Risk of cardiovascular disease in women and men with subfertility: the Trøndelag Health Study

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Objective: To investigate the association between subfertility and risk of cardiovascular disease (CVD) outcomes.
Design: Prospective study.
Setting: Population-based cohort.
Patient(s): We studied 31,629 women and 17,630 men participating in the Trøndelag Health Study.
Intervention(s): Self-reported subfertility. As men were not directly asked about fertility, male partners of female participants were identified through linkage to the Medical Birth Registry of Norway and assigned the fertility information obtained from their partners.
Main Outcome Measure(s): The primary outcomes were stroke and coronary heart disease in women and men with and without a history of subfertility. The secondary outcomes were myocardial infarction and angina (subgroups of coronary heart disease) and any CVD (stroke or coronary heart disease). Information on CVD was available by linkage to hospital records. We used Cox proportional hazards models adjusted for age at participation in the Trøndelag Health Study (linear + squared), birth year, smoking history, cohabitation, and education. Cardiometabolic factors were assessed in separate models.
Result(s): A total of 17% of women and 15% of men reported subfertility. In women, subfertility was modestly associated with an increased risk of stroke (age-adjusted hazard ratio [aaHR], 1.19; 95% confidence interval [CI], 1.02–1.39; adjusted hazard ratio [aHR]; 1.18; 95% CI, 1.01–1.37) and coronary heart disease (aaHR, 1.19; 95% CI, 1.06–1.33; aHR, 1.16; 95% CI, 1.03–1.30) compared

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Consent given by the participants does not open for storage of data on an individual level, in repositories or journals. Researchers who want access to HUNT material for replication should apply to HUNT's Data Access Committee. Access to data sets requires approval from the Regional Committee for Medical and Health Research Ethics in Norway and an agreement with HUNT.
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with fertile women. In men, we observed a weak positive association for stroke (aaHR, 1.11; 95% CI, 0.91–1.34; aHR, 1.10; 95% CI, 0.91–1.33) and a weak inverse association for coronary heart disease (aaHR, 0.92; 95% CI, 0.81–1.05; aHR, 0.93; 95% CI, 0.81–1.06).
Conclusion(s): We observed modestly increased risks of CVD outcomes in women and some weak associations in men, although with no strong statistical evidence on sex differences. We acknowledge that we were only able to include men linked to pregnancies ending at 12 completed gestational weeks or later, potentially resulting in selection bias and misclassification of history of subfertility in analyses of male partners. Despite the large sample size, our results indicate the need for larger studies to obtain precise results in both sexes and determine whether there are true sex differences. (Fertil Steril® 2022;■:■–■. ©2022 by American Society for Reproductive Medicine.)
Key Words: Subfertility, infertility, cardiovascular disease, the HUNT Study

Fertility rates are decreasing in many European countries (1). Subfertility is defined as the inability to conceive after trying for >12 months and is estimated to affect between 10% and 15% of couples (2, 3). It may be caused by underlying female or male characteristics, or both, but remains unexplained in approximately 25%–30% of all cases (3, 4).

Some traits related to subfertility, including polycystic ovary syndrome (PCOS), menstrual irregularities, and endometriosis in women (5–10), and varicocele in men (11–13), share common endocrinologic pathways with cardiovascular diseases (CVDs). Pregnancy-related complications, such as preterm delivery and preeclampsia, may be more common among women with subfertility than among fertile women and could mediate the increased risk of CVD (14–16). Subfertility and CVD also share common risk factors, e.g., high blood pressure, fasting glucose, and cholesterol (17–21).

Previous studies investigating the association between subfertility and risk of CVD have made inconsistent conclusions. Among previous studies investigating the association between subfertility and CVD, four indicated an increased risk of CVD among women with subfertility whereas two studies found no difference in the risk, potentially because of differences in statistical power or different measures of fertility problems (22–27). Our previous study was conducted within The Norwegian Mother, Father, and Child Cohort Study (MoBa) consisting of 64,064 women and 50,533 men (7,863 women and 6,036 men with subfertility, defined as having had regular intercourse without contraception for >12 months before they became pregnant), suggested an increased risk of overall CVD associated with prolonged time-to-pregnancy in both sexes (26).

All previous studies except the one conducted by Magnus et al. (26) included only women, and all studies except the study conducted by Murugappan et al. (27) included only women or couples who eventually conceived. There might be sex-specific factors associated with differences in CVD risk according to subfertility, including sex-specific gene expressions, levels of sex hormones, and underlying disorders related to fertility potential (e.g., PCOS and endometriosis), pregnancy complications, and use of assisted reproductive technologies (28–32). This highlights the value of further investigating the relationship between subfertility and the risk of CVD in both sexes.

Therefore, the objective of the present study was to study the association between subfertility and CVD in both women and men in a large Norwegian cohort setting. We hypothesized that women and men with a history of subfertility were at a greater risk of developing CVD.

MATERIALS AND METHODS

The Trøndelag Health Study

We studied women and men participating in the Trøndelag Health Study (HUNT) (33). Participants were recruited during four separate data collection surveys, and they could participate in more than one survey. The HUNT1 survey was performed in 1984–1986 (77,212 people), the HUNT2 survey in 1995–1997 (65,237 people), the HUNT3 survey in 2006–2008 (50,807 people), and the HUNT4 survey were performed in 2017–2019 (56,042 people) (33, 34). Because information on fertility was only collected in HUNT2, HUNT3, and HUNT4, we restricted our analyses to participants in these surveys. Information from the participants was obtained through questionnaires, clinical measurements, and biologic samples. We linked self-reported information with registrations in the Medical Birth Registry of Norway and the hospital records from the Trøndelag Hospital Trust using unique national identification numbers.

Study Population

If women had participated in more than one of the three surveys, we used the latest time point of participation where they were younger than 50 years old, or closest to if they were older at all time points. Men were not directly asked about fertility, so we assigned the fertility information obtained from women to their male partners. We identified male partners of women participating in HUNT who were participating in HUNT themselves through linkage to the birth registry. This means that we were only able to identify male partners of women who had a registered pregnancy ending at 12 completed gestational weeks or later. We excluded men who were registered in the birth registry as having changed partners, or whose partners were registered as having changed partners, before participation in HUNT, indicated by having given birth to children with different partners.

FIGURE 1

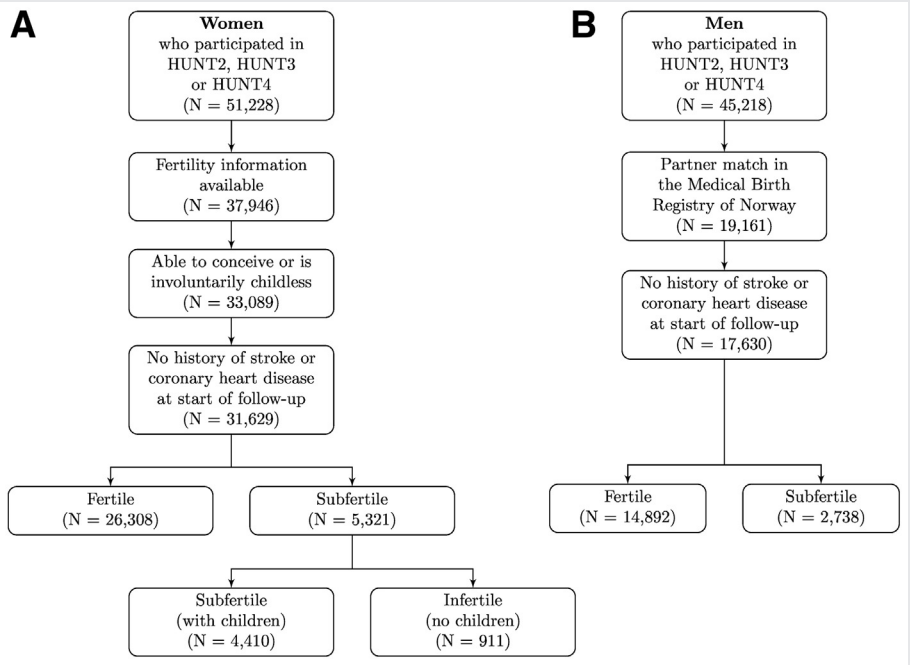

Illustration of the eligible study population for (**A**) women and (**B**) men.

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Fertility

In the HUNT questionnaires, women were asked the question "Have you ever tried for more than a year to become pregnant?" Those who answered "yes" were classified as subfertile, and those who answered "no" were classified as fertile. Women classified as fertile yet who did not report having any children in the HUNT questionnaires nor had a registered pregnancy in the birth registry, would either be too young to have started trying or could be voluntarily childless. Therefore, they were excluded. Women classified as subfertile, and who did not report having any children in the HUNT questionnaires nor had any registered pregnancies in the birth registry, were additionally classified as infertile (Fig. 1). The male fertility status was based on the female report as fertile or subfertile. Because we were only able to identify the male partners of women who had a registered pregnancy in the birth registry, we could not classify any men as infertile. Women with a history of subfertility were also asked the question "How old were you the first time you had trouble getting pregnant?" We had information on all pregnancies ending at 16 completed gestational weeks onwards from the birth registry for the period of 1967–2019 (35).

Cardiovascular Diseases

We used self-reported information on stroke, myocardial infarction, and angina at the time of recruitment and registrations in the hospital records of Nord-Trøndelag Hospital Trust before inclusion in HUNT to identify a history of CVD. Incident cases of CVD in the hospital records were available from September 1987 onwards, and we had follow-up information available until July 2020 (administrative codes shown in Supplemental Table 1, available online). The primary outcomes were stroke and coronary heart disease, and the secondary outcomes were myocardial infarction and angina (subgroups of coronary heart disease) and any CVD (stroke or coronary heart disease).

Covariates

We included a broad range of baseline background characteristics that might influence both subfertility and CVD (Table 1). This included age at participation (continuous), birth year (continuous), body mass index (BMI; measured as weight in kg/height in m^2; underweight, BMI $<$ 18.5 kg/m^2; normal weight, 18.5 kg/m^2 $\leq$ BMI $<$ 25.0 kg/m^2; overweight, 25.0 kg/m^2 $\leq$ BMI $<$ 30.0 kg/m^2; and obese, BMI $\geq$ 30.0 kg/m^2), systolic and diastolic blood pressure (continuous; mm Hg), diabetes (yes or no), serum cholesterol (continuous; mmol/L), pack-years of smoking (smokers with pack years $\leq$20 or $>$20, former smokers with pack years $\leq$20 or $>$20, or never smoked), cohabitation (yes or no), and education level (higher education, upper secondary school, or secondary school).

The underweight and normal weight categories were merged in the statistical analyses because of their low sample sizes. If participants reported the use of blood pressure medication, we added 10 mm Hg to their measured systolic and diastolic blood pressure. This value was

TABLE 1

Distribution of background characteristics among eligible women and men included in our study population.

	Women		Men	
Characteristics	**Fertile**	**Subfertile**	**Fertile**	**Subfertile**
Count, n	26,308	5,321	14,892	2,738
Age at participation, mean (SD)	47.9 (12.1)	45.1 (10.2)	48.2 (11.1)	45.9 (10.6)
Age at participation, n (%)				
19–29	1,537 (5.9)	342 (6.4)	851 (5.7)	200 (7.3)
30–39	4,587 (17.4)	1,126 (21.2)	2,517 (16.9)	559 (20.4)
40–49	10,864 (41.3)	2,592 (48.7)	5,086 (34.2)	1,067 (39.0)
50–59	5,057 (19.2)	766 (14.4)	4,291 (28.8)	644 (23.5)
60–69	3,218 (12.2)	405 (7.6)	1,704 (11.4)	230 (8.4)
≥69	1,045 (4.0)	90 (1.7)	443 (3.0)	38 (1.4)
BMI, n (%)				
Normal weight (18.5 ≤ BMI < 25.0)	10,996 (41.7)	2,133 (40.1)	4,274 (28.7)	765 (27.9)
Underweight (BMI < 18.5)	196 (0.8)	44 (0.8)	24 (0.2)	2 (0.1)
Overweight (25.0 ≤ BMI < 30.0)	9,857 (37.5)	1,877 (35.3)	7,819 (52.5)	1,406 (51.4)
Obese (BMI ≥ 30.0)	5,186 (19.7)	1,248 (23.4)	2,666 (17.9)	543 (19.8)
Missing	73 (0.3)	19 (0.4)	109 (0.7)	22 (0.8)
Blood pressure, mean (SD)				
Systolic	129.3 (20.3)	126.9 (18.7)	135.7 (17.3)	134.0 (16.6)
Diastolic	76.5 (12.2)	75.7 (11.8)	81.6 (11.9)	80.6 (11.8)
Missing	57 (0.2)	10 (0.2)	113 (0.8)	24 (0.9)
Cholesterol, mean (SD)				
Serum cholesterol	5.6 (1.2)	5.5 (1.2)	5.7 (1.1)	5.6 (1.1)
Missing	249 (0.9)	51 (1.0)	194 (1.3)	40 (1.5)
Diabetes, n (%)				
No	25,714 (97.7)	5,167 (97.1)	14,497 (97.3)	2,678 (97.8)
Yes	533 (2.0)	140 (2.6)	365 (2.5)	53 (1.9)
Missing	61 (0.2)	14 (0.3)	30 (0.2)	7 (0.3)
Smoking, n (%)				
Nonsmoker	11,237 (42.7)	2,048 (38.5)	6,332 (42.5)	1,164 (42.5)
Former smoker, pack years 0–20	4,979 (18.9)	1,037 (19.5)	3,080 (20.7)	578 (21.1)
Former smoker, pack years >20	2,884 (11.0)	690 (13.0)	2,102 (14.1)	367 (13.4)
Smoker, pack years 0–20	3,787 (14.4)	795 (14.9)	1,515 (10.2)	304 (11.1)
Smoker, pack years >20	3,029 (11.5)	695 (13.1)	1,685 (11.3)	295 (10.8)
Missing	392 (1.5)	56 (1.0)	178 (1.2)	30 (1.1)
Cohabitation, n (%)				
Living with cohabitant	21,849 (83.1)	4,575 (86.0)	13,708 (92.1)	2,504 (91.5)
Living without cohabitant	4,295 (16.3)	679 (12.7)	792 (5.3)	159 (5.8)
Missing	164 (0.6)	67 (1.3)	392 (2.6)	75 (2.7)
Children, n (%)				
0	0 (0.0)	644 (12.1)	0 (0.0)	82 (3.0)
1	2,950 (11.2)	1,057 (19.9)	1,114 (7.5)	496 (18.1)
2	10,621 (40.4)	1,875 (35.2)	6,167 (41.4)	1,151 (42.0)
≥2	12,737 (48.4)	1,478 (27.8)	7,611 (51.1)	1,009 (36.9)
Missing	0 (0.0)	267 (5.0)	0 (0.0)	0 (0.0)
Education, n (%)				
Higher education	8,759 (33.3)	1,977 (37.1)	4,752 (31.9)	930 (34.0)
Upper secondary school	3,057 (11.6)	700 (13.2)	1,455 (9.8)	320 (11.6)
Secondary school	14,277 (54.3)	2,606 (49.0)	8,580 (57.6)	1,478 (54.0)
Missing	215 (0.8)	38 (0.7)	105 (0.7)	10 (0.4)
Age at first experienced subfertility, n (%)				
19–29		3,580 (67.3)		
30–39		1,041 (19.6)		
>39		48 (0.9)		
Missing		652 (12.2)		
Preterm birth, n (%)				
No	20,476 (77.8)	3,622 (68.0)		
Yes	2,468 (9.4)	605 (11.4)		
Missing	3,364 (12.8)	1,094 (20.6)		

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TABLE 1

Continued.

Characteristics	Women		Men	
	Fertile	Subfertile	Fertile	Subfertile
Preeclampsia				
No	21,563 (82.0)	3,932 (73.9)		
Yes	1,318 (5.2)	295 (5.5)		
Missing	3,364 (12.8)	1,094 (20.6)		

Note: The units for the data are as follows: age (years); BMI (weight in kg/height in m^2); blood pressure (mm Hg); serum cholesterol (mmol/L). BMI = body mass index.

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selected based on previously reported estimates for the effect of medication on reducing blood pressure (36–38). Information about the use of cholesterol-lowering medication was not available. Missing information regarding education was estimated based on the Erikson Goldthorpe Portocarero social class scheme in HUNT2 and HUNT4, and based on the Standard Classification of Occupations (STYRK-08) work codes in HUNT3 (39, 40). In separate analyses in women, we included information on whether they had ever experienced preeclampsia (yes or no) or a preterm birth (birth before 37 weeks of pregnancy; yes or no) obtained from the birth registry (41, 42). Information on gestational diabetes was available in the birth registry but was not included in the statistical analyses because this was strongly underreported in Norway in a large part of our study period (43).

Measures of BMI, systolic and diastolic blood pressure, and serum cholesterol were taken as part of the HUNT examinations by trained health personnel. Although the question about fertility was asked retrospectively, we assumed that the confounding pattern also reflected the values at the time when participants were trying to get pregnant.

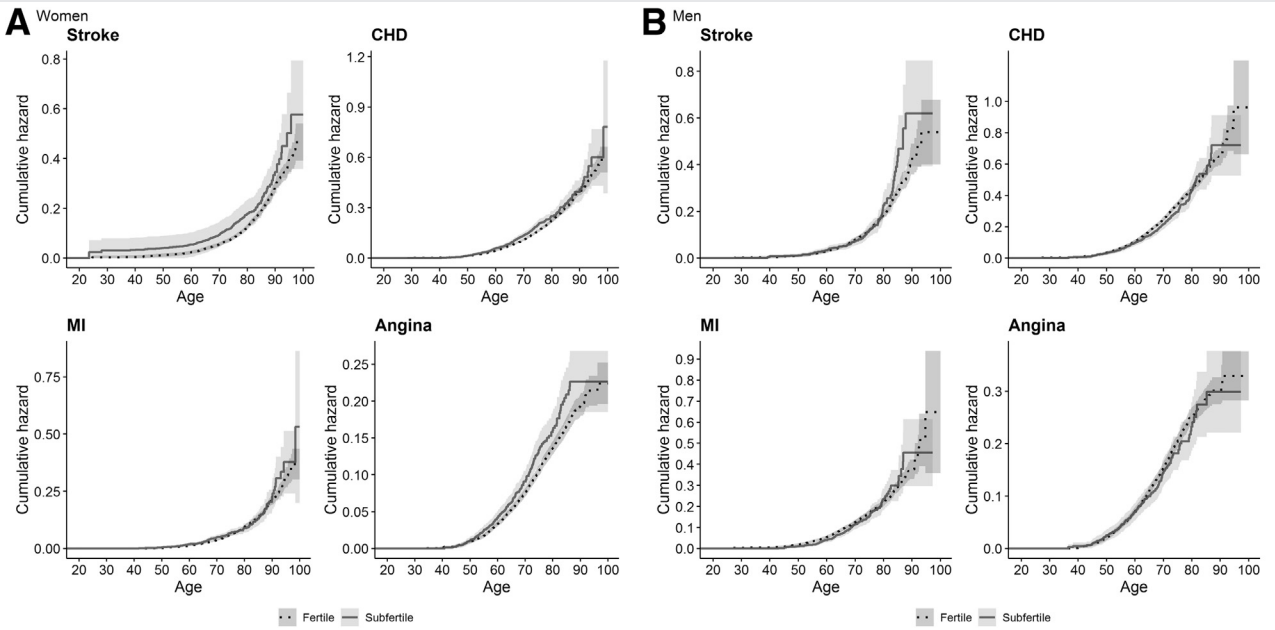
Statistical Analyses

We described the risk of CVD outcomes according to subfertility using Kaplan Meier survival plots and examined the magnitude of the associations using Cox proportional hazards regression. The validity of the proportional hazard assumption was evaluated using Schoenfeld residuals. Participants were observed from the date of HUNT participation, defined as the start of follow-up, until their first registered case of the event of interest, death from other causes, moving out of Trøndelag, or the last day of July 2020 for those who were alive and resident in Trøndelag. We excluded participants with a history of any CVD outcomes at the start of follow-up. In multivariable analyses, we adjusted for age at the start of follow-up (linear + squared) in model 1, for covariates in model 1 + possible confounders related to socioeconomic status (birth year, cohabitation, smoking history, and education level) in model 2, and for covariates in model 2 + possible confounders or mediators related to cardiometabolic health (BMI, cholesterol in serum, systolic and diastolic blood pressure and diabetes) in model 3. Age at the start of follow-up was adjusted for in all models because individuals who were older on the respective participation dates were expected to have higher rates of incident CVD. Because we measured lifetime subfertility, we also expected that the probability of being classified as subfertile was greater among the older population. The birth year was adjusted for to capture differences in birth cohorts, such as paradigm changes for diagnostics of CVD outcomes and subfertility. We adjusted for cardiometabolic health measures in separate models as these were taken at the time of participation in HUNT, several years after the participants experienced fertility problems, and their role as confounders, as opposed to mediators, was unclear (Supplemental Fig. 1, available online). Missing information on covariates, ranging from 0.0% to 2.7% (Table 1), was imputed using multiple imputations by chained equations (number of imputations = 24) and the R package *MICE* (44).

Analyses were performed in women and men separately. In the main analyses, we compared the risk of CVD outcomes between participants with and without subfertility. Additional analyses included stratifying by median birth year (below and above 1956), by age at first experienced subfertility in women (below and above 30 years), and by median years since first experienced subfertility in women (below and above 18 years). We also analyzed women with infertility (no children) separately from women with subfertility (with children), thus dividing the exposure into three groups: fertile, subfertile, and infertile. In a fourth multivariable model (model 4) we investigated pregnancy complications (preeclampsia and preterm birth) as mediators in women aged ≥18 years during the period in which we had data from the birth registry (1967 and onwards). We fitted linear predictive models to test for potential mediators in multiple mediation analyses using the R package *mma* (45). We included interaction terms between subfertility and potential mediators if we found significant exposure-mediator interactions ($P<.5$; Supplemental Table 2). We assumed that the confounders included in our main analyses would also act as confounders of the mediator-outcome relationships. For efficiency and practical reasons, the mediation analyses were performed on complete case data.

We conducted multiple sensitivity analyses, including one analysis in which we restricted our study population of women to those with a registered partner also participating in HUNT, and one where we restricted our study population of both women and men to those with complete cases only before imputation. To investigate the degree of

FIGURE 2



Kaplan Meier curves show the cumulative hazard of stroke, coronary heart disease (CHD), myocardial infarction (MI) and angina across age according to subfertility in (**A**) women and (**B**) men. Subfertility is defined as the failure to achieve pregnancy after 12 months or more of trying.

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misclassification when assigning women's fertility status to the men, we randomly assigned 10%, 20%, 30%, and 40% of men classified with subfertility to be in the reference category (fertile). The random assignment was repeated 1,000 times using bootstrapping.

We assumed that participants who experienced other CVD events were still at risk of the event of interest in each given analysis. If participants had another CVD event before the event of interest, they were neither removed from the analysis nor censored. Because we were considering etiology and not prediction, we did not include death from other causes as a competing event (46). In separate analyses, we included multiplicative interaction terms between sex and subfertility to test whether any associations between subfertility and CVD risk were statistically different between the sexes, clustering the observations by partners to calculate robust standard errors. We also calculated E-values to investigate the robustness of associations (47).

Software

Analyses were performed in R software version 4.0.3. Code for data management and statistical analyses is available at github.com/karolinehskara/HUNT_subfertility_CVD.

Ethical Approval

The current study was approved by the Regional Committee for Medical and Health Research Ethics of South/East Norway (REK 2017/78545).

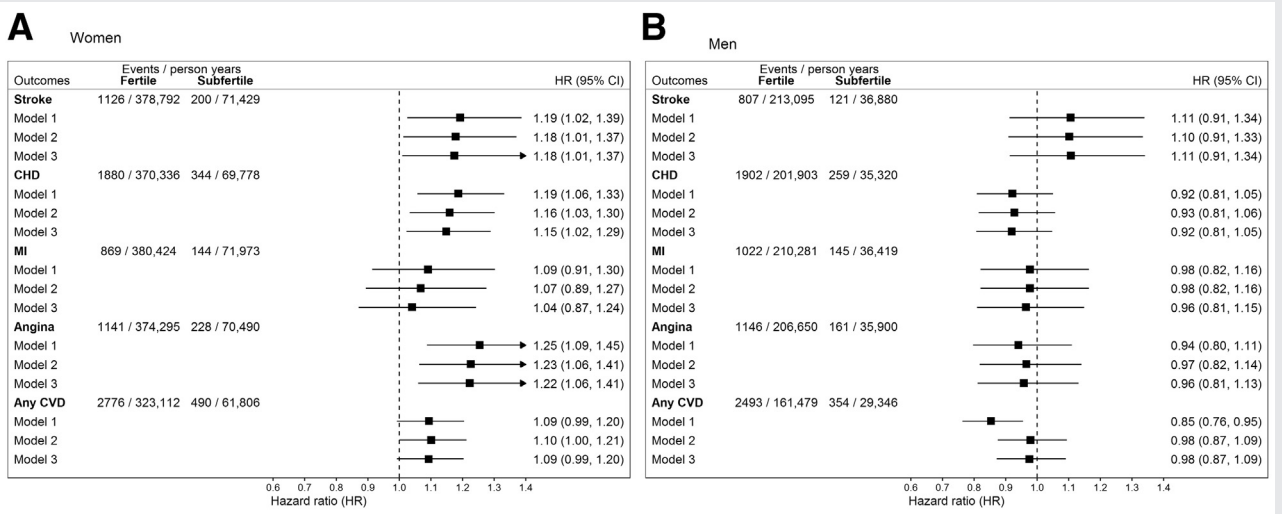
RESULTS

A total of 31,629 women and 17,630 men were included in the analyses (Fig. 1). The average age at the end of follow-up for any CVD event was 60 years for women and 59 years for men. A total of 17% of women and 15% of men experienced subfertility, and 97.1% of all women had been pregnant by the end of 2019. Consequently, 3% of the female population was classified with infertility. The average follow-up time was 14 years (range, 0.01–24.9 years; SD, 9 years). The average ages of onset for the different outcomes in women were 75 years for stroke, 77 years for myocardial infarction, and 71 years for angina. In men, it was 69 years for stroke, 72 years for myocardial infarction, and 73 years for angina. More women with subfertility had higher education, were smokers, and had a cohabitant compared to women who never reported subfertility, although the differences were not large. A tendency toward having higher education was seen among subfertile men (Table 1).

Subfertility and CVD Outcomes in Women

The rates of first-time stroke, coronary heart disease, myocardial infarction, angina, and any CVD in the female population were 30, 50, 22, 31, and 85 per 10,000 person-years, respectively. The Kaplan Meier curves indicated a modest increase in the risk of some CVD outcomes in women (Fig. 2). We found a modest increased risk of coronary heart disease (age-adjusted hazard ratio in model 1 [aaHR], 1.19; 95% confidence interval [CI], 1.06–1.33; adjusted hazard ratio in

FIGURE 3



Risk of stroke, coronary heart disease (CHD), myocardial infarction (MI), angina and any cardiovascular disease (CVD; stroke or CHD) according to subfertility in (**A**) women and (**B**) men. Subfertility is defined as the failure to achieve pregnancy after 12 months or more of trying. Model 1: adjusted for age (linear + squared). Model 2: model 1 + adjusted for birth year, smoking history, cohabitation, and education. Model 3: model 2 + adjusted for body mass index (BMI), systolic and diastolic blood pressure, serum cholesterol and diabetes.

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model 2 [aHR], 1.16; 95% CI, 1.03–1.30), angina (aaHR, 1.25; 95% CI, 1.09–1.45; aHR, 1.23; 95% CI, 1.06–1.41), stroke (aaHR, 1.19; 95% CI, 1.02–1.39; aHR, 1.18; 95% CI, 1.01–1.37) and any CVD (aaHR, 1.09; 95% CI, 0.99–1.20; aHR, 1.10; 95% CI, 1.00–1.21) in women with subfertility (Fig. 3). We found a weak positive association between subfertility and myocardial infarction in women (aaHR, 1.09; 95% CI, 0.91–1.30; aHR, 1.07; 95% CI, 0.89–1.27). There were no strong deviations from the proportional hazards assumption.

Subfertility and CVD Outcomes in Men

The rates of first-time stroke, coronary heart disease, myocardial infarction, angina, and any CVD in men were 37, 91, 47, 54, and 149 per 10,000 person-years, respectively. We found weak and no associations between subfertility and CVD outcomes in men. The HRs for men were 1.11 (95% CI, 0.91–1.34) in model 1 and 1.10 (95% CI, 0.91–1.33) in model 2 for stroke, 0.92 (95% CI, 0.81–1.05) in model 1 and 0.93 (95% CI, 0.81–1.06) in model 2 for coronary heart disease, 0.98 (95% CI, 0.82–1.16) in both model 1 and 2 for myocardial infarction, 0.94 (95% CI, 0.80–1.11) in model 1 and 0.97 (95% CI, 0.82–1.14) in model 2 for angina, and 0.85 (95% CI, 0.76–0.95) in model 1 and 0.98 (95% CI, 0.87–1.09) in model 2 for any CVD (Fig. 3). The coefficients for the multiplicative interaction terms between subfertility and sex were statistically significant in the analyses of angina and coronary heart disease ($P_{interaction} = 0.042$ for angina, $P_{interaction} = 0.022$ for coronary heart disease, and $P_{interaction} \geq 0.26$ for other outcomes, Supplemental Table 3). Randomly assigning men classified with subfertility to be in the reference category (fertile) did not change the results (Supplemental Fig. 2).

Additional Analyses

The stratified analyses by birth year among women and men (Supplemental Fig. 3 and 4), by age at first experience with subfertility among women (Supplemental Fig. 5), and by years since the first experience with subfertility among women (Supplemental Fig. 6) revealed similar results across strata. There was a suggestive increase in the risk of myocardial infarction in women who experienced subfertility during the past 18 years compared with fertile women, but not in women who experienced subfertility >18 years ago. The results from the subgroup analyses exploring the risk of CVD outcomes according to subfertility (with children) and infertility (no children) were also similar to the main results (Supplemental Fig. 7). Including cardiometabolic factors and pregnancy complications in our analyses of women did not substantially change our findings (Fig. 3 and Supplemental Fig. 8), and the mediation analyses revealed no strong evidence of the indirect effects of either cardiometabolic risk factors or pregnancy complications (Supplemental Fig. 9 and 10). We found significant exposure-mediator interactions between subfertility and serum cholesterol in men (Supplemental Table 2). The associations between subfertility and each of the CVD outcomes did not change when only including participants with complete cases of covariates before imputation (Supplemental Fig. 11), nor in the analyses restricted to only women with identified male partners in HUNT (Supplemental Fig. 12).

DISCUSSION

Our results suggest that women with subfertility have an increased risk of some CVD outcomes. Specifically, we found

that women with a history of subfertility had a modest increased risk of coronary heart disease, angina, and stroke compared with fertile women. We also observed a suggestive increase in the risk of myocardial infarction in women with infertility, despite the low number of events. We found a weak positive association of stroke and some weak inverse associations of the other outcomes in men, although with no strong statistical evidence of sex differences.

Our findings are in line with those of some previous studies reporting an increased risk of CVD in women with subfertility (22,24,26,27). Findings from MoBa indicated an increased risk of overall CVD with a time-to-pregnancy of 4–12 months (aHR, 1.07; 95% CI, 1.03–1.09) and >12 months (aHR, 1.14; 95% CI, 1.08–1.20) in women, compared with those conceiving within 3 months of trying (26). Parikh et al. (22) indicated an increased risk of coronary heart disease, stroke, and heart failure in women who reported having tried for >5 years to conceive compared with those who conceived within the first year (aHR, 1.19; 95% CI, 1.02–1.39), whereas they found no increased risk among women who reported having tried for 1–2 (aHR, 1.07; 95% CI, 0.92–1.23) or 3–4 years (aHR, 1.01; 95% CI, 0.83–1.23). Our findings also agree with those of a cross-sectional study of 744 US women aged 20–59 years, in whom those retrospectively reported having tried to conceive for >12 months were 1.83 (95% CI, 1.15–2.89) times more likely to develop heart failure, coronary heart disease, heart attack or stroke (24). A study from the Women's Health Initiative reported an increased risk of atherosclerotic CVD among postmenopausal women who had tried for more than a year to become pregnant (aHR, 1.02; 95% CI, 0.99–1.06). Their result was strengthened when restricting their exposed group to women who had never conceived (27). One of the studies we identified that did not report an increased risk of CVD was a Danish study conducted by Bungum et al. (25) investigating women with infertility diagnoses (aHR, 0.98; 95% CI, 0.85–1.14).

Less is known about the association between subfertility and CVD in men. In our previous analyses in MoBa, we found an increased risk of overall CVD in men with a time-to-pregnancy of 4–12 months (aHR, 1.06; 95% CI, 1.00–1.10) and >12 months (aHR, 1.07; 95% CI, 1.01–1.14), compared with those who conceived within 3 months of trying (26). This contrasts the results of the present study, although we acknowledge that there is potential selection bias and misclassification in the history of subfertility in male partner analyses. Additionally, our analyses in men had lower power than those in women.

Comparisons with other studies are limited by the varying definitions that are used for subfertility and varying covariables that are controlled for in main analyses. Previous studies either failed to adjust for key confounders, such as BMI, smoking, and blood pressure/hypertension, or adjusted for both confounders and potential mediators in main analyses (22,24,25), which can result in biased causal effect estimates. In the studies conducted by Magnus et al. (26) and Parikh et al. (22), diabetes was treated as a confounder, whereas late-onset diabetes could also mediate the relationship between subfertility and risk of CVD through its risk factors, such as hyperglycemia in women with PCOS (48,49).

Endometriosis and PCOS are genetically and clinically linked with subfertility in women (50). Endometriosis may increase women's risk of coronary heart disease, hypercholesterolemia, and hypertension (51,52), and women with PCOS are known to have a worse profile with cardiometabolic risk factors that could increase the risk of developing future CVD (49). We acknowledge that there is a possibility that such diagnoses or other underlying causes of subfertility could cause both subfertility and CVD. Data on the presence of underlying causes of subfertility was not available for our study population, but adjusting for CVD risk factors or pregnancy complications did not change our findings. However, our E-value calculations suggested that any unmeasured confounders would have to be associated with a 1.4-fold increased risk of both subfertility and any CVD to completely attenuate the effect estimate to the null value. This does not seem implausible, with potential unmeasured factors, including diet, medical conditions, familial history of CVD, and shared underlying genetic predisposition (53,54).

Our study presents several strengths. Validation studies indicate high accuracy of the registrations in the hospital records (55–57). The fact that we were able to identify women who never conceived, possibly at a high risk of CVD, is a major strength. We were also able to capture the lifetime history of subfertility and not just subfertility relating to one pregnancy. We had a relatively broad age range in our study population and a long follow-up time. Another advantage of our study is that the HUNT cohort includes directly measured CVD risk factors, such as blood pressure, cholesterol and BMI.

Our study also has limitations. Although we only included men from couples who had not changed partners before they participated in HUNT, we cannot be sure that a woman's fertility information correctly reflected her partner's fertility status, and misclassification of fertility history among men is possible. However, we would expect any misclassification to be nondifferential with respect to the outcome and, therefore, underestimate any true associations. We were also unable to distinguish between female and male causes of fertility problems, as we could only measure couple-level subfertility. Another important limitation of our study is that we did not have information on the possible underlying causes of subfertility, such as PCOS and endometriosis, which could contribute to residual confounding. Therefore, studies with information regarding whether fertility problems were because of female or male causes, or both, are required in the future. In addition, we were unable to include any patients with CVD who died before getting to the hospital. If there is a true association between the CVD outcomes and subfertility, this might attenuate the estimates of lifetime risk.

CONCLUSION

In conclusion, subfertility was modestly associated with all CVD outcomes in women. We found some weak associations in men, although we acknowledge that we did not find robust statistical evidence for sex differences for all outcomes and that selection bias and misclassification of fertility history could be present in the analyses of men. Further large studies

investigating the relationship between subfertility and CVD in women and men that have sex-specific causes of subfertility, can adjust for early life predisposition to CVD, and are large enough to explore sex differences are important.

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