

RESEARCH ARTICLE

Open Access



# Cardiovascular risk factors among women with self-reported infertility

Shruthi Mahalingaiah<sup>1,2\*</sup> , Fangui Sun<sup>3</sup>, J. Jojo Cheng<sup>1</sup>, Erika T. Chow<sup>1</sup>, Kathryn L. Lunetta<sup>3</sup> and Joanne M. Murabito<sup>4</sup>

## Abstract

**Background:** Amongst women with certain types of ovulatory disorder infertility, the studies are conflicting whether there is an increased risk of long-term cardiovascular disease risk. This paper evaluates the associations of several CVD risk factors among Framingham women with self-reported infertility.

**Methods:** Women who completed the Framingham Heart Study Third Generation and Omni Cohort 2 Exam 2 (2008–2011), and reported on past history of infertility and current cardiovascular disease status were included in this cross-sectional study. Directly measured CVD risk factors were: resting blood pressure, fasting lipid levels, fasting blood glucose, waist circumference, and body mass index (BMI). Multivariable models adjusted for age, smoking, physical activity, and cohort. Generalized estimating equations adjusted for family correlations. We performed sensitivity analyses to determine whether the association between infertility and CVD risk factors is modified by menopausal status and menstrual cycle length.

**Results:** Comparing women who self-reported infertility to those who did not, there was an average increase in BMI ( $\beta = 1.03 \text{ kg/m}^2$ , 95% CI: 0.18, 1.89), waist circumference ( $\beta = 3.08 \text{ in.}$ , 95% CI: 1.06, 5.09), triglycerides ( $\beta = 4.47 \text{ mg/dl}$ , 95% CI: -1.54, 10.49), and a decrease in HDL cholesterol ( $\beta = -1.60 \text{ mg/dl}$ , 95% CI: -3.76, 0.56). We estimated that infertile premenopausal women have an increased odds of obesity (BMI  $\geq 30 \text{ kg/m}^2$ ) (OR = 1.56, 95% CI: 1.11, 4.49) and diabetes (OR = 1.96, 95% CI: 0.86, 4.49).

**Conclusions:** BMI and waist circumference were the most strongly correlated CVD risk factors amongst women reporting a history of infertility.

**Keywords:** Infertility, Cardiovascular disease risk, Menstrual cycle length

## Background

Infertility is a multifactorial disease with etiologies attributed to male, female, and unexplained factors. It is defined as attempting conception for 1 year without success, or attempting for 6 months or more without success among those 35 years or older [1]. The main causes of female infertility are ovulatory disorders, including polycystic ovary syndrome (PCOS) and primary ovarian insufficiency (POI); tubal abnormalities, including bilateral tubal occlusion (BTO) and tubal damage; endometriosis; hormonal and endocrine disorders, including thyroid and prolactin abnormalities; cervical mucus

abnormalities; and structural or acquired genital tract disorders including uterine fibroids [2].

Amongst women with ovulatory disorder infertility (PCOS and POI), some studies demonstrate increased prevalence and long term concern for cardiovascular disease risk [3–6]. The age at menopause and menopausal status also alter the risk of cardiovascular morbidity and mortality [7–9]. Amongst women with endometriosis, a recent study using the Nurse's Health Study II cohort found that women with endometriosis had a relative risk of 1.62 (95% CI: 1.39–1.89) for three cardiovascular heart disease end points studied [10].

Aside from ovulatory disorders and endometriosis, the relationship between infertility and CVD risk factors is still unclear. Some recent studies report on the association of infertility history [11], infertility treatment [12] and pre-menopausal cardiovascular disease with no association.

\* Correspondence: shruthi@bu.edu

<sup>1</sup>Department of Obstetrics and Gynecology, Boston University School of Medicine, 85 East Concord Street, Boston, MA 02118, USA

<sup>2</sup>Department of Epidemiology, Boston University School of Public Health, Talbot 3E, 715 Albany Street, Boston, MA 02118, USA

Full list of author information is available at the end of the article



However, due to the conflicting literature, there is still concern that women presenting with infertility may be a susceptible population at risk for cardiovascular disease. Given that cardiovascular disease (CVD) is the leading cause of mortality in women in the U.S [13], identifying risk factors, such as infertility or infertility sub-type, that may be associated with CVD would allow for early identification of risk and initiation of risk reduction strategies.

The objective of this paper was to determine the association between infertility and CVD risk factors (CVD RF) among Framingham Heart Study (FHS) women with self-reported infertility. We hypothesized that women self-reporting for infertility would have more severe markers for CVD. We had the opportunity to conduct this investigation in the FHS, a community-based cohort study unselected for disease status and not skewed to an infertility clinic based sample. To our knowledge, this is the first study that employs a cohort with directly measured CVD RF through a research physical examination and laboratory assay.

## Methods

### Study sample

The Framingham Heart Study (FHS) is a longitudinal population-based cohort study of CVD and any associated risk factors in Framingham, Massachusetts [14]. The current study sample was taken from the Exam 2 data of the FHS Third Generation (Gen 3) and Omni 2 cohorts. A detailed methodologic description of cohort enrollment and follow-up is referenced here [15]. In summary, recruitment for the Gen 3 cohort began in November 2001, and inclusion criteria for the cohort required that participants be at least 20 years of age by the first exam cycle and have at least one parent in the Offspring cohort of the FHS. The Exam 2 cycle for this cohort started in May 2008 and finished February 2011. The Omni 2 cohort was recruited from 2003 to July 2005 and was meant to represent a racially/ethnically diverse group that would be at least 10% of the size of the Gen 3 cohort. The Exam 2 cycle for the Omni 2 cohort occurred at the same time as the Gen 3 Exam 2 cycle. This study was approved by the Institutional Review Board at Boston University School of Medicine. Women who were at risk for pregnancy and who responded to the infertility question were included in the analysis ( $n = 1968$ ).

### Assessment of infertility

Infertility was determined by self-report. At the exam, the physician-administered medical history included the following question: "Have you ever tried to become pregnant for  $\geq 1$  year without becoming pregnant?" If women answered "yes," they were considered to have infertility.

### Assessment of cardiovascular risk factors

For Gen 3/Omni 2 cohorts, the CVD risk factors that were assessed by physical exam and direct measurement by laboratory analysis in this study are: resting blood pressure (diastolic and systolic), fasting lipid levels (total cholesterol, triglycerides, high-density lipoproteins), fasting blood glucose, waist circumference, and body mass index (BMI). Participants were classified as having hypertension if they had a systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or were taking medication for either high blood pressure or hypertension. Participants were classified as having high total cholesterol if they had fasting serum cholesterol  $> 239$  mg/dl, or taking lipid-lowering medications [16]. Diabetes mellitus was defined by either fasting blood glucose  $\geq 126$  mg/dL or receiving treatment for diabetes mellitus. The participants brought medications to the exam and the medications were recorded by the physician.

### Covariates

A participant was determined to be a current smoker if they answered "yes" to the question "Have you smoked cigarettes regularly in the last year?" A measure of physical activity known as the physical activity index was calculated from self-report of responses to questions recording the typical number of hours of sleep and light, moderate, and heavy physical activity, and type of physical activity per day (previously described in Kannel WB 1979).

### Statistical analysis

We performed multivariable regression models to characterize the association between infertility and cardiovascular disease risk factors. Logistic regression was used to assess the association between infertility and dichotomous CVD risk factors (hypertension, diabetes, high total cholesterol, and obesity) separately; generalized estimating equations (GEE) were used to account for family correlations. Linear mixed effect regression models were used to assess the association between infertility and continuous CVD RFs (lipids, SBP, DBP, BMI, waist circumference) separately, taking family structure into account. Covariates in the multivariable models included age, smoking status, physical activity index, and cohort (Gen 3 versus Omni 2). Sensitivity analyses were performed excluding all women who were postmenopausal at the time of the exam ( $N = 711$ ), defined as cessation of menses for 1 year or more. For analyses of cycle length, women who were postmenopausal or did not provide information about cycle length were excluded ( $N = 105$ ). We excluded those with missing data in covariates or CVD RFs. All analyses were performed in R statistical software (R Foundation for Statistical Computing; Vienna, Austria).

**Results**

Of our study sample of 1968 women, 282 reported infertility. Table 1 highlights selected characteristics: average age was similar among those reporting infertility, 47.3 years (standard deviation (sd) = 7.7), compared to not reporting infertility 46.4 (sd = 9.4). The number of live births, age at menarche, and proportion that had reached menopause were also comparable. The distribution of CVD RFs is also reported in Table 1, with slight differences for those reporting infertility compared to those not with regards to BMI 28.0 kg/m<sup>2</sup> (sd = 7.0) vs 26.9 kg/m<sup>2</sup> (sd = 6.1) and total cholesterol 187.8 mg/dL (sd = 35.8) vs 185.7 mg/dL (sd = 33.9).

The results of the primary analyses are summarized in Table 2. Our models estimate that women reporting infertility have an average BMI 1.03 kg/m<sup>2</sup> (95% CI: 0.18, 1.89) higher and an average waist circumference 3.08 (95% CI: 1.06, 5.09) inches larger than women not reporting infertility when adjusting for age, smoking status, physical activity status, and cohort. Similarly, women reporting infertility had 1.43 (95% CI: 1.09, 1.87) times the odds of being obese (BMI ≥ 30 kg/m<sup>2</sup>) compared to women not reporting infertility, after adjustment.

**Table 1** Study population characteristics

|                              | Infertility, no<br>N = 1686 |       | Infertility, yes<br>N = 282 |       |
|------------------------------|-----------------------------|-------|-----------------------------|-------|
|                              | Mean                        | SD    | Mean                        | SD    |
| Age (years)                  | 46.4                        | 9.4   | 47.3                        | 7.7   |
| Live births (#)              | 1.6                         | 1.2   | 1.5                         | 1.2   |
| Age at menarche (years)      | 12.8                        | 1.6   | 12.8                        | 1.5   |
| BMI (kg/m <sup>2</sup> )     | 26.9                        | 6.1   | 28.0                        | 7.0   |
| SBP (mmHg)                   | 112.2                       | 14.1  | 112.6                       | 15.3  |
| DBP (mmHg)                   | 71.7                        | 9.1   | 71.8                        | 8.9   |
| Total Cholesterol (mg/dL)    | 185.7                       | 33.9  | 187.8                       | 35.8  |
| HDL (mg/dL)                  | 67.0                        | 17.3  | 65.7                        | 17.2  |
| Fasting Glucose (mg/dL)      | 93.1                        | 16.4  | 92.2                        | 11.7  |
| Physical activity index      | 35.6                        | 5.0   | 35.7                        | 5.1   |
|                              | Infertility, no             |       | Infertility, yes            |       |
| Count data                   | N                           | %     | N                           | %     |
| Cohort (number from Gen 3)   | 1538                        | 91.2% | 254                         | 90.1% |
| Current smoking              | 169                         | 10.0% | 19                          | 6.7%  |
| Hypertension                 | 296                         | 17.6% | 53                          | 18.8% |
| CVD                          | 31                          | 1.8%  | 5                           | 1.8%  |
| Lipid lowering medication    | 371                         | 22.0% | 63                          | 22.5% |
| Diabetes mellitus            | 70                          | 4.2%  | 11                          | 3.9%  |
| Menopausal                   | 601                         | 35.6% | 93                          | 33.0% |
| Cycle > 35 days <sup>a</sup> | 60                          | 6.1%  | 13                          | 7.7%  |

<sup>a</sup>Among pre-menopausal women who responded

**Table 2** Fully adjusted<sup>a</sup> models for association between infertility and CVD risk factors

| CVD Risk Factors – dichotomous   | N               |                  | Logistic regression estimate |                |
|----------------------------------|-----------------|------------------|------------------------------|----------------|
|                                  | No <sup>b</sup> | Yes <sup>b</sup> | OR                           | 95% CI         |
| Hypertension                     | 1619            | 349              | 1.07                         | (0.77, 1.48)   |
| Total cholesterol > 239 mg/dl    | 1645            | 322              | 1.16                         | (0.83, 1.61)   |
| BMI ≥ 30 kg/m <sup>2</sup>       | 1465            | 503              | 1.43                         | (1.09, 1.87)   |
| Diabetes                         | 1883            | 81               | 0.96                         | (0.49, 1.88)   |
| CVD Risk Factors – continuous    | N               |                  | Linear regression estimate   |                |
|                                  |                 |                  | β                            | 95% CI         |
| Systolic Blood Pressure (mm Hg)  | 1968            |                  | -0.18                        | (-1.94, 1.58)  |
| Diastolic Blood Pressure (mm Hg) | 1967            |                  | -0.05                        | (-1.22, 1.12)  |
| Total cholesterol (mg/dl)        | 1965            |                  | 1.32                         | (-2.90, 5.53)  |
| HDL cholesterol (mg/dl)          | 1965            |                  | -1.60                        | (-3.76, 0.56)  |
| Triglycerides (mg/dl)            | 1965            |                  | 4.47                         | (-1.54, 10.49) |
| Glucose (mg/dl)                  | 1965            |                  | -1.26                        | (-2.94, 0.41)  |
| BMI (kg/m <sup>2</sup> )         | 1968            |                  | 1.03                         | (0.18, 1.89)   |
| Waist circumference (inches)     | 1967            |                  | 3.08                         | (1.06, 5.09)   |

<sup>a</sup>Fully adjusted model includes covariates age, smoking status, physical activity index, and cohort

<sup>b</sup>Counts within the entire study population

We found slightly stronger effects when restricting to premenopausal women (Table 3). Among the premenopausal women, we estimated that the effect size of infertility on HDL is a decrease of 3.2 mg/dl (95% CI: -5.71, -0.74). Likewise, we estimated an effect size of an increase of 6.27 mg/dl in triglycerides among premenopausal women with infertility compared to premenopausal women without infertility. When excluding postmenopausal women, the directionality of the effect sizes changed for diabetes, glucose and total cholesterol. The association between infertility and diabetes increased drastically, from an odds ratio of 0.96 (95% CI: 0.49, 1.88) to 1.96 (95% CI: 0.86, 4.49), and fasting blood glucose for self-reported infertile women became modestly elevated by 0.37 mg/dl (95% CI: -1.63, 2.36). This is likely due to postmenopausal women who are on targeted therapy for glucose control/diabetes. We explored the association between infertility and CVD RFs in a smaller sample of women who also provided information on menstrual cycle length (N = 1152). Among women with cycle length ≤ 35 days, the association between infertility and the risk factors of increased BMI, increased waist circumference, and decreased HDL was similar to the full premenopausal sample, however caution must be exercised in interpretation and generalization as there was a limited number of women with cycle length > 35 days (Table 4).

**Table 3** Fully adjusted<sup>a</sup> models for association between infertility and CVD risk factors in the pre-menopausal subset

| CVD Risk Factors – dichotomous   | N               |                  | Logistic regression estimate |                |
|----------------------------------|-----------------|------------------|------------------------------|----------------|
|                                  | No <sup>b</sup> | Yes <sup>b</sup> | OR                           | 95% CI         |
| Hypertension                     | 1119            | 138              | 0.93                         | (0.55, 1.55)   |
| Total cholesterol > 239 mg/dl    | 1157            | 99               | 0.85                         | (0.48, 1.51)   |
| BMI ≥ 30 kg/m <sup>2</sup>       | 965             | 292              | 1.56                         | (1.11, 2.21)   |
| Diabetes                         | 1225            | 30               | 1.96                         | (0.86, 4.49)   |
| Linear regression estimate       |                 |                  |                              |                |
| CVD Risk Factors - continuous    | N               |                  | β                            | 95% CI         |
| Systolic Blood Pressure (mm Hg)  | 1257            |                  | −0.87                        | (−3.11, 1.36)  |
| Diastolic Blood Pressure (mm Hg) | 1256            |                  | 0.03                         | (−1.51, 1.56)  |
| Total cholesterol (mg/dl)        | 1255            |                  | −1.29                        | (−5.87, 3.28)  |
| HDL cholesterol (mg/dl)          | 1255            |                  | −3.23                        | (−5.71, −0.74) |
| Triglycerides (mg/dl)            | 1255            |                  | 6.27                         | (−1.32, 13.86) |
| Glucose (mg/dl)                  | 1255            |                  | 0.37                         | (−1.63, 2.36)  |
| BMI (kg/m <sup>2</sup> )         | 1257            |                  | 1.35                         | (0.28, 2.43)   |
| Waist circumference (inches)     | 1256            |                  | 3.64                         | (1.11, 6.16)   |

<sup>a</sup>Fully adjusted model includes covariates age, smoking status, physical activity index, and cohort

<sup>b</sup>Counts within the entire study population

## Discussion

This study represents a unique application of the Framingham Heart Study in evaluating the cross-sectional association between infertility and cardio-metabolic disease risk factors. To our knowledge, this is the first study that employs a cohort with directly measured CVD RF outcomes through a physical examination and laboratory assay. In this analysis using FHS participants, the prevalence of infertility was 14.2%, which is similar the figure reported in the 2002 National Survey of Family Growth, 8–12% [17]. In our study, for the women self-reporting for infertility, the odds of having diabetes and an obese BMI were higher than their 1686 counterparts not reporting

**Table 4** Fully adjusted models for association between infertility and CVD risk factors stratified by cycle length

| Cycle Length ≤35                 | Linear regression estimates |       |                |
|----------------------------------|-----------------------------|-------|----------------|
| CVD Risk Factors - continuous    | N                           | β     | 95% CI         |
| Systolic Blood Pressure (mm Hg)  | 1079                        | −0.65 | (−3.13, 1.83)  |
| Diastolic Blood Pressure (mm Hg) | 1078                        | 0.20  | (−1.53, 1.94)  |
| Total cholesterol mg/dl          | 1077                        | 0.38  | (−4.68, 5.44)  |
| HDL cholesterol mg/dl            | 1077                        | −3.66 | (−6.35, 0.97)  |
| Triglycerides mg/dl              | 1077                        | 8.15  | (−0.43, 16.72) |
| Glucose mg/dl                    | 1077                        | 0.73  | (−1.43, 2.89)  |
| BMI (kg/m <sup>2</sup> )         | 1079                        | 1.47  | (0.27, 2.68)   |
| Waist circumference (inches)     | 1078                        | 3.78  | (1.01, 6.55)   |

infertility. We also detected a trend towards abnormal lipid parameters, with an elevation in triglycerides and lower serum HDL in the infertile group, further suggesting an association between self-reported infertility with CVD risk factors. The effect size is small, which makes it uncertain whether the presence of infertility is associated with a small increase in CVD risk metrics for all infertile women, or if a subset carries a disproportionate risk. However, this study limited in its ability to evaluate subpopulations due to a small sample size.

The relationship between female factor infertility subtypes (such as ovulatory disorders, endometriosis, and uterine fibroids) and cardiovascular disease risk may be mediated by different pathways. For example, women with PCOS have greater prevalence of elevated total cholesterol, triglycerides, LDL, as well as lower HDL [18–22]. Increased BMI is well-documented in the three hyperandrogenic Rotterdam phenotypes [23, 24], as is the metabolic syndrome [25, 26]. Daan et al. previously noted that the cardiometabolic profile is worse in the hyperandrogenic phenotypes [27]. Thus, the pathway from infertility to CVD may be mediated by hyperandrogenism, dyslipidemia, obesity, and insulin resistance [28]. Further bolstering the possible implications of PCOS on cardiovascular disease risk, a study using the prospective arm of the Women's Health Initiative employed retrospectively-reported reproductive health outcomes to refine a post-menopausal cardiovascular risk factor model. The study noted that “always having irregular menses” and “sometimes having irregular menses” were positively associated with coronary heart disease, while a history of infertility or cause of infertility were not independently associated with postmenopausal CHD in their model [11]. Thus, it may be that among our study participants self-reporting for infertility, only those with menstrual irregularity carry a greater risk for CVD. One limitation of the study is that they did not evaluate premenopausal cardiovascular events and RFs remotely and retrospectively ascertained history of infertility and infertility cause.

Women with diminished ovarian reserve share a similar inclination towards dyslipidemia as women with PCOS, showing increased levels of triglycerides and LDL, and decreased levels of HDL; markers of insulin resistance like HOMA-IR are also elevated, as well as C-reactive protein, a marker of inflammation [29]. Consequently, among women with premature ovarian insufficiency, the pathway to CVD may be mediated by dyslipidemia [7, 8], chronic inflammation [30], and insulin resistance.

Some earlier studies on women with endometriosis show that serum HDL and LDL are similar to that of age- and adiposity-matched controls, but serum lipoprotein (a) and triglycerides are elevated [31]. The relationship between endometriosis and known CVD risk factors is

complicated by the fact that women with endometriosis have a lower BMI compared to controls [32, 33] and levels of fibroblast growth factor-2 (FGF-2) are elevated in women with endometriosis [34], since FGF-2 is known to protect against myocardial dysfunction [35]. Endometriosis may lead to CVD through pathways involving dyslipidemia, hysterectomy/oophorectomy [10], and chronic inflammation.

One major cardiovascular risk factor associated with the development of uterine fibroids is hypertension [36]. Biological mechanisms between hypertension and fibroids remains elusive, but may be due to hypertension induced tissue-changes at the level of the myoma cells or at the level of promoting vascular proliferation feeding the myoma.

Obesity, defined as a BMI > 25 kg/m<sup>2</sup>, is associated with increased time to pregnancy couples [37, 38], poorer *in-vitro* fertilization outcomes [39, 40], and also associated with ovulatory disorder in females [41]. In regularly ovulating women, obesity is associated with a longer time to pregnancy [42, 43]. Obesity is known longstanding risk factor for coronary heart disease [44], as well as CVD RFs [45] including diabetes [46, 47], hypertension [48], and dyslipidemia [49].

Our study somewhat contrasts with one by Parikh et al. in 2012. They also conducted a study agnostic to the cause of infertility, instead focusing on the association between the degree of subfertility and incidence of CVD among women in Sweden. Even without adjusting for BMI, they found no association between the degree of subfertility and incidence of CVD among women who were moderately infertile (up to 4 years of involuntary childlessness); only the most extreme infertile subjects (5+ years of involuntary childlessness) had an increased risk of CVD [50]. However, our study agrees with a study based on the Japan Nurses' Health Study, which showed that Japanese women with ovarian infertility were at high risk of hypercholesterolemia and diabetes mellitus before age 45 [5]. The group with ovarian infertility were also more likely to be obese than the controls.

Our study has some notable limitations. The ascertainment of infertility is through self-report, and thus we may have had subject misclassification. We neither had information regarding work-up or cause of infertility, nor information on any fertility treatments used. Age at diagnosis, time since diagnosis, and treatment of infertility may be relevant to CVD RF development and were not available for the present cross-sectional analysis. Furthermore, we were limited by small sample sizes in our sensitivity analyses for menstrual cycle length > 35 days.

One concern is that the use of fertility treatment, and not the infertility itself, confers CVD risk. Several treatment options are available and have been utilized by women with subfertility and infertility including superovulation drugs (clomiphene citrate and injectable gonadotropins)

combined with intrauterine insemination or *in-vitro* fertilization. Studies regarding the association of infertility treatment with long-term cardiovascular and metabolic risk in women are inconsistent. One study of 23,498 women in Sweden found that women who underwent *in-vitro* fertilization had an increased risk of hypertension and stroke [51], while another study of 1,186,753 women in Ontario, Canada found that women who delivered after undergoing fertility therapy were not at increased risk of cardiovascular disease [52]. However, there are no published prospective cohort studies that have determined the association of infertility and use of infertility treatment on long-term cardiovascular risk in women.

Our study has several notable strengths. First, there is excellent CVD RF outcome ascertainment with study staff (trained physicians and medical technicians) administered physical exam and study laboratory assessment for CVD RF. This reduces the bias of self-reported CVD RFs noted in other studies. Secondly, this community based cohort may be more representative of the general population compared to hospital or clinic-based cohorts, providing greater generalizability than studies drawn from clinical encounters alone.

## Conclusions

In this study, we found that BMI and waist circumference were the CVD risk factors most strongly correlated with a reported history of infertility among women in their reproductive and menopausal years. Future studies should evaluate CVD RFs in women remote from diagnosis and treatment of infertility, and by infertility sub-type, to better delineate this association.

## Abbreviations

BMI: Body mass index; BTO: Bilateral tubal occlusion; CVD RF: Cardiovascular disease risk factor; CVD: Cardiovascular disease; DAG: Directed acyclic graph; FGF-2: Fibroblast growth factor-2; FHS: Framingham Heart Study; GEE: Generalized estimating equations; Gen 3: Framingham Heart Study Third Generation Cohort; PCOS: Polycystic ovary syndrome; POI: Primary ovarian insufficiency; SD: Standard deviation

## Acknowledgements

We would like to acknowledge the participants of the Framingham Heart Study, including the Omni Cohort participants in their voluntary and selfless service.

## Funding

The results reported herein correspond to specific aims of The Framingham Heart Study, funded by National Institutes of Health contract N01-HC-25195 and HHSN2682015000011. This work was also supported by the NIA R56AG029451 to J.M. and the Reproductive Scientist Development Program from the NIH/NICHD Grant K12 HD000849 to S.M.

## Availability of data and material

The data for this study can be obtained through the NIH Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

## Authors' contributions

All authors made substantial contributions, including interpretation of data and writing of the paper. SM, JM, and KL conceived of the design, FS and KL led data analyses, and JC created figures. The final version of this article was approved by all authors for publication.

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board (IRB) of Boston University.

**Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Author details**

<sup>1</sup>Department of Obstetrics and Gynecology, Boston University School of Medicine, 85 East Concord Street, Boston, MA 02118, USA. <sup>2</sup>Department of Epidemiology, Boston University School of Public Health, Talbot 3E, 715 Albany Street, Boston, MA 02118, USA. <sup>3</sup>Department of Biostatistics, Boston University School of Public Health, Crossstown Center, 801 Albany St, Boston, MA 02118, USA. <sup>4</sup>Framingham Heart Study, Massachusetts. Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA.

Received: 24 January 2017 Accepted: 27 March 2017

Published online: 11 April 2017

**References**

- American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. *Fertil Steril*. 2008;90(5):S60.
- Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, Lopes P, Tabaste JM, Spira A. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). *Hum Reprod*. 1991;6(6):811–6.
- Anderson SA, Barry JA, Hardiman PJ. Risk of coronary heart disease and risk of stroke in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Int J Cardiol*. 2014;176(2):486–7.
- Verit FF, Akyol H, Sakar MN. Low antimüllerian hormone levels may be associated with cardiovascular risk markers in women with diminished ovarian reserve. *Gynecol Endocrinol*. 2016;32(4):302–5.
- Kurabayashi T, Mizunuma H, Kubota T, Hayashi K. Ovarian infertility is associated with cardiovascular disease risk factors in later life: A Japanese cross-sectional study. *Maturitas*. 2016;83:33–9.
- Glueck CJ, Morrison JA, Goldenberg N, Wang P. Coronary heart disease risk factors in adult premenopausal white women with polycystic ovary syndrome compared with a healthy female population. *Metabolism*. 2009;58(5):714–21.
- VanderSchouw YT, VanderGraaf Y, Steyerberg EW, Eijkemans MJC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet*. 1996;347(9003):714–8.
- Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. *Int J Obes Relat Metab Disord*. 2000;24(2):226–31.
- Chern JJ, Muhleman M, Tubbs RS, Miller JH, Johnston JM, Wellons 3rd JC, Blount JP, Oakes WJ, Rozzelle CJ. Clinical evaluation and surveillance imaging in children with spina bifida aperta and shunt-treated hydrocephalus. *J Neurosurg Pediatr*. 2012;9(6):621–6.
- Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and Risk of Coronary Heart Disease. *Circ Cardiovasc Qual Outcomes*. 2016;9(3):257–64.
- Parikh NI, Jeppson RP, Berger JS, Eaton CB, Kroenke CH, LeBlanc ES, Lewis CE, Loucks EB, Parker DR, Rillamas-Sun E, Ryckman KK, Waring ME, Schenken RS, Johnson KC, Edstedt-Bonamy AK, Allison MA, Howard BV. Reproductive Risk Factors and Coronary Heart Disease in the Women's Health Initiative Observational Study. *Circulation*. 2016;133(22):2149–58.
- Farland LV, Grodstein F, Srouji SS, Forman JP, Rich-Edwards J, Chavarro JE, Missmer SA. Infertility, fertility treatment, and risk of hypertension. *Fertil Steril*. 2015;104(2):391–7.
- Heron M. Deaths: Leading Causes for 2013. *Natl Vital Stat Rep*. 2016;65(2):1–95.
- Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci*. 1963;107:539–56.
- Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino Sr RB, Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol*. 2007;165(11):1328–35.
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Sasi CR. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146–e603.
- Chandra A, Martinez GM, Mosher WD, Abma JC, Jones J. Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. *Vital Health Stat*. 2005;25:1–160.
- Meirow D, Raz I, Yossepowitch O, Brzezinski A, Rosler A, Schenker JG, Berry EM. Dyslipidaemia in polycystic ovarian syndrome: different groups, different aetiologies? *Hum Reprod*. 1996;11(9):1848–53.
- Legro RS, Kunesman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med*. 2001;111(8):607–13.
- Zhang J, Fan P, Liu H, Bai H, Wang Y, Zhang F. Apolipoprotein A-I and B levels, dyslipidemia and metabolic syndrome in south-west Chinese women with PCOS. *Hum Reprod*. 2012;27(8):2484–93.
- Cheung LP, Ma RC, Lam PM, Lok IH, Haines CJ, So WY, Tong PC, Cockram CS, Chow CC, Goggins WB. Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. *Hum Reprod*. 2008;23(6):1431–8.
- Valkenburg O, Steegers-Theunissen RP, Smedts HP, Dallinga-Thie GM, Fauser BC, Westerveld EH, Laven JS. A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case-control study. *J Clin Endocrinol Metab*. 2008;93(2):470–6.
- Kumar A, Woods KS, Bartolucci AA, Azziz R. Prevalence of adrenal androgen excess in patients with the polycystic ovary syndrome (PCOS). *Clin Endocrinol (Oxf)*. 2005;62(6):644–9.
- Clark NM, Podolski AJ, Brooks ED, Chizen DR, Pierson RA, Lehotay DC, Lujan ME. Prevalence of Polycystic Ovary Syndrome Phenotypes Using Updated Criteria for Polycystic Ovarian Morphology: An Assessment of Over 100 Consecutive Women Self-reporting Features of Polycystic Ovary Syndrome. *Reprod Sci*. 2014;21(8):1034–43.
- Legro RS, Kunesman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab*. 1999;84(1):165–9.
- Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN, Group PCTS. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2006;91(1):48–53.
- Daan NM, Louwers YV, Koster MP, Eijkemans MJ, De Rijke YB, Lentjes EW, Fauser BC, Laven JS. Cardiovascular and metabolic profiles amongst different polycystic ovary syndrome phenotypes: who is really at risk? *Fertil Steril*. 2014;102(5):1444–51. e3.
- Rizzo M, Rizvi AA, Rini GB, Berneis K. The therapeutic modulation of atherogenic dyslipidemia and inflammatory markers in the metabolic syndrome: what is the clinical relevance? *Acta Diabetol*. 2009;46(1):1–11.
- Verit FF, Keskin S, Omer B, Yalcinkaya S, Sakar N. Is there any relationship between cardiovascular risk markers and young women with diminished ovarian reserve? *Gynecol Endocrinol*. 2014;30(10):697–700.
- Van Wijk DF, Boekholdt SM, Wareham NJ, Ahmadi-Abhari S, Kastelein JJ, Stroes ES, Khaw KT. C-reactive protein, fatal and nonfatal coronary artery disease, stroke, and peripheral artery disease in the prospective EPIC-Norfolk cohort study. *Arterioscler Thromb Vasc Biol*. 2013;33(12):2888–94.
- Crook D, Howell R, Sidhu M, Edmonds DK, Stevenson JC. Elevated serum lipoprotein (a) levels in young women with endometriosis. *Metabolism*. 1997;46(7):735–9.
- Ferrero S, Anserini P, Remorgida V, Ragni N. Body mass index in endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2005;121(1):94–8.
- Lafay Pillet MC, Schneider A, Borghese B, Santulli P, Souza C, Streuli I, De Ziegler D, Chapron C. Deep infiltrating endometriosis is associated with markedly lower body mass index: a 476 case-control study. *Hum Reprod*. 2012;27(1):265–72.
- Bourlev V, Larsson A, Olovsson M. Elevated levels of fibroblast growth factor-2 in serum from women with endometriosis. *Am J Obstet Gynecol*. 2006;194(3):755–9.

35. House SL, Bolte C, Zhou M, Doetschman T, Klevitsky R, Newman G, Schultz JJ. Cardiac-specific overexpression of fibroblast growth factor-2 protects against myocardial dysfunction and infarction in a murine model of low-flow ischemia. *Circulation*. 2003;108(25):3140–8.
36. Boynton-Jarrett R, Rich-Edwards J, Malspeis S, Missmer SA, Wright R. A prospective study of hypertension and risk of uterine leiomyomata. *Am J Epidemiol*. 2005;161(7):628–38.
37. Sundaram R, Mumford SL, Buck Louis GM. Couples' body composition and time-to-pregnancy. *Hum Reprod*. 2017;3:1–7.
38. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. *Hum Reprod*. 2007;22(6):1634–7.
39. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. *Reprod Biomed Online*. 2011;23(4):421–39.
40. Shah DK, Missmer SA, Berry KF, Racowsky C, Ginsburg ES. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. *Obstet Gynecol*. 2011;118(1):63–70.
41. Grodstein F, Goldman MB, Cramer DW. Body mass index and ovulatory infertility. *Epidemiology*. 1994;5(2):247–50.
42. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, Oosterhuis GJ, Bossuyt PM, van der Veen F, Mol BW. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod*. 2008;23(2):324–8.
43. Gesink Law DC, Macle hose RF, Longnecker MP. Obesity and time to pregnancy. *Hum Reprod*. 2007;22(2):414–20.
44. Bogers RP, Bemelmans WJ, Hoogveen RT, Boshuizen HC, Woodward M, Knekt P, Van Dam RM, Hu FB, Visscher TL, Menotti A, Thorpe Jr RJ, Jamrozik K, Calling S, Strand BH, Shipley MJ, Investigators B-CC. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med*. 2007;167(16):1720–8.
45. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983;67(5):968–77.
46. Nguyen NT, Nguyen XM, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey, 1999–2006. *Obes Surg*. 2011;21(3):351–5.
47. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289(1):76–9.
48. Alpert MA, Hashimi MW. Obesity and the heart. *Am J Med Sci*. 1993;306(2):117–23.
49. Grundy SM, Barnett JP. Metabolic and health complications of obesity. *Dis Mon*. 1990;36(12):641–731.
50. Parikh NI, Cnattingius S, Mittleman MA, Ludvigsson JF, Ingelsson E. Subfertility and risk of later life maternal cardiovascular disease. *Hum Reprod*. 2012;27(2):568–75.
51. Westerlund E, Brandt L, Hovatta O, Wallen H, Ekblom A, Henriksson P. Incidence of hypertension, stroke, coronary heart disease, and diabetes in women who have delivered after in vitro fertilization: a population-based cohort study from Sweden. *Fertil Steril*. 2014;102(4):1096–102.
52. Udell JA, Lu H, Redelmeier DA. Long-term cardiovascular risk in women prescribed fertility therapy. *J Am Coll Cardiol*. 2013;62(18):1704–12.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

