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Association between serum unsaturated fatty acids levels and infertility among American women from the National Health and Nutrition Examination Survey 2013–2014

Lifang Wang^{1†}, Xue Bai^{1†}, Limei Zhao¹, Xiaodong Li¹, Fangxiang Mu², Chunyan Liu^{1*} and Qiong Xie^{1*}

Abstract

Background Some research indicates that unsaturated fatty acids (UFAs) in the diet could enhance reproductive outcomes in infertile women. However, other research holds different views, possibly due to differences in the conversion rates of UFAs from various foods and bioavailability in the body. Therefore, this research examined the link between serum UFAs and infertility issues.

Methods This research included reproductive-age women participating in the 2013–2014 American National Health and Nutrition Examination Survey (NHANES). Serum levels of four UFAs, including palmitoleic acid (16:1 n-7), vaccenic acid (18:1 n-7), oleic acid (18:1 n-9), and linoleic acid (18:2 n-6) were measured through gas chromatography-mass spectrometry. Infertility data was collected by affirmative responses to targeted questionnaire items. Associations between serum UFA levels and infertility were evaluated utilizing Poisson regression models and smooth curve fitting methods. Sensitivity analysis was also conducted.

Results This study included 535 women, aged between 18 and 45. Poisson regression analysis, both adjusted and unadjusted for confounders, revealed no associations between palmitoleic acid, vaccenic acid, oleic acid, or linoleic acid and female infertility (all $P > 0.05$). However, four UFAs all showed non-linear relationships with infertility in smooth curve fitting analysis. Sensitivity analysis confirmed the stability of the findings.

Conclusion This research established non-linear associations between serum UFAs and infertility in American women. Specifically, maintaining appropriate serum levels of these UFAs may lower infertility risk. These findings offer new insights and practical dietary recommendations for improving female fertility.

Keywords Unsaturated fatty acids, Infertility, Palmitoleic acid, Oleic acid, Metabolic syndrome

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Introduction

Female infertility is a pivotal medical condition. Women under the age of 35 are advised to seek infertility testing if they and their partners cannot get pregnant after a year of regular, unprotected sex without a known cause [1]. Alarming, female infertility is increasing by 0.37% annually and approximately affects 1.57% of women across 195 countries, a rate double that of male infertility [2]. The consequences of infertility are often devastating for women, leading to loss of social activity, marital instability, and emotional distress such as guilt, shame, worthlessness, and depression [3]. Approximately 85% of infertility cases in couples have identifiable genital causes like ovulatory dysfunction and tubal disease [4, 5], whereas the remaining cases are termed unexplained infertility [6]. Women with unexplained infertility usually have no issues with their reproductive organs [7]. Their infertility may be influenced by unhealthy lifestyle choices, dietary components, and lack of exercise [8], all of which are modifiable risk factors.

Dietary intake is among the most readily modifiable factors. Specific diet components, such as seafood, poultry, fruits, and vegetables could enhance fertility by providing sufficient unsaturated fatty acids (UFAs) [9]. Studies suggest that UFAs play crucial roles during the early reproductive cycle, contributing energy to oocyte maturation [10], improving egg quality [11], and enhancing embryo morphology [12]. Despite their potential positive effects on fertility, existing research reveals a controversial association between dietary-sourced UFAs and female infertility [13], suggesting that increased intake of UFAs may not directly elevate conception success in infertile women. This inconsistency could be due to the dietary intake of UFAs not fully representing their levels in the body. Nevertheless, studies in this area are still lacking. Consequently, this study aimed to target the serum UFAs levels to explore their relationship with female infertility.

The present study hypothesizes that serum levels of four UFAs—palmitoleic acid (16:1n-7), vaccenic acid (18:1n-7), oleic acid (18:1n-9), and linoleic acid (18:2n-6)—which have not been previously investigated in female infertility, may be associated with this condition. Drawing on data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES), this research offers new insights into how UFAs intake might affect infertility in women. The findings could inform clinical dietary advice aimed at improving reproductive health for infertile women.

Methods

Data source

This study used data from the NHANES 2013–2014 cycle, a program designed to evaluate the health and

nutritional condition of Americans. It was approved by the Ethics Review Committee of the National Center for Health Statistics, and all involved participants offered written informed consent. Since NHANES data are collected without direct participant contact, they can be used directly without additional ethics review. This study complied with the Reporting Guidelines for Enhanced Observational Epidemiological Studies.

Study population

NHANES utilized a multi-stage probability sampling design with four stages [14]. In the first stage, primary sampling units (PSUs) were selected from American counties, with most PSUs being individual counties, and some adjacent counties combined. PSUs were selected based on probabilities proportional to their size measure. In the next stage, area segments were selected from the PSUs, with segment size also sampled proportionally to ensure approximately equal sample sizes within each PSU. The third stage involved listing all dwelling units (DUs) within each selected area segment, and a subset of these was screened to maintain approximately equal national sampling probabilities. In the fourth stage, all eligible household members within the selected DUs were listed, and a sample was drawn considering factors like sex, age, race, and income to ensure that subgroup weights were approximately equal. NHANES data were gathered via standardized interviews conducted in person at households and physical examinations at mobile examination centers. Detailed information regarding study design, survey methodologies, and data can be accessed elsewhere (<https://www.cdc.gov/nchs/nhanes/index.htm>).

In this research, women aged 18 to 45 were investigated, as those under 18 are not suitable for infertility evaluation, and those over 45 experience physiological fertility decline. From 10,175 NHANES participants, exclusions were made for men ($n=5,003$), those under 18 years of age ($n=1,975$), or over 45 years of age ($n=1,649$), those with hysterectomy or bilateral oophorectomy ($n=50$), missing infertility data ($n=224$), and missing UFAs data ($n=739$), resulting in 535 participants for analysis. Figure 1 presents the selection process.

Exposure variable

In this study, serum levels of palmitoleic acid (16:1n-7), vaccenic acid (18:1n-7), oleic acid (18:1n-9), and linoleic acid (18:2n-6) (all in $\mu\text{mol/L}$) were used as exposure variables. Given the large range of exposure variable data, results were presented for palmitoleic acid per 100 $\mu\text{mol/L}$, oleic acid per 100 $\mu\text{mol/L}$, vaccenic acid per 10 $\mu\text{mol/L}$, and linoleic acid per 100 $\mu\text{mol/L}$. Serum UFAs were quantified using gas chromatography-mass spectrometry, with detailed procedures available at <https://w>

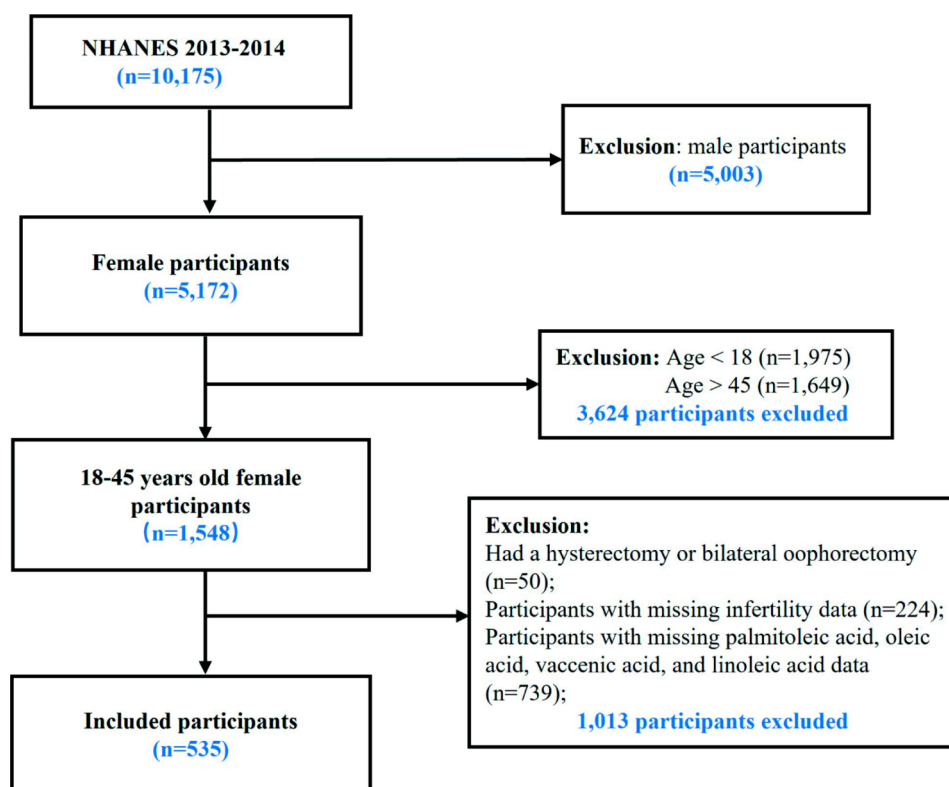


Fig. 1 Participants selection process

www.cdc.gov/Nchs/Nhanes/2013-2014/FAS_H.htm#LBXOL1.

Outcome variable

Infertility was determined from participant responses to the NHANES reproductive questionnaire, which inquired about (1) attempting pregnancy for at least a year without success, and (2) consulting a healthcare provider due to conception difficulties. In the current study, women who responded affirmatively to either question were classified as having a history of infertility [15].

Covariates

Covariates encompassed factors like age, race, educational attainment, poverty income ratio (PIR), marital condition, body mass index (BMI), drinking history, smoking history, sleep difficulties [16, 17], sedentary activity [16, 17], total physical activity, diabetes history, hypertension history, pregnancy history, age at menarche, ever treated for pelvic inflammatory disease, history of hormone use, menstrual cycle regularity, and metabolic syndrome (MetS). Household PIR was divided into low ($PIR \leq 1$), middle ($1 < PIR < 4$), and high ($PIR \geq 4$) [18]. BMI (kg/m^2) was classified into normal or low weight (< 25), overweight ($25 \leq \text{BMI} < 30$), and obese (≥ 30) groups [19]. Smoking history was determined via questionnaire (SMQ020), as were drinking history (ALQ101),

sleep difficulties (SLQ050), and birth control pill use (RHQ420). Total physical activity was divided into adequate exercise (engage in moderate-intensity exercise for 150–300 min or high-intensity for 75–150 min weekly at least, or a combination of moderate-to-high intensity exercise that equates to these) and inactivity [20]. MetS was diagnosed by the National Cholesterol Education Program Adult Treatment Program III [21], requiring three or more out of five specified risk factors. Personal medical history (diabetes and hypertension) and reproductive history (age at menarche, pregnancy, ever treated for pelvic inflammatory disease, hormone use, and menstrual cycle regularity) were obtained from Blood Pressure, Diabetes, and Reproductive Health questionnaires.

Statistical analysis

Mean with standard deviation and percentages were used to represent continuous and categorical variables, respectively. Differences among fertile and infertile women were compared using the χ^2 test or t-test based on data distribution. Poisson regression analysis was applied to assess the serum UFAs-infertility link. Meantime, two models were constructed to control for confounding factors: Model I (controlled for age) and Model II (controlled for age, marital condition, BMI, physical activity, pelvic inflammatory disease treatment, and hypertension history). Subsequently, possible non-linear relationships

that exist in serum UFAs and infertility were explored using smooth curve fitting. Furthermore, sensitivity analysis excluded participants with MetS to confirm the stability of the results.

Missing covariate values were handled with multiple imputation. Sample size was determined by NHANES data, without prior statistical estimates. EmpowerStats 4.2 and R 4.3.1 performed all statistical analyses, with significance set at $P < 0.05$.

Results

Demographic information

Enrollment comprised 535 individuals aged between 18 and 45 (Table 1). Among them, 462 females had no infertility and 73 (13.64%) had infertility. There were no marked differences in serum palmitoleic acid, vaccenic acid, oleic acid, and linoleic acid levels between the two groups. Compared to women without infertility, infertile women were older and differed significantly in marital status, BMI, total physical activity, history of pelvic inflammatory disease treatment, and hypertension history. Other characteristics were comparable between the two groups.

Relationship between UFAs and infertility

Poisson regression models assessed the associations between four serum UFAs with infertility. Two models adjusted for confounding factors (Table 2). Model I adjusted age only. In Model II, age, marital status, BMI, total physical activity, pelvic inflammatory disease treatment, and hypertension history were included. After full adjustment in model II, none of the palmitoleic acid, vaccenic acid, oleic acid, nor linoleic acid were significantly associated with infertility (all $P > 0.05$).

Smooth curve fitting

In smooth curve fitting analysis, serum UFAs showed non-linear relationships with infertility. Specifically, palmitoleic acid had a relatively flat relationship with infertility (Fig. 2A), while both oleic acid and vaccenic acid showed an inverted U-shaped curve (Fig. 2B and C), and linoleic acid exhibited a J-shaped curve (Fig. 2D). These results suggested that the risk of infertility initially decreases, but then increases with rising serum UFA levels.

Sensitivity analysis

After excluding participants with MetS, significant differences in age, BMI, age at menarche, pelvic inflammatory disease treatment, pregnancy history, and history of hypertension were noted between the fertile and infertile groups (Supplementary Table 1). Moreover, the non-linear associations between four UFAs and infertility remained (Supplementary Table 2, Supplementary

Fig. 1A-D). These results demonstrated the robustness of the findings.

Discussion

This national cross-sectional study examined the effect of dietary UFAs on infertility. Poisson regression models revealed no significant link between serum UFAs (palmitoleic acid, vaccenic acid, oleic acid, and linoleic acid) levels and female infertility risk. However, smooth curve fitting indicated non-linear relationships. This study is the first to report the non-linear relationships between these four serum UFAs and infertility, providing new dietary intervention strategies for improving female reproductive health.

Many studies recommend UFAs, such as monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), as key components of a “fertility diet” for women attempting to conceive [22]. A cohort study of 17,544 women found that increased MUFA supplementation decreased the anovulatory infertility risk by 69% [23]. PUFAs and MUFAs are also part of an “anti-inflammatory diet” [24], which combats inflammation contributed to menstrual irregularities and implantation failure, thereby benefiting reproductive outcomes [25]. Increased UFAs intake may enhance fertility by anti-inflammation [26]. Compared to MUFAs, PUFAs may play more crucial roles. PUFAs are essential for human physiological processes and must be diet-derived. Once ingested, PUFAs can be elongated and desaturated to produce other important PUFAs, such as arachidonic acid derived from linoleic acid, as well as eicosapentaenoic acid and docosahexaenoic acid originating from alpha-linolenic acid [27]. Studies have found that supplementing with PUFAs significantly reduces serum follicle-stimulating hormone levels and the risk of anovulation, thereby extending reproductive lifespan and enhancing fertility [28, 29]. Furthermore, couples consuming seafood (rich in PUFAs and MUFAs) more than eight times a month are 61% more fertile than those who consume it less frequently [29, 30].

Some studies suggest that MUFAs and PUFAs do not necessarily lower infertility risk. For instance, Chavarro et al. did not support the influence of MUFA and PUFA consumption on ovulatory infertility, but identified trans fatty acids intake as a risk factor for ovulatory infertility [31]. Similarly, Stanhiser et al. revealed no link between serum PUFAs and female infertility [32]. However, non-linear relationships between UFAs and infertility were observed herein, which implies that appropriate levels of UFAs may reduce infertility risk, whereas excessively high or low levels could be detrimental. Of note, not all UFAs equally promote reproductive health [11]. Studies have found that both linolenic acid and linoleic acid can inhibit the proliferation of cumulus cells and hinder the

Table 1 Baseline characteristics of participants

Characteristics	Total (n = 535)	Fertility (n = 462)	Infertility (n = 73)	P value
Age, years, mean (SD)	30.87 ± 8.58	30.34 ± 8.63	34.21 ± 7.45	< 0.001
Minutes sedentary activity, minute, mean (SD)	407.86 ± 189.69	408.08 ± 185.93	406.44 ± 213.37	0.919
palmitoleic acid, µmol/L, mean (SD)	212.83 ± 146.74	211.60 ± 143.04	220.58 ± 169.22	0.791
Oleic acid, µmol/L, mean (SD)	1769.08 ± 732.94	1758.65 ± 685.65	1835.10 ± 984.45	0.895
Vaccenic acid, µmol/L, mean (SD)	139.13 ± 50.40	139.15 ± 48.97	138.99 ± 59.06	0.583
Linoleic acid, µmol/L mean (SD)	3344.60 ± 839.06	3324.98 ± 765.05	3468.77 ± 1206.60	0.929
Race				0.346
Mexican American	92 (17.20%)	84 (18.18%)	8 (10.96%)	
Other Hispanic	51 (9.53%)	46 (9.98%)	5 (6.85%)	
Non-Hispanic White	204 (38.13%)	170 (36.80%)	34 (46.58%)	
Non-Hispanic Black	106 (19.81%)	90 (19.48%)	16 (21.92%)	
Other Race	82 (15.33%)	72 (15.58%)	10 (13.70%)	
Education level				0.237
Less than 9th grade	15 (2.80%)	13 (2.81%)	2 (2.74%)	
9-11th grade	95 (17.76%)	85 (18.40%)	10 (13.70%)	
High school graduate/GED or equivalent	107 (20.00%)	96 (20.78%)	11 (15.07%)	
Some college or AA degree	179 (33.46%)	146 (31.60%)	33 (45.21%)	
College graduate or above	139 (25.98%)	122 (26.41%)	17 (23.29%)	
Marital status				0.012
Married/living with partner	294 (54.95%)	244 (52.81%)	50 (68.49%)	
Widowed/divorced/separated	56 (10.47%)	47 (10.17%)	9 (12.33%)	
Never married	185 (34.58%)	171 (37.01%)	14 (19.18%)	
PIR				0.310
Low-income (PIR ≤ 1)	178 (33.27%)	157 (33.98%)	21 (28.77%)	
Middle-income (1 < PIR < 4)	252 (47.10%)	219 (47.40%)	33 (45.21%)	
High-income (PIR ≥ 4)	105 (19.63%)	86 (18.61%)	19 (26.03%)	
BMI				0.003
Normal or low weight (< 25)	224 (41.87%)	199 (43.07%)	25 (34.25%)	
Overweight (25 ≤ BMI < 30)	118 (22.06%)	109 (23.59%)	9 (12.33%)	
Obesity (≥ 30)	193 (36.07%)	154 (33.33%)	39 (53.42%)	
Drinking status				0.064
No	183 (34.21%)	165 (35.714%)	18 (24.66%)	
Yes	352 (65.79%)	297 (64.28%)	55 (75.34%)	
Smoking status				0.587
No	389 (72.71%)	334 (72.29%)	55 (75.34%)	
Yes	146 (27.29%)	128 (27.71%)	18 (24.66%)	
Sleep difficulties				0.414
No	443 (82.80%)	385 (83.33%)	58 (79.45%)	
Yes	92 (17.20%)	77 (16.67%)	15 (20.55%)	
Total physical activity				0.033
Sufficient	352 (65.79%)	312 (67.53%)	40 (54.80%)	
Insufficient	183 (34.21%)	150 (32.47%)	33 (45.21%)	
Age at menarche				0.296
< 10	22 (4.11%)	17 (3.68%)	5 (6.85%)	
10 ≤ age < 15	441 (82.43%)	385 (83.33%)	56 (76.71%)	
> 15	72 (13.46%)	60 (12.99%)	12 (16.44%)	
Regular menstruation				0.533
No	500 (93.46%)	433 (93.72%)	67 (91.78%)	
Yes	35 (6.54%)	29 (6.28%)	6 (8.22%)	
Treated for pelvic inflammatory disease				0.002
No	517 (96.64%)	451 (97.62%)	66 (90.41%)	

Table 1 (continued)

Characteristics	Total (n = 535)	Fertility (n = 462)	Infertility (n = 73)	P value
Yes	18 (3.36%)	11 (2.38%)	7 (9.59%)	0.052
Pregnancy history				
No	170 (31.78%)	154 (33.33%)	16 (21.92%)	0.080
Yes	365 (68.22%)	308 (66.67%)	57 (78.08%)	
Ever taken birth control pills?				0.438
No	180 (33.64%)	162 (35.06%)	18 (24.66%)	
Yes	355 (66.36%)	300 (64.94%)	55 (75.34%)	0.006
History of hormones using				
No	511 (95.51%)	440 (95.24%)	71 (97.26%)	0.281
Yes	24 (4.49%)	22 (4.76%)	2 (2.74%)	
Hypertension history				0.387
No	453 (84.67%)	399 (86.36%)	54 (73.97%)	
Yes	82 (15.33%)	63 (13.64%)	19 (26.03%)	
Diabetes history				
Yes	517 (96.64%)	448 (96.97%)	69 (94.52%)	
No	18 (3.36%)	14 (3.03%)	4 (5.48%)	
Metabolic Syndrome				
No	444 (82.99%)	386 (83.55%)	58 (79.45%)	
Yes	91 (17.01%)	76 (16.45%)	15 (20.55%)	

Abbreviations: SD, standard deviation; PIR, poverty income ratio; BMI, body mass index. GED, general educational development; AA, associate of arts

Table 2 The association of palmitoleic acid, oleic acid, vaccenic acid, and linoleic acid with infertility

Exposure	Unadjusted model RR (95%CI)	P value	Adjust model I RR (95%CI)	P value	Adjust model II RR (95%CI)	P value
Palmitoleic acid (μmol/L)	1.001 (0.998,1.004)	0.496	1.001 (0.998,1.003)	0.588	1.000 (0.997,1.003)	0.978
Palmitoleic acid (100 μmol/L)	1.102 (0.817,1.429)	0.496	1.078 (0.806,1.386)	0.588	0.996 (0.735,1.302)	0.978
Oleic acid (μmol/L)	1.000 (0.999,1.001)	0.662	1.000 (0.999,1.001)	0.866	1.000 (0.999,1.001)	0.808
Oleic acid (100 μmol/L)	1.016 (0.942,1.087)	0.662	1.006 (0.931,1.077)	0.866	1.009 (0.931,1.084)	0.808
Vaccenic acid (μmol/L)	0.992 (0.982,1.002)	0.140	0.993 (0.983,1.003)	0.175	0.994 (0.984,1.003)	0.213
Vaccenic acid (10 μmol/L)	0.927 (0.835,1.022)	0.140	0.934 (0.844,1.028)	0.175	0.939 (0.848,1.034)	0.213
Linoleic acid (μmol/L)	1.000 (1.000,1.001)	0.196	1.000 (1.000,1.001)	0.159	1.000 (1.000,1.001)	0.203
Linoleic acid (100 μmol/L)	1.027 (0.986,1.069)	0.196	1.029 (0.989,1.071)	0.159	1.027 (0.986,1.070)	0.203

Adjust model I: Adjusted for age

Adjust model II: Adjusted for age, marital status, body mass index, total physical activity, history of pelvic inflammatory disease treatment, and hypertension history

Abbreviations: RR, relative risk; CI, confidence interval

progression of oocytes to the metaphase II stage, which negatively affects the cumulus-oocyte complex (COC) morphology and ovarian performance [33–35]. This may be due to oxidative stress induced by UFAs intake in the follicular environment [36]. Overall, an ongoing debate exists about the impact of UFAs on reproductive outcomes, yet avoiding trans fatty acids is recommended [37]. Future research should focus on clinical studies to establish the recommended types and quantities of PUFAs and MUFAs for women seeking to improve fertility outcomes.

In this study, after excluding MetS participants, the results remained robust. MetS, marked by obesity, insulin resistance, hypertension, and dyslipidemia, is a global epidemic [38]. A retrospective study revealed that women with MetS face prolonged time to pregnancy and a 62%

increased infertility risk compared to those without MetS [39]. Potential mechanisms may be related to diminished oocyte quality, given that their ovarian reserve is notably less than that of healthy women [40]. Additionally, Robker et al. found that obese women had altered follicular fluid including higher insulin and triglycerides [41], potentially leading to their less favorable reproductive outcomes. Yang et al. also reported similar findings, noting that higher BMI resulted in increased lipid content in follicular fluid [42]. Exposure of mouse COCs to lipid-rich follicular fluid can cause higher oocyte lipid levels, endoplasmic reticulum stress, and nuclear maturation problems, leading to a reduced rate of metaphase II mature oocytes [42]. MetS is also a contributing factor to polycystic ovary syndrome [43], which has been well-documented concerning infertility [44–46]. Moreover,

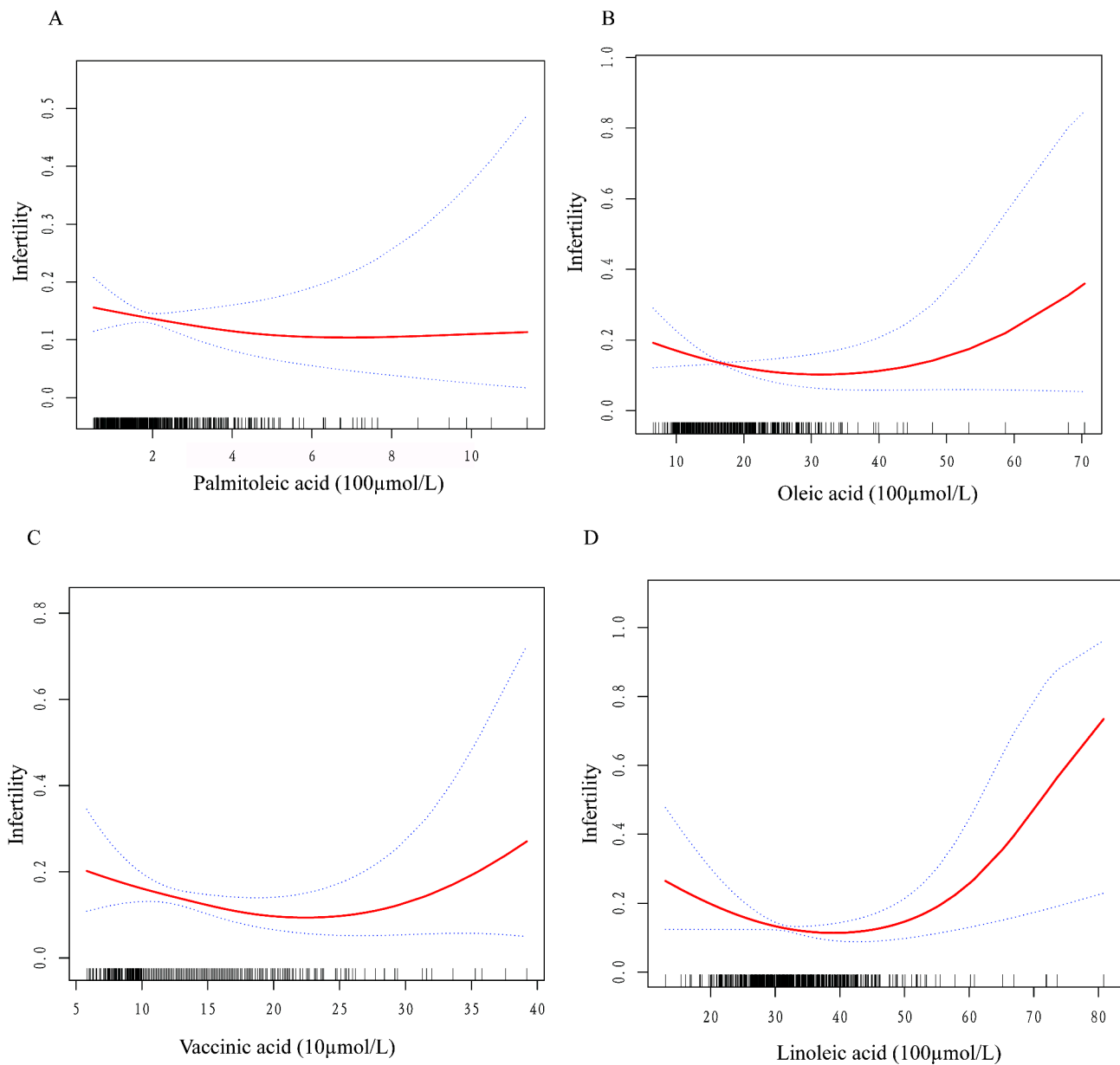


Fig. 2 Smooth curve fitting to evaluate the non-linear associations of palmitoleic acid (A), oleic acid (B), vaccenic acid (C), and linoleic acid (D) with infertility. The solid red line represents a smooth curve fitting between the variables. The blue bars represent the 95% confidence intervals of the fitted results

evidence indicates that mitochondria in patients with MetS exhibit exacerbated oxidative stress when utilizing long-chain fatty acids [47]. This oxidative stress could accelerate oocyte aging and elevate the risk of female infertility [48]. Collectively, addressing MetS through the management of weight, blood pressure, blood lipids, and blood glucose is crucial for improving female fertility outcomes.

Strengths and limitations

This research has several strengths. Firstly, it used NHANES data, which included nationally representative samples, significantly enhancing the evidence base.

Secondly, given a 13.64% infertility prevalence reported in the study population, Poisson regression analysis was applied to evaluate the link between serum UFAs levels and infertility risk, allowing for a more accurate risk evaluation. Lastly, sensitivity analysis confirmed the robustness of the results, further supporting the reliability of the findings.

However, despite these strengths, the research does have certain limitations. The cross-sectional nature of this research prevented establishing causation between UFAs and infertility. Furthermore, serum UFA levels used in the study may not entirely represent the long-term levels in the participants. Moreover, since the participants

were all from America, the findings may not apply to other regions. Last but not least, although confounding factors were adjusted for in the Poisson regression and MetS was excluded in the sensitivity analysis, there could still be additional contributing factors that have not been addressed.

Conclusion

This study concluded non-linear associations between serum palmitoleic acid, vaccenic acid, oleic acid, and linoleic acid with female infertility, suggesting that sustaining appropriate serum UFA levels may reduce the risk of infertility. These findings have valuable implications for clinicians to develop individualized nutrition interventions for infertile women. By altering the dietary patterns and adjusting UFA intake accordingly, it may be possible to enhance reproductive outcomes.

Abbreviations

UFA	Unsaturated fatty acid
NHANES	National Health and Nutrition Examination Survey
PSU	Primary sampling unit
DU	Dwelling unit
PIR	Poverty income ratio
BMI	Body mass index
MetS	Metabolic syndrome
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
COC	Cumulus-oocyte complex

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12944-024-02366-9>.

Supplementary Material 1

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Author contributions

Lifang Wang: Conceptualization, Methodology, and Writing – original draft. Xue Bai: Conceptualization, Validation, and Writing – original draft. Limei Zhao: Data collection, Formal analysis. Xiaodong Li: Data collection, Formal analysis. Fangxiang Mu: visualization. Chunyan Liu: Conceptualization, Writing – review and editing. Qiong Xie: Conceptualization, Writing – review and editing.

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Data availability

The data analyzed in this study were obtained from the NHANES database.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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