Association of infertility with premature mortality among US women: Prospective cohort study

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The Lancet Regional Health - Americas 2022;7: 100122
Published online 16 November 2021
https://doi.org/10.1016/j.lana.2021.100122

Summary

Background Infertility has been associated with common chronic non-communicable diseases. However, the association of infertility with long-term mortality is unclear.

Methods We followed 101,777 women aged 25–42 years at enrollment between 1989 and 2017. Biennial questionnaires updated participants' infertility status and underlying reasons for infertility throughout their reproductive lifespan. Hazard ratios (HRs) for the associations of infertility with the risk of premature mortality (death before age 70 years) were estimated using Cox proportional hazards models.

Findings During 28 years of follow-up, 2174 women died before age 70 years. Infertility was associated with an HR of 1.26 (95% confidence interval: 1.15 to 1.38) for premature death. This relation was largely driven by deaths from cancer (HR = 1.22, 1.08 to 1.39) and was stronger among women reporting infertility at a younger age (HR = 1.35, 1.19 to 1.52 for age ≤ 25 years; 1.23, 1.10 to 1.38 for age 26–30 years; and 1.10, 0.91 to 1.32 for age > 30 years, compared to no infertility). The premature mortality risk was also higher for women who didn't become pregnant after their first report of infertility (HR = 1.39, 1.25 to 1.54) than among women who reported at least one pregnancy after infertility (HR = 1.12, 1.00 to 1.26). When contributing diagnoses of infertility were evaluated, a greater risk of all-cause mortality was associated with infertility due to ovulatory disorders (HR = 1.28, 1.09 to 1.51) and endometriosis (HR = 1.50, 1.22 to 1.83).

Interpretation Infertility may be associated with a greater risk of premature mortality, particularly cancer mortality.

Funding The National Institutes of Health grants.

Key words: Infertility, Premature mortality, Women, Public health

Introduction

Premature mortality from non-communicable diseases (NCDs) is a major public health burden. The absolute number of deaths due to NCDs in people aged 30–69 years increased from 12.5 million in 2000 to 15.2 million in 2016 worldwide.[1,2] Public awareness of the risk factors for NCDs is urgently needed to achieve the Sustainable Development Goal of a one-third reduction in premature mortality from NCDs before 2030.[3] Apart from well-established risk factors (e.g., tobacco smoking, overweight/obesity, unhealthy diet, and

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Research in context

Evidence before this study

Previous studies suggest that women who have experienced infertility may have an elevated risk of common chronic non-communicable diseases. However, the association of infertility with long-term mortality is unclear.

Added value of this study

Our study is the first to explore the associations of infertility and underlying reasons for infertility with the risk of all-cause and cause-specific premature mortality. Among 101,777 women from the Nurses' Health Study II (NHSII), we found that infertility throughout their reproductive lifespan, particularly occurring before age 26 years and without any additional pregnancies, was associated with a greater long-term risk of premature mortality. The relation was mainly driven by the increased risk of mortality due to cancer (i.e., digestive organs and peritoneum, genito-urinary organs, and lymphatic and haematopoietic tissue) and non-malignant diseases of gastrointestinal system. When contributing causes of infertility were evaluated, a greater risk of all-cause mortality was observed among women who reported infertility due to ovulatory disorders and endometriosis.

Implications of all the available evidence

Our results suggest that infertile women with a history of infertility before age 40 years may benefit from further evaluation of premature mortality risk beyond meeting their reproductive needs.

physical inactivity),[4] growing evidence suggests that some key reproductive traits (e.g., gravidity, parity, and pregnancy complications) may be associated with long-term morbidity and mortality due to NCDs.[5–7]

Infertility is characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with their partner.[8] Up to one in six couples in Western countries experience infertility.[9] The rates of infertility are much higher in some regions of the world, reaching 30%, for instance, in South/Central Asia, Sub-Saharan Africa, North Africa/Middle East, and Central/Eastern Europe.[10] Infertility is often physiologically linked with other diseases and disorders (e.g., polycystic ovary syndrome, premature ovarian insufficiency) and has been associated with a greater incidence of diabetes, cardiovascular disease (CVD), and cancer in both men and women,[11,12] suggesting that fertility could serve as an unspecific marker for future overall health status. However, evidence linking infertility with mortality is extremely scarce.[13] Moreover, it is unclear whether different underlying causes of infertility have a similar association with mortality risk. To fill this important knowledge gap, we investigated the association of infertility (overall and according to major underlying diagnoses) with all-cause and cause-specific premature mortality among a cohort of women who have been followed prospectively starting in their reproductive-age years and have repeatedly updated their reproductive, lifestyle and health-related characteristics over three decades.

Methods

Study design

The Nurses' Health Study II (NHSII) is an ongoing prospective cohort following 116,429 female U.S. nurses since1989 (then aged 25–42 years).[14] At baseline and biennially thereafter, participants completed mailed or electronic questionnaires, which collected detailed information on reproductive characteristics, lifestyle, and health-related factors. The response rate of each follow-up cycle was > 90%. The NHS II protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Return of questionnaires indicated informed consent.

NHS II participants were eligible for inclusion in this analysis if they had ever been pregnant or attempted conception without success at baseline (i.e., gravid or reported infertility) or if they became pregnant or reported infertility during follow-up. We excluded women who had missing data on birthday (n = 17), who reported a diagnosis of CVD (n = 875) or cancer (n = 2174) prior to cohort enrollment (1989), or who never returned follow-up questionnaires (n = 1332), leaving 101,777 women in the current analysis (see eFig. S1).

Ascertainment of infertility

Participants were asked on a biennial questionnaire from 1989 to 2001, and every other questionnaire thereafter through 2009, whether they had tried to become pregnant for more than 1 year without success. Assessment of infertility stopped after 2009 because most NHS II participants had completed their reproductive years (youngest participant 45 years old in 2009). Participants who responded 'yes' were asked to select whether their inability to conceive was attributed to one or more following reasons: "no investigation done", "cause not found", "tubal blockage", "ovulatory disorder", "endometriosis", "cervical mucus factors", "spouse/partner factors", or "other reason". Overall infertility was defined as infertility due to any cause. As for infertility treatment, the use of clomiphene and

gonadotropins for ovulation induction was ascertained every 2–4 years since 1993. Self-reported infertility has been validated among a subset of 100 randomly selected women reporting ovulatory infertility from this cohort. Among women who responded to the supplementary questionnaire on infertility diagnosis and treatment (n = 90), 93.3% reported a confirmatory diagnostic test or treatment.[15] Among 40 of the randomly selected 100 women with medical records, 95% of self-reported diagnostic tests or treatments were confirmed through record review.[15]

Assessment of covariates

Height, race/ethnicity, age at delivery of first pregnancy, menstrual cycle length at ages of 18–22 years, age at menarche, and oral contraceptive use before age 18 years were self-reported at baseline. Information on weight, reproductive characteristics, cigarette smoking status, and health-related factors were self-reported at baseline and updated biennially. Time-varying body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared. Physical activity was ascertained at baseline and quadrennially thereafter. Dietary intake, including alcohol consumption, was assessed quadrennially since 1991 using an extensively validated semiquantitative food frequency questionnaire (SFFQ).[16,17] The Alternate Healthy Eating Index (AHEI) score was computed based on SFFQ as a summary measure of diet quality for fruit, vegetables, nuts and legumes, red and processed meat, whole grains, alcohol, sodium, trans fat, long-chain omega-3, and other polyunsaturated fats,[18] with higher scores indicating healthier diet. Phobic anxiety symptom scores were estimated using the Crown-Crisp phobic anxiety scale in 1993 and 2005. The clinician-diagnosed depression was reported in biennial questionnaires since 2003. The history of rotating night shift work was collected through biennial questionnaires since 1989. In subgroups of participants from this cohort or similar nurses from the Nurses' Health Study, the reliability of self-reported body weight, phobic anxiety, reproductive characteristics (e.g., menstrual cycle length and oral contraceptive use), and lifestyle factors (e.g., smoking habit, physical activity, and dietary intake) has been validated in previous studies.[17,19–23]

Ascertainment of mortality

Deaths were ascertained from state vital statistics records and the National Death Index; or by reports from next of kin or the postal authorities, which has been demonstrated to identify > 98% of the deaths.[24] Cause of death was ascertained by physician review of medical records, autopsy reports, or death certificates. We applied the International Classification of Diseases, Eighth Revision (ICD-8), which was widely used at the time when this cohort was established, to distinguish between deaths caused by all CVD, all cancer types, and any other reasons (supplemental Table 2). Premature mortality was defined as death before 70 years of age based on the World Health Organization.[25]

Statistical analysis

Participants were considered exposed after a report of infertility, regardless of the outcome of subsequent attempts to conceive. Infertility reasons were not mutually exclusive, and participants were considered exposed to specific causes throughout follow-up after a report of underlying diagnoses. Gravid women who never reported infertility served as the reference group. To minimize exposure misclassification due to age-related fertility decline,[26] we stopped updating exposure status after age 40 years. Thus, women reporting infertility for the first time after age 40 years were considered unexposed for the entirety of follow-up. Person-years of follow-up were calculated for each eligible participant from the return date of the questionnaire in which the woman reported either infertility or pregnancy until the end of follow-up (June 30, 2017) or death, whichever occurred first. Six women died at or after age 70 years and were treated as censored observations.

Age-stratified Cox proportional hazard models were used to estimate the hazard ratios (HRs) for total and cause-specific premature mortality in relation to infertility status across the reproductive lifespan, overall and according to major underlying diagnoses, while simultaneously adjusting for time-varying confounders and risk factors. Covariates in Cox models were selected *a priori* based on prior findings and were maintained in models if their inclusion changed the age-adjusted HR by ≥ 10%.[27] Multivariable Cox models were adjusted for White race/ethnicity (yes or no), parental history of myocardial infarction or stroke (yes or no), BMI at age 18 years (< 19, 20.5–21.9, 22–24.9, 25–29.9, or ≥ 30 kg/m^2), menstrual cycle length at age 18–22 years (< 26, 26–31, 32–50, or ≥ 50 days or too irregular to estimate), age at menarche (< 12, 12, 13, or ≥ 14 years of age), and oral contraceptive use before age 18 years (never, 2–9 months, or ≥ 10 months per year). In a secondary analysis, multivariable models were further adjusted for updated time-varying marriage status (ever/currently married or never), daily aspirin use (Yes or No), BMI (< 24.9, 25–29.9, 30–34.9, or ≥ 35 kg/m^2), smoking status (never, former, current 1–34 cigarettes/day, or current ≥ 35 cigarettes/day), physical activity (0, 0.1–1.0, 1.1–2.4, 2.5–5.9, or ≥ 6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles). There was no violation of the proportional hazard assumption for age-adjusted and multivariable models based on the likelihood ratio test by adding an interaction term of infertility history with follow–up time. Covariates with missing values at a given time

point (< 5% for all covariates) were carried forward using data from the most recent questionnaire; otherwise, a missing indicator was created.[28] We tested for effect modification by lifestyle and reproductive factors by performing analyzes stratified by current BMI (< 25 vs. ≥ 25 kg/m^2), diet quality (top 40% vs. bottom 60%), physical activity (< 30 vs. ≥ 30 min per day), smoking status (current vs. never/past), nulliparous (Yes vs. No), use of gonadotropins or clomiphene for ovulation induction (Yes vs. No), night shift work (never vs. ever), phobic anxiety symptom scores (< 3 vs. ≥ 3), and depression (No vs. Yes). Multiplicative interaction between infertility status and these stratified variables was assessed using likelihood ratio tests; additive interaction was assessed and by calculating the relative excess risk due to interaction (RERI).[29,30]

Several sensitivity analyzes were conducted. First, we limited the definition of infertility to women who experienced the event before age 37 years to further exclude the potential effects of age-related decline in fertility.[31] Second, we allowed reports of infertility at any age (i.e., > age 40 years) to count as a history of infertility. Third, we defined premature mortality as any deaths occurring before age 65 years to allow for comparison with other studies.[32] Fourth, we included women reporting infertility only due to spouse or partner factors in the reference group. Fifth, we used the Markov chain Monte Carlo (MCMC) method of multiple imputation (MI) procedure to replace covariates with missing data. Sixth, we excluded fertile women reporting a diagnosis of endometriosis or uterine fibroids. Finally, we included nulligravid women without infertility throughout their reproductive lifespan into a separate group. All data were analyzed using SAS 9.4 for UNIX (SAS Institute Inc., Cary, NC, USA).

Results

Our analysis included 101,777 women, with a mean baseline age and BMI of 34.8 ± 4.7 years and 24.1 ± 4.8 kg/m^2, respectively. In total, 28,047 women reported an occurrence of infertility before 40 years of age either at baseline or during follow-up (Table 1). Compared to women without infertility history, women who experienced infertility reported lower gravidity (1.8 ± 1.6 vs. 2.4 ± 1.4) and parity (60.8% vs. 85.1% parous), had higher diet quality score (47.9 ± 10.8 vs. 47.6 ± 10.7) and prevalence of obese (31.0% vs. 28.4%) and parental history of myocardial infarction or stroke (15.6% vs 14.5%), and were less likely to be married (89.8% vs. 92.6%) at baseline. Among parous participants, women reporting infertility had a slightly higher baseline prevalence of gestational diabetes (5.1 vs. 3.6%) and hypertensive disorders of pregnancy (18.3 vs. 14.2%) than fertile women. Ovulatory disorder (n = 7988; 28.5%) was the most common underlying cause reported by women with a history of infertility (Table 1).

During 28 years (2,382,195 person-years) of follow-up, we documented 2174 premature deaths, including 1024 deaths from cancer and 194 from CVD (eTable S1). The crude all-cause mortality incidence was 1.21 and 0.78 per 1000 person-years, respectively, for women with and without a history of infertility. In age-adjusted models, the occurrence of infertility across the reproductive lifespan was associated with an HR of 1.41 (95% CI: 1.29 to 1.54) for premature death during follow-up (Fig. 1). These associations were slightly attenuated but remained statistically significant after additionally adjusting for potential confounding factors (HR = 1.37, 1.26 to 1.50) and lifestyle factors (HR = 1.26, 1.15 to 1.38) (Fig. 1). Analyzes of cause-specific mortality showed that infertility was unrelated to CVD mortality (HR = 1.17, 0.86 to 1.57), but was associated with a greater mortality risk due to cancer (HR = 1.22, 1.08 to 1.39) and other causes of death (HR = 1.32, 1.16 to 1.51) (Fig. 1). When the causes of death were disaggregated and analyzed separately for diagnostic categories with at least 40 deaths attributed, infertility history was associated with a greater risk of mortality due to malignant neoplasm of digestive organs and peritoneum (HR = 1.39; 1.02 to 1.90), genito-urinary organs (HR = 1.38, 1.00 to 1.90), and lymphatic and haematopoietic tissue (HR = 1.53, 1.00 to 2.33), as well as mortality due to non-malignant diseases of gastrointestinal system (HR = 2.15, 1.16 to 3.98) (eTable S2).

The risk of premature mortality was stronger among women who first experienced infertility early in their reproductive life (Table 2). The multivariable-adjusted HRs for all-cause premature death during follow-up were 1.35 (1.19 to 1.52), 1.23 (1.10 to 1.38), and 1.10 (0.91 to 1.32) for infertility occurring at ages ≤ 25, 26–30, and > 30 years, respectively, compared to none. A similar risk of all-cause mortality was observed according to primary and secondary infertility (eTable S3). However, we found a greater risk of all-cause premature mortality among women who did not become pregnant after the initial report of infertility (HR = 1.39, 1.25 to 1.54) than among women who reported at least one pregnancy after infertility (HR = 1.12, 1.00 to 1.26) (Table 3). Analyzes of cause-specific mortality showed that infertility without additional pregnancies was associated with a greater risk of CVD mortality (HR = 1.49, 1.06 to 2.10) (Table 3). When contributing causes of infertility were evaluated (Table 4), multivariable Cox models with adjustment with potential confounders and all other infertility causes showed a greater risk of all-cause mortality among women who reported infertility due to ovulatory disorders (HR = 1.28, 1.09 to 1.51), endometriosis (HR = 1.50, 1.22 to 1.83), and "other" unspecified causes (HR = 1.30, 1.07 to 1.58). In the analyzes of cause-specific mortality (eTable S4), we found positive associations between endometriosis-associated infertility and

Characteristics	Occurrence of infertility	
	No	Yes
No.	73,730	28,047
Age, mean (SD), year[b]	34.8 (4.7)	34.8 (4.6)
Total physical activity, mean (SD), hour/week	3.3 (4.9)	3.4 (5.2)
AHEI-2010 dietary score, mean (SD)	47.6 (10.7)	47.9 (10.8)
White,%	92.1	90.7
Gravidity, mean (SD)	2.4 (1.4)	1.8 (1.6)
Parous,%	85.1	60.8
Gestational diabetes,%	3.6	5.1
Hypertensive disorders of pregnancy,%	14.2	18.3
BMI,%, kg/m^2		
< 18.5	1.3	2.1
18.5–24.9	39.4	37.6
25–29.9	30.9	29.3
≥ 30	28.4	31.0
Aspirin use,%[c]	10.9	10.1
Parental history of myocardial infarction or stroke,%	14.5	15.6
Ever or currently married,%	92.6	89.8
Never smoker,%	36.3	36.7
Causes of infertility, No. (%)[d]		
Ovulatory disorder	NA	7988 (28.5%)
Endometriosis	NA	4398 (15.7%)
Cervical mucus disorder	NA	1526 (5.4%)
Tubal blockage	NA	3017 (10.8%)
Spouse or partner factors	NA	5265 (18.8%)
Other cause	NA	4444 (15.9%)
Cause not found	NA	6237 (22.2%)
Cause not investigated	NA	7633 (27.2%)
Missing	NA	991 (3.5%)

***Table 1*: Age-standardized baseline (1989) characteristics according to the occurrence of infertility either at baseline or during follow-up among 101,777 women (NHS II, 1989–2017).[a]**

NA: not applicable.

[a] Values are given as means (SDs) or percentages and are standardized to the age distribution of the study population.

[b] Value is not age-adjusted.

[c] Aspirin or aspirin-containing products used at least once per week in the past 2 years.

[d] Infertility reasons, which were not mutually exclusive, were gathered at baseline and during follow-ups among those who reported having tried to conceive for at least 12 months.

cancer mortality (HR = 1.37, 1.01 to 1.84) and of infertility due to ovulatory disorders and endometriosis with non-cancer/CVD mortality (HR = 1.44, 1.14 to 1.83 and 1.68, 1.25 to 2.24, respectively). Stratified analyzes indicated that the association of infertility with all-cause mortality was not modified by physical activity, diet quality, smoking status, parity, use of ovulation induction agents, night shift work, phobic anxiety symptom scores, and depression (Table 5). However, this association was slightly stronger among women who had a smoking habit (RERI = 0.28, 0.02 to 0.53).

Sensitivity analyzes showed that the association between infertility and all-cause premature mortality was not affected by further restricting the definition of infertility to first reports before age 37 years, by broadening the definition of infertility to include women who first reported infertility after age 40 years, by defining premature mortality as death before age 65 years, by including women reporting infertility only due to spouse or partner factors in the reference group, by using multiple imputation procedures to replace covariates with missing data, or by excluding women without infertility who reported endometriosis or uterine fibroids (eTable S5). To examine the potential effluence of population selection bias on the risk of cancer mortality, we performed an analysis including nulligravid women without infertility throughout the study period into a separate group and splitting women reporting infertility by gravidity. Compared to gravid women without infertility history, the multivariable-adjusted HR (95% CI) for premature cancer mortality was 1.20 (1.05 to 1.38) for nulligravid women who ever reported infertility, 1.34

Type of death	No infertility	With occurrence of infertility	P-value
All death			
Events, No.	1300	874	NA
Crude incidence per 1000 person years	0.78	1.21	NA
HR (95% CI) for age-adjusted models	1.00 [Reference]	1.41 (1.29 to 1.54)	<0.001
HR (95% CI) for multivariable models	1.00 [Reference]	1.37 (1.26 to 1.50)	<0.001
HR (95% CI) for full models adjusted for lifestyle	1.00 [Reference]	1.26 (1.15 to 1.38)	<0.001
Cancer death			
Events, No.	629	395	NA
Crude incidence per 1000 person years	0.38	0.55	NA
HR (95% CI) for age-adjusted models	1.00 [Reference]	1.33 (1.18 to 1.51)	<0.001
HR (95% CI) for multivariable models	1.00 [Reference]	1.31 (1.15 to 1.48)	<0.001
HR (95% CI) for full models adjusted for lifestyle	1.00 [Reference]	1.22 (1.08 to 1.39)	0.002
CVD death			
Events, No.	120	74	NA
Crude incidence per 1000 person years	0.07	0.10	NA
HR (95% CI) for age-adjusted models	1.00 [Reference]	1.33 (0.99 to 1.78)	0.06
HR (95% CI) for multivariable models	1.00 [Reference]	1.27 (0.94 to 1.70)	0.12
HR (95% CI) for full models adjusted for lifestyle	1.00 [Reference]	1.17 (0.86 to 1.57)	0.32
Other causes			
Events, No.	551	405	NA
Crude incidence per 1000 person years	0.33	0.56	NA
HR (95% CI) for age-adjusted models	1.00 [Reference]	1.51 (1.33 to 1.72)	<0.001
HR (95% CI) for multivariable models	1.00 [Reference]	1.47 (1.29 to 1.68)	<0.001
HR (95% CI) for full models adjusted for lifestyle	1.00 [Reference]	1.32 (1.16 to 1.51)	<0.001

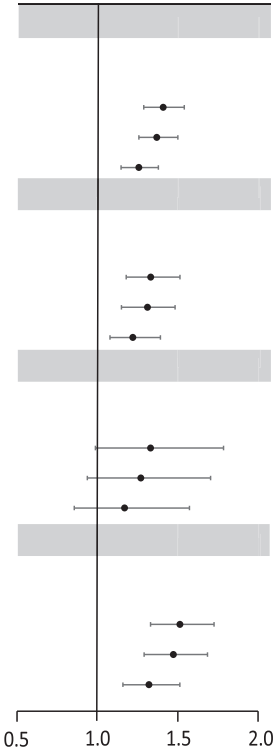

Figure 1. Hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of all-cause and cause-specific premature mortality (before age 70 years) according to the occurrence of infertility among 101,777 women (NHS II, 1989–2017). Age-adjusted models were adjusted for age (continuous). Multivariable models were further adjusted for White race/ethnicity (yes or no), parental history of myocardial infarction or stroke (yes or no), BMI at age 18 years (< 19, 20.5–21.9, 22–24.9, 25–29.9, or ≥ 30 kg/m^2), menstrual cycle length at age 18–22 years (< 26, 26–31, 32–50, or ≥ 50 days or too regular to estimate), age at menarche (< 12, 12, 13, or ≥ 14 years of age), and oral contraceptive use before age 18 years (never, 2–9 month, or ≥ 10 month per year). Full models were further adjusted for time-varying marriage status (ever/currently married or never), daily aspirin use (yes or no), BMI (< 24.9, 25–29.9, 30–34.9, or ≥ 35 kg/m^2), smoking status (never, former, current 1–34 cigarettes/day, or current ≥ 35 cigarettes/day), physical activity (0, 0.1–1.0, 1.1–2.4, 2.5–5.9, or ≥ 6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).

Type of death	No infertility history	Age at first reported infertility			*P* for trend
		Aged > 30 year	aged 26–30 years	aged ≤ 25 years	
All death					
Events, No.	1300	126	411	337	
Crude incidence per 100 person years	0.79	0.95	1.09	1.42	
HRs for age-adjusted model[a]	1.00 [Reference]	1.22 (1.02 to 1.47)	1.34 (1.20 to 1.50)	1.56 (1.38 to 1.76)	< 0.001
HRs for multivariable model[b]	1.00 [Reference]	1.18 (0.98 to 1.42)	1.32 (1.18 to 1.48)	1.50 (1.33 to 1.70)	< 0.001
HRs for full models adjusted for lifestyle[c]	1.00 [Reference]	1.10 (0.91 to 1.32)	1.23 (1.10 to 1.38)	1.35 (1.19 to 1.52)	< 0.001
Cancer death					
Events, No.	629	62	197	136	
Crude incidence per 100 person years	0.38	0.47	0.52	0.57	
HRs for age-adjusted model[a]	1.00 [Reference]	1.24 (0.95 to 1.61)	1.36 (1.16 to 1.59)	1.32 (1.09 to 1.58)	< 0.001
HRs for multivariable model[b]	1.00 [Reference]	1.22 (0.94 to 1.58)	1.34 (1.14 to 1.57)	1.28 (1.06 to 1.54)	< 0.001
HRs for full models adjusted for lifestyle[c]	1.00 [Reference]	1.16 (0.89 to 1.52)	1.26 (1.07 to 1.48)	1.18 (0.98 to 1.43)	0.007
CVD death					
Events, No.	120	11	28	35	
Crude incidence per 100 person years	0.07	0.08	0.07	0.15	
HRs for age-adjusted model[a]	1.00 [Reference]	1.24 (0.66 to 2.30)	1.01 (0.67 to 1.53)	1.77 (1.21 to 2.58)	0.02
HRs for multivariable model[b]	1.00 [Reference]	1.18 (0.63 to 2.21)	0.99 (0.65 to 1.49)	1.64 (1.11 to 2.41)	0.05
HRs for full models adjusted for lifestyle[c]	1.00 [Reference]	1.09 (0.58 to 2.04)	0.94 (0.62 to 1.43)	1.46 (0.98 to 2.16)	0.18
Other causes					
Events, No.	551	53	186	166	
Crude incidence per 100 person years	0.34	0.40	0.49	0.70	
HRs for age-adjusted model[a]	1.00 [Reference]	1.20 (0.90 to 1.59)	1.40 (1.18 to 1.65)	1.78 (1.50 to 2.12)	< 0.001
HRs for multivariable model[b]	1.00 [Reference]	1.14 (0.86 to 1.52)	1.38 (1.17 to 1.63)	1.72 (1.44 to 2.06)	< 0.001
HRs for full models adjusted for lifestyle[c]	1.00 [Reference]	1.03 (0.77 to 1.38)	1.27 (1.07 to 1.50)	1.50 (1.25 to 1.80)	< 0.001

***Table 2*: Hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of all-cause premature mortality (before age 70 years) according to age at first reported infertility among 101,777 women (NHS II, 1989–2017).**

[a] Age-adjusted models were adjusted for age (continuous).

[b] Multivariable models were further adjusted for White race/ethnicity (yes or no), parental history of myocardial infarction or stroke (yes or no), BMI at age 18 years (< 19, 20.5–21.9, 22–24.9, 25–29.9, or ≥ 30 kg/m^2), menstrual cycle length at age 18–22 years (< 26, 26–31, 32–50, or ≥ 50 days or too regular to estimate), age at menarche (< 12, 12, 13, or ≥ 14 years of age), and oral contraceptive use before age 18 years (never, 2–9 month, or ≥ 10 month per year).

[c] Full models were further adjusted for time-varying marriage status (ever/currently married or never), daily aspirin use (yes or no), BMI (< 24.9, 25–29.9, 30–34.9, or ≥ 35 kg/m^2), smoking status (never, former, current 1–34 cigarettes/day, or current ≥ 35 cigarettes/day), physical activity (0, 0.1–1.0, 1.1–2.4, 2.5–5.9, or ≥ 6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).

Type of death	No infertility history	With infertility history	
		No pregnancies after first report of infertility	One or more pregnancies after infertility
All death			
Events, No.	1300	502	372
Crude incidence per 100 person-year	0.78	1.48	0.97
HRs for crude models [a]	1.00 [Reference]	1.59 (1.43 to 1.76)	1.23 (1.09 to 1.38)
HRs for multivariable models [b]	1.00 [Reference]	1.53 (1.38 to 1.70)	1.21 (1.07 to 1.36)
HRs for full models adjusted for lifestyle [c]	1.00 [Reference]	1.39 (1.25 to 1.54)	1.12 (1.00 to 1.26)
Cancer death			
Events, No.	629	208	187
Crude incidence per 100 person-year	0.38	0.61	0.49
HRs for crude models [a]	1.00 [Reference]	1.38 (1.18 to 1.61)	1.29 (1.09 to 1.52)
HRs for multivariable models [b]	1.00 [Reference]	1.35 (1.15 to 1.58)	1.26 (1.07 to 1.49)
HRs for full models adjusted for lifestyle [c]	1.00 [Reference]	1.26 (1.07 to 1.48)	1.19 (1.00 to 1.40)
CVD death			
Events, No.	120	50	24
Crude incidence per 100 person-year	0.07	0.15	0.06
HRs for crude models [a]	1.00 [Reference]	1.76 (1.27 to 2.46)	0.88 (0.56 to 1.36)
HRs for multivariable models [b]	1.00 [Reference]	1.65 (1.18 to 2.30)	0.85 (0.54 to 1.33)
HRs for full models adjusted for lifestyle [c]	1.00 [Reference]	1.49 (1.06 to 2.10)	0.80 (0.51 to 1.24)
Other causes			
Events, No.	551	244	161
Crude incidence per 100 person-year	0.33	0.72	0.42
HRs for crude models [a]	1.00 [Reference]	1.78 (1.53 to 2.07)	1.24 (1.03 to 1.47)
HRs for multivariable models [b]	1.00 [Reference]	1.71 (1.46 to 1.99)	1.22 (1.02 to 1.46)
HRs for full models adjusted for lifestyle [c]	1.00 [Reference]	1.50 (1.29 to 1.76)	1.12 (0.94 to 1.34)

***Table 3*: Hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of all-cause and cause-specific premature mortality (before age 70 years) according to pregnancy history after infertility among 101,777 women (NHS II, 1989–2017).**

[a] Age-adjusted models were adjusted for age (continuous).

[b] Multivariable models were further adjusted for White race/ethnicity (yes or no), parental history of myocardial infarction or stroke (yes or no), BMI at age 18 years (< 19, 20.5–21.9, 22–24.9, 25–29.9, or ≥ 30 kg/m^2), menstrual cycle length at age 18–22 years (< 26, 26–31, 32–50, or ≥ 50 days or too regular to estimate), age at menarche (< 12, 12, 13, or ≥ 14 years of age), and oral contraceptive use before age 18 years (never, 2–9 month, or ≥ 10 month per year).

[c] Full models were further adjusted for time-varying marriage status (ever/currently married or never), daily aspirin use (yes or no), BMI (< 24.9, 25–29.9, 30–34.9, or ≥ 35 kg/m^2), smoking status (never, former, current 1–34 cigarettes/day, or current ≥ 35 cigarettes/day), physical activity (0, 0.1–1.0, 1.1–2.4, 2.5–5.9, or ≥ 6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).

(0.98 to 1.81) for gravid women who ever reported infertility, and 1.19 (0.98 to 1.45) for nulligravid women without a history of infertility.

Discussion

Results from this large prospective study revealed that infertility across the reproductive lifespan was associated with a greater long-term risk of premature mortality. This association was stronger among women first experiencing infertility before age 26 years and among women who did not become pregnant after first experiencing infertility. Analyzes of cause-specific mortality showed that the relation was mainly driven by the increased risk of mortality due to cancer (i.e., digestive organs and peritoneum, genito-urinary organs, and lymphatic and haematopoietic tissue) and non-malignant diseases of gastrointestinal system. When contributing causes of infertility were evaluated, a greater risk of all-cause mortality was observed among women who reported infertility due to ovulatory disorders, endometriosis, and "other" unspecified reasons.

Comparison with other studies

Previous epidemiological studies have found that nulliparity is associated with a greater risk of all-cause mortality.[33–36] Similarly, a recent meta-analysis of 18 studies including 2,813,481 women demonstrated a greater risk of all-cause mortality among nulliparous women compared to those with at least one live birth.[37] However, the assumption that nulliparity is an appropriate surrogate for infertility is overly simplistic, given that nulliparity and infertility are not synonymous and reflect independent pathophysiological and social constructs. To our knowledge, only one previous study to date has assessed the association of infertility with all-

Self-reported causes of infertility	Occurrence of infertility		P
	No	Yes	
Ovulatory disorder			
Events, No.	1300	250	
Crude incidence per 100 person years	0.78	1.21	
HRs for age-adjusted model[a]	1.00 [Reference]	1.53 (1.33 to 1.75)	< 0.001
HRs for full models adjusted for lifestyle[b]	1.00 [Reference]	1.36 (1.18 to 1.57)	< 0.001
HRs for models adjusted for all other infertility causes[c]	1.00 [Reference]	1.28 (1.09 to 1.51)	0.003
Endometriosis			
Events, No.	1300	158	
Crude incidence per 100 person years	0.78	1.40	
HRs for age-adjusted model[a]	1.00 [Reference]	1.68 (1.42 to 1.98)	< 0.001
HRs for full models adjusted for lifestyle[b]	1.00 [Reference]	1.56 (1.32 to 1.84)	< 0.001
HRs for models adjusted for all other infertility causes[c]	1.00 [Reference]	1.50 (1.22 to 1.83)	< 0.001
Cervical mucus disorder			
Events, No.	1300	48	
Crude incidence per 100 person years	0.78	1.23	
HRs for age-adjusted model[a]	1.00 [Reference]	1.52 (1.14 to 2.03)	0.005
HRs for full models adjusted for lifestyle[b]	1.00 [Reference]	1.43 (1.07 to 1.91)	0.02
HRs for models adjusted for all other infertility causes[c]	1.00 [Reference]	1.26 (0.90 to 1.75)	0.17
Tubal blockage			
Events, No.	1300	103	
Crude incidence per 100 person years	0.78	1.34	
HRs for age-adjusted model[a]	1.00 [Reference]	1.54 (1.26 to 1.88)	< 0.001
HRs for full models adjusted for lifestyle[b]	1.00 [Reference]	1.36 (1.11 to 1.67)	0.003
HRs for models adjusted for all other infertility causes[c]	1.00 [Reference]	1.23 (0.98 to 1.55)	0.08
Spouse or partner factors			
Events, No.	1300	155	
Crude incidence per 100 person years	0.78	1.16	
HRs for age-adjusted model[a]	1.00 [Reference]	1.38 (1.16 to 1.62)	< 0.001
HRs for full models adjusted for lifestyle[b]	1.00 [Reference]	1.25 (1.05 to 1.47)	0.01
HRs for models adjusted for all other infertility causes[c]	1.00 [Reference]	1.13 (0.93 to 1.37)	0.22
Other cause			
Events, No.	1300	143	
Crude incidence per 100 person years	0.78	1.31	
HRs for age-adjusted model[a]	1.00 [Reference]	1.55 (1.31 to 1.85)	< 0.001
HRs for full models adjusted for lifestyle[b]	1.00 [Reference]	1.39 (1.17 to 1.65)	< 0.001
HRs for models adjusted for all other infertility causes[c]	1.00 [Reference]	1.30 (1.07 to 1.58)	0.007
Cause not found			
Events, No.	1300	162	
Crude incidence per 100 person years	0.78	1.05	
HRs for age-adjusted model[a]	1.00 [Reference]	1.23 (1.04 to 1.45)	0.01
HRs for full models adjusted for lifestyle[b]	1.00 [Reference]	1.15 (0.97 to 1.35)	0.10
HRs for models adjusted for all other infertility causes[c]	1.00 [Reference]	1.11 (0.94 to 1.32)	0.22

***Table 4*: Hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of all-cause premature mortality (before age 70 years) according to self-reported causes of infertility (NHS II, 1989−2017).**

[a] Age-adjusted models were adjusted for age (continuous).

[b] Full models were further adjusted for White race/ethnicity (yes or no), parental history of myocardial infarction or stroke (yes or no), BMI at age 18 years (< 19, 20.5−21.9, 22−24.9, 25−29.9, or ≥ 30 kg/m^2), menstrual cycle length at age 18−22 years (< 26, 26−31, 32−50, or ≥ 50 days or too regular to estimate), age at menarche (< 12, 12, 13, or ≥ 14 years of age), oral contraceptive use before age 18 years (never, 2−9 month, or ≥ 10 month per year), and time-varying marriage status (ever/currently married or never), daily aspirin use (yes or no), BMI (< 24.9, 25−29.9, 30−34.9, or ≥ 35 kg/m^2), smoking status (never, former, current 1−34 cigarettes/day, or current ≥ 35 cigarettes/day), physical activity (0, 0.1−1.0, 1.1−2.4, 2.5−5.9, or ≥6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).

[c] Based on full models with mutually adjustment for the presence of all other causes of infertility.

Stratified factors	History of infertility	
	No	Yes
Diet quality		
Top 40% (n = 674 deaths)	1.00 [Reference]	1.24 (1.05 to 1.45)
Bottom 60% (n = 1500 deaths)	1.00 [Reference]	1.28 (1.15 to 1.42)
P for multiplicative interaction	0.83	
RERI	0.12 (−0.12 to 0.36)	
P for additive interaction	0.33	
Smoking status		
Never smokers (n = 1112 deaths)	1.00 [Reference]	1.23 (1.08 to 1.39)
Current or ever smokers (n = 1062 deaths)	1.00 [Reference]	1.32 (1.16 to 1.50)
P for multiplicative interaction	0.32	
RERI	0.28 (0.02 to 0.53)	
P for additive interaction	0.03	
BMI		
< 25 kg/m^2 (n = 903 deaths)	1.00 [Reference]	1.26 (1.10 to 1.45)
≥ 25 kg/m^2 (n = 1271 deaths)	1.00 [Reference]	1.27 (1.13 to 1.43)
P for multiplicative interaction	0.98	
RERI	−0.05 (−0.24 to 0.15)	
P for additive interaction	0.64	
Physical activity		
≥ 30 min/day (n = 608 deaths)	1.00 [Reference]	1.25 (1.06 to 1.48)
< 30 min/day (n = 1566 deaths)	1.00 [Reference]	1.27 (1.15 to 1.41)
P for multiplicative interaction	0.73	
RERI	0.10 (−0.17 to 0.36)	
P for additive interaction	0.47	
Nulliparous		
Yes (n = 353 deaths)	1.00 [Reference]	1.05 (0.82 to 1.34)
No (n = 1821 deaths)	1.00 [Reference]	1.22 (1.10 to 1.35)
P for multiplicative interaction	0.50	
RERI	−0.05 (−0.42 to 0.31)	
P for additive interaction	0.78	
Use of gonadotropins or clomiphene for ovulation induction		
Ever (n = 284 deaths)	1.00 [Reference]	1.22 (0.78 to 1.92)
Never (n = 1890 deaths)	1.00 [Reference]	1.31 (1.18 to 1.45)
P for multiplicative interaction	0.96	
RERI	−0.02 (−0.44 to 0.40)	
P for additive interaction	0.92	
Depression		
No (n = 1653 deaths)	1.00 [Reference]	1.32 (1.20 to 1.46)
Yes (n = 521 deaths)	1.00 [Reference]	1.23 (1.02 to 1.47)
P for multiplicative interaction	0.82	
RERI	0.06 (−0.19 to 0.31)	
P for additive interaction	0.64	
Phobic anxiety symptom scores		
< 3 (n = 1587 deaths)	1.00 [Reference]	1.30 (1.17 to 1.44)
≥ 3(n = 587 deaths)	1.00 [Reference]	1.19 (1.00 to 1.41)
P for multiplicative interaction	0.94	
RERI	0.03 (−0.23 to 0.29)	
P for additive interaction	0.81	
Night shift work		
Never (n = 614 deaths)	1.00 [Reference]	1.37 (1.16 to 1.62)
Ever (n = 1560 deaths)	1.00 [Reference]	1.25 (1.13 to 1.39)
P for multiplicative interaction	0.23	

(*continued*)

Table 5 (Continued)

Stratified factors	History of infertility	
	No	Yes
RERI	−0.13 (−0.37 to 0.12)	
P for additive interaction	0.31	

***Table 5*: Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the risk of premature mortality (before age 70 years) according to the occurrence of infertility among 101,777 women, stratified by dietary lifestyle and reproductive factors (NHS II, 1989−2017).**[a]

[a] Models were adjusted for age (continuous), White race/ethnicity (yes or no), parental history of myocardial infarction or stroke (yes or no), BMI at age 18 years (< 19, 20.5−21.9, 22−24.9, 25−29.9, or ≥ 30 kg/m²), menstrual cycle length at age 18−22 years (< 26, 26−31, 32−50, or ≥ 50 days or too regular to estimate), age at menarche (< 12, 12, 13, or ≥ 14 years of age), oral contraceptive use before age 18 years (never, 2−9 month, or ≥ 10 month per year), and time-varying marriage status (ever/currently married or never), daily aspirin use (yes or no), BMI (< 24.9, 25−29.9, 30−34.9, or ≥ 35 kg/m²), smoking status (never, former, current 1−34 cigarettes/day, or current ≥ 35 cigarettes/day), physical activity (0, 0.1−1.0, 1.1−2.4, 2.5−5.9, or ≥ 6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles), excluding the stratifying variable. RERI: relative excess risk due to interaction.

cause or cause-specific mortality. Using data from a multicenter cancer-screening trial including 75,784 post-menopausal women aged 55−74 years, Stentz and colleagues found that women with a history of infertility had an HR for all-cause and cancer-related mortality of 1.10 (95% CI: 1.02 to 1.18) and 1.47 (95% CI: 1.25 to 1.73), respectively, than women without infertility history,[13] which is consistent with our findings. However, their analysis asked participants about their infertility history after menopause which may be prone to misclassification. Besides, they did not collect detailed data on relevant confounders during adolescence and lifestyle factors across the reproductive lifespan. In our study, adjustment for these confounders and lifestyle factors attenuated hazard ratios, indicating that studies that do not control for such variables may have residual confounding. Meanwhile, we found an additive interaction of infertility and smoking on premature mortality, suggesting that infertility might interact synergistically with smoking to further increase the risk of premature mortality. Finally, we were able to advance upon the earlier study by examining age at first reported infertility and heterogeneity in risk across underlying causes of infertility. Our study reveals that these details are critically important in evaluating the relation between infertility and mortality.

We found that the association between infertility and all-cause premature mortality was strongest among women who first experienced infertility before age 26 years, suggesting that infertility occurring early in a women's reproductive life is a more sensitive marker for risk stratification later in life. This is biologically plausible given that infertility occurring at an advanced age is more likely a proxy of age-related changes (e.g., chromosomal abnormalities, decreased ovarian function),[26] rather than an early sign of underlying physiopathology resulting in greater premature mortality risk. We also found that the premature mortality risk, particularly premature CVD mortality, was stronger among women who did not become pregnant after experiencing infertility than among women who conceived after infertility. Women who are unable to conceive after infertility may have more severe infertility and/or systemic disruptions related to infertility that may influence risk of premature mortality. Finally, while it is abundantly clear that infertility is a heterogeneous disease with many contributing causes, the association between individual infertility diagnoses and mortality is poorly investigated. In our present study, a greater risk of all-cause mortality was present among women who reported infertility due to ovulatory disorders, endometriosis, and "other" unspecified reasons. In support of our findings, ovulatory disorders (e.g., polycystic ovary syndrome) and endometriosis have been linked to an increased risk for cancer of genito-urinary organs, such as ovarian and endometrial cancer.[38,39] Previous studies also revealed that women with endometriosis often experienced gastrointestinal symptoms.[40] In crude models, we found infertility due to spouse or partner factors was related to all-death mortality. However, this association attenuated and became no longer statistically significant with additional adjustment for all other infertility causes in fully adjusted models. These results suggest that women with a history of infertility due to male factor are not at an elevated risk of premature mortality and that the associations without co-adjustment for other infertility diagnoses reflect the fact that male factor infertility is a contributing cause of infertility in nearly half of couples who undergo an evaluation for infertility, making this diagnosis more susceptible to residual confounding than other infertility diagnoses.

Underlying mechanisms of the observed relations

The potential mechanisms by which infertility is linked to premature mortality, particularly premature cancer mortality, are related to systemic disruptions associated with the most common causes of infertility. For instance, polycystic ovary syndrome, the leading cause of anovulatory infertility among women of reproductive age,[41] has been associated with ovarian dysfunction (e.g., chronic anovulation), disrupted hormonal

secretion (e.g., excessive androgen and luteinizing hormone production), and metabolic perturbations (e.g., hyperinsulinemia and insulin resistance).[42] The prolonged anovulation and consequent release of estrogen unopposed by progesterone are well-known risk factors of endometrial hyperplasia, eventually leading to carcinoma.[43] Hypersecretion of luteinizing hormone, chronic hyperinsulinemia, and increased serum insulin-like growth factor 1 levels may represent an additional risk for cancer development.[43] Endometriosis is another major cause of infertility in women of reproductive age.[44] The development of endometriosis involves interacting endocrine, immunologic, proinflammatory, and proangiogenic processes,[45] which are also implicated in the development of cancer and diseases of gastrointestinal system.[46–48]

The association between infertility and premature mortality, particularly premature cancer mortality, may also reflect shared genetic, environmental, and lifestyle factors.[49] Growing evidence shows that different infertility etiologies share particular genes and/or molecular pathways with other diseases.[50] For instance, a strong link between diminished ovarian reserve and breast and ovarian cancer has been established among carriers of BRCA1/2 mutations.[51,52] Meanwhile, the influence of environmental and lifestyle factors on female infertility is under increasing scrutiny, given the increasing global prevalence rate of infertility over the past few decades (0.37% per year for females from 1990 to 2017).[53] Several environmental toxins, particularly endocrine-disrupting chemicals (EDCs) in the form of dioxin, phthalates, pesticides, and heavy metals, have been associated with female subfertility by disrupting various hormonal pathways.[54,55] These environmental toxins are exogenous chemicals that can affect hormone action and, eventually, accelerate the risk of cancer.[56] Lifestyle factors such as smoking and obesity are well-known risk factors of cancer,[57] which have also been associated with reduced female fertility.[54]

Strengths and limitations

Strengths of the study include its longitudinal design with a high follow-up rate, large population size, a sufficient number of premature deaths, an extensive follow-up period across the majority of the women's reproductive lifespan, and the collection of various lifestyles factors, reproductive characteristics, and health-related conditions. In addition, our study is the first to assess the heterogeneity of premature mortality risk by infertility subtypes, which enables us to identify the most vulnerable women. Our study also has important limitations. First, infertility and its underlying causes were self-reported. Exposure misclassification cannot be fully excluded, although ovulatory infertility has been validated against medical records in our cohort.[15] However, in this case, the misclassification would be expected to be non-differential with respect to mortality leading to associations biased towards the null. Second, as with any observational study, despite statistical control for many potential confounders and mediating factors, the possibility of residual confounding cannot be fully ruled out. However, our results were robust across different models and consistent in various sensitivity analyzes. Third, the study participants included in our analysis were relatively homogenous in terms of race (mostly White), profession, and educational attainment, which may hamper the generalizability of our results.

Conclusions

Results of this large longitudinal study showed a robust association between infertility across the reproductive lifespan and the long-term risk of female premature mortality. The association was stronger for infertility occurring early in a woman's reproductive years and among women who had a smoking habit. Our findings support the growing evidence that infertility might be served as an early marker of future health risk, including premature mortality. Our results suggest that women with a history of infertility, particularly those first experiencing infertility before 30 years of age and those who are unable to conceive after infertility, may benefit from further screening for common malignancies and cardiovascular disease risk factors. Attempts to meet the reproductive needs of infertile couples should be an initial step in the continuum of care over the life course, rather than an isolated goal.

CRediT authorship contribution statement

Yi-Xin Wang: Formal analysis, Writing – original draft, Conceptualization, Visualization, Writing – review & editing. **Siwen Wang:** Data curation, Writing – review & editing. **Stacey A. Missmer:** Conceptualization, Visualization, Funding acquisition, Project administration, Writing – review & editing. **Jorge E. Chavarro:** Conceptualization, Visualization, Funding acquisition, Project administration, Writing – review & editing. **Leslie V. Farland:** Writing – review & editing. **Audrey J.Gaskins:** Writing – review & editing. **Liang Wang:** Writing – review & editing. **Janet W. Rich-Edwards:** Writing – review & editing. **RullaTamimi:** Writing – review & editing.

Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships

or activities that could appear to have influenced the submitted work.

Acknowledgments

We would like to thank the participants and staff of the Nurses' Health Study II (NHS-II) for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyzes and interpretation of these data.

Data sharing statement

Our data, including code book and analytic code, can be available upon request with permission from our staff. Further information including the procedures for obtaining and accessing data from the Nurses' Health Studies II is described at https://www.nurseshealthstudy.org/researchers (email: nhsaccess@channing.harvard.edu)."

Ethical approval

The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard TH Chan School of Public Health. The completion of the self-administered questionnaire was considered to imply informed consent. Protocol number: 2009-P-002375.

Role of the funding source

This study was supported by grants R01-HD096033, U01-HL145386, U01-CA176726, R01-HL034594, and R01-HL088521 from the National Institutes of Health. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2021.100122.

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