High-Sensitivity C-Reactive Protein is Not Independently Associated with Self-Reported Infertility in National Health and Nutrition Examination Survey 2015-2018 data

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Running title:
C-Reactive Protein in Infertile Women of The U.S.

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High-Sensitivity C-Reactive Protein is Not Independently Associated with Self-Reported Infertility in National Health and Nutrition Examination Survey 2015-2018 data

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Capsule

Although some studies have shown an association between infertility and cardiovascular diseases, we found that the high-sensitivity C-reactive protein (a cardiometabolic marker) was not independently associated with self-reported infertility.

Structured Abstract

Objective:

To study the association between high-sensitivity C-reactive protein (CRP) and infertility among reproductive age women while controlling for obesity and other metabolic markers. Previous studies found a link between infertility and cardiovascular diseases (CVDs). CRP is a sensitive marker of CVDs and its levels are affected by obesity.

Design/Setting:

We conducted a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) from 2015 through 2018.

Patients:

A total of 940 women aged 20-45 years who self-reported infertility, had hs-CRP values measured, and did not have CRP > 10 mg/L, asthma, arthritis, bronchitis, thyroid disease, bilateral oophorectomy, hysterectomy, and who were not breastfeeding or pregnant, premenarchal at the time of study or had menarche after the age of 20.

Interventions: N/A
Main outcome measure(s):
Infertility status (ever reporting inability to conceive with 12 months of trying to become pregnant)

Results:
In comparison to non-infertile women, self-reported infertile women had higher mean of hs-CRP (3.11 mg/L vs 2.40 mg/L, p=0.15) and higher percentage of moderate/high hs-CRP values (77.0% vs 58.8%, p=0.0326). However, after adjusting for metabolic markers, there was a non-significant association between moderate/high hs-CRP and self-reported infertility in the multivariable logistic regression analysis. Odds ratio estimates of the association between hs-CRP and infertility increased over 40% after removing obesity measures and/or HDL from regression models.

Conclusion:
There was no association between hs-CRP and self-reported infertility after controlling for obesity measures and other risk factors for CVDs in a sample of the U.S. women aged 20-45 years.

Keywords
CRP; Infertility; obesity; cardiovascular disease.
Introduction

C-Reactive Protein (CRP) is a non-specific but sensitive marker of inflammation that is synthesized by the liver under the influence of various stimuli, with IL-6 being a dominant regulator. (1) CRP can modulate the immune response and inflammation by affecting the function of the innate and adaptive immune system and the complement system. (1) CRP is associated with and predicts the development of cardiovascular diseases (CVDs) mainly by mediating inflammation-induced endothelium injury. (2-4) Levels of CRP are highly correlated with obesity. (5) In response to chronic low-grade inflammation associated with obesity, the liver increases the synthesis of various acute phase reactants, including CRP. (6) Specifically in women, CRP is associated with high body mass index (BMI) and can predict the development of CVDs. (7) Obesity, especially central obesity, is more closely associated with CRP levels in women than in men. (8) Further, CRP levels were shown to increase with increasing BMI in premenopausal women across different phases of menstrual cycles. (6, 9)

Infertile women were found to have higher risk of chronic metabolic diseases including CVDs. (10-13) The association between fertility impairment and CVDs was postulated to lie in the presence of shared alterations in hormones and inflammatory mechanisms mediated by obesity. Infertility can be associated with disruption of stress hormones linked to sympathetic stimulation and immune disturbance that could subsequently lead to the development of CVDs. (12, 14) For example, disruption of the normal physiology of the hypothalamic-pituitary-adrenal (HPA) axis, which is found in some women with impaired fertility, has been linked to the development of CVDs. (15-18) Activation of the HPA axis leads to high levels of cortisol which may subsequently lead to high blood pressure, fat redistribution with truncal obesity and
disruption of normal menstrual cycle, as manifested in Cushing’s syndrome. (15) In addition to increasing the risk of CVDs, the chronic inflammatory state in obesity could impair the ovarian function and fertility in women. (19) In fact, infertile women have higher inflammatory cytokines partly mediated by obesity. (20, 21)

To date, there is no study that tested the association between CRP and infertility status in reproductive age women using a national sample in the U.S. Therefore, we sought to conduct a cross-sectional study to test the association between high-sensitivity CRP (hs-CRP) and infertility status in reproductive age women (20-45 years) using a sample from National Health and Nutrition Examination Survey (NHANES) for the period 2015-2018. Since CRP level is mainly determined by obesity and metabolic markers in the general population and in premenopausal women, we controlled obesity, serum lipids, some anthropometric measures, hypertension and diabetes in our analyses.

Methods

Data source and sample design

We used NHANES data which is a national cross-sectional study conducted every two years using a complex, multistage and stratified sampling method to represent civilian and non-institutionalized residents of the U.S from all age groups. The surveys gather information using personal interviews, physical examinations and laboratory investigations. NHANES cycle 2015-2016 and 2017-2018 were used for this study since these two cycles contain complete information about hs-CRP, infertility, and most metabolic variables. Our study was deemed
exempt from review by Institutional Review Board of The University of Texas Health Science Center at Houston.

Main dependent and independent variables

Our outcome was the self-reported infertility categorical variable (questionnaire RHQ074) “Have you or your partner ever attempted to become pregnant over a period of at least a year without becoming pregnant?”. Women who responded “yes” were labeled as “ever-infertile” and those who responded “no” were labeled as “non-infertile”. (12) The main independent variable was high-sensitivity C-Reactive Protein (hs-CRP) measured in mg/L. We categorized hs-CRP according to the American Heart Association risk groups (low < 1.0 mg/L, moderate 1.0-3.0 mg/L, and high >3.0 mg/L). (22) Because of limited subjects who had high hs-CRP values, we combined moderate and high hs-CRP (1-10 mg/L) into one category. Values below the lower limit of detection (< 0.11 mg/L) were not included in the domain of our sample.

Covariates: variables that have known association with hs-CRP or infertility were included (e.g., hypertension, diabetes, serum lipids, obesity measures, and demographic factors including age, race, and smoking). (6, 12, 23) Hypertension and diabetes were defined in accordance with previous studies used NHANES data. (23-25) Hypertension categorical variable was created if systolic blood pressure (SBP) was ≥140 mmHg or diastolic blood pressure (DBP) was ≥ 90 mmHg based on average SBP and DBP from four readings recorded for each subject. Subject was also labeled as having hypertension if subject reported taking anti-hypertensive medications (responded yes to the question “now taking medicine for high blood pressure”). Diabetes categorical variable was created if subject had fasting blood glucose ≥ 126 mg/dL or HbA1c ≥ 6.5 or reported taking
insulin or oral hypoglycemic medication (responded yes to questions “now taking pills to lower blood glucose”, “now taking insulin”). Hip circumference was not found in 2015-2016 cycle and therefore it was not included. Because of limited number of subjects who responded to infertility question and had non-obese BMI values, we dichotomized BMI into non-obese (BMI <30) and obese (BMI ≥30). We dichotomized waist circumference as high (≥88 cm) and low (<88 cm), total cholesterol as high (≥200 mg/dL) and low (<200 mg/dL), and HDL as low (<50 mg/dL) and high (≥50 mg/dL) in accordance with previous studies. (26, 27) Trunk percent fat was included as a continuous variable. Smoking respondents were defined as “ever smoker” if they reported smoking at least 100 cigarettes in their entire life. (12) We recoded health insurance coverage as private, Medicaid, other, and none. (12)

Subjects. (Figure-1: flow chart of sample selection)

The sample included female respondents aged 20-45 years who responded to the question RHQ074 and had a valid lab value for high-sensitivity C-reactive protein (hs-CRP) in two cycles of NHANES for the period 2015-2018. A sample domain was specified that excluded subjects who had missing values on the main dependent and independent variables or high missing percentage (>20%) in the covariates. Our sample domain did not include pregnant women (by positive urine pregnancy test), breastfeeding, self-reported having hysterectomy or bilateral oophorectomy, having thyroid disease, were premenarchal or began menarche after the age of 20 at the time of study. Current pregnancy, breastfeeding, history of hysterectomy or bilateral oophorectomy may not indicate the current presence of infertility and thus were excluded. Thyroid diseases can include autoimmune thyroid disorders and might affect the levels of hs-CRP and therefore were excluded. Primary amenorrhea may indicate chromosomal aneuploidy
and genetic disorders that have an increased risk of CVDs in comparison to the general population (e.g., Turner syndrome). There is no variable in NHANES that reflects the definition of primary amenorrhea (absence of secondary sexual characteristics by age of 13 years or absence of menstruation by age of 15 years despite presence of secondary sexual characteristics). Therefore, we excluded premenarchal women or women began menarche after the age of 20 years at the time of the study. Patients with asthma, chronic bronchitis, or arthritis may use steroid or NSAIDs drugs (which could affect the CRP levels) and, therefore, were excluded. Hs-CRP levels higher than 10mg/L most likely indicate infection and were excluded, in accordance with previous studies on CRP in premenopausal women.

**Statistical analysis**

SAS version 9.4 4 (SAS Institute v.9.4, Cary, NC) was used to conduct all analyses. All analyses were performed on weighted sample responses to account for differential probabilities of participant selection and non-response. Use of sample weights in NHANES allows for unbiased parameter estimates to be calculated and generalized to the U.S. population. Rao-Scott F adjusted $\chi^2$ and t-tests were used to report the differences in independent variables between self-reported infertile and non-infertile women in the unadjusted analysis as recommended by NHANES. P value of $< 0.05$ was used to determine the statistical significance.

In the multivariable logistic regression models, we controlled for variables that showed significant differences between non-infertile and infertile women in the unadjusted analysis (age, BMI, waist circumference, and trunk % fat, table-1) as well as known associated factors with hs-CRP or infertility (hypertension, diabetes, total cholesterol, and HDL). We tested the correlation between the covariates and found that BMI, waist circumference and trunk % fat
were highly correlated (r=0.70 - 0.93). Therefore, we included BMI, % trunk fat, and waist circumference each in a separate model of multivariable logistic regression analyses (table-2).

We further examined the change of hs-CRP adjusted estimates of odds ratio after removing some of the metabolic covariates that had significant associations with infertility in the multivariable logistic regression analysis.

**Results:**

There were 2,493 women between age 20 and 45 years who participated in NHANES from 2015 to 2018, of whom 2,102 answered RHQ074 question (response rate 84.32%). The analytic sample included 940 subjects (20-45 years of age) that had no missing values on the selected variables (figure-1). Of the 940 subjects, 79 and 861 women were self-reported having or not having infertility, respectively. Because of NHANES weight, 940 subjects in our sample reflect an estimate of 21,800,049 women aged 20-45 years in the U.S population, 79 infertile women in our sample correspond to 1,735,244, and 861 non-infertile women correspond to 20,064,805 subjects in the U.S population. The estimated prevalence of self-reported infertility among women aged 20-45 years in the U.S was 7.96% for the period 2015 to 2018.

Women with self-reported infertility were older (34.28 years vs 31.12 years), had higher hs-CRP mean (3.11 mg/L vs 2.40 mg/L) and higher moderate-high hs-CRP percentages (77.0% vs 58.8%) than women who did not report infertility. Infertile women were more obese (56.6% vs 29.2%), had higher waist circumference (72.4% vs 51.8%), more mean trunk percent fat (38.7 vs 33.8) and lower HDL mean (54.06 mg/dL vs 59.63 mg/dL) than non-infertile women. There
were no significant differences between infertile and non-infertile women by race, smoking status, health insurance coverage status, total cholesterol, hypertension and diabetes (table-1).

Hs-CRP was no longer significantly associated with infertility in the multivariable logistic regression analyses after adjusting for metabolic factors (table-2). In the model that included BMI but not waist circumference or trunk % fat as measures of obesity (model-a from table-2), women of age group 31-35 years had 3.95 times higher odds of self-reported infertility compared with women of age group 20-25 years (95% CI 1.33, 11.67). In the same model, obese women had 2.86 times higher odds of self-reported infertility compared to non-obese women (95% CI 1.52, 5.34) and women with high HDL (≥50 mg/dL) had almost 50% lower odds of self-reported infertility in comparison to women with low HDL values (<50 mg/dL). In the model that included waist circumference but not BMI or trunk % fat as measures of obesity (model-b from table-2), women of age group 31-35 years had 3.90 times higher odds of self-reported infertility compared with women of age group 20-25 years (95% CI 1.32, 11.55). While in the model that included trunk % fat but not BMI or waist circumference as measures of obesity (model-c from table-2), women of age group 31-35 years had 3.78 times higher odds of self-reported infertility compared with women of age group 20-25 years (95% CI 1.32, 10.85). In the same model, women who had one unit increase in trunk % fat had about 10% higher odds of self-reported infertility (95% CI 1.02, 1.15) and women with high HDL (≥50 mg/dL) had almost 50% lower odds of self-reported infertility in comparison to women with low HDL values (<50 mg/dL).

We further explored the effect of the metabolic covariates that were significantly associated with infertility in the adjusted multivariable logistic regression analysis (obesity, trunk % fat, and...
HDL). Removing obesity, trunk % fat or HDL variables from model-a and model-c resulted in
>40% increase in odds ratio estimates of the association between hs-CRP and self-reported
infertility, however, it was not statistically significant. Taken together, these data indicate that
obesity measures confounded the association between hs-CRP and self-reported infertility.

Discussion
This is the first national study that tested the association between hs-CRP and self-reported
infertility in women aged 20-45 years in the U.S. Using the weighted analysis, the prevalence of
self-reported infertility among women aged 20-45 years was 7.96% for the period 2015-2018
which was within the range of the reported national prevalence from 2002 to 2017 (6%-8.8%).
(30) We found that self-reported infertility among women aged 20-45 increased with increasing
age and with obesity. (31-34) At the national level of the U.S., we found that women who self-
reported infertility had higher hs-CRP (a sensitive cardiometabolic marker) values than non-
infertile women. In the multivariable logistic regression analysis, obese women and women with
increasing trunk percent fat had higher odds of self-reported infertility. High HDL levels, on the
other hand, were associated with lower odds of self-reported infertility. These findings are
consistent with previous reports on the association between metabolic syndrome, markers of
obesity and infertility. (12, 13, 31) However, the association between hs-CRP and self-reported
infertility was not significant after adjustment for metabolic markers which highlights the
possible superior roles of obesity and metabolic pathways in infertility pathogenesis. Our
findings remained consistent across the models that tested obesity measures (BMI, waist
circumference, and trunk % fat) separately. Obesity and low HDL are also associated with high
hs-CRP and higher risk of CVDs, (6, 22) which could delineate the shared mechanism between
infertility and CVDs pathogenesis (or high CRP levels). Our study supported the possible
confounding effects of metabolic dysfunction on the association between hs-CRP and infertility
by showing increased estimates of moderate/high hs-CRP odds ratio (although not significant)
after removing obesity and/or HDL from the models in our adjusted multivariable logistic
regression analysis.

Most published studies have tested the association of infertility with CVDs and not with hs-CRP.
(12, 35-38) Our results are consistent with the subgroup analysis of NHANES data by Gleason and colleagues where they reported no increased odds of CVDs among self-reported infertile women who gave birth but not with their results of overall higher odds of CVDs (83%) among infertile women aged 20-59 years. (12) Gleason and colleagues included a sample of women up to 59 years of age when testing the overall association between infertility and CVDs. Further, they defined CVDs as self-reported “congestive heart failure,” “coronary heart disease,” “heart attack,” or “stroke” rather than using a biomarker (e.g., hs-CRP) in an effort to estimate long term CVDs risk. Our finding of non-statistically significant association between hs-CRP and infertility in the adjusted analysis was not consistent with a single-center Turkish study that reported an association between unexplained infertility and high hs-CRP, high triglycerides, and low HDL in group of normal weight women (of age 20-35 years) with similar exclusion criteria as ours. (13) Criteria of women in the U.S may differ from Turkish women and our study sample included obese infertile women (mean BMI = 30.87 kg/m²) and overweight non-infertile women (mean BMI = 27.39 kg/m²). Parikh et al. found an increased risk of CVDs among Swedish women who self-reported subfertility for five or more years but not in women who experienced subfertility for four or less years. (35) Our NHANES sample likely included women who
experienced infertility for short period of time as we did not have information on the duration of
the experienced infertility in NHANES data. Further, Parikh et al. included normal weight
women in all of their groups and they controlled for hypertension and diabetes in their adjusted
multivariable analysis but not for other metabolic markers. Yldrm et al. found no association
between CRP and the primary ovarian insufficiency (POI) in Turkish women aged 20-40 years.
(39) However, our sample mainly included women with regular menstrual cycle. Some causes of
infertility have been directly attributed to inflammatory damage to the ovary. (19, 39, 40)
Although Yldrm et al. did not find an association between CRP and POI, neutrophil-to-
lymphocyte ratio of less than 1.5 was an independent factor associated with POI. (39) Therefore,
it is important to consider the inflammatory mechanisms in infertility pathogenesis. Further, our
results may highlight the findings from survival analyses of two large-scale studies, Stentz el al.
and Parikh et al., who found no significant difference in the risk of death from CVDs between
infertile and non-infertile women (mean age= 62.5 years) over a period of 10 years and no
association between history of infertility and CVDs in postmenopausal women (mean age= 63.2
years), respectively. (37, 38) Stentz accounted for BMI in their disease risk score-adjusted
survival analysis while Parikh did not control for metabolic markers or BMI in their survival
analysis.

In defined samples, infertility due to polycystic ovarian syndrome (PCOS), endometriosis or
menstrual irregularities showed significant association with CRP and CVDs. (41-45) All of these
conditions can be associated with chronic low-grade inflammation and may exhibit high CRP
values which could explain the associated increased risk of CVDs. (41, 46-48) Our final
analytical sample included only 4.8% of the subjects with irregular menstrual cycle and thus,
might not include a large proportion of women with PCOS, but our sample consisted of obese infertile women and overweight non-infertile women which could explain the non-statistically significant association between infertility and hs-CRP in the models adjusted for metabolic markers and obesity but higher hs-CRP values in infertile compared to non-infertile women. Low grade inflammation (particularly high hs-CRP) can be majorly driven by metabolic dysfunction and obesity. (6, 27) Adipocytes can release various adipocytokines, some of which can augment IL-6 induced hepatic synthesis of CRP. (49) Adipocytes can also secrete leptin which was found to alter the hypothalamic-pituitary-ovarian axis and disrupt the reproductive function. (49) Moreover, obesity can disrupt the ovarian immune microenvironment, oocyte quality, and various cellular mechanisms in the oocytes. (19, 50) Collectively, increased fat mass can impair reproductive function and increase the risk of CVDs through, at least in part, inducing inflammation. Further, obese women (BMI ≥ 30) were found to have significantly lower odds of implantation, clinical pregnancy and having a live birth after conception via first ART cycle. (51) In fact, obese women seeking fertility services have a higher chance of becoming pregnant after losing weight. (52) Since that most infertile women in the U.S would seek fertility services (60%), it is important to consider counseling infertile women on weight loss. (53, 54) Our results underscore the need of counseling women about behavioral changes that could impact their future development of CVDs, reproductive health. Primary care providers should also counsel all women seeking conception on the negative impact of obesity on reproductive health and encourage weight loss.

The results of our study should be interpreted within the scope of its limitations and strengths. Since infertility was assessed through self-reporting, women may not precisely recall how long
they tried to become pregnant which might result in misclassification bias of including women in
the non-infertile group who were otherwise infertile. Similarly, our study could have missed
women who might be infertile but have not tried yet to conceive. We did not have information on
the duration of infertility or the time interval to conceive, thus, we could have missed women
over the age of 35 years who could otherwise be infertile after six months of unsuccessful
attempts to conceive. Since this is a cross-sectional study, we could not derive a causal inference
on the association between hs-CRP and infertility in reproductive age women. Hormonal
contraception could modulate hs-CRP values. (55) It is unknown how many reproductive age
women in our sample were currently on hormonal contraception since NHANES data do not
provide such information. Therefore, it is possible that we included self-reported infertile women
who were using hormonal contraception on the day of the interview and thus on the day of hs-
CRP assessment. Lastly, we did not include women older than 45 years of age; while the risk of
CVDs increases significantly with increasing age, NHANES data do not provide enough
information on CVDs risk factors (e.g., comprehensive family history of CVDs, TGs and LDL
levels).

Despite these limitations, this study has several strengths. This is the first national study to test
the association between a highly sensitive cardiometabolic marker (hs-CRP) and self-reported
infertility in reproductive age women of the U.S using weighted analysis. We accounted for
various metabolic markers and removed various conditions that could modulate hs-CRP values
or infertility. We defined our covariates using biomarkers, thus avoiding recall bias. Although we
did not have information on causes of infertility, we included non-pregnant and non-breast
feeding women aged 20-45 years, and excluded various inflammatory conditions. Thus, it is
reasonable to generalize the results of this study on a similar population of infertile women aged 20-45 years in the U.S.

Our results are important in view of recent studies that found an association between infertility and risk of CVDs or hs-CRP. (12, 13, 35) At the national level of the U.S., we found that the hs-CRP was not independently associated with self-reported infertility after adjustment for metabolic markers and obesity. Prospective studies are warranted to test the causal relationship between infertility and cardiometabolic markers like hs-CRP.
Acknowledgements

We thank Yong-Fang Kuo, PhD from the Department of Preventive Medicine and Population Health, The University of Texas Medical Branch for her scientific opinion on data analysis.

References:


Table 1. General characteristics of women age 20-45 years with self-reported infertility and non-infertility. N=940, weighted n=21,800,049.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ever-infertile women</th>
<th>Non-infertile women</th>
<th>Weighted P value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(Mean or %, SE)</td>
<td>(Mean or %, SE)</td>
<td></td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>3.11, 0.29</td>
<td>2.40, 0.08</td>
<td>0.015</td>
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<td>Hs-CRP categories</td>
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<td></td>
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<tr>
<td>Low (&lt;1 mg/L)</td>
<td>23.0%, 7.18</td>
<td>41.2%, 2.45</td>
<td>0.0326</td>
</tr>
<tr>
<td>Moderate/high (1-10 mg/L)</td>
<td>77.0%, 7.18</td>
<td>58.8%, 2.45</td>
<td></td>
</tr>
<tr>
<td>Age at the time of interview (years)</td>
<td>34.28, 0.69</td>
<td>31.12, 0.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age categories</td>
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<tr>
<td>20-25</td>
<td>11.8%, 5.17</td>
<td>29.6%, 2.14</td>
<td>0.0013</td>
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<tr>
<td>26-30</td>
<td>14.7%, 3.86</td>
<td>21.3%, 1.64</td>
<td></td>
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<tr>
<td>31-35</td>
<td>32.0%, 5.34</td>
<td>18.2%, 1.61</td>
<td></td>
</tr>
<tr>
<td>≥36</td>
<td>41.5%, 5.53</td>
<td>30.9%, 1.91</td>
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<tr>
<td>Race categories</td>
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<td>NHW</td>
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<td>NHB</td>
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<td>20.6%, 2.05</td>
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<tr>
<td>Asian</td>
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<td>16.7%, 1.07</td>
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<tr>
<td>Other</td>
<td>40.5%, 0.72</td>
<td>35.1%, 2.72</td>
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<td>Smoking categories</td>
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<td>No</td>
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<td>Yes</td>
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<td>24.8%, 2.70</td>
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<td>Insurance categories</td>
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<tr>
<td>None</td>
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<td>22.7%, 1.58</td>
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<tr>
<td>Other</td>
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<td>Private</td>
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<td>Medicaid</td>
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<td>16.6%, 1.75</td>
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</tr>
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<td>Measure</td>
<td>Value 1</td>
<td>Value 2</td>
<td>p-value</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>30.87, 0.88</td>
<td>27.39, 0.23</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>BMI categories (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-obese (&lt;30)</td>
<td>43.4%, 7.52</td>
<td>70.8%, 2.33</td>
<td>0.0004</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>56.6%, 7.52</td>
<td>29.2%, 2.33</td>
<td></td>
</tr>
<tr>
<td>Waist circumference categories</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Low (normal) &lt;88cm</td>
<td>27.6%, 6.11</td>
<td>48.2%, 2.54</td>
<td>0.008</td>
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<tr>
<td>High ≥88cm</td>
<td>72.4%, 6.11</td>
<td>51.8%, 2.54</td>
<td></td>
</tr>
<tr>
<td>Trunk % fat</td>
<td>38.70, 0.79</td>
<td>33.80, 0.28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>181.6, 4.10</td>
<td>176.9, 1.08</td>
<td>0.221</td>
</tr>
<tr>
<td><strong>Total cholesterol (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (normal) &lt;200</td>
<td>70.9%, 6.27</td>
<td>78.3%, 1.47</td>
<td>0.200</td>
</tr>
<tr>
<td>High ≥200</td>
<td>29.1%, 6.27</td>
<td>21/7%, 1.47</td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>54.06, 1.35</td>
<td>59.63, 0.53</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>HDL (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low &lt;50</td>
<td>26.5%, 5.86</td>
<td>28.4%, 2.04</td>
<td>0.744</td>
</tr>
<tr>
<td>High (normal) ≥50</td>
<td>73.5%, 5.86</td>
<td>71.6%, 2.04</td>
<td></td>
</tr>
<tr>
<td>Hypertension categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>86.87%, 0.88</td>
<td>95.0%, 1.21</td>
<td>0.045</td>
</tr>
<tr>
<td>Yes</td>
<td>13.13%, 0.50</td>
<td>5.0%, 0.89</td>
<td></td>
</tr>
<tr>
<td>Diabetes categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>93.7%, 0.99</td>
<td>97.9%, 1.20</td>
<td>0.099</td>
</tr>
<tr>
<td>Yes</td>
<td>6.3%, 0.37</td>
<td>2.1%, 0.89</td>
<td></td>
</tr>
</tbody>
</table>

* Bolded values indicate statistical significance at α <0.05
Table 2. Multivariable analyses with adjusted odds ratios and confidence intervals of the association between hs-CRP and self-reported infertility among women 20-45 years of age; NHANES 2015-2018. Outcome is (ever infertile women).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Model a BMI binary</th>
<th>Model b Waist circumference</th>
<th>Model c Trunk % fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-sensitivity CRP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low hs-CRP</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>Moderate/high hs-CRP</td>
<td>1.48 (0.66 – 3.31)</td>
<td>1.83 (0.86 – 3.90)</td>
<td>1.27 (0.61 – 2.63)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-25</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>1.64 (0.52 – 5.17)</td>
<td>1.62 (0.54 – 4.84)</td>
<td>1.55 (0.49 – 4.89)</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>3.95 (1.34 – 11.67)</td>
<td>3.90 (1.32 – 11.55)</td>
<td>3.78 (1.32 – 10.85)</td>
<td></td>
</tr>
<tr>
<td>≥36</td>
<td>2.81 (0.95 – 8.29)</td>
<td>2.65 (0.89 – 7.88)</td>
<td>2.68 (0.91 – 7.85)</td>
<td></td>
</tr>
<tr>
<td>BMI categories (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-obese (&lt;30)</td>
<td>REF</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>2.86 (1.52 – 5.38)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;88cm</td>
<td>N/A</td>
<td>REF</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>≥88cm</td>
<td>N/A</td>
<td>1.73 (0.83 – 3.64)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Trunk % fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.09 (1.02 – 1.15)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>1.01 (0.53 – 1.93)</td>
<td>1.05 (0.54 – 2.03)</td>
<td>1.05 (0.55 – 2.01)</td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td><strong>0.50 (0.27 – 0.96)</strong></td>
<td>0.59 (0.31 – 1.10)</td>
<td><strong>0.51 (0.28 – 0.90)</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>REF</th>
<th>REF</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.33 (0.51 – 3.49)</td>
<td>1.66 (0.61 – 4.58)</td>
<td>1.39 (0.56 – 3.49)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>REF</th>
<th>REF</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.94 (0.46 – 8.20)</td>
<td>1.90 (0.49 – 7.45)</td>
<td>1.65 (0.41 – 6.59)</td>
</tr>
</tbody>
</table>

Abbreviations: NHANES: National Health and Nutrition Examination Survey; hs-CRP: high sensitivity C-reactive protein; BMI: body mass index; REF: Reference group; HDL: high-density lipoprotein.

**Model a** Adjusted for age, **BMI**, total cholesterol, HDL, hypertension, and diabetes.

**Model b** Adjusted for age, **waist circumference**, total cholesterol, HDL, hypertension, and diabetes.

**Model c** Adjusted for age, **trunk % fat**, total cholesterol, HDL, hypertension, and diabetes.

*Low: <1 mg/L, Moderate/High: 1-10 mg/L.*

**Bolded values indicate statistical significance at α <0.05**

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502

503

504 **Figure-1.** Flow chart of sample selection.
Participants screened in NHANES during 2015-2016 and 2017-2018

N1=19,225

All screened female participants

N2=9,776

Females of age 20-45 years

N3=2,493

Excluding: asthma, arthritis, bronchitis, thyroid problem, not started menstruation at the time of study or had menarche after the age of 20, hysterectomy, bilateral oophorectomy, breastfeeding, pregnant, or CRP > 10.

N4=1,571

No missing values in hs-CRP or RHQ074 variables.

N5=1,187

<20% missing covariate data

N6=940