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Maternal dietary pattern characterised by high protein and low carbohydrate intake in pregnancy is associated with a higher risk of gestational diabetes mellitus in Chinese women: a prospective cohort study

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Abstract

Maternal dietary patterns and macronutrients intake have been shown to affect the development of gestational diabetes mellitus (GDM), but the findings are inconsistent. We aimed to identify maternal dietary patterns and examine their associations with GDM risk, and to evaluate the contributions of macronutrients intake to these associations. We included 2755 Chinese pregnant women from the Tongji Maternal and Child Health Cohort. Dietary intakes were assessed using a validated semi-quantitative FFQ 2 weeks before the diagnosis of GDM. GDM (*n* 248) was diagnosed based on the results of a 75-g, 2-h oral glucose tolerance test at 24–28 weeks gestation. We derived five different dietary patterns from a principal component analysis. The results showed that high fish–meat–eggs scores, which were positively related to protein intake and inversely related to carbohydrate intake, were associated with a higher risk of GDM (adjusted OR for quartile 4 *v.* quartile 1: 1·83; 95 % CI 1·21, 2·79; $P_{trend} = 0{\cdot}007$) and higher plasma glucose levels. In contrast, high rice–wheat–fruits scores, which were positively related to carbohydrate intake and inversely related to protein intake, were associated with lower risk of GDM (adjusted OR for quartile 3 *v.* quartile 1: 0·54; 95 % CI 0·36, 0·83; $P_{trend} = 0{\cdot}010$) and lower plasma glucose levels. In addition, dietary protein and carbohydrate intake significantly contributed to the associations between dietary patterns and GDM risk or glucose levels. These findings suggest that a dietary pattern characterised by high protein and low carbohydrate intake in pregnancy was associated with a higher risk of GDM, which may provide important clues for dietary guidance during pregnancy to prevent GDM.

Key words: Dietary patterns: Gestational diabetes mellitus: Plasma glucose: Macronutrients

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, is a common pregnancy complication. GDM reflects a continuum risk of short-term and long-term adverse health outcomes for both mothers and their offspring(1–4). During past decades, its prevalence has increased substantially across a range of multiethnic populations. In China, approximately 10 % of all pregnancies have been reported to be complicated by GDM(5–7).

Maternal diet plays an important role in the development of GDM(8–14). In addition to individual nutrients and specific food groups, such as cholesterol, saturated and trans fats, haem Fe, red and processed meats, several dietary patterns have been identified to be linked to GDM risk(15–21). Only a few studies have examined the association between dietary patterns during pregnancy and risk of GDM(17–21). Results from these studies provided an evidence base for dietary recommendation to prevent GDM, but the findings were compromised by either relatively small sample size(17,18) or variance in study design(19), dietary assessment tools(20,21) and diagnostic criteria for GDM(20,21).

Composition and quality of macronutrients may contribute to the association between dietary patterns and development of GDM. Dietary patterns associated with reduced risk of GDM are

Abbreviations: GDM, gestational diabetes mellitus; NHSII, Nurses' Health Study II; OGTT, oral glucose tolerance test; TMCHC, Tongji Maternal and Child Health Cohort.

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often characterised by high consumption of carbohydrates, mainly complex ones, and low consumption of animal protein and animal fat[18,19,21]. However, there are only a limited number of studies on this issue and the results are inconclusive. Take protein for example, results from a multiethnic Asian cohort suggested that higher intakes of both animal and vegetable protein during pregnancy were associated with a higher risk of GDM[22], in contrast with the findings from the cohort of US nurses, which showed that among women of reproductive age, substitution of vegetable protein for animal protein may potentially lower GDM risk[23].

Therefore, the aim of this study was to identify maternal dietary patterns and examine their associations with GDM using data from a large prospective cohort of pregnant women in central China, furthermore, to evaluate the contributions of macronutrients intake to the associations between dietary patterns and GDM risk.

Methods

Study design

The Tongji Maternal and Child Health Cohort (TMCHC) study is an ongoing population-based prospective cohort to investigate the association between maternal diet and the health outcomes of mother and offspring[24]. The TMCHC study was established in January 2013 and enrolled healthy pregnant women at 8–16 weeks of gestation when they attended their first antenatal visit at a maternity clinic in one of three public hospitals in Wuhan, China. We included TMCHC participants in this analysis if they reported a singleton pregnancy, completed an oral glucose tolerance test (OGTT), and completed the FFQ before their OGTT. Women who developed GDM in a previous pregnancy or had a previous diagnosis of type 2 diabetes or whose fasting plasma glucose value in this early pregnancy ≥5·1 mmol/l were excluded because they may have changed their diets and lifestyles to prevent a recurrence of GDM[13]. Finally, a total of 2755 women were included in the analysis from September 2013 to May 2016 (online Supplementary Fig. S1). This study was approved by the ethics review committee of Tongji Medical College, Huazhong University of Science and Technology. All participants gave informed written consent upon recruitment. This study was registered at clinicaltrials.gov as NCT03099837.

Dietary assessment

The participants reported their dietary intakes during the past 4 weeks using a semi-quantitative FFQ, and completed FFQ 2 weeks before the diagnosis of GDM. The FFQ was validated in a subsample of TMCHC cohort participants, showing that it is a reasonably reliable and valid tool for assessing most food and nutrient intakes of pregnant women in urban areas of central China[24]. The FFQ consisted of sixty-one food items based on the food nutrient composition and eating habits of Chinese individuals, covering more than 200 kinds of food. For each item, trained interviewers conducted face-to-face interviews, the participants were asked to recall the frequency of intake and portion size consumed during the past 4 weeks. To reduce the influence of food intakes with large variances at the expense of those with minor variances[25], we standardised the sixty-one food items and assembled them into sixteen non-overlapping food groups: rice and wheat products, whole grains, poultry, red meat, animal organs and blood, freshwater fish, seafood, eggs, beans and bean products, leafy and cruciferous vegetables, root vegetables, melons and solanaceous vegetables, mushrooms and algae, fruits, nuts, and dairy products. Daily intakes of nutrient and energy were calculated based on the continuously updated China Food Composition Database[26], and each energy-yielding macronutrient intake was expressed as the percentage of total energy intake using the nutrient-density method[14,27].

Ascertainment of gestational diabetes mellitus

The primary outcome was GDM. At 24–28 weeks, participants were routinely offered 75 g, 2-h OGTT. All participants had overnight fasting of at least 8 h before OGTT. Fasting plasma glucose and 1- and 2-h post-load plasma glucose levels were measured by enzymatic assays using an automated biochemical analyser. GDM was diagnosed when any of the glucose values during the diagnostic OGTT met or exceeded the criteria as recommended by the International Association of Diabetes and Pregnancy Study Group: fasting plasma glucose ≥5·1 mmol/l or 1-h plasma glucose ≥10·0 mmol/l or 2-h plasma glucose ≥8·5 mmol/l[28].

Covariates

Covariates were assessed using a structured questionnaire at the enrollment interview. Maternal age (in years) was treated as a continuous variable, except for the descriptive statistics for which we divided age into four groups (≤24, 25–29, 30–35 and ≥36). Ethnicity was divided into two categories (Han Chinese, others). Educational attainment was recorded as the number of completed years of schooling and divided into four categories (≤9, 10–12, 13–15 and ≥16). Average personal income (per month, Chinese Yuan) was divided into five categories (≤1000, 1001–2999, 3000–4999, 5000–9999 and ≥10000). Pre-pregnancy BMI (kg/m^2), which was calculated from self-reported pre-pregnancy weight[29] and measured height, was divided into four categories (<18·5, 18·5–23·9, 24·0–27·9 and ≥28·0) according to the Chinese BMI cutoffs[30]. Gestational weight gains before GDM diagnosis were calculated by subtracting self-reported pre-pregnancy weights from weights measured at OGTT test. Parity were each divided into two categories (0, ≥1). The other covariates, including smoking habits, alcohol consumption habits, family history of diabetes and family history of obesity, were treated as dichotomised variables (yes/no).

Statistical analysis

Principal component analysis with varimax rotation was used to derive the dietary patterns[15,31]. Sensitivity analyses were performed to review the reproducibility and stability of the pattern extraction. Principal component analysis is a data-driven technique that reduces the dimensions of the data and groups correlated variables to identify common factors (i.e. dietary patterns) underlying food consumption[25,31,32]. A total of five factors were determined in this study, and the number of factors retained was based on the eigenvalue, factor interpretability after varimax rotation and a scree plot showing the proportion of the variance of total consumption of the food variables[15,25,33]. The dietary pattern score for each participant was calculated by summing the standardised frequency of food groups weighted by their factor loadings. Each woman received a factor score for each identified pattern, the mean factor score for each pattern is zero, and higher dietary pattern scores indicate greater adherence to the derived pattern[15]. We used dietary pattern scores to rank participants according to the degree to which they conformed to each dietary pattern, and divided dietary pattern scores into quartiles for further analysis. In this study, the food items with loadings of 0·40 or higher on a factor were considered important to the interpretability of each pattern.

The OR and 95 % CI of GDM for each category of dietary pattern compared with the lowest category were estimated using logistic regression models. In addition, the OR and 95 % CI of GDM associated with per SD increment in the dietary pattern scores were also calculated. Stratified analyses were conducted by BMI (<18·5/18·5–23·9/ ≥24·0) and family history of diabetes (yes/no), and other covariates mentioned above were also considered in additional stratified analyses (data not shown). Multivariate linear regression models were estimated to assess the association between dietary patterns and plasma glucose levels. To explore potential dietary contributors for the association between dietary patterns and GDM, we adjusted for macronutrients (e.g. total fat, animal fat, vegetable fat, total protein, animal protein, vegetable protein, total carbohydrate and ratio of total protein to total carbohydrate), other nutrients (e.g. dietary fibre, cholesterol, vitamin C, vitamin E, Mg, K, Ca, total Fe, haem Fe and non-haem Fe), and each food or food group component of each dietary pattern.

Comparisons between groups were performed using χ^2 tests for categorical variables, ANOVA or t tests for continuous variables with normal distribution, or non-parametric Mann–Whitney and Kruskal–Wallis tests for continuous variables with skewed distributions. Frequencies and percentages were used to describe the distributions of categorical variables, and the means and standard deviations were used to describe the distribution of continuous variables. To quantify a linear trend, we assigned the median value for each category and treat the median values as continuous variable in the logistic regression model. All tests of statistical significance were two-sided, and $P < 0·05$ was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM Corporation). All data collected were double entered into the EpiData software program[24].

Results

Dietary patterns

In all, five distinct dietary patterns with eigenvalues above 1·0, as well as factor loadings above 0·40, were extracted from the scree plot (Table 1, online Supplementary Fig. S2). These five patterns accounted for 45·6 % of the total variation in food frequency intakes. The first pattern, beans–vegetables, included higher intakes of root vegetables, melons and solanaceous vegetables, mushrooms and algae, beans and bean products (soyabean, mung bean, soyabean milk), and leafy and cruciferous vegetables. The second pattern, nuts–whole grains, had higher intakes of nuts, whole grains and dairy products (milk, milk powder and yogurt). The third pattern, organs–poultry–seafood, had higher intakes of animal organs, blood, seafood and poultry. The fourth pattern, fish–meat–eggs, had higher

Table 1. Factor loading matrix for the five major dietary patterns identified by principal component analysis using varimax rotation in Tongji Maternal and Child Health Cohort study (*n* 2755)*

	Dietary patterns				
Food groups	Beans–vegetables	Nuts–whole grains	Organs–poultry–seafood	Fish–meat–eggs	Rice–wheat–fruits
Root vegetables	0·71	–	–	–	–
Melon and solanaceous vegetables	0·60	–	–	–	–
Mushrooms and algae	0·59	–	–	–	–
Beans and bean products†	0·54	–	–	–	–
Leafy and cruciferous vegetables	0·42	–	–	–	–
Nuts	–	0·70	–	–	–
Whole grains	–	0·55	–	–	–
Dairy products‡	–	0·45	–	–	–
Animal organs and blood	–	–	0·67	–	–
Seafood	–	–	0·61	–	–
Poultry	–	–	0·60	–	–
Freshwater fishes	–	–	–	0·63	–
Red meat	–	–	–	0·62	–
Eggs	–	–	–	0·59	–
Rice and wheat products	–	–	–	–	0·82
Fruits	–	–	–	–	0·56
Cumulative variance explained (%)§	12·0	21·0	29·9	38·6	45·6

* Values are factor loadings (correlation coefficients) between each food frequency variable and the dietary pattern derived from principal component analysis. Food groups are sorted by size of loading coefficients. Absolute values <0·40 were not listed for simplicity.
† Soyabean, mung bean, soyabean milk, bean curd, and so on.
‡ Milk, milk powder and yogurt.
§ Percentage of variance in total food intake explained by patterns.

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intakes of freshwater fishes, red meat and eggs. The fifth pattern, rice–wheat–fruits, had higher intakes of rice, wheat products and fruits.

Dietary patterns in relation to maternal characteristics

The characteristics of the participants are presented in Table 2. We observed that the beans–vegetables pattern score increased with education level and was higher in women with a family history of obesity, in non-smokers and in multiparous women, while the score was lower in the young (≤24 years) and older (≥36 years) age groups. The nuts–whole grains score increased with maternal age, education level and average personal income, while the score was lower in smokers, in women who habitually consumed alcohol, and in multiparous women. The organs–poultry–seafood pattern scores increased with education level and decreased with increasing pre-pregnancy BMI and were higher in women who consumed alcohol. The fish–meat–eggs pattern score was higher in the few (≤9 years) and high (≥16 years) education groups. The rice–wheat–fruits pattern score was lower in the older age groups, in women with a family history of diabetes, and decreased with increasing pre-pregnancy BMI.

We also analysed the characteristics of the 2755 women according to the quartile of the dietary pattern score and obtained similar results (online Supplementary Table S3).

Dietary patterns in relation to gestational diabetes mellitus

GDM occurred in 248 (9·0 %) of 2755 pregnant women. For the fish–meat–eggs pattern, the adjusted OR for the highest quartile compared with the lowest was 1·83 (95 % CI 1·21, 2·79; P_{trend} = 0·007); each SD of fish–meat–eggs score was associated with a 32 (95 % CI 12, 54) % increment in OR of GDM. For the rice–wheat–fruits dietary pattern, we found that the adjusted OR for the third quartile compared with the lowest was 0·54 (95 % CI 0·36, 0·83; P_{trend} = 0·010); each SD of rice–wheat–fruits score was associated with a 22 (95 % CI 12, 32) % decrement in OR of GDM. No associations were seen for the beans–vegetables, nuts–whole grains or organs–poultry–seafood patterns in relation to GDM (Table 3).

We performed stratified analyses according to the pre-pregnancy BMI (<18·5/18·5–23·9/ ≥ 24·0) and the family history of diabetes (yes/no). We found that in the high BMI (≥24·0) group, a high fish–meat–eggs score was associated with a significantly increased risk of GDM for the highest quartile *v.* the lowest quartile (2·84, 95 % CI 1·03, 7·80; P_{trend} = 0·021), and each SD of the fish–meat–eggs score was associated with a 62 (95 % CI 12, 134) % increment in OR of GDM, while for rice–wheat–fruits dietary pattern, no significant association was observed in the high BMI (≥24·0) group (online Supplementary Table S4). Similarly results were obtained in women with a family history of diabetes: the positive association between fish–meat–eggs pattern and the risk of GDM was stronger, while for rice–wheat–fruits dietary pattern, no significant association was observed in women with a family history of diabetes (online Supplementary Table S4).

Online Supplementary Table S5 shows participants' macronutrient intakes according to the quartiles of dietary pattern scores. The fish–meat–eggs pattern was positively associated with a high intake of energy content from total protein, animal protein, total fat, animal fat and a high ratio of total protein to total carbohydrate, while inversely associated with a high intake of energy content from carbohydrate, vegetable protein and vegetable fat. In addition, we also observed that the rice–wheat–fruits score was positively related to the intake of energy content from carbohydrate, while being inversely related to intake of energy content from total protein, animal protein, vegetable protein, total fat, vegetable fat and ratio of total protein to total carbohydrate.

We further investigated the contributions of energy-yielding macronutrients on the association between dietary patterns and risk of GDM (Table 4). Total carbohydrate intake was inversely associated with risk of GDM, while total fat, animal fat, total protein, animal protein intake and ratio of total protein to total carbohydrate were positively associated with risk of GDM. The association of the fish–meat–eggs score with GDM risk for comparisons of highest with lowest quartiles was no longer significant after additional adjustment for total protein (percentage of energy) (OR 1·42; 95 % CI 0·90, 2·22), or animal protein (percentage of energy) (OR 1·51; 95 % CI 0·94, 2·44), or total carbohydrate (percentage of energy) (OR 1·48; 95 % CI 0·92, 2·36), or ratio of total protein to total carbohydrate (OR 1·35; 95 % CI 0·84, 2·16), which indicated that protein and carbohydrate may be the main contributors to the observed association between the fish–meat–eggs score and GDM risk. Moreover, for the rice–wheat–fruits dietary pattern, the association with GDM was attenuated substantially after adjusting for total protein intake and ratio of total protein to total carbohydrate, respectively.

In addition, we performed similar analyses for both dietary patterns score by adjusting for other nutrients (e.g. dietary fibre, cholesterol, vitamin C, vitamin E, Mg, K, Ca, total Fe, haem Fe and non-haem Fe), and each food or food group component of each dietary pattern. However, these adjustments, except for cholesterol and fruits, did not substantially alter the association.

Dietary patterns in relation to plasma glucose levels

Multivariate linear regression models were constructed to assess the association of dietary patterns with plasma glucose levels in Table 5. The adjusted results showed that per SD increase in the fish–meat–eggs score, the fasting, 1-h and 2-h plasma glucose reading increased by 0·018 mmol/l (95 % CI 0·004, 0·033), 0·136 mmol/l (95 % CI 0·077, 0·195) and 0·074 mmol/l (95 % CI 0·028, 0·120), respectively. With an SD increase in the rice–wheat–fruits score, fasting, 1-h and 2-h plasma glucose decreased by 0·014 mmol/l (95 % CI −0·028, −0·001), 0·100 mmol/l (95 % CI −0·158, −0·042) and 0·093 mmol/l (95 % CI −0·137, −0·048), respectively.

An inverse association was found between plasma glucose levels and total carbohydrate intake, and a positive association was found between plasma glucose levels and total fat, animal fat, total protein, animal protein intake and ratio of total protein to total carbohydrate, respectively. For both dietary patterns, the association with fasting plasma glucose was attenuated

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Table 2. Dietary pattern scores, according to maternal characteristics, in 2755 participants in Tongji Maternal and Child Health Cohort study*
(Numbers and percentages; mean values and standard deviations)

	All participants		Dietary patterns: Beans–vegetables		Nuts–whole grains		Organs–poultry–seafood		Fish–meat–eggs		Rice–wheat–fruits	
Characteristics	*n*	%	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at enrollment (years)												
17–24	311	11·3	−0·17	0·99	−0·16	0·93	−0·19	0·97	−0·01	1·11	0·14	1·05
25–29	1641	59·6	0·00	0·99	0·00	0·98	0·02	0·99	−0·03	0·99	0·02	0·98
30–35	691	25·1	0·09	0·99	0·04	1·05	0·05	1·03	0·06	0·95	−0·11	1·05
36–45	112	4·0	−0·12	1·12	0·26	1·07	−0·05	0·95	0·12	1·04	−0·07	0·73
P	–		0·001		<0·001		0·004		0·146		0·001	
Ethnicity												
Han Chinese	2682	97·4	0·00	1·00	0·00	1·00	0·00	1·00	0·00	1·00	0·00	1·01
Others	73	2·6	0·18	1·00	0·00	0·90	−0·16	1·02	0·12	0·96	0·06	0·62
P	–		0·123		0·979		0·172		0·315		0·632	
Education level (schooling years)												
≤9	79	2·9	−0·39	1·05	−0·47	1·04	−0·39	0·81	0·05	1·13	0·03	1·03
10–12	317	11·5	−0·18	0·98	−0·30	1·11	−0·25	0·97	0·01	1·10	−0·07	1·43
13–15	710	25·7	−0·06	1·05	−0·12	1·00	0·00	1·00	−0·11	1·04	0·08	0·80
≥16	1589	57·7	0·09	0·96	0·13	0·95	0·07	1·01	0·05	0·95	−0·03	0·98
Missing	60	2·2	−0·32	1·00	0·19	0·87	−0·09	0·90	−0·14	0·97	0·10	0·87
P	–		<0·001		<0·001		<0·001		0·005		0·087	
Average personal income (CNY†)												
≤1000	10	0·4	0·24	0·83	−0·27	1·00	0·02	1·11	−0·58	1·06	0·23	0·41
1001–2999	174	6·3	−0·09	0·97	−0·20	1·06	−0·05	0·96	−0·11	1·11	−0·09	1·21
3000–4999	853	31·0	−0·12	1·03	−0·06	1·00	−0·03	1·01	−0·01	0·98	0·01	1·09
5000–9999	1155	41·9	0·05	0·99	0·05	0·98	−0·02	0·99	−0·01	1·00	−0·01	0·97
≥10 000	512	18·6	0·15	0·94	0·06	1·00	0·12	1·00	0·08	0·96	0·04	0·67
Missing	51	1·8	−0·41	1·07	0·00	1·04	−0·09	1·15	0·04	1·08	−0·12	1·80
P	–		<0·001		0·009		0·101		0·111		0·595	
Family history of diabetes												
Yes	236	8·6	−0·04	0·98	0·11	0·98	−0·05	1·04	0·08	1·07	−0·24	1·76
No	2467	89·5	0·01	1·00	−0·01	1·00	0·01	1·00	0·00	0·99	0·02	0·90
Missing	52	1·9	−0·20	1·25	−0·05	0·86	−0·06	0·89	−0·24	1·05	0·09	0·65
P	–		0·283		0·201		0·657		0·100		<0·001	
Family history of obesity												
Yes	47	1·7	0·19	0·95	−0·18	1·12	0·03	0·96	−0·02	1·09	−0·11	0·89
No	2641	95·9	0·01	1·00	0·00	1·00	0·00	1·00	0·00	1·00	0·00	1·01
Missing	67	2·4	−0·37	1·15	−0·01	0·92	−0·21	0·91	−0·03	1·08	0·03	0·83
P	–		0·004		0·461		0·222		0·948		0·713	
Smoking												
Yes	449	16·3	−0·11	1·02	−0·14	1·03	0·01	1·05	−0·04	1·05	0·00	0·90
No	2306	83·7	0·02	0·99	0·03	0·99	0·00	0·99	0·01	0·99	0·00	1·02
P	–		0·009		0·001		0·752		0·307		0·918	
Alcohol												
Yes	409	14·8	0·02	0·94	−0·11	0·94	0·10	0·97	−0·06	1·02	−0·04	1·07
No	2346	85·2	0·00	1·01	0·02	1·01	−0·02	1·00	0·01	1·00	0·01	0·99
P	–		0·592		0·012		0·024		0·156		0·403	
Parity‡												
0	2331	84·6	−0·02	1·00	0·04	0·98	−0·01	1·00	−0·02	1·00	0·00	1·04
≥1	424	15·4	0·12	0·99	−0·20	1·07	0·04	1·01	0·09	0·99	−0·02	0·77
P	–		0·009		<0·001		0·428		0·055		0·661	
Pre-pregnancy BMI (kg/m²)												
<18·5	523	19·0	−0·06	0·98	0·03	0·97	0·06	1·01	−0·01	1·02	0·16	0·65
18·5–23·9	1920	69·7	0·02	0·99	−0·01	0·99	0·01	1·00	0·02	0·97	−0·02	1·07
24·0–27·9	271	9·8	0·00	1·03	0·02	1·09	−0·16	0·97	−0·10	1·09	−0·10	1·03
≥28·0	41	1·5	−0·05	1·24	−0·13	1·03	−0·20	0·84	0·03	1·31	−0·25	0·72
P	–		0·449		0·717		0·016		0·329		<0·001	

CNY, Chinese Yuan.
* Dietary pattern scores created by multiplying factor loadings by corresponding standardised value for frequency intake of each food and adding all these items. Values are mean factor scores, derived by extraction of five dietary factors. Not adjusted for confounders.
† 1 CNY = 0·16 US dollars.
‡ Value 0 means never given birth before.

substantially and was not statistically significant after adjusting for total protein, animal protein, total carbohydrate intake and ratio of total protein to total carbohydrate. No large or statistically significant changes of β (95 %) with 1- and 2-h plasma glucose after adjusting for any macronutrient intake for both dietary patterns were observed.

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Table 3. Dietary pattern scores associated with gestational diabetes mellitus (GDM) (*n* 2755)*†
(Odds ratios and 95 % confidence intervals; numbers and percentages; mean values, minimum and maximum values)

	Quartiles of dietary pattern scores											
	Q1		Q2		Q3		Q4			Per SD increase		
Dietary patterns	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	$P_{for\ trend}$	OR	95 % CI	*P*
Beans–vegetables												
GDM												
n	71		46		71		60					
%	10·3		6·7		10·3		8·7					
Mean	−1·29		−0·30		0·37		1·23					
Min, max	−4·03, −0·66		−0·66, 0·04		0·04, 0·70		0·70, 3·72					
Model 1	1	Ref.	0·62	0·42, 0·92	1·00	0·71, 1·41	0·83	0·58, 1·19	0·731	0·98	0·86, 1·12	0·747
Model 2	1	Ref.	0·63	0·43, 0·94	1·03	0·73, 1·47	0·84	0·58, 1·21	0·847	1·00	0·87, 1·14	0·940
Model 3	1	Ref.	0·68	0·44, 1·04	1·15	0·78, 1·68	0·97	0·64, 1·46	0·649	1·04	0·90, 1·21	0·592
Nuts–whole grains												
GDM												
n	68		51		55		74					
%	9·9		7·4		8·0		10·7					
Mean	−1·33		−0·28		0·40		1·20					
Min, max	−5·00, −0·65		−0·65, 0·09		0·09, 0·72		0·72, 3·06					
Model 1	1	Ref.	0·73	0·50, 1·07	0·79	0·55, 1·15	1·10	0·78, 1·55	0·595	1·04	0·91, 1·18	0·593
Model 2	1	Ref.	0·77	0·53, 1·13	0·84	0·58, 1·22	1·14	0·80, 1·61	0·419	1·06	0·93, 1·21	0·353
Model 3	1	Ref.	0·83	0·55, 1·26	0·89	0·59, 1·35	1·25	0·84, 1·86	0·308	1·09	0·94, 1·26	0·245
Organs–poultry–seafood												
GDM												
n	72		61		54		61					
%	10·5		8·9		7·8		8·9					
Mean	−1·24		−0·38		0·29		1·32					
Min, max	−2·53, −0·73		−0·73, −0·05		−0·05, 0·66		0·66, 3·68					
Model 1	1	Ref.	0·83	0·58, 1·19	0·73	0·50, 1·05	0·83	0·58, 1·19	0·260	0·94	0·82, 1·07	0·329
Model 2	1	Ref.	0·84	0·59, 1·21	0·73	0·50, 1·05	0·86	0·60, 1·23	0·328	0·95	0·83, 1·08	0·430
Model 3	1	Ref.	0·93	0·63, 1·39	0·84	0·57, 1·26	1·01	0·68, 1·51	0·918	1·01	0·87, 1·17	0·900
Fish–meat–eggs												
GDM												
n	53		56		60		79					
%	7·7		8·1		8·7		11·5					
Mean	−1·31		−0·24		0·36		1·19					
Min, max	−4·51, −0·60		−0·60, 0·07		0·07, 0·66		0·66, 3·22					
Model 1	1	Ref.	1·06	0·72, 1·57	1·15	0·78, 1·68	1·55	1·08, 2·24	0·018	1·22	1·07, 1·40	0·003
Model 2	1	Ref.	1·02	0·69, 1·52	1·11	0·75, 1·64	1·51	1·05, 2·18	0·026	1·22	1·06, 1·39	0·005
Model 3	1	Ref.	1·22	0·80, 1·88	1·25	0·81, 1·92	1·83	1·21, 2·79	0·007	1·32	1·12, 1·54	0·001
Rice–wheat–fruits												
GDM												
n	82		69		46		51					
%	11·9		10·0		6·7		7·4					
Mean	−1·02		−0·01		0·33		0·69					
Min, max	−19·91, −0·24		−0·24, 0·20		0·20, 0·47		0·47, 1·69					
Model 1	1	Ref.	0·83	0·59, 1·16	0·53	0·36, 0·77	0·59	0·41, 0·85	<0·001	0·77	0·70, 0·86	<0·001
Model 2	1	Ref.	0·82	0·58, 1·15	0·52	0·35, 0·76	0·60	0·41, 0·86	0·001	0·77	0·69, 0·85	<0·001
Model 3	1	Ref.	0·87	0·60, 1·26	0·54	0·36, 0·83	0·72	0·48, 1·08	0·010	0·78	0·68, 0·88	<0·001

Q, quartile; Ref, reference.
* Mean (minimum, maximum) of scores for each dietary pattern. OR and 95 % CI calculated by logistic regression.
† Model 1 was crude model. Model 2 was adjusted for other dietary patterns. Model 3 was adjusted for model 2 + maternal age, ethnology, maternal education, average personal income, family history of diabetes, family history of obesity, smoking, alcohol, parity, pre-pregnancy BMI, weight gain before GDM diagnosis and total energy intake.

Sensitivity analyses

We randomly selected for different sizes of samples in TMCHC to conduct principal component analysis to identify factors, and the results remained similar, showing that dietary patterns during pregnancy derived in our study were reproducible and stable (data not shown).

Discussion

In this study, we identified five maternal dietary patterns during pregnancy and examined their associations with GDM in Chinese women. Interestingly, there were several important findings about the relationship between dietary patterns and GDM. Firstly, higher adherence to the fish–meat–eggs pattern was associated with an increased risk of GDM and that the association was stronger in overweight women and in women with a family history of diabetes. In contrast, higher adherence to the rice–wheat–fruits pattern was associated with a significantly reduced risk of GDM. Each of these associations was independent of established risk factors for GDM. Secondly, consistent with the findings on the association between dietary patterns and GDM risk, we observed a positive association

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Table 4. Gestational diabetes mellitus (GDM) according to the quartiles (Q) of intake of two dietary patterns and macronutrients intakes in Tongji Maternal and Child Health Cohort study (*n* 2755)†
(Odds ratios and 95 % confidence inervals)

	Q1		Q2		Q3		Q4		
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
Fish–meat–eggs									
Adjusted model	1	Ref.	1·22	0·80, 1·88	1·25	0·81, 1·92	1·83	1·21, 2·79	0·007
Adjusted model + total fat (En%)	1	Ref.	1·17	0·76, 1·80	1·15	0·74, 1·79	1·62	1·03, 2·54	0·049
Adjusted model + animal fat (En%)	1	Ref.	1·19	0·77, 1·84	1·18	0·75, 1·87	1·69	1·06, 2·72	0·037
Adjusted model + vegetable fat (En%)	1	Ref.	1·23	0·80, 1·89	1·28	0·83, 1·97	1·89	1·24, 2·88	0·004
Adjusted model + total protein intake (En%)	1	Ref.	1·13	0·73, 1·74	1·08	0·70, 1·68	1·42	0·90, 2·22	0·162
Adjusted model + animal protein intake (En%)	1	Ref.	1·15	0·74, 1·78	1·11	0·71, 1·75	1·51	0·94, 2·44	0·119
Adjusted model + vegetable protein intake (En%)	1	Ref.	1·27	0·83, 1·96	1·36	0·88, 2·10	2·06	1·34, 3·17	0·001
Adjusted model + total carbohydrate intake (En%)	1	Ref.	1·13	0·73, 1·75	1·09	0·69, 1·71	1·48	0·92, 2·36	0·129
Adjusted model + (total protein)/(total carbohydrate) (%)	1	Ref.	1·12	0·72, 1·72	1·06	0·68, 1·65	1·35	0·84, 2·16	0·263
Rice–wheat–fruits									
Adjusted model	1	Ref.	0·87	0·60, 1·26	0·54	0·36, 0·83	0·72	0·48, 1·08	0·010
Adjusted model + total fat (En%)	1	Ref.	0·88	0·61, 1·29	0·55	0·36, 0·85	0·73	0·48, 1·09	0·013
Adjusted model + animal fat (En%)	1	Ref.	0·87	0·60, 1·26	0·55	0·36, 0·83	0·72	0·48, 1·08	0·011
Adjusted model + vegetable fat (En%)	1	Ref.	0·89	0·61, 1·30	0·56	0·37, 0·85	0·73	0·49, 1·10	0·015
Adjusted model + total protein intake (En%)	1	Ref.	0·92	0·63, 1·34	0·60	0·39, 0·92	0·83	0·55, 1·26	0·105
Adjusted model + animal protein intake (En%)	1	Ref.	0·88	0·60, 1·27	0·56	0·36, 0·85	0·75	0·50, 1·14	0·032
Adjusted model + vegetable protein intake (En%)	1	Ref.	0·89	0·61, 1·30	0·57	0·37, 0·87	0·75	0·50, 1·13	0·037
Adjusted model + total carbohydrate intake (En%)	1	Ref.	0·90	0·62, 1·31	0·57	0·37, 0·87	0·75	0·50, 1·13	0·033
Adjusted model + (total protein)/(total carbohydrate) (%)	1	Ref.	0·94	0·64, 1·37	0·60	0·39, 0·92	0·82	0·54, 1·24	0·094
Total fat (En%)‡	1	Ref.	1·47	0·96, 2·27	1·31	0·84, 2·04	1·85	1·21, 2·81	0·010
Animal fat (En%)‡	1	Ref.	1·38	0·89, 2·14	1·76	1·15, 2·69	1·81	1·18, 2·77	0·003
Vegetable fat (En%)‡	1	Ref.	1·00	0·64, 1·57	0·87	0·53, 1·43	1·36	0·81, 2·29	0·244
Total protein intake (En%)‡	1	Ref.	1·70	1·08, 2·68	1·60	1·01, 2·53	2·67	1·71, 4·14	<0·001
Animal protein intake (En%)‡	1	Ref.	1·21	0·78, 1·88	1·55	1·01, 2·36	1·97	1·30, 3·00	0·001
Vegetable protein intake (En%)‡	1	Ref.	1·10	0·74, 1·65	0·99	0·66, 1·49	1·07	0·71, 1·60	0·897
Total carbohydrate intake (En%)‡	1	Ref.	0·73	0·50, 1·05	0·79	0·55, 1·14	0·43	0·28, 0·66	0·001
(Total protein)/(total carbohydrate) (%)‡	1	Ref.	1·15	0·71, 1·86	2·32	1·49, 3·60	2·41	1·56, 3·72	<0·001
Per 1 percentage point increase‡	1·05***	1·03, 1·07							
Per 5 percentage point increase‡	1·26***	1·14, 1·40							

Ref., reference; En%, percentage energy.
*** $P < 0.001$.
† Adjusted model was adjusted for maternal age, ethnology, maternal education, average personal income, family history of diabetes, family history of obesity, smoking, alcohol, parity, pre-pregnancy BMI, weight gain before GDM diagnosis, other dietary patterns and total energy intake.
‡ Adjusted for maternal age, ethnology, maternal education, average personal income, family history of diabetes, family history of obesity, smoking, alcohol, parity, pre-pregnancy BMI, weight gain before GDM diagnosis and total energy intake.

between the fish–meat–eggs score and plasma glucose levels and an inverse association between the rice–wheat–fruits score and plasma glucose levels. Moreover, we specifically designed to investigate the association of dietary patterns with GDM risk or plasma glucose levels with adjustment for dietary macronutrient intakes, and we found the association between dietary pattern and GDM may be at least partially attributed to intake of dietary protein and carbohydrate. The results suggested that a high-protein and low-carbohydrate dietary pattern in pregnancy was associated with a higher risk of GDM in Chinese women.

Several recent studies of Caucasian populations have reported that a maternal diet high in red meat, processed meat and eggs was associated with a higher risk of GDM[15,34]. Our results were in line with these studies, demonstrating that the fish–meat–eggs pattern – a maternal diet high in freshwater fish, red meat and eggs, similar to the Western pattern which was defined in the Nurses' Health Study II (NHSII)[15] – was associated with a higher risk of GDM. Despite similarities in the association with dietary pattern and GDM, the contribution of red meat to fish–meat–eggs pattern in the present study was different from its contribution to Western pattern in NHSII, by the evidence that the strong association of fish–meat–eggs pattern with GDM risk remained significant in the present study after adjustment for red meat intake, but was no longer significant in the NHSII[15,23]. One possible reason for this may be that the red meat consumption (approximately 105 g/d on average) in NHSII[23] was substantially higher than the average daily intake (49·5 g/d) in our study.

In addition, the rice–wheat–fruits pattern was associated with a significantly reduced risk of GDM, which was also in line with the findings from the NHSII[15,16]. Women adherence to the prudent pattern characterised by a high intake of fruit, vegetables and green leafy vegetables were associated with decreased risks for GDM[15]. Importantly, our analysis of diet was conducted in the second trimester, which was different from the time in pre-pregnancy of NHSII, suggesting that our similar findings in pregnant Chinese women may confirm the association of dietary pattern with the risk of GDM found in NHSII. Moreover, a vegetable–fruit–rice-based dietary pattern resembled the rice–wheat–fruits dietary pattern was observed to be associated with lower fasting blood glucose concentrations in a Multi-Ethnic Asian Cohort[20].

Table 5. Associations between two dietary pattern scores and plasma glucose levels (*n* 2755)*
(*β*-Coefficients and 95 % confidence intervals)

	Fasting plasma glucose			1-h plasma glucose			2-h plasma glucose		
Dietary patterns	*β*	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P*
Fish–meat–eggs									
Crude	0·013	−0·001, 0·027	0·072	0·102	0·046, 0·158	<0·001	0·051	0·008, 0·094	0·020
Adjusted model	0·018	0·004, 0·033	0·012	0·136	0·077, 0·195	<0·001	0·074	0·028, 0·120	0·001
Adjusted model + total fat (En%)	0·014	−0·002, 0·029	0·086	0·140	0·075, 0·204	<0·001	0·076	0·026, 0·126	0·003
Adjusted model + animal fat (En%)	0·011	−0·006, 0·027	0·210	0·132	0·063, 0·200	<0·001	0·058	0·006, 0·111	0·030
Adjusted model + vegetable fat (En%)	0·018	0·003, 0·032	0·015	0·134	0·074, 0·193	<0·001	0·071	0·025, 0·117	0·003
Adjusted model + total protein intake (En%)	0·008	−0·008, 0·024	0·310	0·116	0·051, 0·180	<0·001	0·055	0·005, 0·105	0·031
Adjusted model + animal protein intake (En%)	0·005	−0·012, 0·022	0·553	0·124	0·052, 0·195	0·001	0·055	0·000, 0·110	0·048
Adjusted model + vegetable protein intake (En%)	0·020	0·005, 0·035	0·009	0·147	0·085, 0·209	<0·001	0·080	0·032, 0·128	0·001
Adjusted model + total carbohydrate intake (En%)	0·010	−0·006, 0·027	0·209	0·134	0·066, 0·201	<0·001	0·070	0·018, 0·122	0·008
Adjusted model + (total protein)/(total carbohydrate) (%)	0·006	−0·010, 0·023	0·472	0·117	0·049, 0·185	0·001	0·056	0·004, 0·109	0·036
Rice–wheat–fruits									
Crude	−0·021	−0·035, −0·007	0·003	−0·135	−0·191, −0·080	<0·001	−0·114	−0·156, −0·071	<0·001
Adjusted model	−0·014	−0·028, −0·001	0·049	−0·100	−0·158, −0·042	0·001	−0·093	−0·137, −0·048	<0·001
Adjusted model + total fat (En%)	−0·013	−0·027, 0·001	0·064	−0·099	−0·158, −0·041	0·001	−0·092	−0·137, −0·048	<0·001
Adjusted model + animal fat (En%)	−0·014	−0·028, 0·000	0·058	−0·099	−0·157, −0·040	0·001	−0·091	−0·136, −0·046	<0·001
Adjusted model + vegetable fat (En%)	−0·014	−0·028, −0·001	0·047	−0·102	−0·160, −0·044	0·001	−0·096	−0·140, −0·051	<0·001
Adjusted model + total protein intake (En%)	−0·010	−0·024, 0·004	0·168	−0·087	−0·146, −0·028	0·004	−0·082	−0·128, −0·037	<0·001
Adjusted model + animal protein intake (En%)	−0·012	−0·026, 0·002	0·100	−0·094	−0·152, −0·035	0·002	−0·087	−0·132, −0·042	<0·001
Adjusted model + vegetable protein intake (En%)	−0·014	−0·028, 0·000	0·058	−0·098	−0·156, −0·039	0·001	−0·092	−0·136, −0·047	<0·001
Adjusted model + total carbohydrate intake (En%)	−0·012	−0·027, 0·002	0·085	−0·097	−0·155, −0·038	0·001	−0·090	−0·135, −0·045	<0·001
Adjusted model + total protein)/(total carbohydrate) (%)	−0·010	−0·024, 0·005	0·194	−0·086	−0·146, −0·027	0·005	−0·082	−0·128, −0·036	<0·001
Total fat intake (En%)†	0·003	0·001, 0·005	0·008	0·009	0·001, 0·018	0·034	0·005	−0·001, 0·012	0·105
Animal fat (En%)†	0·003	0·001, 0·006	0·005	0·014	0·004, 0·023	0·005	0·011	0·004, 0·019	0·003
Vegetable fat (En%)†	0·000	−0·004, 0·004	0·986	−0·005	−0·023, 0·013	0·565	−0·009	−0·023, 0·004	0·184
Total protein intake (En%)†	0·014	0·007, 0·021	<0·001	0·060	0·030, 0·089	<0·001	0·049	0·026, 0·071	<0·001
Animal protein intake (En%)†	0·012	0·006, 0·019	<0·001	0·054	0·026, 0·081	<0·001	0·042	0·020, 0·063	<0·001
Vegetable protein intake (En%)†	0·000	−0·010, 0·010	0·967	0·001	−0·041, 0·043	0·966	0·005	−0·027, 0·038	0·747
Total carbohydrate intake (En%)†	−0·003	−0·005, −0·001	0·001	−0·012	−0·019, −0·004	0·003	−0·008	−0·014, −0·002	0·011
(Total protein)/(total carbohydrate) (%)†	0·005	0·002, 0·007	<0·001	0·020	0·011, 0·030	<0·001	0·015	0·008, 0·022	<0·001

En%, percentage energy; GDM, gestational diabetes mellitus.
* Adjusted model was adjusted for maternal age, ethnology, maternal education, average personal income, family history of diabetes, family history of obesity, smoking, alcohol, parity, pre-pregnancy BMI, weight gain before GDM diagnosis, other dietary patterns and total energy intake. Values are linear regression coefficients and 95 % CI.
† Adjusted for maternal age, ethnology, maternal education, average personal income, family history of diabetes, family history of obesity, smoking, alcohol, parity, pre-pregnancy BMI, weight gain before GDM diagnosis and total energy intake. Values are linear regression coefficients and 95 % CI.

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Previous studies have indicated that macronutrient intake was associated with GDM[10,11,13,14,22]. Our results were in line with previous findings that a higher pre-pregnancy intake of protein or fat, in particular animal origin, was significantly associated with a greater risk of GDM[13,14], and a lower intake of carbohydrate during mid-pregnancy was associated with an increased risk of GDM later in pregnancy[11]. In addition, a major characteristic of the fish–meat–eggs pattern is high intakes of total protein, animal protein, total fat and animal fat, while a major characteristic of rice–wheat–fruits pattern is a high intake of carbohydrate. In the present study, the positive association between fish–meat–eggs pattern and GDM risk became non-significant after adjustment for total protein, animal protein and total carbohydrate intake, respectively, and the inverse association between rice–wheat–fruits pattern and GDM became non-significant after adjustment for total protein, and ratio of total protein to total carbohydrate, respectively, suggesting that the observed association of dietary patterns with GDM may have been due to the distribution intakes of protein and carbohydrate across quartiles of the dietary patterns. Similar to our results, in the NHSII, a pre-pregnancy low-carbohydrate dietary pattern with high protein and fat from animal-food sources was positively associated with GDM risk[23]. However, the associations between dietary patterns and GDM were not significantly modified by adjusting for intake of total fat or animal fat, although there was a positive association of total fat intake or animal fat intake with GDM risk in the present study.

Our findings are biologically plausible, although the underlying mechanisms remain to be elucidated. First, dietary proteins and amino acids are important modulators of glucose metabolism and insulin sensitivity[14,35], and a short-term increase in plasma amino acid concentrations has been shown to directly induce insulin resistance in skeletal muscle and stimulate endogenous glucose production[36]. Further research is needed to evaluate the associations between dietary patterns and insulin resistance such as insulin values and homeostasis model assessment of insulin resistance (HOMA-IR). Second, prospective studies provided evidence that branched-chain amino acids (BCAA), aromatic amino acids, were associated with the incidence of prediabetes and type 2 diabetes[37]. Moreover, metabolomics studies have demonstrated that increased fasting concentrations of circulating BCAA are associated with an increased risk of type 2 diabetes and insulin resistance in humans and in some rodent models[38]. Finally, another potential explanation is related to the complex carbohydrate. In the present study, average 61·8 % of total carbohydrates are from grains, suggesting the components of carbohydrate were mainly complex carbohydrates. A prospective, randomised crossover trial demonstrated that a short-term diet with liberalised complex carbohydrate and limited fat effectively controlled maternal glycemia and postprandial lipids[39]. Moreover, a high-carbohydrate diet represents combinations of a higher content of carbohydrate and lower contents of fat and protein from the diet, which may also explain the associations found between the dietary patterns and GDM risk in the present study[13,14].

In addition, we also examined the other nutrients' potential contributions on the association between dietary patterns and risk of GDM, including total dietary fibre, dietary vitamin C and dietary vitamin E which are shown to reduce GDM risk in previous studies[11,40,41], and cholesterol and haem Fe which might contribute to the increased risk of GDM[9]. However, the association between dietary patterns and GDM risk remained strong after adjusting for dietary fibre, dietary vitamin C, dietary vitamin E and haem Fe, suggesting that these nutrients were not contributors to the association of dietary pattern with GDM risk in the present study. Interestingly, the strong association of fish–meat–eggs pattern with GDM risk became non-significant after further adjustment for dietary cholesterol intake, which mainly came from red meat and eggs, indicating that cholesterol might also be related to the pathogenesis of GDM. Further studies are warranted to validate this interaction and explore potential mechanisms.

Considering the role of a high pre-pregnancy BMI and the family history of diabetes in the development of GDM[42,43], the stratified analysis were performed in the present study. The results showed that the association between the fish–meat–eggs pattern and the risk of GDM was stronger in overweight women and in women with a family history of diabetes, which is clinically important. Understanding dietary patterns in relation to GDM in obese pregnant women will provide potential targets for future interventions to improve pregnancy outcomes[42]. However, the protective effect of the rice–wheat–fruits pattern was not significant in the high BMI group or in women with a family history of diabetes, suggesting that for overweight women or women with a family history of diabetes, other environmental factors or genetic components may play a more important role than rice–wheat–fruits pattern in the development of GDM[43,44].

The strengths of our study include its prospective design, the uniform criteria for diagnosis of GDM and the availability of abundant information on covariates that allowed us to diminish potential confounders as much as possible[16]. Another strength is the prospective assessment of the pregnancy diet, which means that women completed an FFQ before their OGTT; thus, a diagnosis of GDM could not affect dietary reporting. In addition, the FFQ used in our study has been validated in a TMCHC subsample[24]. Finally, a key strength is the focus on dietary patterns, rather than individual dietary components, and the design of investigating the association between dietary pattern and GDM with adjustment for dietary macronutrient intakes.

We also acknowledge that our study has limitations. First, the data-driven approach of deriving dietary patterns is observational, making a comparison with results from other studies challenging. However, the results of sensitivity analysis by using different sample size from the TMCHC demonstrated the internal validity and reproducibility (data not shown). In addition, the rice–wheat–fruits and fish–meat–eggs patterns shared some similarities with the prudent diets and Western diets, respectively, and our findings are largely consistent with most existing studies on prudent diets and Western diets[14,16,33,34]. Second, our study population consisted mostly of Han Chinese, thus we are unable to ascertain whether the association is similar in other ethnic groups. However, the relative homogeneity of our population advantageously reduced unmeasured confounding. Third, self-reported weight before pregnancy may lead to under-estimation of overweight or obese[45]. However, the self-reported pre-pregnancy weight is widely used in observational studies[29,46]. Fourth, a relative shortened FFQ consisting of sixty-one food items was used to classify dietary intake in the present study. Finally, despite careful consideration of the known risk factors and potential confounding factors, residual confounding cannot be ruled out.

In conclusion, the present prospective study, which was conducted in central China, showed that a maternal dietary pattern characterised by high protein and low carbohydrate intake in pregnancy was associated with a higher risk of GDM. These findings of our study provide important clues for dietary guidance during pregnancy to prevent GDM.

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The authors' responsibilities are as follows: X. Z., X. Y. and N. Yang designed the research. L. H., X. Y. and N. Yang supervised the study conduct. X. Z., R. C., C. Z., J. W., X. L., Q. L., W. C., N. Yi, M. X., H. Y., G. X. and W. H. conducted the research. X. Z. and X. Y. analysed and interpreted the data. X. Z. wrote the manuscript. X. Y. and N. Yang reviewed and edited the manuscript and contributed to discussion. N. Yang had primary responsibility for final content. All authors read and approved the final version of the manuscript.

None of the authors has any conflicts of interest to declare.

Supplementary materials

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114518002453

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