

Association of Dietary Polyamines with the Prevalence of Gestational Diabetes Mellitus: A Cross-Sectional Study in Chinese Pregnant Women

Tianru Mei

1.Clinical Research Center, The International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University School of Medicine, 910 Hengshan Road, 200030,

Yiting Song

1.Clinical Research Center, The International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University School of Medicine, 910 Hengshan Road, 200030,

Rui Zhang

4.College of Public Health, Shanghai University of Medicine and Health Sciences, No. 279 Zhouzhu Road, Pudong New District, 201318

Xinyu Deng

School of Public Health, China Medical University, 110122,

Yan Wang

2.Hainan Branch,Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, 572000

Min Song

2.Hainan Branch,Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, 572000

Dan Wang

2.Hainan Branch,Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, 572000

Xuchen Yang

6.School of Public Health, Shanghai Jiao Tong University, 200025, China

Yifei Shao

6.School of Public Health, Shanghai Jiao Tong University, 200025, China

Sihan Jing

6.School of Public Health, Shanghai Jiao Tong University, 200025, China

Rennan Feng

Department of Nutrition and Food Hygiene, School of Public Health, Harbin Medical University, Harbin, Heilongjiang 150081, PR China.

Liqiang Zheng

liqiangzheng@126.com

1.Clinical Research Center, The International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University School of Medicine, 910 Hengshan Road, 200030,

Wenqian Ji

2.Hainan Branch,Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, 572000

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Abstract

Objective

To investigate the associations between dietary intake of spermidine, spermine, and putrescine and the prevalence of gestational diabetes mellitus (GDM).

Methods

This cross-sectional study included 1,007 pregnant women (287 GDM, 720 non-GDM) who received prenatal care at the Hainan Hospital of Shanghai Jiao Tong University School of Medicine from August 2024 to April 2026. Dietary polyamine intake was calculated based on a food frequency questionnaire and a nutrient database. Multivariable logistic regression and restricted cubic spline (RCS) models were used to assess associations and dose-response relationships.

Results

After multivariable adjustment, participants in Q2 and Q3 of spermidine intake had 52% (OR = 1.52, 95% CI: 1.00–2.31, $P = 0.049$) and 73% (OR = 1.73, 95% CI: 1.09–2.75, $P = 0.021$) higher odds of GDM, respectively. For putrescine, Q3 was associated with 57% increased odds (OR = 1.57, 95% CI: 1.00–2.46, $P = 0.049$). No significant association was observed for spermine. RCS analyses did not reveal significant nonlinear dose-response relationships. Sensitivity analyses excluding participants with polycystic ovary syndrome yielded consistent results (spermidine Q3: OR = 1.90, 95% CI: 1.18–3.06, $P = 0.008$).

Conclusion

Higher dietary spermidine and putrescine intakes were associated with increased GDM prevalence, while spermine showed no significant association. These findings suggest that dietary polyamines may influence glucose metabolism during pregnancy.

1. Introduction

Gestational diabetes mellitus (GDM), defined as hyperglycaemia with first onset or recognition during pregnancy^[1], is one of the most common metabolic complications of pregnancy. The global prevalence of GDM has risen markedly over recent decades, with current estimates affecting approximately 14%–20% of pregnancies worldwide, though rates vary considerably by region and diagnostic criteria^[2, 3]. In China, the prevalence increased sharply from 4% in 2010 to 21% in 2020, largely attributed to rising maternal age and obesity^[4, 5]. GDM not only increases the risk of adverse perinatal outcomes but also predisposes affected women to a substantially elevated lifetime risk of type 2 diabetes mellitus (T2DM), while their offspring face increased long-term risks of obesity and glucose intolerance^[6, 7]. The pathophysiology of GDM is multifactorial, centrally involving pregnancy-induced insulin resistance—a physiological adaptation mediated by placental hormones such as progesterone, cortisol, and human placental lactogen—and inadequate compensatory insulin secretion from pancreatic β -cells^[8, 9]. Established risk factors include advanced maternal age, elevated pre-pregnancy body mass index (BMI), and family history of diabetes^[2]. Identifying modifiable dietary determinants remains a priority for primary prevention strategies.

Polyamines—ubiquitous aliphatic polycationic compounds including putrescine, spermidine, and spermine—are bioactive dietary constituents derived from foods such as meat, fish, legumes, and certain vegetables^[10]. They play essential roles in cell proliferation, differentiation, and gene expression^[11]. Emerging evidence from animal and cell studies suggests that polyamines influence glucose homeostasis through multiple mechanisms, including the regulation of glucose transporter proteins, insulin signaling pathways (e.g., PI3K/AKT and AMPK), and pancreatic β -cell function.^[12, 13] Notably, pregnancy is characterized by profound alterations in systemic polyamine metabolism driven by placental synthesis and fetal demands, with polyamines playing critical roles in implantation, placentation, and embryonic development^[14].

Despite biological plausibility, epidemiological evidence linking dietary polyamine intake to GDM remains scarce. A recent large prospective cohort study from the UK Biobank (n = 168,137) demonstrated significant associations between dietary polyamines and incident T2DM in the general population^[15], but no previous study has specifically examined this association in pregnant populations. Therefore, the present study aimed to investigate the association between dietary intake of spermidine, spermine, and putrescine and the prevalence of GDM in a population of Chinese pregnant women, with dietary intake assessed using a validated food frequency questionnaire (FFQ).

2. Materials and Methods

2.1 Study Population

This study employed a cross-sectional design and was conducted as part of the Hainan Provincial Health and Wellness Science and Technology Innovation Joint Project undertaken by the Hainan Hospital of the Shanghai Children's Medical Center, affiliated with the School of Medicine at Shanghai Jiao Tong University. The study was conducted from August 2024 to April 2026 and the target population consisted of pregnant women who had registered for prenatal care at the hospital and had completed the Oral Glucose Tolerance Test (OGTT) and FFQ as scheduled. A total of 1,286 pregnant women who voluntarily signed informed consent forms were recruited. The inclusion criteria for this study were as follows: (1) Pregnant women who completed OGTT screening during the current pregnancy; (2) All participants had singleton pregnancies; (3) Participants signed an informed consent form, voluntarily participated in the study, were able to cooperate in completing dietary surveys and questionnaires, and demonstrated good compliance. Exclusion criteria included: (1) Participants diagnosed with type 1 or type 2 diabetes prior to pregnancy, or those with a history of gestational diabetes in previous pregnancies; (2) Participants with missing key biochemical test data (for example, OGTT blood glucose values) or incomplete clinical records; (3) Abnormal dietary energy intake data (for example, daily energy intake > 5,000 kcal or < 500 kcal^[16, 17]). A total of 1,007 valid study participants were ultimately enrolled. Based on OGTT results, 287 pregnant women were diagnosed with GDM, and 720 were included in the non-GDM group, as shown in Fig. 1. This study was approved by the hospital's Medical Ethics Committee (Ethics No.: SYFYIRB2024078).

2.2 Data Collection

All surveys were conducted jointly by experienced obstetricians and public health professionals who had undergone training and passed the relevant assessments. On-site epidemiological surveys were conducted face-to-face with all study participants using a standardized questionnaire. The data collected included the following: (1) Questionnaire Survey: A standardized questionnaire was used to conduct on-site epidemiological surveys with all study participants in a face-to-face format. Specific content included: sociodemographic data (name, gender, date of birth, residential address, educational level, ethnicity, marital status, and average monthly income); personal lifestyle factors (smoking, alcohol consumption, sleep patterns, etc.); medical history (diabetes, polycystic ovary syndrome, etc.); and dietary assessment (food frequency questionnaire). (2) Physical examination: Including measurements of height, weight, etc. (3) FFQ: To assess the study participants' dietary intake over the past month, administered via one-on-one face-to-face

interviews. The FFQ covers 10 food categories: grains, tubers, legumes, vegetables, fruits, nuts, meat, dairy and eggs, seafood, and beverages. Frequency options range from “never” to “3 times or more per day,” divided into 8 levels. Participants are asked to select from the provided options the average frequency of consumption for each food item over the past month, as well as the average portion size (in grams or milliliters) for each food item. Based on the participants’ selections, researchers will calculate the average daily intake (in grams or milliliters) for each food item and further estimate the average daily intake of nutrients and polyamines.

2.3 Detection and Measurement of Dietary Polyamines

To systematically and accurately assess the average daily intake of dietary spermidine, spermine, and putrescine among the study participants, we constructed a dedicated dietary polyamine database. This database covers approximately 162 common food items and integrates the food polyamine database previously established by our research group, internationally reported measurement data, and our laboratory test results. The specific construction and integration procedures are detailed below. (1) For the polyamine content of common foods included in this study, approximately 78 food items were preferentially derived from the dietary polyamine database previously compiled by our research group. This database was developed by systematically retrieving and strictly matching food polyamine values from internationally published literature. Its validity for dietary exposure estimation has been established in our previous UK Biobank-based epidemiological studies on dietary polyamines and disease risk.^[16, 18] (2) For the 76 food items from our dietary questionnaire not found in the routine database, our research group conducted laboratory test to supplement the data. Commonly available commercial varieties of the aforementioned foods were purchased as test samples and analyzed using Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-MS/MS). In brief, samples were ground in liquid nitrogen and extracted with 80% acetonitrile containing 0.1% formic acid. Following homogenization, ultrasonication, and centrifugation, the supernatant was derivatized with dansyl chloride, extracted with n-hexane, and reconstituted after nitrogen evaporation. Chromatographic separation was achieved on a Kinetex C18 column using a water–acetonitrile mobile phase (0.1% formic acid) under gradient conditions. Mass spectrometric detection was performed in electrospray positive ion mode with multiple reaction monitoring for spermidine, spermine, and putrescine quantification. (3) Furthermore, for the few food items for which measurements were unavailable, the missing data were supplemented using values derived from the Japanese Food Polyamine Composition Report.^[19, 20]

2.4 Diagnostic Criteria for Gestational Diabetes Mellitus

The diagnosis of GDM for study participants in this project followed the IADPSG criteria^[21]. First, patients were scheduled for relevant tests and instructed to maintain their normal diet for 3 days prior to testing. They underwent an OGTT between 24 and 28 weeks of gestation. For the test, 75 g of glucose was dissolved in 300 mL of water and consumed within 5 minutes. 2 mL of venous blood was drawn three times over a 3-hour period. Blood glucose levels were measured using a fully automated biochemical analyzer and reagents. A diagnosis of GDM was made if any one of the following three thresholds was met during the OGTT: a) fasting blood glucose ≥ 5.1 mmol/L; b) 1-hour blood glucose concentration ≥ 10.0 mmol/L; c) 2-hour blood glucose concentration ≥ 8.5 mmol/L.

2.5 Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) or median (interquartile range), and categorical variables are expressed as frequency (percentage). Comparisons of characteristics between groups were performed using the t-test, the Mann-Whitney U test, or the chi-square test. Categorical data were expressed as the number of cases and proportion (%), and the χ^2 test was used to compare differences between groups. This study employed logistic regression models to assess the association between dietary spermidine, spermine, and putrescine and the prevalence of gestational diabetes, after adjusting for age, BMI, ethnicity, educational level, monthly income, parity, history of polycystic ovary syndrome, smoking status, alcohol consumption, and total daily energy intake. A sensitivity analysis was performed after excluding pregnant women with a history of polycystic ovary syndrome to further assess

the robustness of the results. Statistical analyses were performed using SPSS 29.0 (IBM Corp., Armonk, NY, USA) and R 4.6.0, and P less than 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics of the Study Population

This study included a total of 1,007 participants, comprising 287 cases (28.5%) in the GDM group and 720 cases (71.5%) in the non-GDM group. The baseline characteristics of the two groups are shown in Table 1. The mean age in the GDM group was 32.0 ± 4.4 years, which was significantly higher than that of the non-GDM group (30.5 ± 4.4 years; $P < 0.001$); the pre-pregnancy BMI in the GDM group was 22.2 ± 3.0 kg/m², which was also significantly higher than that of the non-GDM group (21.5 ± 3.2 kg/m²) ($P = 0.003$). In terms of ethnic distribution, there was a statistically significant difference between the two groups ($P = 0.013$); the proportion of Li ethnic group members in the GDM group was 33.8%, higher than the 25.4% in the non-GDM group. Additionally, the proportion of participants with a history of polycystic ovary syndrome in the GDM group was 5.6%, slightly higher than the 3.1% in the non-GDM group, with the difference approaching statistical significance ($P = 0.067$). There were no statistically significant differences between the two groups in baseline characteristics such as educational level, monthly income, smoking history, alcohol consumption history, and obstetric history (all $P > 0.05$).

Table 1
Demographic and Biochemical Characteristics of the Participants

Variable	Total(n = 1007)	GDM group(n = 287)	Non-GDM group(n = 720)	P value
Age*, years	31.0 ± 4.4	32.0 ± 4.4	30.5 ± 4.4	<0.001
BMI, kg/m ²	21.7 ± 3.1	22.2 ± 3.0	21.5 ± 3.2	0.003
Ethnicity, n(%)				0.013
Han	700(69.5)	180(62.7)	520(72.2)	
Li	280(27.8)	97(33.8)	183(25.4)	
Other ethnic groups	27(2.7)	10(3.5)	17(2.4)	
Education level, n(%)				0.411
High school or below	383(38.0)	118(41.1)	265(36.8)	
Community college	326(32.4)	86(30.0)	240(33.3)	
College or higher	298(29.6)	83(28.9)	215(29.9)	
Income, n(%)				0.822
<5000	806(80.0)	231(80.5)	575(79.9)	
≥ 5000	201(20.0)	56(19.5)	145(20.1)	
Smoking, n(%)	13(1.3)	3(1.0)	10(1.4)	0.656
Drinking, n(%)	5(0.5)	2(0.7)	3(0.4)	0.581
History of PCOS, n (%)	38(3.8)	16(5.6)	22(3.1)	0.067
Obstetric history, n (%)				0.150
Primipara	666(66.1)	180(62.7)	486(67.5)	
Multipara	341(33.9)	107(37.3)	234(32.5)	
History of HDP, n(%)	12(1.2)	7(2.4)	5(0.7)	0.326
FPG ^{&} , mmol/L	4.42(4.17,4.69)	4.65(4.37,5.04)	4.37(4.10,4.58)	<0.001
1h-PPG ^{&} , mmol/L	8.40(7.17,9.49)	10.08(9.28,10.89)	7.84(6.70,8.75)	<0.001
2h-PPG ^{&} , mmol/L	7.01(6.09,8.26)	8.95(8.43,9.60)	6.55(5.82,7.27)	<0.001
* Mean ± SD				
^{&} Expressed as median (Q1-Q3),				
Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; PCOS:Polycystic Ovary Syndrome; HDP:Hypertensive Disorders of Pregnancy; FPG:Fasting Plasma Glucose; 1h- PPG:1-hour postprandial plasma glucose; 2h-PPG:2-hour postprandial plasma glucose.				

3.2 Dietary Polyamine and Nutrient Intake in Study Participants

The dietary polyamine, food category, and nutrient intakes of the study participants are presented in Table 2. The mean intake of dietary spermidine was 85.55 ± 54.17 $\mu\text{mol/day}$ in the GDM group and 81.97 ± 56.42 $\mu\text{mol/day}$ in the non-GDM group ($t = 0.919$, $P = 0.358$). The median (P25, P75) intakes of dietary spermine and putrescine were 24.80 (15.28, 38.10) and 161.12 (109.71, 229.45) $\mu\text{mol/day}$ in the GDM group, respectively, both slightly higher than those in the non-GDM group [21.26 (14.57, 36.18) and 149.05 (104.76, 228.94) $\mu\text{mol/day}$]; however, none of these differences reached statistical significance ($Z = 1.777$, $P = 0.076$; $Z = 1.596$, $P = 0.111$).

Table 2 Comparison of Diet and Nutrient Intake Among Study Participants

Variable	Total (n=1007)	GDM group (n=287)	Non-GDM group (n=720)	t/Z value	P value
Dietary Polyamines					
Dietary Spermidine, $\mu\text{mol/day}^*$	82.99 ± 55.79	85.55 ± 54.17	81.97 ± 56.42	0.919	0.358
Dietary Spermine, $\mu\text{mol/day}^\#$	22.47 (14.73, 36.80)	24.80 (15.28, 38.10)	21.26 (14.57, 36.18)	1.777	0.076
Dietary Putrescine, $\mu\text{mol/day}^\#$	153.63 (105.69, 229.08)	161.12 (109.71, 229.45)	149.05 (104.76, 228.94)	1.596	0.111
Food Category					
Grains, g/d*	375.91 ± 156.41	370.42 ± 145.83	378.09 ± 160.48	-0.702	0.483
Tubers, g/d [#]	56.70 (25.29, 104.96)	52.96 (24.91, 95.50)	57.66 (25.46, 106.65)	-1.071	0.284
Legumes, g/d [#]	64.25 (28.00, 151.25)	64.75 (26.25, 144.19)	64.25 (28.50, 152.00)	-0.033	0.974
Vegetables, g/d [#]	402.08 (253.46, 616.99)	425.19 (271.26, 648.89)	395.27 (251.36, 607.82)	1.579	0.114
Fruits, g/d [#]	196.40 (109.92, 306.80)	204.11 (119.01, 319.44)	191.83 (109.47, 304.46)	1.397	0.162
Nuts, g/d [#]	2.19 (0.44, 6.25)	2.19 (0.44, 6.25)	2.19 (0.44, 5.75)	-0.316	0.750
Meat, g/d [#]	107.00 (75.00, 171.00)	114.00 (78.07, 176.77)	100.00 (74.57, 169.51)	1.970	0.048
Dairy and Eggs, g/d [#]	211.38 (98.88, 258.75)	222.38 (114.75, 272.50)	206.12 (92.62, 254.69)	2.505	0.012
Seafood, g/d [#]	58.84 (30.40, 81.45)	61.70 (35.22, 83.04)	57.34 (28.26, 80.59)	1.802	0.072
Beverages, g/d [#]	8.75 (0.00, 31.50)	8.75 (0.00, 31.50)	8.75 (0.00, 29.75)	-0.147	0.880
Nutrient Intake					
Total Energy, Kcal/d*	2339.34 ± 895.19	2366.91 ± 827.74	2328.34 ± 921.02	0.617	0.537
Protein, g/d*	109.03 ± 50.44	111.86 ± 47.47	107.90 ± 51.57	1.124	0.261
Fat, g/d*	72.55 ± 30.25	74.32 ± 27.81	71.85 ± 31.16	1.173	0.241
Carbohydrates, g/d*	326.99 ± 138.95	327.32 ± 126.72	326.86 ± 143.62	0.048	0.962

* Normally distributed variables are expressed as mean ± SD; group comparisons were performed using independent samples t-test. # Non-normally distributed variables are expressed as median (P25, P75); group comparisons were performed using the Mann-Whitney U test (Z value). *P* < 0.05 indicates a statistically significant difference (values shown in bold). Abbreviations:GDM,gestational diabetes mellitus.

Regarding food intake, the GDM group consumed significantly higher amounts of meat [114.00 (78.07, 176.77) vs. 100.00 (74.57, 169.51) g/d, *Z* = 1.970, *P* = 0.048] and dairy/eggs [222.38 (114.75, 272.50) vs. 206.12 (92.62, 254.69) g/d, *Z* = 2.505, *P* = 0.012] than the non-GDM group, whereas no significant differences were observed for grains, tubers, legumes, vegetables, fruits, nuts, seafood, or beverages (all *P* > 0.05). Regarding nutrient intake, the GDM group exhibited slightly higher mean intakes of total energy (2366.91 ± 827.74 vs. 2328.34 ± 921.02 kcal/d, protein (111.86 ± 47.47 vs. 107.90 ± 51.57 g/d), fat (74.32 ± 27.81 vs. 71.85 ± 31.16 g/d), and carbohydrates (327.32 ± 126.72 vs. 326.86 ± 143.62 g/d) compared with the non-GDM group, with none of these differences being statistically significant (all *P* > 0.05).

3.3. Association Between Dietary Polyamine Intake and the Prevalence of GDM

The study included a total of 1,007 participants, of whom 287 were diagnosed with GDM, resulting in an overall prevalence of 28.5%. As dietary spermidine intake increased, the prevalence of GDM initially rose and then leveled off. A multivariate logistic regression model was used to analyze the association between dietary polyamine intake and the prevalence of GDM. Polyamine intake was grouped by quartiles, with the lowest quartile (Q1) serving as the reference group; the results are shown in Table 3.

Table 3

Logistic Regressions Investigating the Associations Between Dietary Polyamines and Gestational Diabetes

Spermidine, μmol/day	Case/N	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value	Model 3 OR (95% CI)	P value
Q1(≤ 39.27)	57(19.9)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(39.27, 64.22)	76(26.5)	1.47(0.99, 2.19)	0.059	1.48(0.99, 2.23)	0.059	1.52(1.00, 2.31)	0.049
Q3(64.22,112.35)	80(27.9)	1.57(1.06, 2.34)	0.025	1.62(1.07, 2.44)	0.021	1.73(1.09,2.75)	0.021
Q4(≥ 112.35)	74(25.8)	1.42(0.95, 2.13)	0.085	1.48(0.97, 2.27)	0.073	1.71(0.90, 3.26)	0.100
Spermine, μmol/day							
Q1(≤ 14.73)	62(21.6)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(14.73,22.47)	69(24.0)	1.16(0.78, 1.72)	0.477	1.13(0.75, 1.70)	0.552	1.17(0.77, 1.76)	0.469
Q3(22.47, 36.80)	77(26.8)	1.36(0.92, 2.01)	0.128	1.31(0.87, 1.98)	0.203	1.42(0.90, 2.23)	0.134
Q4(≥ 36.80)	79(27.5)	1.40(0.95, 2.07)	0.092	1.47(0.97, 2.25)	0.071	1.73(0.98, 3.03)	0.059
Putrescine, μmol/day							
Q1(≤ 105.69)	63(22.0)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(105.69,153.63)	65(22.6)	1.04(0.69, 1.55)	0.858	0.99(0.66, 1.50)	0.976	1.02(0.67, 1.54)	0.943
Q3(153.63,229.08)	86(30.0)	1.54(1.05, 2.26)	0.029	1.47(0.99, 2.18)	0.058	1.57(1.00, 2.46)	0.049
Q4(≥ 229.08)	73(25.4)	1.22(0.83,1.82)	0.316	1.28(0.83,1.95)	0.265	1.47(0.80,2.71)	0.215
Model 1: Unadjusted; Model 2: Adjusted for age, BMI, ethnicity, history of polycystic ovary syndrome, educational level, income,smoking,,alcohol consumption and obstetric history; Model 3: Adjusted for average daily total energy intake in addition to the factors in Model 2.							

Regarding the association between dietary spermidine and GDM, in the unadjusted model (Model 1), the odds of GDM in the Q3 group was 57% higher than in the Q1 group (OR = 1.57, 95% CI: 1.06–2.34, $P = 0.025$). After adjusting for confounding factors (Model 3), the odds of GDM in the Q2 and Q3 groups were 52% higher (OR = 1.52, 95% CI: 1.00–2.31, $P = 0.049$) and 73% higher (OR = 1.73, 95% CI: 1.09–2.75, $P = 0.021$), respectively, while the Q4 group had an OR of 1.71 (95% CI: 0.90–3.26, $P = 0.100$). The Q2 and Q3 findings were statistically significant, suggesting a significant positive correlation between dietary spermidine intake and the prevalence of GDM, with moderate-to-high intake significantly increasing the prevalence of GDM. Regarding dietary putrescine, in Model 3, the Q3 group had a 57% higher odds of GDM (OR = 1.57, 95% CI: 1.00–2.46, $P = 0.049$); however, no significant association was observed in either the Q2 or Q4 groups, and no clear dose-response trend was observed. However, no significant association was found between dietary spermine and GDM.

To further explore the dose-response relationship between dietary polyamines and GDM, this study employed a RCS regression model for analysis. After adjusting for all confounding factors, the results, as shown in Fig. 2, indicates that there is no significant nonlinear dose-response relationship between dietary polyamines and GDM (P -overall for spermidine = 0.094, P -nonlinear = 0.058).

3.4 Sensitivity Analysis

To verify the robustness of the results, a sensitivity analysis was conducted after excluding participants with a history of polycystic ovary syndrome. The results showed that the association between the dietary spermidine Q3 group and GDM remained significant after adjusting for confounding factors (Model 3) (OR = 1.90, 95% CI: 1.18–3.06, $P = 0.008$), and the effect size was stronger than in the main analysis. The trends in OR values for the dietary spermine subgroups were consistent with those in the main analysis but did not reach statistical significance. The association between dietary putramine Q3 and GDM remained significant in Model 3 (OR = 1.58, 95% CI: 1.00–2.49, $P = 0.048$). The results of the sensitivity analysis were generally consistent with those of the primary analysis, indicating that the findings of this study are robust.

4. Discussion

In this cross-sectional study of 1,007 Chinese pregnant women, we found that higher dietary intakes of spermidine and putrescine were significantly associated with an increased prevalence of GDM, particularly at moderate intake levels. No significant association was observed for spermine, and no clear dose-response relationship was identified for any of the three polyamines. Sensitivity analyses confirmed the robustness of these findings.

To our knowledge, this is the first study to examine the association between dietary polyamines and GDM. The positive association between spermidine and GDM is consistent with a recent UK Biobank prospective cohort study ($n = 168,137$), which reported that dietary spermidine and putrescine intake was positively associated with incident type 2 diabetes mellitus in the general population^[15]. Notably, a nested case-control study from Beijing (47 GDM cases vs. 47 controls) demonstrated that maternal serum putrescine levels in the first trimester were significantly elevated in women who subsequently developed GDM, with a single putrescine measurement achieving an area under the curve (AUC) of 0.904 for predicting GDM^[22, 23]. These complementary lines of evidence—linking both dietary intake and circulating levels of putrescine to adverse glycemic outcomes—strengthen the biological plausibility of our findings. Furthermore, a Mendelian randomization analysis incorporating 13,039 GDM cases and 197,831 controls identified the spermidine/spermine biosynthesis pathway as causally associated with GDM risk, providing genetic evidence supporting a causal role of polyamine metabolism in GDM pathogenesis^[24]. Experimental studies have demonstrated that polyamines play essential roles in pancreatic β -cell proliferation and insulin secretion^[11], and animal models have revealed a dual role of polyamines^[25]—being both necessary for normal β -cell function and detrimental under inflammatory conditions^[26]. This context-dependent nature of polyamine biology underscores the value of population-based investigations.

Several mechanisms may explain our findings. Spermidine serves as the sole aminobutyl donor for hypusine modification of eukaryotic translation initiation factor 5A (eIF5A), a post-translational modification essential for translating mRNAs associated with cellular stress and inflammation^[27]. Under the chronic low-grade inflammatory state of pregnancy, excessive polyamine availability may dysregulate this pathway, impairing β -cell compensatory capacity^[28]. Indeed, dysregulation of the polyamine-hypusine circuit in β -cells has been implicated in diabetes pathogenesis under inflammatory conditions^[29]. Polyamines also modulate insulin signaling through the PI3K/Akt pathway in a concentration-dependent manner, with supraphysiological levels potentially impairing GLUT4 translocation via oxidative stress^[10]. Additionally, gut microbiota represent a major source of colonic polyamines^[30], and metabolomics studies have revealed that fecal putrescine abundance is significantly altered in women with GDM, suggesting that host-microbe interactions may mediate the metabolic effects of dietary polyamines^[13, 28]. The polyamine catabolic pathway generates hydrogen peroxide, contributing to oxidative stress and systemic inflammation^[11]. The differential effect observed—significant for spermidine and putrescine but not spermine—may

reflect distinct metabolic roles and bioavailability. Spermidine is directly linked to hypusine formation, whereas spermine may be subject to tighter homeostatic regulation or more rapid catabolism ^[10].

The absence of a clear dose-response relationship in our restricted cubic spline analysis, coupled with the finding that the odds increase was significant only in the Q3 group and attenuated in Q4, suggests a threshold-like rather than linear pattern. This may reflect tight homeostatic regulation of intracellular polyamine levels through feedback inhibition of ornithine decarboxylase—the rate-limiting enzyme in polyamine biosynthesis—and induction of antizyme, which promotes polyamine degradation and export ^[11]. The "polyamine paradox"—where both deficiency and excess are detrimental—underscores the importance of maintaining polyamine levels within a narrow physiological window ^[12]. Additionally, the Q4 group may include individuals with differential absorption or metabolism of dietary polyamines, contributing to the plateauing of the effect.

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes determination of temporal sequence and causal inference. Second, dietary intake assessed via FFQ captured only the preceding month, which may not fully represent the critical exposure window for GDM development ^[17]. Third, we cannot rule out residual confounding effects from unmeasured factors, such as genetic variations in polyamine-metabolizing enzymes ^[8, 9, 31]. Fourth, the single-center population in Hainan Province, China, may limit generalizability to other populations. Additionally, the lack of circulating polyamine measurements precluded examination of the correlation between dietary intake and physiological exposure. Despite these limitations, the present study has notable strengths. First, to our knowledge, this is the first study to investigate the association between dietary polyamines and GDM. Second, a validated FFQ was administered via face-to-face interviews by trained personnel. Finally, UPLC-MS/MS was employed for accurate polyamine quantification, comprehensive confounder adjustment was performed, and robust sensitivity analyses confirmed the stability of our findings.

5. Conclusion

In summary, dietary spermidine and putrescine intake were significantly positively associated with the prevalence of gestational diabetes, with a marked increase in prevalence observed particularly at moderate intake levels; no statistically significant association was found between dietary spermine and GDM, and no clear dose-response trend was observed for any of these compounds. These findings suggest that dietary polyamines, particularly spermidine, may play an important role in the regulation of glucose metabolism during pregnancy. However, given the cross-sectional nature of this study, further research and mechanistic experiments are needed to clarify the causal relationship between dietary polyamines and GDM, as well as its potential biological mechanisms.

Abbreviations

AUC

Area Under the Curve

BMI

Body mass index

CI

Confidence interval

Food frequency questionnaire

FPG

Fasting plasma glucose

GDM

Gestational diabetes mellitus

HDP

Hypertensive disorders of pregnancy

OGTT

Oral glucose tolerance test

OR

Odds ratio

PCOS

Polycystic ovary syndrome

PPG

Postprandial plasma glucose

RCS

Restricted cubic spline

SD

Standard deviation

T2DM

Type 2 diabetes mellitus

UPLC-MS/MS

Ultra-high-performance liquid chromatography–tandem mass spectrometry

Declarations

Authors contributions

Tianru Mei completed the statistical analysis and co-authored the manuscript with Yiting Song; Rui Zhang systematically searched the literature and screened articles; Xinyu Deng, Dan Wang, Min Song, Yan Wang, and Wenqian Ji collected the data; Xuchen Yang, Yifei Shao, and Sihan Jing assessed the quality of the studies; Liqiang Zheng and Rennan Feng designed the study and critically revised the manuscript to enhance its academic substance. All authors read and approved the final version of the manuscript.

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Institutional Review Board Statement

This project was approved by the Ethics Committee of Hainan Hospital, Shanghai Children's Medical Center, affiliated with Shanghai Jiao Tong University School of Medicine, on July 18, 2024 (Approval No.: SYFYIRB2024078). All research procedures were carried out following the ethical principles for medical research involving human subjects outlined in the Declaration of Helsinki.

Informed Consent Statement

All participants signed informed consent forms.

Data Availability Statement

The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

Acknowledgements

Not applicable.

Conflicts of Interest

There are no conflicts of interest.

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Figures

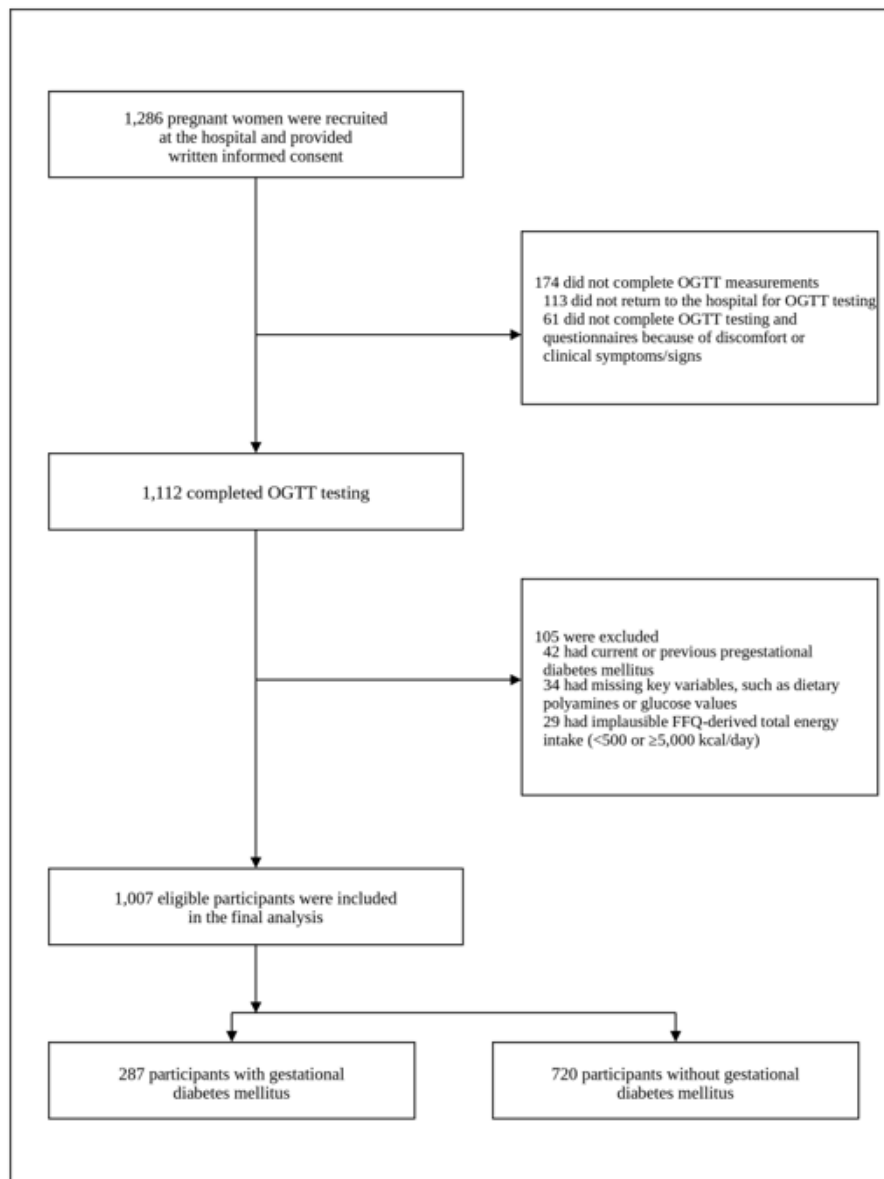


Figure 1

Flow chart of included and excluded study population

Abbreviations: OGTT, Oral Glucose Tolerance Test; FFQ, food frequency questionnaire.

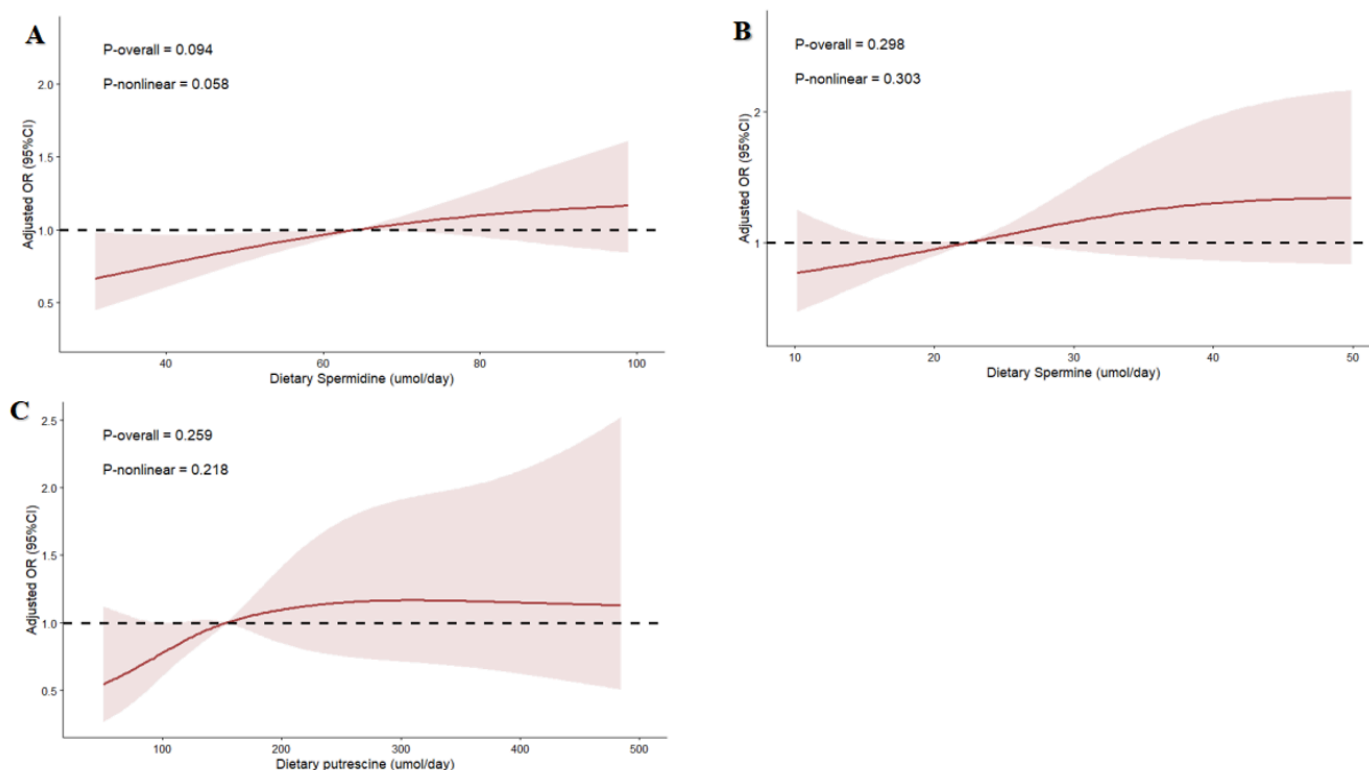


Figure 2

Relationship between dietary polyamines and gestational diabetes using restricted cubic splines.

The multivariate-adjusted odds ratio (OR) and 95% confidence interval (CI) were obtained using restricted cubic splines. The solid red line represents the multivariate-adjusted OR, and the red shaded area represents the 95% CI. The model was adjusted for factors including age, body mass index, ethnicity, education level, income, parity, history of polycystic ovary syndrome, smoking, alcohol consumption, and total daily energy intake. OR, odds ratio; CI, confidence interval. ...