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ORIGINAL ARTICLE

Erectile Dysfunction

Relationship between dietary niacin intake and erectile dysfunction: a population-based study

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Existing research on the precise link between dietary niacin intake and erectile dysfunction (ED) is scarce. Thus, this study aimed to investigate the potential association between dietary niacin intake and the risk of ED. Multivariate logistic regression and restricted cubic splines (RCSs) were used to examine the relationship between dietary niacin intake and ED. Subgroup interaction analysis was performed to assess the impact of different subgroups on the study outcomes. In addition, 1:1 propensity score matching (PSM) was employed to adjust for potential confounding factors, ensuring the reliability of the results. The analyzed data were collected from the 2001–2004 National Health and Nutrition Examination Survey (NHANES) in the USA. The study encompassed 3184 adults, among whom 863 participants were identified as having ED. Following adjustments for potential confounders, the findings revealed that higher niacin intake, specifically in the highest tertile, was associated with a decreased risk of ED compared to that in the lowest tertile, showing an odds ratio (OR) of 0.56 (95% confidence interval [CI]: 0.37–0.85). Analysis of dose–response curves illustrated a negative correlation between dietary niacin intake and the risk of ED. Subgroup and interaction analyses fortified the consistency of these results. Furthermore, PSM corroborated the validity of the findings. This study suggests an inverse association between dietary niacin intake and the risk of ED. However, establishing a cause-and-effect relationship remains elusive, and defining the safe threshold of niacin intake to prevent ED requires further investigation.

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INTRODUCTION

Erectile dysfunction (ED), a prevalent multifactorial disorder, is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[1] An epidemiological survey highlights a roughly 19% prevalence of ED among adult males aged 20 years and older in the USA.[2] In addition, the prevalence of ED tends to rise with age.[3] The contributors to ED vary, stemming from psychological, neurological, hormonal, arterial, to cavernous damage.[4] However, there is a general consensus that underlying vascular causes, particularly atherosclerosis, primarily lead to ED.[5] Previous studies indicate ED as a potential risk indicator for cardiovascular disease (CVD),[6] sharing vascular endothelial dysfunction as a common pathophysiological basis with CVD.[5] Moreover, the likelihood of developing ED may increase with obesity, diabetes, hypertension, and hypercholesterolemia.[7–9] Lifestyle adjustments can impact the risk of ED, with smoking and alcohol consumption showing positive associations, while regular, moderate physical activity might reduce the risk.[4]

Niacin, also known as nicotinic acid or Vitamin B3, serves as the precursor to nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), pivotal in energy metabolism and redox reactions.[10] Studies indicate that niacin supplementation can regulate abnormal lipid metabolism, enhance vascular endothelial function, and demonstrate antioxidant and anti-inflammatory properties.[11,12] Human bodies acquire niacin through both endogenous and exogenous pathways. Dietary niacin primarily originates from various meat products, animal organs, seafood, and diverse grains.[13,14] Several studies have revealed that higher dietary niacin intake levels aid in reducing or delaying the risk of dyslipidemia.[15] In a study on the correlation between dietary niacin intake and hypertension in Chinese adults, when dietary niacin intake fell below 15.6 mg per day, the risk of hypertension gradually declined with increasing niacin consumption. Conversely, when dietary niacin intake exceeded 15.6 mg per day, the results were contradictory.[16]

Severe niacin deficiency in humans results in pellagra, characterized by dermatitis, dementia, diarrhea, and potentially death.[17] Contrastingly, excessive niacin intake can lead to skin flushing, gastrointestinal disorders, abnormal liver function, and insulin resistance.[18–20] However, most adverse effects associated with excessive niacin intake stem from overconsumption of dietary niacin supplements or high doses of niacin medication. Adverse events associated with excessive dietary niacin intake are rarely reported. Notably, a recent cross-sectional study has highlighted that increased dietary niacin consumption elevates the risk of developing diabetes.[21]

Considering the aforementioned points, niacin demonstrates protective effects on the vascular endothelium and harbors antioxidant and anti-inflammatory properties. The pathogenesis of ED could potentially be linked to vascular endothelial dysfunction, inflammation, and oxidative stress. Hence, we hypothesize that dietary niacin might

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offer assistance in preventing and treating ED. However, there is a scarcity of studies investigating this aspect. As a result, this study delves into utilizing data from the National Health and Nutrition Examination Survey (NHANES) to investigate the potential relationship between dietary niacin intake and the risk of ED.

PARTICIPANTS AND METHODS

Study population

The NHANES, conducted by the Centers for Disease Control and Prevention (CDC), stands as an ongoing survey program, scrutinized and sanctioned by the National Health Statistics Research Council Center in the USA. Its primary objective is to assess the health and nutritional well-being of both adults and children across the USA. Employing a stratified multistage sampling technique, the study aims to comprehensively evaluate the health and nutritional status of the American population. Studies involving human participants are reviewed and approved by the National Center for Health Statistics (NCHS) Ethics Review Committee (Approval No. Protocol #98-12). Each participant involved in the survey provided written informed consent before participation.

Given that data on erectile function questionnaires were only available from 2001 to 2004, this study utilized data from the 2001 to 2004 NHANES, encompassing 4116 males aged ≥20 years who completed an erectile ability questionnaire. To ensure accuracy, several exclusion criteria were applied: (1) individuals lacking dietary niacin data (n = 241); (2) participants with a history of prostate cancer (n = 101); and (3) those with incomplete survey details on body mass index (BMI; n = 93), educational level (n = 1), smoking status or drinking status (n = 8), poverty-to-income ratio (PIR; n = 199), marital status (n = 2), recreational activities (n = 1), CVD status (n = 1), and hypertension status (n = 3). In addition, 282 participants with unreliable data on total daily energy intake, consuming <800 kcal or >4200 kcal per day, were excluded.[22] Ultimately, the study included a total of 3184 participants. **Figure 1** provides a participant flowchart for visual reference.

Exposure variable

In this study, dietary niacin intake emerged as the primary exposure variable. Trained diet interviewers utilized the NHANES computer-assisted diet interview (CADI) system to gather data on dietary intake. Information regarding individual levels of niacin intake in the diet was acquired from NHANES diet interview days 1 and 2 questionnaires, specifically designed to document the total dietary intake of the participants over two distinct 24-h periods. The initial day of the diet interview was conducted face to face, while the subsequent day was conducted via telephone 3–10 days later. Each mobile examination center (MEC) diet interview room adhered to standardized measurement guidelines, aiding respondents in reporting the quantity and size of food consumed. The United States Department of Agriculture (USDA)'s Food and Nutrient Database for Dietary Studies (FNDDS) supplied the nutritional value of all diet items, offering detailed nutritional profiles for each food reported in NHANES. Dietary niacin intake was calculated by averaging the results of 2 days of dietary interviews; if only the data from day 1 were available, that value was used. This study exclusively focused on niacin obtained from food sources and excluded supplements.

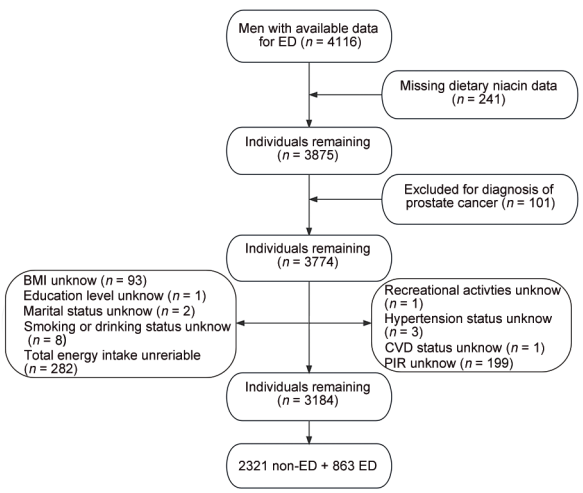

Figure 1: The selection process of the National Health and Nutrition Examination Survey (NHANES) 2001–2004. ED: erectile dysfunction; BMI: body mass index; PIR: poverty-to-income ratio; CVD: cardiovascular disease.

Outcome variable

ED was assessed using a direct and uncomplicated questionnaire developed by the Massachusetts Male Aging Study (MMAS),[23] which asked, "how would you describe your ability to get and maintain an erection sufficient for satisfactory intercourse?" Respondents could choose from four options: "always or almost always", "usually", "sometimes", or "never". Research has shown that the outcomes of this direct ED questionnaire align with those of the International Index of Erectile Function (IIEF).[23] In this questionnaire, individuals who reported being "sometimes able" or "never able" to maintain an erection were categorized as having ED, while those who reported being "usually able" or "always or almost always able" were classified as not having ED. **Supplementary Figure 1** shows a flowchart outlining the selection criteria for ED.

Covariates

In addition to investigating the primary outcome variables, this study explored potential confounding factors that might influence the relationship between dietary niacin intake and ED. These factors included age, race (Caucasian, African American, or others), marital status (married/living with a partner or single/divorced/widowed), educational level (less than high school, high school or equivalent, or college or above), BMI (<30.00 kg m^{-2} or ≥30.00 kg m^{-2}), PIR (≤1.30, 1.31–3.50, or >3.50), smoking status (never, former, or now), drinking status (never, former, or now), recreational physical activity (vigorous, moderate, or no activity), hypercholesterolemia (yes or no), CVD (yes or no), hypertension (yes or no), diabetes (yes or no), testosterone levels (low, normal, or unknown), and total daily energy intake.

Statistical analyses

To counterbalance the influence of NHANES's complex multi-stage sampling design, we applied appropriate sample weights following NHANES guidelines and conducted weighted analyses to enhance data accuracy. Demographic characteristics are presented as weighted mean ± standard error (s.e.) for continuous variables and weighted percentages (%) for categorical variables. Subsequently, a Student's t-test and a Chi-square test were employed to assess baseline features based on ED status. Weighted logistic regression models were used to determine the adjusted odds ratios (aORs) and their respective 95% confidence intervals (CI) concerning ED across niacin intake tertiles. We constructed four weighted logistic regression models: model 1 without variable adjustment; model 2 adjusting for age and race; model 3 adjusting for age, race, PIR, BMI, marital status, education, smoking status, drinking status, recreational activities, and total daily

energy intake; and model 4 additionally adjusted for hypertension, diabetes, hypercholesterolemia, CVD, and testosterone levels. We employed weighted restricted cubic splines (RCSs) to elucidate the dose–response relationship between dietary niacin intake and the risk of ED. Subsequently, we stratified the participants by age, race, BMI, smoking status, drinking status, recreational activity, hypertension, diabetes, hypercholesterolemia, and CVD and conducted interaction analyses to explore potential differential associations among subgroups. In addition, sensitivity analyses were performed by excluding participants using medications potentially affecting erectile function, such as phosphodiesterase type 5 (PDE5) inhibitors,[24] sex hormones,[25] corticosteroids,[25] antidepressants,[26] and antipsychotics.[27] Furthermore, we conducted 1:1 propensity score matching (PSM) to mitigate differences in the baseline characteristics among participants and re-analyzed the PSM data to validate the findings. Statistical analyses were conducted using R software (R4.2.3; http://www.R-project.org; The R Foundation, Vienna, Austria). A bilateral $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Table 1 shows the inclusion of 3184 participants in this study. The prevalence of ED was 27.1%, revealing significant differences in various demographic and health factors among groups. Significant differences in age, marital status, education level, BMI, PIR, smoking status, drinking status, recreational activities, hypercholesterolemia, CVD, hypertension, diabetes, testosterone level, and total energy intake were observed (all $P < 0.05$). Those participants with ED exhibited a higher average age and were predominantly Caucasian. The mean daily dietary niacin intake among participants was 26.8 (s.e.: 0.3) mg per day. Notably, the non-ED group displayed a significantly higher mean daily dietary niacin intake (27.6 [s.e.: 0.4] mg per day) compared to the ED group (23.4 [s.e.: 0.5] mg per day; $P < 0.001$).

Associations between niacin intake and ED

The dose–response curve analysis of RCS demonstrated a decrease in the risk of ED with an increase in dietary niacin intake (P for overall < 0.001; P for nonlinearity = 0.453; **Figure 2**). **Table 2** illustrates that weighted multivariate logistic regression analysis identified an inverse association between daily dietary niacin intake and the risk of ED. In model 1 (OR: 0.97; 95% CI: 0.96–0.98; $P < 0.0001$), model 2 (OR: 0.98; 95% CI: 0.97–0.99; $P < 0.001$), and model 3 (OR: 0.98; 95% CI: 0.97–0.99; $P = 0.01$), this association remained significant. Notably, in model 4, the significance persisted even after adjusting for all covariates (OR: 0.98; 95% CI: 0.97–0.99; $P = 0.01$). In addition, we transformed dietary niacin intake into a categorical variable (tertiles) for further analysis. In model 4, after adjusting for all potential covariates, participants in the highest tertile (T3) of daily dietary niacin intake exhibited a 56% lower risk of ED compared to those in the lowest tertile (T1; T3 *vs* T1, OR: 0.56; 95% CI: 0.37–0.85; $P = 0.01$, P for trend = 0.009).

Subgroup analyses

We conducted stratified analyses to evaluate the stability of the association between dietary niacin intake and ED across various subgroups (**Figure 3**). On adjusting for covariates, our findings indicated no significant differences in dietary niacin intake concerning ED within any subgroups (all P for interaction > 0.05). Specifically, the relationship between dietary niacin intake and the risk of ED remained consistent across subgroups based on age, race, BMI category, recreational activity, smoking status, drinking status, hypertension, diabetes, hypercholesterolemia, and CVD.

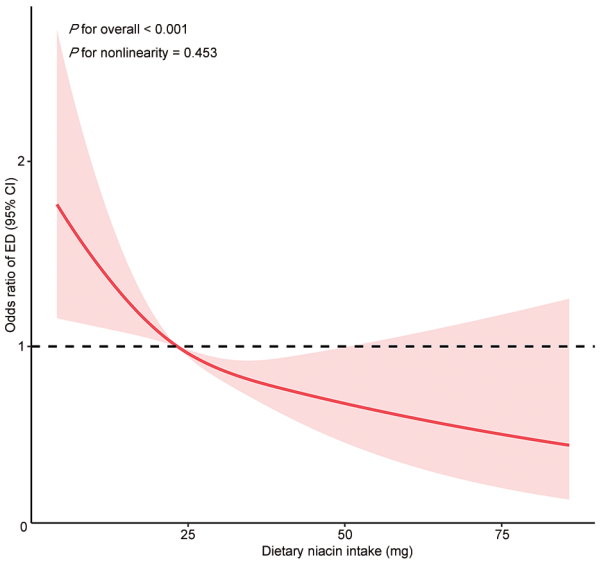

Figure 2: Dose–response relationship analysis between dietary niacin intake and erectile dysfunction before PSM. RCS regression was adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking status, drinking status, total daily energy intake, CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels (Model 4). The red solid line represents ORs, and red-shaded region represents 95% CI. PSM: propensity score matching; ED: erectile dysfunction; CI: confidence interval; RCS: restricted cubic spline; BMI: body mass index; PIR: poverty-to-income ratio; CVD: cardiovascular disease; OR: odds ratio.

Sensitivity analysis

In the sensitivity analysis shown in **Table 3**, the logistic regression outcomes remained consistent even after excluding medications that could potentially influence ED, such as PDE5 inhibitors, sex hormones, cortisol hormones, antidepressants, and antipsychotic medications. In model 4, following adjustment for all covariates, in comparison to the lowest tertile of dietary niacin intake, the OR for ED was 0.66 (95% CI: 0.44–0.98; $P = 0.04$) for the second tertile and 0.57 (95% CI: 0.37–0.89; $P = 0.02$) for the highest tertile (P for trend = 0.008).

PSM analysis

We implemented a 1:1 PSM approach to mitigate the impact of differing baseline characteristics among participants. Following PSM, both the ED and non-ED groups comprised 863 participants each. **Supplementary Table 1** illustrates the post-PSM baseline characteristics of the study population. On re-examining the outcomes of PSM, the dose–response curve analysis of RCS reaffirmed the negative linear correlation between dietary niacin intake and ED (P for overall < 0.001; P for nonlinearity = 0.678; **Supplementary Figure 2**). In addition, the weighted multivariate logistic regression outcomes following PSM indicated a significant decrease in the risk of ED associated with higher dietary niacin intake (**Supplementary Table 2**). Subgroup analysis post-PSM revealed no influence of different subgroups on the study's results (**Supplementary Figure 3**). Moreover, sensitivity analyses once again confirmed the stability of the findings (**Supplementary Table 3**).

DISCUSSION

This study is an exploration into the association between niacin intake and ED. With this nationally representative study, we found a strong

Table 1: Baseline characteristics of the study population before propensity score matching

Characteristic	*Total*	*ED*		*P*
		No	*Yes*	
Patients, *n* (%)	3184 (100.0)	2321 (72.9)	863 (27.1)	
Age (year), mean (s.e.)	45.4 (0.4)	41.6 (0.4)	61.5 (0.6)	<0.0001
Race, *n* (%)				0.01
Caucasian	1750 (55.0)	1227 (73.4)	523 (79.7)	
African American	569 (17.9)	450 (10.4)	119 (7.4)	
Others	865 (27.2)	644 (16.2)	221 (12.9)	
Marital status, *n* (%)				<0.0001
Married/living with a partner	2253 (70.8)	1598 (68.3)	655 (78.5)	
Single/divorced/widowed	931 (29.2)	723 (31.7)	208 (21.5)	
Education level, *n* (%)				<0.0001
Less than high school	849 (26.7)	517 (13.2)	332 (27.9)	
High school or equivalent	786 (24.7)	605 (26.2)	181 (24.5)	
College or above	1549 (48.7)	1199 (60.7)	350 (47.6)	
BMI (kg m^{-2}), *n* (%)				<0.001
<30.00	2278 (71.6)	1691 (72.3)	587 (62.7)	
≥30.00	906 (28.5)	630 (27.7)	276 (37.3)	
PIR, *n* (%)				<0.001
≤1.30	732 (23.0)	515 (16.6)	217 (16.7)	
1.31–3.50	1258 (39.5)	869 (32.6)	389 (43.7)	
>3.50	1194 (37.5)	937 (50.8)	257 (39.6)	
Smoking status, *n* (%)				<0.0001
Never	1286 (40.4)	1027 (45.3)	259 (29.8)	
Former	1049 (33.0)	616 (26.1)	433 (48.1)	
Now	849 (26.7)	678 (28.6)	171 (22.2)	
Drinking status, *n* (%)				<0.0001
Never	211 (6.6)	152 (7.5)	59 (7.2)	
Former	648 (20.4)	366 (13.3)	282 (30.2)	
Now	2325 (73.0)	1803 (79.2)	522 (62.7)	
Recreational activity, *n* (%)				<0.0001
Vigorous	1097 (34.5)	949 (45.3)	148 (18.2)	
Moderate	895 (28.1)	600 (26.9)	295 (39.6)	
Inactivity	1192 (37.4)	772 (27.7)	420 (42.2)	
Hypercholesterolemia, *n* (%)				<0.0001
No	1998 (62.8)	1547 (66.1)	451 (47.4)	
Yes	1186 (37.3)	774 (33.9)	412 (52.6)	
CVD, *n* (%)				<0.0001
No	2761 (86.7)	2161 (94.6)	600 (71.2)	
Yes	423 (13.3)	160 (5.5)	263 (28.8)	
Hypertension, *n* (%)				<0.0001
No	1909 (60.0)	1588 (69.5)	321 (41.3)	
Yes	1275 (40.0)	733 (30.5)	542 (58.7)	
Diabetes, *n* (%)				<0.0001
No	2747 (86.3)	2136 (94.0)	611 (71.9)	
Yes	437 (13.7)	185 (6.0)	252 (28.1)	
Testosterone, *n* (%)				0.001
Low	80 (2.5)	41 (1.6)	39 (4.6)	
Normal	430 (13.5)	332 (12.8)	98 (11.8)	
Unknown	2674 (84.0)	1948 (85.6)	726 (83.7)	
Total energy (kcal), mean (s.e.)	2395.2 (25.1)	2460.7 (28.3)	2116.8 (43.1)	<0.0001
Dietary niacin (mg), mean (s.e.)	26.79 (0.3)	27.60 (0.4)	23.40 (0.5)	<0.0001

BMI: body mass index; PIR: poverty-to-income ratio; CVD: cardiovascular disease; PSM: propensity score matching; s.e.: standard error; ED: erectile dysfunction

association between dietary niacin intake and ED. Both univariate and multivariate logistic regression analyses underscored the link between higher niacin intake and a reduced risk of ED. When transitioning niacin intake from continuous to categorical, heightened dietary niacin significantly lowered the risk of ED compared to lower intake levels. In addition, a comprehensive dose–response analysis underscored a consistent, inverse linear relationship between dietary niacin and ED. Subgroup analyses further fortified the stability of this association

Table 2: Association of dietary niacin intake and erectile dysfunction risk before propensity score matching

Variable	*Model 1*		*Model 2*		*Model 3*		*Model 4*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Dietary niacin	0.97 (0.96–0.98)	<0.0001	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	0.01	0.98 (0.97–0.99)	0.01
Stratified by dietary niacin tertiles								
Tertile 1	1		1		1		1	
Tertile 2	0.66 (0.49–0.88)	0.01	0.67 (0.48–0.93)	0.02	0.69 (0.50–0.96)	0.03	0.67 (0.46–0.99)	0.05
Tertile 3	0.43 (0.32–0.58)	<0.0001	0.51 (0.37–0.71)	<0.001	0.58 (0.41–0.82)	0.01	0.56 (0.37–0.85)	0.01
P for trend		<0.0001		<0.001		0.004		0.009

Model 1: unadjusted; Model 2: adjusted for age and race; Model 3: adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking status, drinking status, and total daily energy intake; Model 4: additionally adjusted for CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels. OR: odds ratio; CI: confidence interval; BMI: body mass index; PIR: poverty-to-income ratio; CVD: cardiovascular disease

Table 3: Sensitivity analyses before propensity score matching

Variable	*Model 1*		*Model 2*		*Model 3*		*Model 4*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Dietary niacin	0.97 (0.96–0.98)	<0.0001	0.98 (0.96–0.99)	<0.001	0.98 (0.97–0.99)	0.01	0.98 (0.97–0.99)	0.02
Stratified by dietary niacin tertiles								
Tertile 1	1		1		1		1	
Tertile 2	0.63 (0.46–0.86)	0.01	0.65 (0.46–0.93)	0.02	0.68 (0.48–0.95)	0.03	0.66 (0.44–0.98)	0.04
Tertile 3	0.43 (0.32–0.59)	<0.0001	0.53 (0.37–0.76)	0.001	0.61 (0.42–0.87)	0.01	0.57 (0.37–0.89)	0.02
P for trend		<0.0001		<0.001		0.003		0.008

Sensitivity analyses excluded participants taking medications that could affect erectile function. Model 1: unadjusted; Model 2: adjusted for age and race; Model 3: adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking status, drinking status, and total daily energy intake; Model 4: additionally adjusted for CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels. OR: odd ratio; CI: confidence interval; BMI: body mass index; PIR: poverty-to-income ratio; CVD: cardiovascular disease

across diverse subgroups. Moreover, the meticulous re-examination following 1:1 PSM reinforced the consistency and reliability of the study outcomes.

The pathophysiology of ED encompasses a multifaceted interplay of factors. A normal penile erection relies on the harmonious functioning of neural integrity, a robust vascular system, and healthy cavernous tissue. Conventionally, ED has been categorized into organic, psychogenic, and mixed types based on its etiology. However, this classification might present limitations due to the prevalent mixed nature of ED cases. Hence, as per the recommendations of the European Association of Urology (EAU) sexual and reproductive health guidelines, ED can be dichotomized into two categories: primary organic ED and primary psychogenic ED.[28] In a European cross-sectional study involving 2009 patients with ED, a substantial 86.2% of patients with ED were classified under primary organic ED.[29]

Primary organic ED primarily stems from vascular, endocrine, or pharmaceutical causes, with vascular issues being the predominant factor.[30] The erection process hinges on the synthesis of NO by endothelial NO synthase (eNOS).[31] Within the smooth muscle of the cavernous body, NO activation of the guanosine cyclase elevates cyclic guanosine monophosphate (cGMP) levels, including smooth muscle hyperpolarization and relaxation by opening potassium channels and inhibiting calcium channels, culminating in penile erection.[31] Hence, NO synthesized by the vascular endothelium serves as the chief mediator of erection.[32] Nevertheless, dysfunction in vascular endothelium curtails NO production, thereby contributing to ED.[33] Hormonal disorders notably impact vascular endothelial dysfunction, with testosterone playing a pivotal role.[34] Testosterone exerts a catabolic effect on the expression and activity of hydrolases involved in cGMP degradation and upregulates PDE5, the principle enzyme responsible for cGMP degradation.[35] These actions positively influence NO synthesis. Conversely, testosterone deficiency prompts increased production of endothelin-1, a potent vasoconstrictor, exacerbating cellular hypoxia and prompting apoptosis.[36] Consequently, testosterone deficiency exacerbates vascular endothelial dysfunction and diminishes NO synthesis by the vascular endothelium, culminating in ED. Intriguingly, research indicates that NO inhibits Leydig cell conversion of cholesterol to pregnenolone, ultimately reducing testosterone production.[37]

Oxidative stress is believed to have a significant impact on ED. Prior studies have highlighted the role of oxidative stress-induced nitric oxide synthase (NOS)-dependent endothelial dysfunction in the initiation and progression of diabetic ED.[38] High levels of reactive oxygen species (ROS) accompanying oxidative stress can interact with NO, forming peroxynitrite, subsequently reducing the available NO.[39] Moreover, peroxynitrite and superoxide can elevate endothelial cell apoptosis rates,[40] leading to endothelial damage and a further decline in available NO. Therefore, strategies aimed at repairing endothelial dysfunction and employing antioxidant therapy hold promise for preventing and treating ED.

Niacin, an essential nutrient derived from dietary sources, fulfills crucial bodily requirements. Nicotinic acid, a precursor of NAD (NADP), and reduced glutathione (GSH), play a pivotal role in cellular processes. GSH, an intracellular nonprotein mercaptan, is instrumental in preserving the intracellular redox balance and shielding cells against oxidative stress.[41] Dietary niacin intake contributes to elevating GSH levels within the human body. A study by Wu *et al.*[42] showed that niacin can mitigate vascular inflammation and enhance endothelial function by augmenting vascular GSH, a vital agent in clearing ROS generated by myeloperoxidase from neutrophils within the blood vessel walls. Previous research indicates that increased dietary niacin intake correlates with enhanced endothelial function and reduced vascular and systemic oxidative stress in middle-aged and older adults.[43] In addition, findings from Ganji *et al.*[44] suggest that niacin reduces vascular inflammation by inhibiting endothelial cell ROS production to reduce subsequent LDL oxidation and inflammatory

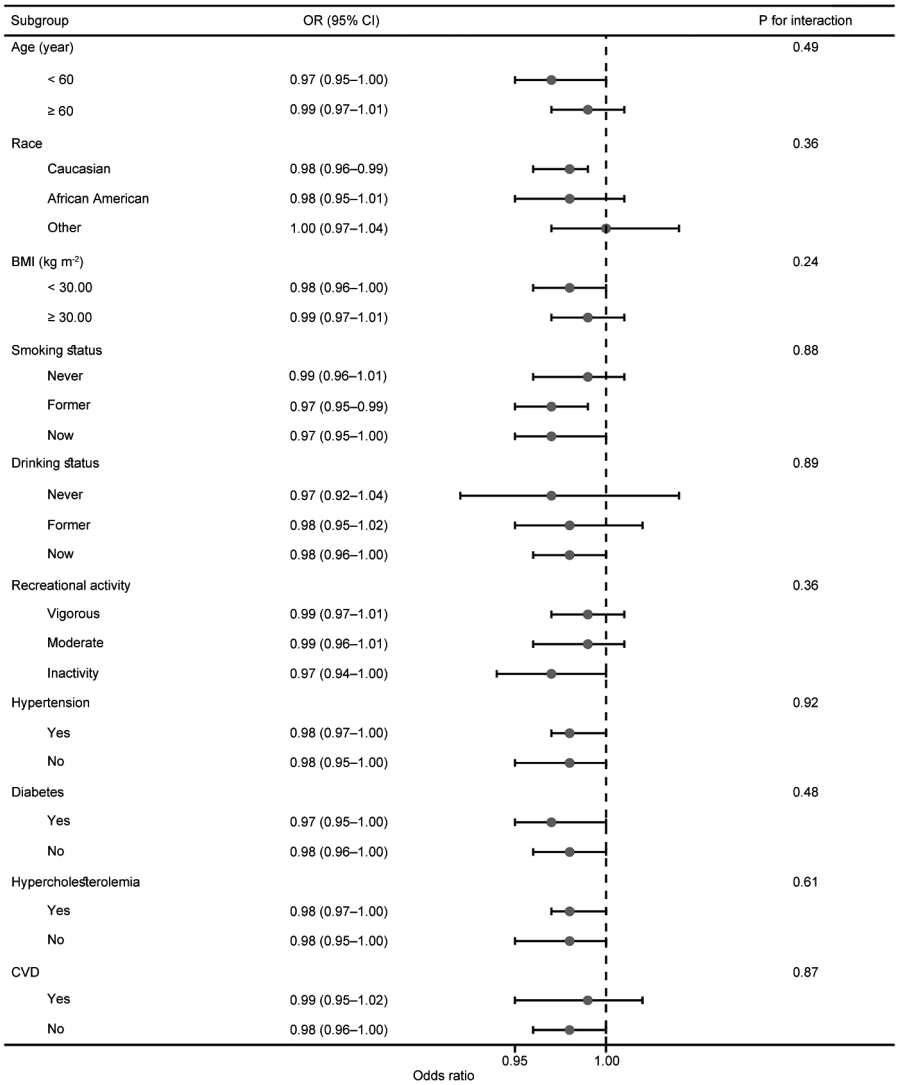

Figure 3: Association between dietary niacin intake and erectile dysfunction in different subgroups before PSM. Analyses were adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking status, drinking status, total daily energy intake, CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels. OR: odds ratio; CI: confidence interval; BMI: body mass index; CVD: cardiovascular disease; PSM: propensity score matching; PIR: poverty-to-income ratio.

cytokine production, thereby reducing the risk of atherosclerosis. Current preclinical evidence further reinforces the notion that niacin shields blood vessel cells from oxidative stress triggered by diverse stressors.[45,46] Considering these findings, it is hypothesized that niacin may influence the risk of ED by improving vascular endothelial function and diminishing oxidative stress.

In this observational study, we evaluated the impact of dietary niacin intake on ED by examining dietary data from the study population. Through a series of statistical analyses, we found that a higher dietary niacin intake is associated with a reduced risk of ED. To further explore potential causality, we recommend that future studies employ a longitudinal study design combined with interventions for dietary niacin. In addition, conducting mechanistic studies would be beneficial in elucidating the biological pathways through which niacin might influence erectile function.

The study has several advantages and limitations. One key advantage lies in its extensive sample size, which allows for a representation of characteristics mirroring those of the national population. Concurrently, appropriate sampling weights were considered during the analysis to mitigate oversampling bias, bolstering the reliability of our conclusions. However, the study does have limitations. Primarily, being a nutritional and epidemiological cross-sectional study, it cannot establish a causal relationship between dietary niacin intake and the development of ED. Moreover, it lacks measurements of serum or blood levels of niacin in humans. Secondly, the ED diagnosis in NHANES relies predominantly on a questionnaire format, which not only diminishes accuracy but also constrains our ability to further categorize ED. Finally, the data on ED in NHANES are confined to the period from 2001 to 2004, curtailing our ability to ascertain the applicability of our findings to the current population.

CONCLUSIONS

In this observational, population-based study, there seems to be an inverse association between dietary niacin intake and the risk of ED. However, the cause-and-effect relationship remains unclear, and the safe threshold of niacin intake to prevent ED remains unknown.

AUTHOR CONTRIBUTIONS

WLL, WZ, and MEL designed the study; performed statistical analysis; interpreted the analysis, wrote, revised, and reviewed the manuscript; and supervised all processes. CZ and HXW wrote and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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Supplementary Table 1: Baseline characteristics of the study population after propensity score matching

Characteristic	*Total*	*ED*		*P*
		No	*Yes*	
Patients, *n* (%)	1726	863 (50.00)	863 (50.00)	
Age (year), mean (s.e.)	58.24 (0.5)	55.55 (0.5)	61.50 (0.6)	<0.0001
Race, *n* (%)				0.24
Caucasian	997 (57.8)	474 (76.0)	523 (79.7)	
African American	248 (14.4)	129 (8.4)	119 (7.4)	
Others	481 (27.9)	260 (15.6)	221 (12.9)	
Marital status, *n* (%)				0.8
Married/living with a partner	1312 (76.0)	657 (77.8)	655 (78.5)	
Single/divorced/widowed	414 (24.0)	206 (22.2)	208 (21.5)	
Education level, *n* (%)				0.06
Less than high school	609 (35.3)	277 (20.3)	332 (27.9)	
High school or equivalent	391 (22.7)	210 (27.3)	181 (24.5)	
College or above	726 (42.1)	376 (52.4)	350 (47.6)	
BMI (kg m^{-2}), *n* (%)				0.93
<30.00	1160 (67.2)	573 (63.1)	587 (62.7)	
≥30.00	566 (32.8)	290 (37.0)	276 (37.3)	
PIR, *n* (%)				0.05
≤1.30	411 (23.8)	194 (16.7)	217 (16.7)	
1.31–3.50	733 (42.5)	344 (36.2)	389 (43.7)	
>3.50	582 (33.7)	325 (47.1)	257 (39.6)	
Smoking status, *n* (%)				0.1
Never	534 (30.9)	275 (31.0)	259 (29.8)	
Former	781 (45.3)	348 (41.1)	433 (48.1)	
Now	411 (23.8)	240 (27.9)	171 (22.2)	
Drinking status, *n* (%)				0.18
Never	104 (6.0)	45 (6.7)	59 (7.2)	
Former	509 (29.5)	227 (24.1)	282 (30.2)	
Now	1113 (64.5)	591 (69.2)	522 (62.7)	
Recreational activity, *n* (%)				0.4
Vigorous	318 (18.4)	170 (22.1)	148 (18.2)	
Moderate	596 (34.5)	301 (37.7)	295 (39.6)	
Inactivity	812 (47.1)	392 (40.2)	420 (42.2)	
Hypercholesterolemia, *n* (%)				0.46
No	915 (53.0)	464 (50.1)	451 (47.4)	
Yes	811 (47.0)	399 (49.9)	412 (52.6)	
CVD, *n* (%)				0.002
No	1316 (76.3)	716 (82.9)	600 (71.2)	
Yes	410 (23.8)	147 (17.1)	263 (28.8)	
Hypertension, *n* (%)				0.01
No	747 (43.3)	426 (48.6)	321 (41.3)	
Yes	979 (56.7)	437 (51.4)	542 (58.7)	
Diabetes, *n* (%)				0.004
No	1304 (75.6)	693 (81.0)	611 (71.9)	
Yes	422 (24.5)	170 (19.0)	252 (28.1)	
Testosterone, *n* (%)				0.25
Low	70 (4.1)	31 (3.4)	39 (4.6)	
Normal	224 (13.0)	126 (14.3)	98 (11.8)	
Unknown	1432 (83.0)	706 (82.4)	726 (83.7)	
Total energy (kcal), mean (s.e.)	2183.98 (27.8)	2239.09 (40.5)	2116.81 (43.1)	0.06
Dietary niacin (mg), mean (s.e.)	24.53 (0.3)	25.49 (0.4)	23.37 (0.5)	0.002

BMI: body mass index; PIR: poverty income ratio; CVD: cardiovascular disease; s.e.: standard error; ED: erectile dysfunction

Supplementary Table 2: Association of dietary niacin intake and erectile dysfunction risk after propensity score matching

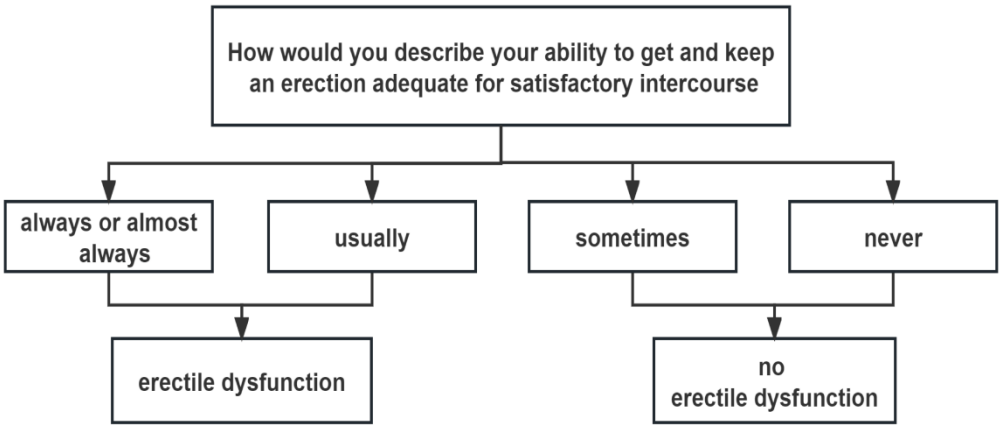
Variable	*Model 1*		*Model 2*		*Model 3*		*Model 4*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Dietary niacin	0.98 (0.97–0.99)	0.003	0.98 (0.97–1.00)	0.01	0.98 (0.97–1.00)	0.01	0.98 (0.97–1.00)	0.02
Stratified by dietary niacin quartiles								
Tertile 1	1		1		1		1	
Tertile 2	0.85 (0.58–1.24)	0.38	0.81 (0.56–1.20)	0.28	0.82 (0.55–1.23)	0.31	0.82 (0.53–1.27)	0.31
Tertile 3	0.59 (0.44–0.81)	0.002	0.61 (0.44–0.83)	0.003	0.59 (0.41–0.84)	0.01	0.58 (0.39–0.86)	0.01
P for trend		0.002		0.004		0.02		0.012

Model 1: unadjusted; Model 2: adjusted for age and race, marital status, education level, PIR, and BMI categories; Model 3: adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking, drinking status, and total daily energy intake; Model 4: additionally adjusted for CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels. OR: odd ratio; CI: confidence interval; BMI: body mass index; PIR: poverty income ratio; CVD: cardiovascular disease

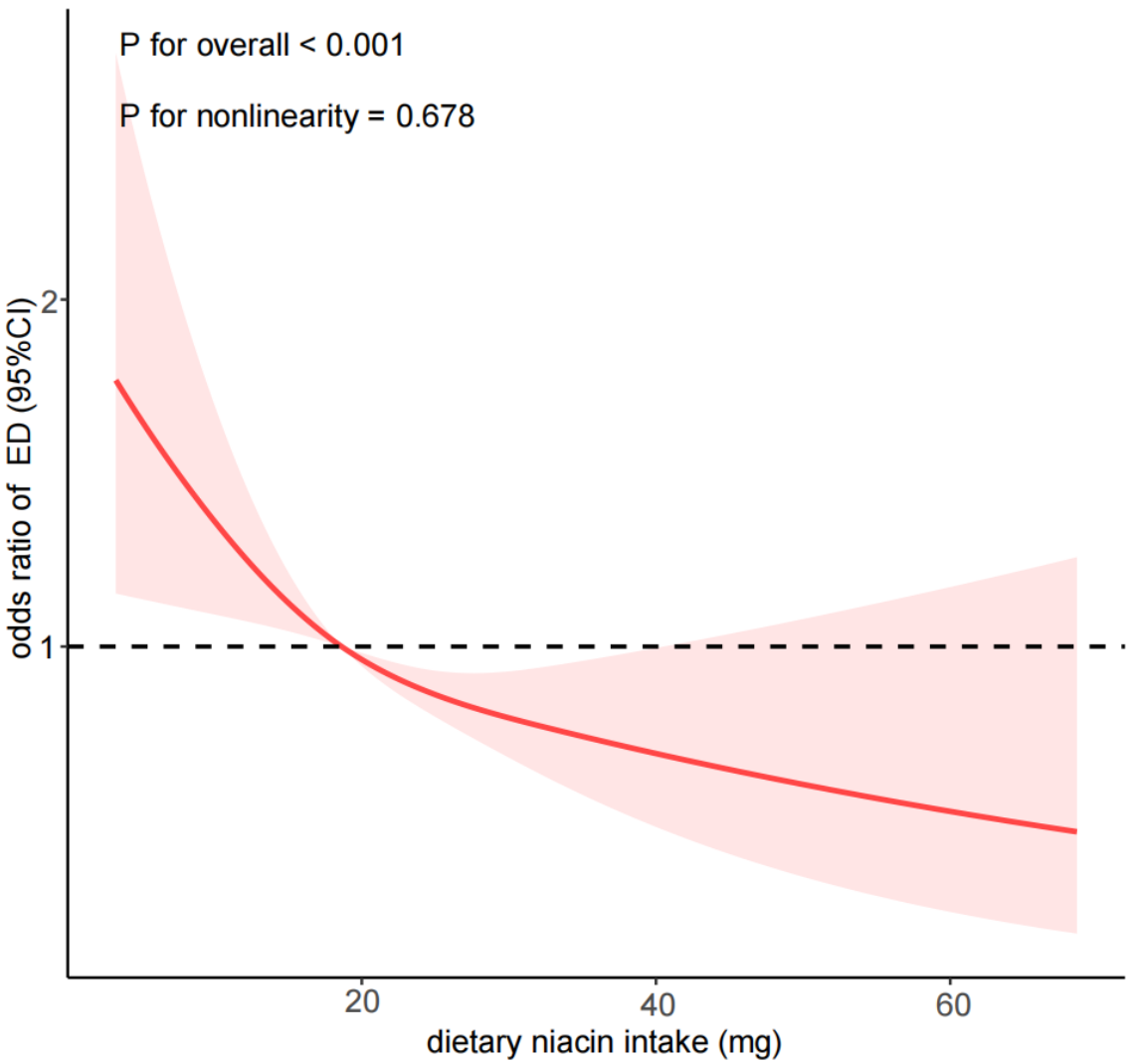
Supplementary Table 3: Sensitivity analyses after propensity score matching

Variable	*Model 1*		*Model 2*		*Model 3*		*Model 4*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Dietary niacin	0.98 (0.97–0.99)	0.01	0.98 (0.97–1.00)	0.02	0.99 (0.97–1.00)	0.03	0.98 (0.97–1.00)	0.02
Stratified by dietary niacin quartiles								
Tertile 1	1		1		1		1	
Tertile 2	0.86 (0.60–1.24)	0.41	0.86 (0.60–1.23)	0.39	0.90 (0.61–1.34)	0.58	0.87 (0.57–1.33)	0.45
Tertile 3	0.59 (0.43–0.82)	0.003	0.61 (0.43–0.86)	0.003	0.66 (0.46–0.96)	0.03	0.57 (0.37–0.89)	0.02
P for trend		0.002		0.006		0.023		0.016

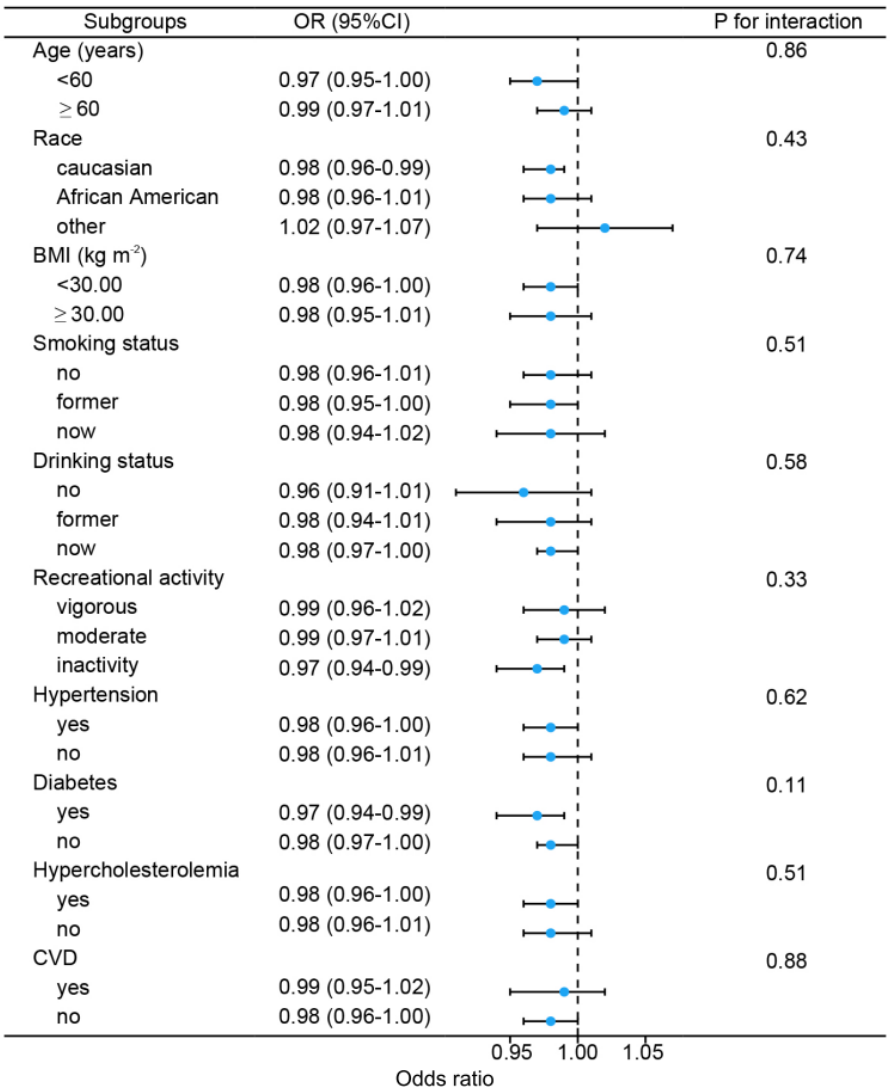
Sensitivity analyses excluded participants taking medications that could affect erectile function. Model 1: unadjusted; Model 2: adjusted for age and race, marital status, education level, PIR, and BMI categories; Model 3: adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking, drinking status, and total daily energy intake; Model 4: additionally adjusted for CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels. OR: odd ratio; CI: confidence interval; BMI: body mass index; PIR: poverty income ratio; CVD: cardiovascular disease



Supplementary Figure 1: Selection criteria for erectile dysfunction.



Supplementary Figure 2: Dose–response relationship analysis between dietary niacin intake and erectile dysfunction after PSM. RCS regression was adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking status, drinking status, total daily energy intake, CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels (Model 4). The red solid line represents ORs, and red-shaded region represents 95% CI. ED: erectile dysfunction; CI: confidence interval; CVD: cardiovascular disease; PSM: propensity score matching; RCS: restricted cubic spline; OR: odds ratio.



Supplementary Figure 3: Association between dietary niacin intake and erectile dysfunction in different subgroups after PSM. Analyses were adjusted for age, race, marital status, education level, PIR, BMI categories, recreational activity, smoking, drinking status, total daily energy intake, CVD, hypercholesterolemia, hypertension, diabetes, as well as testosterone levels. OR: odds ratio; CI: confidence interval; BMI: body mass index; CVD: cardiovascular disease; PSM: propensity score matching.