


Association Between Body Mass Index and Female Infertility in the United States: Data from National Health and Nutrition Examination Survey 2013–2018

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Purpose: This study aimed to investigate the effects of body mass index (BMI) on infertility in women of childbearing age.

Patients and Methods: We performed a cross-sectional study using data from 3624 participants from the National Health and Nutrition Examination Survey (NHANES). We used BMI and fertility status in the survey as independent and dependent variables, respectively. We evaluated their relationship and used smoothed curve fitting and multivariate logistic regression analysis as well as a generalized additive model (GAM) to determine the effect of BMI.

Results: Logistic regression model analysis linked BMI and infertility after adjusting for potential confounders OR 1.03, 95%CI: 1.02–1.05). There was a non-linear relationship between BMI and infertility, with each unit increase in BMI reducing the risk of infertility by 33% when BMI was <19.5 kg/m². In contrast, when BMI ≥19.5 kg/m², each unit increase in BMI predicted a 3% increase in the risk of infertility.

Conclusion: The relationship between infertility and BMI presented a U-shaped curve. Therefore, a BMI that lay at the extremes of the spectrum tended to predict infertility. We believe that this study will support the maintenance of suitable BMI levels in women preparing for pregnancy.

Keywords: BMI, infertility, nonlinear, NHANES

Introduction

Infertility is the inability to conceive despite regular unprotected intercourse without using any contraception for more than 1 year. It affects millions of families worldwide, touching approximately one in seven couples in developed countries and one in four couples in developing countries.¹ In the United States, infertility affects approximately 6.7%–15.5% of women of reproductive age.^{2,3} As a result, the Centers for Disease Control and Prevention (CDC) have prioritized its diagnosis and treatment.⁴

Although it is clearly a global health concern, research has not fully elucidated the factors of its determinants. Infertility stems from occupational factors [eg, shift work, stress, physical (radiation), and toxic (chemicals) sources] or various lifestyle factors (age, nutrition, exercise, obesity, psychological stress, smoking, or alcohol consumption) in addition to environmental pollution factors.^{5–7}

Obesity (BMI ≥ 30 kg/m²) amongst women of reproductive age has increased significantly in the last decades.^{8,9} This is pertinent because obesity factors increase the time it takes to conceive, reduce conception rates, and render patients less responsive to fertility treatments.¹⁰ Several studies have shown that obesity increases the risk of prenatal complications such as gestational hypertension and gestational diabetes.^{11–13} It is also responsible for prolonging labor, increasing the

risk of obstructed labor and cesarean delivery,¹⁴ and has notable effects on the fetus.^{12,15,16} Recent animal experiments have shown that lean and obese animals are typically less fertile, but not necessarily in humans.¹⁷ Few high-quality studies have explored the nonlinear relationship between body mass index and infertility. Data in a large 15-year population-based cohort study from Australia shows that higher BMI positively correlates with fertility problems.¹⁸ However study shows that low BMI is also associated with infertility.¹⁹

A literature review concerning nutrient intake and its effects on female fertility revealed many studies that reported a *J*-shaped association between infertility and BMI.²⁰ However, they suggest that the effect of body mass on fecundity could be bimodal. We summarized previous studies of the relationship between BMI and infertility and found it to be limited and inconclusive. Therefore, the current study aimed to determine the relationship between BMI and infertility, in terms of linearity, using a large sample from the NHANES database from 2013 to 2018.

Materials and Methods

Data Source

We obtained the original data for this study from the National Health and Nutrition Examination Survey (NHANES), a program that began in the early 1960s. Published by the National Center for Health Statistics (NCHS), it includes surveys on various populations and health topics under the jurisdiction of the US Centers for Disease Control and Prevention (CDC). NHANES is a research program of studies designed to assess the health and nutritional status of the US population, combining interviews and physical examinations. It employs a complex, multistage sampling design to select a nationally representative sample of about 5000 individuals each year.²¹ Thereafter, it provides comprehensive information on nutrition and health every 2 years for a representative sample of the noninstitutionalized civilian population in the US. The NCHS Research Ethics Review Committee approved the NHANES survey protocol, and all participants of the study provided informed written consent.²²

Population

We selected data from the 2013–2018 cycle of the NHANES because only those cycles included health questionnaires concerning infertility issues.²³ A total of 29,400 adults participated in this survey over that period. Our study excluded male participants ($n=14,452$), women older than 45 ($n=4995$) and younger than 18 ($n=5630$). Similarly, the study also excluded responses with incomplete fertility information ($n=656$), missing BMI information ($n=43$) and special abnormalities ($n=1$). Thus, the final sample population for the purposes of this study was 3623 participants (Figure 1).

Dependent and Independent Variable

The dependent variable of infertility derived from each woman's self-report from the Reproductive Health Questionnaire (variable name in questionnaire: RHQ074). In this questionnaire, the investigators asked questions such as, "Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?"²⁴ The affirmative answer "yes" denoted an "infertile" case; if not, the assumed response would be "fertile."

The independent variable was BMI. Conventionally, practitioners calculate this value as mass in kilograms divided by height in meters squared, rounded to one decimal place. The NHANES website provides detailed description.²⁵ In accordance with previous literature, we classified BMI into four groups: "Low" (<18.5), "Normal" (18.5 – 24.9), "Overweight" (24.9 – 29.9), and "Obese" (>29.9).²⁶

Other Variables

In accordance with previous studies, we used additional covariates in our study. We classified these covariates as demographic or potential confounders that may affect BMI, or fertility status in the NHANES database.^{2,18,19,24,27,28} They were derived from self-reported data, examination data. Covariates included: age (18–45 years), race/ethnicity (Mexican-American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, Other Race), educational attainment (Less than high school, High school, More than high school), marital status (Married or Living with partner, Living alone), ratio of family income to poverty (ratio of household income to poverty indicators²⁹), alcohol

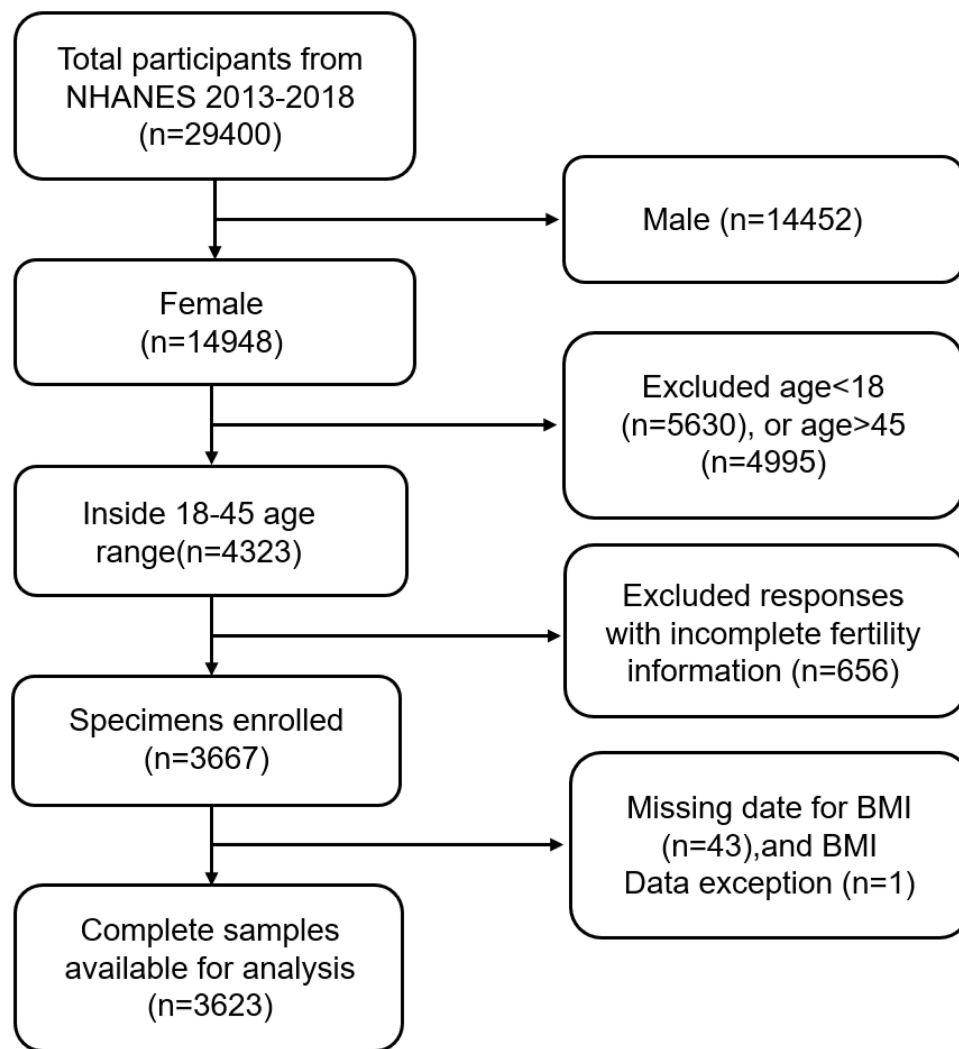


Figure 1 Flow chart of sample selection from the NHANES 2013–2018.

consumption (at least 12 drinks of alcoholic beverages in the last year), active smoking (at least 100 cigarettes/year), diabetes mellitus, hypertension, and prior pregnancy.

In addition, there are studies that suggest that lifestyle behaviors affect BMI, such as lack of physical activity, thus affecting fertility directly or indirectly. In particular, physical activity induces vasodilation and improves the perfusion of many organs including the female reproductive system and its follicular development.^{30,31} In contrast, sedentary activity increases the likelihood of conditions such as cardiovascular disease and cancer, while also contributing to weight gain.^{32–34} Thus, our study included physical activity and sedentary time in the covariates. We divided physical activity into two categories: “vigorous exercise” and “moderate recreational activities.”³⁵ The questionnaire data also from the NHANES database.

Statistical Analysis

In our study, we described continuous variables using the mean and standard deviation, and presented categorical variables as percentages. The main analysis included three steps. First, we used a multiple regression model to test the independent correlation between BMI and infertility. Specifically, we used three models to assess this relationship: 1) no adjustment; 2) adjustment for socio-demographic data only; 3) other covariates shown in Table 1. Second, we detected a nonlinear relationship between BMI and infertility. We calculated the volume inflection point by using a recursive

Table I Baseline Characteristics of Participants (N =3623)

	Fertile N=3246(89.59%)	Infertile N=377(10.41%)	P-value
Age, mean \pm SD (years)	30.75 \pm 8.43	34.79 \pm 7.13	<0.001
Ratio of family income to poverty	2.24 \pm 1.59	2.51 \pm 1.64	0.002
Minutes sedentary activity, mean \pm SD(min)	378.30 \pm 201.03	384.01 \pm 207.88	0.603
Glycohemoglobin, mean \pm SD (%)	5.37 \pm 0.71	5.58 \pm 1.10	<0.001
Body Mass Index (kg/m ²)	29.04 \pm 8.20	32.05 \pm 9.19	<0.001
Race/Hispanic, n (%)			0.155
Mexican American	572 (17.62)	61 (16.18)	
Other Hispanic	345 (10.63)	31 (8.22)	
Non-Hispanic White	1034 (31.85)	146 (38.73)	
Non-Hispanic Black	719 (22.15)	78 (20.69)	
Non-Hispanic Asian	408 (12.57)	44 (11.67)	
Other Race	168 (5.18)	17 (4.51)	
Education, n (%)			0.758
Less than high school	455 (15.94)	54 (14.52)	
High school	549 (19.24)	71 (19.09)	
More than high school	1850 (64.82)	247 (66.40)	
Marital status, n (%)			<0.001
Married or Living with partner	1601 (56.10)	272 (73.12)	
Live alone	1253 (43.90)	100 (26.88)	
Drinking, n (%)			0.031
Yes	2244 (69.13)	281 (74.54)	
No	1002 (30.87)	96 (25.46)	
Vigorous recreational activities, n (%)			<0.001
Yes	1038 (31.98)	88 (23.34)	
No	2208 (68.02)	289 (76.66)	
Moderate recreational activities, n (%)			0.243
Yes	1463 (45.07)	158 (41.91)	
No	1783 (54.93)	219 (58.09)	
Smoking, n (%)			<0.001
Yes	831 (25.60)	133 (35.28)	
No	2413 (74.34)	244 (64.72)	
NA	2 (0.06)	0 (0.00)	
Diabetes Mellitus, n (%)			<0.001
Yes	117 (3.60)	31 (8.22)	
No	3079 (94.86)	339 (89.92)	
Borderline	47 (1.45)	7 (1.86)	
NA	3 (0.09)	0 (0.00)	
Hypertension, n (%)			<0.001
Yes	427 (13.15)	78 (20.69)	
No	2817 (86.78)	299 (79.31)	
NA	2 (0.06)	0 (0.00)	
Health insurance, n (%)			0.156
Public	922 (28.40)	87 (23.08)	
Private	1600 (49.29)	198 (52.52)	
None	720 (22.18)	91 (24.14)	
NA	4 (0.12)	1 (0.27)	
Ever been pregnant			<0.001
Yes	2065 (72.38)	317 (85.44)	
No	788 (27.62)	54 (14.56)	

algorithm. Third, we constructed a logistic regression model at the inflection point co-test. The model that gave the best fit based on likelihood-ratio tests and *P*-values was included.

We performed data analyses using the R[®] statistics package (v.3.4.3, <http://www.r-project.org>) and Empower[®] software (v.2.0, <http://www.empowerstats.com>, X&Y Solutions, Inc. Boston, MA, USA). We expressed statistical significance as two-sided *P* < 0.05.

Results

Baseline Characteristics of Study Participants

Figure 1 shows the inclusion and exclusion criteria of selected participants, after the exclusion of all participants with incomplete or ambiguous responses. In total, 3623 participants took part in this study and Table 1 presents the baseline characteristics of the selected female participants, with respect to infertility (dichotomous variable).

Results of Multiple Regression Models

We constructed three models to explore the independent effect of BMI on infertility and analyzed its independent effect on infertility, using binary logistic regression with single and multiple variables. Table 2 shows the relevant effect size [odds ratio [OR]], 95% confidence intervals (CI), and *P*-values. There was a significant association between BMI and infertility in models 1, 2, and 3 and the generalized additive model (GAM). The association between body mass index and infertility was positive regardless of the type of adjusted covariates. In the initial model (model 1), each 1-unit increase in body mass index increased the risk of infertility by 4% (OR=1.04; 95% CI: 1.03–1.05). In model 2 (OR: 1.03, 95% CI: 1.02–1.05) and model 3 (OR=1.03; 95% CI: 1.02–1.05), we converted BMI into a categorical variable from the continuous variable (four groups of “Low,” “Normal,” “Overweight,” and “Obese”) for sensitivity analysis. There was a nonlinear relationship between BMI and infertility, and the trends in effect size were analogous for different BMI groups. To solve the nonlinear problem, we used GAM to adjust all the continuous variables in covariates (shown in Table 1) (OR=1.03; 95% CI: 1.00–1.05), which remained largely consistent with model 3. This sensitivity analysis confirmed the robustness of the results (Table 2).

Stratified Analysis by Potential Effect Modifiers

We then performed subgroup analysis to assess the effect of BMI on infertility. As shown in Figure 2, the interactions tested were not statistically significant among the different ethnic/racial groups, different education groups, or household income to poverty ratio. The same was true with regard to physical activity, alcohol consumption, smoking habits, history of hypertension, or type of insurance. The interactions of the abovementioned values were 0.70, 0.10, 0.93, 0.52, 0.64, 0.97, 0.28 0.46, 0.22, 0.73 respectively. Conversely, we found statistically significant differences (*P* < 0.05) with respect to age groups, marital status, history of diabetes, and whether or not the couple had undergone a prior pregnancy. Therefore, there was an evident interaction between BMI and age, marital status, history of diabetes mellitus, and prior pregnancy.

Table 2 Relationship Between Body Mass Index (Kg/M²) and Fertile or Infertile

Exposure	Model 1 N=3623, 100% (OR,(95% CI), P value)	Model 2 N=3623 100% (OR, (95% CI), P value)	Model 3 N=2847, 78.58% (OR, (95% CI), P value)	GAM* N= 2847, 78.58% (OR, (95% CI), P value)
Body Mass Index (kg/m ²)	1.04 (1.03, 1.05), <0.0001	1.03 (1.02, 1.05), <0.0001	1.03 (1.02, 1.05), <0.0001	1.03(1.00, 1.05), <0.0001
Normal	Ref	Ref	Ref	Ref
Low	0.90 (0.41, 2.00), 0.7959	1.18 (0.53, 2.65), 0.6815	1.48(0.61, 3.62), 0.3861	1.45 (0.60, 3.54), 0.4123
Overweight	1.01 (0.73, 1.40), 0.9534	0.92 (0.66, 1.29), 0.6456	0.85 (0.59, 1.23), 0.3989	0.85 (0.59, 1.23), 0.3938
Obesity	2.05 (1.58, 2.66), <0.0001	1.85 (1.40, 2.44), <0.0001	1.74 (1.28, 2.37), 0.0004	1.74(1.28,2.37), 0.0004
P for trend	<0.001	<0.001	<0.001	<0.001

Notes: Model 1 adjust for: none. Model 2 adjust for: social demographic covariables. Model 3 adjust for: all covariates listed in Table 1 were adjusted, and continuous covariates were adjusted as non-linearity. * Covariates adjustment results of GAM were close to Model 3.

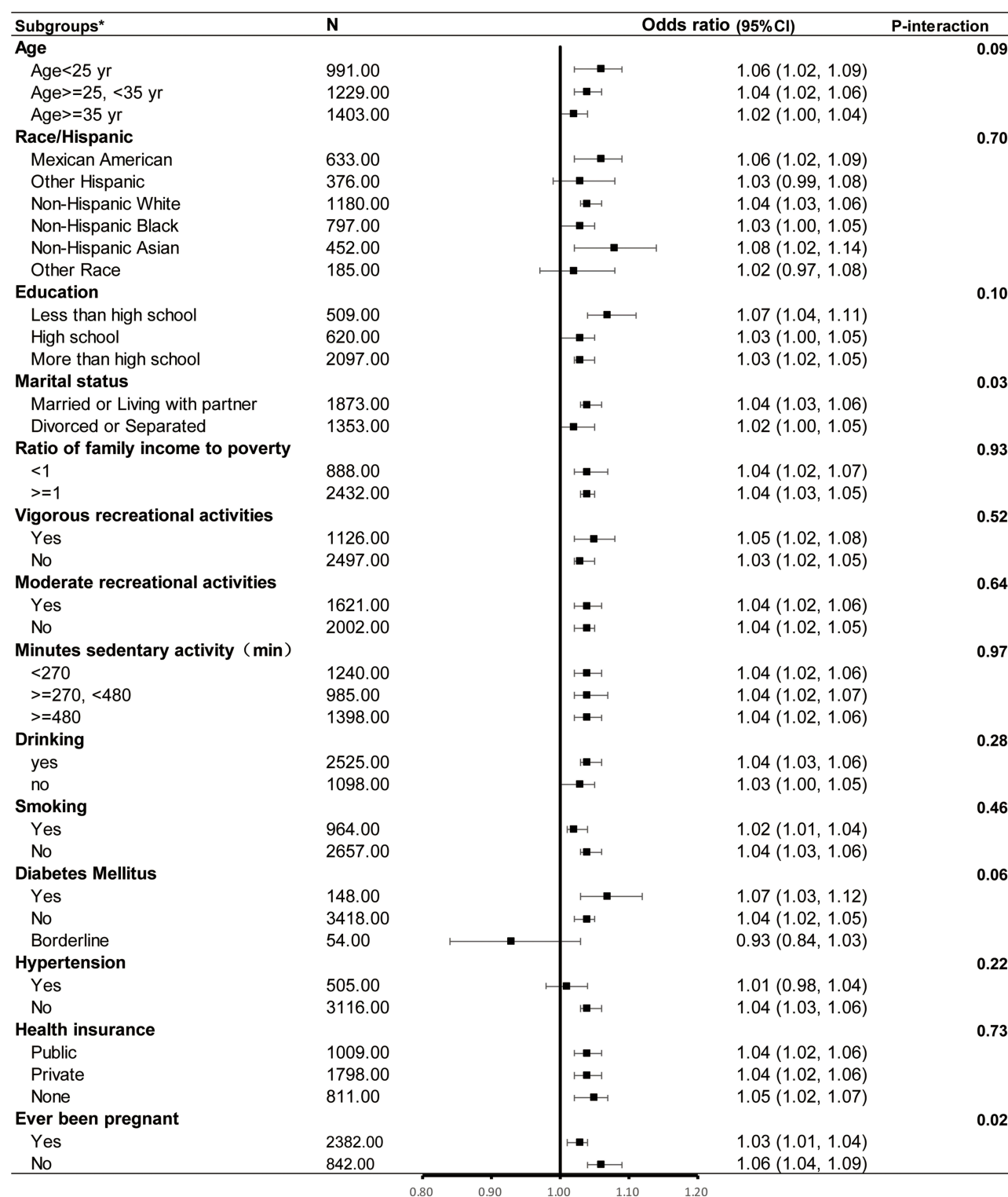


Figure 2 Subgroups* analyses of the effect of BMI on infertility.

Moreover, BMI was positively associated with infertility in the subgroup with a history of diabetes with or without diabetes stratification, negatively associated with infertility in the critical status subgroup, and positively associated with infertility with respect to age, marital status, and prior pregnancy.

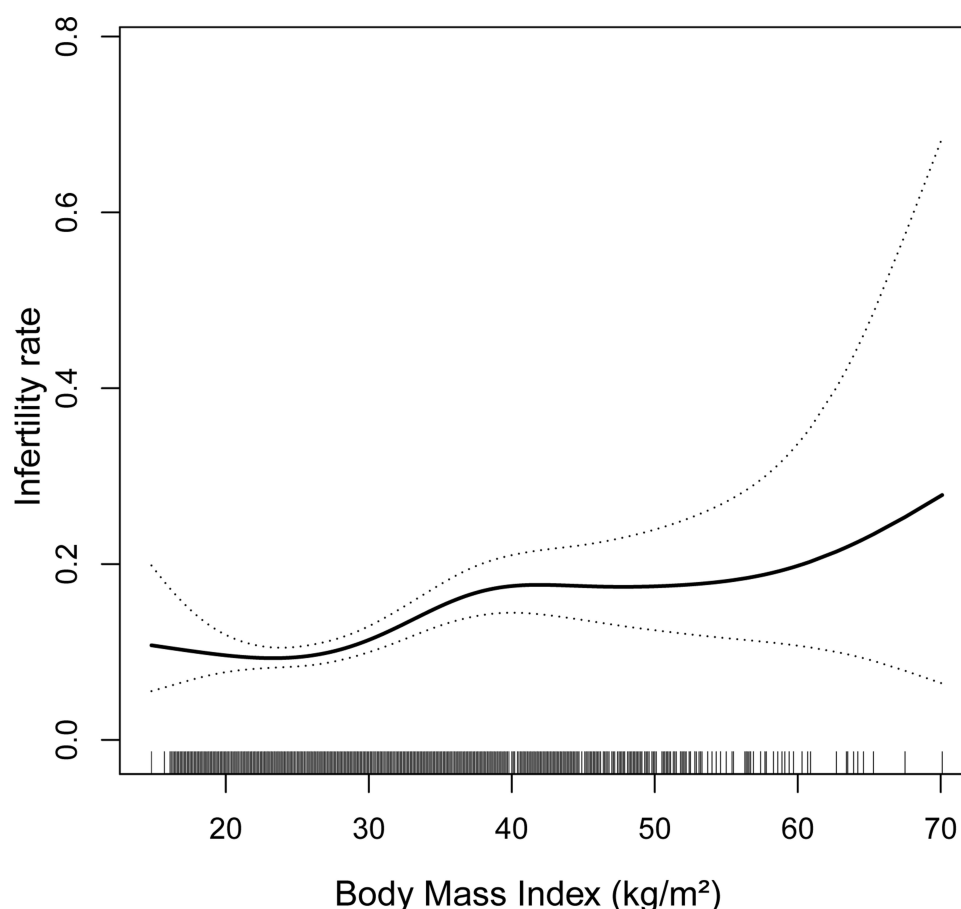


Figure 3 The correlation between BMI and infertility rate (using penalized spline method).

Results of Nonlinear of BMI and Infertility

We fitted the GAM and the smoothed curve (penalized curve method) to explore the potential nonlinear relationship between BMI and infertility (Figure 3) and found a nonlinear U-shaped relationship. We calculated the volume inflection point using a recursive algorithm, resulting in a value of 19.5 (Table 3). The OR and 95% CI on the left side of the inflection point were 0.67 and 0.47–0.95, respectively. Similarly, the OR and 95% CI on the right side were 1.03 and 1.02–1.05, respectively.

Discussion

Our cross-sectional study used data from women of childbearing age enrolled in NHANES from 2013–2018 in the US to investigate the existence of an independent relationship between BMI and infertility. After adjusting for other covariates, BMI positively associated with infertility. After transforming BMI into a categorical variable, we observed the possibility of a nonlinear relationship with univariate and multifactorial logistic regression. Hence, we considered a smooth curve fit and a bipartite linear regression model and determined the inflection point to be 19.5 kg/m². The trends of the effect size were not consistent on the two sides of the inflection point [left side OR: 0.67, 95% CI (0.47, 0.95); right side OR: 1.03, 95% CI (1.02, 1.05)]. The above results presented a U-shaped curve relationship between BMI and infertility.

Infertility is a prevalent problem that has a significant impact on individuals, families, and communities. Modifiable lifestyle factors may affect the chances of conceiving and delivering a baby. Among these lifestyle factors, BMI is an important component.

Table 3 Threshold Effect Analysis of Body Mass Index (Kg/M^2) and Infertility Rate Using Piece-Wise Linear Regression

Outcome:	Infertility (OR, 95% CI)	p value
	1.03 (1.02, 1.05)	<0.0001
Inflection point (K)	19.5	
<19.5	0.67 (0.47, 0.95)	0.0249
≥ 19.5	1.03 (1.02, 1.05)	<0.0001
Log likelihood ratio	0.029	

Notes: Effect: body mass index (kg/m^2). Cause: infertility rate. Adjusted: all covariate adjusted were same as Model 3 presented in Table 3.

Abbreviation: CI, confidence interval; OR, odds ratio.

Previous studies have pointed out the non-negligible effect of leanness on the menstrual cycle and female infertility, where it causes gonadotropin dysregulation and subsequent anovulation.³⁶ In another study, researchers used a weight gain regimen to treat 29 slim women with unexplained infertility.³⁷ As they gradually gained weight, the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) of the subjects gradually reached normal ratios. This accompanied the gradual improvement of ovulatory cycles and amenorrhea symptoms, culminating in conception in 19 of the subjects. These studies suggest that a low BMI can lead to infertility in women of reproductive age, which is consistent with the findings in our study.

In addition, obesity is a growing global health concern, especially for women of reproductive age and infertility has been attributable to a variety of chronic diseases such as polycystic ovary syndrome (PCOS), hypertension, and diabetes.^{38–40} Similarly, reduced fertility has been attributable to obesity resulting in biochemical pregnancies, ectopic and spontaneous abortions.⁴¹ A Danish study showed a slight increase in the chance of infertility in children of overweight mothers compared to those of mothers of normative weight.³⁹ Additional reports suggest that obese women tend to present dysregulation of the hypothalamic-pituitary-gonadal axis.⁴² This results in reduced gonadotropin levels, producing symptoms such as irregular menstruation and anovulation, causing infertility. These studies on obesity and infertility correspond with the findings of our study that suggest the probability of infertility increasing as BMI increases.

In our study, we noted the existence of a threshold effect between BMI and infertility, such that different association were evident when BMI levels were below or above $19.5 \text{ kg}/\text{m}^2$.

Overall, there was some clinical value in our novel study. First, it detected a U-shaped curve association between infertility and BMI for the first time in a large-scale cross-sectional study in US women. Second, the GAM model and smoothed curve fit (penalized curve method) explored the nonlinear relationship between infertility and BMI, which offers a more significant clinical application than previous studies. Third, we based our study on a national survey with a large sample size. To support the robustness of our findings, we also used a series of sensitivity analyses on the relationship between BMI and female infertility, which fully explained this nonlinear relationship. Fourth, the results of our study will contribute to the development of strategies to improve infertility treatment and add to the body of knowledge concerning female reproductive health.

However, our study also has limitations. First, we conducted our study on 3623 women in the US, aged 18–45 years, thus it is not applicable to women outside this age range or men. In addition, the findings may not apply to women outside the US. Second, we were unable to draw a causal relationship between BMI and infertility because of the cross-sectional nature of our study. As with other studies, ours had inevitable and inherent flaws. We noted that most participants in the study were multipara. Owing to the lack of supplementary information in the NHANES database, we were unable to determine whether they experienced primary or secondary infertility, thus, we could not ascertain the duration of their infertility. Finally, we could not assess additional indicators related to obesity, such as body fat, waist, hip circumference, or waist-to-hip ratio.

Conclusion

In our study, we found a U-shaped curve between infertility and BMI. Therefore, a BMI that was too low or too high was a potential hazard for infertility in women. We believe that this study will support the maintenance of more appropriate BMI levels in women preparing for pregnancy.

Such measures are useful for increasing the possibility of pregnancy in women with infertility, for the improvement of social population has a certain effect.

Abbreviations

BMI, body mass index; NHANES, National Health and Nutrition Examination Survey; GAM, generalized additive model; CI, confidence interval; OR, odds ratio.

Data Sharing Statement

All the data sets we used for this study are publicly available from the NHANES website <https://wwwn.cdc.gov/nchs/nhanes/Default.aspx>.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Ethics Committee of the Lishui Central Hospital, Zhejiang Province (N0.2021-224). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The NCHS Research Ethics Review Committee approved the NHANES survey protocol (<https://www.cdc.gov/nchs/nhanes/irba98.htm>), and all participants of the study provided informed written consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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