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The associations between dietary advanced glycation-end products intake and self-reported infertility in U.S. women: data from the NHANES 2013–2018

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Evidence suggest that dietary advanced glycation end products (AGEs) might exert harmful effects on female reproductive function. However, population-based studies exploring the associations between dietary AGEs intake and female infertility remain lacking. This studyaimed to determine the relationship between dietary AGEs intake and female infertility based on National Health and Nutrition Examination Survey (NHANES). A cross-sectional analysis of 2863 participants in the NHANES 2013–2018 were included. The dietary AGEs, i.e. Nε-(carboxymethyl)lysine(CML), Nε-(1-carboxyethyl) lysine (CEL), and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1) were estimated using the combination of ultra-performance LC-tandem MS dietary AGEs database and two 24-h dietary recall interviews. Multivariate Logistic regression analyses were adopted to explore the relationships between dietary AGEs intake and self-reported infertility risk. Compared to the lowest tertile, total dietary AGEs (P-trend = 0.089) and CML (P-trend = 0.032) in the upper tertile were positively correlated with female infertility, and the corresponding odds radios (ORs) (95% confidence interval (CI)) were 1.44 (1.01, 2.06) and 1.64 (1.10, 2.45) respectively. Subgroups analysis found that in participants with overweight and obese, each 1-SD increment in dietary AGEs, CML and MG-H1 level was associated with 18% (95% CI: 1-38%), 21% (95% CI: 1-46%), and 16% (95% CI: 0-36%) elevated risk of infertility. Elevated dietary AGEs intake was associated with the higher risk of infertility for female subjects, this positive association was more pronounced in women with excess body weight.

Keywords Dietary advanced glycation end products, Infertility, Multivariate regression analysis, National Health and Nutrition Examination Survey, Obesity

Infertility is defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse[1]. Globally, from 1990 to 2017, the age-standardized prevalence of women with infertility increased by 14.9% in 195 countries and regions[2]. It was estimated that the prevalence of infertility ranged from 6.7 to 19.4% in the U.S. women at reproductive age between 2011 and 2019 based on the information from the U.S. National Center for Health Statistics[3,4]. Infertility affects an individual's personal, social and economic life and the family as a whole[5]. Therefore, it is of great importance to clarify risk factors associated with infertility.

A variety of factors may increase the risk of female infertility, such as smoking, alcohol consumption, desire for offspring and dietary risk factors including popularity of fast foods and high-calorie foods[6]. Among the dietary risk factors, dietary advanced glycation end products (AGEs) might be an emerging risk factor associated with female infertility[7]. Dietary AGEs are stable heterogenous compounds which are formed by the spontaneous reaction between the amino groups of protein, lipid and nucleic acid and the aldehyde group of reducing carbohydrate during cooking or food preparation involving dry high-temperature conditions, such as baking, frying, or grilling[8]. In addition, AGEs could also be formed endogenously in the body especially under conditions like hyperglycemia and oxidative stress[9]. Recently, Roushenas et al.[10]reviewed that AGEs in

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follicular fluid were associated with the ovarian response, follicle number, retrieved oocyte number, mature (MII) oocyte number, fertilization rate, embryo number, embryo quality, and successful pregnancy. At human level, in women with polycystic ovary syndrome (PCOS), a high AGEs diet intake for 2 months elevated serum levels of AGEs, testosterone, oxidative stress, insulin and homeostasis model assessment-insulin resistance (HOMA-IR) index[11]. In women with infertility undergoingassisted reproduction technology (ART) including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) therapy, accumulation of pentosidine, Nε-carboxymethyllysine (CML), and glyceraldehyde-derived AGEs, i.e. toxic advanced glycation end products (TAGEs) in follicular fluid and TAGEs in serum correlated negatively and significantly with follicular growth, fertilization and embryonic development[12]. At animal level, given C57BL/6 mice high AGEs diets for 13 weeks disrupted folliculogenesis and steroidogenesis and upregulated inflammatory markers in ovarian tissue compared to mice on low AGEs diet[13]. Increased plasma testosterone and decreased plasma estradiol and progesterone was also reported post 2 months high-AGEs diet compared to rats on low-AGE diets[14]. Recently, it was also reported that in isolated human granulosa cells, AGEs induced hormonal dysfunction as evidenced by reduction in estradiol and elevation in progesterone and total testosterone level[15]. These evidence underscores an irrefutable correlation between dietary AGEs intake and reproductive hormone abnormalities, as well as ovarian dysfunction, solidifying the hypothesis that dietary AGEs might be an emerging risk factor for female infertility. However, currently population-based studies exploring the direct associations between dietary AGEs intake and female infertility remain lacking.

Given the rising obesity rates worldwide among women of reproductive age, it is of great necessity to take excess body weight into consideration when exploring the associations between dietary AGEs intake and female infertility. On the one hand, women with excess body weight often suffer from irregular menstrual cycle, ovulation disorders, endometrial pathology, and infertility[16]. On the other hand, dietary AGEs intake might further increase the risk of obesity and associated metabolic dysfunction. For example, a 5-year prospective cohort study from 10 European countries found that dietary intake of AGEs was positively associated with weight gain[17]. Besides, a recent randomized controlled clinical study reported that dietary restriction of AGEs for 8 weeks improved central obesity (i.e. significantly reduced waist circumference), insulin resistance, and inflammation in patients with metabolic syndrome[18]. Therefore, it is likely that the notorious effects of dietary AGEs intake on female infertility might be affected by women's body weight.

This study hypothesized that increased dietary intakes of AGEs might be associated elevated risk of infertility in U.S. women, and this positive association might be more pronounced in women with excess body weight. In this study, National Health and Nutrition Examination Survey (NHANES) 2013 and 2018 were utilized to determine the associations between dietary AGEs intake and female infertility.

Methods

Study design

The data of this study was extracted from three continuous cycles (2013–2014, 2015–2016 and 2017–2018) of National Health and Nutrition Examination Survey (NHANES), because only those cycles assembled the reproductive health questionnaire for infertility items. The NHANES survey uses a complex, multistage sampling design[19], they provide comprehensive information on health and nutrition every 2 years for a representative sample of the civilian and non-institutionalized U. S. population. The survey protocols of NHANES were approved by the National Center for Health Statistics Research Ethics Review Board (no.#2011-17), and documented signed informed consent was obtained from every participant.

In the present study, a total of 29,400 participants in the NHANES during 2013–2018 were included. Firstly, male participants ($n=14452$) were excluded. Then, those aged <20 years old ($n=6098$) or >44 years old ($n=5143$) were excluded. We additionally excluded those with missing data for ever infertility ($n=586$) and with incomplete dietary AGEs data ($n=142$). Meanwhile, those who ever had hysterectomy or bilateral ovariectomy ($n=116$) were excluded. Eventually, a total of 2863 participants with complete data were included for analysis (Fig. 1). We primarily focused on those aged ranging from 20 to 44 years old was based on previously published researches[20]. The NHANES was approved by National Center for Health Statistics Research Ethics Review Board, this research has been performed in accordance with the Declaration of Helsinki and analyzing the public domain data from NHANES does not require additional institutional review board approval.

Infertility assessment

The primary outcome was self-reported infertility. It was extracted from the reproduction health questionnaire (Variable Name in NHANES: RHQ074), i.e. "Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?". Those who responded "yes" were considered as "ever infertile", and those who responded "no" were considered as "fertile", and otherwise the data would be considered as missing[21].

Dietary AGEs intake measurement

All NHANES participants are eligible for two 24-hour dietary recall interviews. The first dietary recall interview is collected in-person in the Mobile Examination Center (MEC) and the second interview is collected by telephone 3 to 10 days later. The averaged data collected from two 24-h dietary recall interviews was used for assessing dietary AGEs contents by coupling with the dietary AGEs database developed by Scheijen et al.[22]. In this dietary AGEs database, the concentrations of representative AGEs including Nε-(carboxymethyl) lysine (CML), Nε-(1-Carboxyethyl)-l-lysine (CEL) and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1) in the protein fractions of 190 kinds of food were provided via a highly sensitive, specific and fast method of ultra-performance liquid chromatography tandem mass-spectrometry (UPLC-MS/MS). In brief, for food and beverage items existed in the database, the levels of CML, CEL and MG-H1 were calculated directly by matching the food items in the dietary AGEs database. For food and beverage items not existed in the database,

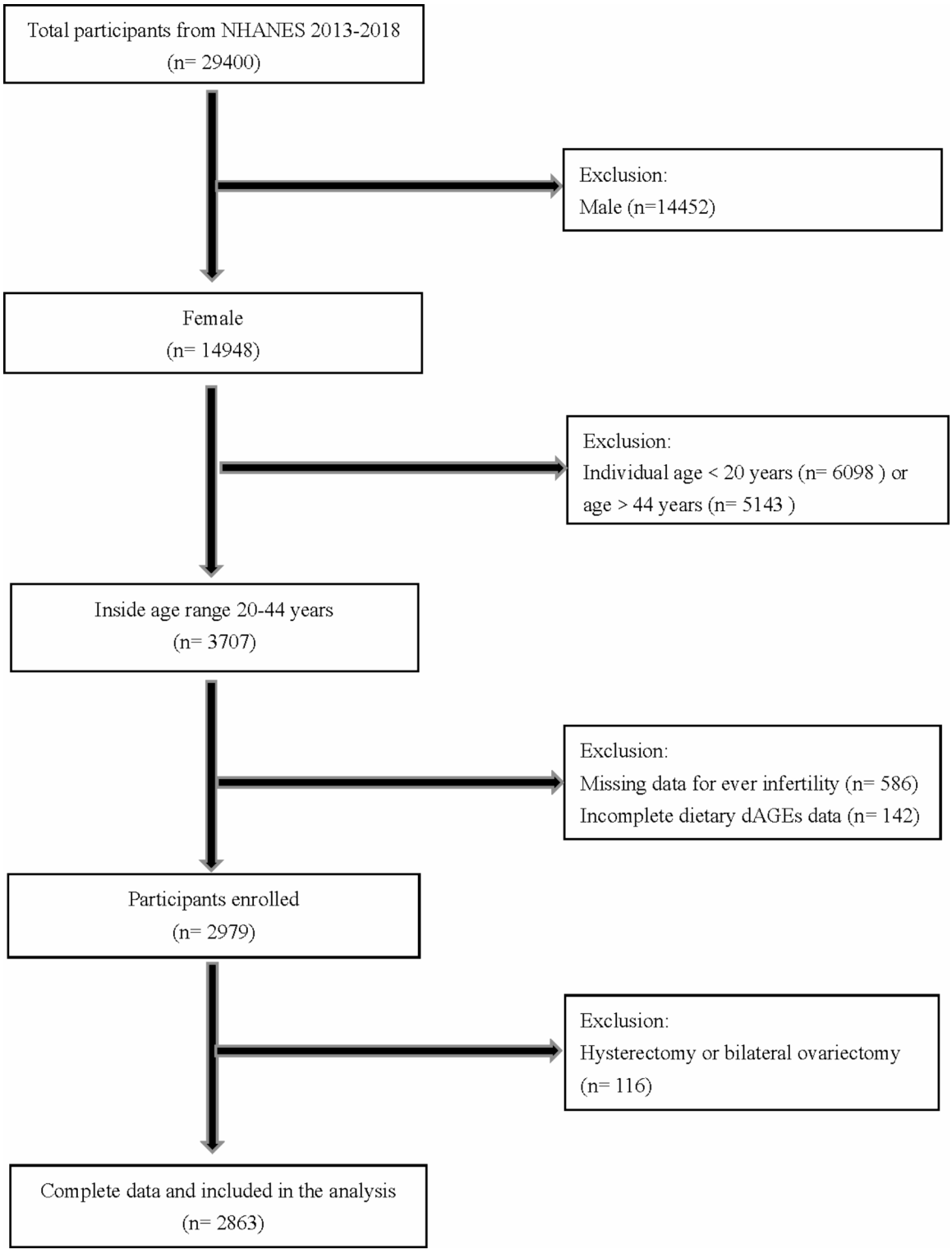

Fig. 1. Flowchart of participants selection. A total of 29,400 participants in the NHANES during 2013–2018 were included. After excluding male participants, those aged < 20 years old or > 44 years old, with missing data for ever infertility and with incomplete dietary AGEs data, and those who ever had hysterectomy or bilateral ovariectomy, a total of 2863 participants were included for analysis. *NHANES* national health and nutrition examination survey, *AGEs* advanced glycation end products.

we estimated the intake of dietary AGEs from the average of similar foods as described previously by others[23,24]. In addition, we averaged the Z-score of each dietary AGEs (i.e. CML, CEL and MG-H1) to obtain the overall dietary AGEs. The amount of overall and individual dietary AGEs intake was adjusted for daily energy intake for the final analysis.

Covariates

According to previous studies[20,25,26], we included various covariates that are related to infertility and/or dietary AGEs intake. Demographic variables included age, race/ethnicity (Mexican American, Non-Hispanic white, Non-Hispanic black, and other race), education (high school or less, some college or AA degree, and college graduate or above), marital status (married and others), poverty-income ratio (PIR, <1.3, $1.3\sim3.5$, >3.5). Health and laboratory related variables included had health insurance (yes or no), body mass index, vigorous recreational activities (yes or no), moderate recreational activities (yes or no), moderate work activity (yes or no), minutes of sedentary activity, glycohemoglobin, ever treated for a pelvic inflammatory disease (PID, yes or no), and ever been pregnant (yes or no), drinking status (non-drinkers or drinkers) and smoking status (non-smokers or smokers). Vigorous recreational activities and moderate recreational activities were defined as yes if participants had ≥ 1/day for the activities. Moderate work activity was defined as yes based on the questionnaire "Does your work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking or carrying light loads for at least 10 minutes continuously?". Glycohemoglobin was measured via the Tosoh G8 glycohemoglobin analyzer from whole blood specimens. Non-drinkers were defined as drinking <1 drink/day and heavy drinkers were defined as ≥ 1 drink/day in women[27]. Non-smokers or smokers were defined as serum cotinine level $<$ or ≥ 3.0 ng/ml, respectively[28].

Statistical analyses

Because we combined three cycles of the NHANES data, new sample weights (the original sample weight divided by 3) was constructed according to the analytical guidelines of the NHANES[29]. Firstly, the characteristics of participants were presented as means (standard deviation (SD)) and number (percentages) for continuous and categorical variables, respectively. ANOVA test was performed for continuous variables, and Chi-square test was performed for categorical variables, respectively. Then logistic regression analyses with enter method in different models were applied to analyze the association between dietary AGEs intake (divided into tertiles, and as continuous variables) and infertility status. Meanwhile, adjustment was done for potential covariates. Model 1 was adjusted for age in years at screening, education, marital status, race/ethnicity, and the ratio of family income to poverty. Model 2 was additionally adjusted for health insurance, smoking status, drinking status, body mass index, glycohemoglobin, vigorous recreational activities, moderate recreational activities, minutes of sedentary activity, ever been pregnant and PID. Subgroup analyses were further performed to explore the relationship between total and individual dietary AGEs and female infertility, according to BMI (normal, or overweight and obese). The statistical software SAS 9.4 was used to perform all analysis. P values <0.05 were considered statistically significant.

Results

Baseline characteristics of study participants

The baseline characteristics of recruited participants were presented in Table 1. The average age of 2863 subjects in this study were 31.91 (SD = 7.21) years old. Participants in the highest tertiles of dietary AGEs intake were more likely to be older, married, non-Hispanic White, not current drinkers, not current smokers and those who had not ever been treated for a PID, and had higher glycohemoglobin levels, while lower BMI level (all p-values <0.05). There was no significant difference in education, PIR, vigorous and moderate recreational activities, moderate work activity, minutes of sedentary activity, health insurance and ever been pregnant among T1, T2 and T3 groups.

Associations between total dietary AGEs, CML, CEL, MG-H1 and infertility risk

After adjusting for all potential confounders, higher intakes of dietary AGEs (P-trend = 0.076) and CML (P-trend = 0.030) were positively correlated with infertility, and the corresponding ORs (95% CI) were 1.42 (1.00, 2.01) and 1.60 (1.08, 2.38) respectively for the upper tertile vs. the lowest tertile. Each 1-SD increase in dietary AGEs and CML were associated with a 18% (95% CI: 1-37%) and 19% (95% CI: 2-38%) higher risk of the infertility events, respectively. No significant associations between CEL and MG-H1 level and infertility risk were observed (Table 2). Further subgroup analysis demonstrated that the positive associations between dietary AGEs intake and infertility risk mainly existed in subjects with BMI ≥ 25 kg/m^2. Each 1-SD increment in dietary AGEs, CML (1.63 mg/d) and MG-H1 (10.72 mg/d) level was associated with 18% (95% CI: 1-38%), 21% (95% CI: 1-46%), and 16% (95% CI: 0-36%) elevated risk of infertility. However, a significant interaction between dietary AGEs, CML and BMI with infertility was observed (P interaction = 0.025 and 0.018, respectively) (Fig. 2). The results remain consistent for those aged between 20 and 40 years old (supplementary Table 1).

Discussion

In this study, using the NHANES (2013–2018) database, it was found that total dietary AGEs and dietary CML were significantly associated with self-reported infertility. Further subgroup analysis demonstrated the positive associations between total dietary AGEs, CML, MG-H1 and self-reported infertility appeared more pronounced in U.S. women with overweight and obesity.

Existing evidence have suggested that dietary AGEs intake might be positively associated with female infertility. Female-specific causes of infertility include deterioration of oocyte quality; ovulatory disorders, most

Variables	Total	Tertiles of dietary AGEs			P^a
		T1	T2	T3	
N	2863	953	956	954	
Age in years at screening, Mean ± SD (years)	31.91 ± 7.21	31.75 ± 7.18	31.74 ± 7.22	32.24 ± 7.24	< 0.001
Education, n (%)					0.639
High school or less	997 (31.08)	346 (32.56)	328 (28.96)	323 (31.72)	
Some college or AA degree	1053 (35.04)	346 (34.02)	361 (35.59)	346 (35.53)	
College graduate or above	812 (33.89)	261 (33.42)	267 (35.45)	284 (32.75)	
Marital status, n (%)					0.005
Married	1217 (44.42)	347 (38.50)	432 (48.34)	438 (46.50)	
Others	1216 (40.97)	449 (45.33)	386 (38.70)	381 (38.80)	
Race /ethnicity, n (%)					< 0.001
Mexican American	494 (12.00)	153 (10.84)	170 (12.36)	171 (12.81)	
Non-Hispanic White	941 (55.75)	324 (56.57)	327 (57.74)	290 (52.82)	
Non-Hispanic Black	628 (13.49)	253 (16.43)	213 (13.51)	162 (10.43)	
Other race	800 (18.77)	223 (16.16)	246 (16.38)	331 (23.94)	
Ratio of family income to poverty, n (%)					0.396
< 1.3	941 (26.34)	345 (28.16)	308 (25.38)	288 (25.45)	
1.3–3.5	972 (34.03)	313 (32.56)	322 (33.79)	337 (35.80)	
> 3.5	697 (32.20)	218 (32.45)	246 (34.18)	233 (29.91)	
Vigorous recreational activities, n (%)					0.960
Yes	887 (35.50)	278 (35.02)	295 (35.82)	314 (35.66)	
No	1976 (64.50)	675 (64.98)	661 (64.18)	640 (64.34)	
Moderate recreational activities, n (%)					0.787
Yes	1312 (50.61)	407 (49.45)	443 (50.90)	462 (51.51)	
No	1551 (49.39)	546 (50.55)	513 (49.10)	492 (48.49)	
Moderate work activity, n (%)					0.225
Yes	1177 (44.05)	403 (46.32)	383 (41.41)	391 (44.43)	
No	1686 (55.95)	550 (53.68)	573 (58.59)	563 (55.57)	
Health insurance, n (%)					0.722
Yes	2206 (81.21)	716 (80.78)	756 (82.08)	734 (80.76)	
No	653 (18.79)	236 (19.22)	200 (17.92)	217 (19.24)	
PID, n (%)					0.031
Yes	132 (4.17)	56 (5.71)	42 (3.75)	34 (3.02)	
No	2714 (95.47)	890 (93.93)	908 (95.88)	916 (96.63)	
Ever been pregnant, n (%)					0.139
Yes	2046 (67.05)	656 (64.91)	714 (69.80)	676 (66.41)	
No	815 (32.95)	296 (35.09)	241 (30.20)	278 (33.59)	
Drinking status, n (%)					0.003
Drinkers	1310 (47.72)	421 (32.87)	436 (33.73)	453 (33.39)	
Non-drinkers	680 (18.64)	193 (27.99)	224 (34.17)	263 (37.84)	
NA	873 (33.64)	339 (37.52)	296 (35.70)	238 (26.80)	
Cotinine n (%)					< 0.001
Smokers	646 (22.82)	275 (45.09)	200 (27.92)	171 (26.99)	
Non-smokers	1226 (40.28)	396 (31.32)	414 (35.12)	416 (33.56)	
NA	991 (36.90)	282 (28.79)	342 (37.83)	367 (33.38)	
Minutes of sedentary activity, Mean ± SD (min)	371.64 ± 201.67	363.96 ± 197.54	378.49 ± 205.42	372.44 ± 201.91	0.098
BMI, Mean ± SD (Kg/m^2)	29.60 ± 8.40	29.75 ± 8.43	29.88 ± 8.41	29.18 ± 8.34	< 0.001
Glycohemoglobin, Mean ± SD (%)	5.39 ± 0.77	5.40 ± 0.78	5.37 ± 0.67	5.40 ± 0.86	< 0.001

Table 1. Baseline characteristics of recruited participants from NHANES 2013–2018. Values are mean ± SD (continuous variables) or n, % (categorical variables) are weighted; *T1* tertile 1, *T2* tertile 2, *T3* tertile 3, *AGEs* advanced glycation end products, *PID* Pelvic inflammatory disease, *BMI* body mass index. [a] ANOVA test was performed for continuous variables, and Chi-square test was performed for categorical variables.

	Tertiles of AGEs				
	T1	T2	T3	P trend	Continuous (per SD increase)
Z score for all dietary AGEs					
Median, mg/day	-0.82	0.04	0.82		—
Events, %	119(12.49)	100(10.46)	103(10.80)		(322) 11.25
Model 1	Ref	1.29(0.95–1.74)	1.38(0.97–1.97)	0.122	**1.16(1.01–1.35)**
Model 2	Ref	1.31(0.98–1.75)	**1.42(1.00–2.01)**	0.076	**1.18(1.01–1.37)**
Energy-adjusted dietary CML					
Median, mg/day	2.07	3.24	4.93		—
Events, %	122(12.79)	103(10.79)	97(10.17)		(322) 11.25
Model 1	Ref	1.30(0.91–1.87)	**1.52(1.02–2.27)**	0.067	**1.16(1.02–1.33)**
Model 2	Ref	1.35(0.95–1.91)	**1.60(1.08–2.38)**	**0.030**	**1.19 (1.02–1.38)**
Energy-adjusted dietary CEL					
Median, mg/day	1.68	2.78	4.56		—
Events, %	115(12.07)	96(10.04)	111(11.64)		(322) 11.25
Model 1	Ref	1.22(0.86–1.73)	1.20(0.86–1.69)	0.357	1.11(0.97–1.28)
Model 2	Ref	1.28(0.89- 1.84)	1.27(0.89- 1.81)	0.239	1.13(0.98- 1.30)
Energy-adjusted dietary MG-H1					
Median, mg/day	14.56	21.67	32.03		—
Events, %	114(11.96)	106(11.09)	102(10.69)		(322) 11.25
Model 1	Ref	1.04(0.73–1.49)	1.27(0.87–1.85)	0.296	1.17(1.00–1.38)
Model 2	Ref	0.98(0.70- 1.38)	1.22(0.86- 1.71)	0.289	1.16(0.99–1.36)

Table 2. Relationship between dietary AGEs and female infertility from NHANES 2013–2018. Conditional logistic regression models were used to calculate the ORs (95% CIs). Crude model was adjusted for none. Significant values are given in bold. Model 1 was adjusted for age in years at screening, education, marital status, race/ethnicity, and the ratio of family income to poverty. Model 2 was adjusted for model 1 + health insurance, drinking status, smoking status, body mass index, glycohemoglobin, vigorous recreational activities, moderate recreational activities, moderate work activity, minutes of sedentary activity, ever been pregnant, and PID. *T* tertiles, *AGEs* advanced glycation end products, *CML* Nε-(carboxymethyl)lysine; CEL, Nε-(1-carboxyethyl)lysine; MG-H1, Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine.

notably PCOS; history of salpingitis; uterine cavity abnormalities; and endometriosis[30]. In women with PCOS, elevated serum levels of AGEs, testosterone, oxidative stress, insulin and HOMA-IR index were elevated post a 2 months high AGEs isocaloric diet intake[11]. In women with assisted reproduction technology (ART), toxic AGE(TAGE), pentosidine (Pent) and CML accumulated in follicular fluid, and was negatively correlated with serum estradiol level, follicular growth, fertilization and embryonic development. Especially women with serum TAGE above 7.24 U/ml showed decreased oocyte numbers and ongoing pregnancy rates[12]. Our study is the very first to demonstrate that higher intake of dietary AGEs, and especially dietary CML was correlated with increased risk of female infertility. To be specific, each SD increase in CML level (i.e. 1.63 mg/d) was associated with 20% increased risk of infertility in U.S. women. Also the findings remain consistent after including a wide range of covariates. The average intake of dietary AGEs (expressed as CML and pyrraline) ranged from 25 to 75 mg/d in a traditionally Western diet[31]. It was also reported that the addition of fat-, sugar- and protein-rich ingredients greatly increased the CML content in bakery products[32]. Thus, our findings suggested that it is of great necessity to reduce dietary intake of AGEs to reduce the risk of infertility in women of childbearing age. Additionally, priority should be given to the restriction of bakery products. It should be mentioned that phytochemicals such as phenolic acids, flavonoids, stilbenes and lignans possess anti-AGE activity[33], which might be beneficial for infertile individuals with high dietary AGE intake. Especially, α-lipoic acid, which is highly available from green vegetables, could reduce the formation of AGEs in vitro[34]. Recent in vitro study also reported that α-lipoic acid ameliorated AGEs induced impaired steroidogenesis[15]. Likewise, the combination of taurine, α-lipoic acid and vitamin B6 improved methylglyoxal induced impaired developmental competence of immature mouse oocytes[35]. Nevertheless, further studies are required to determine whether α-lipoic acid supplementation is capable of improving AGEs associated female infertility.

Excess body weight might be one of the critical factors affecting the associations between dietary AGEs intake and female infertility. Obesity in women is associated with ovulatory dysfunction, reduced ovarian responsiveness, altered oocyte as well as endometrial function, all of these factors could result in infertility[16]. Higher dietary AGEs intake might also be associated with increased risk of obesity[17]. Also metabolic disorder could be both the cause and the consequences of AGEs[36]. Compared with women of normal weight, women with overweight and obesity had significantly lower serum soluble receptor for AGEs (sRAGE) levels[37]. Our subgroup analysis also demonstrated that the positive associations between dietary AGEs intake and female infertility risk mainly existed in women with overweight and obesity. It is further suggested that women with overweight

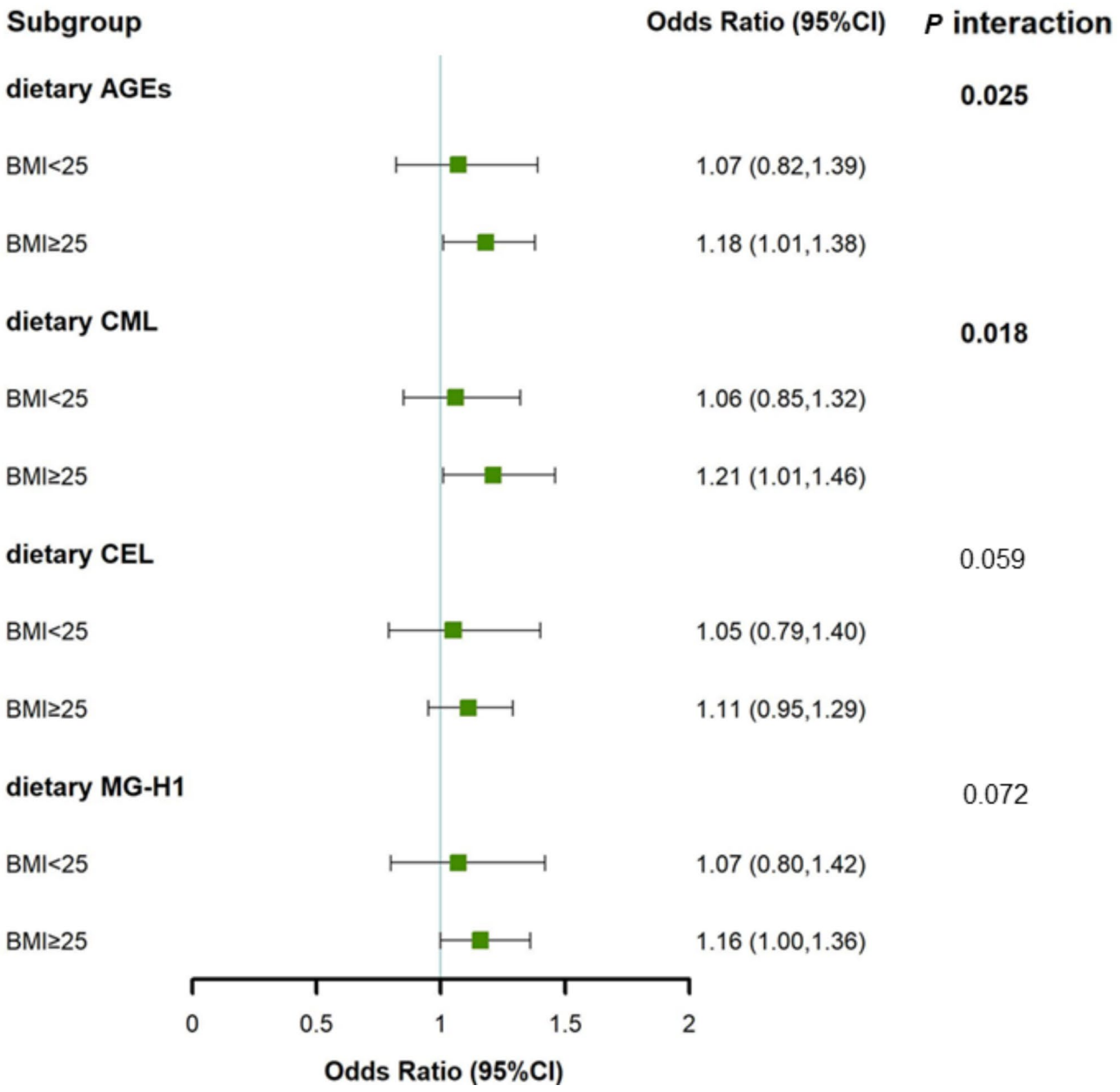

Fig. 2. Subgroup analysis via BMI demonstrated that the positive associations between dietary AGEs, CML, CEL and MG-H1 and female infertility mainly existed in those BMI ≥ 25 kg/m^2. Forest plots of subgroup analysis via BMI on the associations between dietary AGEs (**A**), CML (**B**), CEL (**C**), MG-H1 (**D**) and infertility. Adjusted for age, education, marital status, race/ethnicity, and the ratio of family income to poverty, health insurance, body mass index, vigorous recreational activities, moderate recreational activities, moderate work activity, minutes of sedentary activity, glycohemoglobin, ever been pregnant and PID. *AGEs* advanced glycation end products, *BMI* body mass index, *CML* N$^{\varepsilon}$-(carboxymethyl)lysine, *CEL* N$^{\varepsilon}$-(1-carboxyethyl)lysine; MG-H1, N$^{\delta}$-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine, *PID* pelvic inflammatory diseases.

and obesity are the main targeted population for restricting dietary AGEs intake to reduce the risk of infertility. Collectively, in order to improve the female infertility, dietary AGEs intake levels should be should be monitored and controlled, in the meantime, α-lipoic acid supplementation, or sufficient green vegetables intake might be a promising strategy for counteracting the potential deleterious effects of dietary AGEs intake on female infertility.

Potential mechanisms exist for explaining how dietary AGEs intake might increase the risk of female infertility. Binding of AGEs to its receptor (i.e.RAGE) could activate inflammatory pathways and oxidative stress, and the downstream signalling cascades[38]. In women with PCOS and polycystic ovary animal models, several studies have found that dietary AGEs can induce inflammatory responses and oxidative stress[39], which cause anovulation, hyperandrogenism, insulin resistance, and obesity, ultimately resulting in infertility among females[7,40,41]. A high AGEs diet in C57BL/6J female mice for 13 weeks had prolonged diestrus phases, disrupted

mRNA expression involved in folliculogenesis, steroidogenesis and increased ovarian inflammation, indicating that high amounts of dietary AGEs intake could lead to abnormal estrous cyclicity[13]. High-AGEs diet in rats have also been reported to increase plasma testosterone and decreased plasma estradiol and progesterone[14]. AGEs deposition in the ovaries has a negative impact on oocyte development and maturation, and also might affect meiotic and developmental competence of the oocyte at the level of chromosome rearrangement[41,42].

To the best of our knowledge, this is the very first study exploring the direct association between dietary AGEs and self-reported infertility in women representative of U.S. population. Also, the UPLC-MS/MS-based dietary AGEs database and 24 h food recall were coupled to generate the majority sources of AGEs, leading to relatively precise estimates of dietary AGEs intake. However, some limitations need to be addressed. First, the current study is a cross-sectional survey, limiting our ability to establish the temporality of dietary AGEs intake and the occurrence of infertility. Second, the dietary AGEs database was based on foodstuff in the Netherlands, which may not exactly match with the Food and Nutrition Database in the United States. Third, our findings are vulnerable to unconsidered confounding factors such as male semen quality and endogenous AGEs level. Therefore, the results should be interpreted with caution, large prospective cohort studies are needed to further confirm the relationship between dietary AGEs and infertility in women. Additionally, the potential modifying effects of male factors on female infertility couldn't be adjusted and considered in the present study. Last but not the least, this study primarily focused on dietary AGEs. Endogenous AGEs are formed during physiological glycation processes in the organs, tissues and body fluids. The associations between endogenous AGEs and infertility risk remain unclear, also whether a non-toxic AGEs level might exist remain unanswered.

In conclusion, elevated dietary AGEs intake might increase the risk of infertility for female subjects; and that the positive associations between dietary AGEs intake and female infertility mainly existed in women with overweight and obesity. For women who are willing to be pregnant, attention should be paid to the dietary AGEs intake, especially for those with excess body weight. Strategies for counteracting the deleterious effects of AGEs on the body, especially on female infertility are highly required. Additional longitudinal studies are needed to confirm the associations between dietary AGEs intake and infertility risk in women.

Data availability

The data set analyzed in this study is available on the NHANES' official website (https://www.cdc.gov/nchs/nhanes/index.htm).

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References

1. Carson, S. A. & Kallen, A. N. Diagnosis and management of infertility: a review. *JAMA* **326**, 65–76. https://doi.org/10.1001/jama.2021.4788 (2021).
2. Sun, H. et al. Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990–2017: results from a global burden of disease study, 2017. *Aging.* **11**, 10952–10991. https://doi.org/10.18632/aging.102497 (2019).
3. Key Statistics from the National Survey of Family Growth – 2015–2019. https://www.cdc.gov/nchs/nsfg/key_statistics/i-keystat.htm#Infertility (2023).
4. Key Statistics from the National Survey of Family Growth – 2011–2015. https://www.cdc.gov/nchs/nsfg/key_statistics/i.htm#infertility (2023).
5. Nik Hazlina, N. H., Norhayati, M. N. & Bahari, S. Nik Muhammad Arif, N. A. Worldwide prevalence, risk factors and psychological impact of infertility among women: a systematic review and meta-analysis. *BMJ Open.* **12**, e057132. https://doi.org/10.1136/bmjopen-2021-057132 (2022).
6. Lakoma, K., Kukharuk, O. & Sliz, D. The influence of metabolic factors and Diet on Fertility. *Nutrients* https://doi.org/10.3390/nu15051180 (2023).
7. Mouanness, M. & Merhi, Z. Impact of Dietary Advanced Glycation End products on Female Reproduction: review of potential mechanistic pathways. *Nutrients*. https://doi.org/10.3390/nu14050966 (2022).
8. Zhang, Q., Wang, Y. & Fu, L. Dietary advanced glycation end-products: perspectives linking food processing with health implications. *Compr. Rev. Food Sci. Food Saf.* **19**, 2559–2587. https://doi.org/10.1111/1541-4337.12593 (2020).
9. van Dongen, K. C. W. et al. Differences in kinetics and dynamics of endogenous versus exogenous advanced glycation end products (AGEs) and their precursors. *Food Chem. Toxicol. Int. J. Br. Ind. Biol. Res. Assoc.* **164**, 112987. https://doi.org/10.1016/j.fct.2022.112987 (2022).
10. Roushenas, F. et al. Follicular fluid advanced glycation end products in assisted reproduction: a systematic review. *Clin. Chim. Acta.* **549**, 117560. https://doi.org/10.1016/j.cca.2023.117560 (2023).
11. Tantalaki, E. et al. Impact of dietary modification of advanced glycation end products (AGEs) on the hormonal and metabolic profile of women with polycystic ovary syndrome (PCOS). *Hormones.* **13**, 65–73. https://doi.org/10.1007/BF03401321 (2014).
12. Jinno, M. et al. Advanced glycation end-products accumulation compromises embryonic development and achievement of pregnancy by assisted reproductive technology. *Hum. Reprod.*. **26**, 604–610. https://doi.org/10.1093/humrep/deq388 (2011).
13. Thornton, K. et al. Dietary Advanced Glycation End products (AGEs) could alter ovarian function in mice. *Mol. Cell. Endocrinol.* **510**, 110826. https://doi.org/10.1016/j.mce.2020.110826 (2020).
14. Chatzigeorgiou, A. et al. Dietary glycotoxins affect scavenger receptor expression and the hormonal profile of female rats. *J. Endocrinol.* **218**, 331–337. https://doi.org/10.1530/JOE-13-0175 (2013).
15. Derakhshan, Z. et al. Alpha-lipoic acid ameliorates impaired steroidogenesis in Human Granulosa cells Induced by Advanced Glycation End-products. *Iran. J. Med. Sci.* **49**, 515–527. https://doi.org/10.30476/ijms.2023.99512.3168 (2024).
16. Silvestris, E., de Pergola, G., Rosania, R. & Loverro, G. Obesity as disruptor of the female fertility. *Reprod. Biol. Endocrinol.* **16**, 22. https://doi.org/10.1186/s12958-018-0336-z (2018).
17. Cordova, R. et al. Dietary intake of advanced glycation end products (AGEs) and changes in body weight in European adults. *Eur. J. Nutr.* **59**, 2893–2904. https://doi.org/10.1007/s00394-019-02129-8 (2020).
18. Goudarzi, R., Sedaghat, M., Hedayati, M., Hekmatdoost, A. & Sohrab, G. Low advanced glycation end product diet improves the central obesity, insulin resistance and inflammatory profiles in Iranian patients with metabolic syndrome: a randomized clinical trial. *J. Diabetes Metab. Disord.* **19**, 1129–1138. https://doi.org/10.1007/s40200-020-00614-0 (2020).

19. Chen, T. C., Clark, J., Riddles, M. K., Mohadjer, L. K. & Fakhouri, T. H. I. National Health and Nutrition Examination Survey, 2015–2018: Sample Design and Estimation procedures. *Vital Health Stat.* **2**, 1–35 (2020).
20. Arya, S., Dwivedi, A. K., Alvarado, L. & Kupesic-Plavsic, S. Exposure of U.S. population to endocrine disruptive chemicals (parabens, Benzophenone-3, Bisphenol-A and Triclosan) and their associations with female infertility. *Environ. Pollut.* **265**, 114763. https://doi.org/10.1016/j.envpol.2020.114763 (2020).
21. Gleason, J. L., Shenassa, E. D. & Thoma, M. E. Self-reported infertility, metabolic dysfunction, and cardiovascular events: a cross-sectional analysis among U.S. women. *Fertil. Steril.* **111**, 138–146. https://doi.org/10.1016/j.fertnstert.2018.10.009 (2019).
22. Scheijen, J. et al. Analysis of advanced glycation endproducts in selected food items by ultra-performance liquid chromatography tandem mass spectrometry: presentation of a dietary AGE database. *Food Chem.* **190**, 1145–1150. https://doi.org/10.1016/j.foodchem.2015.06.049 (2016).
23. Jiao, L. et al. Dietary consumption of meat, fat, animal products and advanced glycation end-products and the risk of Barrett's oesophagus. *Aliment. Pharmacol. Ther.* **38**, 817–824. https://doi.org/10.1111/apt.12459 (2013).
24. Linkens, A. M. A. et al. Habitual intake of dietary advanced glycation end products is not associated with generalized microvascular function-the Maastricht Study. *Am. J. Clin. Nutr.* **115**, 444–455. https://doi.org/10.1093/ajcn/nqab302 (2022).
25. Zhu, F. et al. Elevated blood mercury level has a non-linear association with infertility in U.S. women: data from the NHANES 2013–2016. *Reprod. Toxicol.*. **91**, 53–58. https://doi.org/10.1016/j.reprotox.2019.11.005 (2020).
26. Zhu, L. et al. Association between Body Mass Index and female infertility in the United States: data from National Health and Nutrition Examination Survey 2013–2018. *Int. J. Gen. Med.* **15**, 1821–1831. https://doi.org/10.2147/IJGM.S349874 (2022).
27. Chen, C., Ye, Y., Zhang, Y., Pan, X. F. & Pan, A. Weight change across adulthood in relation to all cause and cause specific mortality: prospective cohort study. *BMJ* **367**, l5584. https://doi.org/10.1136/bmj.l5584 (2019).
28. Benowitz, N. L., Bernert, J. T., Caraballo, R. S., Holiday, D. B. & Wang, J. Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial/ethnic groups in the United States between 1999 and 2004. *Am. J. Epidemiol.* **169**, 236–248. https://doi.org/10.1093/aje/kwn301 (2009).
29. Huang, J. S. et al. Effect of nitric oxide-cGMP-dependent protein kinase activation on advanced glycation end-product-induced proliferation in renal fibroblasts. *J. Am. Soc. Nephrology: JASN*. **16**, 2318–2329. https://doi.org/10.1681/asn.2005010030 (2005).
30. Expert Panel on Women's. ACR Appropriateness Criteria(R) female infertility. *J. Am. Coll. Radiol.* **17**, S113–S124. https://doi.org/10.1016/j.jacr.2020.01.018 (2020).
31. Henle, T. AGEs in foods: do they play a role in uremia? *Kidney Int. Suppl.* https://doi.org/10.1046/j.1523-1755.63.s84.16.x (2003).
32. Boz, H. N(ε) -(carboxymethyl)lysine in bakery products: a review. *J. Food Sci.* **88**, 901–908. https://doi.org/10.1111/1750-3841.16475 (2023).
33. Del Castillo, M. D. et al. Healthy eating recommendations: good for reducing dietary contribution to the body's advanced glycation/lipoxidation end products pool? *Nutr. Res. Rev.* **34**, 48–63. https://doi.org/10.1017/S0954422420000141 (2021).
34. Ghelani, H., Razmovski-Naumovski, V., Pragada, R. R. & Nammi, S. Attenuation of Glucose-Induced Myoglobin Glycation and the Formation of Advanced Glycation End Products (AGEs) by (R)-alpha-Lipoic Acid In Vitro. *Biomolecules*. https://doi.org/10.3390/biom8010009 (2018).
35. Mokhtari, S. et al. Taurine, alpha lipoic acid and vitamin B6 ameliorate the reduced developmental competence of immature mouse oocytes exposed to methylglyoxal. *Sci. Rep.* **14**, 17937. https://doi.org/10.1038/s41598-024-66785-5 (2024).
36. Twarda-Clapa, A., Olczak, A., Bialkowska, A. M. & Koziolkiewicz, M. Advanced Glycation End-Products (AGEs): Formation, Chemistry, Classification, Receptors, and Diseases Related to AGEs. *Cells*. https://doi.org/10.3390/cells11081312 (2022).
37. Merhi, Z., Irani, M., Doswell, A. D. & Ambroggio, J. Follicular fluid soluble receptor for advanced glycation end-products (sRAGE): a potential indicator of ovarian reserve. *J. Clin. Endocrinol. Metab.* **99**, E226–233. https://doi.org/10.1210/jc.2013-3839 (2014).
38. Merhi, Z. Advanced glycation end products and their relevance in female reproduction. *Hum. Reprod.* **29**, 135–145. https://doi.org/10.1093/humrep/det383 (2014).
39. Cai, W. et al. Oxidative stress-inducing carbonyl compounds from common foods: novel mediators of cellular dysfunction. *Mol. Med.*. **8**, 337–346 (2002).
40. Mouanness, M., Nava, H., Dagher, C. & Merhi, Z. Contribution of Advanced Glycation End Products to PCOS Key Elements: A Narrative Review. *Nutrients*. https://doi.org/10.3390/nu14173578 (2022).
41. Siddiqui, S., Mateen, S., Ahmad, R. & Moin, S. A brief insight into the etiology, genetics, and immunology of polycystic ovarian syndrome (PCOS). *J. Assist. Reprod. Genet.* https://doi.org/10.1007/s10815-022-02625-7 (2022).
42. Tatone, C., Eichenlaub-Ritter, U. & Amicarelli, F. Dicarbonyl stress and glyoxalases in ovarian function. *Biochem. Soc. Trans.* **42**, 433–438. https://doi.org/10.1042/BST20140023 (2014).

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Author contributions

Z.X.W., H.Z., and L.X.T. designed the study; L.X.T. and X.H.Z. performed the statistical analyses; L.X.T. drafted and X.H.Z., J.S.C., H.Y.H. , W.Z.Z., H.Z. and Z.X.W. revised the manuscript; H.Z. and Z.X.W. supervised the data analysis and interpretation; H.Z. had the primary responsibility for the final content. All authors critically reviewed the manuscript and approved the final draft.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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