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ORIGINAL RESEARCH

Associations Between Total and Regional Fat-to-Muscle Mass Ratio with the Prevalence of Infertility: A Cross-Sectional Study

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Purpose: The fat-to-muscle mass ratio (FMR) is a novel anthropometric parameter that integrates the antagonistic effects of fat and muscle mass. The current study aimed to examine the associations between total and region-specific FMR with the prevalence of self-reported infertility in US women.

Methods: US women aged 20 to 44 years from the 2013–2018 National Health and Nutrition Examination Survey were included. Total, trunk, arm, and leg FMR were calculated from fat mass and muscle mass in the corresponding body part by dual-energy X-ray absorptiometry. Binary logistic regression, restricted cubic spline analysis and subgroup analysis were primarily used for statistical analyses.

Results: Infertility prevalence was 12.77% among the 1958 women included. Arm and leg FMR were not associated with infertility prevalence, while the odds ratio and 95% confidence intervals for infertility by each 0.1 point increase in trunk and total FMR were 1.19 (1.07–1.33) and 1.16 (1.04–1.30), respectively. Restricted cubic spline analysis indicated a positive and linear relationship between trunk or total FMR and infertility prevalence. Subgroup analysis consistently demonstrated that the associations between trunk or total FMR with infertility prevalence were more pronounced in women without a pregnancy history than in those with a pregnancy history. The receiver-operating characteristic curves indicated that the trunk FMR outperformed total, arm, and leg FMR in discriminating infertility from women without infertility.

Conclusion: Trunk and total FMR, rather than arm or leg FMR, were associated with an increased risk of infertility in US women, especially those without a prior pregnancy history.

Keywords: cross-sectional, dual-energy X-ray absorptiometry, fat-to-muscle mass ratio, infertility, NHANES

Introduction

Infertility is a common reproductive disorder affecting approximately one in five married women between the age of 15 to 49 years in the United States.[1] Although the majority of patients with infertility have no clinical symptoms, the psychological distress and social stigmatization associated with infertility may incur significant burden to the patient and the family. Currently, the causes of female infertility are complex and heterogeneous, and can be dichotomized into primary and secondary, depending on whether an underlying cause can be found.[2] Therefore, identification of risk factors are very helpful for the prevention and management of infertility.

It has been increasingly recognized that obesity is intimately associated with an increased risk of infertility.[3] Common causes of female infertility include a wide range of factors, such as ovarian and ovulation disorders, fallopian tube abnormalities and pelvic disease, uterine anomalies, endocrine disorders, and genetic predisposition.[4,5] Previous studies have indicated that obesity not only significantly increases the risk of ovulatory dysfunction but also adversely affects the

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outcomes of assisted reproductive technology.[6] Moreover, obesity is closely linked to hyperandrogenemia, a hallmark of polycystic ovary syndrome, which represents one of the leading causes of infertility in women.[7] The underlying mechanisms linking obesity and female infertility are multifaceted, involving metabolic perturbation, alterations in cytokines and adipokines, ovulatory malfunction, and gut microbiota dysbiosis.[8] The work by Zhu's group showed that the risk of infertility increased by 3% for each unit increase in body mass index (BMI) when BMI > 19.5 kg/m^2.[9] A recent meta-analysis that included 8 studies on assisted reproduction and 1 study on natural conception showed that the odds ratio (OR) and 95% confidence interval (CI) for clinical pregnancy in those with a BMI ≥ 25 and ≥ 30 kg/m^2 were 0.76 (0.62–0.93) and 0.61 (0.39–0.98), respectively.[10] It should be noted, however, that BMI is a suboptimal marker of excess adiposity, as it does not differentiate between fat and muscle mass. Individuals with the same BMI can have drastically disparate body composition and fat distribution. Echoing this notion, it has been proposed that body roundness index, a more accurate biomarker of abdominal obesity, is positively and linearly associated with risk of infertility and outperforms BMI in predicting infertility.[11]

The fat-to-muscle mass ratio (FMR) is a novel anthropometric parameter that integrates the metabolic load from adiposity and metabolic capacity from muscle.[12] Prior studies have consistently demonstrated that the FMR is predictive of type 2 diabetes and mortality risk, independent of BMI.[13,14] However, the relationship between region-specific FMR (arms, legs, and trunk) and the prevalence of infertility remains largely unknown. Existing studies have shown that visceral adipose tissue and abdominal subcutaneous tissue are major contributors to insulin resistance, a well-established risk factor for infertility.[15] Based on these findings, we hypothesize that trunk-specific and total FMR exhibit a stronger association with an increased risk of infertility. To test this hypothesis, the current study investigated the associations between total and regional FMR and the risk of infertility in adult women using data from the US National Health and Nutrition Examination Survey (NHANES).

Methods

Data Source and Study Population

The NHANES is an ongoing biennial national survey to collect data on the health and nutritional status of the community-dwelling US citizens. Protocols and detailed information for data gathering have been made available on the NHANES website and can also be accessed at other publications.[16] The Research Ethics Review Board of the NCHS approved the NHANES protocol, and all participants provided written informed consent.

Considering data availability on dual-energy X-ray absorptiometry and reproductive health questionnaire, we restricted our sample to women from the 2013–2018 NHANES dataset. Participants were also excluded from the final analysis for age range outside 20 to 44 years, pregnancy at the time of interview, missing data of infertility or dual-energy absorptiometry, and missing data of other covariates. As shown in Figure 1, the final study sample is composed of 1,958 women.

Primary Exposure Assessments

The primary exposure in this study is total and regional FMR measured by the gold-standard method of dual-energy X-ray absorptiometry,[17] which also has the advantages of low radiation exposure, a lower cost, and a shorter scan time. Whole-body dual-energy absorptiometry was performed with the Hologic Discovery model A densitometers (Hologic, Inc., Bedford, Massachusetts). The data were analyzed with the Hologic APEX version 4.0 software with NHANES BCA option to obtain both fat and lean mass from the whole body, trunk, right arm, left arm, right leg, and left leg. The fat mass or lean mass in both arms or legs were combined to calculate the FMR using the equation FMR = Fat mass/Lean mass in the corresponding body part.[18]

Primary Outcome

The primary outcome for this study is self-reported infertility, which is obtained from the Reproductive Health Questionnaire (RHQ074). Women were considered to have infertility if responded yes to the question.

> Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?.[19]

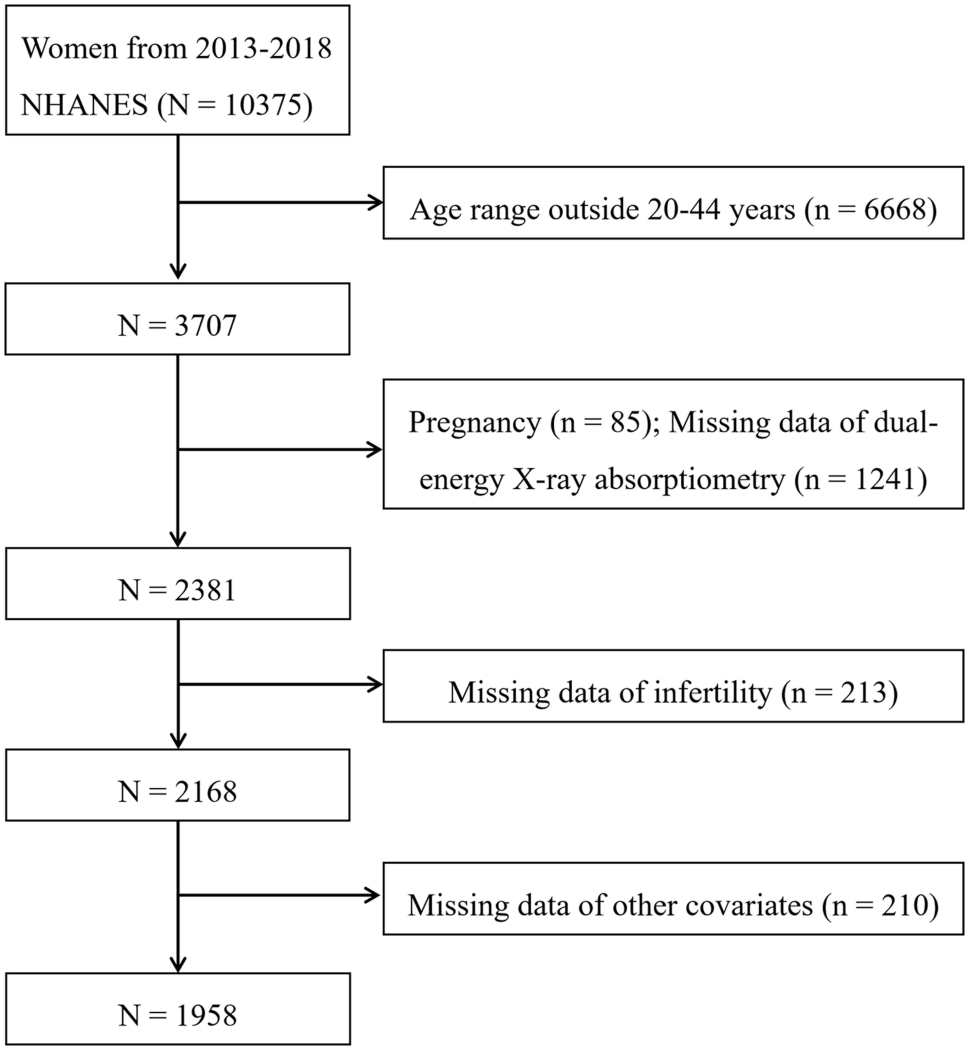

Figure 1 Flowchart for participant inclusion and exclusion.
Abbreviation: NHANES, National Health and Nutrition Examination Survey.

Covariate Measurements

In accordance with prior similar studies,[20–22] the following variables were selected as covariates: participant's age, race/ethnicity, education level, poverty-income ratio, marital status, body mass index, smoking, drinking, physical activity, comorbidities (hypertension, diabetes, and cardiovascular disease), and reproductive factors (age at menarche, hormone use, pelvic infections, pregnancy history, and menstrual regularity). Body mass index was calculated as body weight in kilograms divided by height in meters squared. Smoking and drinking was defined as lifetime use over 100 cigarettes and consumption of over 12 drinks, respectively.[23] Positive pregnancy history was defined as at least 1 live birth. Information on reproductive factors were obtained from the Reproductive Health Questionnaire. Participants were considered to have used hormone pills when responded affirmatively to the question

> Have you ever used female hormones such as estrogen and progesterone? Please include any forms of female hormones, such as pills, cream, patch, and injectables, but do not include birth control methods or use for infertility.

The criteria for diabetes, hypertension, and poverty-income ratio were the same as those reported previously.[24,25]

Statistical Analysis

Descriptive analyses and comparisons of women with and without infertility were performed with the Student's *t*-test or chi-squared test, as appropriate. Associations between total or regional FMR and infertility prevalence were analyzed with the univariate and multivariate binary logistic regression analysis, with FMR as a continuous or categorical variable (Q1, lowest quartile; Q4, highest quartile). The effect size was calculated and presented as OR with 95% CI. A total of 4 statistical models were created during logistic regression. The Model 1 was unadjusted, and the Model 2 was adjusted for participant's age, race/ethnicity, marital status, education level, and poverty-income ratio. Model 3 was further adjusted for body mass index, smoking, drinking, physical activity, diabetes, hypertension, and cardiovascular disease. Model 4 was the final model, which was further adjusted for menstrual regularity, menarche age, female hormone use, pelvic infections, and history of pregnancy. To identify any potential non-linear associations between FMR and infertility, we performed restricted cubic spline analysis with knots automatically determined using the Akaike Information Criterion.[26] Restricted cubic spline analysis is a statistical transformation method for continuous predictors that provides a flexible approach to modeling nonlinear relationships in regression models. Subgroup analysis was also done to observe the relationships between FMR and infertility across different sub-populations. Finally, we constructed receiver-operating characteristic curves to assess and compare the capabilities of total and regional FMR for discriminating infertility from fertility. All analyses were appropriately weighted according to analytic recommendations. A two-sided P value < 0.05 signified statistical significance.

Results

Baseline Characteristics

Among the 1958 participants enrolled, there were 234 women with infertility, representing 12.77% of the population. As shown in Table 1, compared with women without infertility, those with infertility were significantly older, economically advantaged, had a higher BMI, and were associated with a higher prevalence of comorbidities of diabetes and hypertension. In addition, women with infertility had a significantly higher prevalence of history of pelvic infection, use of female hormones, and history of previous pregnancy. Women with infertility had significantly higher arm, trunk and total FMR than women without infertility.

Table 1 Comparison of Baseline Characteristics Between US Women with and without Infertility

	Total (n=1958)	Non-Infertility (n=1724)	Infertility (n=234)	P
Age, years	31.66±0.25	31.20±0.24	34.80±0.62	< 0.001
Race/ethnicity (n, %)				0.40
Non-Hispanic White	700 (59.21)	616 (58.81)	84 (61.97)	
Other	1258 (40.79)	1108 (41.19)	150 (38.03)	
Marital status (n, %)				< 0.001
Non-single	1120 (59.04)	957 (56.71)	163 (74.91)	
Single	838 (40.96)	767 (43.29)	71 (25.09)	
Educational level (n, %)				0.76
Less than high school	80 (2.51)	74 (2.60)	6 (1.84)	
High school	540 (24.34)	476 (24.37)	64 (24.12)	
Higher than high school	1338 (73.15)	1174 (73.03)	164 (74.04)	
Poverty-income ratio	2.70±0.07	2.67±0.08	2.92±0.13	0.04
Body mass index, kg/m^2	28.59±0.25	28.23±0.27	31.07±0.76	0.001

(*Continued*)

Table 1 (Continued).

	Total (n=1958)	Non-Infertility (n=1724)	Infertility (n=234)	P
Smoking (n, %)	552 (31.50)	475 (30.79)	77 (36.34)	0.10
Drinking (n, %)	1630 (87.09)	1429 (86.79)	201 (89.15)	0.41
Physical activity (n, %)				0.97
None	1084 (52.86)	951 (52.71)	133 (53.84)	
Moderate	536 (29.60)	477 (29.67)	59 (29.09)	
Vigorous	338 (17.54)	296 (17.62)	42 (17.07)	
Diabetes (n, %)	136 (5.61)	112 (4.91)	24 (10.39)	0.007
Hypertension (n, %)	299 (13.60)	243 (12.21)	56 (23.06)	< 0.001
CVD (n, %)	30 (1.16)	27 (1.17)	3 (1.11)	0.94
Menarche age, years	12.59±0.05	12.60±0.05	12.55±0.13	0.67
History of pelvic infections (n, %)	86 (3.98)	60 (3.05)	26 (10.33)	< 0.001
Female hormone use (n, %)	60 (4.25)	42 (3.00)	18 (12.74)	< 0.001
Regular menstruation (n, %)	1771 (89.66)	1556 (90.08)	215 (86.79)	0.30
Pregnancy history (n, %)	1349 (64.34)	1159 (61.67)	190 (82.59)	< 0.001
Left arm fat, gram	1860.52±30.02	1821.35±33.09	2128.07±84.01	0.002
Left arm muscle mass, gram	2229.37±15.27	2208.45±16.33	2372.24±42.25	< 0.001
Right arm fat, gram	1852.94±30.58	1814.11±32.99	2118.19±88.74	0.003
Right arm muscle mass, gram	2396.283±17.552	2373.889±18.936	2549.232±37.699	< 0.001
Left leg fat, gram	5596.53±70.56	5514.34± 78.66	6157.90±167.28	0.002
Left leg muscle mass, gram	6998.93±44.90	6935.22± 50.41	7434.02±122.65	< 0.001
Right leg fat, gram	5722.77±74.00	5640.04± 81.39	6287.83±176.90	0.002
Right leg muscle mass, gram	7206.40±45.78	7135.78± 51.03	7688.70±129.57	< 0.001
Trunk fat, gram	13588.95±231.56	13,176.43±241.56	16,406.39±735.75	< 0.001
Trunk muscle mass, gram	22510.29±149.20	22,264.50±158.66	24,189.01±450.16	< 0.001
Total fat, gram	29691.93±427.83	29,031.95± 458.16	34,199.48±1219.57	< 0.001
Total muscle mass, gram	44243.11±262.03	43,809.70±283.95	47,203.22±761.76	< 0.001
Arm FMR	0.78±0.01	0.78±0.01	0.84±0.02	0.01
Leg FMR	0.79±0.01	0.78±0.01	0.81±0.02	0.12
Trunk FMR	0.58±0.01	0.57±0.01	0.65±0.02	< 0.001
Total FMR	0.65±0.01	0.65±0.01	0.70±0.02	0.001

Notes: Continuous variables with normal distribution were presented as mean±standard error and categorical variables were expressed as number (weighted percentages). P denotes the comparison between women with and without infertility.
Abbreviations: CVD, cardiovascular disease; FMR, fat-to-muscle mas ratio.

Associations Between Total and Regional FMR with Risk of Infertility

As summarized in Table 2, arm and leg FMR did not appear to be associated with infertility prevalence in the fully adjusted Model 4. The ORs and 95% CIs for each 0.1 point increase in trunk and total FMR were 1.19 (1.07–1.33) and 1.16 (1.04–1.30), respectively, in the fully adjusted Model 4. Compared to the lowest quartile, the ORs and 95% CIs for the Q2, Q3 and Q4 group

Table 2 Associations Between Total or Regional Fat to Muscle Mass Ratio with Risk of Infertility in US Women Aged 20 to 44 years

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Arm FMR (per 0.1 point increase)	1.09 (1.02–1.17)	0.01	1.08 (1.01–1.16)	0.04	1.07 (1.00–1.15)	0.08	1.07 (0.99–1.15)	0.10
Arm FMR quartile								
Q1	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
Q2	1.78 (0.99–3.19)	0.06	1.78 (1.01–3.15)	0.05	1.75 (0.98–3.14)	0.07	1.72 (0.98–3.02)	0.07
Q3	1.54 (0.90–2.66)	0.13	1.43 (0.83–2.46)	0.21	1.36 (0.78–2.39)	0.29	1.48 (0.83–2.63)	0.20
Q4	2.15 (1.21–3.82)	0.01	2.01 (1.12–3.58)	0.02	1.87 (1.03–3.40)	0.05	1.84 (0.98–3.45)	0.07
P for trend	0.02		0.04		0.10		0.10	
Leg FMR (per 0.1 point increase)	1.07 (0.99–1.16)	0.11	1.06 (0.97–1.15)	0.20	1.07 (0.98–1.16)	0.17	1.06 (0.96–1.16)	0.26
Leg FMR quartile								
Q1	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
Q2	1.03 (0.63–1.70)	0.90	1.00 (0.62–1.60)	0.98	1.01 (0.62–1.64)	0.96	0.93 (0.59–1.47)	0.77
Q3	1.37 (0.92–2.03)	0.13	1.27 (0.84–1.91)	0.26	1.29 (0.85–1.98)	0.24	1.23 (0.80–1.89)	0.36
Q4	1.34 (0.87–2.07)	0.20	1.22 (0.80–1.88)	0.36	1.27 (0.80–2.01)	0.32	1.20 (0.75–1.91)	0.46
P for trend	0.11		0.24		0.22		0.31	
Trunk FMR (per 0.1 point increase)	1.23 (1.11–1.36)	<0.001	1.21 (1.09–1.35)	0.001	1.20 (1.08–1.33)	0.002	1.19 (1.07–1.33)	0.003
Trunk FMR quartile								
Q1	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
Q2	2.60 (1.47–4.61)	0.002	2.45 (1.41–4.24)	0.003	2.46 (1.42–4.26)	0.003	2.56 (1.52–4.31)	0.002
Q3	2.03 (1.16–3.56)	0.02	1.84 (1.06–3.18)	0.04	1.77 (1.03–3.03)	0.05	1.84 (1.06–3.19)	0.04
Q4	3.41 (1.94–6.00)	<0.001	3.07 (1.73–5.48)	<0.001	2.82 (1.58–5.02)	0.001	2.93 (1.68–5.11)	<0.001
P for trend	<0.001		0.003		0.007		0.005	
Total FMR (per 0.1 point increase)	1.20 (1.08–1.33)	0.002	1.18 (1.06–1.32)	0.006	1.17 (1.04–1.31)	0.01	1.16 (1.04–1.30)	0.02
Total FMR quartile								
Q1	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
Q2	2.04 (1.21–3.42)	0.01	1.90 (1.15–3.13)	0.02	1.89 (1.14–3.12)	0.02	2.03 (1.29–3.21)	0.006
Q3	1.81 (1.00–3.29)	0.06	1.60 (0.89–2.88)	0.12	1.53 (0.85–2.74)	0.17	1.53 (0.84–2.79)	0.18
Q4	2.73 (1.57–4.73)	<0.001	2.47 (1.40–4.35)	0.004	2.33 (1.33–4.08)	0.006	2.41 (1.40–4.15)	0.004
P for trend	0.003		0.01		0.02		0.02	

Notes: Model 1 was crude analysis. Model 2 was adjusted for age, race, education level, marital status, and poverty-income ratio. The Model 3 was further adjusted for body mass index, smoking, drinking, physical activity, diabetes, hypertension, and cardiovascular disease. The Model 4 is the final model that was further adjusted for menstrual regularity, age at menarche, female hormone use, history of pelvic infection and pregnancy history.

Abbreviations: CI, confidence interval; FMR, fat to muscle mass ratio; OR, odds ratio.

were 2.56 (1.52–4.31), 1.84 (1.06–3.19), and 2.93 (1.68–5.11), respectively, for trunk FMR (P for trend = 0.005), and 2.03 (1.29–3.21), 1.53 (0.84–2.79), and 2.41 (1.40–4.15), respectively, for total FMR (P for trend = 0.02).

Restricted Cubic Spline Analysis

The restricted cubic spline analysis (Figure 2) indicated that there were no associations between arm or leg FMR with infertility prevalence. However, a positive and linear relationship were identified between trunk or total FMR with infertility prevalence.

Subgroup Analysis

The subgroup analysis (Figure 3) consistently showed that the associations of trunk or total FMR with infertility prevalence were not modified by participant's age, race, BMI, menarche age and diabetes status. However, the associations of trunk or total FMR with infertility prevalence were more pronounced in women without a pregnancy history than those with a pregnancy history. Interestingly, the associations between arm or leg FMR with infertility prevalence were also significant in women without a pregnancy history.

Receiver-Operating Characteristic Curves

The receiver-operating characteristic curves (Figure 4 and Table 3) indicated that the trunk FMR had the largest area under the curve for discriminating infertility from women without infertility.

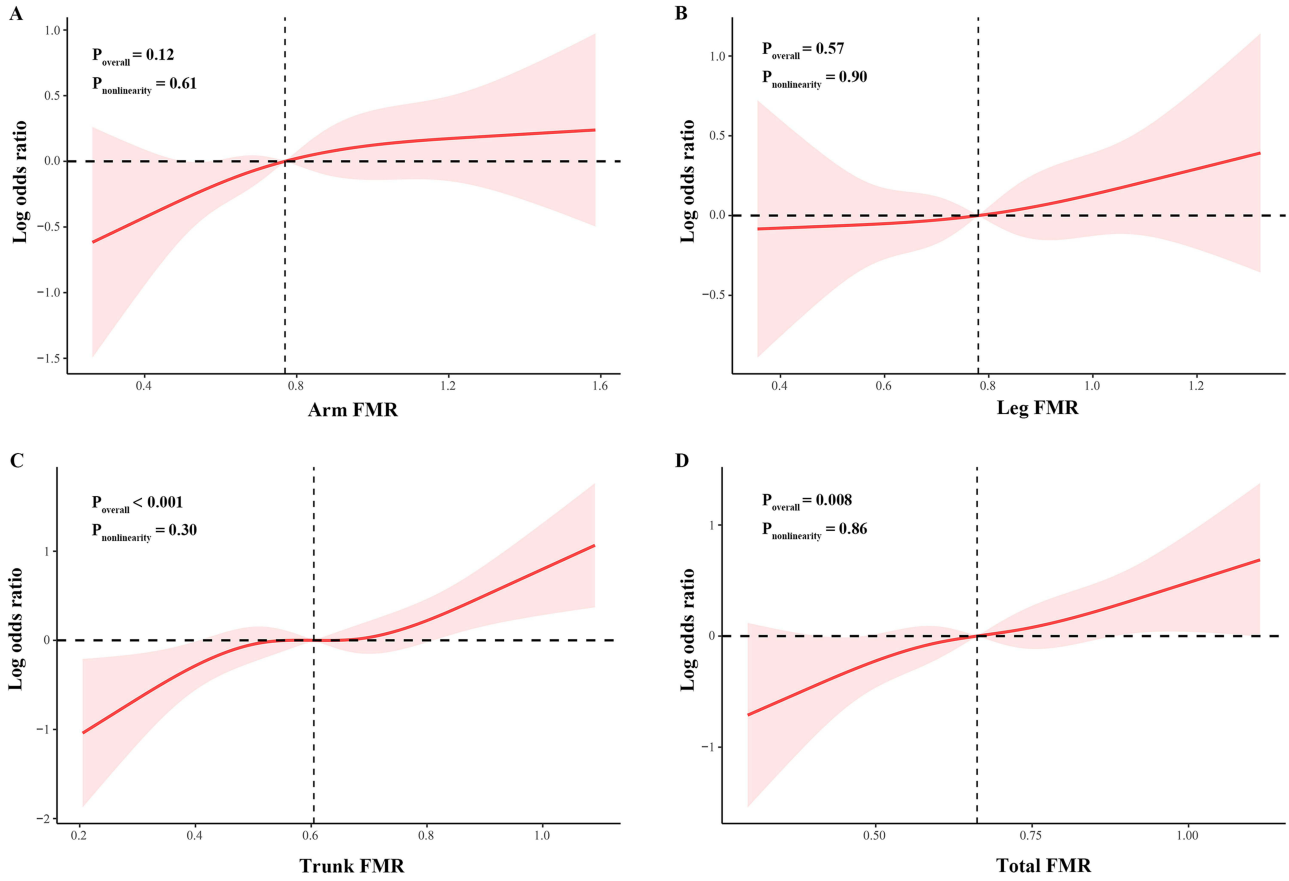

Figure 2 Restricted cubic spline analysis for the associations between arm (**A**), leg (**B**), trunk (**C**), and total (**D**) fat to muscle mass ratio (FMR) and risk of infertility in US women aged 20 to 44 years. The results indicated that arm and leg FMR were unrelated to infertility prevalence, whereas the trunk and total FMR were positively and linearly associated with infertility prevalence.

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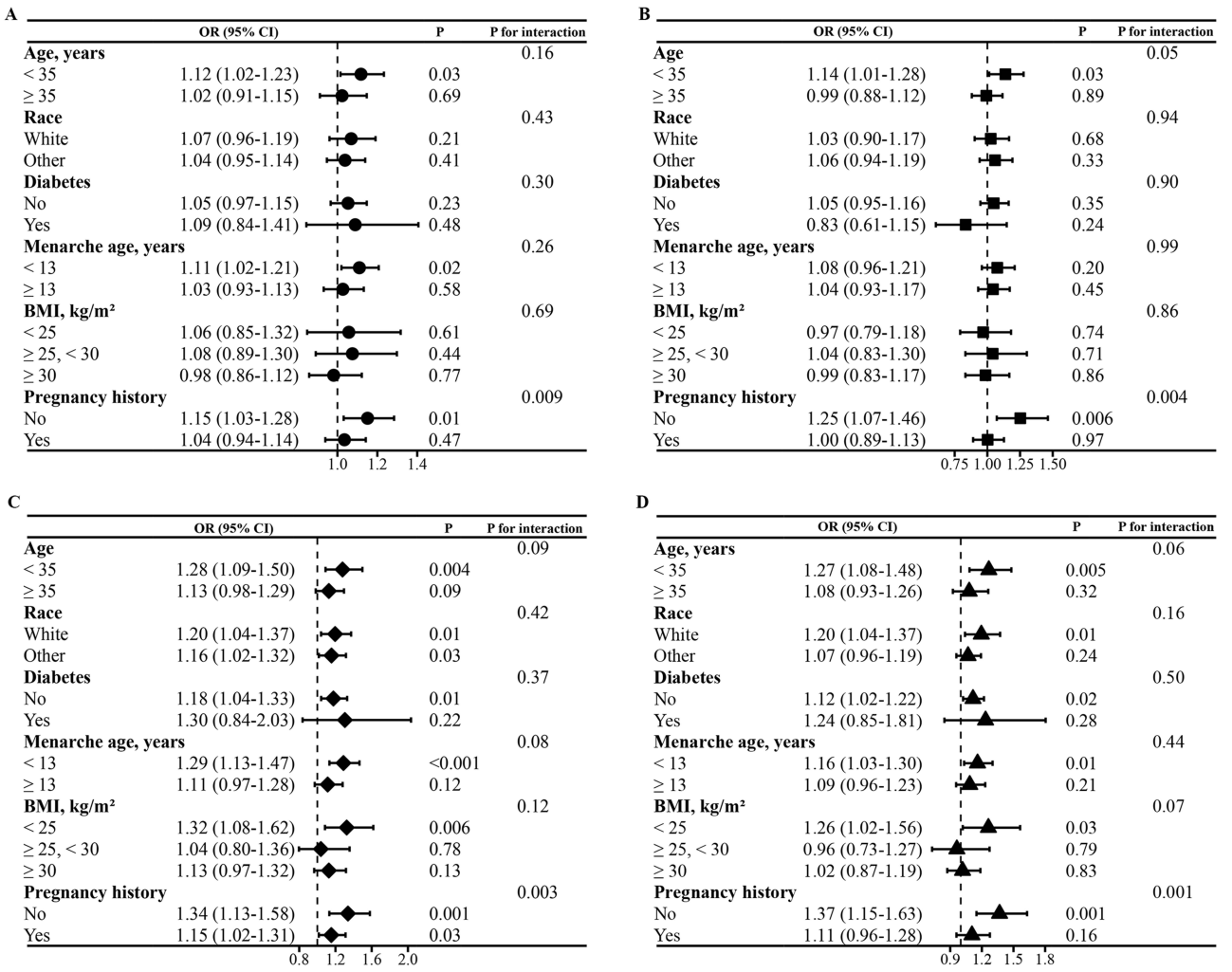

Figure 3 Subgroup analysis for the associations between arm (**A**), leg (**B**), trunk (**C**), and total (**D**) fat to muscle mass ratio (FMR) and risk of infertility in US women aged 20 to 44 years.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Discussion

In this large-scale nationally representative study, we found that total and trunk FMR, but not arm or leg FMR, were cross-sectionally and linearly associated with an increased risk of infertility prevalence in US women aged 20 to 44 years. Furthermore, the association between trunk or total FMR and infertility prevalence was more stronger among women without a prior history of pregnancy. The trunk FMR appeared to be the most useful indicator for discriminating infertility from fertility, as suggested by the receiver-operating characteristic curve. Taken together, this study represents the first investigation to potentially suggest that excess adiposity in different body compartments may have different impacts on infertility in US women aged 20–44 years.

Previous studies have consistently shown that obesity is an important independent risk factor for infertility in women. Mechanistically, obesity has been found to affect uterine receptivity by modulating the expression of several critical signaling pathways to induce a hostile endometrial environment.[27] Consistent with this notion, several earlier studies have shown that weight loss through lifestyle modification, pharmacologic intervention, or bariatric surgery, can significantly improve the success rate of in vitro fertilization and reduce the risk of infertility.[28–30] Although a myriad of anthropometric indices have been proposed to characterize excess adiposity in obesity, the BMI remains the most convenient and widely used indicator. However, it is increasingly recognized that fat distribution has a dramatic impact

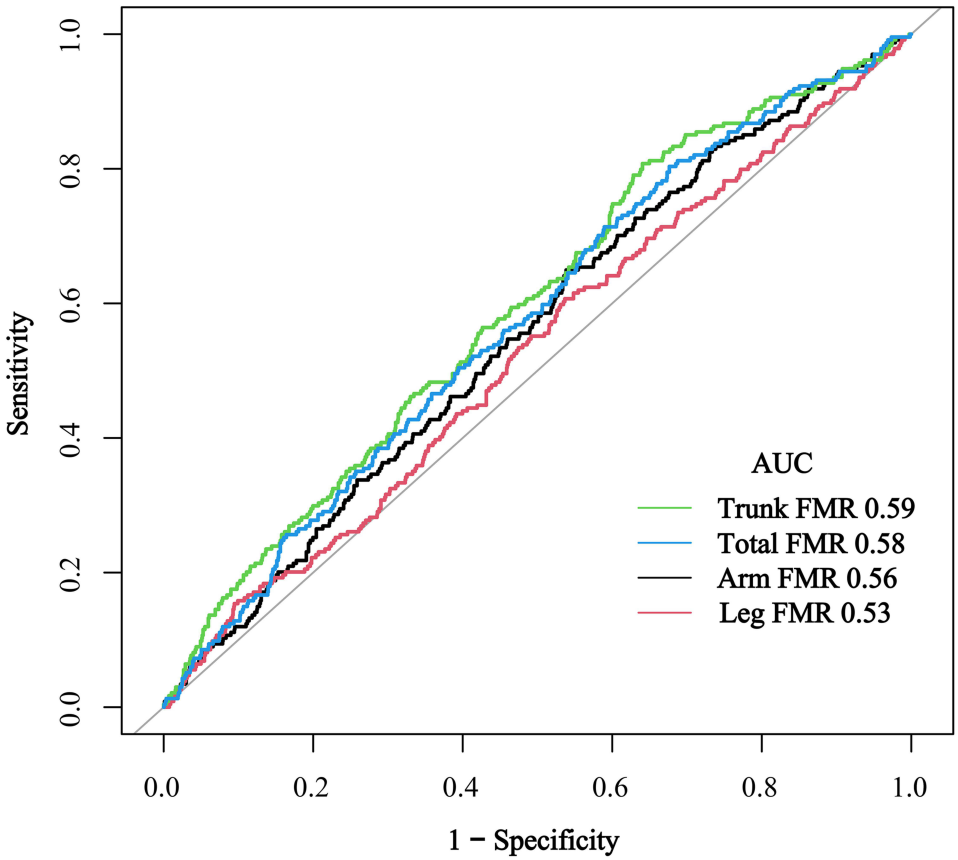

Figure 4 Receiver-operating characteristic curves comparing the capabilities of arm, leg, trunk, and total fat to muscle mass ratio (FMR) to discriminate infertility in US women aged 20 to 44 years.
Abbreviation: AUC, area under the curve.

on health outcomes. In particular, studies have indicated that abdominal adiposity is metabolically unhealthy and is associated with micro-inflammation, insulin resistance, and even a higher mortality rate.[31]

To the best of our knowledge, this study represents the first to explore the associations between total/regional relative adiposity with risk of infertility. Compared to the BMI, FMR from the dual-energy absorptiometry could provide a relatively accurate characterization of relative adiposity within various body parts. This study found that arm, trunk, and total FMR were significantly higher in women with infertility than those without. Subsequent multivariate-adjusted logistic regression analysis indicated that trunk and total FMR, rather than arm or leg FMR, were positively and linearly associated with the risk of infertility.

Table 3 Results of the Receiver-Operating Characteristic Curve for Discriminating Infertility in US Women Aged 20–44 years by Total or Regional FMR

	Cut-Off	AUC (95% CI)	Specificity (%)	Sensitivity (%)	P
Trunk FMR	0.509	0.59 (0.56–0.63)	35.96	80.77	Reference
Arm FMR	0.738	0.56 (0.52–0.60)	46.17	64.96	<0.001
Leg FMR	0.759	0.53 (0.49–0.57)	46.35	60.68	<0.001
Total FMR	0.568	0.58 (0.54–0.61)	32.37	80.34	0.007

Abbreviations: AUC, area under the curve; CI, confidence interval; FMR, fat to muscle mass ratio.

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The FMR is a novel anthropometric parameter that combines the effects of fat mass and skeletal muscle mass, and thus may be a more promising index for assessing cardiometabolic risk. The skeletal muscles directly counteract the biological functions of white adipose tissue by glucose uptake, catabolism and maintain toward energy expenditure. Moreover, the skeletal muscle is also an endocrine organ that secretes myokines that improve insulin sensitivity, enhance energy metabolism and hormonal regulation, all of which contribute to maintaining good metabolic homeostasis.[32] Previous studies have successfully applied the total and regional FMR in the evaluation of cardiometabolic, dementia and mortality risk.[33–35] For instance, Zhou et al reported that higher total FMR was related to a 63% and 83% increased risk of cardiovascular mortality in UK men and women, respectively.[36] Wang's group observed that total and leg FMR to be the most strongest predictor for incident type 2 diabetes among men and women, respectively.[13] Interestingly, this sex-specific association of total or regional FMR has also been documented with regard to cardiometabolic risk, as leg FMR presented the strongest associations for cardiometabolic risk factors.[33] Our study showed that although both total and trunk FMR were associated with infertility risk, the latter appeared to outperform the former in predicting infertility.

Currently, the exact mechanisms underscoring the disparate associations between FMR in different regions and risk of infertility remain largely elusive. This study supports the notion that trunk FMR, which predominantly includes visceral and abdominal subcutaneous fat, contributes most to the risk of infertility. Previous studies have consistently demonstrated that surrogate markers of visceral adiposity, such as visceral adiposity index and visceral adipose tissue area, are significantly related to the risk of infertility.[37,38] There are several plausible mechanisms underlying the associations between trunk FMR and infertility. First, abdominal adiposity was associated with insulin resistance, and the elevated circulating insulin could stimulate androgen synthesis.[39] Following androgen conversion to the estrogen, the hypothalamic-pituitary-ovarian axis was then inhibited, leading to follicular dysplasia and gonadal insufficiency. Changes in adipokines secreted by visceral adipose tissue, such as leptin, adiponectin, resistin, visfatin, and omentin, have been linked to insulin resistance and a pro-inflammatory state, which negatively impact ovarian function.[40] Second, abdominal adipose tissue could also secrete a variety of bioactive adipokines that have a dramatic and negative effects on reproduction, immune response, and glucose and lipid metabolism.[41] Ultimately, abdominal adiposity has also been shown to increase systemic micro-inflammation and oxidative stress that disrupts follicle and oocyte maturation, ovarian steroidogenesis, and embryo and placental development.[42]

Subgroup analysis revealed the relationships between trunk or total FMR and infertility prevalence were not modified by the BMI. Most importantly, there was still an elevated risk of infertility with increasing trunk or total FMR even among those with a BMI < 25 kg/m^2, suggesting that the FMR is probably more accurate than BMI for predicting infertility risk. Another notable finding is that a prior history of pregnancy significantly modified the relationship between total or regional FMR and risk of infertility. Specifically, a prior history of pregnancy attenuated the effect of total and regional FMR on infertility risk. Similar findings have also been reported in previous studies exploring the association between other obesity indices, such as relative fat mass and android to gynoid fat ratio, and risk of infertility.[43,44] This finding is compatible with the notion that obesity represents a major cause of secondary infertility. We also observed that the significance of trunk and total FMR on infertility tends to be more pronounced in women aged under 35 years. We speculated that this phenomenon could be attributed to the potential influence of other biological factors, such as age-related decline in ovarian function, which may play a more dominant role in infertility among females aged over 35 years.[45]

The main strengths of this study include national representativeness, accurate measurement by dual-energy absorptiometry, inclusion of multiple covariates allowing for rigorous adjustment, and assessment of region-specific FMR. However, we must also acknowledge the shortcomings associated with the current investigation. A major limitation of this study is the lack of data on the specific causes of infertility, which hinders the ability to analyze the associations between region-specific FMR and various underlying causes of infertility. Second, a causal relationship between FMR and infertility remains to be established by prospectively designed studies, as the current cross-sectional study could only suggest an association. Third, the diagnosis of infertility was based on self-report, which may introduce recall bias. Fourth, the unavailability of reproductive hormone levels, such as anti-Müllerian hormone and follicle-stimulating hormone, prevented us from further analyzing the underlying molecular mechanisms. At last, although we adequately controlled for potential confounding factors by considering a host of known and putative risk factors, we cannot completely exclude the possibility of residual confounding.

Conclusion

In conclusion, this nationwide study from NHANES showed a positive and linear association between total and trunk FMR with the prevalence of infertility in US women aged 20 to 44 years, especially those without a history of pregnancy. Additional prospective and animal studies are needed to establish causal relationships and to elucidate the underlying operating molecular mechanisms.

Ethical Considerations

The study was approved by the Ethics Review Board of the National Center for Health Statistics. According to the Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects of the People's Republic of China, ethical approval from local Institutional Review Board is not necessary.

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Disclosure

The authors report no conflicts of interest in this work.

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