age group of 40 to 59 years, though BAC was also an independent predictor among women ages 60 to 74 years. Our results are concordant with those of Minssen et al**21** who found that the diagnostic accuracy (~ 84%) for BAC with CACs was the highest in patients under the age of 60 years. Results from this study and others suggest that BAC may develop at an earlier age than other traditional cardiovascular risk factors, and thus could serve as an early biomarker of underlying ASCVD risk.**22** These findings are important since they suggest that early risk stratification with BAC in younger women may help identify new candidates for lifestyle modification and preventative therapies and may ultimately help improve their outcomes. Moreover, we find that quantifying BAC allows us to better stratify risk with a graded association for both mortality and the composite outcome. Thus, simply reporting BAC presence or absence is insufficient and leaves valuable information underutilized.

Even with engagement from cardiologists and patients, the success of BAC implementation hinges on buy-in and education of the radiology

community. A survey of the members of the Society of Breast Imaging found that 85% were aware of the association of BAC with CVD, but only 15% routinely included BAC data on mammogram reports.**6** One of the major barriers to universal BAC reporting is the lack of radiology society guidelines on reporting and appropriate use of BAC.**6**,**9** Automated quantification and reporting methods for BAC will be critical to ensure that the current radiology workflow is not compromised.**11** Therefore, it will be important for cardiologists to advise and collaborate with the breast imaging community to develop clear BAC reporting guidelines and apply automated quantification tools into clinical workflow.

If the development and implementation of BAC can follow a similar pathway as CACs, BAC may someday be used to improve CVD risk stratification beyond current tools such as the pooled cohort equation, the ASCVD Risk Score, and the Framingham Risk Score. Reclassification of risk will help identify those who will benefit from more aggressive lifestyle modifications and medical therapy (ie, statins, antihypertensives).

Recently, the MINERVA (Multiethnic Study of Breast Arterial Calcium Gradation and Cardiovascular Disease) demonstrated that presence of BAC conferred additional risk at every category (ie, low, medium, and high risk) of the pooled cohort equation.**17** While our study does not address CVD risk discrimination modeling, we demonstrate that BAC can reliably be quantified using a novel AI algorithm and is independently associated with mortality and various CVD outcomes, which is a crucial and impactful step in this field. Future work will assess whether BAC scores can improve existing risk assessments for CVD outcomes, especially among women of intermediate ASCVD risk to guide initiation of preventive measures, such as statins, similar to CAC scores as suggested in the 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines.**23** Ultimately, BAC scores may offer important and

personalized risk stratification information, especially for younger women, without additional time, cost, and radiation.**24**

Study limitations

First, the retrospective nature of the study does not prove causality. Although attempts at reducing confounding factors using multivariable models were used, residual risk remains. Second, clinical data including outcomes relied on the use of ICD-10 codes from EHR data extraction, which introduces the possibility of misclassification. Also, mortality information only included all-cause mortality, but data on cause-specific mortality including CVD-related death were not available. Third, although EHRs allow for large aggregation of data and study populations with ICD codes for outcome ascertainment, misclassification still occurs. Additionally, while EHRs are becoming increasingly connected across hospital systems, follow-up information is still lost, especially among those who received care in other health systems. Fourth, follow-up varied for women in the study due to use of a strict censoring date, loss to follow-up, and development of events. However, regarding the composite outcome, there were only 146 women with less than 1 year of follow-up, and by the ninth year, there were still 9,804 women with follow-up data available (out of the 16,638 assessed for loss to follow-up; 17,720 total eligible for the composite outcome analyses and 1,082 developed events). Fifth, data on menopausal status were not available. Sixth, most subjects in this study identified as White, making results most applicable to this population. Seventh, our study design adjusted for history of several cardiovascular conditions based on ICD codes, including history of MI, CAD, HF, and PAD. However, we do not have available information on specific CV interventions, such as PCI, coronary artery bypass graft, or valve replacements. Lastly, this study shows the characteristics and outcomes from a single-center, albeit with a large cohort of women. Our ongoing work focuses on assessing the implications of BAC across more diverse populations to increase

external validity of this potential screening tool and to identify additional areas to improve risk assessment.

Conclusions

In this large, retrospective study, both BAC presence and quantity are significantly and independently associated with mortality and CVD outcomes. BAC appears to be especially predictive of CVD risk among younger women. Reporting of BAC was feasible and reliable using an automated AI algorithm, which could facilitate reporting uptake within the radiology community. Further studies are needed to determine the appropriate clinical response to BAC, and whether such a response can improve CVD outcomes in women.

4.Atrial Fibrillation Recurrence Risk After Ablation Is Greater in Women vs Men

Researchers conducted a multicenter, retrospective cohort study to determine the risk for AF recurrence post-ablation and explore potential sex-based variations in this recurrence risk. Adults who had an index radiofrequency ablation for AF between January 2018 and June 2020 were eligible for inclusion. The association between racial disparities in AF recurrence and readmission within 3 years of the index ablation was evaluated using chi-square analysis. Logistic regression was also used in statistical analyses.

A total of 23,558 patients (mean age, 66; men, 63.46%; mean body mass index [BMI], 32 kg/m2; mean length of stay, 1.5 days) were included in the analysis, 10,447 (44.4%) of whom had recurrent AF.

The risk for AF recurrence in women vs men was 6.52% (95% CI, 1.0344-1.0968) greater.

After controlling for race, sex remained significantly associated with the likelihood of AF recurrence. The risk for AF recurrence in women vs men was 12.1% (95% CI, 1.062-1.182).

According to logistic regression analyses, when controlling for race and age group, sex continued to be significantly related to the likelihood of AF recurrence. Compared with men, women had a 7.8% (95% CI, 1.021-1.138) greater risk for AF recurrence.

"These findings underline the need for further research to explore potential gender variations in response to different treatments and their impact on procedural choices," the study authors concluded.

5. ANCORS-YW: Higher BMI Associated With Higher CV Risk in Women

Women with a higher BMI may have a higher prevalence of cardiovascular risk factors, according to an analysis of the ANCORS-YW study presented during ACC Middle East 2024.

The multicenter study matched young women aged 18-50 (mean age 42.9 years old) with atherosclerotic cardiovascular disease at a 1:2 ratio to those without, based on age, gender, ethnicity and marital status.

Results showed that of the 626 participants, women who were classified as overweight or obese had a higher prevalence of hypertension (31.43% vs. 23.78%, $p<0.001$), diabetes mellitus (19.52% vs. 10.49%), hypertensive disease of pregnancy (26.67% vs. 18.18%, $p=0.026$) and persistent weight gain after pregnancy (16.19% vs. 9.09%, $p<0.001$).

Those with a higher BMI were also significantly more likely to be older, with a low level of education (58.57% vs. 49.65%, $p<0.001$) and less likely to smoke (33.33% vs. 37.06%, $p=0.001$).

“This demographic is often underrepresented in global research and literature especially when it comes to the Middle East, despite the region’s high rates of obesity and cardiovascular disease,” said **Mohammad Adnan Bani Baker, MD**, one of the study’s authors. “I was drawn to this topic because of the alarming rise in these conditions in Middle Eastern women, which poses a significant public health challenge.”

He recommended targeted interventions including lifestyle modification programs, public health campaigns, educational programs and socioeconomic support.

Bani Baker et al.’s analysis was just one of the studies presented during ACC Middle East 2024, a virtual conference co-hosted by the ACC and the Egyptian Society of Cardiology centered on cardiovascular health issues affecting the Middle East.

“Heart disease is the leading cause of death in the world and causes one-third of all deaths in the Middle East and North Africa each year,” said **Mohamed A. Sobhy, MD, FACC**, ACC Middle East 2024 conference co-chair. “The ACC Middle East conference aims to provide clinicians from the region the opportunity to learn from global experts and consider new strategies to reduce the burden of heart disease on our patients.”

Sessions include:

- AI in Cardiology: Bridging US and European Union Perspectives
- Unlocking Imaging Modalities: Maximizing Clinical Utility Across Scenarios
- Addressing Cardiovascular Risk: Cases and Discussions on Novel Therapies and Genetic Considerations
- International Guidelines in Chronic Coronary Disease: Contrasting ACC and ESC Approaches

ACC Middle East 2024 will be presented virtually from Oct. 16-18. Read the full agenda here and follow the ACC on social media for live updates from the meeting.

6.Beyond Parental Leave: Addressing Infertility, Pregnancy, and Postpartum Complications Among Cardiologists

Introduction

Cardiologists experience a disproportionately greater risk of complications on the road to parenthood as compared to their nonphysician counterparts. For many, difficulties begin with infertility, which is experienced at a reported rate of 1 in 4 surveyed physicians.**1** A recent *JACC* paper reported about 38% of female cardiologists also experienced pregnancy complications, a rate nearly double that of their nonphysician counterparts.**2** Issues including infertility and pregnancy complications are amplified among physician trainees, as training years often parallel periods of life in which individuals and/or their partners contemplate parenthood. As such, the focus on complications around parenthood as well as the search for effective support mechanisms is paramount.

Unique to physicians, young adult life is often filled with physical, emotional, and financial strains, including long working hours, complex tasks in the hospital, interrupted sleep, extended training into the late 30s, and the specter of repayment of significant education debt. Many of these aspects of training and early career practice may underscore the disproportionate rates of complications surrounding planning for parenthood among cardiologists and cardiology-trainees.

A recent focused session on this topic at the 2024 American College of Cardiology Annual Scientific Sessions highlighted programmatic and policy changes enacted at academic centers throughout the country that addressed challenges surrounding achieving parenthood (**Figure 1**). We highlight approaches undertaken by national physician organizations and the authors of this paper with their respective

institutions from this session and from other sources. We also outline future focus areas for change.

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Figure 1

Implemented Policies and Programs Toward Addressing Parenthood Complications

Policies and programs as well as future directions targeting infertility, complication support networks, and lactation. AMWA = American Women's Medical Association.

Implemented programs and policies

Infertility summit/coverage at work toolkit

National multispecialty organizations, including the American Women's Medical Association (AMWA) have spearheaded efforts toward actionable change to address infertility.**3** Their 5-part strategic approach includes:

1. to increase fertility awareness starting with early education in college and continuing through medical training,
2. to target both insurance coverage and access to fertility assessment and care among all physicians,
3. to ensure support systems among physicians that can provide both emotional support and wisdom during the fertility treatment journey,
4. to focus research highlighting the economic benefits of supporting fertility treatment among the physician workforce,
5. and to enact supportive policy from state to a national level.**1**,**3**

In partnership with RESOLVE, a national infertility association, AMWA organized annual physician infertility summits spanning 2021

to 2023 to accomplish these aims. One of their most actionable items features a “Coverage at Work” toolkit. This toolkit includes documents like letter templates for physicians to advocate for infertility coverage at their organizations at multiple levels, from human resources to institutional leadership. Their toolkit also includes infertility insurance coverage facts and resources. All seminar lectures and toolkits are readily downloadable from their website.**3**

Infertility, pregnancy, and postpartum complications support network

One of AMWA and RESOLVE’s strategic approaches is to ensure support systems for physicians provide emotional backing and wisdom regarding reproductive life events. Responsive to this, the University of Pittsburgh has created a support network for physician and physician-trainees to provide support and information about topics from infertility through postpartum complications.

To “construct a village” of support, a committee, including multispecialty program directors, convened a leadership team who were both impacted on a personal level and/or were passionate about supporting physicians who had experienced difficulties around reproductive issues. They constructed a 10-question/5-minute survey that was inclusive, short, and anonymous. Embedded in the survey were requests for personal recommendations on resources including supportive groups, mental health professionals, physicians, doulas, and faculty peers that they had found useful. From this, a list of local resources was created. The survey also sought to obtain qualitative information with open-ended questions including “what other topics can you provide support for” and “how else can we best support you?” A total of 11 support topics were identified: infertility, high-risk pregnancy, multigestational pregnancy, miscarriage, late pregnancy loss, neonatal illness, adoption, postpartum anxiety and/or depression, unplanned childlessness, breastfeeding difficulties, and egg cryopreservation/donation.

A Department of Medicine Grand Rounds at the University of Pittsburgh was held to raise awareness of issues surrounding parenthood and to introduce the support network.**4** A best practice document was developed for support members, which included crisis and suicide network emergency contacts. There was also dissemination of the network both on physician and trainee listservs, as well as engagement of outside institutions to disseminate program implementation and solicit advice for future additions.

Breastfeeding/lactation support

Updated guidance by the American Academy of Pediatrics recommends breastfeeding for up to 2 years "as mutually desired by mother and child."**5** Physicians and trainees who breastfeed can incur many challenges in achieving this recommended guidance. Prior to returning to work, one barrier includes low breastmilk supply.**6** This is an aspect of breastfeeding among physicians that is sparsely covered in studies amidst growing scientific evidence that focuses on benefits of breastmilk in both maternal and infant health. This can deeply impact physicians who may be well acquainted with the benefits of breastfeeding from the scientific literature, but data on low breastmilk supply is not adequately covered.

For cardiologists and trainees able and willing to breastfeed, additional barriers to recommended breastfeeding durations become apparent once returning to work. A prior survey by the American College of Cardiology noted that around 68% of cardiologists reported barriers to breastfeeding at work. Some of these barriers included trouble finding space to pump, time constraints for pumping, and trouble with low breastmilk supply.**6** The Mayo Clinic conducted a trainee-specific single center survey and found that half of trainees (including cardiology trainees) reported breastfeeding cessation prior to 6 months.**7** Several authors have undertaken approaches to address these barriers. At least one institution arranged for the location of lactation rooms, including portable/temporary units, close

to procedural and operating room suites to accommodate physicians who have the greatest time constraints for pumping.

One academic medical center, the University of Pennsylvania, instituted a university-wide faculty lactation policy. This policy outlined a reduction in outpatient clinical effort equivalent to up to 30 minutes for every 4 clinical hours for up to 12 months after the birth of a child. It also mandated target relative value units to be prorated for leave as per allotted by the Family and Medical Leave Act. Further, it calls for equity on incentive opportunities otherwise available to faculty based on this prorated relative value units adjustment. Their strategic approach has been published for adaptation at other institutions.**8**

As noted, challenges around breastfeeding can impact trainees even more than practicing cardiologists. To help mitigate resource challenges, Vanderbilt University Medical Center obtained funding for at-work wearable breast pumps to be shared among physicians and physician trainees. In addition, a best practice document was created for resident trainees. This includes a stepwise approach to securing time for pumping during rotations. Support documents include letter templates to send for upcoming rotations to supervisors and established communication lines between the resident-parent and leadership advocates within medicine.

Focus areas for change

Improving insurance coverage for infertility treatment and cryopreservation

As noted, data suggest around 25% of birthing-capable physicians reported infertility diagnoses.**1** This exceeds the reported national 13% rate of infertility.**9** Investigations and treatment for infertility are often a time-consuming and expensive process. Physicians will often undergo numerous fertility specialist visits, lab work and imaging, followed by pharmacologic and invasive therapeutic interventions

toward achieving a successful pregnancy. Prior surveys have noted costs from around $1,100 for fertility medications and exceeding $60,000 until pregnancy via in vitro fertilization was successfully achieved.**10**

These costs are typically unaffordable under trainee salaries and for young clinicians. A recent study collected information on insurance coverage for physicians among several top academic institutions throughout the country. They found many institutions do not provide enough coverage for even one cycle of in vitro fertilization, while many individuals require 3 or more cycles for successful egg retreival.**10** For those looking to preserve fertility via egg, embryo, or sperm cryopreservation, an even smaller percentage of academic medical institutions offered specific insurance coverage for cryopreservation.**10**

Rethinking bereavement leave

The United States is one of the few countries for which there are no policies to ensure paid parental leave. Time off for up to 12 weeks following the birth of a child, including adoption, or for the care of one's own medical condition is detailed under the Family and Medical Leave Act. However, there may be financial difficulties that result from this unpaid policy, which may compound if a trainee must extend their training time.

One solution may include expansion of these policies to include initiatives like flexible work hours. Bereavement policies exist among many training programs and hospital employers to offer time and support for physicians and their families following the loss of a partner or close family member. Pregnancy loss is not consistently included in these policies. While some physicians feel being at work with their colleagues may be helpful, they should be afforded flexibility and protected time if they prefer privacy. The current structure at most fellowships and health care institutions is such that you are either at work or not. This inflexibility can serve to create more stress

for physicians who may only need short time periods off intermittently to attend therapy, support groups, or physician appointments. A progressive structure of paid time-off for bereavement in the setting of pregnancy loss should be offered by training programs and healthcare systems.

Directed counseling services

The emotional bereavement process following reproductive difficulties can be complex. As mentioned, the stigmatization of experiences including infertility and miscarriage can further complicate individual coping and support networks. Many hospitals and associated trainee programs have established confidential referral services. These include therapists and psychiatrists as well as peer-to-peer physician support. Both trainee institutions and hospital systems should ensure their resources adequately cover support for these topics for both physicians and physician-trainees. Support resources and networks should be readily accessible and available to their trainees. Trainees and practicing cardiologists should also be provided resources to help navigate the legal requirements of institutions and hospitals for pregnancy and parental leave, such as The Center for Work Life Law (www.worklifelaw.org).**2**

Conclusions

For cardiologists who choose to pursue parenthood, the road can be physically taxing, emotionally difficult, and financially burdensome. Cardiologists and cardiology-trainees must be provided with support, flexibility, and counseling resources to change a culture of silent coping with infertility, pregnancy, and postpartum complications toward a destigmatized, caring community at work. Those in leadership positions, specifically training program leadership, division leadership, and hospital administration, must create progressive parenthood policies and build robust support structures so that physicians and physician-trainees who encounter parenthood

complications have the tools, financial/insurance coverage, and community network to overcome these hardships.

7.Characteristics of Young Women Presenting With Acute Myocardial Infarction

BACKGROUND

The percentage of women <50 years of age hospitalized with myocardial infarction is increasing. We describe the clinical, morphological, and biological characteristics, as well as the clinical outcomes of this population.

METHODS AND RESULTS

This prospective, observational study included consecutive women <50 years of age admitted for myocardial infarction at 30 centers in France (May 2017-June 2019). The primary outcome was the composite of net adverse clinical events: all-cause death, cardiovascular death, recurrent myocardial infarction, stent thrombosis, any stroke, or major bleeding occurring during hospitalization with a 12-month follow up. Three hundred fourteen women were included. The mean age was 43.0 (±5.7) years, 60.8% presented with ST-segment-elevation myocardial infarction, 75.5% were current smokers, 31.2% had a history of complicated pregnancy, and 55.1% reported recent emotional stress. Most (91.6%) women presented with typical chest pain. Of patients on an estrogen-containing contraceptive, 86.0% had at least 1 contraindication. Of patients with ST-segment-elevation myocardial infarction, 17.8% had myocardial infarction with nonobstructive coronary arteries and 14.6% had spontaneous coronary artery dissection, whereas 29.3% presented with multivessel vessel disease. During hospitalization, 11 net adverse clinical events occurred in 9 (2.8%) women, but no deaths or stent thromboses occurred. By 12 months, 14 net adverse clinical events occurred in 10 (3.2%) women; 2 (0.6%) died (from progressive

cancer) and 25 (7.9%) had an ischemia-driven repeat percutaneous coronary intervention.

CONCLUSIONS

Most young women with myocardial infarction reported typical chest pain and had modifiable cardiovascular risk factors. History of adverse pregnancy outcomes and prescription of combined oral contraceptive despite a contraindication were prevalent, emphasizing the need for comprehensive cardiological and gynecological evaluation and follow-up.

8. **Gender and contemporary risk of adverse events in atrial fibrillation**

Introduction

Atrial fibrillation (AF) remains a common, costly, and high-morbidity condition impacting patients across the whole spectrum of healthcare. The high and ultimately preventable risk of stroke and other thromboembolic events associated with AF1 has driven the generation of clinical risk scores to help determine which patients would benefit from oral anticoagulation. These range from simple clinical classification systems, which have dominated routine practice,2,3 to more complex algorithms4 and the use of biomarkers.5 However, most clinical risk scores have broadly similar performance and may not accurately predict those that will go on to suffer from strokes, may not account for the use of direct oral anticoagulants (DOACs), and ignore other thromboembolic outcomes, such as vascular dementia.

A further challenge with AF risk scores has been their inclusion of gender as a risk stratifier. Higher rates of stroke in women with AF have been reported in historical data,6 although this is likely confounded by the contribution of other risk factors. This includes

older age and lower anticoagulation rates in women and higher mortality in men, which is a competing risk for stroke. More recently, gender has been reconsidered as a risk modifier;7,8 however, international guidelines vary considerably (*Figure 1*; Supplementary data online, *Table S1*). The inclusion of gender in risk scores has typically been circumvented by using different risk cut-offs for each gender, for example, a CHA_2DS_2-VASc score of 2 for men, but 3 for women, to qualify for a class I indication for oral anticoagulation.

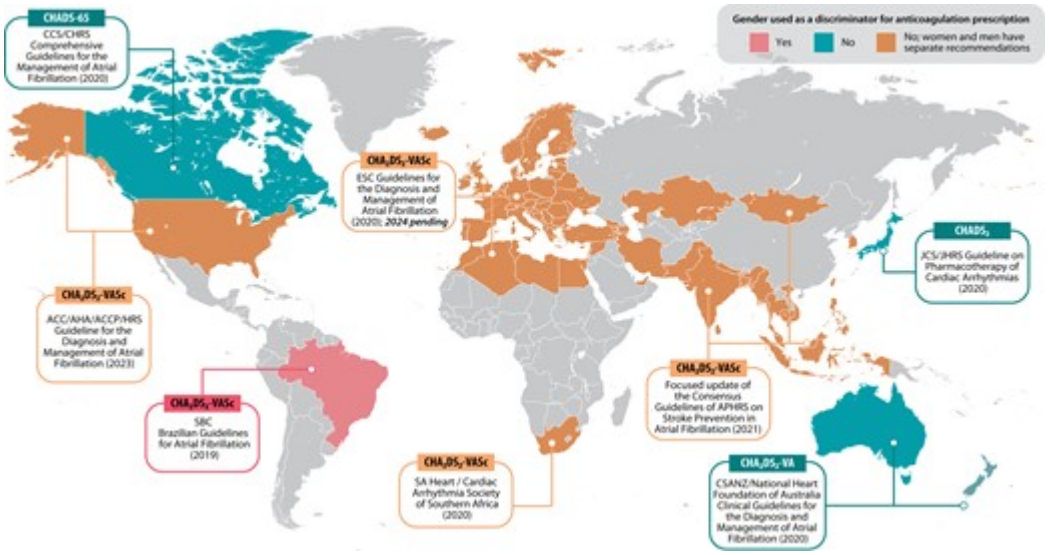


Figure 1

Variation in global use of gender for risk stratification in atrial fibrillation. Guidelines from different global regions showing marked variability in the use of gender as a discriminating factor for the prescription of oral anticoagulation in patients with AF. Further details are presented in Supplementary data online, *Table S1*. CCS = Canadian Cardiovascular Society; CHRS = Canadian Heart Rhythm Society; ESC = European Society of Cardiology; AHA = American Heart Association; ACC = American College of Cardiology; ACCP = American College of Clinical Pharmacy; HRS = Heart Rhythm Society; JCS = Japanese Circulation Society; JHRS = Japanese Heart Rhythm Society; SBC = Brazilian Society of Cardiology; SA Heart = South African Heart

Association; APHRS = Asia-Pacific Heart Rhythm Society; CSANZ = Cardiac Society of Australia and New Zealand.

This population cohort study was performed to address a key evidence gap in patients with AF, where gender plays a role in the decision for anticoagulation. The study specifically excluded those with prior stroke or age ≥75 years where there is strong confounding of clinical outcomes and guideline-recommended indication for oral anticoagulation, irrespective of the patient's gender. The aim of this study was to provide real-world evidence on the value of gender for risk stratification in contemporary patients with AF where anticoagulation is being considered.

Methods

Study design and data source

A population-based, retrospective cohort study was conducted between 1 January 2005 and 31 December 2020 using data obtained from the IQVIA Medical Research Database (IMRD), a proprietary database of Cegedim SA (France). IMRD is a primary care database containing pseudonymized medical records of patients registered within general practices across the UK using the VISION clinical system.9 IMRD comprises over 18 million patient records from 832 general practices in the UK, representing a snapshot of around 6% of the UK population. The database contains information on patient demographics and coded records of diagnoses using the Read code clinical classification system, dispensed prescriptions, and additional health information, such as physical and biochemical measurements. The primary care coded database is used for billing and reimbursement purposes in the UK National Health Service (NHS), with high data quality incentivized through the Quality and Outcomes Framework.10 Data extraction was conducted using the DExtER software.11 This study meets all five of the CODE-EHR framework

minimum standards for the use of structured healthcare data in clinical research, with three out of five standards meeting the preferred criteria; see Supplementary data online, *Table S2* for CODE-EHR domains and Appendix 1 for the CODE-EHR checklist.12 All codes used in this study were predefined and pre-published for transparency and re-use by other researchers in concordance with the CODE-EHR framework.

Ethics

Data collection for IMRD was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. Under the terms of this approval, each study protocol undergoes independent review from the Scientific Review Committee, with approval obtained in July 2017 (SRC reference number: SRC 17THIN061).

Study population

Practices were considered eligible 1 year after the establishment of the VISION clinical system within their practice or 1 year after reporting mortality rates comparable to national averages,13 whichever was the latest. In eligible general practices, adults aged 40 years or older and registered during the study period for at least a year were included. For patients with an existing AF diagnosis, the index date was assigned as the date of patient eligibility (1 year after their registration date with an eligible general practice). For patients with a new diagnosis of AF after they became eligible, the index date was assigned as the date of AF diagnosis.

Exclusions

Individuals aged ≥75 years or with a history of stroke in their medical record were excluded as these patients have an undisputed indication for oral anticoagulation for stroke prevention reasons regardless of gender. In addition, patients with an active prescription for a vitamin

K antagonist or DOAC were excluded irrespective of stroke risk assessment.

Covariates

This study uses the term gender as it relates to personal identity and recording of such within the patient's medical record. Gender is documented as female or male, with no current option to record transgender status or specify sex at birth. Age, socioeconomic status, and diagnoses of hypertension, diabetes mellitus, heart failure, and vascular disease were considered as confounders. Age was modelled as a continuous variable. Socioeconomic deprivation was recorded as the Townsend deprivation index categorized into quintiles,14 with missing data specifically encoded as such to avoid embedding bias. The listed comorbidities were extracted from the medical record according to the pre-published coding scheme. The CHA_2DS_2-VASc score was calculated with 2 points given for prior stroke, transient ischaemic attack or thromboembolism, 2 points for age ≥75 years, and 1 point for heart failure, hypertension, age 65–74 years, diabetes mellitus, vascular disease, or female gender. The CHA_2DS_2-VA score was similarly calculated, but without considering gender.

Follow-up and outcomes

The primary outcome was the composite of all-cause mortality, ischaemic stroke, or arterial thromboembolism. Including mortality within the primary outcome was essential as death is a competing risk for thromboembolic events (dead patients cannot be admitted with a stroke), and mortality risks are higher in men, leading to further bias. Secondary outcomes were: (1) ischaemic stroke or arterial thromboembolism; (2) any stroke (ischaemic or haemorrhagic) or any thromboembolism (arterial or venous); (3) vascular dementia; and (4) all-cause mortality. Strokes with an unspecified cause were included in the ischaemic category. Outcomes were considered from the index

date until the earliest of the following time points: (1) recording of the outcome of interest; (2) patient censorship due to death or de-registration from their registered practice; (3) practice censorship due to ceasing of their data contribution to IMRD; and (4) study end date of 31 December 2020.

Statistical analysis

Summary results are presented as percentages, median, and interquartile range (IQR; displayed as 25th to 75th quartiles), or mean and standard deviation (SD). Group comparisons were made using the Kruskal–Wallis non-parametric rank test adjusted for multiple comparisons. Outcomes were analysed using Cox proportional hazards regression models for women vs. men reported for univariate analysis and multivariate adjustment for the aforementioned confounders. Hazard ratios (HR) and 95% confidence intervals (CI) are presented, along with corresponding *P*-values. Proportional hazards were tested using a log–log plot of scaled Schoenfeld residuals to ensure that the hazard related to gender remained constant over time. Effect modification was assessed using *P*-values from interaction terms fitted in the multivariable models. Kaplan–Meier plots were used to graph the unadjusted outcomes according to gender, and failure plots to present the adjusted data from the multivariate model. The interaction of age as a continuous variable with gender on the primary outcome was assessed using cubic splines in the Cox model and a Royston–Parmar flexible parametric survival model.15 Two pre-defined sensitivity analysis were conducted for the primary outcome: (1) censoring at the time of treatment with any oral anticoagulant; and (2) censoring for patients with incident AF only. Post-hoc analyses were: (1) competing risk for ischaemic stroke or arterial thromboembolism with death using the method of Fine and Gray; and (2) separation into three time periods (index AF date 2005–09, 2010–14 and 2015–20) for assessment of the primary outcome with censoring at 1 year.

The area under the receiver operating characteristic curve (AUROC) was determined using logistic regression, with group comparisons using a *x2* test. Robust methods for model comparisons are presented in the online supplement. Net reclassification improvement and integrated discrimination improvement were evaluated to assess the impact of gender on risk prediction for the primary outcome; bootstrapping to calculate CI was not required due to the lack of any reclassification.

A two-tailed *P*-value of .05 was considered statistically significant. Analyses were performed on Stata Version 17 (StataCorp LP, College Station, TX, USA).

Results

A total of 16 587 749 patients from 828 eligible primary care practices in the UK were evaluated, of which 5 199 994 were eligible and aged 40–75 years, including 290 525 with an AF diagnosis code (5.6%). In total, 78 852 patients had AF, were aged 40–75 years, had no prior stroke, and were not prescribed oral anticoagulants (see Supplementary data online, *Figure S1*). There were 28 590 women (36.3%) and 50 262 men (63.7%). Median age was 65.7 years (IQR 58.5–70.9), with women older by a median difference of 2.5 years compared to men. Women had higher rates of coexisting hypertension and lower rates of heart failure, diabetes, and vascular disease compared to men (*Table 1*). All comparisons between women and men were statistically significant ($P < .001$). The mean CHA_2DS_2-VASc and CHA_2DS_2-VA scores were 1.74 (SD 1.27) and 1.38 (SD 1.16), respectively. There was a statistical, but not a clinically significant difference in CHA_2DS_2-VA scores between women and men (mean 1.42 vs. 1.36; $P < .0001$), and the distribution across scores was similar (*Structured Graphical Abstract*). The total follow-up period for outcome assessment was 159 355 person-years for women (mean 5.6 years

per-patient; SD 4.1) and 271 731 person-years for men (mean 5.4 years per-patient; SD 4.0).

Table 1

Baseline demographics by gender

Baseline characteristic	**All (*n* = 78 852)**	**Women (*n* = 28 590)**	**Men (*n* = 50 262)**
Age, median years (IQR)	65.7 (58.5–70.9)	67.3 (60.6–71.6)	64.8 (57.4–70.4)
Women, *n* (%)	28 590 (36.3%)		
CHA_2DS_2-VASc, mean score (SD)	1.74 (1.27)	2.42 (1.12)	1.36 (1.19)
CHA_2DS_2-VA, mean score (SD)	1.38 (1.16)	1.42 (1.12)	1.36 (1.19)
Hypertension, *n* (%)	36 478 (46.3%)	14 058 (49.2%)	22 420 (44.6%)
Heart failure, *n* (%)	5704 (7.2%)	1698 (5.9%)	4006 (8.0%)
Diabetes mellitus, *n* (%)	11 411 (14.5%)	3763 (13.2%)	7648 (15.2%)
Vascular disease, *n* (%)	8275 (10.5%)	2034 (7.1%)	6241 (12.4%)
Townsend deprivation score, *n* (%)			
Quintile 1 (least deprived)	17 692 (22.4%)	6151 (21.5%)	11 541 (23.0%)

Baseline characteristic	All (*n* = 78 852)	Women (*n* = 28 590)	Men (*n* = 50 262)
Quintile 2	16 102 (20.4%)	5721 (20.0%)	10 381 (20.7%)
Quintile 3	14 421 (18.3%)	5288 (18.5%)	9133 (18.2%)
Quintile 4	11 706 (14.9%)	4480 (15.7%)	7226 (14.4%)
Quintile 5 (most deprived)	8086 (10.3%)	3094 (10.8%)	4992 (9.9%)
Missing deprivation data	10 845 (13.8%)	3856 (13.5%)	6989 (13.9%)

Primary outcome

The composite of all-cause mortality, ischaemic stroke, or arterial thromboembolism occurred in 6172 women (21.6%) and 10 721 men (21.3%). There was no difference between women and men in univariate analysis (HR .98, 95% CI .96–1.02; *P* = .37; *Table 2*), with superimposed Kaplan–Meier curves (*Figure 2*). After adjustment for age, socioeconomic status, and comorbidities, women had a lower rate of the primary outcome, with adjusted HR .89 vs. men (95% CI .87–.92; *P* < .001).

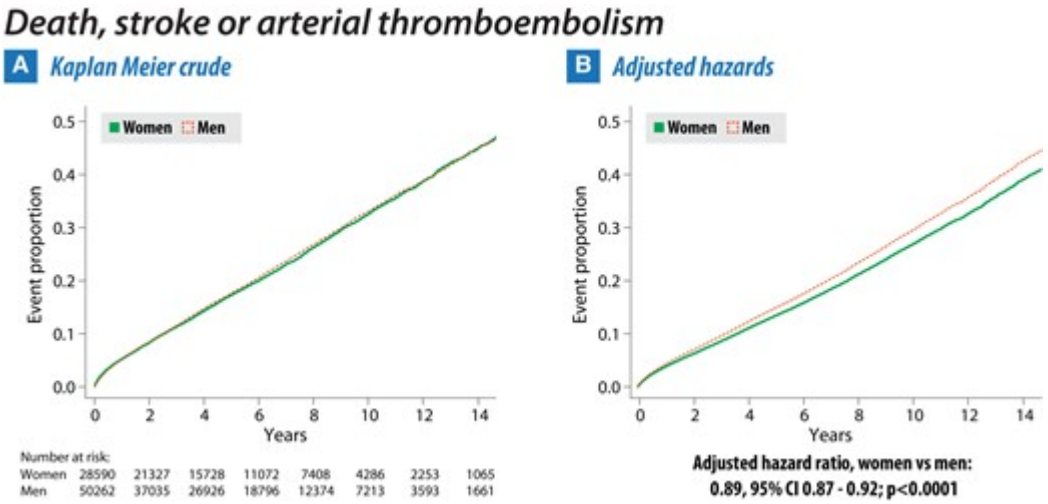


Figure 2

Crude and adjusted primary outcome by gender. Cumulative event curves for the composite of all-cause mortality, ischaemic stroke, or arterial thromboembolism for women (solid green line) and men (dashed orange line). Presented as crude Kaplan–Meier curves (panel A) and after adjustment for age, socioeconomic deprivation status, and diagnoses of hypertension, diabetes mellitus, heart failure, and vascular disease (panel B)

Table 2

Primary and secondary outcomes

Outcome	**Events, *n* (%)**	**Unadjusted event rate, per 1000 person-years**	**Women vs. men**

	Women (*n* = 28 590)	**Men (*n* = 50 262)**	**Women (159 355 person-years of follow-up)**	**Men (271 731 person-years of follow-up)**	**Unadjusted hazard ratio (95% CI)**	**Adjusted hazard ratio[a] (95 % CI)**
All-cause mortality, ischaemic stroke, or arterial thromboembolism	6172 (21.6%)	10 721 (21.3%)	38.7	39.5	.98 (.96–1.02); *P* = .37	.89 (.87–.92); *P* < .001
Ischaemic stroke or arterial thromboembolism	1467 (5.1%)	2288 (4.6%)	9.2	8.4	1.10 (1.03–1.17); *P* = .004	1.00 (.94–1.07); *P* = .87
Any stroke (ischaemic or haemorrhagic) or any thromboembolism (arterial or venous)	2186 (7.7%)	3417 (6.8%)	13.7	12.6	1.10 (1.04–1.16); *P* < .001	1.02 (.96–1.07); *P* = .58
Vascular dementia	323 (1.1%)	380 (0.8%)	2.0	1.4	1.44 (1.24–1.67); *P* < .001	1.13 (.97–1.32); *P* = .11
All-cause mortality	5079 (17.8%)	9090 (18.1%)	31.9	33.4	.95 (.92–.99); *P* = .005	.86 (.83–.89); *P* < .001

aAdjusted for age, socioeconomic deprivation status, and diagnoses of hypertension, diabetes mellitus, heart failure, and vascular disease.

During follow-up, 17 133 women (60.0%) and 30 307 men (60.3%) received oral anticoagulants (P = .31 for comparison). In a sensitivity analysis that censored patients at the time of commencement of oral anticoagulation, there was no impact on results for the primary outcome with adjusted HR of .87 for women vs. men (95% CI .83–.91; P < .001; Supplementary data online, *Figure S2*). Results for those with incident AF (n = 57 107) were the same as the total population of any AF exposure, with unadjusted HR .98 for women vs. men (95% CI .95–1.02; P = .37) and adjusted HR .92 (95% CI .89–.96; P < .001). A post-hoc analysis demonstrated similar 1-year event rates after adjusting for risk factors when comparing 2005–09, 2010–14, and 2015–20 (see Supplementary data online, *Figure S3*).

Secondary outcomes

There were numerically more events in women for ischaemic stroke or arterial thromboembolism, and any stroke or any thromboembolism, with a 10% increased hazard in women for both outcomes compared with men in crude analysis (*Table 2* and *Figure 3*). After adjusting for confounders, no difference was identified between women and men for either outcome (HR 1.00, 95% CI .94–1.07, P = .87 and 1.02, 95% CI .96–1.07, P = .58). The lack of difference between genders was confirmed in a post-hoc analysis to account for competing risk between ischaemic stroke or arterial thromboembolism and death (HR 1.03, 95% CI .96–1.10; P = .40).

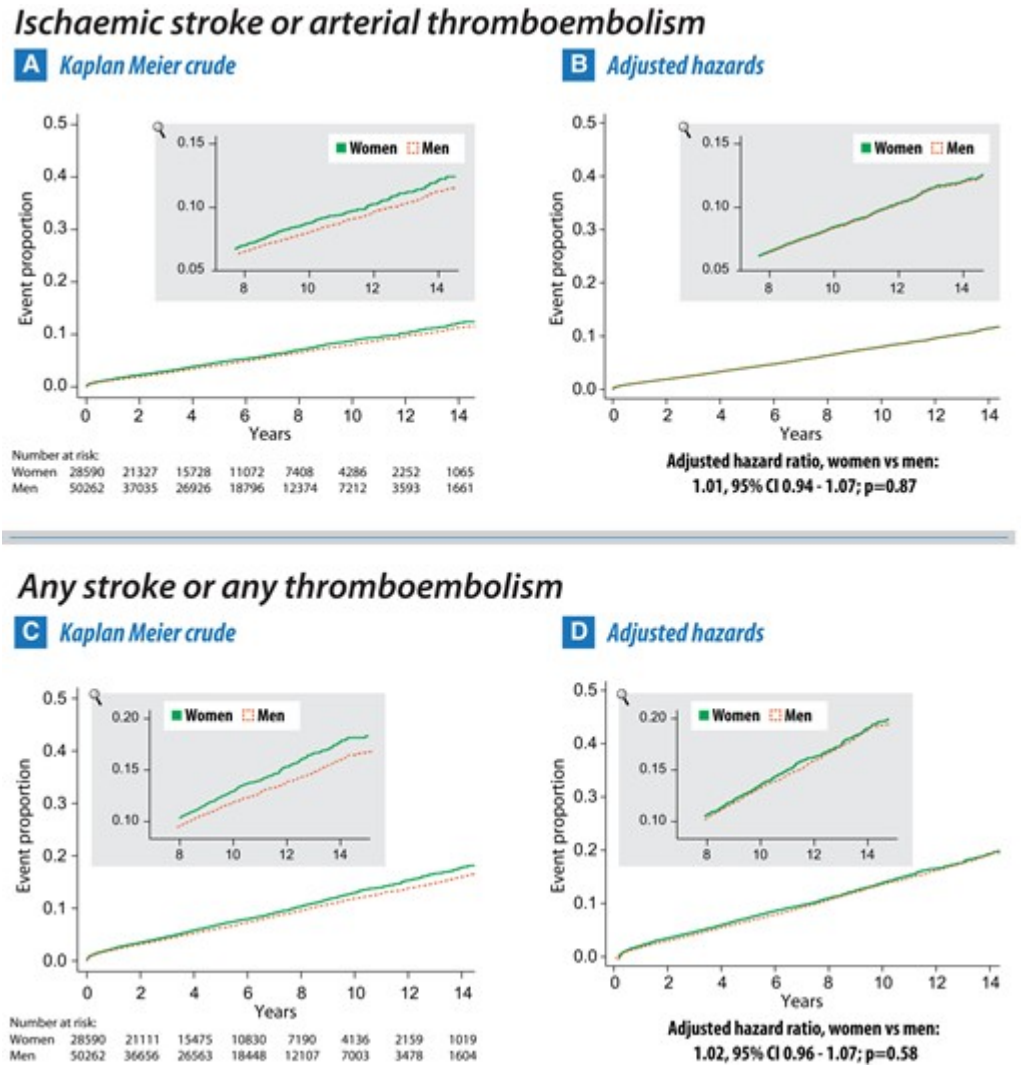


Figure 3

Crude and adjusted secondary outcomes by gender. Cumulative event curves for ischaemic stroke or arterial thromboembolism and any stroke (ischaemia or haemorrhagic) or any thromboembolism (arterial or venous). Presented as crude Kaplan–Meier curves (panels A and C) and after multivariate adjustment (panels B and D) for women (solid green line) and men (dashed orange line)

Vascular dementia followed the same pattern as thromboembolic outcomes, with no significant difference between women and men after risk factor adjustment (HR 1.13, 95% CI .97–1.32; *P* = .11; *Table 2* and Supplementary data online, *Figure S4*).

Death occurred in 14 169 patients (18.0%) during follow-up, with a rate of 31.9 per 1000 patient-years in women and 33.5 per 1000 patient-years in men. All-cause mortality rates were significantly lower in women after adjusting for age, socioeconomic status, and comorbidities (HR .86, 95% CI .83–.89; *P* < .001) (*Table 2* and Supplementary data online, *Figure S4*).

Comparison of risk scoring with and without gender

CHA_2DS_2-VA and CHA_2DS_2-VASc were only modest predictors of adverse outcomes in this selected cohort of patients with AF, with AUROC values consistently showing relatively poor discrimination. As a continuous score, CHA_2DS_2-VA was superior to CHA_2DS_2-VASc for the primary outcome with AUROC .651 vs. .639 (*P* < .001) (*Figure 4*). Further robust comparison is presented in the online supplement. CHA_2DS_2-VA was also superior to CHA_2DS_2-VASc when used as a categorical score (2 or above), with AUROC .611 vs. .604 (*P* < .001) (see Supplementary data online, *Figure S5*). There were no differences between CHA_2DS_2-VA and CHA_2DS_2-VASc for ischaemic stroke or arterial thromboembolism, and any stroke or any thromboembolism.

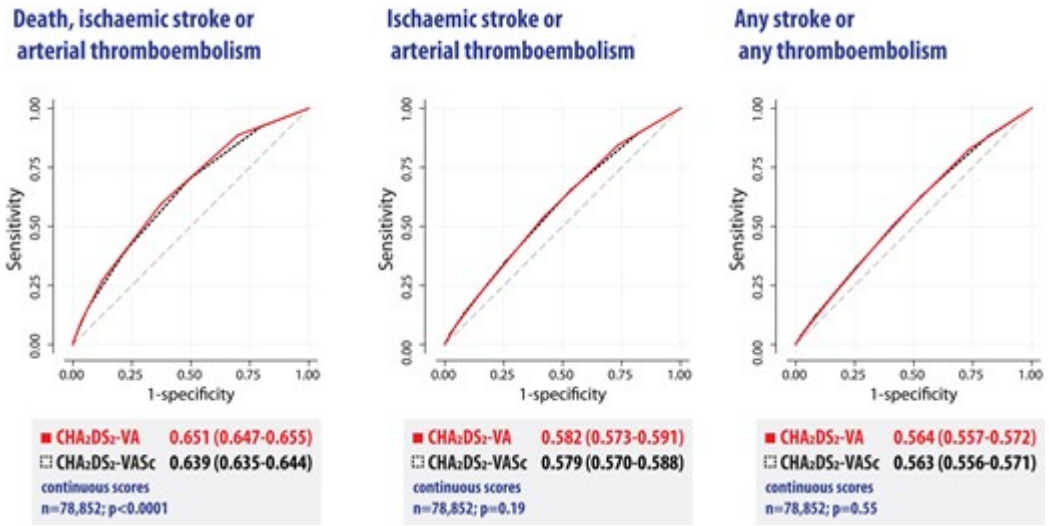


Figure 4

Comparison of risk scores with and without gender. Comparison of the area under the receiver operator characteristic curve for the

CHA_2DS_2-VA score (solid red line) and CHA_2DS_2-VASc score (dashed black line) for each outcome. Higher values indicate better accuracy, with the dashed grey line indicating accuracy no better than chance. Note patients with prior stroke or age ≥75 years were excluded to focus on a population where gender was a contributor to decision-making on oral anticoagulation; hence, these performance figures do not reflect the standard use of these risk scores

The CHA_2DS_2-VA score as a continuous variable was superior to age alone using a cut-off of 65 years, with AUROC .651 vs. .618 ($P < .001$). This was not the case when using CHA_2DS_2-VA as a categorical score (2 or above), with AUROC .611 vs. .618 for age 65 years ($P = .009$) (see Supplementary data online, *Figure S6*).

Other components of clinical risk scoring (heart failure, hypertension, diabetes, and vascular disease) were individually associated with higher risk of the primary outcome (see Supplementary data online, *Figure S7*). For each 1 point increase in CHA_2DS_2-VA score, the hazard of all-cause mortality, ischaemic stroke, or arterial thromboembolism increased by 1.48 (95% CI 1.46–1.50; $P < .001$; Supplementary data online, *Figure S8*). There was no interaction noted between CHA_2DS_2-VA as a continuous score and gender ($P = .45$). Except for those at the highest risk, crude primary outcome event rates were similar between women and men in each CHA_2DS_2-VA score categories, with an annualized rate of 3.56% and 3.66% for CHA_2DS_2-VA = 1 and 4.84% and 5.33% for CHA_2DS_2-VA = 2 (*Figure 5A*; Supplementary data online, *Figure S9* for ischaemic stroke/arterial thromboembolism). No reclassification was seen with the addition of gender to CHA_2DS_2-VA for either cases (death, ischaemic stroke, or arterial thromboembolism) or controls (no primary outcome events). Net reclassification improvement was zero when gender was added to the model, and integrated discrimination improvement was not significant ($P > .5$). There was no difference

between women and men in the association of age (as a continuous variable) with primary outcome events (*Figure 5B*).

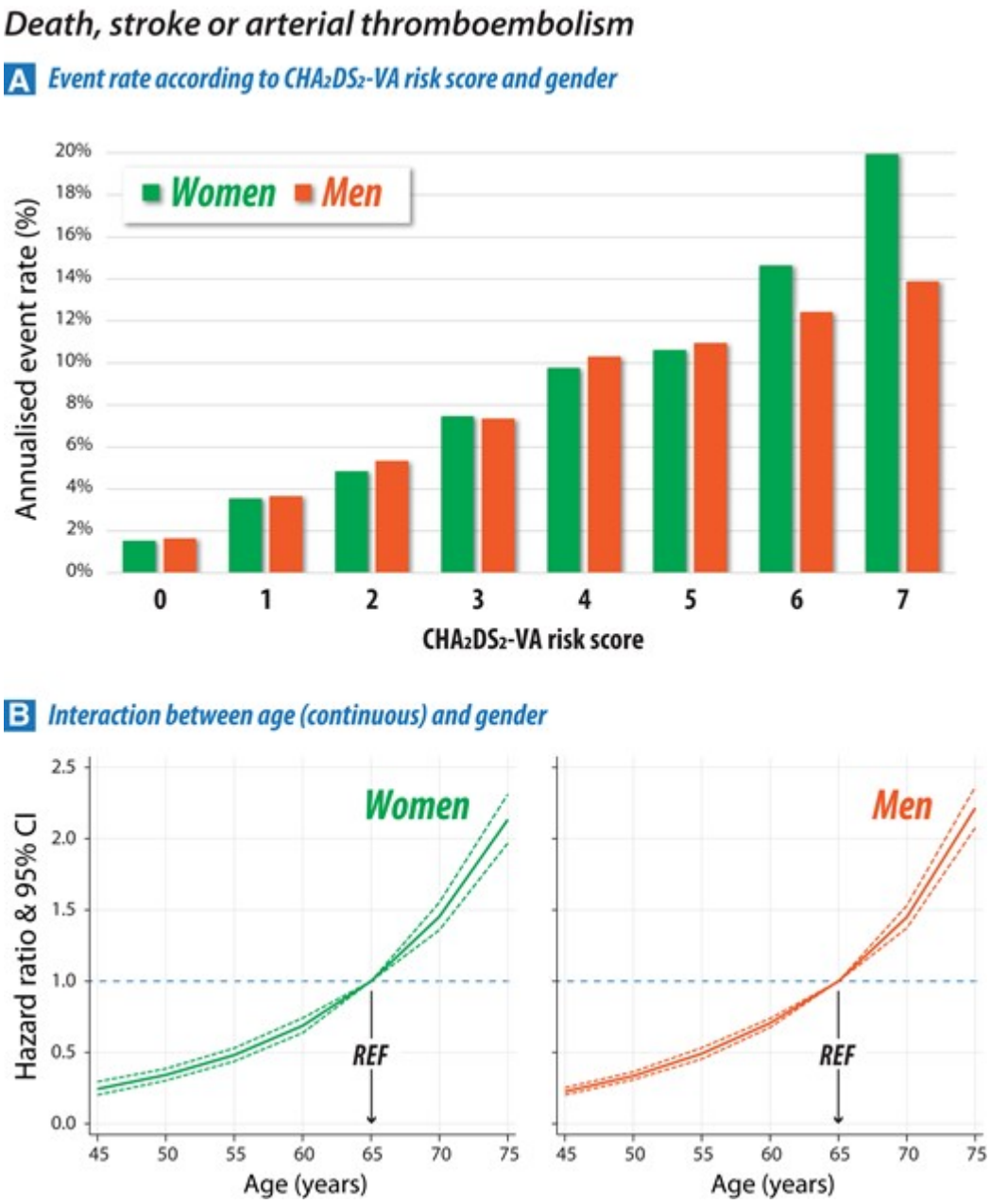


Figure 5

Primary outcome according to risk stratification. (A) Annualised crude event rate for the composite of all-cause mortality, ischaemic stroke, or arterial thromboembolism for each CHA_2DS_2-VA score according to gender; refer to Supplementary data online, *Figure S7* for the secondary outcome of ischaemic stroke or arterial thromboembolism. (B) Age as a continuous variable using a cubic spline model in

reference to age = 65 years and presented separately for women and men

Discussion

This study used a large, contemporary, primary care population to assess the impact of gender on adverse outcomes in patients with AF. To approximate the population where gender could potentially play a role in treatment selection for oral anticoagulation, those with a prior stroke or age ≥75 years were specifically excluded, as there is already a clear indication in these groups for oral anticoagulation regardless of gender. After accounting for various confounders, including age, comorbidities, anticoagulation use, and the differential rate of death, there was no indication in this study that gender should play a major part in risk stratification for anticoagulation therapy. There was no difference between women and men in this population for different types of stroke or different types of thromboembolism, with higher age in women likely offsetting the greater vascular comorbidity burden in men. Mortality rates and, hence, the incidence of the composite primary outcome were overall higher in men than women. CHA_2DS_2-VA (ignoring gender) had better performance than CHA_2DS_2-VASc in this selected population, although both scores can oversimplify treatment decisions and have limited accuracy for prediction of adverse outcomes in individual patients.

Gender has always been a controversial issue with regard to decisions on prevention of stroke and thromboembolism in the context of AF. It became part of routine practice in 2010 after validation of the CHA_2DS_2-VASc score in 1084 patients from the 2003–04 Euro Heart Survey of hospitalized patients with AF.3 The association between female gender and ischaemic stroke is changing over time, with a large registry cohort finding that the incidence of ischaemic stroke in more recent years was no longer different between women and men.16 Numerous cohort studies have validated the CHA_2DS_2-VASc

score in different populations and against other risk scores;17–19 however, the issue of gender has never been settled. International guideline committees have tended to get around the issue by suggesting different cut-off points for women and men (*Figure 1*).20,21 It is possible that this may have inadvertently contributed in the past to lower reported rates of appropriate anticoagulation in women.22,23 Of note, using a score for risk assessment may be different from threshold-based decisions for oral anticoagulation.

The association between gender and outcomes in AF is confounded by substantial differences in age, comorbidity burden, symptoms, and access to interventional therapy when comparing women with men.24 In addition, comorbidities and risk factors are known to change over time. This study adjusted for relevant clinical factors that may have impacted previous observational studies,7 and as a result, we saw similar event rates over different time-periods. Substantive differences were noted between the unadjusted and adjusted analyses for every outcome, highlighting the dependence of prognosis on individual patient profiles and the importance of considering these confounders. The differential rate of death amongst women and men is also important to consider as dying precludes the possibility of developing a stroke or another thromboembolic event. This is of particular relevance in older multimorbid populations (such as patients with AF), and why death was included within the primary outcome of this study. In recent years, the complexities of gender identity have led to new challenges, with the potential for transgender patients to not receive appropriate therapy, even though they have high rates of cardiovascular events.25 Removing all aspects of gender from risk stratification in AF could have additional benefit on securing equality in the provision of evidence-based therapy.

The accuracy of risk scores and their relatively poor ability to discriminate patients who go on to suffer from the sequelae of AF is a concern. Most clinical risk scores for stroke prevention in AF have

AUROC values of .6–.7, indicating that a substantial number of patients will not be appropriately classified, and the chance of missing people where oral anticoagulation could have prevented thromboembolic events. The median AUROC for CHA_2DS_2-VASc in a meta-analysis of eight studies was .600 as used in clinical practice (i.e. as a categorical cut-off).26 Of note, AUROC values of .5 indicate that the risk model is no better than a random guess or toss of a coin. Although the main objective of this study was to assess the value of gender in risk profiling, our results also confirm that stratification based on clinical categories is far from ideal. Attempts to improve these scores have led to more complex calculators27 and the inclusion of biomarkers to refine risk assessment.28 These approaches have not been as widely validated, and the transition away from simple clinical scores may have unintended consequences or lead to health inequalities. Healthcare professionals and patients should be made aware of the poor performance of available risk scores and seek to personalize prescription of oral anticoagulation where possible. This includes considering the broad range of other clinical factors that may modulate thromboembolic risk in AF and could contribute to decision-making on oral anticoagulation, such as kidney disease.29 Robust evidence for clinical risk scores from randomized trials is lacking, with a cluster randomized study of automated CHA_2DS_2-VASc to advise on anticoagulant prescription finding no difference in thromboembolic outcomes compared to usual care,30 and a biomarker-guided approach still under evaluation (NCT03753490). Other ongoing trials are exploring the use of DOACs in younger populations at lower established risk (DaRe2THINK, NCT0470082631; BRAIN-AF, NCT0238722932), which may in the future remove the need for risk scores entirely. Although lifetime risk of AF is similar in women and men, AF onset occurs around 10 years later in women,33 making the feasibility of trials uncertain to address the question of gender in low or intermediate risk patients.

Observational datasets are prone to reflect prescription biases common in routine clinical practice, and larger sample sizes do not necessarily ameliorate these effects.34 This contemporary study showed a lower mortality in women after careful multivariable adjustment, which differs from historical studies.35 The mortality data in this study of patients with AF are consistent with the overall and unselected UK population figures, where the median age at death in 2018–20 was 85.8 years for women and 82.3 years for men, and life expectancy at age 65 years was 21.0 years for women and 18.5 years for men.36 This study used a population-based design within primary care to avoid patient selection biases common to registry and hospital-based studies. We restricted the population to address the clinical question of whether gender was useful in risk stratification in AF, considering patients not currently anticoagulated and without an established indication for anticoagulation irrespective of gender. It should be noted that by excluding patients with prior stroke and age ≥75 years, this study is not assessing the full CHA_2DS_2-VASc and CHA_2DS_2-VA scores, but where gender is clinically relevant to making a decision on oral anticoagulation. Hence, the overall values of performance will not be comparable to studies with unselected inclusion. Restricting the sample also limited complex confounding from various factors in those with high risk, but we cannot exclude impact from unmeasured or unknown confounders. There are also factors that this study did not include that are associated with AF and thromboembolism and may vary according to gender, such as kidney function and body mass index. Biases in outcomes can arise due to delays between disease onset and diagnosis,37 so participants in this study were only eligible after an AF diagnosis was clinically made. However, gender disparities are known in the presentation and diagnosis of AF.24

Our data confirm that age is the key driver of thromboembolic risk in patients with AF and augments the impact of other comorbidities. Age

alone (at a cut-off point of 65 years) was inferior to CHA_2DS_2-VA when used as a continuous score, but had numerically similar precision when used as a categorical score. This reinforces that thromboembolic risk is a continuum, and that while risk score categories can guide the prescription of oral anticoagulation, they should not be the absolute determinant. Further, the artificial categorisation of age has the potential to obscure appropriate decision-making for individual patients.38 Although risk scoring without the gender criterion had better statistical performance, there were only small differences, which may not impact clinical significance. Detailed assessment of different risk scores was not within scope of this study, which was focused on the value of gender within clinical decision making. It could be argued that the primary outcome for this study should have been the anticoagulant-censored analysis; however, that was prespecified as a sensitivity analysis and was no different to the main analysis for the primary outcome. This study did not collect information on anticoagulation dosage or time in therapeutic range. The presentation, morbidity and management of AF are known to vary across different ethnicity groups.39,40 Information on ethnicity was available for 39 619 patients (50.2% of this cohort), of which 1446 (3.7%) were non-white; hence, these data cannot be generalized beyond those of European ancestry.

Conclusion

Women and men with AF have similar rates of thromboembolic events, such as stroke, arterial or venous clots and vascular dementia after accounting for confounding factors. The rate of the primary composite outcome of all-cause death, ischaemic stroke, or arterial thromboembolism was significantly lower in women than men without prior stroke and aged <75 years, even after censoring for oral anticoagulant use, driven by lower mortality. Clinical risk scores only have a modest ability to predict events in AF, but excluding gender

leads to better precision without affecting reclassification or discrimination.

9.Effect of Preexisting Maternal CVD on the Risk of Offspring CVD From Infancy to Early Adulthood

BACKGROUND AND AIMS

A variety of maternal heart conditions are associated with abnormal placentation and reduced foetal growth. However, their impact on offspring's long-term cardiovascular health is poorly studied. This study aims to investigate the association between intrauterine exposure to pre-existing maternal cardiovascular disease (CVD) and offspring CVD occurring from infancy to early adulthood, using paternal CVD as a negative control.

METHODS

This nationwide cohort study used register data of live singletons without major malformations or congenital heart disease born between 1992 and 2019 in Sweden. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models, adjusted for essential maternal characteristics. Paternal CVD served as a negative control for assessment of unmeasured genetic and environmental confounding.

RESULTS

Of the 2 597 786 offspring analysed (49.1% female), 26 471 (1.0%) were born to mothers with pre-existing CVD. During a median follow-up of 14 years (range 1-29 years), 17 382 offspring were diagnosed with CVD. Offspring of mothers with CVD had 2.09 times higher adjusted HR of CVD (95% CI 1.83, 2.39) compared with offspring of mothers without CVD. Compared with maternal CVD, paternal CVD showed an association of smaller magnitude (HR 1.49, 95% CI 1.32,

1.68). Increased hazards of offspring CVD were also found when stratifying maternal CVD into maternal arrhythmia (HR 2.94, 95% CI 2.41, 3.58), vascular (HR 1.59, 95% CI 1.21, 2.10), and structural heart diseases (HR 1.48, 95% CI 1.08, 2.02).

CONCLUSIONS

Maternal CVD was associated with an increased risk of CVD in offspring during childhood and young adulthood. Paternal comparison suggests that genetic or shared familial factors may not fully explain this association.

10. Congenital heart defects in children born after assisted reproductive technology: a CoNARTaS study

Abstract

Background and Aims

Children born after assisted reproductive technology (ART) have worse perinatal outcomes compared with spontaneously conceived children. This study investigates whether children conceived after ART have a higher risk of congenital heart defects (CHDs) compared with children born after spontaneous conception (SC).

Methods

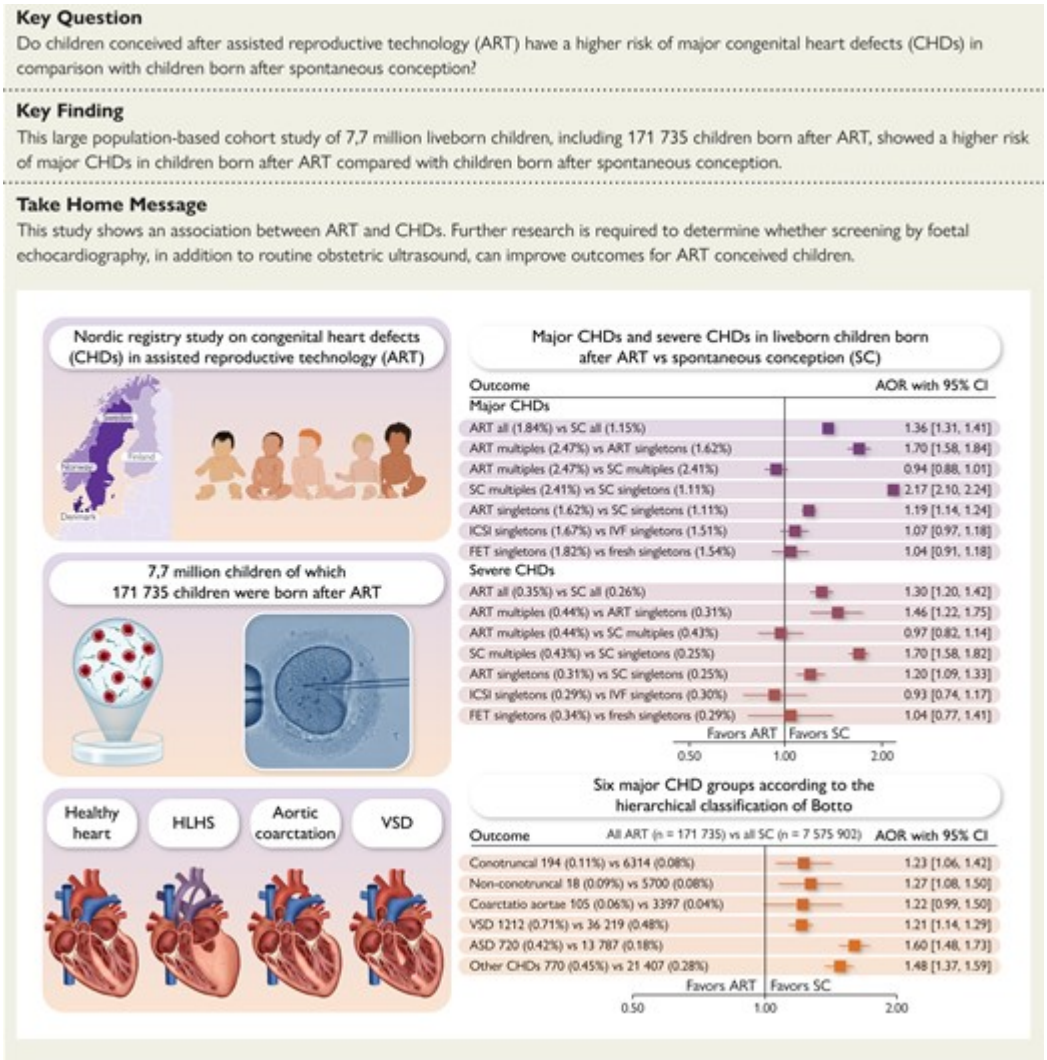
All 7 747 637 liveborn children in Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015), and Sweden (1987–2015), where 171 735 children were conceived after ART, were included. National ART and medical birth registry data were cross-linked with data from other health and population registries. Outcomes were major CHDs, severe CHDs, 6 hierarchical CHD lesion groups, and 10 selected major CHDs, diagnosed prenatally or up to 1 year of age (Denmark, Finland, and Sweden) and prenatally or at birth (Norway). The association between ART and CHDs was assessed with multivariable logistic regression analysis, with adjustment for available confounders.

Results

Major CHDs were detected in 3159 children born after ART (1.84%) and in 86 824 children born after SC [1.15%; adjusted odds ratio (AOR) 1.36; 95% confidence interval (CI) 1.31–1.41]. Risk was highest in multiples, regardless of conception method. Severe CHDs were detected in 594 children born after ART (0.35%) and in 19 375 children born after SC (0.26%; AOR 1.30; 95% CI 1.20–1.42). Risk was similar between ICSI and IVF and between frozen and fresh embryo transfer.

Conclusions

Assisted reproductive technology–conceived children have a higher prevalence of major CHDs, being rare, but severe conditions. The absolute risks are, however, modest and partly associated with multiple pregnancies, more prevalent in ART.



Structured Graphical Abstract

The main findings were that assisted reproductive technology (ART) was associated with an increased risk of major congenital heart defects (CHDs) as well as severe CHDs in liveborn children with follow-up to 1 year of age, compared with spontaneous conception (SC). Children born from a multifetal pregnancy had the highest risk of CHDs, but ART was also associated with an increased risk in singletons. No significant difference was found between singletons born after intracytoplasmic sperm injection (ICSI) and *in vitro* fertilization (IVF) or between fresh and frozen embryo transfer. AOR, adjusted odds ratio; ASD, atrial septal defect; CI, confidence interval; FET, frozen embryo transfer; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect.

Introduction

The field of reproductive medicine is growing due to advancements in assisted reproductive technology (ART).1 More than 10 million children are so far conceived through ART worldwide, and currently, 3.0% of children in Europe and 2.3% in the USA are born after ART.2–4

Health outcomes for children born after ART continue to be in focus due to the widespread use of ART, the increasing number of children born after ART, and the fast development of new ART procedures. Many systematic reviews, meta-analyses, and large observational studies show an association between ART and low birth weight (LBW) and preterm birth (PTB). Although multiple births are the most important cause of the increased risk of PTB and LBW in ART-conceived children compared with children born after spontaneous conception, risk of these outcomes is also higher in ART-conceived singletons.5–8 Several meta-analyses and original studies have found that birth defects are more common in children born after ART

compared with children born after spontaneous conception. Estimates of excess risk range between 30% and 70%.7–10 A systematic review, including 29 studies, by Qin *et al.*7 reported birth defects in 5.7% [95% confidence interval (CI) 4.7%–6.9%] of singletons born after *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and in 3.9% (95% CI 3.1%–4.8%) of singletons born after spontaneous conception. Most studies show no difference in the frequency of birth defects in children born after IVF vs. ICSI, nor in children born after fresh vs. frozen-thawed embryo transfer (FET).10,11 The increased rate of birth defects found among children born after ART could partly be explained by parental subfertility according to a recent study from Australia.12

Congenital heart defects (CHDs) refer to structural anomalies of the heart and the intrathoracic vessels present during pregnancy or at birth.13 Congenital heart defects are the most commonly occurring birth defects, accounting for ~ 50% of all major birth defects, affecting ~ 1%–2% of children in the general population.14–17 Although many CHDs are recorded at birth and a few later in life, the true incidence of CHDs remains largely unknown due to lack of identification in pregnancies ending in miscarriages, terminations, or stillbirths.13,18,19 Heart defects are a major paediatric health concern and remain the leading cause of mortality from birth defects.20 Several systematic reviews and cohort studies have found an increased risk of CHDs in children born after ART.21–23 A recent review including 41 cohort and case–control studies with 25 856 children born after ART showed an increased risk of CHDs in the ART-conceived group as compared with spontaneous conception [SC; pooled odds ratio (OR) 1.45; 95% CI 1.20–1.76].21 Congenital heart defects are more common in twins compared with singletons,24,25 and a recent study found that most of the association between ART and CHD was mediated by twinning.26 For specific CHDs, conflicting results have been reported.21,27

Using nationwide data from four Nordic countries, we assessed the risk of major CHDs in ART-conceived liveborn children compared with children born after spontaneous conception. We further explored if risk of any specific CHD was increased in children born after ART and if specific assisted reproductive techniques were associated with CHDs.

Methods

Data sources

The Committee of Nordic ART and Safety (CoNARTaS) was established in 2008 to evaluate short- and long-term health consequences of ART in children and their mothers.28 The unique personal identity number, assigned to all residents in the Nordic countries, enabled individual-level data linkage between children and their mothers and between different registries.29 Data from national ART registries, medical birth registries (MBRs), national patient registries (NPRs), cause of death registries, and population registries were cross-linked. Data for this study were obtained from Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015), and Sweden (1987–2015). Due to incompleteness of the Swedish ICD-8 codes for 1985 and 1986, we chose to exclude these 2 years for Sweden. Details on our cohort and the registries used are given in Supplementary data online, *Table S1*.

Study population

Inclusion criteria were all liveborn singletons, twins, and higher-order multiples born after ART and SC (i.e. conception without ART) during the study period. Assisted reproductive technology is defined according to Zegers-Hochschild *et al.*,30 i.e. 'all interventions that include the *in vitro* handling of both human oocytes and sperm or of embryos for the purpose of reproduction'.

Stillbirths were excluded due to low data quality on birth defects in these pregnancies. Information on terminations of pregnancies due to birth defects was not available.

Outcome variables

We defined children with CHDs as having a CHD diagnosis at birth and up to 1 year of age, in the MBR, NPR, or cause of death registry. For Norway, follow-up stopped at birth. All diagnoses were coded according to the International Classification of Diseases (ICD), Eighth Revision (ICD-8); Ninth Revision (ICD-9); and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).31

The primary outcome was major CHDs diagnosed up to 1 year of age. Major CHDs were defined according to the European Concerted Action on Congenital Anomalies and Twins (EUROCAT) as ICD-10 Q20-Q26, and with corresponding ICD-8 and ICD-9 codes32 (see Supplementary data online, *Table S2*). In line with EUROCAT, we did not consider minor defects such as patent ductus arteriosus in preterm babies (<37 weeks) and isolated patent foramen ovale as major CHDs.33

Secondary outcomes were (i) severe CHDs, (ii) CHDs according to the hierarchical classification of Botto *et al.*,34 and (iii) 10 selected specific major CHDs. The severe CHD subgroup consists of 26 major CHDs classified as severe CHDs according to EUROCAT, which is based on Dolk *et al.*35 (see Supplementary data online, *Table S2*). The Botto classification of CHDs has been designed for use in aetiological and observational studies.34,36,37 Here, all CHDs are grouped in a hierarchical arrangement into six lesion groups, lesion group 1 being the most severe (see Supplementary data online, *Table S3*). Lesion group 1 includes conotruncal defects (such as tetralogy of Fallot, transposition of the great vessels, common arterial trunk, and aortopulmonary septal defects); lesion group 2 includes non-

conotruncal defects [such as endocardial cushion defects, a common ventricle, and hypoplastic left heart syndrome (HLHS)]; lesion group 3 coarctation of the aorta; lesion group 4 ventricular septal defects (VSDs); and lesion group 5 atrial septal defects. Lesion group 6 includes all other CHD diagnoses and circulatory system anomalies not included in lesion groups 1–5. In individuals with several CHDs, only the most severe CHD was included. The 10 selected specific major CHDs were common arterial truncus, double outlet right ventricle, complete transposition of the great vessel, isomerism of atrial appendages with asplenia or polysplenia, atrioventricular septal defect, tetralogy of Fallot, pulmonary valve atresia, tricuspid atresia and stenosis, HLHS, and coarctation aortae (see Supplementary data online, *Table S2*). These specific CHDs were mainly selected based on medical knowledge and previous studies.38,39

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.40

Statistical methods

Logistic regression analysis was performed estimating crude and adjusted ORs for CHD, with 95% CIs. We estimated the risk of major CHDs, severe CHDs, the 6 CHD lesion groups, and the 10 selected major CHDs within 1 year of age for Danish, Finnish, and Swedish children, and by the time of birth for Norwegian children since data on CHDs in Norway were available solely from the birth records.

Children born after ART were compared with children conceived spontaneously. Multiples included twins, triplets, and higher-order multiple births. Moreover, ART-conceived singletons were compared with spontaneously conceived singletons, ART-conceived multiples with spontaneously conceived multiples, ART-conceived multiples with ART-conceived singletons, and spontaneously conceived multiples

with spontaneously conceived singletons. Where data were available (Denmark, Norway, and Sweden), we further compared singletons conceived using ICSI with singletons conceived using conventional IVF, and singletons conceived using frozen embryos with singletons conceived using fresh embryos. Singletons born after ICSI, IVF, or frozen embryo transfer (FET) were also compared with spontaneously conceived singletons.

The choice of covariates was based on previous studies and a thorough consideration of the existing knowledge of risk factors.38,41–44 Adjustments were made for child's year of birth (continuous variable), country of birth, maternal age at delivery (continuous variable), parity (nulliparous/parous), maternal smoking, maternal pre-gestational diabetes types 1 and 2, and history of maternal non-chromosomal CHDs. There were few missing data for most of these covariates except for smoking (*Table 1*). Missing data for smoking were set as no smoking in the main analysis. No imputation was conducted for other missing data. The significance level was set to 5%. All data analyses were calculated using STATA (version 18).

Table 1

Characteristics of study population by mode of conception and country of birth (Denmark 1994–2014, Finland 1990–2014, Norway 1984–2015, and Sweden 1987–2015)

	All countries	**Denmark**	**Finland**	**Norway**	**Sweden**
	n **= 7 747 637 liveborn children**	***n*** **= 1 355 267 liveborn children**	***n*** **= 1 497 341 liveborn children**	***n*** **= 1 865 484 liveborn children**	***n*** **= 3 029 545 liveborn children**
	ART SC	**ART SC**	**ART SC**	**ART SC**	**ART SC**

	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
Child characteristics										
Year of birth, n (%)										
1984–90	1610 (0.9)	898 290 (11.9)	0	0	53 (0.2)	65 393 (4.5)	877 (2.6)	383 757 (21.0)	680 (1.1)	449 140 (15.1)
1991–95	11 681 (6.8)	1 321 614 (1.4)	1299 (2.8)	138 138 (10.6)	2864 (9.7)	321 476 (21.9)	2464 (7.2)	297 356 (16.2)	5054 (8.1)	564 644 (19.0)
1996–2000	28 709 (16.7)	1 333 763 (17.6)	8532 (18.6)	327 305 (25.0)	6941 (23.4)	283 333 (19.3)	4313 (12.7)	292 015 (15.9)	8923 (14.4)	431 110 (14.

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	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
										5)
2001–05	36 092 (21.0)	1 332 414 (17.6)	11 798 (25.8)	313 094 (23.9)	6359 (21.4)	276 400 (18.8)	6586 (19.4)	276 926 (15.1)	11 349 (18.3)	465 994 (15.7)
2006–10	45 519 (26.5)	1 414 225 (18.7)	13 156 (28.7)	310 143 (23.7)	6974 (23.5)	291 949 (19.9)	9411 (27.7)	293 014 (16.0)	15 978 (25.7)	519 119 (17.5)

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	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
2011–15	48 124 (28.0)	1 275 596 (16.8)	11 016 (24.1)	220 786 (16.9)	6500 (21.9)	229 099 (15.6)	10 391 (30.5)	288 374 (15.8)	20 217 (32.5)	537 337 (18.1)
Birth weight, *n* (%)										
Very low, <1500 g	5215 (3.1)	54 992 (0.7)	1566 (3.5)	10 331 (0.8)	845 (2.9)	9504 (0.7)	1233 (3.6)	14 584 (0.8)	1571 (2.5)	20 573 (0.7)
Low,	27448	319	8463	61	4783	56	6103	81	809	12

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	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	***n* = 171 735**	***n* = 7 575 902**	***n* = 45 801**	***n* = 1 309 466**	***n* = 29 691**	***n* = 1 467 650**	***n* = 34 042**	***n* = 1 831 442**	***n* = 62 201**	***n* = 2 967 344**
<2500, g	(16.0)	685 (4.2)	(18.5)	229 (4.7)	(16.1)	334 (3.8)	(17.9)	588 (4.5)	9 (13.0)	0 534 (4.1)
Macrosomia, ≥4000g	20 516 (12.0)	1 425 820 (18.8)	4725 (10.3)	238 103 (18.2)	3521 (11.9)	272 464 (18.6)	3933 (11.6)	355 748 (19.4)	8337 (13.4)	559 505 (18.9)
Missing data on birth weight	755 (0.4)	36 271 (0.5)	463 (1.0)	24 570 (1.9)	13 (0.04)	3405 (0.2)	35 (0.1)	1556 (0.1)	244 (0.4)	6740 (0.

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	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
										2)
Gestational age, *n* (%)										
Extremely preterm, <28 + 0 weeks	1984 (1.2)	20 482 (0.3)	626 (1.4)	3640 (0.3)	325 (1.1)	3613 (0.3)	455 (1.3)	5352 (0.3)	578 (0.9)	7877 (0.3)
Very preterm, <32 + 0 weeks	6120 (3.6)	64 821 (0.9)	1869 (4.1)	12 178 (0.9)	970 (3.3)	10 834 (0.7)	1400 (4.1)	16 984 (0.9)	1881 (3.0)	24 825 (0.8)
Preterm, <37 + 0 weeks	31 367 (18.3)	436 471 (5.8)	9264 (20.2)	78 548 (6.0)	5725 (19.3)	77 520 (5.3)	6867 (20.2)	108 524 (5.9)	9511 (15.	171 87

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	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	***n* = 171 735**	***n* = 7 575 902**	***n* = 45 801**	***n* = 1 309 466**	***n* = 29 691**	***n* = 1 467 650**	***n* = 34 042**	***n* = 1 831 442**	***n* = 62 201**	***n* = 2 967 344**
									3)	9 (5.8)
Post-term, ≥42 + 0 weeks	3296 (5.3)	513 869 (6.8)	1491 (3.3)	82 959 (6.3)	924 (3.1)	67 415 (4.6)	1557 (4.6)	158 092 (8.6)	3296 (5.3)	205 403 (6.9)
Missing data on gestational age	652 (0.4)	128 984 (1.7)	298 (0.7)	28 949 (2.2)	57 (0.2)	6755 (0.5)	246 (0.7)	89 599 (4.9)	51 (0.1)	3681 (0.1)
Plurality, *n* (%)										

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	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
Singletons	127 275 (74.1)	7 380 916 (97.4)	31 077 (67.9)	1 269 638 (97.0)	22 044 (74.2)	1 431 723 (97.6)	24 117 (70.8)	1 783 926 (97.4)	50 037 (80.4)	2 895 629 (97.6)
Twins	42 459 (24.7)	190 426 (2.5)	14 332 (31.3)	38 810 (3.0)	7198 (24.2)	35 222 (2.4)	9364 (27.5)	46 356 (2.5)	11 565 (18.6)	70 038 (2.4)
Triplets and higher	2001 (1.2)	4504 (0.1)	392 (0.9)	1018 (0.1)	449 (1.5)	705 (0.1)	561 (1.7)	1160 (0.1)	599 (1.0)	1621

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										(0.1)
Missing data on plurality, *n*	0	56	0	0	0	0	0	0	0	56
Male sex, *n* (%)	87 785 (51.1)	3 887 791 (51.3)	23 211 (50.7)	672 079 (51.3)	15 197 (51.2)	749 952 (51.1)	17 456 (51.3)	940 571 (51.4)	31 921 (51.3)	1 525 189 (51.4)
Missing	0	7	0	0	0	0	0	0	0	7

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	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
data on sex, *n*										
Maternal characteristics										
Age at delivery years, mean (SD)	33.4 (4.2)	29.3 (5.2)	33.1 (4.2)	29.7 (4.9)	33.4 (4.7)	29.3 (5.3)	33.2 (4.7)	28.8 (5.2)	33.7 (4.2)	29.3 (5.2)
Age at delivery (years), *n* (%)										
<25	2773 (1.6)	1 401 083 (18.5)	715 (1.6)	186 390 (14.2)	695 (2.3)	280 446 (19.1)	506 (1.5)	394 183 (21.5)	857 (1.4)	540 064 (18.

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										2)
25–29	28 888 (16.8)	2 574 096 (34.0)	8278 (18.1)	454 202 (34.7)	5424 (18.3)	489 753 (33.4)	6098 (17.9)	637 419 (34.8)	9088 (14.6)	992 722 (33.5)
30–34	70 849 (41.3)	2 371 342 (31.3)	19 848 (43.3)	453 307 (34.6)	11 776 (39.7)	446 451 (30.4)	14 402 (42.3)	538 859 (29.4)	24 823 (39.9)	932 725 (31.4)

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35–39	56 593 (33.0)	1 027 140 (13.6)	13 813 (30.2)	184 443 (14.1)	8956 (30.2)	204 704 (14.0)	11 203 (32.9)	221 121 (12.1)	22 621 (36.4)	416 872 (14.1)
>40	12 632 (7.4)	202 241 (2.7)	3147 (6.9)	31 124 (2.4)	2840 (9.6)	46 296 (3.2)	1833 (5.4)	39 860 (2.2)	4812 (7.7)	84 961 (2.9)
Primiparous, *n* (%)	116 520 (67.9)	3 163 682	30 490 (66.6)	554 283 (42.3)	2138 (67.8)	593 361 (40.4)	21 733 (63.8)	756 578 (41.3)	44 159 (71.	1 259

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		(41.8)							0)	460 (42.4)
Missing data on parity, *n* (%)	569 (0.33)	19 165 (0.3)	560 (1.2)	17 719 (1.4)	9 (0.03)	1374 (0.1)	0	0	0	0
BMI (kg/m2), *n* (% of non-missing)										
<18.5	2565 (2.4)	132 058 (3.5)	942 (3.4)	25 980 (4.2)	391 (2.6)	22 448 (3.7)	310 (0.2)	10 619 (4.1)	922 (1.7)	73011 (3.1)

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18.5–24.9	68 169 (63.4)	2 415 098 (63.4)	18 050 (64.6)	385 134 (62.5)	9840 (65.3)	375 550 (62.6)	5878 (61.0)	158 114 (61.7)	34 411 (62.8)	1 496 300 (64.0)
25.0–29.9	25 989 (24.2)	851 663 (22.4)	6196 (22.2)	129 398 (21.0)	3302 (21.9)	130 144 (21.7)	2298 (23.8)	56 411 (22.0)	14 193 (25.9)	535 710 (22.9)

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
≥30	10 746 (10.0)	410 734 (10.8)	2774 (9.9)	75 920 (12.3)	1543 (10.2)	72 271 (12.0)	1154 (12.0)	31 139 (12.2)	5275 (9.6)	231 404 (9.9)
Missing data for BMI, *n* (% of total)	64 256 (37.4)	3 766 349 (49.7)	17 839 (39.0)	693 037 (52.9)	14 615 (49.2)	867 237 (59.1)	24 402 (71.7)	1 575 159 (86.0)	7400 (11.9)	630 919 (21.3)
Smoking, *n* (%)	10 120	934 433	3956 (8.6)	194 514	1815 (6.1)	224 950	1735 (5.1)	129 171	2614	385

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
	(5.9)	(12.3)		(14.9)		(15.3)		(7.1)	(4.2)	798 (13.0)
Missing data on smoking, *n* (%)	12 938 (7.5)	1 199 059 (15.8)	3217 (7.0)	132 470 (10.1)	449 (1.5)	37 317 (2.5)	5703 (16.8)	868 891 (47.4)	3569 (5.7)	160 381 (5.4)
Educational levela,b, *n* (%)										
Low	59 160	2 972	24 096	775 820	8675 (29.2)	604 510	NA	NA	26 389	159

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
	(43.0)	924 (51.7)	(52.6)	(59.3)		(41.2)			(42.4)	2 594 (53.7)
Middle	45 314 (32.9)	1 604 375 (27.9)	13 662 (29.8)	342 853 (26.2)	11 349 (38.2)	466 541 (31.8)	NA	NA	20 303 (32.6)	794 981 (26.8)
High	27 952	765 000	7 463	154 271	8078 (27.2)	237 162	NA	NA	12 411	373

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
	(20.3)	(13.3)	(16.3)	(11.8)		(16.2)			(20.0)	567 (12.6)
Missing data on education, *n* (%)	5267 (3.8)	402 161 (7.0)	580 (1.3)	36 522 (2.8)	1589 (5.4)	159 437 (10.9)	NA	NA	3098 (5.0)	20620 2 (6.7)
Pre-gestational diabetes *n* (%)	1515 (0.88)	53 709 (0.71)	517 (1.13)	16 105 (1.23)	372 (1.25)	14 266 (0.97)	268 (0.79)	9352 (0.51)	358 (0.58)	13986 (0.

	All countries		**Denmark**		**Finland**		**Norway**		**Sweden**	
	***n* = 7 747 637 liveborn children**		***n* = 1 355 267 liveborn children**		***n* = 1 497 341 liveborn children**		***n* = 1 865 484 liveborn children**		***n* = 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	***n* = 171 735**	***n* = 7 575 902**	***n* = 45 801**	***n* = 1 309 466**	***n* = 29 691**	***n* = 1 467 650**	***n* = 34 042**	***n* = 1 831 442**	***n* = 62 201**	***n* = 2 967 344**
										47)
Non-chromosomal CHD, *n* (%)	648 (0.38)	26 017 (0.34)	167 (0.36)	4649 (0.36)	159 (0.54)	7868 (0.54)	54 (0.16)	1739 (0.09)	268 (0.43)	11 761 (0.40)
Chromosomal defects, *n* (%)	661 (0.38)	5925 (0.08)	232 (0.51)	1368 (0.10)	107 (0.36)	2066 (0.14)	28 (0.08)	872 (0.05)	294 (0.47)	1619 (0.05)
Paternal characteristics										

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
Non-chromosomal CHD, *n* (%)	NA	NA	NA	NA	NA	NA	NA	NA	243 (0.14)	10448 (0.35)
Chromosomal defects, *n* (%)	NA	NA	NA	NA	NA	NA	NA	NA	217 (0.35)	768 (0.03)
Assisted reproduction methodc, *n* (%)										
IVF	81 900	-	25 024	-	NA	-	20 093	-	36 783	-

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
	(57.7)		(54.6)				(59.0)		(59.1)	
ICSI	55 126 (38.8)	-	18 118 (39.6)	-	NA	-	11 590 (34.1)	-	25 418 (40.9)	-
Missing data on IVF/ICSI	5018 (3.5)	-	2659 (5.8)	-	NA	-	2359 (6.9)	-	0	-
Single embryo transfer	52 130 (36.7)	-	10 191 (22.3)	-	NA	-	10 303 (30.3)	-	31 636 (50.9)	
Fresh	115	-	41	-	NA	-	25	-	48	-

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
embryo transfer	408 (81.2)		022 (89.6)				630 (75.3)		756 (78.4)	
Frozen embryo transfer	22 630 (15.9)	-	4761 (10.4)	-	NA	-	4424 (13.0)	-	13 445 (21.6)	-
Missing data on fresh/frozen cycle	4006 (2.8)	-	18 (0.04)	-	NA	-	3988 (11.7)	-	0	-
Cleavage stage embryo	130 079 (91.6)	-	43 621 (95.2)	-	NA	-	30 219 (88.8)	-	56 239 (90.	-

	All countries		Denmark		Finland		Norway		Sweden	
	n **= 7 747 637 liveborn children**		***n*** **= 1 355 267 liveborn children**		***n*** **= 1 497 341 liveborn children**		***n*** **= 1 865 484 liveborn children**		***n*** **= 3 029 545 liveborn children**	
	ART	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**	**ART**	**SC**
	n **= 171 735**	***n*** **= 7 575 902**	***n*** **= 45 801**	***n*** **= 1 309 466**	***n*** **= 29 691**	***n*** **= 1 467 650**	***n*** **= 34 042**	***n*** **= 1 831 442**	***n*** **= 62 201**	***n*** **= 2 967 344**
									4)	
Blastocysts	7663 (5.4)	-	1287 (2.8)	-	NA	-	414 (1.2)	-	596 2 (9.6)	-
Missing data on embryo stage	4302 (3.0)	-	893 (2.0)	-	NA	-	3409 (10.0)	-	0	-
Donated oocytes	1410 (1.0)	-	710 (1.6)	-	NA	-	0e	-	700 (1.1)	-
Donated spermd	2994 (2.8)	-	1911 (4.2)	-	NA	-	NA	-	108 3 (1.7)	-

ART, assisted reproductive technology; BMI, body mass index; CHD, congenital heart defect; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; NA, not available; SC, spontaneous conception.

aData for Denmark, Finland, and Sweden (denominator ART, 137 693; SC, 5 744 460).

bHighest educational level according to the International Standard Classification of Education (ISCED2011): ISCED < 5, primary, secondary, or post-secondary non tertiary education; ISCED 5–6, first stage of tertiary education (bachelor or equivalent); and ISCED 7–8, second stage of tertiary education (master, doctorate, or more).45.

cData for Denmark, Norway, and Sweden (denominator ART = 142 044).

dData for Denmark and Sweden (denominator ART = 108 002).

eOocyte donation not permitted in Norway during the study period.

Sensitivity analyses

We performed several sensitivity analyses on major CHDs. First, we performed a sensitivity analysis restricting the analysis to those with known data on smoking. Second, maternal highest educational level (low, medium, and high)45 was included as a covariate when this information was available (Denmark, Finland, and Sweden). Third, a sensitivity analysis was performed including Finnish data with validated data on major CHDs and excluding those which after further evaluation by the Finnish malformation registry were considered as minor CHDs (see Supplementary data online, *Table S1*).46 A fourth sensitivity analysis on major CHDs and severe CHDs was performed restricting the cohort to infants born 2006–15. Between 2004 and 2007, all countries had introduced the second trimester ultrasound including foetal anomaly screening (gestational week 18–21). Lastly, a sensitivity analysis was performed on Swedish data, adjusting also for paternal CHD.

Results

Baseline characteristics

A total of 7 747 637 liveborn children were included, 171 735 (2.2%) were born after ART and 7 575 902 (97.8%) were born after SC (*Figure 1*). The proportion of multiples was 25.9% (44 460 of 171 735) in the ART group and 2.6% (194 930 of 7 575 902) in the spontaneously conceived group.

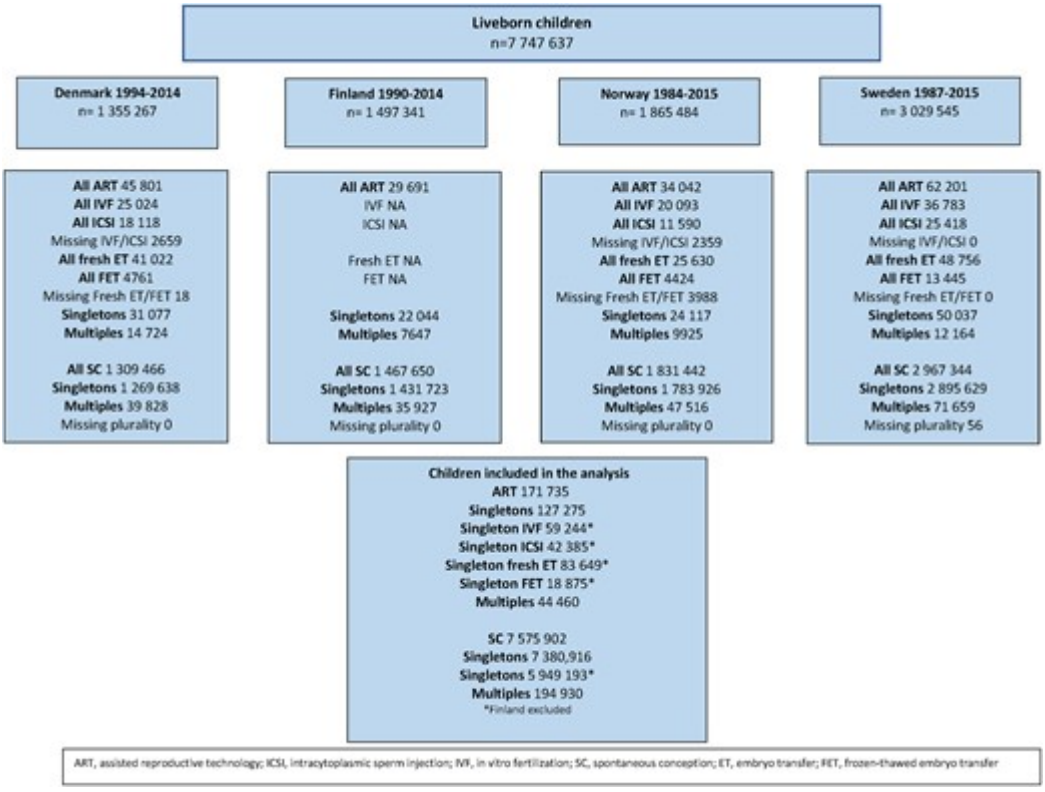


Figure 1

Flow chart of the study population

Baseline characteristics are presented in *Table 1*. Children conceived by ART were more often born preterm (<37 weeks; 18.3% vs. 5.8%) or with LBW (<2500 g; 16.0% vs. 4.2%) than children born after SC. Women who conceived by ART were more likely to be older at birth (≥35 years; 40.4% vs. 16.3%), to be primiparous (67.9% vs. 41.8%), to have a high educational level (16.3% vs. 10.1%), and to be non-

smokers (86.6% vs. 71.9%). The prevalence of pre-gestational diabetes was 0.88% in women who conceived using ART vs. 0.71% in women who conceived spontaneously. Corresponding figures for maternal non-chromosomal CHDs were 0.38% vs. 0.34% and for obesity (body mass index ≥ 30 kg/m2) 10.0% vs. 10.8%.

Major congenital heart defects

The rate of major CHDs varied somewhat between countries as indicated in *Table 2* and *Figure 2*.

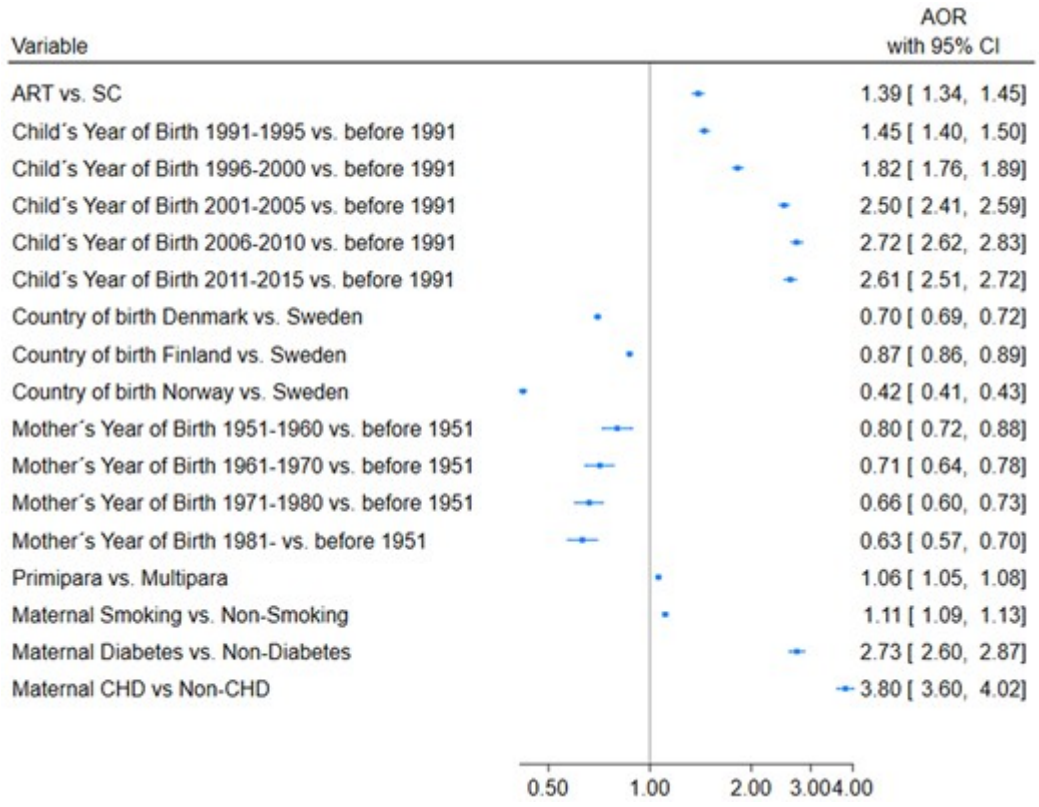


Figure 2

Forest plot showing the ORs for independent covariates of risk of major congenital heart defects in children born after assisted reproductive technology vs. children conceived spontaneously. Footnote: Please observe that in this figure, child's year of birth and maternal age are expressed in categories for better visualization. In all statistical models, however, both variables are analysed as continuous

variables, resulting in slightly different AOR and 95% CI for comparison ART vs. SC

Table 2

Risk of congenital heart defects in liveborn children conceived by assisted reproductive technology vs. spontaneous conception for all countries and by country (Denmark 1994–2014, Finland 1990–2014, Norway 1984–2015, and Sweden 1987–2015)

	No. of liveborn children		**Risk of CHD, ART vs. spontaneous conception**	
	ART	**Spontaneous conception**	**Crude OR (95% CI) *P* value**	**Adjusted OR**a **(95% CI) *P* value**
Major CHDsb **diagnosed within the first year of life**				
All countries *n*/*N* (%)	3159/171 735 (1.84)	86 575 (1.15)	824/7 902 1.62 (1.56–1.68) < .001	1.36 (1.31–1.41) < .001
Denmark *n*/*N* (%)	879/45 801 (1.92)	14 309 (1.10)	467/1 466 1.75 (1.64–1.88) < .001	1.70 (1.58–1.82) < .001
Finland *n*/*N* (%)	592/29 691 (1.99)	19 467 (1.32)	341/1 650 1.52 (1.40–1.65) < .001	1.33 (1.22–1.45) < .001
Norway (at birth) *n*/*N* (%)	380/34 042 (1.12)	10 831 (0.58)	630/1 442 1.93 (1.74–2.14) < .001	1.34 (1.21–1.49) < .001
Sweden *n*/*N* (%)	1308/62	42	386/2 1.48 (1.40–1.57)	1.22 (1.16–1.29)

	No. of liveborn children		Risk of CHD, ART vs. spontaneous conception	
	ART	**Spontaneous conception**	**Crude OR (95% CI) *P* value**	**Adjusted OR**a **(95% CI) *P* value**
	201 (2.10)	967 344 (1.43)	< .001	< .001
Severe CHDsb **diagnosed within the first year of life**				
All countries *n*/*N* (%)	594/171 735 (0.35)	19 375/7 575 902 (0.26)	1.35 (1.25–1.47) < .001	1.30 (1.20–1.42) < .001
Denmark *n*/*N* (%)	137/45 801 (0.30)	3042/1 309 466 (0.23)	1.29 (1.09–1.53) .004	1.28 (1.07–1.53) .006
Finland *n*/*N* (%)	117/29 691 (0.39)	4320/1 467 650 (0.29)	1.34 (1.11–1.61) .002	1.27 (1.06–1.54) .011
Norway (at birth) *n*/*N* (%)	90/34 042 (0.26)	3642/1 831 442 (0.20)	1.33 (1.08–1.64) .008	1.23 (0.99–1.52) .060
Sweden *n*/*N* (%)	250/62 201 (0.40)	8371/2 967 344 (0.28)	1.43 (1.26–1.62) < .001	1.37 (1.20–1.56) < .001
Major CHDs diagnosed within the first year of life according to the hierarchic classification of Botto *et al.*c				

	No. of liveborn children		Risk of CHD, ART vs. spontaneous conception	
	ART	**Spontaneous conception**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
Lesion group 1 conotruncal				
All countries *n*/*N* (%)	194/171 735 (0.11)	6314/7 575 902 (0.08)	1.36 (1.18–1.56) < .001	1.23 (1.06–1.42) .006
Denmark *n*/*N* (%)	49/45 801 (0.11)	1255/1 309 466 (0.10)	1.12 (0.84–1.49) .450	1.14 (0.86–1.52) .366
Finland *n*/*N* (%)	36/29 691 (0.12)	1205/1 467 650 (0.08)	1.48 (1.06–2.06) .021	1.46 (1.04–2.04) .027
Norway (at birth) *n*/*N* (%)	35/34 042 (0.10)	965/1 831 442 (0.05)	1.95 (1.39–2.74) < .001	1.45 (1.03–2.04) .033
Sweden *n*/*N* (%)	74/62 201 (0.12)	2889/2 967 344 (0.10)	1.22 (0.97–1.54) .088	1.20 (0.95–1.51) .134
Lesion group 2 Non-conotruncal				
All countries *n*/*N* (%)	158/171 735 (0.09)	5700/7 575 902 (0.08)	1.22 (1.04–1.43) .013	1.27 (1.08–1.50) .003

	No. of liveborn children		Risk of CHD, ART vs. spontaneous conception	
	ART	**Spontaneous conception**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
Denmark *n*/*N* (%)	42/45 801 (0.09)	835/1 309 466 (0.06)	1.44 (1.05–1.96) .022	1.40 (1.02–1.92) .035
Finland *n*/*N* (%)	34/29 691 (0.11)	1038/1 467 650 (0.07)	1.62 (1.15–2.28) .006	1.45 (1.02–2.04) .036
Norway (at birth) *n*/*N* (%)	32/34 042 (0.09)	1787/1 831 442 (0.10)	0.96 (0.68–1.37) .834	1.19 (0.84–1.70) .325
Sweden *n*/*N* (%)	50/62 201 (0.08)	2040/2 967 344 (0.07)	1.17 (0.88–1.55) .274	1.12 (0.84–1.48) .441
Lesion group 3 coarctation aortae				
All countries *n*/*N* (%)	105/171 735 (0.06)	3397/7 575 902 (0.04)	1.36 (1.12–1.66) .002	1.22 (0.999–1.49) .051
Denmark *n*/*N* (%)	20/45 801 (0.04)	522/1 309 466 (0.04)	1.10 (0.70–1.71) .689	1.06 (0.67–1.66) .815
Finland *n*/*N* (%)	19/29 691	1081/1 467 650 (0.07)	0.87 (0.55–1.37) .543	0.79 (0.50–1.24) .305

	No. of liveborn children		Risk of CHD, ART vs. spontaneous conception	
	ART	**Spontaneous conception**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
	(0.06)			
Norway (at birth) *n*/*N* (%)	10/34 042 (0.03)	313/1 831 442 (0.02)	1.72 (0.92–3.23) .092	1.14 (0.60–2.15) .689
Sweden *n*/*N* (%)	56/62 201 (0.09)	1481/2 967 344 (0.05)	1.80 (1.38–2.36) < .001	1.57 (1.20–2.06) .001
Lesion group 4 VSD				
All countries *n*/*N* (%)	1212/171 735 (0.71)	36 219/7 575 902 (0.48)	1.48 (1.40–1.57) < .001	1.21 (1.14–1.29) < .001
Denmark *n*/*N* (%)	185/45 801 (0.40)	3812/1 309 466 (0.29)	1.39 (1.20–1.61) < .001	1.39 (1.20–1.62) < .001
Finland *n*/*N* (%)	333/29 691 (1.12)	10 677/1 467 650 (0.73)	1.55 (1.39–1.73) < .001	1.39 (1.25–1.56) < .001
Norway (at birth)	153/34 042 (0.45)	3661/1 831 442 (0.20)	2.25 (1.92–2.65) < .001	1.41 (1.20–1.66) < .001

	No. of liveborn children		Risk of CHD, ART vs. spontaneous conception	
	ART	**Spontaneous conception**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
Sweden *n*/*N* (%)	541/62 201 (0.87)	18 069/2 967 344 (0.61)	1.43 (1.31–1.56) < .001	1.16 (1.06–1.26) .001
Lesion group 5 ASD				
All countries *n*/*N* (%)	720/171 735 (0.42)	13 787/7 575 902 (0.18)	2.31 (2.14–2.49) < .001	1.60 (1.48–1.73) < .001
Denmark *n*/*N* (%)	288/45 801 (0.63)	3372/1 309 466 (0.26)	2.45 (2.17–2.77) < .001	2.21 (1.96–2.50) < .001
Finland *n*/*N* (%)	23/29 691 (0.08)	1038/1 467 650 (0.07)	1.10 (0.72–1.66) .666	0.90 (0.59–1.37) .623
Norway (at birth) *n*/*N* (%)	82/34 042 (0.24)	1559/1 831 442 (0.09)	2.83 (2.27–3.54) < .001	1.75 (1.40–2.19) < .001
Sweden *n*/*N* (%)	327/62 201 (0.53)	7818/2 967 344 (0.26)	2.00 (1.79–2.24) < .001	1.38 (1.23–1.54) < .001
Lesion group 6 other CHDs				

	No. of liveborn children		Risk of CHD, ART vs. spontaneous conception	
	ART	**Spontaneous conception**	**Crude OR (95% CI) *P* value**	**Adjusted OR**a **(95% CI) *P* value**
All countries *n*/*N* (%)	770/171 735 (0.45)	21 407/7 575 902 (0.28)	1.59 (1.48–1.71) < .001	1.48 (1.37–1.59) < .001
Denmark n/N (%)	295/45 801 (0.64)	4671/1 309 466 (0.36)	1.81 (1.61–2.04) < .001	2.09 (1.85–2.35) < .001
Finland *n*/*N* (%)	147/29 691 (0.50)	4302/1 467 650 (0.29)	1.69 (1.44–2.00) < .001	1.50 (1.27–1.77) < .001
Norway (at birth) *n*/*N* (%)	68/34 042 (0.20)	2345/1 831 442 (0.13)	1.56 (1.23–1.99) < .001	1.13 (0.88–1.44) .332
Sweden *n*/*N* (%)	260/62 201 (0.42)	10 089/2 967 344 (0.34)	1.23 (1.09–1.39) .001	1.27 (1.12–1.44) < .001

ART, assisted reproductive technology; ASD, atrial septal defect; CHD, congenital heart defects; CI, confidence interval; OR, odds ratio; VSD, ventricular septal defect.

a*Major CHDs and severe CHDs:* Adjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, and maternal CHD, in the analysis of all countries. Adjustment for child's year of birth, maternal age, parity, maternal smoking, maternal diabetes, and maternal CHD, in the analysis of the

specific countries. *Botto lesion groups 1–6:* Adjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, and maternal CHD in the analysis of all countries. Only adjustment for child's year of birth and maternal age in the analysis of the specific countries.

bMajor CHDs and severe CHDs according to the EUROCAT 1.5 definition.32,33.

cLesion groups 1–6 according to Botto *et al.*34

Major CHDs diagnosed up to 1 year of age were detected in 3159 children born after ART (1.84%) and in 86 824 children born after SC (1.15%; adjusted OR 1.36; 95% CI 1.31–1.41; *P* < .001; *Table 2*). Among children with major CHDs, 193 children (6.1%) in the ART group and 5472 (6.3%) in the spontaneously conceived group had a concomitant chromosomal aberration. Associations of each covariate with major CHDs are illustrated in *Figure 2*. The strongest associations were seen for maternal pre-gestational diabetes (OR 2.72; 95% CI 2.59–2.86) and maternal CHDs (OR 3.80; 95% CI 3.59–4.02).

Major CHDs were detected among 1.62% (*n* = 2059) of singletons born after ART and among 1.11% (*n* = 82 119) of singletons born after SC (adjusted OR 1.19; 95% CI 1.14–1.24; *P* < .001; *Table 3*). No significant difference was seen for multiples conceived after ART vs. multiples conceived after SC (*Table 3*).

Table 3

Risk of congenital heart defects in singletons conceived by assisted reproductive technology vs. spontaneous conception and multiples conceived by assisted reproductive technology vs. spontaneous conception (Denmark 1994–2014, Finland 1990–2014, Norway 1984–2015, and Sweden 1987–2015)

	No. of singletons		No. of multiples		Risk of CHD in AR singletons vs. singletons bor after spontaneous conceptio			
	ART *n* = 127 275	**Spontaneous conception *n* = 7 380 916**	**ART *n* = 44 460**	**Spontaneous conception *n* = 194 930**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95 % CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
Major CHDsb diagnosed within the first year of life, *n* (%)	2059 (1.62)	82 119 (1.11)	1100 (2.47)	4707 (2.41)	1.46 (1.40–1.53) < .001	1.19 (1.14–1.24) < .001	1.03 (0.96–1.10) .455	0.94 (0.88–1.01) .085
Severe CHDsb diagnosed within the first year of life, *n* (%)	399 (0.31)	18 539 (0.25)	195 (0.44)	836 (0.43)	1.25 (1.13–1.38) < .001	1.20 (1.09–1.33) < .001	1.02 (0.87–1.20) .778	0.97 (0.82–1.14) .669
Major CHDs diagnosed within								

	No. of singletons		No. of multiples		Risk of CHD in AR singletons vs. singletons bor after spontaneous conceptio			
	ART *n* = 127 275	**Spontaneous conception *n* = 7 380 916**	**ART *n* = 44 460**	**Spontaneous conception *n* = 194 930**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95 % CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
the first year of life according to the hierarchic classification of Botto *et al.*c								
Lesion group 1 conotruncal, *n* (%)	138 (0.11)	6057 (0.08)	56 (0.13)	257 (0.13)	1.32 (1.12–1.56) .001	1.20 (1.01–1.42) .042	0.96 (0.72–1.28) .757	0.84 (0.62–1.24) .273
Lesion group 2 non-conotrun	99 (0.08)	5499 (0.07)	59 (0.13)	201 (0.10)	1.04 (0.86–1.27) .671	1.12 (0.92–1.37) .260	1.29 (0.96–1.72)	1.14 (0.83–1.55) .420

	No. of singletons		No. of multiples		Risk of CHD in AR singletons vs. singletons bor after spontaneous conceptio			
	ART *n* = 127 275	**Spontaneous conception *n* = 7 380 916**	**ART *n* = 44 460**	**Spontaneous conception *n* = 194 930**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95 % CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
cal, *n* (%)							.088	
Lesion group 3 coarctation aortae, *n* (%)	64 (0.05)	3221 (0.04)	41 (0.09)	176 (0.09)	1.15 (0.90–1.48) .261	1.00 (0.78–1.28) .988	1.02 (0.73–1.44) .903	1.03 (0.72–1.49) .855
Lesion group 4 VSD, *n* (%)	882 (0.69)	34 552 (0.47)	330 (0.74)	1667 (0.86)	1.48 (1.39–1.59) < .001	1.15 (1.07–1.23) < .001	0.87 (0.77–0.98) .018	0.90 (0.79–1.02) .086
Lesion group 5 ASD, *n* (%)	427 (0.34)	12 569 (0.17)	293 (0.66)	1218 (0.62)	1.97 (1.79–2.17) < .001	1.30 (1.17–1.43) < .001	1.06 (0.93–1.20) .412	0.95 (0.83–1.09) .400
Lesion	449	20 221	321	1186	1.29	1.20	1.19	1.01

	No. of singletons		No. of multiples		Risk of CHD in AR singletons vs. singletons bor after spontaneous conceptio			
	ART *n* = 127 275	**Spontaneous conception *n* = 7 380 916**	**ART *n* = 44 460**	**Spontaneous conception *n* = 194 930**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95 % CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
group 6 other CHDs, *n* (%)	(0.35)	(0.27)	(0.72)	(0.61)	(1.17–1.42) < .001	(1.09–1.32) < .001	(1.05–1.34) .006	(0.88–1.15) . 879

ART, assisted reproductive technology; ASD, atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; VSD, ventricular septal defect.

aAdjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, and maternal CHD.

bMajor CHDs and severe CHDs according to the EUROCAT 1.5 definition.32,33.

cLesion groups 1–6 according to Botto *et al.*34

Multiples born after ART had an absolute risk of major CHDs of 2.47% (*n* = 1100; adjusted OR 1.70; 95% CI 1.58–1.84; *P* < .001 vs. singletons conceived after ART; *Table 4*). Multiples born after SC had an absolute risk of major CHDs of 2.41% (*n* = 4705; adjusted OR 2.17; 95% CI 2.10–2.24; *P* < .001 vs. spontaneously conceived singletons; *Table 4*).

Table 4

Risk of congenital heart defects in multiples born after ART vs. singletons born after assisted reproductive technology and multiples born after spontaneous conception vs. singletons born after spontaneous conception (Denmark 1994–2014, Finland 1990–2014, Norway 1984–2015, and Sweden 1987–2015)

ART, assisted reproductive technology; ASD, atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; SC, spontaneous conception; VSD, ventricular septal defect.

aAdjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, and maternal CHD.

bMajor CHDs and severe CHDs according to the EUROCAT 1.5 definition.32,33.

cLesion groups 1–6 according to Botto *et al.*34

Table 5 shows the results for singletons born after ICSI (*n* = 42 385), IVF (*n* = 59 244), and SC (*n* = 5 949 193). Major CHDs were detected among 1.67% (*n* = 709) of singletons born after ICSI and among 1.51% (*n* = 895) singletons born after IVF (adjusted OR 1.07; 95% CI 0.97–1.18; *P* = .200; *Table 5*).

Table 5

Risk of congenital heart defects by type of *in vitro* fertilization treatment (intracytoplasmic sperm injection or *in vitro* fertilization) in singletons conceived by assisted reproductive technology and spontaneous conception (Denmark 1994–2014, Norway 1984–2015, and Sweden 1987–2015)

	No of singletons	**Risk of CHD, ICSI vs. IVF**	**Risk of C**

	ICSI *n* = 42 385	**IVF *n* = 59 244**	**SC *n* = 5 949 193**	**Crude OR (95% CI) *P* value**	**Adjusted**a **OR (95% CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted**b **OR (95% CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted**b **OR (95% CI) *P* value**
Major CHDsc *n* (%)	709 (1.67)	895 (1.51)	63 675 (1.07)	1.11 (1.00–1.22) .041	1.07 (0.97–1.18) .200	1.57 (1.46–1.69) < .001	1.21 (1.12–1.31) < .001	1.42 (1.33–1.52) < .001	1.14 (1.07–1.22) < .001
Severe CHDsc *n* (%)	124 (0.29)	180 (0.30)	14 390 (0.24)	0.96 (0.77–1.21) .746	0.93 (0.74–1.17) .536	1.21 (1.01–1.44) .035	1.17 (0.98–1.40) .085	1.26 (1.08–1.46) .002	1.19 (1.03–1.39) .019
Major CHDs diagnosed within the first year of life according to the hierarchic classification of Botto *et al.*d									
Lesion group	37	70	489	0.74	0.73	1.06	0.94	1.44	1.28

	No of singletons			Risk of CHD, ICSI vs. IVF					Risk of C
	ICSI *n* = 42 385	**IVF *n* = 59 244**	**SC *n* = 5 949 193**	**Crude OR (95% CI) *P* value**	**Adjusted[a] OR (95% CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted[b] OR (95% CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted[b] OR (95% CI) *P* value**
1 conotruncal, *n* (%)	(0.09)	(0.12)	6 (0.08)	(0.50–1.10) .136	(0.49–1.10) .130	(0.77–1.47) .721	(0.68–1.30) .688	(1.13–1.82) .003	(1.01–1.62) .046
Lesion group 2 non-conotruncal, *n* (%)	31 (0.07)	42 (0.07)	4500 (0.08)	1.03 (0.65–1.64) .895	1.03 (0.64–1.67) .889	0.97 (0.68–1.38) .852	1.14 (0.80–1.63) .459	0.94 (0.69–1.27) .676	1.00 (0.74–1.36) .995
Lesion group 3 coarctation aortae, *n* (%)	21 (0.05)	28 (0.05)	2185 (0.04)	1.05 (0.60–1.85) .870	0.99 (0.56–1.76) .977	1.35 (0.88–2.07) .172	1.06 (0.69–1.63) .795	1.29 (0.89–1.87) .185	1.07 (0.73–1.56) .733
Lesion group 4 VSD, *n* (%)	270 (0.64)	356 (0.60)	24 349 (0.41)	1.06 (0.90–1.24) .468	1.03 (0.87–1.21) .752	1.56 (1.38–1.76) < .001	1.08 (0.96–1.22) .198	1.47 (1.32–1.63) < .001	1.09 (0.98–1.21) .115

	No of singletons			Risk of CHD, ICSI vs. IVF					Risk of C
	ICSI *n* = 42 385	**IVF *n* = 59 244**	**SC *n* = 5 949 193**	**Crude OR (95% CI) *P* value**	**Adjusted**a **OR (95% CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted**b **OR (95% CI) *P* value**	**Crude OR (95% CI) *P* value**	**Adjusted**b **OR (95% CI) *P* value**
Lesion group 5 ASD, *n* (%)	191 (0.45)	209 (0.35)	11 598 (0.19)	1.28 (1.05–1.56) .014	1.18 (0.97–1.44) .101	2.32 (2.01–2.67) < .001	1.42 (1.23–1.64) < .001	1.81 (1.58–2.08) < .001	1.22 (1.06–1.41) .005
Lesion group 6 other CHDs, *n* (%)	159 (0.38)	190 (0.32)	16 147 (0.27)	1.17 (0.95–1.45) .144	1.17 (0.94–1.45) .163	1.38 (1.18–1.62) < .001	1.33 (1.14–1.56) < .001	1.18 (1.02–1.36) .022	1.14 (0.99–1.32) .079

ART, assisted reproductive technology; ASD, atrial septal defect; CHD, congenital heart defect; CI, confidence interval; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilisation; OR, odds ratio; SC, spontaneous conception; VSD, ventricular septal defect.

aAdjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, maternal CHD, and fresh and frozen embryo transfer.

bAdjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, and maternal CHD.

cMajor CHDs and severe CHDs according to the EUROCAT 1.5 definition.32,33.

dLesion groups 1–6 according to Botto *et al.*34

Table 6 presents the results for singletons born after frozen (n = 18 875) and fresh (n = 83 649) embryo transfer and SC (n = 5 949 193). The occurrence of major CHDs among singletons born after FET was 1.82% (n = 343) and among singletons born after fresh embryo transfer 1.54% (n = 1286; adjusted OR 1.04; 95% CI 0.91–1.18; P = .603).

Table 6

Risk of congenital heart defects by frozen and fresh embryo transfer in singletons conceived by assisted reproductive technology and spontaneous conception (Denmark 1994–2014, Norway 1984–2015, and Sweden 1987–2015)

ART, assisted reproductive technology; ASD, atrial septal defect; CHD, congenital heart defect; CI, confidence interval; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilisation; OR, odds ratio; SC, spontaneous conception; VSD, ventricular septal defect.

aAdjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, maternal CHD, and IVF/ICSI.

bAdjustment for child's year of birth, country of birth, maternal age, parity, maternal smoking, maternal diabetes, and maternal CHD.

cMajor CHDs and severe CHDs according to the EUROCAT 1.5 definition.32,33.

dLesion groups 1–6 according to Botto *et al.*34

Severe congenital heart defects

Severe CHDs were detected in 594 children born after ART (0.35%) and in 19 375 children born after SC (0.26%; adjusted OR 1.30; 95% CI 1.20–1.42; *P* < .001; *Table 2*). Severe CHDs occurred among 0.31% (*n* = 399) singletons born after ART and among 0.25% (*n* = 18 539) singletons born after SC (adjusted OR 1.20; 95% CI 1.09–1.33; *P* < .001; *Table 3*). In multiples born after ART, the prevalence of severe CHDs was 0.44% (*n* = 195; adjusted OR 1.46; 95% CI 1.22–1.75; *P* < .001 vs. singletons conceived after ART; *Table 4*). In multiples born after SC, the prevalence of severe CHDs was 0.43% (*n* = 836; adjusted OR 1.70; 95% CI 1.58–1.82; *P* < .001 vs. spontaneously conceived singletons; *Table 4*). No significant difference in risk of severe CHDs was seen for multiples born after ART vs. multiples born after SC (*Table 3*).

Severe CHDs occurred among singletons born after ICSI in 0.29% (*n* = 124) and among singletons born after IVF in 0.30% (*n* = 180; adjusted OR 0.93; 95% CI 0.74–1.17; *P* = .536; *Table 5*). In singletons born after FET, the prevalence of severe CHDs was 0.34% (*n* = 64), and among singletons born after fresh embryo, transfer the prevalence was 0.29% (*n* = 244; adjusted OR 1.04; 95% CI 0.77–1.41; *P* = .784).

Sensitivity analyses

Information on smoking was missing in ~ 15% of the study population. A sensitivity analysis with no imputation on smoking did not alter results (adjusted OR for major CHDs 1.35; 95% CI 1.30–1.40, *P* < .001 for all countries combined, singletons and multiples).

In a second sensitivity analysis, we excluded observations from Norway and added an adjustment for maternal highest educational level, data which were not available for Norway. Including singletons and multiples from Denmark, Finland, and Sweden, the adjusted OR for major CHDs was 1.36 (95% CI 1.30–1.41, *P* < .001).

The analysis including Finnish data with validated major CHDs showed similar results as the main analysis (adjusted OR for major CHDs 1.35; 95% CI 1.30–1.41, $P < .001$ for all countries combined, and adjusted OR 1.31; 95% CI 1.19–1.44, $P < .001$ for Finland).

Including 2 783 464 infants born between 2006 and 2015, small differences in rates of any major CHDs and severe CHDs were found, compared with the whole time period (see Supplementary data online, *Table S4*). For major CHDs, all countries combined, the absolute rates during this period were 1.88% for ART and 1.42% for SC and 0.34% and 0.25% for severe CHDs, respectively. For Denmark, the absolute rates for both major CHDs and severe CHDs decreased, while for the other Nordic countries, the rates during the more recent time period stayed almost unchanged or varied slightly up or down. The adjusted ORs remain, however, rather unchanged (major CHDs, adjusted OR 1.31, 95% CI 1.24–1.37, $P < .001$; severe CHDs, adjusted OR 1.35, 95% CI 1.20–1.52, $P < .001$). Lastly, including only Swedish data and adding paternal CHDs as a covariate did not change the results for major CHDs (adjusted OR 1.22; 95% CI 1.16–1.29, $P < .001$).

Congenital heart defects according to the classification of Botto

According to the hierarchical CHD classification, the risk of CHDs was higher in children born after ART than in spontaneously conceived children for five of the six lesion groups: conotruncal defects, non-conotruncal defects, VSD, ASD, and other CHDs (*Table 2*).

Singletons born after ART had increased risk for four lesion groups compared with spontaneously conceived singletons: conotruncal defects, VSD, ASD, and other CHDs (*Table 3*).

For multiples born after ART vs. singletons born after ART a higher risk was seen for five of the six lesion groups: non-conotruncal defects, coarctation aortae, VSD, ASD, and other CHDs, and for multiples

born after SC vs. spontaneously conceived singletons, the risk was increased for all six lesion groups (*Table 4*).

In singletons born after ART, no difference was seen between ICSI and IVF (*Table 5*), or between frozen and fresh embryo transfer (*Table 6*) for any of the six lesion groups.

Selected specific congenital heart defects

We analysed 10 selected major CHDs (*Table 7*). In singletons, significantly increased risks in ART were seen for three CHDs: isomerism of atrial appendages, atrioventricular septal defects, and tetralogy of Fallot. Also including multiples, increased risk was seen also for pulmonary valve atresia (see Supplementary data online, *Table S5*).

Table 7

Risk of selected major congenital heart defects in singletons conceived by assisted reproductive technology vs. spontaneous conception (Denmark 1994–2014, Finland 1990–2014, Norway 1984–2015, and Sweden 1987–2015)

	No. of children		**Risk of CHD, ART vs. spontaneous conception**	
	ART *n* = 127 275	**SC *n* = 7 380 916**	**Crude OR (95% CI) *P* value**	**Adjusted OR**a **(95% CI) *P* value**
Common arterial truncus (Q20.0b), *n* (%)	15 (0.01)	613 (0.01)	1.42 (0.85–2.37) .180	1.50 (0.89–2.52) .126
Double outlet	23 (0.02)	831	1.61 (1.06–	1.26 (0.83–

	No. of children		Risk of CHD, ART vs. spontaneous conception	
	ART *n* = 127 275	**SC *n* = 7 380 916**	**Crude OR (95% CI) *P* value**	**Adjusted ORa (95% CI) *P* value**
right ventricle (Q20.1b), *n* (%)		(0.01)	2.43) .025	1.91) .281
Complete transposition of the great vessel (Q20.3b), *n* (%)	46 (0.04)	2676 (0.04)	1.00 (0.74–1.33) .983	0.99 (0.74–1.33) .949
Isomerism of atrial appendages with asplenia or polysplenia (Q20.6b), *n* (%)	11 (0.01)	196 (0.003)	3.25 (1.77–5.97) < .001	2.79 (1.50–5.18) < .001
Atrioventricular septal defect (Q21.2b), *n* (%)	90 (0.07)	3327 (0.05)	1.57 (1.27–1.93) < .001	1.28 (1.03–1.58) .023
Tetralogy of Fallot (Q21.3b), *n* (%)	60 (0.05)	2272 (0.03)	1.53 (1.19–1.98) < .001	1.34 (1.03–1.73) .028
Pulmonary valve atresia (Q22.0b), *n* (%)	29 (0.02)	1407 (0.02)	1.20 (0.83–1.73) .342	1.45 (1.00–2.10) .052
Tricuspid atresia and stenosis (Q22.4b), *n* (%)	9 (0.01)	447 (0.01)	1.17 (0.60–2.26) .645	1.37 (0.70–2.67) .357

	No. of children		Risk of CHD, ART vs. spontaneous conception	
	ART *n* = 127 275	**SC *n* = 7 380 916**	**Crude OR (95% CI) *P* value**	**Adjusted OR**a **(95% CI) *P* value**
Hypoplastic left heart syndrome (Q23.4b), *n* (%)	26 (0.02)	1607 (0.02)	0.94 (.64–1.38) .747	1.05 (0.71–1.54) .825
Coarctation aortae (Q25.1b), *n* (%)	80 (0.06)	4112 (0.06)	1.13 (0.90–1.41) .285	0.97 (0.78–1.22) .808

ART, assisted reproductive technology; CI, confidence interval; OR, odds ratio.

aAdjustment for child's year of birth, country of birth, maternal age.

bICD-10 codes. Corresponding included ICD-8 and ICD-9 codes are shown in Supplementary data online, *Table S2*. A child can have more than one CHD diagnosis.

Discussion

In this large cohort study of 7.7 million liveborn children, including more than 171 000 children born after ART, we found that ART was associated with an increased risk of major CHDs as well as severe CHDs in both the overall ART population and in the ART singleton population, compared with spontaneously conceived children. Multiples, regardless of conception method, were associated with the highest risk of CHDs. Similar risks were observed in multiples conceived by ART and spontaneous conception, but this comparison is limited by the fact that we were missing information about chorionicity. The lower rate of monochorionic multiples in ART may

give a false low risk in ART. Children conceived with ICSI did not seem to have an increased risk for CHDs compared with children conceived with IVF, and no significant difference was found between fresh and FET (*Structured Graphical Abstract*). The estimates were robust without any major changes after adjustments for available confounders or in sensitivity analyses.

Consistent with previous studies, our data showed higher occurrence of CHDs in pregnancies conceived by ART compared with spontaneously conceived pregnancies.21–23 For specific CHDs, conflicting results have been reported. A large US study, including more than 11 million live births (singletons and multiples), of which 71 050 were conceived by ART, found a nearly three-fold increased risk of cyanotic CHDs in children born after ART, compared with children born after spontaneous conception, in adjusted analysis.47 In a meta-analysis from 2018, Giorgione *et al.* analysed some specific CHDs in ART and spontaneously conceived singletons and multiples. They found lower occurrence of tetralogy of Fallot and transposition of the great arteries in the ART group. However, results were based on few events in the ART group.21 In contrast, a French case–control study of 1583 CHD cases and 4104 controls (singletons and multiples) assessing four different major structural CHDs found 2.4-fold odds of tetralogy of Fallot in children born after ART.27

The overall risk of birth defects in our cohort has been explored in a previous study.11 The study showed an increased risk of major birth defects in singletons conceived using ICSI with fresh embryo transfer compared with spontaneously conceived singletons. The risk was increased for most organ systems including the heart. Detailed data on type of CHD group or specific diagnoses were not reported. Further, multifetal pregnancies, an important mediator in risk of CHDs, were not included in our previous study.

Congenital heart defects are a heterogeneous group of diseases including both severe, life-threatening defects and minor abnormalities.34,48,49 While most children with CHDs survive to adulthood, health issues persist for many children with CHDs when they grow up.50,51 Children and adolescents with CHDs have an 11-fold increased risk of ischaemic stroke, compared with the general population, although absolute risk is low.48,52 For adults with CHDs, the risks of pulmonary arterial hypertension and endocarditis are increased.53,54 Further, for young adults with CHDs, 1 in 12 develop atrial fibrillation, and 1 in 10 of these develop congestive heart failure, before 42 years of age.52,55

The aetiology of CHDs is mainly unknown, but chromosomal abnormalities and other genetic and environmental factors are considered to predispose to CHDs.36,56 Congenital heart defects may be part of a malformation syndrome due to chromosomal aneuploidy, such as Down syndrome (trisomy 21), Edward syndrome (trisomy 18), Patau syndrome (trisomy 13), Turner syndrome (monosomy X), and Klinefelter syndrome (XXY), or Mendelian syndromes as Alagille–Holt–Oram syndrome and Noonan syndrome. Several environmental risk factors have been identified for CHDs, including both young and advanced maternal age, high parity, smoking, obesity, maternal diabetes, and use of drugs during pregnancy, e.g. antiepileptic and antidepressant drugs.38,41–44,57–61 Furthermore, women with a history of CHDs are considered to be at increased risk of having offspring with CHDs.38,39,62,63 Also, low socioeconomic status has been found to be associated with CHDs.64,65

Prenatal screening with foetal echocardiography for CHDs has been proposed to be beneficial for ART-conceived pregnancies.21,66,67 and screening by foetal echocardiography is recommended by the American Heart Association for ART pregnancies.66 Improved detection rate prenatally may offer the possibility for foetal therapy and/or specialized planning of delivery. However, this screening is still

controversial and may cause increased costs and anxiety for the parents.68–70 Further research is required to determine whether screening with foetal echocardiography, in addition to routine prenatal screening, will reduce morbidity and mortality for ART-conceived children when a major CHD is detected prenatally. In addition, preimplantation genetic testing may identify some CHDs of genetic origin and thereby contribute to decrease the CHDs among liveborn children.

Recent research has hypothesized that the placenta has a role in the development of CHDs, since placental vascular resistance has a direct impact on foetal circulation and thereby the developing foetal heart.71 Children born with CHDs have smaller placentas with increased vascular abnormalities.72 Further, studies also show a strong association between preeclampsia and CHDs, especially in early-onset and severe preeclampsia.73,74 Pregnancies conceived with ART, in particular after FET, are associated with increased risk of preeclampsia, both for singleton and multifetal pregnancies.75–77 An association between preeclampsia and CHD would, however, be expected to translate into a higher risk of CHD after FET which was not observed in the present study.

Twin pregnancies, especially monochorionic twins are associated with a higher risk of CHDs.78 In recent years, multi-foetal pregnancies in ART have been declining, due to the introduction of the single embryo transfer policy.79 However, the incidence of twin pregnancies continues to be elevated in ART-conceived pregnancies.3,80

The main strength of this study is the large population with pooled nationwide data cross-linked from several high-quality national registries. Moreover, we explored specific CHD groups and specific assisted reproductive techniques. Detailed information enabled sub-analysis and adjustment for several confounders and comparisons according to multiplicity.

Some limitations should be considered when interpreting the results. Despite similar demography and healthcare systems, the rate of CHDs varied somewhat between countries. The follow-up for Norway was limited to birth, explaining the lower rate of CHDs in Norway. The reason for discrepancies between the other Nordic countries is not known but may be due to differences in registration policies and screening for foetal anomalies. The detection rate of major CHDs prenatally has increased substantially over time, as shown in Denmark leading to an increased termination of pregnancies, with a subsequent decrease in live-birth incidence of major CHDs.18 This change might have had an impact on the results in this study, particularly since a greater proportion of the ART cohort are born in later years in this study. There were some differences in prenatal screening routines in the four Nordic countries during the study period. All countries had introduced a second trimester ultrasound (gestational week 18–21) between 2004–07 including foetal organ screening and where the large majority of women participated. Norway had a second trimester prenatal screening ultrasound during the whole study period. A first-trimester ultrasound to assess the nuchal fold and determine the risk of aneuploidy was more variably introduced with a higher frequency in Denmark and Finland. Although sensitivity analyses showed some differences in rates of major and severe CHDs in live births in the later years, this seemed to occur in similar way for both ART and spontaneous conception, resulting in only minor changes in adjusted ORs. However, still these changes over time in combination with the much increasing ART population are considered a limitation.

Furthermore, a limitation of this study is the lack of information on CHDs in miscarriages, termination of pregnancies, and stillbirths. This may result in bias if ART-conceived pregnancies have a different probability of prenatal diagnosis with subsequent termination compared with spontaneously conceived pregnancies. A French study

by Tararbit *et al.*81 found however no difference between ART and SC when evaluating the probability of prenatal diagnosis or termination of pregnancy for CHDs. A previous study on singletons from our cohort indicated similar risk of stillbirth after fresh and frozen embryo transfer compared with singletons conceived without medical assistance.82 One study limitation is that we relied only on registry data and ICD codes with the potential for miscoding. Some ICD codes, e.g. the codes for VSDs, do not differentiate between severe and less severe CHDs, and we should have needed more data on echocardiography and surgical and other procedures for correct classification. However, we have used different classifications of major CHDs to identify the most complex CHDs. Furthermore, a sensitivity analysis using data from the Finnish birth defects registry with validated major CHDs showed similar results as the main result.

Children conceived after ovulation induction and intrauterine insemination were included in the SC group. This misclassification will, if anything, dilute the association between ART and CHD.12 Other limitations are that we did not have information about causes of infertility and data on specific techniques used in assisted reproduction was not available from Finland. Finally, as in all observational studies residual confounding by unknown or unmeasured factors may remain.

Conclusions

Congenital heart defects are serious, although rare conditions. This large study reports a higher occurrence of CHDs after ART conception, both severe and less severe. The highest rates of CHDs were observed in children born in multiple pregnancies. No difference in CHDs was found between ICSI and IVF and neither between children born after fresh or frozen transfer. The findings of the current study should be conveyed to patients undergoing counselling before ART. Although the risk for major CHDs is higher in children born after ART, the absolute

increase in risks seems to be modest. This study also emphasizes the importance of single embryo transfer to avoid the increased risks in multifetal pregnancies.

11.In-Hospital Mortality Higher When Female CABG Patients Have Male Surgeons

Women undergoing CABG surgery seem to have a higher rate of in-hospital mortality if they are treated by a male versus female surgeon, according to a single-center analysis from the United Kingdom. Yet the same could not be said about male patients treated by female surgeons or patients treated by surgeons of the same gender.

While the data as they stand are hypothesis-generating, they show trends consistent with larger analyses looking at all surgeries from the United States and Canada, and they are in line with similar studies on acute MI.

“These are really interesting findings which seem to follow a pattern, even in much larger studies, and something that we have to tease down as to what may be responsible,” said Indu Deglurkar, MBBS (University Hospital of Wales, Cardiff), who presented the data here Friday at the European Association for Cardio-Thoracic Surgery 2024 meeting during a session on unresolved questions in CABG.

“If there is something correctable that we can do to improve female outcomes, then we should do it,” she told TCTMD. “But that can only come with detailed analysis.”

Male Surgeons, Female Patients

For the analysis, Deglurkar looked at all 3,317 isolated CABG surgeries (mean patient age 67 years; mean logistic EuroSCORE 6.41) done at her institution between April 2010 and March 2023. The cases were grouped by self-reported gender:

- Male patient and male surgeon (n = 2,181)

- Male patient and female surgeon (n = 567)
- Female patient and male surgeon (n = 460)
- Female patient and female surgeon (n = 109)

Overall, 28 patients died in the hospital. When stratified by groups, nine women (2.0%) treated by a male surgeon died compared with 0.7% of men who had a male surgeon, 0.3% of men who had a female surgeon, and 0.9% of women who had a female surgeon (P = 0.043 for interaction). However, this pattern was not seen when the procedures were broken down into elective, urgent, and emergency cases. There was also no significant interaction by gender concordance overall or by surgeon gender.

Deglurkar and colleagues found no difference in secondary outcomes including any postoperative complications, reoperation for bleeding, deep sternal wound infection, stroke, and renal impairment by group, gender concordance, or surgeon gender.

The study is subject to several limitations, including low numbers of the primary outcome and the involvement of only one female surgeon, as well as the lack of information on the potential effects of other members of the care team, Deglurkar acknowledged.

'Some Underappreciated Phenomena'

"There has been a lot said about patient and surgeon sociocultural aspects, structural sexism, unconscious bias, and potential communication styles based on surgeon and patient gender concordance or nonconcordance that could potentially affect the decision-making by referring physicians for elective cases," she said. "But if our findings were actually causal, these results suggest that increasing gender diversity in the surgeon workforce has the potential to improve the quality of surgeon care and patient outcomes."

Deglurkar said she would be pursuing a larger study encompassing the entire United Kingdom to look at the effects of patient-surgeon gender concordance on CABG outcomes. "I think there [are] some underappreciated phenomena," she said.

“Patients can't always choose their surgeons. But when you have data that is lacking and when you have publications like these, there will be concerns by female patients who are undergoing surgery,” Deglurkar stressed. “What is definitely the truth in all these discussions is that there is an eminent paucity of female surgeons globally.”

> **There is an eminent paucity of female surgeons globally.**Indu Deglurkar

Session co-chair Jennifer Lawton, MD (Johns Hopkins School of Medicine, Baltimore, MD), estimated that 5-7% of US cardiothoracic surgeons are female, while Deglurkar said that figure is around 9-10% in the UK.

Questioning the mechanism at play, Stephen Fremes, MD (University of Toronto, Canada), who also served as session co-chair, asked whether gender is the only driver or if age and racial/ethnic concordance might also be contributing.

Deglurkar said this remains a question that needs “deep reflection,” but noted that “if it was a discordance issue, then when female surgeons are operating on male patients, there should be some discordance. That doesn't seem to show up.”

What also needs further thought is why female patients undergoing CABG consistently have higher short-term mortality compared with male patients. “We know that women are less likely to receive arterial grafts than men, at least in the US, and they're also less likely to get complete revascularization,” she said. “But those affect long-term outcomes. Maybe we're missing something in the short term.”

Notably, Deglurkar warned against making statements like: “female surgeons are much better than male surgeons, or any nonsensical judgement.”

“I think a lot of things are needed before you can make interpretations completely pertaining to the gender of the surgeon or the patient,” she stressed.

In the meantime, Lawton made a suggestion to help reduce some potential gender-based bias in cardiac surgery. “Perhaps in a heart team discussion, you may discuss a patient as a 55-year-old patient and see what the consensus of treatment is, rather than saying woman [or] man,” she said.

Audience member Diana Reser, MD, PhD (HerzKlinik Hirslanden, Zurich, Switzerland), agreed the impact of gender concordance is “a very hot topic.” Still, “it's really important not to fight against each other—male and female surgeons or doctors,” she cautioned.

12.Exercise effects on maternal vascular health and blood pressure during pregnancy and postpartum: a systematic review and meta-analysis

Abstract

Aims

This systematic review aimed to assess the effects of exercise training during pregnancy and the postpartum period on maternal vascular health and blood pressure (BP).

Methods and results

The outcome of interest was pulse wave velocity (PWV), flow-mediated dilation (FMD), and BP from pregnancy to 1-year postpartum. Five databases, including Ovid MEDLINE, EMBASE, CINAHL, Web of Science, and Cochrane Library, were systematically searched from inception to August 2023. Studies of randomized controlled trials (RCTs) comparing the effects of prenatal or postpartum exercise to a non-exercise control group were included. The risk of bias and the certainty of evidence were assessed. Random-effects meta-analyses and sensitivity analyses were conducted. In total, 20 RCTs involving 1221 women were included. Exercise training, initiated from Week 8 during gestation or between 6 and 14 weeks after delivery, with the programme lasting for a minimum of 4 weeks up to 6 months, showed

no significant impact on PWV and FMD. However, it resulted in a significant reduction in systolic BP (SBP) [mean difference (MD): −4.37 mmHg; 95% confidence interval (CI): −7.48 to −1.26; *P* = 0.006] and diastolic BP (DBP) (MD: −2.94 mmHg; 95% CI: −5.17 to −0.71; *P* = 0.01) with very low certainty. Subgroup analyses revealed consistent trends across different gestational stages, types of exercise, weekly exercise times, and training periods.

Conclusion

Exercise training during pregnancy and the postpartum period demonstrates a favourable effect on reducing maternal BP. However, further investigations with rigorous methodologies and larger sample sizes are needed to strengthen these conclusions.

13.Large-Scale Proteomics in Early Pregnancy and HDP

IMPORTANCE

There is no consensus regarding the best method for prediction of hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia.

OBJECTIVE

To determine predictive ability in early pregnancy of large-scale proteomics for prediction of HDP.

DESIGN, SETTING, AND PARTICIPANTS

This was a nested case-control study, conducted in 2022 to 2023, using clinical data and plasma samples collected between 2010 and 2013 during the first trimester, with follow-up until pregnancy outcome. This multicenter observational study took place at 8 academic medical centers in the US. Nulliparous individuals during first-trimester clinical visits were included. Participants with HDP were selected as cases; controls were selected from those who delivered at or after 37 weeks without any HDP, preterm birth, or

small-for-gestational-age infant. Age, self-reported race and ethnicity, body mass index, diabetes, health insurance, and fetal sex were available covariates.

EXPOSURES

Proteomics using an aptamer-based assay that included 6481 unique human proteins was performed on stored plasma. Covariates were used in predictive models.

MAIN OUTCOMES AND MEASURES

Prediction models were developed using the elastic net, and analyses were performed on a randomly partitioned training dataset comprising 80% of study participants, with the remaining 20% used as an independent testing dataset. Primary measure of predictive performance was area under the receiver operating characteristic curve (AUC).

RESULTS

This study included 753 HDP cases and 1097 controls with a mean (SD) age of 26.9 (5.5) years. Maternal race and ethnicity were 51 Asian (2.8%), 275 non-Hispanic Black (14.9%), 275 Hispanic (14.9%), 1161 non-Hispanic White (62.8%), and 88 recorded as other (4.8%), which included those who did not identify according to these designations. The elastic net model, allowing for forced inclusion of prespecified covariates, was used to adjust protein-based models for clinical and demographic variables. Under this approach, no proteins were selected to augment the clinical and demographic covariates. The predictive performance of the resulting model was modest, with a training set AUC of 0.64 (95% CI, 0.61-0.67) and a test set AUC of 0.62 (95% CI, 0.56-0.68). Further adjustment for study site yielded only minimal changes in AUCs.

CONCLUSIONS AND RELEVANCE

In this case-control study with detailed clinical data and stored plasma samples available in the first trimester, an aptamer-based proteomics panel did not meaningfully add to predictive utility over and above clinical and demographic factors that are routinely available.

14. Inflammation, Cholesterol, Lp(a) Levels, and 30-Year Cardiovascular Outcomes in Women

BACKGROUND

High-sensitivity C-reactive protein (CRP), low-density lipoprotein (LDL) cholesterol, and lipoprotein(a) levels contribute to 5-year and 10-year predictions of cardiovascular risk and represent distinct pathways for pharmacologic intervention. More information about the usefulness of these biomarkers for predicting cardiovascular risk over longer periods of time in women is needed because early-life intervention represents an important risk-reduction method.

METHODS

We measured high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels at baseline in 27,939 initially healthy U.S. women who were subsequently followed for 30 years. The primary end point was a first major adverse cardiovascular event, which was a composite of myocardial infarction, coronary revascularization, stroke, or death from cardiovascular causes. We calculated the adjusted hazard ratios and 95% confidence intervals across quintiles of each biomarker, along with 30-year cumulative incidence curves adjusted for age and competing risks.

RESULTS

The mean age of the participants at baseline was 54.7 years. During the 30-year follow-up, 3662 first major cardiovascular events occurred.

Quintiles of increasing baseline levels of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) all predicted 30-year risks. Covariable-adjusted hazard ratios for the primary end point in a comparison of the top with the bottom quintile were 1.70 (95% confidence interval [CI], 1.52 to 1.90) for high-sensitivity CRP, 1.36 (95% CI, 1.23 to 1.52) for LDL cholesterol, and 1.33 (95% CI, 1.21 to 1.47) for lipoprotein(a). Findings for coronary heart disease and stroke appeared to be consistent with those for the primary end point. Each biomarker showed independent contributions to overall risk. The greatest spread for risk was obtained in models that incorporated all three biomarkers.

CONCLUSIONS

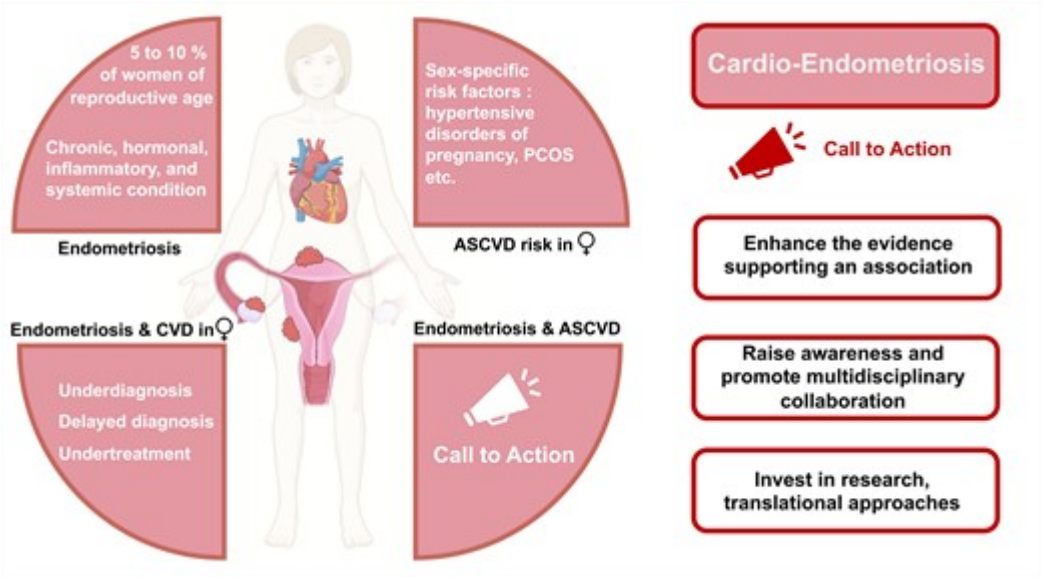
A single combined measure of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels among initially healthy U.S. women was predictive of incident cardiovascular events during a 30-year period. These data support efforts to extend strategies for the primary prevention of atherosclerotic events beyond traditional 10-year estimates of risk.

15.Fostering cardio-endometriosis: a call to action for a comprehensive understanding of cardiovascular disease in endometriosis

Abstract

Recently, a growing body of evidence has highlighted a concerning link between endometriosis and cardiovascular disease. Endometriosis, a chronic, inflammatory, hormone-dependent condition affecting 5–10% of reproductive-aged women worldwide, has long been associated with reproductive and gynaecological consequences. However, emerging research has suggested that it may also contribute to adverse cardiovascular outcomes. This paper aims to shed light on the importance of recognizing cardio-endometriosis as a new and

developing sphere of research in the field of cardiology, thereby urging the medical community to address this pressing issue.



Graphical Abstract

Endometriosis, Cardiology, Women's heath, Cardiovascular research, Sex specific

Topic:

- cardiovascular diseases
- endometriosis
- cardiovascular system

Issue Section:

Clinical Practice > Gender-Specific Conditions

See the editorial comment for this article 'Women's cardiovascular health prevention: are we ready to change the road?', by S. Castelvecchio and R.E. Nappi, https://doi.org/10.1093/eurjpc/zwae115.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in both women and men.1,2 As its incidence continues to rise, so does the economic burden, which was an estimated €77 billion for coronary heart disease and €76 billion for stroke in the European

Union countries in 2021.3 The most rapid relative increase in ASCVD mortality is occurring among middle-aged women (aged 45–64 years),1,2 highlighting this demographic as a noteworthy high-risk group deserving special attention.

While men and women share traditional risk factors (e.g. smoking and diabetes), recent advances have emphasized sex-specific factors, including polycystic ovary syndrome (PCOS),4 hypertensive disorders of pregnancy,5–7 and primary ovarian insufficiency,8,9 which are associated with a greater risk of cardiovascular disease (CVD), specifically ASCVD. Endometriosis is a common medical condition that affects ~ 5–10% of reproductive-aged women worldwide10 (*Figure 1*). Responsible for pelvic pain and infertility, endometriosis has a significant impact on quality of life and is characterized by the presence of endometrial-like tissue outside the uterus, which leads to inflammation, scarring, and adhesion formation. These pathological processes can contribute to the release of pro-inflammatory molecules, cytokines, and growth factors that may have systemic effects, including on the cardiovascular system.11–13 Recent studies have demonstrated an association between endometriosis and an increased risk of adverse cardiovascular outcomes, particularly atherosclerosis and ASCVD.14–19 While the precise mechanisms in this association are still under investigation, chronic inflammation, oxidative stress, hormonal imbalances, and vascular dysfunction may play crucial roles.13

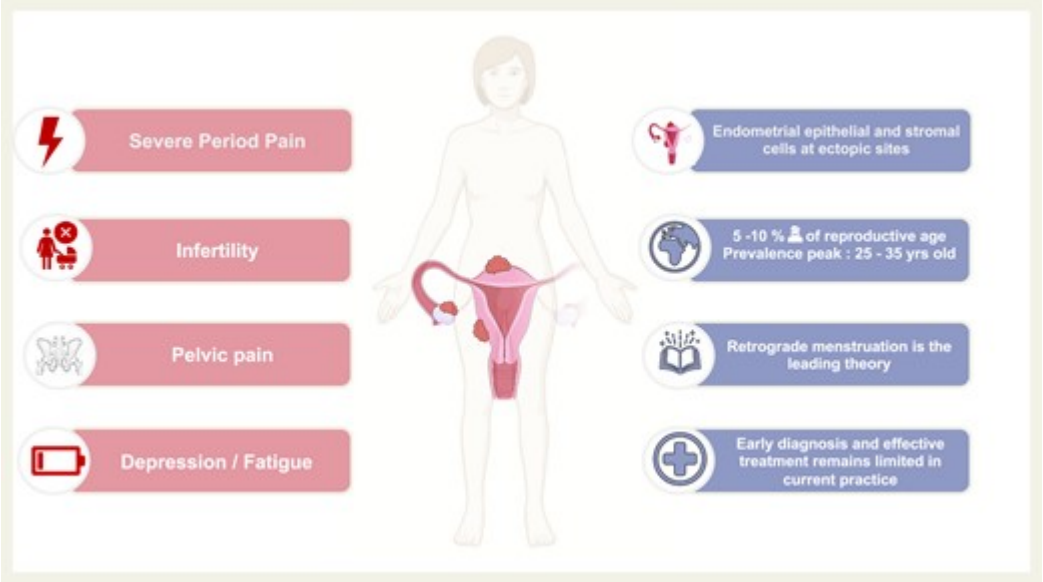


Figure 1

Endometriosis: key points.

This manuscript combines expertise from diverse disciplines, including cardiology, gynaecology, translational science, clinical trials, epidemiology, biostatistics, and clinical medicine. These experts deliberated upon a spectrum of evidence and directions that warrant immediate and future attention in the context of endometriosis and CVD. Consequently, the positions and recommendations presented here reflect the viewpoints and suggestions of the participants and do not constitute the official policy or priorities endorsed by any international society. Rather, this position statement serves as a call to action to enhance ASCVD prevention strategies in women with endometriosis. It emphasizes the importance of empowering both cardiologists and gynaecologists with knowledge regarding the potential cardiovascular implications of endometriosis. Furthermore, it underscores the necessity for detailed research aimed at comprehending the underlying mechanisms connecting endometriosis and ASCVD. The paper discusses whether the current body of evidence is sufficient to warrant routine ASCVD risk evaluation in individuals with endometriosis and whether endometriosis screening should be considered for young female patients presenting with

ASCVD events. Given the limited evidence concerning the intersection of CVD in general that include heart failure, arrhythmias, venous thromboembolic events, and endometriosis, our focus has primarily been on the most studied aspect: ASCVD.

Understanding cardio-endometriosis

Recent guidelines and position papers have provided limited commentary on the correlation between endometriosis and adverse cardiovascular outcomes,20–22 even though recent studies have demonstrated an association between endometriosis and an increased risk of ASCVD, particularly coronary heart disease and stroke (*Table 1*). This cautious stance of current expert panels concerning the association between endometriosis and ASCVD is largely due to the limited level of evidence, which has several cofounders to be considered. First, the current evidence generally relies on observational cohorts with self-completed questionnaires or data extracted from electronic health records. Those study designs possess inherent drawbacks that affect the reliability and applicability of the evidence they generate. Additionally, inhomogeneity in the definition of both endometriosis (e.g. surgical confirmation and clinical suspicion) and cardiovascular endpoints (e.g. acute myocardial infarction and coronary stenosis) limit the comparison and generalization of these data. Finally, and most significantly, hormonal status either due to oophorectomy after surgery or the role of hormonal treatment strategies for endometriosis [including combined oral contraceptives, progestins, and gonadotrophin-releasing hormone (GnRH) analogues] may worsen patients' lipid and cardiovascular risk profiles, thereby acting as a major cofounder (*Table 1*).

Table 1

Association between endometriosis and atherosclerotic cardiovascular disease

First author, year	Study setting	Population	Adverse cardiovascular outcomes	Limitations
Mu *et al.*14	Cohort study	Nurses' Health Study II (NHSII) : 4244 women with laparoscopically confirmed endometriosis and 91 554 control women	Myocardial infarction (RR 1.52, 95% CI 1.17–1.98); angiographically confirmed angina (RR 1.91, 95% CI 1.59–2.29); CABG/coronary angioplasty procedure/stent (RR 1.35, 95% CI 1.08–1.69)	42% of the association between endometriosis and CAD could be explained by greater frequency of hysterectomy/oophorectomy and earlier age at surgery following endometriosis diagnosis
				Laparoscopically confirmed endometriosis: severe cases
				Self-completed questionnaire
				Specific population: nurses with greater knowledge of access to medical care
				Unexposed group may include asymptomatic endometriosis or symptomatic without confirmatory diagnosis
Okoth *et al.*15	Cohort study	UK cohort: 56 090 women	Composite outcome: IHD,	No information about surgically confirmed cases

First author, year	Study setting	Population	Adverse cardiovascular outcomes	Limitations
		with endometriosis and 223 669 matched control women	HF, cerebrovascular disease (aHR 1.24, 95% CI 1.13–1.37); IHD (aHR 1.40, 95% CI 1.22–1.61); cerebrovascular disease (aHR 1.19, 95% CI 1.04–1.36); arrhythmia (aHR 1.26, 95% CI 1.11–1.43)	vs. other methods Electronic health records Asymptomatic cases in the unexposed cohort
Farland *et al.*16	Cohort study	NHSII: 5244 women with laparoscopically confirmed endometriosis and 106 812 control women	Stroke (aHR 1.34, 95% CI 1.10–1.62)	The association between endometriosis and stroke was partially mediated by occurrence of hysterectomy or oophorectomy (percent mediated: 39%), postmenopausal hormone therapy (15.5%), age at menopause <45 (12.3%), history of hypertension (8.4%), or history of high cholesterol (4.9%) Laparoscopically confirmed

First author, year	Study setting	Population	Adverse cardiovascular outcomes	Limitations
				endometriosis: severe cases
				Self-completed questionnaire
				Specific population: nurses with greater knowledge of access to medical care
				Unexposed group may include asymptomatic endometriosis or symptomatic without confirmatory diagnosis
Chiang *et al.*17	Cohort study	17 543 women with endometriosis and 70 172 matched control women	Composite outcome: myocardial infarction, HF, stroke (aHR 1.17, 95% CI 1.05–1.29)	No details regarding lifestyle and risk factors (e/G smoking, BMI, hormonal treatments, etc.)
				Electronic health records
Farland *et al.*18	Cohort study	NHSII: 8611 women with infertility and 103 729 control women	Greater risk of CHD in women with infertility [HR 1.13 (95% CI 1.01–1.26)]. Elevated risk of	Self-completed questionnaire and diagnosis of infertility
				Specific population: nurses with greater knowledge of access to medical care

First author, year	Study setting	Population	Adverse cardiovascular outcomes	Limitations
			CHD was observed among women with infertility and endometriosis (HR 1.42, 95% CI 1.09–1.85)	Women without infertility group may include asymptomatic or symptomatic women with endometriosis

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CAD, Coronary Artery Disease; CHD, coronary heart disease; HF, Heart Failure; IHD, ischemic Heart Disease ; OR, odds ratio; RR, relative risk.

However, despite these inherent limitations and the nuanced nature of the available evidence, this panel believes it is reasonable to emphasize the potential acceleration of cardiovascular risk in women with endometriosis. Through exploring the interaction between endometriosis and CVD (referred to as cardio-endometriosis), the panel underscores the imperative for additional, rigorous research aimed at identifying causality and correlations between endometriosis, stratified by severity and stages, and a broad spectrum of adverse cardiovascular outcomes. Furthermore, comprehending the underlying mechanisms linking endometriosis and CVD is essential. These initial steps are essential to establish a solid background linking endometriosis and ASCVD, as well as to further develop strategies for the applicability of cardiovascular primary prevention in women with endometriosis and how to specifically target the link between endometriosis and cardiovascular risk (*Figure 2*).

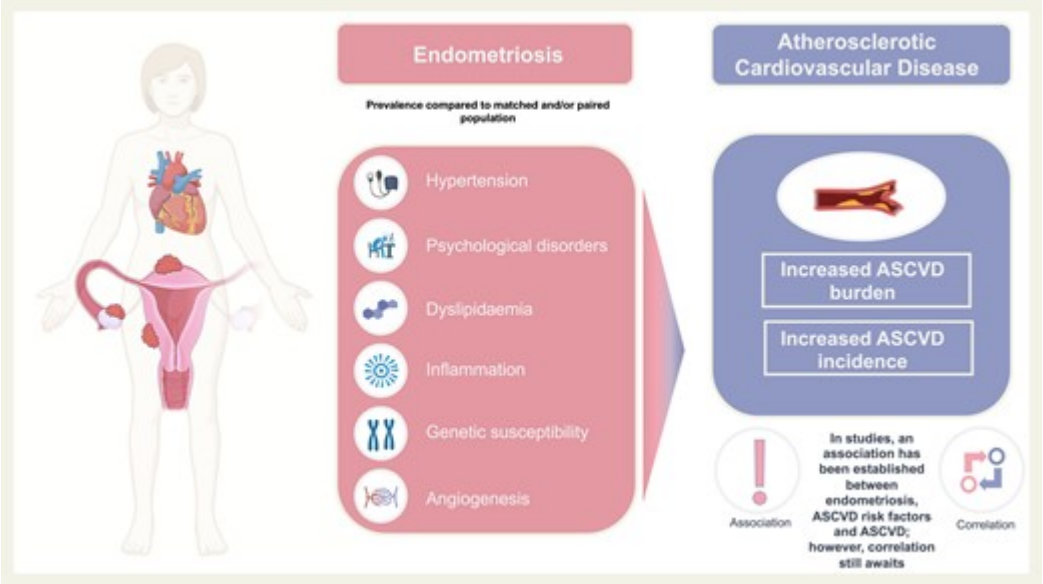


Figure 2

Epidemiological insights into the association between endometriosis and atherosclerotic cardiovascular disease. Endometriosis has been associated with an increased risk of atherosclerotic cardiovascular disease, a greater burden of atherosclerotic cardiovascular disease, and increased atherosclerotic cardiovascular disease morbidity in dedicated studies. While an association has been established in studies, the determination of whether endometriosis by itself drives atherosclerotic cardiovascular disease still awaits clarification. ASCVD, atherosclerotic cardiovascular disease.

Enhancing research intensity: approaches for rapid advancement in the field of cardio-endometriosis

Future research should concentrate on both epidemiological cohorts and data aimed at establishing a definite causality between endometriosis and adverse cardiovascular outcomes. Additionally, research efforts should encompass preclinical and translational evidence designed to enhance our understanding of the molecular pathways involved in an increased risk of CVD in individuals with endometriosis. Finally, studies exploring how psychological and social factors, hormonal treatments, anti-inflammatory agents, and lifestyle

modifications influence cardio-endometriosis are needed to develop evidence-based therapeutic strategies. *Figure 3* provides a summary of the recommendations for future studies on cardio-endometriosis.

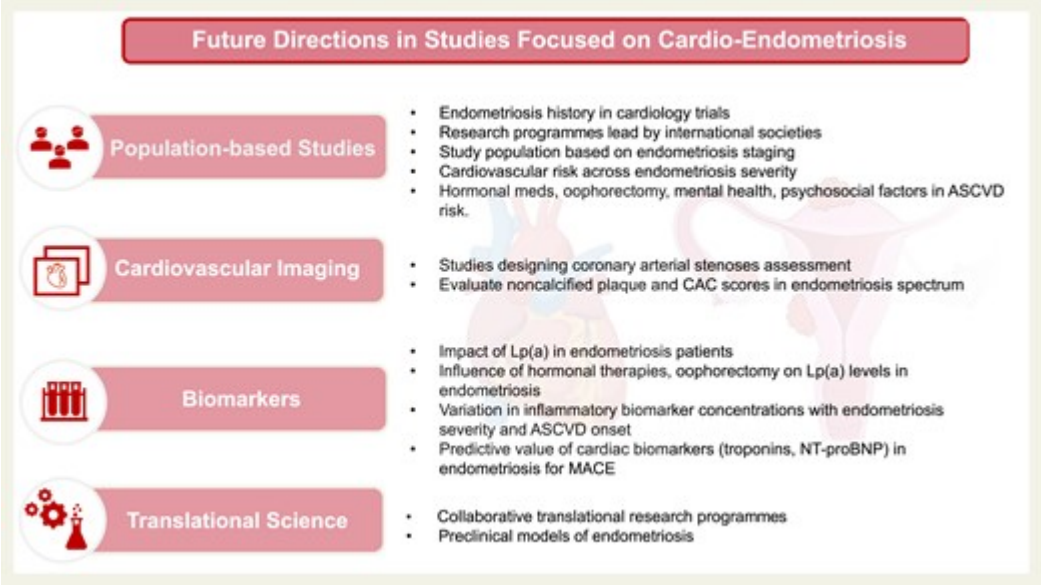


Figure 3

Future directions in studies focused on cardio-endometriosis. ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events.

Population-based cohorts

Due to a lack of endometriosis history in most existing cohorts and clinical trials in cardiology, particularly coronary artery disease (CAD), examining whether there is a difference in the pathophysiologic development of atherosclerosis in women with endometriosis has been difficult. The current understanding of the association between endometriosis and CVD is primarily based on population-based cohorts, predominantly derived from the Nurses' Health Study II (NHSII), the results of which are published in three studies14,16,18 (*Table 1*). The NHSII has several strengths, including its prospective design, large sample size, confirmation of endometriosis via laparoscopy, and 30 years of longitudinal follow-up.

However, notable limitations must also be considered. The study exclusively focused on presumed severe and symptomatic cases of endometriosis, as indicated by the inclusion of laparoscopically confirmed endometriosis. Further, the studied population comprised US healthcare professionals with greater access to medical care. Last, the unexposed group in these studies may have included individuals with asymptomatic endometriosis or those with symptoms but lacking a confirmatory diagnosis. These factors collectively limit the generalizability of the evidence. Moreover, all population-based cohort studies in endometriosis acknowledge a fundamental limitation: the potential confounding effects of treatments for endometriosis, such as hormonal medications and oophorectomy, which may modify the risk of ASCVD. Disentangling the relative contributions of chronological exposure to endometriosis and oophorectomy to cardiovascular risk is challenging. Surgically induced menopause increases the risk of adverse cardiometabolic changes, and data from longitudinal studies are likely to provide valuable insights but are currently unavailable in women with endometriosis. Likewise, mental and psychosocial risk factors are of paramount significance in endometriosis; these factors have long been recognized for their intricate interplay with the risk of developing CAD and for their potential to worsen clinical outcomes.23,24 However, the current population-based cohorts have yet to investigate these influential confounders comprehensively.

The advancement of new, non-invasive diagnostic essays, such as saliva-based micro-ribonucleic acid (miRNA) signature for endometriosis,25 will ease the design of studied aimed at elucidating the incidence of endometriosis for young female patients presenting with ASCVD events. Future studies should replicate the prior successes observed in epidemiological cardiology initiatives. For example, the FAST-MI programme, which involved 1-month surveys of patients admitted to hospitals in France for acute myocardial infarction, has been ongoing since 2005.26 In line with its design,

implementing a 1-month programme for screening the history of endometriosis in all cardiology departments across multiple institutions would be worthwhile. This could occur in March, which is Endometriosis Awareness Month. The ethical implications surrounding awareness of endometriosis status will undoubtedly pose significant challenges in designing a trial aimed at assessing the incidence of endometriosis in a female population with significant cardiovascular outcomes (e.g. stroke, Non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI).

International initiatives and multicentre registries may provide novel insights leading to improved knowledge. Research programmes supported by international societies, such as the European Society of Cardiology (ESC), the American Heart Association (AHA), the European American Society of Gynecology, and the American College of Obstetricians and Gynecologists (ACOG), are likely to garner attention and facilitate recruitment.

Finally, endometriosis has been associated with a higher risk of adverse pregnancy outcomes, particularly preeclampsia,27,28 which has been extensively studied for cardiovascular risk. The latest evidence highlights a striking increase in the risk of ASCVD in women with preeclampsia.5,7 Women with preeclampsia had a higher likelihood of experiencing heart attacks and strokes within just 7 years of delivery.7 These risks remain elevated for >20 years, as shown in a study involving >1 million pregnant women.5 Incorporating women with endometriosis and adverse pregnancy outcomes into CVD risk calculators might bring about a significant transformation in the classification of diseases and the approach to preventive care.

Staging of endometriosis

The two most commonly used endometriosis-staging systems are the revised American Society for Reproductive Medicine (rASRM) staging system and the recently updated ENZIAN classification. The rASRM system is based on a point scale that considers the location, extent, and severity of endometriosis lesions. It assigns a score ranging from I (minimal) to IV (severe) based on visual assessment of endometriosis lesions during laparoscopic surgery.29 The recently updated ENZIAN classification extends the previous ENZIAN score to incorporate all types of endometriosis.30 The use of gold standard staging systems in future cardio-endometriosis studies is mandatory to enable comparative analysis, confirm the association between endometriosis and adverse cardiovascular outcomes, evaluate a potential gradation of risk with endometriosis severity, and define the targeted population for future clinical trials aimed at reducing CVD risk (either in primary or secondary prevention). Whether cardiovascular risk increases with the severity of endometriosis, as it is the case with other chronic inflammatory conditions, must still be demonstrated.31,32

Cardiovascular imaging in endometriosis

The design of cardiovascular imaging studies is meaningful for establishing a robust connection between endometriosis and ASCVD. Coronary computed tomography (CT) angiography is a highly accurate, non-invasive diagnostic test that can be used to assess the presence of obstructive epicardial coronary arterial disease with high sensitivity and negative predictive value. Similarly, the coronary artery calcium (CAC) score has demonstrated a positive correlation with the evaluation of future cardiovascular risk.33,34

Evaluating the presence, severity, and extent of atherosclerotic coronary arterial stenoses, as well as the presence of non-calcified plaque, and determining the CAC score across a wide spectrum of

women with endometriosis, ranging from asymptomatic to severe cases, will likely contribute to the advancement of knowledge and provide insights into the heightened risk of asymptomatic CAD in individuals with endometriosis. The use of this imaging prism has proven to be beneficial in examining other sex-specific factors associated with an increased risk of CVD in women, such as PCOS35 and hypertensive disorders of pregnancy.6,36,37 Sederholm Lawesson *et al.*6 showed an increased prevalence of any coronary atherosclerosis in women with a history of adverse pregnancy outcomes compared to those without. Furthermore, they provide evidence that, in women with a history of preeclampsia who had <5% predicted disease risk according to the SCORE2 system, the burden of significant stenosis was similar to women who had no adverse pregnancy outcome history and intermediate predicted cardiovascular risk. This finding confirmed that women with a history of preeclampsia could benefit from reclassification at a higher level of risk. Similar imaging studies could implement knowledge of a potentially accelerated vascular age in endometriosis.

Biomarkers linking endometriosis and adverse cardiovascular outcomes

The availability of reliable non-invasive biomarkers for the diagnosis, prediction of response to treatment, and monitoring of endometriosis progression remains a major unmet need.38 Furthermore, no robust biomarker to date has linked endometriosis with subclinical atherosclerosis.

Lipoprotein(a)

Convincing evidence supports a causal relationship between lipoprotein(a) [Lp(a)] and ASCVD. Recent guidelines acknowledge that Lp(a) concentrations increase in women during pregnancy, as well as from the onset of menopause.39 High Lp(a) levels are more common in

women than in men after the age of 50, which may impact ASCVD risk. However, evidence regarding an association between LP(a) and endometriosis remains scarce.40,41 As the interplay between Lp(a) concentration and low-grade inflammation and the time course of inflammatory disease remains controversial,42,43 as is the effect of hormones on Lp(a) concentrations,44 assessing Lp(a) over the time course of endometriosis and in conjunction with exogenous factors, such as hormonal therapies, is an area of future research.

Inflammatory biomarkers

Several studies have documented an association between inflammatory disorders,45–47 inflammatory markers such as high-sensitivity C-reactive protein, white blood cell count, fibrinogen and cytokines, and ASCVD, with a gradation of risk across the measured ranges.48–50 Defined as a systemic and inflammatory disease, endometriosis is characterized by elevated levels of inflammatory biomarkers in both the serum and peritoneal environment. Low-grade inflammation is likely at the root of endometriosis pathogenesis leading to endothelial dysfunction, a surrogate marker of CV risk. Therefore, a comprehensive set of screening tests targeting biological markers for disease activity (e.g. high-sensitivity C-reactive protein, GDF15, TNF-α, IL-10, IL-6, MCP-1, and prostaglandins) may enhance the understanding of endometriosis.

Cardiac biomarkers

The predictive value of existing biomarkers indicating subclinical myocardial injury and stress, such as cardiac troponins and the N-terminal prohormone of brain natriuretic peptide (NT-proBNP), has not been investigated within the context of endometriosis where they might forecast the risk of major adverse cardiovascular events.

Inherited risk, genetic analysis, and polygenic risk scores

While the pathogenesis of endometriosis is not fully understood, genetic factors have been acknowledged to play a crucial role in its development. Recent advances in biotechnology and high-throughput sequencing platforms, including whole-genome sequencing (WGS), whole-exome sequencing (WES), and single nucleotide polymorphism (SNP) array with derivation of a polygenic risk score (PRS), have described a shared genetic susceptibility between endometriosis and atherosclerosis.51–55 CDKN2B-AS variants on chromosome 9p21 have been linked to endometriosis susceptibility, also associated with atherosclerotic conditions such as intracranial and abdominal aortic aneurysms, peripheral vascular disease, diabetes, and strokes.51,52 Chronic inflammation ties atherosclerosis and endometriosis, emphasizing the 7q22 locus' association with CAD and endometriosis.53 Genome-wide association studies (GWAS) and SNPs may unveil increased genetic susceptibility to CVD in women, potentially overlapping with endometriosis. CDKN2B-AS transcript levels correlate with atherosclerosis severity, and the rs10965235 SNP in CDKN2B-AS significantly links to endometriosis.54 Thus, genetic contributions to endometriosis and their potential interplay with CVD hold potential for promising diagnostics.

Basic and translational science in endometriosis

Endometriosis is a chronic, inflammatory, hormone-dependent condition that presents the challenge of modelling a multifactorial disease of unknown aetiology in preclinical models.56–58 Preclinical development relies on the use of appropriate animal models that accurately reflect human disease. However, spontaneous endometriosis occurs only in humans and non-human primates. Thus, the primate model has long been used for studying the pathogenesis and potential treatment for endometriosis. Additionally, cost-effective rodent models of endometriosis have been developed using either heterologous or autologous models and xenotransplantation of human endometrium into immunodeficient mouse models.59–61 Investigating

the co-culture of endometriotic cells with various cell types of significance in endometriosis has recently yielded valuable insights into the interplay between these cells and their microenvironment.59 All these model systems present benefits and limitations and do not fully mimic the architecture and function of endometriosis. However, due to the rapid growth of artificial intelligence (AI), models may be created in the future that can extract data patterns and serve as inputs for developing preclinical models with qualities and accuracies superior to those of conventional methods and current tools used in research standards.

Endometriosis is characterized by a pro-inflammatory, pro-angiogenic, and aberrant immune-endocrine environment, all of which are intimately involved in the pathophysiology, growth, and survival of endometriotic lesions. The scope of future research should first address the molecular pathways likely to favour atherosclerosis in endometriosis. Accordingly, current research should focus on the following:

A better understanding of the underlying biology that links endometriosis to endothelial dysfunction, a surrogate marker of atherosclerosis. Past studies have indeed demonstrated enhanced endothelial dysfunction in endometriosis patients62 and a regression of endothelial dysfunction at 2-year follow-up in patients with endometriosis after surgical treatment.63 In this prospect, translational studies aimed at defining how endometriosis cell-derived secretory factors impact vascular endothelial function would provide a first strong insight linking endometriosis and atherosclerosis.

The contribution of endometriosis to magnitude, effect, and temporal/cyclic changes of low-grade inflammation and hormonal load on atherosclerosis.

Evaluation potential differences between stages, as well as the specific topography of endometrial deposits in terms of their ability to favour an atherosclerosis response.

Defining the molecular basis aimed at disentangling the relative contributions of chronological exposure to endometriosis and treatment effects (oophorectomy, hormonal therapy) to cardiovascular risk.

Defining the molecular basis that may link the pathophysiology of heart failure and endometriosis, as the immune system is intimately involved in both processes.

Define molecular targets accessible to pharmacological regulation.

Exploring the eicosanoid signalling pathways holds promise. Eicosanoids initiate and propagate diverse signalling cascades and have been recognized as key players in both endometriosis64,65 and CVD.66 Oestradiol increases prostaglandin E2 production in a feed-forward mechanism by activating cyclooxygenase (COX)-2 within uterine endothelial cells. COX-2 regulates the survival, migration, and invasion of human endometriotis.67 As such, Non-steroidal anti-inflammatory drugs (NSAID) therapy stands as a first-line therapy for endometriosis-associated pain. The role of aspirin in cardiovascular prevention and the potential implications of NSAID treatment regarding the risk of cardiovascular and bleeding events are topics that merit further investigation in future studies. Furthermore, the roles of eicosanoids in activating molecular cascades within the peritoneal cavity, coupled with their potential concurrent systemic effects on cardiovascular tissues, will offer deeper insights into the cardio-endometriosis relationship. A more profound comprehension of this axis and its mechanisms may even pave the way for the development of targeted pharmaceutical approaches.

Fertility therapy

Assisted reproductive therapies encompass a wide spectrum of interventions, ranging from ovarian stimulation and induction drugs to intrauterine insemination and *in vitro* fertilization (IVF). In a meta-analysis of 41 910 women who received fertility therapy and 1 400 202 women who did not, Dayan *et al.*68 found no increased risk of a cardiac event. The authors acknowledge that the small number of studies (only six observational studies included) and the heterogeneity must be accounted for in the analysis of these results. A similar observation by Udell *et al.*69 found that successful fertility therapy was not associated with an increased risk of CVD during a median follow-up of 9.7 years. These finding should be tempered by an increased incidence of adverse pregnancy outcomes (e.g. preeclampsia and gestational diabetes) observed in patients treated with fertility therapy.68 These features are associated and may serve as surrogate markers indicating long-term increased cardiovascular risks. Moreover, most of the women evaluated in these reports were young, and the follow-up was of limited extent. Studies with longer follow-up periods, specifically designed for the field of endometriosis, are imperative to explore the potential influence of fertility treatments on cardiovascular events.

Cardiovascular risks factors, early intervention, and management of endometriosis

In endometriosis, women may experience a worsening lipid profile, potentially contributing to accelerating ASCVD risk.70–73 However, the current body of evidence is insufficient to advocate for additional screening or the early implementation of aggressive management of cardiovascular risk factors and intensified primary prevention in patients with endometriosis. Therefore, this panel emphasizes the importance of early assessment of cardiovascular risk and prompt treatment of dyslipidaemia in women, particularly those with familial

hypercholesterolaemia. Based on current evidence, this panel does not recommend any additional interventions beyond the existing guidelines.74,75

Heightened awareness and collaboration

One of the significant challenges in addressing cardio-endometriosis lies in the underdiagnosis and misdiagnosis of endometriosis. As the symptoms of the disease are non-specific, many women may go undiagnosed for years, delaying the identification and management of modifiable cardiovascular risk factors earlier in these women. Additionally, the lack of awareness among cardiologists and gynaecologists regarding the link between endometriosis and cardiovascular health further compounds the problem. Recent media footage on endometriosis including the fact it affects 5–10% of reproductive-aged women; the development of endometriosis expert centres; the prominent role of patient associations; and the advancement of new, non-invasive diagnostic essays25 and AI tools76 will likely offer new perspectives in the near future. This panel urges the medical community to collaborate across specialties, fostering a multidisciplinary approach that involves gynaecologists, cardiologists, and researchers. The role of gynaecologists is essential in addressing CV health in young women. Their unique position as primary healthcare providers for many young women allows for early intervention and management of modifiable CV risk factors. Being present in the early stages of women's lives, their voices are essential to raise awareness of CV disease and ensure comprehensive care, including proactive measures to address CV risk factors beyond the scope of endometriosis alone. Increased awareness of the interaction between CVD and endometriosis, along with its potential implications in both fields, will facilitate earlier diagnosis and appropriate management. Moreover, empowering both cardiologists and gynaecologists with knowledge about the potential cardiovascular

implications of endometriosis will foster proactive care and lead to better-informed decisions about women's health.

Conclusions

Cardio-endometriosis is an emerging area of research with significant implications for both cardiologists and gynaecologists. Addressing the link between endometriosis and adverse cardiovascular outcomes requires a collaborative effort, increased research, and tailored studies. Indeed, further studies to understand the effects of endometriosis on atherosclerosis development and progression are needed. By recognizing and acting upon this call for action, the medical community can improve the lives of countless women affected by this challenging condition.

16.Managing menopause after cancer

Summary

Globally, 9 million women are diagnosed with cancer each year. Breast cancer is the most commonly diagnosed cancer worldwide, followed by colorectal cancer in high-income countries and cervical cancer in low-income countries. Survival from cancer is improving and more women are experiencing long-term effects of cancer treatment, such as premature ovarian insufficiency or early menopause. Managing menopausal symptoms after cancer can be challenging, and more severe than at natural menopause. Menopausal symptoms can extend beyond hot flushes and night sweats (vasomotor symptoms). Treatment-induced symptoms might include sexual dysfunction and impairment of sleep, mood, and quality of life. In the long term, premature ovarian insufficiency might increase the risk of chronic conditions such as osteoporosis and cardiovascular disease. Diagnosing menopause after cancer can be challenging as

menopausal symptoms can overlap with other common symptoms in patients with cancer, such as fatigue and sexual dysfunction. Menopausal hormone therapy is an effective treatment for vasomotor symptoms and seems to be safe for many patients with cancer. When hormone therapy is contraindicated or avoided, emerging evidence supports the efficacy of non-pharmacological and non-hormonal treatments, although most evidence is based on women older than 50 years with breast cancer. Vaginal oestrogen seems safe for most patients with genitourinary symptoms, but there are few non-hormonal options. Many patients have inadequate centralised care for managing menopausal symptoms after cancer treatment, and more information is needed about cost-effective and patient-focused models of care for this growing population.

This is the fourth in a **Series** of four papers about menopause. All papers in the Series are available at www.thelancet.com/series/menopause-2024

Introduction

The average age at natural menopause is 51 years in high-income countries (HICs).1 A systematic review and meta-analysis in 2014 showed an earlier age at menopause in low-income and middle-income countries (LMICs) across Asia, India, Latin America, and the Middle East.2 Menopause is more likely to be premature (ie, occurring before age 40 years) or early (ie, at age 41–44 years) after cancer and burgeoning evidence indicates that young age at menopause can be a risk factor for chronic disease.3 A 2017 meta-analysis of 45 studies in female patients who had survived cancer found a median age at menopause of 44 years.4 Guidelines from the UK National Institute for Health and Care Excellence (NICE) recommend menopausal hormone therapy (MHT) for younger postmenopausal women without contraindications,5 but often the safety and efficacy of MHT after cancer is uncertain. Crucially, most patients who have troublesome menopausal symptoms after cancer do not have access to effective

treatments, even in HICs.6 This Series paper will address the prevention and management of menopausal symptoms after cancer, including evidence about health disparities if available.7

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in some instances, we have referred to "people" rather than "women" to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people. Evidence on menopause in gender-diverse people is scarce and this area needs more attention.8

17. Optimising health after early menopause

Summary

The typical age at menopause is 50–51 years in high-income countries. However, early menopause is common, with around 8% of women in high-income countries and 12% of women globally experiencing menopause between the ages of 40 years and 44 years. Menopause before age 40 years (premature ovarian insufficiency) affects an additional 2–4% of women. Both early menopause and premature ovarian insufficiency can herald an increased risk of chronic disease, including osteoporosis and cardiovascular disease. People who enter menopause at younger ages might also experience distress and feel less supported than those who reach menopause at the average age. Clinical practice guidelines are available for the diagnosis and

management of premature ovarian insufficiency, but there is a gap in clinical guidance for early menopause. We argue that instead of distinct age thresholds being applied, early menopause should be seen on a spectrum between premature ovarian insufficiency and menopause at the average age. This Series paper presents evidence for the short-term and long-term consequences of early menopause. We offer a practical framework for clinicians to guide diagnosis and management of early menopause, which considers the nature and severity of symptoms, age and medical history, and the individual's wishes and priorities to optimise their quality of life and short-term and long-term health. We conclude with recommendations for future research to address key gaps in the current evidence.

This is the second in a **Series** of four papers about menopause. All papers in the Series are available at www.thelancet.com/series/menopause-2024

Introduction

Menopause marks the permanent cessation of menstrual cycles, usually confirmed after 12 consecutive months of amenorrhoea. Natural menopause typically occurs at around age 50–51 years in high-income countries (HICs).1,2 In clinical practice, the onset of menstrual changes and menopausal symptoms generally indicates the start of perimenopause or menopausal transition. While the menopause is marked by the final menstrual period, symptoms can persist for years into the postmenopause.3 Early menopause is usually defined as occurring between the ages of 40 years and 44 years, whereas premature ovarian insufficiency indicates menopause before age 40 years. Both can be either spontaneous or iatrogenic, with iatrogenic causes including bilateral oophorectomy and chemotherapy or pelvic radiation treatment for cancer.

In this Series paper, we outline the evidence suggesting that both premature ovarian insufficiency and early menopause are linked with

increased risk of chronic conditions in later life, such as cardiovascular disease and osteoporosis, although data are generally scarce around early menopause. Similarly, although consensus guidance exists for diagnosing and managing premature ovarian insufficiency, no guidance is available for early menopause. Given the scarcity of specific evidence regarding the long-term health implications of early menopause, we argue that early menopause should be considered as being on a spectrum between premature ovarian insufficiency and the typical age of menopause. To prevent patients from falling through this gap in care, we offer a practical framework to guide diagnosis and management of early menopause and identify evidence-based approaches for individuals either with or at risk of early menopause to optimise their health and quality of life in the short and long term. This process has identified key evidence gaps for further research and areas where people with early menopause require greater support.

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in some instances, we have referred to “people” rather than “women” in order to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used “women” in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people.4

Search strategy and selection criteria

We conducted a review of published articles up to July, 2023, on the PubMed, Embase, Scopus, and Cochrane databases. The search was restricted to studies published in English with the following keywords

and medical subject heading terms in PubMed (MeSH) and Embase (Emtree): “menopause”; “premature menopause”; “premature ovarian insufficiency”; “early menopause”; “menopausal symptoms”; “vasomotor symptoms”; “menopausal hormone therapy”; “hormone therapy”; “hormone replacement therapy”; and “non-hormonal therapy”. For long-term health outcomes, we combined these terms with “chronic disease”, “non-communicable disease”, “osteoporosis”, “fracture”, “cardiovascular disease”, “heart disease”, “stroke”, “depression”, “dementia”, “cancer”, and “mortality”. We prioritised the most robust evidence from clinical trials, systematic reviews, meta-analyses, and pooled studies. We also reviewed guidelines and position statements from the period 2010–23 on menopause management.

18. Hypertension in Pregnancy: 5 Things Clinicians Should Know

Hypertension is a serious public health concern, and it is the primary risk factor for the first and fifth leading causes of death, both globally[1]and in the United States. In recent years, hypertension in pregnancy has increased notably.[2]

Hypertension in pregnancy encompasses chronic hypertension and pregnancy-associated hypertension, including gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia or eclampsia. Pregnancy-associated hypertension heightens cardiovascular risks for mothers and babies, both immediate and in the long term. These risks may be reduced through timely, effective hypertension management.

Healthcare teams can use the Hypertension in Pregnancy Change Package, which features ready-to-implement strategies, to improve detection and management and reduce complications related to uncontrolled hypertension during and following pregnancy.

Healthcare professionals are also invited to join the Hypertension in Pregnancy Action Forum, an opportunity for clinical, public health, and community-based partners to exchange best and promising practices, identify solutions to common obstacles, and share resources to improve hypertension management during and after pregnancy.

Here are five things healthcare teams should know:

1. A lower target blood pressure is safe and better for mom and baby.

On the basis of compelling findings from the Chronic Hypertension and Pregnancy (CHAP) randomized controlled trial, clinical guidance has been updated to recommend 140/90 mm Hg (rather than 160/110) as either the threshold to initiate treatment or as the upper limit target blood pressure for mild chronic hypertension in pregnancy.[3,4]

Hypertension in pregnancy is defined as two or more blood pressure readings of at least 140 mm Hg systolic or 90 mm Hg diastolic, measured 4 hours apart. Severe hypertension in pregnancy is defined as blood pressure of at least 160 mm Hg systolic or 110 mm Hg diastolic. For treatment purposes, severe hypertension can be diagnosed with measurements at least 15 minutes apart. Results from the CHAP trial found that women with chronic hypertension who were treated to a blood pressure target of < 140/90 mm Hg had better pregnancy outcomes than the control group, with no increase in births that were small for gestational age.[5]

2. Low-dose aspirin (81 mg) reduces preeclampsia and hypertension-related illness and death.

Most pregnancy-related deaths stemming from hypertension are preventable, with one California study suggesting that 60% of deaths

attributed to preeclampsia or eclampsia had a "good-to-strong chance of being prevented."[6] To help prevent preeclampsia and its complications, healthcare teams can develop a system to identify and treat pregnant women who can benefit from aspirin prophylaxis.

3. Healthcare teams play pivotal roles in helping ensure health equity.

Striking health disparities exist among different racial and ethnic groups. For instance, the prevalence of hypertension during delivery hospitalization is highest among non-Hispanic Black (20.9%) and American Indian and Alaska Native (16.4%) women.[2] By understanding risks based on data stratified by race/ethnicity, age, insurance status, preferred language, and other social drivers of health, teams can better identify and address care gaps and ensure equitable outcomes.

Trainings can help staff practice respectful and culturally safe communication; address communication needs, such as health literacy and language barriers; and understand family structures and cultural practices. The Hypertension in Pregnancy Change Package also includes tools for implicit-bias training and other recommended resources.

4. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) should not be used during pregnancy.

ACE inhibitors and ARBs are teratogenic or known to cause fetal abnormalities. Oral medications that are safe in pregnancy include labetalol, nifedipine (extended release), and methyldopa as first-line agents. Second-line agents include hydralazine, chlorthalidone or hydrochlorothiazide, and clonidine. Safe medications in lactation

include nifedipine (extended release), enalapril, captopril, benazepril, labetalol, hydrochlorothiazide, and hydralazine.[7,8]

Many antihypertensives do not have robust data related to their safety for use in pregnancy and lactation but may be appropriate in life-threatening emergencies. More information is provided in Table 1 of the Hypertension in Pregnancy Change Package.

5. More than 50% of pregnancy-related deaths occur 7 days to 1 year after the end of pregnancy, and hypertensive disorders are a leading cause.

The postpartum period is full of transitions — across settings, between clinical teams, and also in blood pressure. Almost half of women who have pregnancy-related hypertension continue to have high readings at 6 weeks postpartum.[9,11] Home or self-measured blood pressure monitoring (SMBP) is an effective tool for managing blood pressure and can help women and care teams recognize these elevated blood pressures and respond quickly. Find information about starting an SMBP program using devices validated for pregnancy, along with other important strategies to improve hypertension care during and following pregnancy, in the Hypertension in Pregnancy Change Package.

The Hypertension in Pregnancy Change Package was developed by Million Hearts® with CDC's Division of Reproductive Health and in partnership with the American Academy of Family Physicians, American College of Nurse-Midwives, American College of Obstetricians and Gynecologists, American College of Osteopathic Obstetricians and Gynecologists, American Medical Association, National Association of Nurse Practitioners in Women's Health, and the Society for Maternal-Fetal Medicine. The change package offers valuable resources for clinical teams in outpatient settings. If these resources are implemented, efficient and effective systems can be

created to support patients with hypertension and, ultimately, improve maternal and fetal health.

19.Pre-eclampsia and long-term risk of arrhythmias

Abstract

Aims

Pre-eclampsia (PE), a pregnancy-induced hypertensive disorder, affects 4–5% of pregnancies worldwide. It is well known that hypertension is associated with an increased risk of arrhythmias; however, data on the association between PE and arrhythmias are sparse.

Methods and results

In this observational cohort study, we identified all primiparous women who gave birth in Denmark (1997–2016) using Danish nationwide registries. The women were stratified on whether they developed PE during primiparous pregnancy and followed from primiparous pregnancy to incident arrhythmia, emigration, death, or end of study (31 December 2018). A total of 523 271 primiparous women with a median age of 28 years were included, and 23 367 (4.5%) were diagnosed with PE. During a median follow-up of 10.1 years, women with and without PE were associated with a higher incidence of arrhythmias (1.42 vs. 1.02%): (i) composite of cardiac arrest, ventricular tachycardia/fibrillation, or implantable cardioverter defibrillator implantation [adjusted hazard ratio (HR) 1.60, 95% confidence interval (CI) 1.14–2.24], (ii) composite of advanced second- or third-degree atrioventricular block, sinoatrial dysfunction, or pacemaker implantation [adjusted HR 1.48 (95% CI 0.97–2.23)], (iii) composite of supraventricular tachyarrhythmias or extra systoles [adjusted HR 1.34 (95% CI 1.19–1.51)], and (iv) composite of all the above-mentioned arrhythmias [adjusted HR 1.37 (95% CI 1.23–1.54)].

Conclusion

Pre-eclamptic women were associated with a significantly and at hitherto unknown long-term increased rate of arrhythmias. This finding suggests that women with PE may benefit from cardiovascular risk assessment, screening, and preventive education.

20.The Pandora's Box of Hypertensive Heart Disease in Women

Introduction

Recently, there has been significant advancement in the recognition of sex and gender-based differences in cardiovascular health and disease. However, while hypertension remains the most common medical diagnosis and modifiable cardiovascular risk factor regardless of sex, a sex- and gender-based approach to diagnosis and management of hypertension has not been explored.**1-4** Of note, although the terms sex and gender are used interchangeably in the literature, it should be recognized that sex is a biologic construct, while gender is a social construct; analysis and reporting frequently blur these definitions, as exemplified in this editorial, due to imprecision of source documents.
Autonomic and hormonal function are key contributors to the regulation of blood pressure (BP).**3**,**4** Females experience unique events over the course of their lifespan related to reproductive biology including menarche and menstruation, pregnancy, and menopause. After the onset of menopause, hypertension is more prevalent in females than males.**3**,**4** Despite this, underdiagnosis of hypertension is more common in women than men, and when women are treated with antihypertensive medications, it has been found to be less well controlled than men.**3**,**4** Additionally, women have a unique profile when it comes to efficacy and adverse effects of some antihypertensive medical therapies.**4** There is also a sex-specific cardiac response to chronic hypertension and pressure overload.**4** It was initially demonstrated within the analysis of the Framingham Heart Study that women with systolic hypertension experience higher rates of

hypertensive left ventricular concentric remodeling and hypertrophy,**5** a finding has since been corroborated in several observational studies.**6-8** Once established, hypertensive left ventricular hypertrophy (LVH) is less modifiable by antihypertensive treatment in females than males.**8** Although the overall risk for cardiovascular disease is lower in premenopausal women, this protection is lost after the onset of menopause. Interestingly, it has been shown that the presence of LVH in hypertension offsets the female sex-protection in cardiovascular risk, such that among hypertensive subjects with LVH, both sexes have comparable cardiovascular risk.**9** It has also been observed that although healthy young women have lower BP than men at similar age, they experience a steeper increase in BP from the third decade of life onward, and women with hypertension more often develop heart failure with preserved ejection fraction and atrial fibrillation, whereas men more often develop acute myocardial infarction and heart failure with reduced ejection fraction.**4**,**9**,**10** While sex-related differences in hypertension and left ventricular geometry have been clearly demonstrated,**5-8** to date these observations have not translated into mechanistic understandings for these differences, potentially leading to the creation of sex-specific diagnosis or management guidelines in clinical practice. This is primarily due to a lack of sex- and gender-specific analysis and reporting in large clinical trials on treatment and outcomes in hypertension.

In this issue of *JACC: Advances,* Canciello et al**11** add to the substantial data supporting sex-based differences in hypertensive heart disease by demonstrating the longitudinal impact of hypertension on ventricular morphology and remodeling. This study reports on a post-hoc sex-disaggregated analysis of echocardiograms from 6,427 patients (43% female) in the Campania Salute Network observational registry of hypertensive patients and found over twice the rate of left ventricular remodeling and hypertrophy in females at both baseline and follow-up (mean of 6.1 years) when compared to

males. These increased rates of abnormal geometry were found despite exclusion of patients with established cardiovascular disease or significant chronic kidney disease. Female sex was independently associated with abnormal left ventricular geometry in multivariate analysis with an odds ratio of 2.36 (95% CI: 2.12-2.62; $P < 0.001$).

An unexpected result was that the majority of females with abnormal geometry had eccentric hypertrophy, a finding previously thought to be more common in males.**12** No clear hypothesis was given for this observation, but it is possible that this may represent a longer duration of undertreated hypertension, and an associated increased predisposition to subclinical microvascular coronary artery disease in this female population, leading to more extensive fibrotic changes and eccentric dilation. In a recent study evaluating altered left ventricular geometry using cardiac magnetic resonance imaging and adjusted for epicardial coronary artery disease, it was shown that concentric hypertrophy was associated with increased all-cause mortality in both sexes, while eccentric hypertrophy was associated with increased all-cause mortality only in females.**12** Bairey Merz et al**13** pointed to the disproportionate burden of microvascular coronary dysfunction in females as a possible explanation for the increased adverse mortality.

Although observational studies of this nature cannot determine causal relationships, Canciello et al**11** report findings that are in keeping with previous similar cross-sectional studies and uniquely add to this growing body of information by providing longitudinal evidence for persistent sex disparities over time, shedding light on the prognostic importance of early identification of these sex-specific morphologic changes in response to altered physiology using the readily accessible tool of echocardiography. In addition to LVH, which has been considered the cardinal echocardiographic biomarker of pressure overload and associated cardiac damage, strain assessment of the left ventricle and left atrium are emerging areas of exploration providing more sensitive markers of hypertensive changes preceding chamber enlargement or hypertrophy and may eventually play a greater role in

earlier recognition of cardiac alterations and response to antihypertensive treatment.**14** Sex-differences have been identified in both ventricular and atrial strain, and the establishment of sex-specific strain reference values would be an essential step for unlocking strain assessments as potential tools aiding in mechanistic understanding and management.**15**,**16**

Limitations to retrospective analysis of observational data are acknowledged by the group, including the undefined role of potential underlying subclinical coronary artery disease and lack of detail regarding individual antihypertensive therapies. In addition, there is no data addressing the potential for associations with cardio-obstetric sex-specific cardiovascular risk factors such as hypertensive pregnancy disorders (preeclampsia, eclampsia), polycystic ovary syndrome, menopausal status, and hormonal drug therapies.

In summary, this latest observational study by Canciello et al**11** confirms sex disparities in the physiologic response to hypertension adding to the growing body of research demonstrating sex-specific differences of hypertensive heart disease and prognostic implications of these differences, and in so doing raises many questions that urgently require answers. Why do female hypertensive patients exhibit a higher propensity for left ventricular remodeling than their male counterparts? Is eccentric hypertrophy truly more prevalent in females? If so, what is the adaptive impact and association with increased clinical prevalence of coronary microvascular dysfunction and heart failure with preserved ejection fraction in females? What new pharmacologic strategies could be indicated? There is a clear need to better understand the underlying mechanisms of these sex differences in adaptive ventricular geometry in order to develop optimal sex-specific diagnostic and prognostic strategies to guide the optimal management of hypertension in women. Moreover, this work underscores the importance of considering sex- and gender-specific factors in risk assessment and management strategies and demonstrates that analysis of data through a sex-

specific lens is essential to our understanding of cardiovascular pathophysiology. Integrating sex-specific risk factors into risk stratification models is a crucial step toward more tailored and effective clinical interventions.

21.Sex-specific differences in alive hospital discharge following infrarenal abdominal aortic aneurysm repair

Abstract

Background and Aims

A longer time to alive hospital discharge following infrarenal abdominal aortic aneurysm (AAA) repair is associated with reduced patient satisfaction and increased length of stay, hospital-acquired deconditioning, infection, and costs. This study investigated sex-specific differences in, and drivers of, the rate of alive hospital discharge.

Methods

Examination of UK National Vascular Registry (UK NVR), 2014–19, and Swedish National Patient Registry (SE NPR) elective AAA patients, 2010–18, for endovascular (EVAR) or open aneurysm repair (OAR). Cox models assessed sex-specific difference in the rate of alive hospital discharge, adjusting for co-morbidity, anatomy, standard of care, post-operative complications, and year, with in-hospital death as the competing risk.

Results

A total of 29 751 AAA repairs (UK NVR: EVAR 12 518:1532; OAR 6803:837; SE NPR: EVAR 4234:792; OAR 2638:497, men:women) were assessed. For EVAR, the unadjusted rate of alive hospital discharge was ~ 25% lower for women [UK NVR: hazard ratio (HR) 0.75 (0.71–0.80), $P < .001$; SE NPR: HR 0.75 (0.69–0.81), $P < .001$]. Following adjustment, the sex-specific HR narrowed but remained significant [UK NVR: HR 0.83 (0.79–0.88), $P < .001$; SE NPR: HR 0.83

(0.76–0.89), *P* < .001]. For OAR, the rate of alive hospital discharge was 23%–27% lower for women [UK NVR: HR 0.73 (0.67–0.78), *P* < .001; SE NPR: HR 0.77 (0.70–0.85), *P* < .001]. Following adjustment, the sex-specific HR narrowed [UK NVR: HR 0.82 (0.76–0.88), *P* < .001; SE NPR: HR 0.79 (0.72–0.88), *P* < .001] but remained significant.

Conclusions

Women have a 25% lower rate of alive discharge after aortic surgery, despite adjustment for pre/peri- and post-operative parameters. Efforts to increase the rate of alive hospital discharge for women should be sought.

22. Sex Differences in Hospital Survival After AAA Repair

Methods:

The investigators systematically examined the UK National Vascular Registry (UK NVR), 2014-2019 and Swedish National Patient Registry (SE NPR) of elective AAA patients, 2010-2018, for endovascular (EVAR) or open (OAR) aneurysm repair. Cox models assessed sex-specific differences in the rate of alive hospital discharge, adjusting for comorbidity, anatomy, standard-of-care, postoperative complications, and year, with in-hospital death as the competing risk.

Results:

A total of 29,751 AAA repairs (UK NVR – EVAR 12,518:1,532; OAR 6,803:837; SE NPR – EVAR 4,234:792; OAR 2,638:497, men:women) were assessed. For EVAR, the unadjusted rate of alive hospital discharge was approximately 25% lower for women (UK NVR: hazard ratio [HR] 0.75 [0.71-0.80], p < 0.001; SE NPR: HR 0.75 [0.69-0.81], p < 0.001). Following adjustment, the sex-specific HR narrowed but remained significant (UK NVR: HR 0.83 [0.79-0.88], p < 0.001; SE NPR: HR 0.83 [0.76-0.89], p < 0.001). For OAR, the rate of alive hospital discharge was 23-27% lower for women (UK NVR: HR 0.73

[0.67-0.78], p < 0.001; SE NPR: HR 0.77 [0.70-0.85], p < 0.001). Following adjustment, the sex-specific HR narrowed (UK NVR: HR 0.82 [0.76-0.88], p < 0.001; SE NPR: HR 0.79 [0.72-0.88], p < 0.001) but remained significant.

Conclusions:

The authors report that women have a 25% lower rate of alive discharge after aortic surgery, despite adjustment for pre/peri- and postoperative parameters.

Perspective:

This study reports that women stayed longer in the hospital after aortic repair (consistent for both EVAR and OAR) as well as experienced a higher in-hospital mortality rate. Furthermore, this sex-specific difference narrows slightly but remains significant despite adjustment for age, comorbidities, anatomical complexity, anesthetic, year, standard-of-care, and postoperative complications. There is an urgent need for efforts to increase the rate of alive hospital discharge for women after aortic repair. Further research is also needed to explore the role of gender and social support networks that might impact the rate of alive hospital discharge in the AAA population.

23. Sex-Specific Differences in Alive Hospital Discharge After Infrarenal Abdominal Aortic Aneurysm Repair

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality for women and responsible for 35% of total deaths in women in 2019.1 Over the past 30 years, CVD in women has remained understudied, underrecognized, underdiagnosed, and undertreated.2 The prevalence of CVD in women has surpassed that in men in 2019.3 Therefore, the Lancet Women and Cardiovascular

Disease Commission has identified the reduction in the global burden of CVD in women as a key focus of its work through the year 2030.4

Polycystic ovary syndrome (PCOS) is a highly prevalent and profoundly hereditary complex multigenic and multifactorial disorder.5 Polycystic ovary syndrome has already affected 5–15% of reproductive-age females, characterized primarily by pathophysiological abnormalities in gonadotropin secretion, ovarian follicle generation, steroidogenesis, insulin secretion, and adipose tissue function.6,7 Over the past decades, the disease burden of PCOS has exhibited a steep upward trend, gradually evolving into a significant public health concern affecting the overall health of the global female population.8,9 This rising prevalence of PCOS may contribute to multiple factors, such as foetal life, birth weight, neonatal and childhood events, and even epigenetics.10,11 Studies have indicated that PCOS increases the risk of CVD in women, particularly with respect to myocardial infarction (MI) and stroke.12,13 Meta-analyses indicated that individuals with PCOS have a higher risk of CVD than non-PCOS individuals, although their reported CVD events are inconsistent.14 The increased cardiovascular risk in PCOS patients may be due to metabolic disorders like insulin resistance, diabetes, or obesity. Additionally, Gao *et al.*15 proposed a non-metabolic mechanism, particularly chronic inflammation, for the high CVD risk in PCOS patients. Considering the evidence presented above, the increasing global prevalence of PCOS may be one of the contributing potential factors exacerbating the disease burden of CVDs in females. However, there is no systematic study that assesses the contribution of PCOS to CVD and explores the global burden of PCOS-associated CVD.

Herein, we conducted an updated meta-analysis to thoroughly assess the relationship between PCOS and CVD. Furthermore, we evaluated the global incidence of PCOS-associated CVD in different regions and countries, utilizing a population attributable fraction (PAF) and CVD

epidemiological data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019.

Methods

Search strategy

The study protocol was registered on PROSPERO (https://www.crd.york.ac.uk/prospero/; CRD42023472564). A systematic search was conducted in PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus up to 25 September 2023, following the PICOS principle (see Supplementary material online, *Appendix S1*). Primary key words included CVD (defined by the International Classification of Diseases (ICD) version 10), PCOS, and their respective equivalents (detailed information is provided in Supplementary material online, *Appendix S1*). We extracted studies that met the inclusion criteria and included pertinent risk measures, such as risk ratio (RR), odds ratio (OR), and hazard ratio (HR), along with their corresponding 95% confidence intervals (95% CIs).

Data extraction and quality assessment

Literature screening was conducted using Endnote software (version X9.2). Data extraction and quality assessment were independently conducted by Z.S. and J.Z., with discrepancies resolved through consultation or arbitration by Z.W. (additional details are available in Supplementary material online, *Appendix S1* and *Table S1*). We utilized the Agency for Healthcare Research and Quality (https://www.wjx.cn/m/85284180.aspx) to classify the included articles into high-, medium-, and low-risk categories.

Data sources

We obtained PCOS prevalence data among all-age-group and 10- to 55-year-old group, along with the number incidence of CVD from

1990 to 2019, according to the ICD codes 9 and 10 (see Supplementary material online, *Table S2*). Age-standardized incidence rate (ASIR) per 100 000 population of incidence and the corresponding 95% CI were calculated, based on the age-specific all-cause CVD incidence and the world standard population reported in GBD 2019, as introduced before (see Supplementary material online, *Appendix S3*).16 These data were collected globally, in World Bank–defined regions, and in 204 countries (https://vizhub.healthdata.org/gbd-results/). The GBD database employed a five-tier sociodemographic index (SDI) to categorize the 204 locations into low, low–middle, middle, high–middle, and high regions (https://ghdx.healthdata.org/search/site/SDI; see Supplementary material online, *Table S3*). The SDI was estimated based on the country development and composite of the country's total fertility rate for women younger than 25 years, educational attainment, and lag-distributed income per capita.17 The World Bank defines the world into seven regions, including East Asia and Pacific, Europe and Central Asia, Latin America and Caribbean, Middle East and North Africa, North America, South Asia, and Sub-Saharan Africa (see Supplementary material online, *Table S4*).

Pooled risk ratio estimation

We utilized a random-effects model to calculate an aggregate RR with a 95% CI to scrutinize the link between PCOS and CVD. Heterogeneity was appraised using Cochrane's *Q* statistic via *x2* test, alongside a quantitative assessment through Higgins's *I2* metric. We undertook subgroup analyses and meta-regression trying to find the source of heterogeneity, based on the characteristics of the study region, study type, study setting, study period, CVD outcome events, age group, and sex. For subgroups with ≤5 studies, the Hartung–Knapp–Sidik–Jonkman approach was applied.18 We integrated external adjustments for potential confounders absent in unadjusted study reports.19 Sensitivity analyses were performed by omitting studies

one by one, or those with high risk levels. We employed Egger's linear regression and funnel plots to investigate potential publication bias. To address and correct for bias, we utilized the trim-and-fill method. Meta-analyses were conducted using the R software (version 4.2.2) with the 'metafor' package.

Estimation of population attributable fraction and polycystic ovary syndrome–attributed cardiovascular disease incidence

Using the pooled RR value and PCOS prevalence data from GBD 2019, we calculated the PAF (%) through Levin's formula (1)20:

PAF=PCOSprevalence*(RR-1)1+PCOSprevalence*(RR-1).

In calculating the PAF, we modeled RRs with log-normal distributions and prevalence data with beta distributions. A Monte Carlo simulation of 10 000 iterations in R established 95% CIs (see Supplementary material online, *Appendix S3*). Polycystic ovary syndrome–attributable incidence numbers and ASIRs were derived by applying PAF to all-cause data. An example using Zimbabwe's data illustrates the calculation in Supplementary material online, *Figure S1and Figure S2*.

We utilized an estimated annual percentage change (EAPC) with 95% CI to assess the trends in ASIRs from 1990 to 2019 using a regression model fitted by logarithmic ASR, as indicated below (y is the ASIR, x is the calendar year; see Supplementary material online, *Appendix S2*)21:

Additionally, the association between the SDI score and both all-cause and PCOS-associated ASIRs, as well as EAPCs, was estimated using a Spearman test implemented in R software (version 4.2.2).

Results

Characteristics and quality of included studies

Seventeen studies qualified for the present systematic review from 14 430 initially identified articles (see Supplementary material online, *Figure S3*). Supplementary material online, *Tables S5* and *S6*, summarize the key characteristics of the included studies. The 17 included articles comprised 14 cohort studies and 3 case–control studies. Eight studies provided adjusted effect sizes and 95% CIs, while nine studies provided unadjusted or original data, which enabled us to calculate the adjusted effect sizes according to external adjustments (see Supplementary material online, *Table S7*). According to the World Bank–defined regions, roughly seven of the included studies were performed in North America (USA), two in East Asia and Pacific (Australia, Taiwan in China), and eight studies in Europe and Central Asia (UK, Denmark, Netherland, and Norway). Eight studies diagnosed CVD according to the ICD criteria 9 (ICD-9), while four used ICD-10, and one study did not report detailed criteria. In addition, only three primary reports with five studies in our meta-analysis had a clear age baseline and follow-up end age under 55, with two reports performed in the USA and one in the UK. The other reports included participants under 55 years old, and followed up excluded over 55 years or did not provide clear follow-up information (see Supplementary material online, *Table S6*). Based on the Newcastle-Ottawa Quality Assessment Scale (NOS), 11 studies had a low risk of bias in their methodology, and 5 had a moderate risk of bias (see Supplementary material online, *Table S8*). The PRISMA-DTA checklist for abstracts can be found in Appendix S4.

The risk of cardiovascular disease among people living with polycystic ovary syndrome

Overall, the pooled risk of CVD was significantly higher among participants with PCOS than in their PCOS-negative counterparts (pooled RR = 1.51; 95% CI 1.36–1.69), with significant heterogeneity across the studies ($I2$ = 66%; P < 0.01; *Figure 1*). Similar pooled RR values were observed in women under 55 years old (1.37; 95% CI 1.17–1.59; *Figure 1A*). Subgroup analysis revealed that the heterogeneity did not differ by variables of study region, study type, study setting, and study quality (see Supplementary material online, *Table S9*). Similar results were found in major CVDs [stroke, MI, and coronary heart disease (CHD)], and non-significant RR values were found among these subtypes (see Supplementary material online, *Table S9*). Furthermore, univariate meta-regression analyses failed to establish a significant difference for these variables (see Supplementary material online, *Table S10* and *Figure S4*).

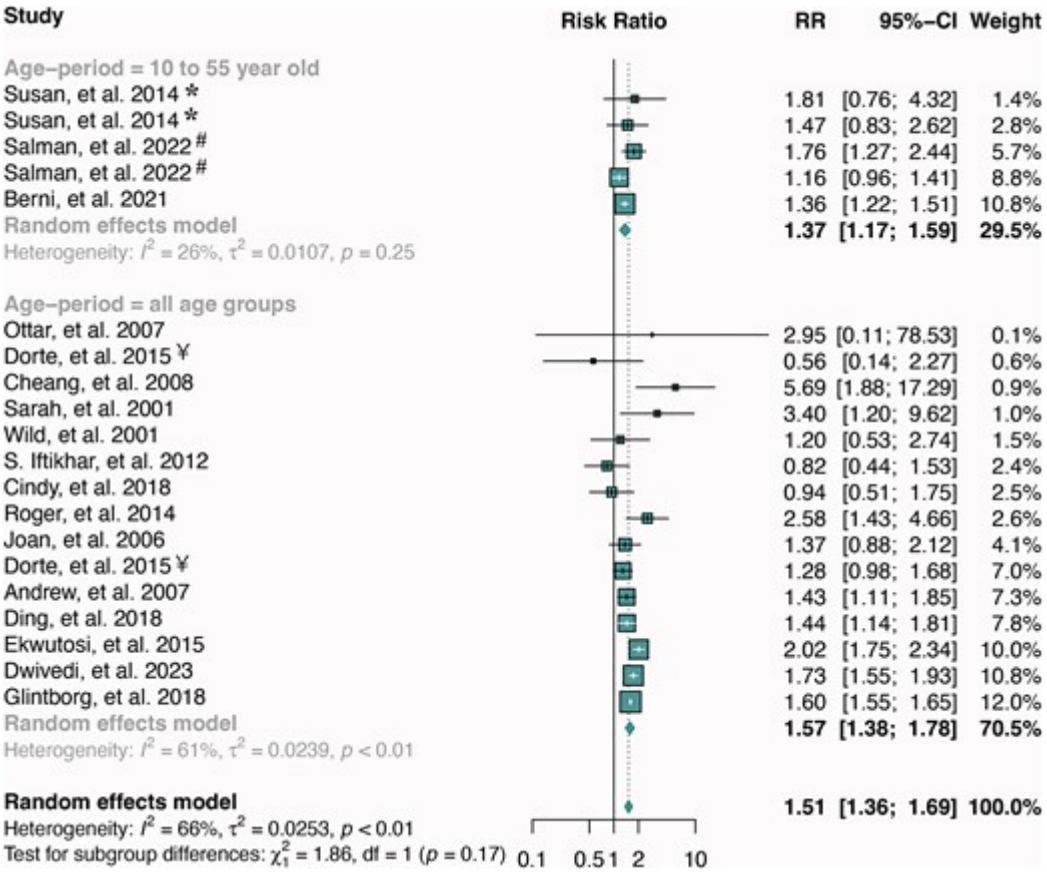


Figure 1

Pooled risk ratio estimation for the association of cardiovascular disease in the population with polycystic ovary syndrome. *Susan *et al.* provided ischaemic stroke and coronary heart disease for study outcome. #Salman *et al.* provided stroke and heart failure for study outcome. ¥ Dorte *et al.* reported cardiovascular disease risk of polycystic ovary syndrome in two populations (Odense University Hospital, OUH; Denmark population).

We further performed a sensitivity analysis employing a leave-one-out method. We found that the pooled risk of CVD varied between 1.54 (95% CI 1.45–1.62) and 1.60 (95% CI 1.56–1.65; see Supplementary material online, *Figure S5*). Sensitivity analyses were also performed by removing studies that manually calculated the effect sizes. After analysing the original data, 70 results were still stable (1.53, 95% CI 1.35–1.72; see Supplementary material online, *Figure S6*). We also estimated the pooled RR values from 8 unadjusted studies (RR 1.29, 95% CI 1.18–1.42), with no significant difference from the 12 adjusted studies (RR 1.60, 95% CI 1.30–1.91), even the external adjusted RR value (RR 1.36, 95% CI 1.25–1.49; see Supplementary material online, *Table S11*). No potential publication bias was observed by funnel plot (see Supplementary material online, *Figure S7*) or Egger's test (t = 0.34, P = 0.736) in our study.

Global burden of polycystic ovary syndrome–attributed cardiovascular disease

Table 1 shows the results of global and regional PCOS-associated CVD burden for women in all-age group and 10 to 54 years old. Regarding the all-age group, the estimated PAF for POCS-associated CVD in the global population increased from 0.64% (95% CI 0.39–0.98) in 1990 to 0.85% (95% CI 0.52–1.30) in 2019. This was accompanied by a more than two-fold increase in the number of PCOS-associated CVD cases from 102 530 (95% CI 62 130–157 540) in 1990 to 235 560 (95% CI

142 720–361 960) in 2019 (see Supplementary material online, *Table S12*). In addition, the global POCS-attributed ASIR (per 100 000 population) of CVD increased from 1990 to 2019, demonstrating an EAPC of 0.34% (95% CI 0.27–0.41; see Supplementary material online, *Table S12*; *Figures 2* and *3*). Decreasing trend at the global level was observed for all-cause ASIR (EAPC −0.57%, 95% CI −0.61 to −0.52; see Supplementary material online, *Table S12* and *Figures S8* and *S9*). For women in between 10 and 54 years old, higher PAF (0.71; 0.29–1.26) was found globally in 1990 and consistent to 2019 (0.95; 0.39–1.65; *Table 1*). Meanwhile, higher worldwide increase trends of PCOS-associated CVD ASIR was observed (EAPC 0.49%; 0.41–0.56), compared with the all-age group (*Figures 2* and *3*).

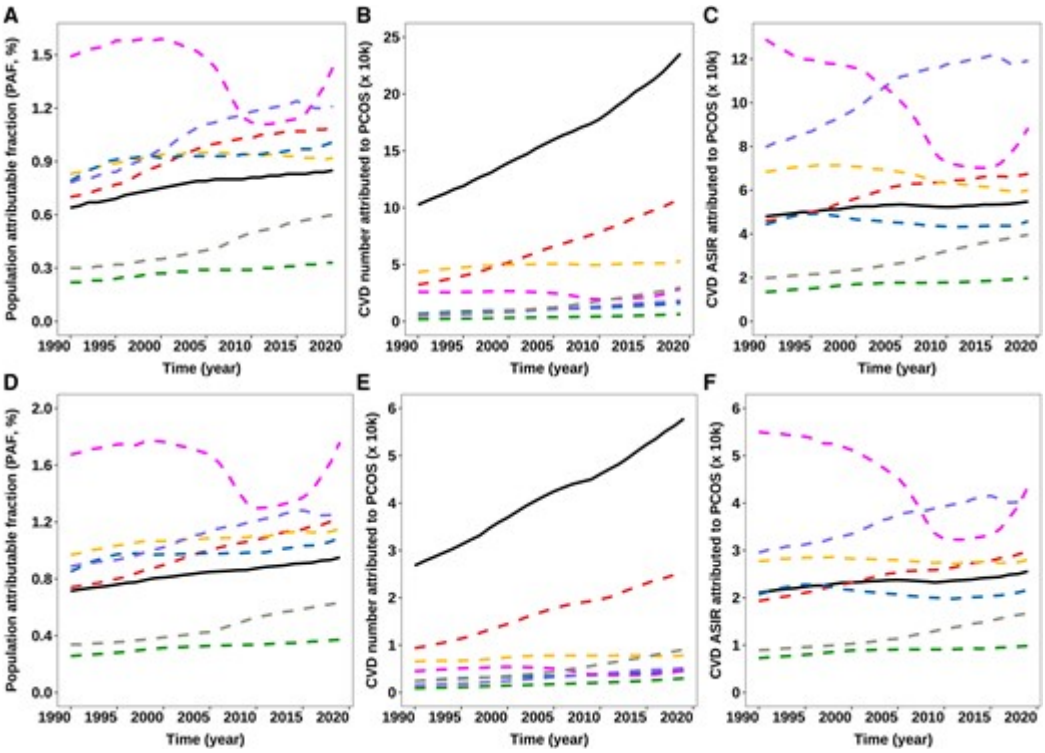


Figure 2

Terminal trend of population attributable fraction, polycystic ovary syndrome–associated new cases, and age-standardized incidence rates for the global and World Bank–defined regions, in all-age group (*A*–*C*) and 10- to 54-year-old (*D*–*F*) women, from 2010 to 2019. (*A*, *D*) Population attributable fractions (%). (*B*, *E*) Incidence number due to

polycystic ovary syndrome (×1000). (*C*, *E*) Polycystic ovary syndrome–associated age-standardized incidence rates per 100 000 population.

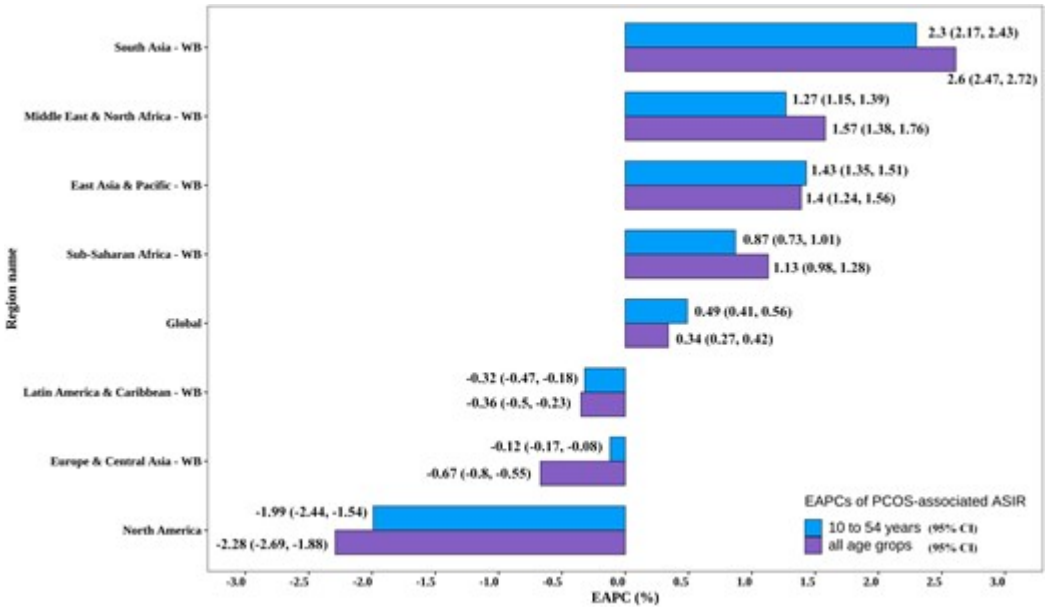


Figure 3

The estimated annual percentage changes of polycystic ovary syndrome–associated cardiovascular disease age-standardized incidence rate for the global and World Bank–defined regions, in all-age group and 10- to 54-year-old women, from 2010 to 2019. Abbreviations: WB, World Bank; EAPCs, estimated annual percentage changes; PCOS, polycystic ovary syndrome; ASIR, age-standardized incidence rate.

Table 1

Population attributable fraction using prevalence data of polycystic ovary syndrome for women and age-standardized cardiovascular disease incidence rates ones by global and regions

World Bank region	**Age group** a	**PCOS prevalence (%)**	**PAF (%)**	**PCOS-associated number (×1000)**	**PCOS-associated ASIR (per 100 000)**

		1990	2019	1990	2019	1990	2019	1990	2019
Global	All-age group	1.32 (0.91, 1.74)	1.76 (1.22, 2.3)	0.64 (0.39, 0.98)	0.85 (0.52, 1.3)	102.53 (62.13, 157.54)	235.56 (142.72, 361.96)	4.8 (2.91, 7.35)	5.48 (3.32, 8.37)
	10–54 years old	2.04 (1.4, 2.67)	2.7 (1.88, 3.53)	0.71 (0.29, 1.26)	0.95 (0.39, 1.65)	26.80 (10.91, 47.57)	57.82 (23.19, 101.63)	2.10 (0.86, 3.70)	2.56 (1.04, 4.43)
East Asia and Pacific	All-age group	1.45 (0.97, 1.95)	2.24 (1.55, 2.96)	0.7 (0.41, 1.1)	1.09 (0.66, 1.66)	32.3 (18.9, 50.56)	108.43 (66.09, 166.15)	4.59 (2.69, 7.2)	6.75 (4.07, 10.31)
	10–54 years old	2.11 (1.42, 2.84)	3.46 (2.4, 4.58)	0.74 (0.29, 1.33)	1.22 (0.5, 2.15)	9.40 (3.78, 17.05)	25.33 (10.37, 45.09)	1.93 (0.77, 3.48)	2.97 (1.22, 5.24)
Europe and Central Asia	All-age group	1.71 (1.17, 2.26)	1.9 (1.3, 2.52)	0.83 (0.5, 1.26)	0.92 (0.56, 1.42)	43.31 (26.09, 66.21)	52.94 (31.8, 81.63)	6.83 (4.12, 10.45)	6 (3.59, 9.24)
	10–54 years old	2.76 (1.89, 3.65)	3.28 (2.25, 4.36)	0.97 (0.4, 1.71)	1.15 (0.46, 2.03)	6.55 (2.67, 11.66)	7.83 (3.18, 14.01)	2.77 (1.13, 4.89)	2.8 (1.13, 4.94)
Latin America and Caribbean	All-age group	1.61 (1.09, 2.16)	2.06 (1.41, 2.78)	0.79 (0.47, 1.23)	1.01 (0.61, 1.56)	6.72 (3.99, 10.5)	16.25 (9.64, 25.13)	4.43 (2.64, 6.91)	4.58 (2.73, 7.06)
	10–54 years old	2.41 (1.63, 3.24)	3.08 (2.12, 4.15)	0.85 (0.35, 1.49)	1.09 (0.44, 1.93)	1.55 (0.62, 2.78)	5.17 (2.108, 9.29)	2.95 (1.2, 5.26)	4.05 (1.65, 7.19)
Middle	All-	1.61	2.5	0.78	1.21	4.93	18.32	7.97	11.93

World Bank region	Age group a	PCOS prevalence (%)		PAF (%)		PCOS-associated number (×1000)		PCOS-associated ASIR (per 100 000)	
		1990	2019	1990	2019	1990	2019	1990	2019
East and North Africa	age group	(1.08, 2.15)	(1.68, 3.37)	(0.46, 1.21)	(0.71, 1.9)	(2.89, 7.7)	(10.8, 28.75)	(4.66, 12.5)	(7.07, 18.86)
	10–54 years old	2.55 (1.7, 3.42)	3.58 (2.4, 4.84)	0.89 (0.36, 1.58)	1.26 (0.51, 2.23)	1546 (621, 2780)	5173 (2098, 9291)	2.95 (1.2, 5.26)	4.05 (1.65, 7.19)
North America	All-age group	3.07 (2.06, 4.18)	2.87 (2.27, 3.53)	1.49 (0.89, 2.32)	1.43 (0.92, 2.04)	25.96 (15.34, 40.73)	28.73 (18.34, 41.14)	12.89 (7.58, 20.24)	8.84 (5.66, 12.7)
	10–54 years old	4.76 (3.2, 6.5)	4.92 (3.9, 6.02)	1.67 (0.69, 2.98)	1.76 (0.73, 2.88)	4.50 (1.82, 8.04)	4.70 (1.96, 7.78)	5.50 (2.26, 9.81)	4.34 (1.80, 7.10)
South Asia	All-age group	0.61 (0.41, 0.82)	1.24 (0.84, 1.66)	0.3 (0.18, 0.46)	0.6 (0.36, 0.94)	5.88 (3.47, 9.22)	29.54 (17.46, 46.13)	1.98 (1.17, 3.11)	3.96 (2.35, 6.18)
	10–54 years old	0.96 (0.64, 1.28)	1.81 (1.22, 2.42)	0.34 (0.13, 0.6)	0.63 (0.26, 1.12)	2.43 (0.97, 4.37)	9.04 (3.68, 16.14)	0.9 (0.36, 1.58)	1.67 (0.69, 2.95)
Sub-Saharan Africa	All-age group	0.45 (0.28, 0.62)	0.69 (0.44, 0.95)	0.22 (0.12, 0.35)	0.33 (0.19, 0.53)	1.89 (1.08, 3.08)	6.33 (3.68, 10.24)	1.34 (0.77, 2.19)	1.98 (1.15, 3.19)
	10–54	0.74	1.06	0.26	0.37	0.90	2.98	0.73	0.98

World Bank region	Age group a	PCOS prevalence (%)		PAF (%)		PCOS-associated number (×1000)		PCOS-associated ASIR (per 100 000)	
		1990	2019	1990	2019	1990	2019	1990	2019
	years old	(0.47, 1.02)	(0.69, 1.46)	(0.1, 0.48)	(0.15, 0.68)	(0.35, 1.69)	(1.18, 5.55)	(0.28, 1.34)	(0.39, 1.79)

PAF, population attributable fraction; CVD, cardiovascular disease; ASIR, age-standardized incidence rate.

aBurden of PCOS-associated CVD was estimated in all-age group and 10- to 54-year-old women.

The POCS-attributed CVD burden exhibited regional disparities across eight World Bank regions, with North America experiencing the highest PAF (1.49%, 95% CI 0.89–2.32) in all-age group women, in 2019 (*Table 1*). The East Asia and Pacific had the highest POCS-attributed new CVD cases (108 430, 95% CI 66 090–166 150; see Supplementary material online, *Table S12*), while the Middle East and North Africa recorded the highest POCS-attributed CVD ASIR (11.93 per 100 000 population, 95% CI 7.07–18.86; *Table 1*). Similar results were observed in women under 55 years old (10–54; *Table 1*). From 1990 to 2019, increased POCS-attributed CVD new cases were observed in seven World Bank regions (*Table 1* and *Figure 2*). Specially, the South Asia region noted the most significant increase trend (EAPC 2.61%, 95% CI 2.49–2.73), followed by Middle East and North Africa (1.58%), East Asia and Pacific (1.39%), and Sub-Saharan Africa (1.13%; see Supplementary material online, *Table S12*; *Figures 2* and *3*). Additionally, all-cause ASIR for CVD remained stable or slightly decreased across regions (see Supplementary material online, *Table S12* and *Figure S8*). Specific PAFs calculated by specific RRs for major CVDs (stroke, MI, and CHD) by global and regions are

shown in Supplementary material online, *Table S13*. The results indicated that globally, ~ 0.83, 0.82, and 0.52% of incidences of stroke, CHD, and MI were associated with PCOS, respectively. Regarding the women between 10 and 54 years old, the highest PAF (1.76; 0.73–2.88) was also found in North America, which is higher than that in all-age group (*Table 1*). Similar differences and trends apply to all other regions as well (*Figures 2* and *3*).

At the national level, among the global all-age group women in 2019, five countries with the highest PAFs were observed in Italy (3.14%), Japan (2.53%), New Zealand (2.49%), Brunei (2.34%), and Malaysia (2.37%), as well as the ASIRs (see Supplementary material online, *Table S14*; *Figure 4*). Regarding the new CVD cases attributed to PCOS, China observed the highest number (50 639; 95% CI 30 113–78 765), followed by the USA, India, and Japan (see Supplementary material online, *Table S14*; *Figure 4*). Among the 204 countries, 151 (75.00%) countries exhibited an increasing trend in CVD ASIR due to PCOS from 1990 to 2019, with the highest increases located in Maldives, Vietnam, and Equatorial Guinea (see Supplementary material online, *Table S15* and *Figure S10*). In contrast, only 40 countries were observed to have a significant increase in the all-cause CVD ASIR (see Supplementary material online, *Table S15* and *Figure S10*).

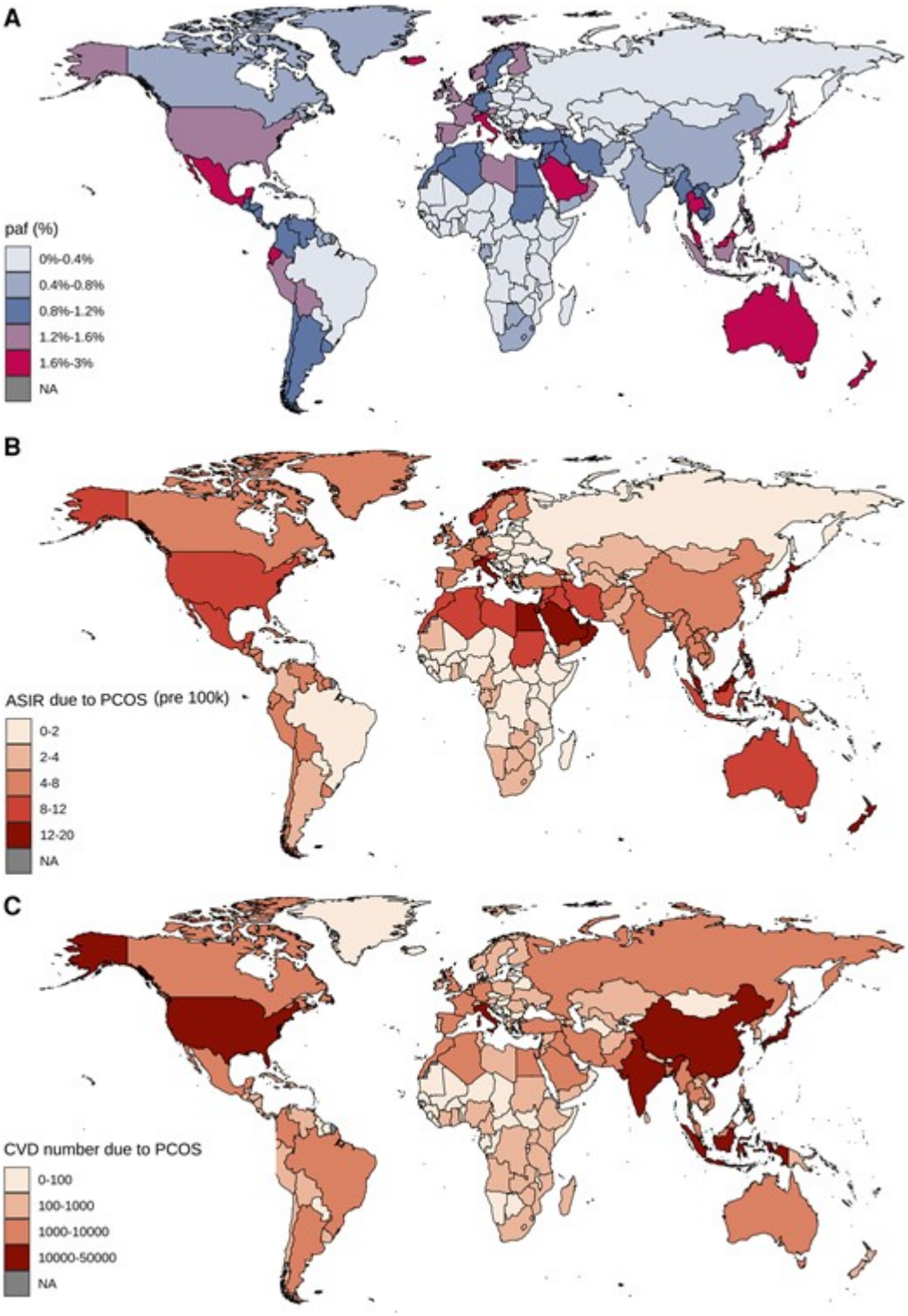


Figure 4

Map of population attributable fraction, polycystic ovary syndrome–associated cardiovascular disease incidence number, and age-standardized incidence rates for the 204 countries in all-age group, 2019. (*A*) Population attributable fraction (%). (*B*) Cardiovascular

disease incidence number due to polycystic ovary syndrome (×1000). (*C*) Polycystic ovary syndrome–associated age-standardized incidence rate per 100 000 population. Abbreviations: paf, population attributable fraction; ASIR, age-standardized incidence rate; PCOS, Polycystic Ovary Syndrome; CVD, Cardiovascular Disease; NA, not available.

We detected a correlation between the burden of CVD and the SDI. Generally, a negative correlation was detected between the all-cause ASIR (2019) and SDI (2019) for CVD, but it was not significant (r = −0.02, 95% CI 0.16 to 0.13, P = 0.779; *Figure 5A*). However, a significant positive correlation was detected between the POCS-attributed ASIR (2019) and SDI (2019; r = 0.40, 95% CI 0.28–0.51, P < 0.001; *Figure 5B*). Meanwhile, the EAPC was negatively correlated with the SDI (2019) for all-cause ASIR (r = −0.46, 95% CI −0.56 to −0.34, P < 0.001; *Figure 5C*). A similar negative relationship was observed between the SDI (2019) and EAPC for POCS-attributed ASIRs (r = −0.49, 95% CI −0.59 to −0.38, P < 0.001; *Figure 5D*).

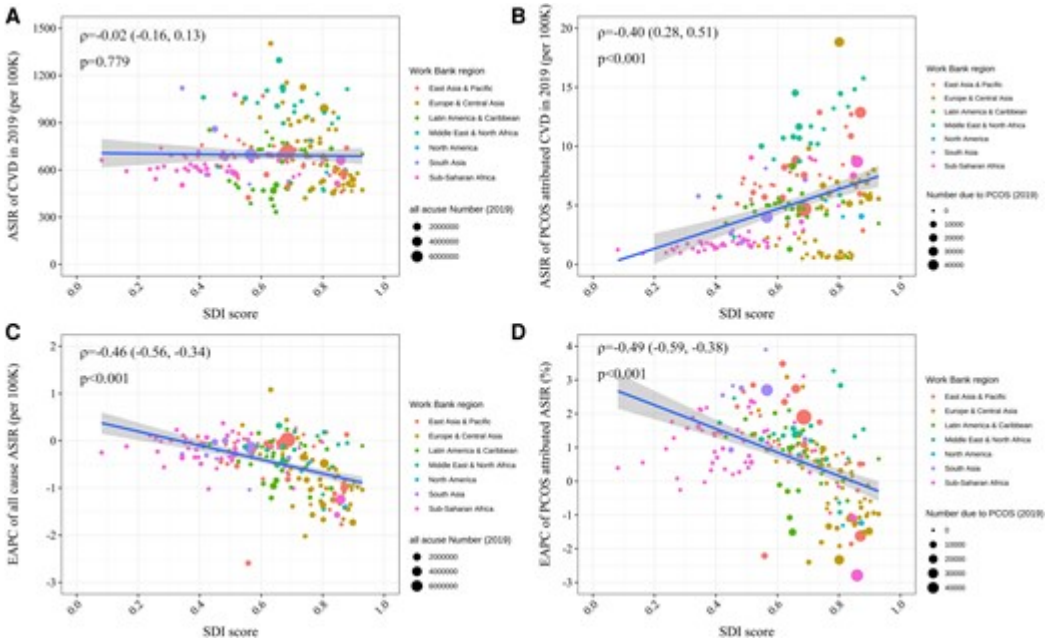


Figure 5

The relationship between cardiovascular disease incidence burden of 204 countries and sociodemographic index in all-age group, 2019. (*A*) Correlation between all-cause age-standardized rates and sociodemographic index. (*B*) Correlation between the polycystic ovary syndrome–associated age-standardized rate and sociodemographic index. (*C*) Correlation between the estimated annual percentage change of all-cause age-standardized rate from 2010 to 2019 and sociodemographic index. (*D*) Correlation between the estimated annual percentage change of polycystic ovary syndrome–associated age-standardized rate from 2010 to 2019 and sociodemographic index. The size of the circle is increased with all-cause incidence numbers and polycystic ovary syndrome–associated incidence numbers in 2019, respectively. ASIR, age-standardized rate; EAPC, estimated annual percentage change; CVD, cardiovascular disease; SDI, sociodemographic index.

Discussion

Our study performed an updated assessment of the association between PCOS and CVD risk, and first evaluated the global, regional, and national burden of CVD associated with PCOS. Our results indicated that the risk of incident CVD was 1.51 times higher in PCOS patients than in the non-PCOS all-age group population. Correspondingly, over the past three decades, there has been a more than two-fold increase in the incidence number of CVD associated with PCOS. There were substantial regional variations, with the highest PAF, the incident number, and rates of PCOS-associated CVD observed within North America, Middle East and North Africa, and East Asia and Pacific, respectively. Countries in the low or middle–low SDI category observed a more pronounced upward trend in PCOS-related CVD incidence, particularly in South Asia. In addition, our result found similar increase trends and regional variations of PCOS-

associated CVD incidence in 10- to 54-year-old women but higher PAFs than that in all-age group women.

Wekker *et al.*12 reported the long-term cardiometabolic disease risk in women with PCOS, focusing on altering serum metabolic indicators such as lipid concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). In addition, Osibogun *et al.*22 reported the association between PCOS and coronary artery calcification. Our meta-analysis comprehensively estimated the association between PCOS and CVD, and found a significant CVD risk for PCOS patients. The mechanisms underlying this association remain poorly understood. Metabolic syndrome, characterized by factors such as hyperinsulinaemia,23 obesity due to insulin resistance,24 hypertension,25 and lipid abnormalities,26 may contribute to cardiovascular events in PCOS patients by directly promoting the development of atherosclerosis.27 This is further supported by Wekker *et al.*'s12 findings of increased risk of hypertension, elevated TC levels, and decreased HDL-C levels in PCOS patients. In addition, a novel study suggests that PCOS may exacerbate cardiac inflammation and alter heart structure after MI by promoting the accumulation of macrophages in cardiac tissue through increased extramedullary myelopoiesis.16 This underscores the importance of PCOS screening in predicting the prognosis of women with coronary artery disease (CAD). Additionally, the research indicates that targeting the suppression of splenic myelopoiesis might be an effective strategy for preventing heart disease in women with PCOS.

It is noteworthy that our research findings indicated an observable upward trajectory in both ASIRs and new case numbers. This trend is evident on a global scale, within specific regions (South Asia, Middle East and North Africa, East Asia and Pacific, and Sub-Saharan Africa), and in most countries studied. However, when specifically examining

the all-cause CVD, we found a declining trend in the ASIRs over the past three decades globally and regionally, which is consistent with the other reports.28 While the PAF for CVD burden still remains higher for some traditional risk factors such as high-salt diet, elevated systolic blood pressure, and smoking,29 our findings suggest that the global increase in PCOS prevalence has contributed to a gradually rising PAF for CVD incidence. This suggests that the prevention, control, and management of CVD in female PCOS patients should receive significant attention. Simultaneously, we acknowledge the potential regional differences highlighted in our meta-analysis. Our subgroup analysis indicates that in the Europe and Central Asia, East Asia and Pacific, and North America regions, the pooled RRs for PCOS women are 1.40, 1.80, and 1.59, respectively. Although the statistical differences among them are not significant, it is crucial to note that the risk of PCOS–CVD in the East Asia and Pacific region is slightly higher than in the other two regions. Therefore, in our analysis, the incidence of PCOS–CVD in the East Asia and Pacific region is underestimated. Additionally, for regions where the CVD risk in PCOS patients has not been reported in the literature, a uniform RR value was applied in our analysis. The heterogeneity within this approach requires further clarification in future studies.

Our study identified a regional pattern in PCOS-associated CVD reduction, with North America experiencing the most significant decrease, followed by Latin America and the Caribbean, and Europe and Central Asia. These trends may be attributed to the earlier CVD management in PCOS in these regions, where labelled women are ‘at risk’ for factors like obesity or hypertension and ‘high risk’ if they have metabolic syndrome, type 2 diabetes mellitus (T2DM), or evident vascular/renal disease.30,31 In addition, the PCOS clinical trials were concentrated in North America and Europe, with extensive meta-analyses indicating that studies assessing the impact of pharmaceutical treatments on the endocrine and metabolic symptoms

in adolescents and adults with PCOS are predominantly conducted in these regions.32 Moreover, non-pharmacological interventions such as lifestyle changes, including diet modification and increased exercise, have been proven to positively affect symptom relief in North America women with PCOS.33 These measures were mostly promoted through the middle or high SDI regions, which align with our subsequent findings, where changes in PCOS-associated CVD ASIRs appeared inversely correlated with the SDI index, which may reflect the enthusiasm for research on the treatment and non-pharmacological interventions of PCOS in these regions and suggest the necessity of conducting relevant treatment studies in other regions. And the above reasons can explain the significant decline in PCOS-associated CVD incidence trend in regions like North America. Our results raise another concern: since PCOS primarily occurs in females before menopause (under 55 years), the prevalence of PCOS in the population under 55 will be higher than the estimated prevalence across the all-age group, which leads to higher PAFs of CVD cases attributed to PCOS in our results, compared with those in the all-age group. Meanwhile, we further found a faster increase trend of PCOS-associated CVD under 55-year-old females. These highlight the importance of focusing on the early occurrence of CVD in PCOS women under 55.

Our research found that the Asian-Pacific and European regions have the highest number of CVD incidences related to PCOS. This can be attributed to the large population base in these regions. In addition, the latest GBD reported high prevalence rates of PCOS and CVD in the Asian-Pacific and European regions,8,28 contributing to higher incidences of PCOS-related CVD in these areas compared with others. In addition, regarding countries, we found more than half (6/10) of the top 10 countries come from these regions (including China, Japan, the UK, and Germany), which collectively contribute to >60% of the global PCOS-associated CVD incidence. The deeper reasons for this

might be multifaceted, including demographic,34 obesity and dietary habit,35 and psychosocial elements, with significant roles played by race and ethnicity. For example, over the past three decades, the rapid economic ascension in the Asia-Pacific region, notably in China, has coincided with an escalation in the prevalence of PCOS-related CVD. This phenomenon is multifactorial: heightened societal pressures accompanying economic growth have engendered alterations in female lifestyle dynamics, including disrupted circadian rhythms, identified as contributory factors to PCOS and CVD.36 Additionally, economic progress has induced shifts in dietary patterns, such as increased sugar consumption, potentially culminating in obesity or insulin resistance, thereby amplifying the risk of PCOS and CVD.36 Concurrently, the economic upturn has spurred an enhanced focus on healthcare, exemplified by China's 'Healthy China 30-year' initiative, fostering heightened vigilance and early intervention in PCOS and CVD among women.37 This highlights the need for increased attention in countries with a significant dual burden of PCOS and CVD, with far-reaching implications for regional health policies, guidelines, and resource allocation.

This study has certain limitations that may affect the accuracy of the results. First, a primary limitation of our study is the heterogeneity within the meta-analysis, which undermines the precision of our estimative results. Despite conducting subgroup and meta-regression analyses based on study characteristics such as region, type, setting, and risk level, potential sources of heterogeneity were not explored. The heightened risk of CVD due to PCOS may be predominantly due to other traditional factors like obesity, insulin resistance, and hypertension. Although we extracted some of these factors, inconsistent reporting in the primary data precluded further subgroup and regression analyses. The heterogeneity in these CVD risk factors may potentially impact the robustness of our risk estimates for CVD occurrence in the PCOS population. Second, as no sufficient

literatures were included for seven World Bank–defined regions, instead we did only include studies for three regions (North America, Europe and Central Asia, and East Asia and Pacific), and the subgroup analysis did not reveal significant differences in RRs by these regions. Thus, we applied the pooled RR value to global and regions without stratification, which is typical in this type of analysis.38–40 Third, our PCOS prevalence and CVD incidence burden data were derived from the GBD Study, which utilizes modeling techniques and incorporates data from varying quality cancer registries in low- and middle-income countries. Fourth, we ultimately synthesized RR, OR, and HR values in our meta-analysis, which need to be cautious about the potential heterogeneity between different measures. Fifth, the research findings indicate that the global incidence of PCOS is slowly increasing, likely due to multiple factors such as improved accessibility to medical resources, increased awareness of women's health, and rising rates of female obesity.9 The growth and distribution of medical resources impact the early detection and management of PCOS in different regions. Another factor is the proposed Rotterdam criteria from 2003,41 which are currently the most widely used diagnostic criteria for PCOS worldwide and significantly enhance the accuracy of PCOS diagnosis. Overall, multiple factors introduced ascertainment bias in the diagnosis of PCOS, emphasizing the need for cautious consideration. Sixth, the principle of PAF requires adjustment for all confounding variables in the analysis. Therefore, we used external adjustment methods19 to obtain all the adjusted effect values for the final meta-analysis and PAF calculation. However, although we externally adjusted unadjusted effect values to obtain adjusted effect values and ultimately included adjusted effect values in the meta-analysis, not every study adjusted for the same variables, which may introduce unavoidable potential bias. Seventh, our study calculated the incidence number of PCOS-associated CVD of women between 10 and 55 years old. However, due to the limited number of studies included, this result should be

interpreted with caution. Finally, considering different criteria of PCOS diagnostic and pathology services in some countries, underestimation of PCOS prevalence and CVD incidence may lead to potential limitations.

In conclusion, our study first estimated the global burden of CVD associated with PCOS. We demonstrated a 1.51-fold higher risk of CVD among PCOS patients than among those without PCOS in the all-age group. Correspondingly, ~ 0.85% of global CVD cases in 2019 were associated with PCOS based on the PAF model and a more than two-fold increase in new PCOS-associated CVD cases from 1990 to 2019. In addition, we found high regional variation in the PCOS-attributed CVD burden, with the highest ASIR increase trend in South Asia. Meanwhile, according to the higher estimated PCOS prevalence in women between 10 and 54 years old, we found higher worldwide and regional PAFs than that in all-age group women. It is worth noting that both the pooled RR values and subsequently calculated incidence rates of PCOS-associated CVD may be influenced by regional and PCOS–CVD-related risk factors. These potential heterogeneities require more specific and detailed research in the future to address and clarify. Current findings emphasize the significance of implementing targeted prevention and control policies in countries with a high PCOS prevalence, especially premature CVD in women with PCOS under 55 years.