Miao et al. Nutrition Journal (2025) 24:77
https://doi.org/10.1186/s12937-025-01141-5

Nutrition Journal

RESEARCH Open Access

Association between the dietary index for gut microbiota and atherosclerotic cardiovascular disease risk among US elderly adults: a cross-sectional study

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Abstract

Background Gut microbes are important for the development of atherosclerotic cardiovascular disease (ASCVD), and the dietary index for gut microbiota (DI-GM), a new measure of gut flora-friendly diets, has not been systematically investigated in relation to ASCVD.

Objective This study aimed to evaluate the correlation between DI-GM and the risk of ASCVD in American older adults, also to analyze the mediating role of body mass index (BMI).

Methods Researchers selected 2234 elderly participants ≥ 65 years of age from the National Health and Nutrition Examination Survey (NHANES) from 2015 to 2018 for a cross-sectional cohort study. Stratified analyses were taken based on DI-GM quartile. To achieve our research objectives, we employed logistic regression analysis, smooth curve fitting, interaction effects analysis, and mediation analysis.

Results After adjusting for confounders, individuals with higher DI-GM had a significantly lower risk of ASCVD (highest quartile vs. lowest quartile OR = 0.73, 95% CI: 0.52–1.01, P < 0.001). DI-GM was linearly negatively associated with ASCVD (P = 0.13) and the association was stable in the diabetes subgroup (interaction P > 0.05), but age, gender and BMI may modify the association between DI-GM and ASCVD (interaction P < 0.05). BMI mediated 11.51% of the association between DI-GM and ASCVD (95% CI: 2.54%-54.1%, P = 0.016).

Conclusion DI-GM is likely to be a promising indicator for the assessment of the risk of ASCVD, with BMI exhibiting a partial mediating effect in this association. Future studies should prioritize a comprehensive investigation of the underlying mechanisms by which DI-GM contributes to atherogenesis, with the aim of enhancing the efficacy of early prevention strategies for ASCVD.

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Keywords Dietary index for gut microbiota (DI-GM), Body mass index (BMI), Atherosclerotic cardiovascular disease (ASCVD), Cohort analysis, National health and nutrition examination survey (NHANES)

Introduction

Cardiovascular disease (CVD) is the main chronic noncommunicable disease (NCD) threatening human life and health globally, affecting more than 523 million people worldwide. Atherosclerotic cardiovascular disease (ASCVD)-predominant CVDs (e.g., ischemic heart disease (IHD) and ischemic stroke, etc.) are the main cause of the CVD burden and trend, with IHD accounting for approximately half of CVD deaths (49.2%) [1]. The clinical presentation of ASCVD is highly variable, and its diagnosis usually comprises medical history, physical examination, laboratory tests, and imaging [2]. Control of risk factors is one of the important management strategies for ASCVD, including lifestyle changes and pharmacologic therapy [3–4]. Despite the progress made in the prevention and treatment of ASCVD, it still places a significant burden on the healthcare system. Therefore, identifying factors that predict the risk of ASCVD is essential to promote early prevention, early diagnosis, and early treatment of the disease.

Kase et al. [5]. proposed the dietary index for gut microbiota (DI-GM) in April 2024, based on multiple longitudinal intervention studies as a novel index containing 14 dietary components that have positive or negative effects on the gut microbiota (GM) and is able to estimate the diet quality related to keeping a healthy GM. As a novel dietary assessment tool, DI-GM has been applied to the study of various diseases in recent years. For example, Zhang et al. [6] found that DI-GM was significantly and negatively associated with the risk of depression (OR = 0.85, 95% CI: 0.76–0.95), and that this association was partially mediated by BMI and phenotypic age. In addition, the original study by Kase et al. [5]. demonstrated a 23% reduction in the risk of metabolic syndrome in those with higher DI-GM scores (HR = 0.77), suggesting that it improves insulin sensitivity and lipid metabolism by modulating gut flora metabolism. A preliminary study also found that DI-GM was associated with a reduced risk of stroke in U.S. adults (OR = 0.93, 95% CI: 0.89–0.98) [7], although the data need further validation. These findings highlight the potential of DI-GM in cross-disease health assessment, with the core strength of directly correlating dietary quality with microbiome function, providing new perspectives for mechanism-driven intervention strategies.

Thus, the DI-GM may become a standardized tool for evaluating a balanced diet for the GM [6] and serve as an intervention target for risk stratification in multiple diseases. Several studies have revealed the correlation between GM and ASCVD [8–10], indicating that modulating GM may be a potential pathway for early ASCVD prevention and treatment [11], while improving dietary quality contributes to cardiovascular health [12]. DI-GM is considered a potential indicator of gut health due to its positive correlation with biomarkers of gut microbiome diversity (urinary glycerol and intestinal esters) [5]. And studies have shown that intestinal esters are associated with a lower risk of CVD death [13]. Based on this, we hypothesized that DI-GM, an index that integrates gut microbiology and dietary quality, could also reflect the whole-body nutritional and risk status of ASCVD, thus providing a new perspective for risk assessment of CVD.

Method and materials

Data sources

The U.S. National Health and Nutrition Examination Survey (NHANES) database is a survey project based on a cross-sectional population-based investigation performed by the National Center for Health Statistics (NCHS) to acquire information on the health and nutrition of the U.S. household people. The project consisted of two parts: a household interview and a physical assessment. The interview section encompassed demographic, socioeconomic, nutritional, and health-related inquiries. The physical evaluation encompassed physiological assessments and laboratory analyses [14]. The NCHS Research Ethics Review Board authorized the project. The information for this inquiry came from the official website (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm). It was a cross-sectional research project that used publicly accessible data from NHANES (2015–2018). After receiving official authorization, the original study protocol can be found on the NHANES Ethics Review Board website (https://www.cdc.gov/nchs/nhanes/irba98.htm). Participants provided their written informed cons ent when they were enrolled. The Protocol for Reporting Observational Studies in Epidemiology (STROBE) was followed by this study [15].

Study population

Herein, inclusion criteria for individuals were: age ≥ 65 years and finished an interview and assessment at the Mobile Examination Center (MEC). Exclusion criteria: participants with missing data on ASCVD status, DI-GM data, and covariates. The detailed flow chart is shown in Fig. 1.

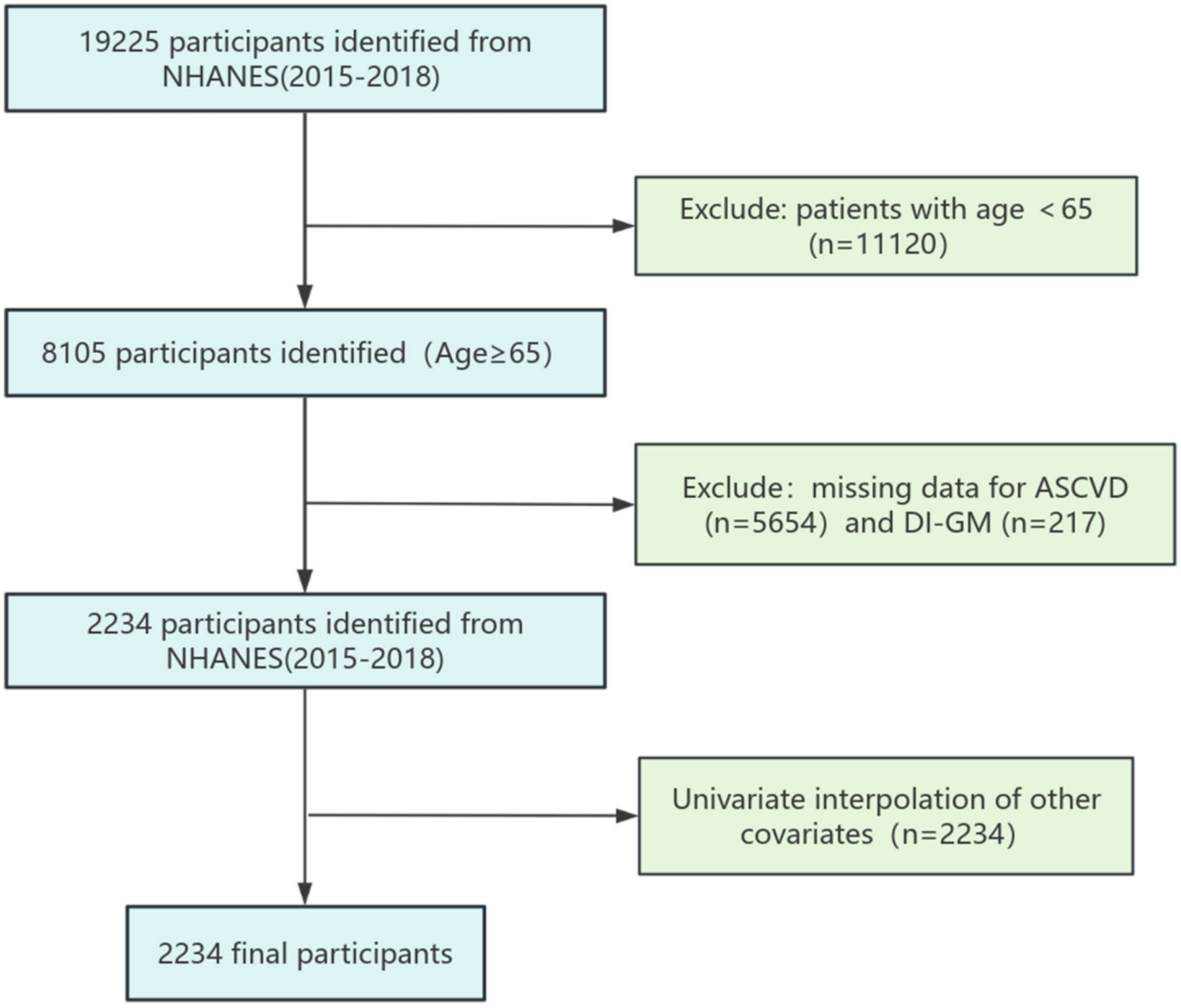

Fig. 1 The flowchart of NHANES 2015–2018 Participant

Diagnosis of ASCVD, DM, and hypertension (HTN)

The diagnosis of ASCVD is detected by a self-reported physician diagnosis obtained through the use of a standardized medical condition questionnaire in a personal interview and is diagnosed when the following conditions are met [14]: According to the 2013 Guidelines for the Treating Blood Cholesterol to Decrease ASCVD Risk in Adults, published by the American College of Cardiology (ACC) and the American Heart Association (AHA), this condition is identified by one or more of the following: A prognosis of myocardial infarction, angina, cardiac arrest, or cerebrovascular accident. Hard criteria were established as a previous occurrence of a heart attack or stroke [14].

Based on previous studies, diagnoses of DM and HTN were detected by self-reported physician diagnoses gained through personal interviews using a standardized medical status questionnaire. Individuals were asked, "Did your doctor tell you that you have DM/ HTN?" If the participant answered yes, he was considered to have DM/ HTN. Diagnosis of DM/ HTN by a physician was an outcome variable [16].

Assessment of DI-GM

In Fig. 2, DI-GM consists of 14 nutrients: 10 beneficial (avocado, broccoli, chickpeas, coffee, cranberries, fermented dairy products, fiber, green tea (it may be excluded in certain assessments because of NHANES not specifically documenting green tea intake), soy, and whole grains) and 4 harmful (red, processed meats, refined grains, and high-fat diets (fat provide ≥ 40% of total energy) [5]. A 24-hour recall approach developed by the U.S. Department of Agriculture (USDA) (Automated Multiple-Pass approach, AMPM) was employed

Table 2. Components of the DI-GM identified based on the systematic review.

Component	Included Foods within the Component	Scoring
Beneficial to gut microbiota		
Avocados	Avocados	For each component, a score of 1 if consumption at or above the sex-specific median, else 0
Broccoli	Broccoli	
Chickpea	Chickpeas	
Coffee	Coffee	
Cranberries	Cranberries	
Fermented dairy	Yogurt, cheese, kefir, sour cream, buttermilk	
Fiber	Not applicable	
Green tea	Green tea	
Soybean	Soy products—Soy milk, Tofu	
Whole grains	Grains defined as whole grains, containing the entire grain kernel—the bran, germ, and endosperm	
Unfavorable to gut microbiota		
High-fat diet (% energy)	Not applicable	0 if consumption at or above 40% energy from fat, else 1 For each remaining component, a score of 0 if consumption at or above the sex-specific median, else 1
Processed meat	Frankfurters, sausages, corned beef, and luncheon meat that are made from beef, pork, or poultry	
Red meat	Beef, veal, pork, lamb, and game meat; excludes organ meat and cured meat	
Refined grains	Refined grains that do not contain all of the components of the entire grain kernel	

Fig. 2 Components of DI-GM [5]. DI-GM consists of 14 food or nutrient components, including 10 considered beneficial for gut microbiota diversity—avocado, broccoli, chickpeas, coffee, cranberries, fermented dairy products, fiber, green tea (this component may be omitted in some analyses due to NHANES not specifically recording green tea consumption), soy, and whole grains—and 4 components considered detrimental to gut microbiota diversity—red meat, processed meats, refined grains, and high-fat diets (≥ 40% of total energy from fat)

to retrieve the dietary data from NHANES [17]. We used two 24-hour food recall data calculated for DI-GM. The first recall was obtained from a mobile examination center, while the second was conducted through telephone interviews [18]. All of the food and drink consumed in the last 24 h is recorded using this standardized interview technique, which is carried out by interviewers with professional training. By standardizing processes and equipment and instituting universal training for interviewers, NHANES was able to minimize interviewer bias and participant memory bias during data collection [19]. To score DI-GM, the gender-specific median intake for each component was calculated, except for high-fat diets, which used a fixed threshold of 40% fat energy. For participants whose consumption of each beneficial component exceeds the gender-specific median, and for those whose consumption of each adverse component is below the gender-specific median, the score is 1. For participants whose consumption of each beneficial component is below the gender-specific median, and for participants whose consumption of each adverse component is above the gender-specific median, the score is 0 [5]. By summing up the scores of each component, since the NHANES 24-hour recall data does not include specific tea consumption, a DI-GM score of 0–13 is obtained and grouped into quartiles: 0–3, 4, 5, and ≥ 6 [6].

Other covariates

We intended to lessen any confounding bias in the analysis by the selection of factors grounded in prior research and clinical validity. Our goal in choosing covariates was to minimize the influence of confounding factors by relying on previous research and clinical validity. Factors such as age, gender, race, education, marital status, household income to poverty ratio (HIPR), body mass index (BMI), alcohol intake, smoking, HTN, history of diabetic exacerbations, and activity status (PAQ) were among the covariates that were chosen [20, 21]. Race was classified into 5 groups: Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and other Race - Including Multi-Racial. The education is classified into 3 classes: Less than high school, High school or equivalent, and above high school. Marital status is categorized into 4 categories: Married, Never married, Living with a partner, and other. HIPR is divided into 3 categories: <1.3 (low), 1.3–3.5 (medium), and ≥ 3.5 (high) [22]. The BMI calculation was as weight (kg)/height $(m)^2$ and was classified into three classes: <25, 25–30, and ≥ 30 kg/m^2. Respondents were considered drinkers if they had at least 12 drinks/year during their lifetime [23]. Smoking status was classified into 3 classes: (1) never-smokers who had not smoked 100 cigarettes in their lifetime and did not smoke now; (2) ex-smokers who had smoked at least 100 cigarettes in their lifetime but did not smoke now; and

(3) current smokers who had smoked at least 100 cigarettes in their lifetime and currently smoked every day or a few days [24]. HTN was described by an average systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, self-reported diagnosis, or use of antihypertensive pharmaceuticals [25]. Activity was categorized into 5 categories: vigorous work activity, moderate work activity, walk or bicycle, vigorous recreational activities, and moderate recreational activities [23].

Comprehensive measurement protocols are available at https://www.cdc.gov/nchs/nhanes [26], accessed Novem ber 12, 2024.

Statistical analysis

Herein, statistical assessments were two-sided, with $P = 0.05$ considered significant. R 4.22 (http://www.R-project.org, The R Foundation) and Free Statistics software versions 2.0 were employed for all assessments [27]. When describing data for continuous variables, we used the mean ± standard deviation (SD) or median and interquartile range (IQR). When describing data for categorical variables, we used frequencies (percentages). We used the t-test (for normally distributed data) and the Kruskal-Wallis test (for skewed variables) to look at continuous variables [27].

The DI-GM was categorized into 4 quartiles (Q1: 0–3; Q2: 4; Q3:5; Q4: 6–9), with the first quartile (Q1) designated as the reference quartile. We utilized univariate and multivariate binary logistic regression to further examine the association between DI-GM and ASCVD. In multivariate logistic regression, we delineated (1) unadjusted models, (2) Model 1: adjusted for covariates including age and sex, (3) Model 2: adjusted for race, education, marital status, HIPR, BMI, activity status, alcohol and smoking status on top of the variables in Model 1 ($p < 0.001$); and (4) Model 3: comorbidities, such as (HTN + DM) ($p < 0.001$). Additionally, we employed restricted cubic spline curve (RCS) regression with three sections (10th, 50th, and 90th percentile) to check whether the correlation between DI-GM and ASCVD was linear. Subgroup assessments of age, gender, BMI, smoking status, alcohol intake, DM, and HTN were performed to examine the presence of significant interactions of these covariates with the correlation between DI-GM and ASCVD. The Sobel test and bootstrap method were used in mediation analyses to investigate the roles of BMI. The 95% CIs of the mediation effect were calculated from 1,000 simulations. This mediated proportion served as an indicator of the mediation effect.

Results

Baseline characteristics of the research cohort

Table 1 shows the demographic and health characteristics of 2,234 older adults (50.3% male and 49.7% female) categorized by DI-GM quartile, with their ages ranging from 65 to 80 years and a mean age of 73.1 ± 5.3 years. The data showed that in the group with higher DI-GM values, there were more non-Hispanic whites/blacks and other races, higher levels of education, higher proportions of none or former smokers and none-drinkers, higher household incomes, higher levels of BMI, and lower levels of sports and recreation. In addition, as DI-GM tertiles increased, participants' mean age and prevalence of CVD, ASCVD, DM, and HTN also increased. Notably, as DI-GM quartiles increased, the proportion of participants who had vigorous work activity increased. These findings may have important implications for understanding the relationship between DI-GM and cardiovascular health (Table 1).

DI-GM affected the risk of ASCVD

Univariate analyses showed that age, sex, race, marital status, education level, household income ratio, smoking status, alcohol intake, BMI, DI-GM, and advantageous or harmful to GM, HTN, and DM were linked to ASCVD (Table 2).

Table 3 illustrates the outcomes of the weighted logistic regression analysis. In the uncorrected model, DI-GM was negatively linked to the risk of ASCVD (OR,0.87; 95% CI, 0.85 ~ 0.88). The outcomes remained consistent after controlling for age and sex (OR, 0.88; 95% CI, 0.87 ~ 0.90). Following the adjustment of potential confounds such as race, education, marital status, household income ratio, body mass index (BMI), alcohol intake, smoking status, and activity, Model 2 employed a multifactor regression model to reveal a significant inverse association ($P < 0.001$). Model 3 was adjusted for the comorbidity indices HTN + DM based on model 2, and DI-GM remained significantly negatively related to the risk of ASCVD (OR,0.92; 95% CI, 0.85 ~ 0.99, $P < 0.001$). When the DI-GM transformation was conducted into a categorical variable, the same significant positive correlation was found in the full model ($P < 0.001$).

Dose-response relationships

In Fig. 3, we used RCS analysis to evaluate the relationship between the DI-GM, advantageous or harmful to GM, and ASCVD. Upon the adjustment of all covariates in Model 3 above, we detected a linear relationship between the DI-GM and ASCVD ($P = 0.13$) and a nonlinear relationship between the advantageous and harmful to GM and ASCVD ($P = 0.001$, $P < 0.001$).

In the threshold analysis, there was a significant negative link between the beneficial GM score and ASCVD when it was < 4.186, which means that for every 1-unit increase in the beneficial to GM score, there was a 0.78-fold reduction in the risk of ASCVD. When the beneficial GM score was ≥ 4.186, there was a significant positive

Table 1 Baseline characteristics of the elderly participants by DI-GM scores

Variables	Total (*n* = 2234)	DI-GM				*P*-Value
		Q1 (*n* = 473)	Q2 (*n* = 500)	Q3 (*n* = 582)	Q4 (*n* = 679)	
Age (year), Mean ± SD	73.1 ± 5.3	72.7 ± 5.4	73.3 ± 5.4	73.2 ± 5.4	73.0 ± 5.2	0.302
Gender, n (%)						0.067
Male	1123 (50.3)	248 (52.4)	271 (54.2)	284 (48.8)	320 (47.1)	
Female	1111 (49.7)	225 (47.6)	229 (45.8)	298 (51.2)	359 (52.9)	
Ethnicity, n (%)						**< 0.001**
MA	261 (11.7)	48 (10.1)	54 (10.8)	80 (13.7)	79 (11.6)	
OH	238 (10.7)	40 (8.5)	55 (11)	71 (12.2)	72 (10.6)	
NHW	1089 (48.7)	219 (46.3)	235 (47)	287 (49.3)	348 (51.3)	
NHB	417 (18.7)	119 (25.2)	108 (21.6)	93 (16)	97 (14.3)	
Other	229 (10.3)	47 (9.9)	48 (9.6)	51 (8.8)	83 (12.2)	
Marital status, n (%)						0.198
Mrd	1194 (53.4)	241 (51)	266 (53.2)	312 (53.6)	375 (55.2)	
NM	101 (4.5)	31 (6.6)	20 (4)	28 (4.8)	22 (3.2)	
LWP	62 (2.8)	14 (3)	18 (3.6)	18 (3.1)	12 (1.8)	
Other	877 (39.3)	187 (39.5)	196 (39.2)	224 (38.5)	270 (39.8)	
Education, n (%)						**< 0.001**
< HS	581 (26.0)	121 (25.6)	150 (30)	153 (26.3)	157 (23.1)	
HS	518 (23.2)	139 (29.4)	109 (21.8)	134 (23)	136 (20)	
> HS	1135 (50.8)	213 (45)	241 (48.2)	295 (50.7)	386 (56.8)	
HIPR, Median (IQR)	2.1 (1.2, 3.8)	2.0 (1.1, 3.2)	2.0 (1.2, 3.6)	2.0 (1.2, 3.7)	2.3 (1.4, 4.3)	**0.002**
Smoking, n (%)						**< 0.001**
Never	1111 (49.7)	218 (46.1)	239 (47.8)	291 (50)	363 (53.5)	
Former	891 (39.9)	192 (40.6)	197 (39.4)	224 (38.5)	278 (40.9)	
Current	232 (10.4)	63 (13.3)	64 (12.8)	67 (11.5)	38 (5.6)	
Drinking alcohol, n (%)						0.834
No	1426 (63.8)	295 (62.4)	317 (63.4)	373 (64.1)	441 (64.9)	
Yes	808 (36.2)	178 (37.6)	183 (36.6)	209 (35.9)	238 (35.1)	
BMI (kg/m^2), Mean ± SD	29.7 ± 7.2	26.1 ± 5.0	29.8 ± 6.1	30.6 ± 7.2	33.4 ± 8.3	**< 0.001**
Physical activity, n (%)						
Vigorous	1899 (85.0)	396 (83.7)	425 (85)	500 (85.9)	578 (85.1)	0.803
Moderate	1470 (65.8)	327 (69.1)	346 (69.2)	379 (65.1)	418 (61.6)	0.015
Walk or bicycle	1828 (81.8)	393 (83.1)	414 (82.8)	474 (81.4)	547 (80.6)	0.656
Vigorous recreational	2003 (89.7)	441 (93.2)	454 (90.8)	530 (91.1)	578 (85.1)	< 0.001
Moderate recreational	1435 (64.2)	347 (73.4)	335 (67)	379 (65.1)	374 (55.1)	< 0.001
CHF, n(%)	203 (9.1)	54 (11.4)	54 (10.8)	48 (8.2)	47 (6.9)	**0.026**
CHD, n(%)	280 (12.5)	63 (13.3)	74 (14.8)	74 (12.7)	69 (10.2)	0.106
Angina, n(%)	119 (5.3)	25 (5.3)	27 (5.4)	32 (5.5)	35 (5.2)	0.994
Heart attack, n(%)	248 (11.1)	57 (12.1)	61 (12.2)	66 (11.3)	64 (9.4)	0.39
Stroke, n(%)	205 (9.2)	57 (12.1)	51 (10.2)	51 (8.8)	46 (6.8)	**0.017**
CVD, n(%)	599 (26.9)	140 (29.6)	147 (29.6)	160 (27.5)	152 (22.4)	**0.013**
ASCVD, n(%)	401 (17.9)	97 (20.5)	97 (19.4)	108 (18.6)	99 (14.6)	**0.042**
DM, n(%)	660 (29.5)	168 (35.5)	158 (31.6)	171 (29.4)	163 (24)	**< 0.001**
Hypertension, n(%)	1408(63.0)	306 (64.7)	307 (61.4)	370 (63.6)	425 (62.6)	0.738

Education, n (%): < HS (Less than High School) / HS (High School or Equivalent) / > HS (Above High School). Ethnicity: MA = Mexican American; OH = Other Hispanic; NHW = Non-Hispanic White; NHB = Non-Hispanic Black. Marital Status: Mrd = Married; NM = Never Married; LWP = Living with Partner; BMI = Body Mass Index; CHD = Coronary Heart Disease; CHF = Congestive Heart Failure; ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota; PIR = Poverty-Income Ratio; HIPR = Household Income to Poverty Ratio. 99% of the data are displayed

correlation between the risk and ASCVD, and even a 22.24-fold elevation in the risk of ASCVD for each 1-unit elevation in the advantageous to GM score. The harmful GM fraction exhibited a significant positive correlation with ASCVD risk when below 2.862 (OR, 95% CI: 1.49, 1.18–1.88, $P < 0.001$) but demonstrated a significant negative correlation with ASCVD risk when ≥ 2.862 (OR, 95% CI: 0.34, 0.23–0.50, $P < 0.001$) (Table 4).

Table 2 Single-factor analysis associated with ASCVD in U.S. Older adults. (one-way regression analysis OR (95% CI))

Variable	OR_95CI	P_value
Age (year)	1.05 (1.03 ~ 1.07)	**< 0.001**
Gender, n (%)		
Male	1 (reference)	
Female	0.61 (0.49 ~ 0.76)	**< 0.001**
Race/ethnicity, n (%)		
Mexican American	1 (reference)	
MA	1.46 (0.9 ~ 2.35)	0.123
OH	1.56 (1.06 ~ 2.28)	0.023
NHW	1.24 (0.8 ~ 1.92)	0.335
NHB	1.09 (0.66 ~ 1.81)	0.739
Marital status, n (%)		
Mrd	1 (reference)	
NM	0.76 (0.42 ~ 1.39)	0.375
LWP	1.65 (0.9 ~ 3)	0.105
Other	1.32 (1.06 ~ 1.66)	0.015
Education, n (%)		
< HS	1 (reference)	
HS	0.89 (0.66 ~ 1.19)	0.43
> HS	0.73 (0.56 ~ 0.94)	0.014
HIPR, n (%)	0.85 (0.78 ~ 0.92)	**< 0.001**
BMI (kg/m^2), n (%)	1.01 (1 ~ 1.03)	**0.003**
Smoking, n (%)		
Never	1 (reference)	
Former	1.59 (1.26 ~ 2.01)	**< 0.001**
Current	1.96 (1.39 ~ 2.77)	**< 0.001**
Drinking alcohol, n (%)		
No	1 (reference)	
Yes	0.91 (0.73 ~ 1.14)	0.42
Physical activity, n (%)		
Vigorous	1 (0.74 ~ 1.36)	0.984
Moderate	1.15 (0.91 ~ 1.45)	0.239
Walk or bicycle	1.53 (1.12 ~ 2.08)	0.007
Vigorous recreational	1.73 (1.14 ~ 2.63)	0.01
Moderate recreational	1.55 (1.22 ~ 1.96)	< 0.001
DI-GM, n (%)	0.91 (0.85 ~ 0.98)	**0.010**
Beneficial to gut microbiota, n (%)	0.86 (0.79 ~ 0.95)	**0.002**
Unfavorable, n (%)	0.99 (0.89 ~ 1.1)	0.847
DM, n (%)	1.75 (1.39 ~ 2.19)	**< 0.001**
Hypertension, n (%)	2.17 (1.69 ~ 2.79)	**< 0.001**

Education, n (%): < HS (Less than High School) / HS (High School or Equivalent) / > HS (Above High School). Ethnicity: MA = Mexican American; OH = Other Hispanic; NHW = Non-Hispanic White; NHB = Non-Hispanic Black. Marital Status: Mrd = Married; NM = Never Married; LWP = Living with Partner; BMI = Body Mass Index; ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota; DM = Diabetes Mellitus; HIPR = Household Income to Poverty Ratio. 99% of the data are displayed

We also used box plots to illustrate the differences in DI-GM indices between participants with and without ASCVD. As shown in Fig. 4, the ASCVD group had a lower DI-GM than the non-ASCVD group, and the variation between both groups was significant (4.53 vs. 4.75, $P = 0.008$).

Table 3 Multifactor Analysis - the correlation between DI-GM and ASCVD risk among U.S. Older adults. (multifactor regression OR (95% CI))

Variable	Non-adjusted model	Model 1	Model 2	Model 3
DI-GM	0.87 (0.85 ~ 0.88)	0.88 (0.87 ~ 0.90)	0.91 (0.85 ~ 0.98)	0.92 (0.85 ~ 0.99)
P-value	< 0.001	< 0.001	< 0.001	< 0.001
Beneficial	0.76 (0.71 ~ 0.81)	0.78 (0.72 ~ 0.83)	0.81 (0.75 ~ 0.88)	0.81 (0.75 ~ 0.88)
P-value	< 0.001	< 0.001	< 0.001	< 0.001
Unfavorable	1.03 (0.95 ~ 1.12)	1.04 (0.96 ~ 1.13)	1 (0.92 ~ 1.09)	1.01 (0.93 ~ 1.1)
P-value	0.423	0.305	0.968	0.804
DI-GM, quartile				
Q1(0–3)	1(Ref)	1(Ref)	1(Ref)	1(Ref)
Q2(4)	0.93 (0.68 ~ 1.28)	0.86 (0.79 ~ 0.92)	0.88 (0.69 ~ 1.12)	0.99 (0.71 ~ 1.37)
Q3(5)	0.88 (0.65 ~ 1.20)	0.51 (0.47 ~ 0.55)	0.52 (0.39 ~ 0.68)	0.88 (0.64 ~ 1.23)
Q4(6–9)	0.66 (0.49 ~ 0.90)	0.59 (0.55 ~ 0.63)	0.62 (0.48 ~ 0.79)	0.73 (0.52 ~ 1.01)
P-trend	< 0.001	< 0.001	< 0.001	< 0.001

ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota; CI = Confidence interval; OR = Odd Ratio. Adjusted for key demographics, health factors, and lifestyle. 99% data shown

Sensitivity analysis

In several subgroups, stratified analysis was performed to assess the potential effect of modifications on the relationship between the DI-GM and ASCVD. After stratifying by age, sex, BMI, and diabetes, we found significant interactions for all subgroups except diabetes (Fig. 5).

Mediating function of BMI in DI-GM and ASCVD

Existing evidence demonstrates that BMI is independently associated with both ASCVD risk and DI-GM scores [6, 28], a finding corroborated by the significant BMI-DI-GM-ASCVD correlations observed in this study (Tables 1 and 2). To elucidate the mechanistic pathway underlying the DI-GM–ASCVD relationship, we performed a mediation analysis with BMI as the hypothesized mediator. Key findings from the analysis (Fig. 6) reveal:

DI-GM's inverse association with BMI: Higher DI-GM scores significantly predicted lower BMI values (β = −0.0018, 95% CI: −0.0034 to − 0.0006; $P = 0.015$).

BMI's positive association with ASCVD: Reduced BMI was independently linked to lower ASCVD risk (β = 0.003, 95% CI: 0.0012–0.0298; $P = 0.009$).

Significant mediation effect: BMI accounted for 11.51% (95% CI: 2.54–54.1%; $P = 0.016$) of the total effect of DI-GM on ASCVD, confirming its partial mediating role.

These results suggest that the cardioprotective effect of favorable gut microbiota dietary patterns (reflected by

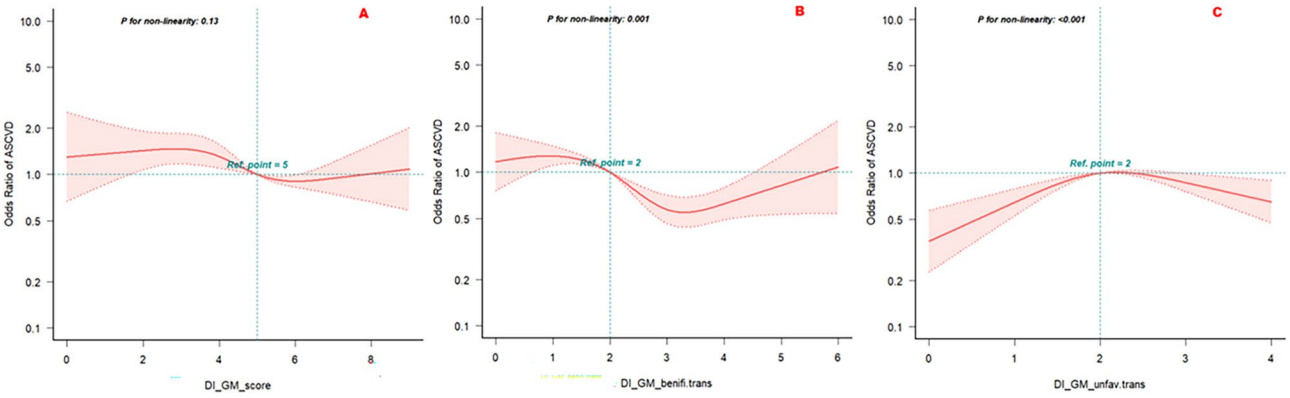

Fig. 3 Association Between DI-GM, Gut Microbiota (Beneficial & Unfavorable), and ASCVD by RCS. ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota; Fig. 3A represents the linear relationship between DI-GM and ASCVD; Fig. 3B and C represent Nonlinear Beneficial / Unfavorable Gut Microbiota and ASCVD

Table 4 Dose-response relationships - threshold effect of gut microbiota (beneficial and unfavorable) on ASCVD

Beneficial	Adjusted Model		Unfavorable	Adjusted Model	
	OR (95% CI)	*p*-value		OR (95% CI)	*p*-value
< 4.186	0.78 (0.72 ~ 0.86)	< 0.001	< 2.862	1.49 (1.18 ~ 1.88)	< 0.001
≥ 4.186	22.24 (21.62 ~ 23.55)	< 0.001	≥ 2.862	0.34 (0.23 ~ 0.50)	< 0.001
Log-likelihood ratio test		0.001	Log-likelihood ratio test		< 0.001

ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota; CI = Confidence interval; OR = Odd Ratio. Adjusted for key demographics, health factors, and lifestyle. 99% data shown

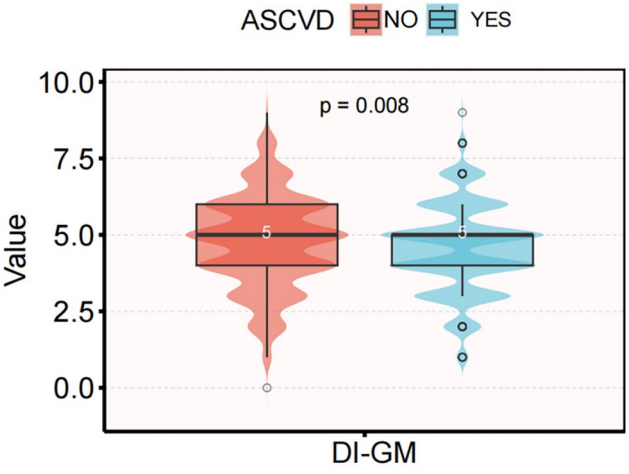

Fig. 4 Distribution of the DI-GM in participants with or without ASCVD (box diagram). ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota;

higher DI-GM) may be partially mediated through BMI reduction. However, the modest proportion of mediation (11.51%) implies that additional pathways (e.g., inflammation modulation, metabolite production) likely contribute to the DI-GM–ASCVD association, warranting further investigation.

Discussion

This study explored the association between DI-GM, beneficial/unfavorable to gut microbiota score and ASCVD based on NHANES, 2015–2018 data and assessed the mediating role of BMI. The results showed that higher DI-GM levels were significantly associated with a lower risk of ASCVD, and the association was more stable in patients with DM.

DI-GM was developed based on existing literature and research and contains 14 dietary ingredients that are either beneficial or harmful to the gut microbiota. The selection of these ingredients was based on conclusions drawn from previous longitudinal intervention studies showing significant effects on the gut microbiota. Therefore, we believe that the DI-GM is theoretically sound and able to reflect the potential effects of diet on the gut microbiota. This study is the first to find a linear negative association between DI-GM and ASCVD, i.e., higher DI-GM scores were associated with a lower risk of ASCVD, and this result held in a model adjusted for all covariates. In addition, BMI partially mediated the association, suggesting that DI-GM may reduce ASCVD risk by improving BMI. This finding complements the diet-gut flora-cardiovascular health association and provides new perspectives for future research.

Previous studies have shown that gut microbiome imbalance is closely associated with the occurrence of ASCVD [29], and improving dietary structure can effectively reduce CVD risk [30]. In recent years, it has been found that changes in intestinal microflora such as Trichosporonaceae, Ruminalococcaceae, and E. pulaefaciens can reduce the probability of ASCVD in patients [31] and mitigate cardiovascular risk factors. Meanwhile, low dietary quality has surpassed other causes of death as the leading cause of CVD mortality risk [32]. The DASH

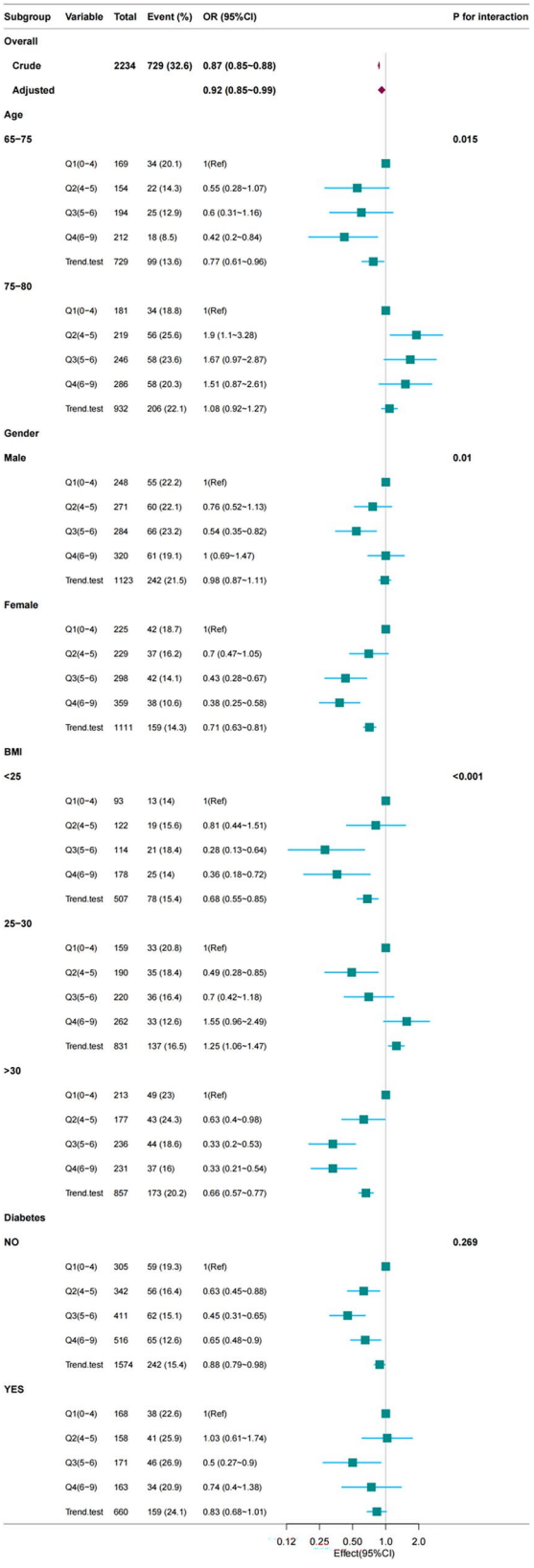

Fig. 5 Subgroup Analysis of DI-GM and ASCVD (Forest Plot, Adjusted for Key Factors). ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota; BMI = body mess index; CI = Confidence interval; OR = Odd Ratio. Adjusted for key demographics, health factors, and lifestyle

(Dietary Approaches to Stop HTN) diet is a dietary pattern rich in beneficial to gut microbiota components that effectively reduces the risk of blood pressure, lipid levels, and ASCVD in patients [32]. This study found that individuals with higher DI-GM scores have a lower risk of ASCVD, consistent with findings from dietary patterns such as Mediterranean Diet (MED) [33–34] and DASH [35]. Furthermore, Rienks et al. [13] found that higher levels of gut metabolites, such as enterolactone, are associated with a lower risk of CVD, a finding that was partially confirmed in this study.

In contrast, the uniqueness of the DI-GM compared to traditional dietary indices (e.g., the Mediterranean Diet Score or the DASH Diet Score) lies in its microbiome-centered design logic [5]. Although the Mediterranean diet is strongly associated with cardiovascular health, its scoring criteria are mainly based on macro-nutrients and food groups (e.g., olive oil, fish intake), and lack the quantification of gut flora-specific effects. In contrast, the DI-GM is able to more accurately reflect diet-microbiome-host interactions by incorporating fermented dairy products, dietary fiber, and other components that directly modulate the flora [5]. For example, whole grain and coffee intake in DI-GM is associated with increased abundance of Roseburia spp. whose butyrate synthesizing capacity has been shown to have anti-inflammatory and anti-atherosclerotic effects [36, 37]. This mechanism-oriented design makes DI-GM more targeted in personalized nutritional interventions.

The results of this study suggest that DI-GM scores are linearly and negatively associated with the risk of ASCVD, and that DI-GM may reduce ASCVD risk through the following mechanisms: first, it regulates the gut microbiome, and individuals with high DI-GM scores may have healthier gut microbiota, fewer pro-inflammatory microorganisms (such as Firmices) and inflammatory mediators, thereby lowering the risk of atherosclerosis [38]. Secondly, DI-GM can improve metabolism. Research has found that gut microbiome metabolites, such as short-chain fatty acids, can enhance insulin resistance and lipid metabolism, helping to control metabolic risk factors for ASCVD [39]. Finally, this study found that BMI partially mediates between DI-GM and ASCVD, suggesting that DI-GM may reduce the risk of ASCVD by regulating weight and fat metabolism.

However, the present study further found a 21.24-fold increased risk of ASCVD with a beneficial component of gut flora score > 4.186, whereas a 66% reduction in the risk of ASCVD was observed with a harmful component of gut flora score ≥ 2.862. In this regard, we believe that this seemingly contradictory result (high scores of beneficial components increase risk and high scores of harmful components decrease risk) actually reflects a complex mechanism of interaction between gut flora and ASCVD,

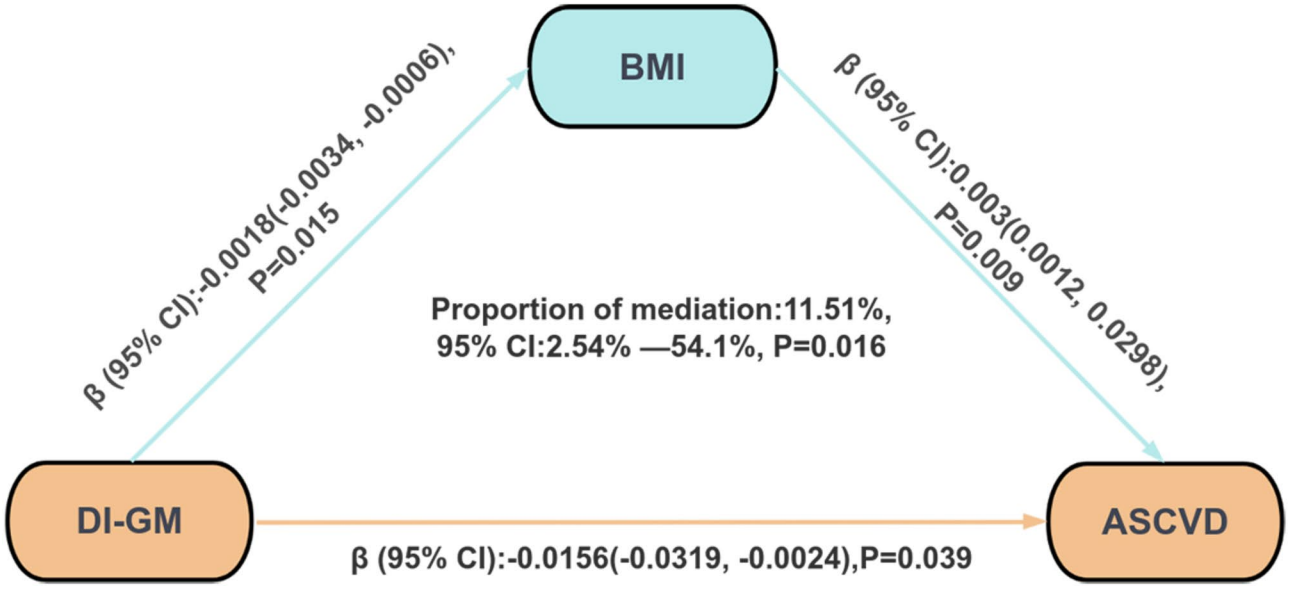

Fig. 6 Mediation Analysis: BMI in DI-GM and ASCVD Link (Adjusted for Key Factors). ASCVD = Atherosclerosis Cardiovascular Disease; DI-GM = Dietary Index for Gut Microbiota; BMI = body mess index; CI = Confidence interval; OR = Odd Ratio. Adjusted for key demographics, health factors, and lifestyle

which may involve the following explanations: 1. The "double-edged sword" effect of bacterial metabolites. Metabolites of certain"beneficial bacteria" (e.g., TMAO, secondary bile acids) may promote AS under certain conditions [40]. Above a threshold (e.g., score > 4.186), the flora balance may be disrupted, inducing inflammation instead. Some "harmful bacteria" may reduce inflammation by competitively inhibiting more dangerous pathogens (e.g., lipopolysaccharide-producing Gram-negative bacteria), or by modulating immune tolerance [41]. 2. Diet-flora-host interactions. High "Beneficial Ingredient" scores may counteract the flora benefits if they also consume large amounts of red meat/choline (TMAO precursor) [42]; A diet rich in polyphenols/fiber for those with high "harmful component" scores may be protective by inhibiting pathogenic bacterial virulence [43]. Individual differences (e.g., genotype, baseline inflammatory status) may lead to distinct effects of flora on ASCVD (e.g., ApoE mutation carriers are more sensitive to flora metabolism [44]). 3. Methodological considerations. The categorization of "beneficial/harmful" components may be oversimplified. The "beneficialness" of certain flora at the phylum level (e.g., phylum Thick-walled Bacteria/Hyphomycetes) depends on the specific species and functional genes. In ASCVD patients, disease states (e.g., chronic medication, vascular inflammation) may lead to changes in the intestinal microenvironment, which in turn affects the composition of the flora (i.e., disease → flora change, not vice versa) [45].

Therefore, the clinical use of DI-GM requires individualized assessment of the patient: a combination of colony function tests (e.g., macro-genomic sequencing) rather than score alone, with a focus on specific metabolic pathways (e.g., TMAO production, short-chain fatty acid synthesis). Dynamic monitoring of people with very high scores (e.g., > 4.186) for "beneficial components" should include screening for TMAO and inflammatory markers (e.g., hs-CRP) to identify potential risks. For those with high "harmful component" scores but low risk, the current colony structure can be preserved while further optimizing function through diet (e.g., increased dietary fiber).

The DI-GM score can be used as a new predictor of ASCVD risk with important clinical and public health implications. Its potential clinical applications include: (1) personalized dietary advice (e.g., probiotic/prebiotic supplementation for those with low scores); (2) refined stratification of ASCVD risk (combining traditional scores and flora metabolic markers); and (3) dynamic monitoring of intervention effects (improvement of DI-GM and metabolic indicators after dietary adjustment). In the future, further studies on the causal mechanisms are needed to develop clinical guidelines based on DI-GM. Dietary modification and improvement of DI-GM scores are effective strategies for the prevention of ASCVD, especially for high-risk elderly populations. Controlling body mass index can be a key mediator in reducing the risk of ASCVD.

Advantages and limitations

This research possesses multiple strengths: This investigation is the inaugural examination of the correlation between DI-GM and ASCVD, examining the mediating role of BMI in this context. A suitably large sample size

was provided by the research population, which was an older American population typical of the nation. Since DI-GM is a new metric that has not been clinically validated, we have enhanced the reliability of this study through various means, such as NHANES using standardized data collection methods to reduce interviewer biases and participant memory biases. At the same time, we conducted two 24-hour recalls and adjusted all covariates in multi-factor regression analysis, performing stratified and sensitivity analyses to comprehensively reduce the potential impact of these factors on the results. Therefore, the research results have a certain degree of reliability. This study identified a negative correlation between DI-GM and ASCVD, highlighting significant clinical implications for early identifying, preventing, and treating ASCVD. We conducted a dose-response assessment to quantitatively evaluate the link between DI-GM and ASCVD. Our study is consistent with previous findings on the relationship between diet, gut microbiota and cardiovascular health. This consistency increases the authors' confidence in DI-GM and further validates the reliability of DI-GM as a new indicator.

Nonetheless, our investigation has evident limitations. Firstly, cross-sectional studies do not allow for causal inferences, and baseline DI-GM data do not allow for assessment of the influence of time status on experimental outcomes. Secondly, the study's DI-GM components and covariates relied on self-report, coupled with the fact that the study population was elderly and may suffer from memory loss. As a result, there may be misinterpretation of the survey or recall questions, especially in the case of ASCVD patients who may have changed their diet after diagnosis, resulting in high DI-GM indices. Although the DI-GM index is based on a synthesis of intervention studies and has some reliability, its calculation does not cover all foods associated with the gut microbiome. In addition, the cross-sectional nature of the study limited our ability to obtain dynamic DI-GM data, and it was not possible to confirm whether ASCVD patients improved their diet after diagnosis, which may have influenced the results. Therefore, future studies could incorporate actual gut microbiota measurements (e.g., 16 S rRNA sequencing or macrogenomic sequencing) to verify whether DI-GM accurately reflects changes in the gut microbiota. The dynamic relationship between DI-GM and gut microbiota can also be better understood through a longitudinal study design and incorporating broader demographic data to track changes in participants' diet and gut microbiota over time. In addition, samples from clinical ASCVD patients could be collected for metabolomics analysis in order to explore the specific mechanisms by which DI-GM intervenes in ASCVD.

Conclusion

This study reveals for the first time a negative correlation between DI-GM and ASCVD, and finds that BMI plays a partial intermediary role in this association. DI-GM could become a powerful tool for ASCVD risk assessment, and future research may further explore the specific mechanisms by which DI-GM plays a role in the formation of ASCVD.

Abbreviations

BMI	Body Mass Index
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
DI-GM	Dietary Index for Gut Microbiota
PIR	Poverty-Income Ratio
HIPR	Household Income to Poverty Ratio. OR: Odds ratio
CI	Confidence interval

Acknowledgements

We thank Home for Researchers editorial team (www.home-for-researchers.com) for language editing service. Also, we thank Dr. Jie Liu (Dept. of Vascular & Endovascular Surgery, Chinese PLA General Hospital) for statistical support, study design insights, and paper feedback.

Author contributions

MM and SQ: Providing ideas and first drafts of manuscript writing; WP and ZX: responsible for collecting and organizing data; WL and CL: Responsible for reviewing and proofreading this manuscript and funding.

Funding

This work was supported by the Fujian Medical University's Startup Fund for Scientific Research (2021QH1240), high-level scientific and technological innovation team project of Kunshan Traditional Chinese Medicine Hospital (032025KCTD01).

Data availability

This study did not need ethical review or authorization since the secondary analysis did not necessitate any extra IRB approval.

Declarations

Competing interests

The authors declare no competing interests.

Institutional review board (IRB) statement

This study did not need ethical review or authorization since the secondary analysis did not necessitate any extra IRB approval.

Ethics statement

Consent was obtained post-NCHS Ethics approval of NHANES.

Declaration of conflicting interest

None.

Disclosures

None.

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Received: 8 February 2025 / Accepted: 22 April 2025
Published online: 11 May 2025

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