Self-reported infertility, metabolic dysfunction, and cardiovascular events: a cross-sectional analysis among U.S. women

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Objective: To explore associations between infertility and metabolic syndrome, and cardiovascular events. Infertility is increasingly a public health issue, with emerging links to chronic disease. Existing literature on infertility focuses primarily on known causes, which likely excludes a substantial number of women for whom there is no known cause or formal diagnosis.
Design/Setting: We conducted a cross-sectional analysis examining the association between self-reported infertility (i.e., ever experiencing inability to conceive after 12 months of trying to become pregnant) and metabolic syndrome and cardiovascular events (i.e., congestive heart failure, coronary heart disease, heart attack, or stroke). Data were analyzed using multivariate logistic regression.
Patient(s): A total of 744 U.S. women, 20–59 years of age, from the National Health and Nutrition Examination Survey (2013–2014), participated in the study. Among them, 15.7% reported ever experiencing infertility, 27.6% met the definition of metabolic syndrome, and 2.84% reported ever having a cardiovascular event.
Intervention(s): N/A.
Main Outcome Measure(s): Metabolic syndrome and cardiovascular events.
Results: Compared to women who had never experienced infertility, women who reported infertility had a 1.79 (95% confidence interval [CI] 1.04, 3.08) higher odds of reporting symptoms of metabolic syndrome and 1.83 (95% CI 1.15, 2.89) times higher odds of having experienced a cardiovascular event. Furthermore, women with self-reported infertility had a 71% higher odds of reporting a cardiovascular event after controlling for metabolic syndrome (95% CI 1.01, 3.00).
Conclusions: Our results suggest that among U.S. women, the experience of infertility at any point in a woman's reproductive window may be associated with later-life cardiovascular health. (Fertil Steril® 2019;111:138–46. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Infertility, cardiovascular disease, reproductive health

With links being found between infertility and later onset of chronic conditions such as cancer, diabetes, and cardiovascular disease (1, 2), infertility is being considered an indicator of overall health (3). The high prevalence of U.S. women (12–16%) who report experiencing infertility in their lifetime underscores the need to identify long-term sequelae of infertility (4, 5). From a public health perspective, metabolic syndrome (MetS) and cardiovascular disease are leading causes of mortality in the United States (6) and important potential sequelae of infertility.

The notion that infertility may predict MetS and development of cardiometabolic disease is supported by two lines of evidence. The first regards the link between neuroendocrine functioning and fertility (7, 8). Critical to optimal fertility is regulation of reproductive hormones, such as luteinizing hormone and follicle-stimulating hormone, which influence menstruation, ovulation, implantation,

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and pregnancy viability (7, 8). Disruption of any of these processes can lead to reproductive dysfunction. Infertility has been linked to disruptions in both the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenal-medullary (SAM) pathway (7, 8). Generally, HPA activation stimulates the release of corticotropin-releasing hormone, which suppresses the release of reproductive hormones, including luteinizing hormone and follicle-stimulating hormone (7). Disruption during critical windows in the conception process can adversely affect ovarian innervation and further inhibit release of luteinizing hormone and follicle-stimulating hormone (7, 9, 10). Similarly, stimulation of adrenocorticotropin-releasing hormone during neuroendocrine activation inhibits release of gonadotropin-releasing hormone, which, under normal functioning, regulates luteinizing and follicle-stimulating hormones (11).

The second line of evidence implicates activation of HPA and SAM in the development of the MetS (12, 13). Defined by a combination of dyslipidemia, elevated blood pressure, insulin resistance, hypercholesterolemia, and abdominal obesity, MetS is a reliable predictor of lifetime risk of developing cardiovascular disease (14). Further support for the existence of HPA and SAM activity in the development of MetS comes from animal studies that have linked MetS to hyperandrogenemia through alterations in luteinizing hormone, follicle-stimulating hormone, and progesterone levels (15).

One recognized cause of infertility, polycystic ovary syndrome (PCOS), has been linked to an elevated risk of developing MetS (16, 17). However, only about 25% of female-factor infertility is attributed to anovulation due to PCOS, and a significant proportion of infertility remains idiopathic (18, 19). Whether MetS is a likely sequela among the broader population of infertile women remains an open question, as many studies on infertility are conducted among women seeking fertility treatment, which consequently excludes women who never seek clinical diagnosis or treatment (20, 21). Given the large prevalence of women with idiopathic or undiagnosed infertility, and given that CVD is a leading cause of morbidity and mortality among women (22), it is important to examine whether the association between infertility and cardiovascular health is observed among a nonreferred population of women who report having experienced infertility. Therefore, we examine the association among infertility, MetS, and cardiovascular events in a nationally representative sample of U.S. women.

MATERIAL AND METHODS

Data Source and Sample

We analyzed data from the 2013–2014 cycle of the National Health and Nutrition Examination Survey (NHANES), which combines in-home interviews with biomarker data to assess the health of the U.S. population. NHANES uses complex stratified sampling methods to obtain a nationally representative sample of children and adults in 2-year cycles. This cycle is currently the only available cycle with a complete complement of biomarker variables and infertility-related questions (23).

Our analytic sample was restricted to women 20–59 years of age who both completed the reproductive health interview and answered questions related to cardiovascular disease. Furthermore, because two components of MetS required respondents to fast for at least 8 hours, we used the fasting subsample of NHANES for all analyses to ensure comparability of the sample across the outcomes examined in this study (24). All procedures for biometric collection and home interviews are available through the survey operations manual for each (25, 26).

Dependent Variables

Respondents were determined to have conditions consistent with MetS if at least three of the following five conditions were met, in accordance with the American Heart Association criteria (27): elevated waist circumference ($\geq$88 cm), elevated triglycerides ($\geq$150 mg/dL), reduced high-density lipoprotein (HDL) cholesterol ($<$50 mg/dL), elevated blood pressure ($\geq$130 mm Hg systolic blood pressure or $\geq$85 mm Hg diastolic blood pressure, averaged over three readings), or elevated fasting glucose ($\geq$100 mg/dL), consistent with previous NHANES studies (17). Respondents were also considered to have elevated blood pressure or glucose if they reported taking prescribed antihypertensive or antidiabetic (oral agents or insulin) medications, respectively.

Respondents were determined to have had a cardiovascular event if they had ever been told by a doctor that they had "congestive heart failure," "coronary heart disease," "heart attack," or "stroke." Because the prevalence of any specific cardiovascular events was less than 3%, we developed a binary composite variable (1 = any event, 0 = no event).

Independent Variable

Infertility was defined as a binary variable based on how women responded to the question, "Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?" Those who responded yes were considered ever infertile (1= ever infertile, 0 = never infertile) (19).

Covariates

Directed acyclic graph (DAG) informed variable selection for adjusted models (Supplementary Fig. 1). Covariates were considered based on known associations of behavior and health variables with infertility and cardiovascular health based on prior literature (27–29). Age was a continuous variable in years. Race and ethnicity were categorized in NHANES as non-Hispanic white, non-Hispanic black, Asian, Mexican American, other Hispanic, or other/multiracial. The "other race/multiracial" subgroup was included in the analysis, but results are not reported because of the small number of participants and racial/ethnic heterogeneity of this subgroup, consistent with NHANES analytic guidelines (24). For insurance type, respondents reported having private insurance, Medicaid, Medicare, military health insurance, state-sponsored, Indian Health Service, other government, single-service health plan, or no health insurance. These were recoded into four groups: private insurance, Medicaid, no insurance, and other, to include all other insurance

categories. Poverty-to-income ratio (PIR) was calculated by dividing family income by the federal poverty level (24).

Behavioral and health covariates were considered based on their association with the independent and dependent variables, as established in previous studies (27–29). We examined smoking history, current medication use, and BMI. Smoking status was a binary variable, wherein respondents were considered ever smokers if they reported having smoked at least 100 cigarettes in their lifetime (28). Current medication use was coded as a binary variable coded as "yes" if respondents indicated that they were currently taking medication prescribed for high blood pressure, high cholesterol, or diabetes, including insulin and oral medication to lower glucose levels (29). BMI was calculated by dividing weight (kg) by squared height (m^2), and coded into three categories, based on National Institutes of Health guidelines (30): underweight/normal weight (<25), overweight (25–29.9), and obese (30+).

The study procedures were submitted to the Institutional Review Board (IRB) at the University of Maryland for review. The IRB determined that this study was exempt from review, and thus no approval was required or obtained.

Data Analysis

We conducted all analyses in SAS version 9.4, using survey commands and survey weights developed by NHANES for the fasting subsample to account for complex stratified sampling procedures (24). Both χ^2 and *t*-tests were conducted to test for differences between outcomes for each covariate.

Two logistic regression models were fit to assess the association between infertility and MetS and cardiovascular events separately for each outcome: an unadjusted model, and an adjusted model that included age, race, insurance type, poverty-to-income ratio, smoking, use of medication, and BMI. Because the definition of MetS included use of medication and waist circumference, which is strongly correlated with BMI, we did not include these two covariates in models examining MetS. In addition, MetS was added to the adjusted model of cardiovascular events to determine whether MetS was a confounder of the association of infertility and cardiovascular events.

We also conducted several sensitivity analyses to assess assumptions of our models. First, because a portion of the never infertile group may have included women who did not yet try to become pregnant, we restricted each analysis to [1] women who had a previous birth and [2] women who were aged 35 years or older at the time of interview, to ensure more comparability in ever having tried to become pregnant. Second, because our main analysis of MetS did not control for BMI due to its strong correlation with waist circumference ($r = 0.92$, $P<.01$), we excluded waist circumference from the definition of MetS and subsequently adjusted for BMI, to assess the extent to which BMI influenced our findings.

RESULTS

The analytic sample included 744 women, 20–59 years of age, weighted to be representative of the U.S. population (Table 1). Approximately 28% of the sample met the definition of having MetS, and 2.84% reported having a cardiovascular event. Women with self-reported infertility (15.7%) were more likely than other women either to meet the definition of MetS (21.2% vs. 13.6%) or to have reported a CVD event (20.6% vs. 15.6%) ($P<.01$).

Results of the multivariate analyses for MetS and cardiovascular events appear in Tables 2 and 3, respectively. After controlling for all demographic as well as behavioral and health covariates, women who reported ever having experienced infertility had 79% (confidence interval [CI] 1.04, 3.08) higher odds of having MetS and 83% (CI 1.15, 2.89) higher odds of having reported a cardiovascular event than women who did not report infertility. This association remained significant in sensitivity analyses controlling for MetS (odds ratio [OR] = 1.71; CI 1.01, 3.00). In this model, MetS was also significantly associated with reporting a cardiovascular event (OR 3.05; CI 1.99, 4.67).

In two sensitivity analyses restricted to women who either had a previous birth or who were aged 35 or older at the time of interview (Tables 2 and 3), we found that point estimates remained generally consistent with those of the full sample; however, the significance of our estimates varied depending on outcome and subsample examined. Among women who had given birth to at least one child (n = 530), women who ever reported infertility were 73% more likely to present with conditions consistent with MetS (CI 1.01, 3.23) compared with never infertile women, but we did not find a significant association with cardiovascular events. Among women aged 35 years or older (n = 458), women reporting infertility were more likely to have ever experienced a cardiovascular event (OR 1.83; CI 1.11, 3.10) compared with never infertile women, but we did not find a significant association with MetS.

In sensitivity analyses that applied a modified MetS outcome definition that excluded waist circumference and controlled for BMI in adjusted models (Table 4), women with self-reported infertility had 2.31 (CI 1.12, 4.78) times higher odds of having MetS than never infertile women (Table 4). These findings were consistent across subgroup analyses. For women who had ever given birth, women with self-reported infertility were 2.38 times more likely to meet the modified definition of MetS (CI 1.05, 5.39) compared to never infertile women. Among women aged 35 years and older, ever infertile women were 2.25 times (CI 1.02, 4.99) more likely to meet the modified definition of MetS compared to never infertile women.

DISCUSSION

In this first national study of the association between self-reported infertility and MetS and cardiovascular events, we found that among U.S. women 20–59 years of age, infertility was associated with risk of MetS and experiencing a cardiovascular event. Given that cardiovascular disease is most likely to occur after the age of 55 years among women (6), whereas MetS can develop at any age (31), the examination of both outcomes separately and within the same models

TABLE 1

Characteristics of U.S. women aged 20–59 y who reported ever or never infertility (n = 744), National Health and Nutrition Examination Survey, 2013–2014, weighted.

		Metabolic syndrome		CV event	
	Total (n = 744)	Yes (28%)	No (72%)	Yes (2.8%)	No (97.1%)
Age, y, mean (SD)	39.7 (11.44)	44.5 (10.23)	37.7 (11.33)	47.44 (6.92)	39.48 (11.48)
PIR, mean (SD)	2.44 (1.68)	2.18 (1.55)	2.55 (1.72)	1.44 (1.02)	2.47 (1.69)
Race/ethnicity					
Non-Hispanic white	62.93%	66.09%	61.72%	64.72%	62.88%
Non-Hispanic black	13.09%	12.31%	13.39%	16.19%	13.00%
Asian	5.52%	2.48%	6.69%	0%	5.68%
Mexican American	9.59%	11.37%	8.91%	10.30%	9.57%
Other Hispanic	6.44%	6.67%	6.35%	8.79%	6.37%
Infertility					
Ever	15.71%	21.23%	13.59%	20.64%	15.56%
Never	84.29%	78.77%	86.41%	79.36%	84.44%
Insurance type					
Private	55.18%	52.79%	56.09%	17.60%	56.27%
Medicaid	10.06%	12.92%	8.96%	45.74%	9.03%
Other	14.70%	14.13%	14.92%	28.45%	14.30%
None	20.06%	20.16%	20.02%	8.21%	20.40%
Medications					
Yes	31.02%	44.68%	10.45%	78.09%	18.25%
No	68.98%	55.32%	89.55%	21.91%	81.75%
Smoker					
Ever	35.07%	41.26%	32.70%	77.60%	33.84%
Never	64.93%	58.74%	67.30%	22.40%	66.16%
BMI					
Underweight–normal	32.21%	2.93%	43.43%	24.11%	32.44%
Overweight	24.43%	21.38%	25.60%	29.23%	24.29%
Obese	43.36%	75.69%	30.97%	46.66%	43.27%

Note: Missing values were 6.4% for PIR, and <3% for the following: metabolic syndrome (2.8%), medications (0.3%), insurance type (0.3%), and BMI (0.4%). BMI = body mass index; PIR = family income-to-poverty ratio.

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provides evidence that infertility may be an indicator of metabolic dysfunction, regardless of age.

Despite the low prevalence of cardiovascular events in this sample, we found self-reported infertility to be significantly associated with MetS and cardiovascular events in our main models. Furthermore, subgroup analyses were conducted to make the ever infertile and never infertile groups more comparable with respect to having attempted pregnancy. We found that the magnitude of associations remained consistent across sensitivity analyses, despite variation in

TABLE 2

Adjusted odds ratios and confidence intervals for the association between ever infertility and risk of metabolic syndrome for U.S. women aged 20–59 y, National Health and Nutrition Examination Survey, 2013–2014, with subgroups.

	Crude model	Adjusted model (n = 744)	Women who gave birth (n = 530)	Women 35+ (n = 458)
Ever infertile	1.65 (1.01, 2.71)	1.79 (1.04, 3.08)	1.73 (1.01, 3.23)	1.83 (0.90, 3.73)
Age		1.06 (1.05, 1.08)	1.06 (1.03, 1.09)	1.07 (1.03, 1.11)
Race/ethnicity				
Non-Hispanic white		1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Hispanic black		0.77 (0.43, 1.38)	0.77 (0.39, 1.52)	0.94 (0.51, 1.72)
Asian		0.46 (0.22, 0.96)	0.49 (0.22, 1.09)	0.44 (0.20, 0.96)
Mexican American		1.57 (0.94, 2.62)	0.98 (0.53, 1.83)	1.43 (0.78, 2.62)
Other, Hispanic		1.19 (0.47, 3.06)	1.14 (0.43, 3.07)	1.37 (0.43, 4.39)
Insurance type				
Private		1.0 (ref)	1.0 (ref)	1.0 (ref)
Medicaid		1.16 (0.51, 2.65)	1.09 (0.49, 2.42)	1.00 (0.37, 2.73)
Other		0.80 (0.40, 1.60)	0.81 (0.36, 1.85)	0.51 (0.24, 1.05)
None		0.82 (0.44, 1.51)	0.86 (0.41, 1.78)	0.71 (0.30, 1.70)
PIR		0.82 (0.70, 0.96)	0.83 (0.68, 1.01)	0.83 (0.70, 0.97)
Smoker (ever regular)		1.19 (0.80, 1.77)	1.78 (0.94, 3.33)	1.11 (0.65, 1.89)

Note: ref = Reference; PIR = family income-to-poverty ratio.

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TABLE 3

Adjusted odds ratios and confidence intervals for the association between ever infertility and risk of cardiovascular events for U.S. women aged 20–59–y, National Health and Nutrition Examination Survey, 2013–2014, with subgroups.

	Crude model	Adjusted model (n = 744)	Women who gave birth (n = 530)	Women aged 35+ (n = 458)
Ever infertile	1.41 (0.96, 2.25)	1.83 (1.15, 2.89)	1.77 (0.55, 5.65)	1.83 (1.11, 3.10)
Age (mean)		1.08 (1.05, 1.12)	1.09 (1.05, 1.14)	1.02 (0.97, 1.08)
Race/ethnicity				
Non-Hispanic white		1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Hispanic black		0.94 (0.21, 4.27)	1.39 (0.35, 5.60)	0.88 (0.19, 4.00)
Asian		NS[a]	NS[a]	NS[a]
Mexican American		1.80 (0.46, 7.05)	2.27 (0.57, 9.10)	1.48 (0.46, 4.75)
Other, Hispanic		1.99 (0.64, 6.19)	1.98 (0.52, 7.54)	2.03 (0.64, 6.50)
Insurance type				
Private		1.0 (ref)	1.0 (ref)	1.0 (ref)
Medicaid		10.57 (0.94, 118.27)	8.00 (0.99, 64.75)	10.16 (0.98, 105.87)
Other		4.40 (0.52, 37.39)	5.01 (0.59, 42.24)	4.34 (0.47, 39.80)
None		0.69 (0.11, 4.27)	0.72 (0.14, 3.69)	0.74 (0.11, 5.08)
PIR		0.58 (0.40, 0.84)	0.53 (0.35, 0.80)	0.58 (0.41, 0.81)
Smoker (ever regular)		4.79 (1.44, 15.93)	4.72 (1.31, 17.02)	5.02 (1.52, 16.59)
Medications		10.03 (2.57, 39.20)	6.10 (1.52, 24.56)	8.55 (2.29, 31.94)
BMI				
Underweight–normal		1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight		1.53 (0.40, 5.90)	1.06 (0.36, 3.16)	1.33 (0.32, 5.59)
Obese		1.01 (0.34, 3.04)	0.87 (0.19, 4.03)	1.05 (0.30, 3.69)

Note: BMI = body mass index; NS = not significant; ref = reference.
[a] No individuals in this category experienced a cardiovascular event.

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statistical significance when restricted to women who had given birth or who were over age 35 years. In particular, findings for MetS and cardiovascular events became insignificant when restricted to women aged 35 and older and women who had ever given birth, respectively. In the absence of direct information on pregnancy attempt from NHANES, restriction to these subgroups allows greater similarity in pregnancy attempt. However, determining whether a woman is trying to conceive is a common issue in population-based studies of infertility (32). Furthermore, cardiovascular events are already a rare outcome in our full sample and became rarer in subsample analyses. This may have limited our ability to detect associations in all groups. Overall, MetS and cardiovascular events are complicated multifactorial outcomes, and we

TABLE 4

Adjusted odds ratios and confidence intervals for the association between ever infertility and risk of metabolic syndrome, waist circumference removed from definition of metabolic syndrome, with subgroups.

	Crude model	Adjusted model (n = 744)	Women who gave birth (n = 530)	Women 35+ (n = 458)
Ever infertile	2.07 (1.20, 3.58)	2.31 (1.12, 4.78)	2.38 (1.05, 5.39)	2.26 (1.02, 4.99)
Age (mean)		1.08 (1.05, 1.11)	1.08 (1.04, 1.13)	1.09 (1.04, 1.14)
Race/ethnicity				
Non-Hispanic white		1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Hispanic black		0.26 (0.10, 0.67)	0.27 (0.10, 0.71)	0.16 (0.05, 0.51)
Asian		0.92 (0.33, 2.58)	0.84 (0.25, 2.88)	0.98 (0.34, 2.82)
Mexican American		0.86 (0.39, 1.90)	0.50 (0.25, 2.00)	0.57 (0.31, 1.07)
Other, Hispanic		1.48 (0.54, 4.09)	1.25 (0.40, 2.92)	1.71 (0.68, 4.33)
Insurance type				
Private		1.0 (ref)	1.0 (ref)	1.0 (ref)
Medicaid		0.86 (0.29, 2.57)	1.02 (0.29, 3.59)	0.98 (0.29, 3.34)
Other		0.66 (0.28, 1.56)	0.61 (0.23, 1.60)	0.49 (0.15, 1.54)
None		0.57 (0.18, 1.82)	0.63 (0.15, 2.61)	0.49 (0.12, 2.09)
PIR		0.85 (0.68, 1.08)	0.93 (0.75, 1.15)	0.84 (0.66, 1.06)
Smoker (Ever regular)		2.05 (1.08, 3.89)	2.43 (1.22, 4.85)	2.08 (0.94, 4.59)
BMI				
Underweight–normal		1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight		6.47 (2.30, 18.22)	6.01 (2.21, 16.33)	6.56 (2.36, 18.26)
Obese		13.71 (6.63, 28.36)	10.37 (5.54, 19.39)	11.15 (5.56, 22.34)

Note: BMI = body mass index; ref = reference; PIR = family income-to-poverty ratio.

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cannot fully explain these two divergent results in subsample analyses.

In models that adjusted for MetS, the association between infertility and cardiovascular events remained significant. This suggests that the associations between infertility and each of these two outcomes may be independent of one another. Sensitivity analyses in which waist circumference was omitted from the definition of MetS to allow inclusion of BMI as a covariate in models testing the association between infertility and MetS yielded similar results to our original findings, with a greater magnitude of association, suggesting a potential pathway between infertility and MetS that may be independent of abdominal adiposity. This finding is also supported by other research demonstrating that women with PCOS-related infertility are likely to present with symptoms of MetS, independent of their BMI (33). In subgroup analyses, infertility is associated with MetS for women who have ever given birth and women aged 35 years and older. This highlights the sensitivity of the definition of MetS to waist circumference, which has been subject to some controversy, with some researchers arguing that waist circumference cut-offs should vary by gender and race/ethnicity (34).

Our findings are consistent with most (28, 35–39), but not all (29), studies that have examined long-term health sequelae of infertility. Parikh et al. (28) found higher risk of cardiovascular morbidity among subfertile women, although their sample was limited to women who eventually gave birth. Our sensitivity analysis among a subpopulation of women who had given birth did not yield significant results to suggest an association between infertility and cardiovascular morbidity, although our subsample may have had limited power to detect such an effect. Other studies have found an elevated risk of cardiovascular and metabolic dysfunction among women diagnosed with PCOS (35, 36), endometriosis (37), or menstrual irregularity (38, 39). Again, these studies are somewhat limited in scope, in that they do not consider idiopathic or undiagnosed cases of infertility. Our findings are inconsistent with the only other study of self-reported infertility and cardiovascular events, in which there was no independent association, although the definition of cardiovascular events in this study was limited to coronary heart disease (29).

Our findings are also consistent with evidence that suggest an overlap in mechanisms underlying both infertility and cardiovascular disease, itself a complicated multifactorial syndrome. For example, HPA activation has been implicated in both conditions (11, 12). Through activation of neuroendocrine pathways, stress has been linked independently to MetS, cardiovascular disease, and infertility (12, 13). As such, infertility may be a harbinger of cardiometabolic conditions that could be triggered by neuroendocrine or other shared pathways and that could be prevented with earlier intervention. Furthermore, with this in mind, when women present with infertility in a health care setting, providers have a unique opportunity to counsel women during their reproductive years about behavioral changes that may decrease future risk of chronic disease, when they are young enough to make these changes (40). This point may be particularly salient for women who present with infertility at a younger age who would generally be considered low risk for both infertility and cardiovascular disease.

This study should be viewed in light of its limitations and strengths. There are limitations of infertility as a self-report measure; women may not recall how long they tried to conceive, which could result in a misclassification of the length of time trying to conceive. Similarly, women clinically diagnosed with infertility prior to trying to conceive for 12 months or who had not tried to conceive may not have been included in our measure of infertility. This could include women with endometriosis or PCOS, or women over the age of 35 years, who would be considered infertile after 6 months of unsuccessful conception attempts. In addition, our conclusions are limited by an incomplete knowledge of participants' history of pregnancy attempts. To address this, we conducted two subgroup analyses, one among women who had ever given birth and the other among women aged 35 years or older, to minimize the number of women included in the "never infertile" group who had never tried to conceive. Assuming nondifferential misclassification, our estimate of the associations between infertility and our dependent variables is conservative. The results of sensitivity analyses were similar to those conducted in the full sample, highlighting the robust nature of our results.

Our conclusions are subject to limitations inherent to cross-sectional surveys, in that we cannot establish the temporality of the occurrence of infertility, onset of MetS, and occurrence of cardiovascular events. We note that the observed epidemiologic associations do not allow causal inference, so results should be interpreted with caution and in the context of previous research. However, because we defined MetS based on laboratory measures at the time of the survey, we know that these symptoms were present at the time of the survey. In addition, because cardiovascular disease typically occurs after a woman's reproductive years, it may be reasonable to consider that infertility likely occurred before cardiovascular events. Our sample was relatively young, between the ages of 20 and 59 years, limiting our ability to test this last assertion. It is striking that an association between infertility and cardiovascular events was detected in a sample of younger women, who may be at relatively low risk for cardiovascular events. Finally, although stress has been linked to infertility, MetS, and CVD, as described previously (8, 11), the 2013–2014 cycle of NHANES does not include indicators of stress, such as cortisol or C-reactive protein, which limited our ability to account for stress in our models. Furthermore, stress could arguably be considered a mediator in the causal pathway between infertility and MetS or CVD.

This study also has several strengths. Although infertility-related diagnoses, such as PCOS and endometriosis, have been examined in relation to chronic disease (36, 37), this study is the first to consider self-reported infertility and its association with current and later health outcomes. We also used biomarkers to define MetS, thus avoiding recall bias. Furthermore, it is the first to use a nationally representative sample, which substantially increases the generalizability of our findings.

Our work is particularly salient in light of a recent call from the Centers for Disease Control and Prevention and the National Institute of Child Health and Human Development regarding infertility as a predictor of overall health (3). Our main contribution is that we found associations between infertility and cardiometabolic outcomes among a nonreferred population-based sample of U.S. women with self-reported infertility. Infertility is a multifactorial syndrome in which reproductive dysfunction can be traced to a known cause such as PCOS, but in any given community a large proportion of women are experiencing undiagnosed infertility. Our findings that self-reported infertility is associated with metabolic and cardiovascular events underscore the need for a view of infertility beyond clinical diagnoses, and continued research into the link between fertility and later health status.

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Infertilidad, disfunción metabólica y problemas cardiovasculares referidos por la propia mujer: un análisis transversal en mujeres estadounidenses.

Objetivo: Explorar las asociaciones entre la infertilidad y el síndrome metabólico, y los problemas cardiovasculares. La infertilidad es cada vez más un problema de salud pública que tiende a convertirse en enfermedad crónica. La literatura existente sobre la infertilidad se enfoca principalmente en causas conocidas, lo que probablemente excluye a un considerable número de mujeres para quienes no existe una causa conocida o un diagnóstico formal.

Diseño/Entorno: Realizamos un análisis transversal analizando la asociación entre la infertilidad referida por la propia mujer (es decir, la incapacidad para concebir después de 12 meses intentando el embarazo) y el síndrome metabólico y problemas cardiovasculares (por ejemplo, insuficiencia cardíaca congestiva, enfermedad coronaria, infarto cardíaco o accidente cerebrovascular). Los datos fueron analizados mediante regresión logística multivariable.

Paciente(s): En el estudio participaron un total de 744 mujeres estadounidenses, de 20 a 59 años de edad, de la Encuesta nacional de examen de salud y nutrición (2013-2014). Entre ellas, el 15.7% informó haber sufrido infertilidad en algún momento, el 27.6% cumplían la definición de síndrome metabólico, y el 2.84% informó haber tenido algún problema cardiovascular.

Intervención(es): N/A

Principales medidas de resultado: Síndrome metabólico y problemas cardiovasculares.

Resultados: En comparación con las mujeres que nunca habían experimentado infertilidad, las mujeres que refirieron infertilidad tuvieron una razón de probabilidad de 1.79 [intervalo de confianza (IC) del 95% 1.04, 3.08] de referir síntomas de síndrome metabólico, y de 1.83 (IC95%: 1.5, 2.89) de referir un problema cardiovascular. Además, las mujeres con infertilidad referida por ellas mismas tuvieron un 71% más de probabilidades de informar de un problema cardiovascular después de controlar el síndrome metabólico (IC 95%: 1.01, 3.00).

Conclusiones: Nuestros resultados sugieren que, entre las mujeres estadounidenses, el sufrir infertilidad en cualquier momento de su etapa reproductiva puede estar asociada con la salud cardiovascular en la edad avanzada.