Plasma Alkylresorcinol Metabolite, a Biomarker of Whole-Grain Wheat and Rye Intake, and Risk of Type 2 Diabetes and Impaired Glucose Regulation in a Chinese Population

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OBJECTIVE

To examine the association of plasma alkylresorcinol metabolite 3-(3,5-dihydroxyphenyl)-1-propanoic acid (DHPPA), a biomarker of whole-grain wheat and rye intake, with type 2 diabetes (T2D) and impaired glucose regulation (IGR) in a Chinese population.

RESEARCH DESIGN AND METHODS

A total of 1,060 newly diagnosed T2D patients, 736 newly diagnosed IGR patients, and 1,443 control subjects with normal glucose tolerance were recruited in the case-control study. Plasma DHPPA concentrations were determined by high-performance liquid chromatography–tandem mass spectroscopy. Multivariate logistic regression analysis was used to evaluate the independent association of plasma DHPPA concentrations with the likelihood of T2D and IGR.

RESULTS

After adjustment for age, sex, BMI, and family history of diabetes, the odds ratios (95% CI) of T2D and IGR were 0.57 (0.45, 0.73) and 0.66 (0.50, 0.85), respectively, comparing the lowest with the highest quartile of plasma DHPPA concentrations. Further adjustment for current smoking status, current alcohol consumption, physical activity, history of hypertension, and educational level did not change the observed association materially. Similar results were also obtained in T2D and IGR groups combined. The inverse association of plasma DHPPA with T2D persisted in stratified analyses according to age, sex, BMI, current smoking status, current alcohol consumption, physical activity, family history of diabetes, and history of hypertension.

CONCLUSIONS

These findings suggested that higher plasma DHPPA concentrations were associated with lower odds of T2D and IGR. Further studies are warranted to confirm these findings in prospective cohorts.

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The prevalence of type 2 diabetes (T2D) has dramatically increased over the past few decades worldwide (1), leading to considerable increases in related mortality and economic cost. Although there are several modifiable risk factors for T2D, diet is clearly of paramount importance (2).

Recently, whole-grain intake has been confirmed to have an inverse association with the risk of developing T2D in several prospective cohort studies (3–5). A meta-analysis on nutritional studies (6) also found beneficial effects of whole grains on several cardiometabolic risk factors such as fasting glucose, blood insulin, and blood lipids. The abundance of dietary fiber, minerals, vitamins, and phytochemicals may contribute to the protective effects (7,8).

Available prospective studies on the association between whole grains and risk of T2D have generally assessed whole-grain intake through self-administered food frequency questionnaires. However, it is always challenging in free-living populations to accurately measure food and nutrient intakes, especially for whole-grain intake because of the limitations of whole-grain food composition data (9,10). Inaccurate identification of different whole-grain constituents as well as incorrect estimation of whole-grain foods can lead to measurement errors and underestimates of health benefits of whole grains (11). These together make dietary biomarkers significant as additional estimates of dietary intake.

Alkylresorcinols are phenolic lipids abundant in the outer layers of rye and wheat grain, but absent in highly refined white flour and most other cereal products (12,13). In human subjects, intact alkylresorcinols and their main metabolites (3,5-dihydroxybenozoic acid, DHBA; 3-(3,5-dihydroxyphenyl)-1-propanoic acid, DHPPA) are measurable in plasma (14–16). Recently, they have been suggested as biomarkers of whole-grain wheat and rye intake in epidemiological studies (17–19). Considering that the estimated half-life is significantly longer for DHPPA (16.3 h) than DHBA (10.1 h) and alkylresorcinols (5 h) (20), plasma DHPPA appears to be a good and specific biomarker of whole-grain wheat and rye intake (14,17,21).

In this study, we aimed to examine the association between plasma DHPPA, a biomarker of whole-grain wheat and rye intake, and risk of T2D and impaired glucose regulation (IGR) in a case-control study conducted among a Chinese Han population.

RESEARCH DESIGN AND METHODS

Study Population and Data Collection

This study population consisted of 3,239 participants: 1,060 newly diagnosed T2D patients, 736 newly diagnosed IGR patients, and 1,443 control subjects with normal glucose tolerance (NGT). All cases were consecutively recruited from individuals who, for the first time, received a diagnosis of T2D in the Department of Endocrinology, Tongji Hospital, Tongji Medical College, Wuhan, China, from February 2012 to December 2015. Concomitantly, we recruited control subjects from the general population undergoing a routine health checkup in the same hospital. All cases were frequency matched with control subjects based on sex and age (±5 years). The inclusion criteria were age ≥30 years, BMI <40 kg/m^2, and no history of a diagnosis of diabetes or receiving pharmacological treatment for hyperlipidemia and hypertension. Subjects with clinically significant neurological, endocrinological, or other systemic diseases, as well as those with acute illness and chronic inflammatory or infective diseases, were excluded from the study. All the participants enrolled were of Chinese Han ethnicity.

The diagnostic criteria for IGR and T2D were recommended by the World Health Organization in 1999, incorporating both fasting plasma glucose and a 2-h oral glucose tolerance test (75 g of glucose) (22). IGR was defined as impaired fasting glucose (fasting plasma glucose ≥6.1 mmol/L and <7.0 mmol/L, and 2-h postglucose load <7.8 mmol/L) and/or impaired glucose tolerance (fasting plasma glucose <7.0 mmol/L, and 2-h postglucose load ≥7.8 mmol/L and <11.1 mmol/L). T2D was confirmed when fasting plasma glucose was ≥7.0 mmol/L and/or 2-h postglucose load was ≥11.1 mmol/L.

Basic characteristics, including age, sex, smoking status, alcohol consumption, physical activity, history of hypertension, family history of diabetes, and educational level, were obtained by a standardized questionnaire. Anthropometric measurements such as weight (kg) and height (cm) were measured by trained project staff. BMI was calculated as weight (kg)/square of height (m^2). All participants underwent a physical examination in the morning after an overnight fast and venous blood samples drawn from the antecubital vein were collected. This study was approved by the ethics committee of Tongji Medical College (Huazhong University of Science and Technology, Wuhan, China). All participants provided written informed consent.

Laboratory Measurements

The collected blood samples were separated for plasma within 1 h and then stored at −80°C until analysis. Plasma levels of biochemical parameters, including fasting plasma glucose, 2-h postglucose load, total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol, were measured as previously described (23).

Plasma DHPPA was analyzed by high-performance liquid chromatography–tandem mass spectroscopy (LC-MS/MS) (AB Sciex QTRAP 4500; Applied Biosystems, Foster City, CA). Briefly, 50 μL of plasma sample was spiked with the internal standard (1 ng of syringic acid). The sample was hydrolyzed overnight at 37°C with β-glucuronidase/sulfatase (16) and then extracted with acetonitrile. After centrifuge, the supernatant was collected, and the procedure was repeated once. The combined supernatants were evaporated to dryness under vacuum at 35°C. The residue was then reconstituted in 50 μL of solvent (acetonitrile/water, 1:1, v/v) for LC-MS/MS analysis. Four replicate quality control samples were analyzed in each batch (n = 48). The within- and between-batch coefficients of variation were both <10%. Validation of this method is described in the Supplementary Data.

Statistical Analysis

The differences in plasma DHPPA and basic characteristics between case and control subjects were assessed using Mann-Whitney U test (continuous variables, skewed distribution), Student t test (continuous variables, normal distribution), and χ^2 test (categorical variables). Multiple logistic regression analysis was used to estimate the association between plasma DHPPA concentration and risk of T2D and IGR. To calculate the odds ratios (ORs) for T2D and IGR, plasma DHPPA concentrations were categorized in quartiles according to the control group: quartile 1, <6.56 nmol/L; quartile 2, 6.56 to <10.21 nmol/L; quartile 3, 10.21 to <17.98 nmol/L; and quartile 4, ≥17.98 nmol/L. The regression models were

adjusted for potential confounders including age, sex, BMI, family history of diabetes, history of hypertension, current smoking status (yes/no), current alcohol consumption (yes/no), educational level (none or elementary school, middle school, high school, or college), and vigorous physical activity (at least once/week or no). Because of skewed distribution of plasma DHPPA levels, the normal distribution was approximated by logarithmic transformation. We further explored the potential nonlinear relationship between plasma DHPPA and T2D using a restricted cubic spline with four knots at the 20th, 40th, 60th, and 80th percentiles of ln (plasma DHPPA concentrations). To estimate the consistency of the findings according to participant characteristics, we conducted stratified analyses by sex, age ($<$55 and $\geq$55 years), BMI (BMI $<$24 and $\geq$24 kg/m^2) (24), current smoking status, current alcohol consumption, physical activity, family history of diabetes, and history of hypertension. Interaction tests with multiplicative terms were also performed to determine whether risks differed between the subgroups. Statistical analyses were done with SPSS 17.0 (SPSS Inc., Chicago, IL) and Stata/SE 12.0 (StataCorp LP, College Station, TX). *P* values presented are two-tailed with a significance level of 0.05.

RESULTS

Demographic and clinical characteristics of the 3,239 participants with T2D, IGR, and NGT are summarized in Table 1. Plasma DHPPA concentrations were significantly lower in T2D and IGR patients compared with the control subjects (median: 9.06 nmol/L, 9.66 nmol/L, and 10.21 nmol/L, respectively, $P < 0.005$). In addition, T2D and IGR cases had a higher BMI and greater prevalence of family history of diabetes and history of hypertension. As expected, higher plasma levels of total cholesterol, triglyceride, and fasting plasma glucose but lower HDL cholesterol levels were observed in T2D and IGR case subjects than in the control subjects ($P < 0.005$).

Table 2 demonstrates logistic regression results for T2D and IGR associated with plasma DHPPA concentrations, categorized into quartiles according to the distribution in control subjects. After adjustment for age, sex, BMI, and family history of diabetes, the ORs (95% CI) of T2D and IGR were 0.57 (0.45, 0.73) and 0.66 (0.50, 0.85), respectively, comparing the highest with the lowest quartile of plasma DHPPA concentrations. Further adjustment for current smoking status, current alcohol consumption, physical activity, history of hypertension, and educational level did not change the observed association materially. Similar results were also obtained in T2D and IGR groups combined. We further conducted analyses stratified by categories of the potential confounding factors. The inverse association of plasma DHPPA with T2D was consistently observed across all categories except when stratifying by alcohol habits and family history of diabetes (Table 3). The association seemed to be stronger in subjects without smoking or alcohol drinking habits. In this study, tests for multiplicative interaction were not statistically significant.

In the spline regression models, the OR of T2D decreased significantly with increasing ln-transformed DHPPA at less than 2.05 (7.77 nmol/L plasma DHPPA), followed by a slight plateau (Fig. 1). The nonlinear spline terms were statistically significant ($P = 0.0009$), suggesting a potential nonlinear relationship between plasma DHPPA levels and T2D.

CONCLUSIONS

To the best of our knowledge, this was the first study to examine the relationship between plasma DHPPA concentration as a biomarker of whole-grain intake and risk of T2D and IGR. We found that higher plasma DHPPA concentration was associated with lower ORs of T2D. Adjustment for potential confounding factors did not affect the above results materially. Plasma DHPPA concentration was also inversely associated with risk of IGR, but this association was somewhat attenuated.

Our findings are suggestive of an inverse association of whole-grain intake with T2D risk, which is in accordance with previous epidemiological studies using food frequency questionnaires (3,5,25). A meta-analysis of cohort studies also found a consistent inverse association between whole-grain intake and risk of T2D (32% reduction in the relative risk per three servings per day) (26). A recent study in a Scandinavian population reported a nonsignificant association between plasma alkylresorcinols concentration as a biomarker of whole-grain intake and risk of T2D (27). However, whole-grain intake in that population was much higher than other populations (28). The nonsignificant association might result from a lack of the increased benefits of whole-grain intake when increasing intake from intermediate or high levels (5,25). In our population, plasma DHPPA concentration was significantly lower compared with that in European populations (21.9 nmol/L in elderly Swedish men [19] and 50.6 nmol/L in German men and women [29]). This could be attributed to dietary patterns in Asian countries where rice and wheat are the staple foods. Additionally, the advance of grain-processing technology made possible large-scale production of refined grains in Asian countries (30). Daily whole-grain intake in China was estimated to have decreased from 104 g in 1982 to 24 g in 2002 (31), and it is likely to have continued to decline since 2002. Similar results were also reported by a study in Singapore that suggested low intake of whole-grain wheat among Singaporeans (32).

The inverse association between plasma DHPPA and T2D risk may be explained by other healthy lifestyle factors associated with high whole-grain intake. However, the inverse association persisted in multiple logistic regression models that adjusted for these known risk factors. Moreover, these findings remained robust among individuals with a greater BMI ($\geq$24 kg/m^2) and among nonsmokers, nondrinkers, and individuals with lower physical activity levels. Certain mechanisms have been suggested to be responsible for the observed inverse association. Whole-grain foods higher in insoluble fiber can improve insulin sensitivity and lower insulin secretion as assessed by insulin clamp (33,34). Additionally, minerals, vitamins, and phytochemicals that whole grains are rich in may also contribute to the inverse association between whole-grain intake and T2D (7,35).

In this study, there was evidence of a nonlinear inverse association between plasma DHPPA and T2D, with a steep reduction in the risk at the lower range of plasma DHPPA concentration. This finding is in line with the results from a previous meta-analysis of cohort studies, which indicates a consistent inverse association between whole-grain intake and risk of T2D and that the relative risk reduction was nonlinear, with most of the reduction observed at a lower range of

Table 1—Demographic and clinical characteristics of NGT, T2D, and IGR groups

				P value	
	NGT (*n* = 1,443)	T2D (*n* = 1,060)	IGR (*n* = 736)	T2D vs. NGT	IGR vs. NGT
Age (years)	52.78 (11.04)	51.56 (10.75)	53.33 (11.08)	0.002	0.254
Male, *n* (%)	854 (59.18)	625 (58.96)	458 (62.23)	0.912	0.169
BMI (kg/m^2)	23.47 (3.09)	25.41 (3.43)	24.82 (3.36)	<0.001	<0.001
Fasting plasma glucose (mmol/L)	5.47 (0.39)	9.27 (3.30)	6.28 (0.43)	<0.001	<0.001
Triglyceride (mmol/L)	1.28 (0.85–1.99)	1.59 (0.99–2.54)	1.38 (0.93–2.12)	<0.001	0.003
Total cholesterol (mmol/L)	4.40 (3.44–5.37)	4.75 (4.09–5.47)	4.68 (3.68–5.47)	<0.001	<0.001
HDL cholesterol (mmol/L)	1.36 (1.10–1.65)	1.09 (0.87–1.43)	1.23 (0.98–1.56)	<0.001	<0.001
LDL cholesterol (mmol/L)	2.73 (2.20–3.38)	2.86 (2.04–3.78)	2.81 (2.00–3.56)	0.009	0.912
Hypertension, *n* (%)	279 (19.33)	382 (36.04)	236 (32.07)	<0.001	<0.001
Current smoker, *n* (%)	480 (33.26)	376 (35.47)	260 (35.33)	0.250	0.336
Current drinker, *n* (%)	424 (29.38)	373 (35.19)	276 (37.50)	0.002	<0.001
Family history of diabetes, *n* (%)	105 (7.28)	255 (24.06)	110 (14.95)	<0.001	<0.001
Vigorous activity (at least once/week), *n* (%)	547 (37.91)	373 (35.19)	277 (37.64)	0.163	0.902
Educational level				<0.001	<0.001
None or elementary school	352 (24.39)	221 (20.85)	180 (24.46)		
Middle school	538 (37.28)	352 (33.21)	270 (36.68)		
High school	474 (32.85)	373 (35.19)	212 (28.80)		
College	79 (5.47)	114 (10.75)	74 (10.05)		
Plasma DHPPA (nmol/L)	10.21 (6.56–17.98)	9.06 (5.30–15.78)	9.66 (5.82–15.62)	<0.001	0.002

Data are presented as *n* (%) for categorical data, mean (SD) for parametrically distributed data, or median (interquartile range) for nonparametrically distributed data.

whole-grain intake (26). In the spline regression model, a slightly raised curve was observed at intermediate DHPPA concentration. This may be due to chance or random statistical variations. In addition, refined-grain foods rather than whole grains are mainly consumed in this population, and we could not exclude the possibility that the participants in different quartiles had different amounts of refined-grain intake. Unfortunately, the data on refined-grain intake versus whole-grain intake was not available in this study. Moreover, although we carefully adjusted or matched on the confounding factors such as sex, age, BMI, smoking status, and alcohol consumption, residual confounding could not be ruled out.

Our study has several strengths. Plasma concentration of alkylresorcinol metabolites is a novel and independent biomarker of whole-grain intake with modest long-term reproducibility (29), and it has been used in several studies to estimate the effect of whole-grain wheat and rye on human health (19,36). Moreover, participants in this study were confined to the newly diagnosed to avoid possible changes in diet and lifestyle, which may distort the association between whole-grain intake and T2D risk. Furthermore, despite the relatively low DHPPA concentrations in this population, most of the plasma DHPPA values (98.4%) were detectable by the sensitive, reliable, and validated LC-MS/MS method. Finally,

Table 2—ORs (95% CI) of T2D and IGR, by quartiles of plasma DHPPA concentrations

	Quartile of plasma DHPPA concentrations (nmol/L)				
	Q1 (referent), <6.56	Q2, 6.56 to <10.21	Q3, 10.21 to <17.98	Q4, ≥17.98	*P* for trend
T2D vs. NGT					
Case/control subjects, *n*	376/361	207/363	273/358	204/361	
Crude OR (95% CI)	1	0.55 (0.44, 0.68)	0.73 (0.59, 0.91)	0.54 (0.43, 0.68)	<0.0001
Adjusted OR* (95% CI)	1	0.57 (0.45, 0.73)	0.78 (0.62, 0.98)	0.57 (0.45, 0.73)	0.0002
Adjusted OR† (95% CI)	1	0.58 (0.45, 0.74)	0.76 (0.60, 0.96)	0.56 (0.44, 0.72)	0.0001
IGR vs. NGT					
Case/control subjects, *n*	221/361	170/363	196/358	149/361	
Crude OR (95% CI)	1	0.76 (0.60, 0.98)	0.89 (0.70, 1.14)	0.67 (0.52, 0.87)	0.0099
Adjusted OR* (95% CI)	1	0.74 (0.57, 0.95)	0.90 (0.70, 1.15)	0.66 (0.50, 0.85)	0.0108
Adjusted OR† (95% CI)	1	0.77 (0.59, 1.00)	0.90 (0.70, 1.15)	0.66 (0.51, 0.86)	0.0088
T2D&IGR vs. NGT					
Case/control subjects, *n*	597/361	377/363	469/358	353/361	
Crude OR (95% CI)	1	0.63 (0.52, 0.76)	0.79 (0.66, 0.96)	0.59 (0.49, 0.72)	<0.0001
Adjusted OR* (95% CI)	1	0.62 (0.51, 0.77)	0.82 (0.67, 1.00)	0.59 (0.48, 0.73)	0.0001
Adjusted OR† (95% CI)	1	0.64 (0.52, 0.78)	0.81 (0.66, 0.99)	0.59 (0.48, 0.73)	0.0001

T2D&IGR, T2D and IGR groups combined. *Model 1, adjusted for age, sex, BMI, and family history of diabetes. †Model 2, adjusted for Model 1, current smoking status, current alcohol consumption, physical activity, history of hypertension, and educational level.

Table 3—Stratified analyses of T2D risk and plasma DHPPA concentrations by sex, age, BMI, current smoking status, current alcohol consumption, physical activity, family history of diabetes, and history of hypertension

	Quartile of plasma DHPPA concentrations (nmol/L)				
Group (*n*)	Q1 (referent), <6.56	Q2, 6.56 to <10.21	Q3, 10.21 to <17.98	Q4, ≥17.98	*P* value for interaction
Sex					0.407
Male (1,479)	1	0.58 (0.42, 0.80)	0.88 (0.65, 1.18)	0.66 (0.48, 0.91)	
Female (1,024)	1	0.58 (0.40, 0.84)	0.68 (0.47, 0.97)	0.47 (0.32, 0.68)	
Age, years					0.953
<55 (1,363)	1	0.60 (0.43, 0.83)	0.80 (0.59, 1.08)	0.54 (0.39, 0.75)	
≥55 (1,140)	1	0.58 (0.40, 0.85)	0.81 (0.57, 1.15)	0.61 (0.42, 0.88)	
BMI, kg/m^2					0.438
<24 (1,221)	1	0.67 (0.47, 0.96)	0.81 (0.58, 1.13)	0.53 (0.36, 0.76)	
≥24 (1,282)	1	0.51 (0.37, 0.70)	0.76 (0.56, 1.05)	0.61 (0.44, 0.85)	
Current smoking					0.645
Yes (856)	1	0.61 (0.40, 0.93)	0.82 (0.55, 1.21)	0.71 (0.47, 1.07)	
No (1,647)	1	0.55 (0.41, 0.74)	0.76 (0.57, 1.01)	0.51 (0.38, 0.69)	
Current drinking					0.067
Yes (797)	1	0.69 (0.46, 1.08)	1.00 (0.67, 1.50)	0.92 (0.60, 1.41)	
No (1,706)	1	0.54 (0.40, 0.72)	0.70 (0.53, 0.93)	0.46 (0.34, 0.61)	
Vigorous activity	1				0.383
At least once/week (920)	1	0.50 (0.33, 0.74)	0.87 (0.60, 1.28)	0.68 (0.46, 1.01)	
No (1,583)	1	0.62 (0.46, 0.84)	0.74 (0.56, 0.99)	0.53 (0.39, 0.71)	
Family history of diabetes					
Yes (360)	1	0.67 (0.34, 1.32)	0.68 (0.36, 1.28)	0.53 (0.27, 1.04)	0.822
No (2,143)	1	0.56 (0.43, 0.72)	0.80 (0.62, 1.02)	0.58 (0.45, 0.75)	
History of hypertension					0.060
Yes (661)	1	0.87 (0.55, 1.39)	0.93 (0.59, 1.46)	0.53 (0.34, 0.83)	
No (1,842)	1	0.48 (0.36, 0.63)	0.74 (0.57, 0.96)	0.59 (0.45, 0.78)	

Data are OR (95% CI). The multivariate model was adjusted for age, sex, BMI, and family history of diabetes.

because of the apparent long half-life of approximately 16.3 h (17), plasma DHPPA as a biomarker of whole-grain intake has advantages over alkylresorcinols ($t_{1/2}$ = 5 h), given that blood samples are usually taken after overnight fasting.

Several limitations should also be acknowledged. First, the case-control study design did not allow us to establish a causal relationship, and the likelihood of recall and selection biases could not be excluded. Second, the lack of information on dietary factors (especially refined-grain intake) and socioeconomic factors precluded us from assessing their confounding effects on the results. Third, plasma levels of alkylresorcinol metabolites can be influenced by between-subject differences in metabolism (29,37), which may distort the association under investigation. This problem is further accentuated when intake of whole grains is irregular. Finally, plasma DHPPA is only a biomarker of whole-grain wheat and rye intake, meaning that intakes of other whole grains such as brown rice and corn, which are also consumed in this population, could not be assessed using this biomarker.

In conclusion, we observed that higher plasma DHPPA concentrations were associated with lower ORs of T2D and IGR. Further studies are warranted to confirm our results in prospective cohorts.

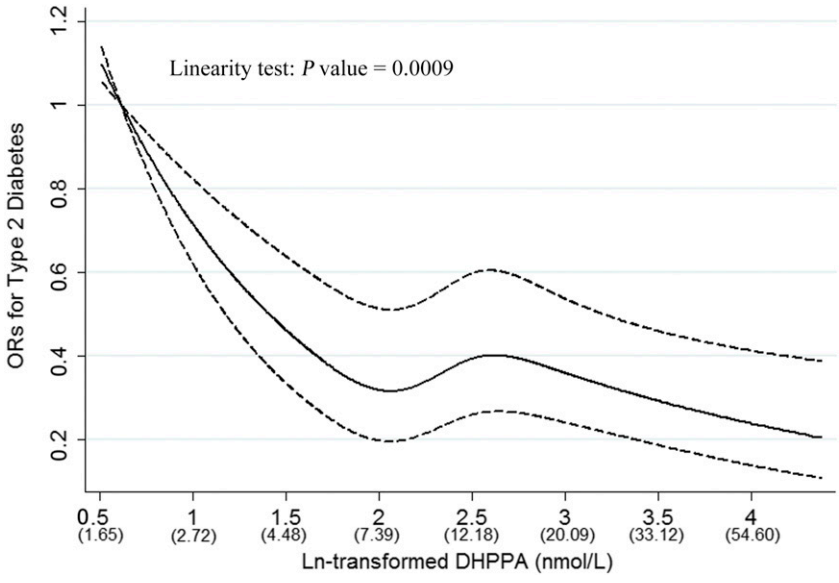

Figure 1—Representation of restricted cubic spline logistic regression models for ln-transformed DHPPA and risk of T2D. Knots were placed at the 20th, 40th, 60th, and 80th percentiles of ln (plasma DHPPA concentrations). Solid line, OR as a function of ln-transformed DHPPA adjusted for age, sex, BMI, family history of diabetes; dashed lines, 95% CIs.

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