Association of insulin resistance with chronic diarrhea: based on the NHANES database 2005-2010

Keywords
chronic diarrhea, insulin resistance, NHANES

Abstract

Introduction

The evidence regarding the association of insulin resistance (IR) with chronic diarrhea (CD) remains scarce, especially without robust epidemiological support from large-scale population cohorts. Therefore, we aimed to explore the association of IR with CD by a cross-sectional study of data drawn from the National Health and Nutrition Examination Survey(NHANES) from 2005 to 2010.

Material and methods

Multiple logistic regression models combined with subgroup analyses were leveraged to explore the association of IR(triglyceride-glucose[TyG] index, metabolic score for IR [METS-IR] score, and Homeostasis Model Assessment of IR [HOMA-IR] score) with the prevalence of CD. Nonlinear correlations were measured by restricted cubic spline(RCS) curves. Finally, the diagnostic efficacy of these indicators was calculated and examined with the receiver operating characteristic(ROC) curve and area under the curve(AUC).

Results

After full adjustment for covariates(e.g., sex, age, race, education, poverty-to-income ratio (PIR), body mass index (BMI), smoking status), the TyG index(OR: 1.35, 95% CI: 1.12-1.63), METS-IR score(OR: 2.00, 95% CI: 1.31-3.06), and HOMA-IR score (OR: 1.02, 95% CI: 1.00-1.03) showed positive associations with the prevalence of CD. The RCS curve analysis showed a non-linear association between HOMA-IR and CD (P-non-linear=0.003), with an inflection point at 2.423. METS-IR and TyG showed a significant positive linear association with CD(both P-non-linear > 0.05). The ROC curve analysis identified METS-IR score as the optimal diagnostic indicator for CD (AUC=0.645, 95% CI: 0.619-0.672).

Conclusions

The present research discovered a significant positive association of IR with CD among a demographically representative cohort of US adults. Elevated IR scores are significantly associated with the prevalence of CD.

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Conclusion: The present research discovered a significant positive association of IR with CD among a demographically representative cohort of US adults. Elevated IR scores are significantly associated with the prevalence of CD.

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1. Introduction

Chronic diarrhea (CD) represents a notable public health concern. While this condition does not increase mortality risk, patients with CD exhibit significantly higher prevalence of detected organic pathologies—including colon polyps and ulcerative colitis—relative to the general population [1]. The condition causes physical and mental distress, affects the patients' quality of life and nutrient absorption capacity, and places a greater economic strain on the health care system. CD is usually defined as having more than 3 stools per day, or a total stool volume of >200 g/d, with water content of over 85%, for more than 4 weeks [2]. CD is estimated to be present in 1%-5% of adults [3].

CD can be triggered by various diseases, such as functional and organic diseases. The pathophysiological mechanisms of diarrhea caused by different etiologies are different. Previous studies have shown that intestinal function is somewhat affected in patients with type 2 diabetes compared with the normal population [4]. It may be related to autonomic neuropathy, hyperglycemia-stimulated intestinal microangiopathy and gastrointestinal hormone secretion disorders[5, 6], which seriously affect the quality of life and blood glucose control of patients[7]. Insulin resistance (IR) is not only the main feature of type 2 diabetes and prediabetes, but also a systemic metabolic disorder that triggers chronic low-grade inflammation, autonomic dysfunction, and changes in hormone levels. These can act directly or indirectly on the gastrointestinal tract, thereby causing or aggravating chronic diarrhea. However, currently, most studies on CD focus on its association with intestinal microecology, inflammatory response, and abnormalities in gastrointestinal mucosal function [8-9]. Studies on the association of IR with CD remain sparse, especially without robust epidemiological evidence from large-scale population cohorts. To quantify IR, there are a number of methods. The

hyperinsulinemic-euglycemic clamp (HEGC) test is considered the gold standard for detecting IR [10]. Nevertheless, it is time-consuming, costly, and technically difficult to apply in extensive epidemiological research and clinical practice. Homeostasis Model Assessment of IR (HOMA-IR), computed from fasting insulin (FINS) and fasting plasma glucose (FPG) measurements, is considered a reliable surrogate for HEGC test and is the most extensively utilized index in current practice [11]. Triglyceride-glucose (TyG) index is extensively acknowledged to be a recommended tool for evaluating IR [12]. It is simpler, more economical, and more suitable for clinical studies. Collectively, the TyG index, metabolic score for IR (METS-IR), and HOMA-IR score are widely adopted metrics for assessing IR because of their simplicity, availability, and low cost [13-16]. They have been extensively utilized to study the association of IR with type 2 diabetes, obesity, and cardiovascular disease.

Although the National Health and Nutrition Examination Survey (NHANES) lacks direct evidence demonstrating that IR independently contributes to CD, IR may be associated with CD through indirect mechanisms such as metabolic abnormalities, dysbiosis, and inflammation. Therefore, the present study examined the association of IR (TyG index, METS-IR score, and HOMA-IR score) with the prevalence of CD based on NHANES 2005-2010 data. The research aimed to provide new epidemiological evidence for CD and a potential clinical reference for early intervention and management of the disease.

2. Materials and Methods

2.1 Study population

In total, there were 31,034 participants in the NHANES [17] (2005-2010) of the United States of America. Eventually, 5,606 individuals were included in this research. The inclusion criteria

were as follows: (i) age ≥20 years; (ii) with complete data of FPG, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and FINS; (iii) with complete data of Bristol Stool Form Scale (BSFS), and without constipation; (iv) with complete data of age, sex, race, education, PIR, body mass index (BMI), smoking status, alcohol consumption, caffeine intake, depression scale score, and history of diabetes mellitus (DM). The filtering process is demonstrated in Figure 1. All the data were obtained from the official website of NHANES. All the study protocols in the survey were approved by the Ethics Review Committee of the National Center for Health Statistics (NCHS). Informed consent was documented for all participants. Because the data retrieved in this research were publicly available and de-identified, no additional ethical approval was required.

2.2 Exposure variables

The TyG index [18] was computed as ln(TG × FPG/2) (units: TG and FPG in mg/dL). The METS-IR score [19] was defined by ln[BMI × (TG + 2 × FPG)] / ln(HDL-C) (units: TG, FPG, HDL-C in mg/dL; BMI in kg/m²). HOMA-IR [20] was determined using (FPG × FINS)/22.5 (FPG in mmol/L; FINS in μU/mL). The TyG index, METS-IR score, and HOMA-IR score were divided into T1, T2, and T3 groups according to tertiles.

2.3 Outcome variables

During the NHANES survey, participants were issued a color card with images and a description card of the BSFS types (1 to 7). They were then asked, “Select the number corresponding to your usual or most common stool type.” Participants were confirmed with CD if they identified their usual or most common stool type as BSFS type 6 (fluffy with ragged edges, mushy) or type 7 (watery, no solid pieces). They were confirmed with chronic constipation when they chose type 1 (separate hard lumps, like nuts) or type 2 (sausage-shaped, frequent use of laxatives) [21, 22].

The present study included the normal and diarrhea populations.

2.4 Covariates

The researchers identified potential covariates based on previous studies and clinical expertise. Covariates included age, sex, race, education, PIR, BMI, smoking status, alcohol consumption, DM, depression, and caffeine intake (mg/d). Age was categorized as under 40 years, 40-60 years, and over 60 years. Race was categorized as non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, and other races. Education was categorized as less than high school, high school and equivalent, and beyond high school. PIR denoted a household's income relative to the federal poverty guidelines, and is categorized as less than 1.3, 1.3-3.5, and more than 3.5. Based on smoking status, participants were divided into former smokers, never smokers, and current smokers. Never smokers were those who have smoked fewer than 100 cigarettes. Former smokers were those who had smoked more than 100 cigarettes, but were non-smokers at the time. Current smokers were those who had smoked more than 100 cigarettes and still smoked on a few days or every day. Alcohol consumption was grouped into drinking and non-drinking. Drinking was characterized by having at least twelve alcoholic drinks a year, based on questionnaires administered via the Computer-Assisted Personal Interview (CAPI) system at the Mobile Examination Center (MEC). History of DM was categorized as either present or absent. A present history of DM was defined as those who had been previously informed by a physician that the respondent had diabetes or those with a glycosylated hemoglobin level > 6.5%. Depression was characterized by a score of>10 in the Patient Health Questionnaire (PHQ). Caffeine intake was examined with a standardized 24-hour dietary recall interview at the dietary assessment center.

2.5 Statistical methods

All continuous variables conforming to a normal distribution were expressed as mean (SD), and inter-group comparisons were examined with the independent samples t-test. Non-normally distributed continuous variables were expressed as [M(P25, P75)], and inter-group comparisons were conducted with the Mann-Whitney U-test. Categorical variables were expressed as percentages(%), and inter-group disparities were compared with the X^2 test. Variance inflation factor (VIF) was leveraged to examine potential multicollinearity between covariates. All included covariates showed a VIF value of less than 5, denoting no significant multicollinearity in the current study. Logistic regression models were leveraged to ascertain the association of TyG index, METS-IR score, and HOMA-IR score with CD, respectively. Model 1 was unadjusted; model 2 was adjusted for age, sex, and race; and model 3 was further adjusted for education, PIR, BMI, smoking status, alcohol consumption, caffeine intake, history of depression, and history of DM, based on model 2. METS-IR, HOMA-IR, and TyG were included in regression models both in continuous form and in tertile groups, with OR and 95% CI calculated. Stratified analyses and interaction analyses were implemented by sex, age, race, PIR, education, smoking status, alcohol consumption, caffeine intake, history of depression, and history of DM. Also, restricted cubic spline (RCS) plots were leveraged to further examine the nonlinear relationships of TyG index, METS-IR score, and HOMA-IR score with CD. Additionally, receiver operating characteristic (ROC) curves and area under the curve (AUC) analyses were employed to appraise the prognostic performance of IR indices in the full cohort. All data analyses were executed with the R 4.4.3 package (http://www.R-project.org), and differences were deemed to be statistically significant at $P<0.05$ (two-sided).

3. Results

3.1 Baseline characteristics of the participants

In total, 5,606 participants were included, of whom 49.92% were males and 50.08% were females, and 511 (9.12%) had CD. The prevalence of CD was considerably higher in females, current smokers, individuals aged 40-60 years old, individuals with DM, depression, PIR less than 3.5, education less than high school education. A statistically significant difference was noted ($P<0.05$). The IR scores in individuals with CD [TyG: 8.78 (8.41,9.24); METS-IR: 2.14 (1.95,2.34); HOMA-IR: 2.79 (1.62,4.97)] were all higher than those of the individuals without CD [TyG: 8.62(8.24,9.04), METS-IR: 2.26 (1.37,4.01), HOMA-IR: 2.06 (1.89,2.25)], with statistically significant differences ($P<0.001$). The details are delineated in Table 1.

3.2 Association of TyG index, METS-IR score, and HOMA-IR score with CD

As continuous variables, IR (TyG index, METS-IR score, and HOMA-IR score) were positively associated with the prevalence of CD. The unadjusted logistic regression analyses yielded the following ORs with 95% CIs: METS-IR (OR: 2.13, 95% CI: 1.52-2.98), HOMA-IR (OR: 1.03, 95% CI: 1.01-1.04), and TyG index (OR: 1.47, 95% CI: 1.26-1.73), as demonstrated in Table 2. After fully adjusting for covariates, the IR remained positively associated with CD prevalence. Specifically, per unit increase in METS-IR (OR: 2.00, 95% CI: 1.31-3.06) was associated with approximately a 1-fold increase in the prevalence of CD. Significant positive associations were also observed for HOMA-IR (OR: 1.02; 95% CI: 1.00-1.03) and TyG index (OR: 1.35; 95% CI: 1.12-1.63). Further analyses supported this finding. With the tertile T1 as a reference, the third quartile groups of METS-IR, HOMA-IR, and TyG were associated with increased prevalence of CD, regardless of model adjustment ($P<0.05$), as shown in Table 2. To better understand the nonlinear association of IR with CD prevalence, we plotted RCS curves. The results showed that HOMA-IR exhibited a nonlinear positive association with the prevalence of CD

(P-non-linear=0.003) with an inflection point at 2.423, and METS-IR and TyG demonstrated significant positive linear associations with CD (P-non-linear = 0.056 and 0.567, respectively) (Figure 2A-C).

3.3 Subgroup analyses of the association of METS-IR score, TyG index, and HOMA-IR score with CD

The results of the subgroup analyses indicated inconsistent associations of the METS-IR score, TyG index, and HOMA-IR score with CD (Table 3).

In subgroup analyses, the positive association of METS-IR with CD was consistent in the subgroups of females, non-Hispanic whites, non-Hispanic blacks, other Hispanics, aged < 40 years, PIR < 3.5, beyond high school education, less than high school education, current smokers, non-drinking, with history of DM, no history of DM, and no depression (P<0.05). The interaction test yielded that sex and alcohol consumption could influence the positive association between METS-IR score and CD (P for interaction<0.05), and no interaction was observed for the remaining components (Table 3).

The positive association of TyG index with CD was consistent across the subgroups of females, non-Hispanic whites, non-Hispanic blacks, and other Hispanics, aged <40 years, PIR <3.5, beyond high school education, less than high school education, current smokers, no depression, drinking, and non-drinking (P<0.05). The interaction test yielded that education could impact the positive association of TyG index with CD (P for interaction<0.05), and no interaction was observed for the remaining components (Table 3).

The positive association of HOMA-IR scores with CD was consistent in the subgroups of females, non-Hispanic whites, beyond high school education, current smokers, and depression (P<0.05). Interaction tests showed that no interaction was noted for all components (P for

interaction>0.05), as shown in Table 3.

3.4 ROC curve analysis of METS-IR score, TyG index, and HOMA-IR score with CD

The ROC curves were adopted (Figure 3A-C) to further examine the predictive utility of IR for the prevalence of CD. The AUC of METS-IR was 0.645 (95% CI: 0.619-0.672), which was higher than that of the TyG index (AUC=0.644,95% CI:0.617-0.671) and the HOMA-IR score (AUC=0.641,95% CI:0.614- 0.668), as shown in Figure 3A-C.

4. Discussions

Using cross-sectional data from U.S. adults (≥20 years) in NHANES (2005-2010), we discovered that HOMA-IR exhibited a nonlinear positive correlation with CD. Separately, both METS-IR and TyG demonstrated significant positive linear correlations with CD after adjustment for key demographic and lifestyle confounders. Furthermore, ROC curve analysis showed that METS-IR score had the strongest diagnostic performance for CD. This indicates that high scores of IR (METS-IR, HOMA-IR, and TyG) are highly associated with the prevalence of CD, suggesting the therapeutic potential of targeting IR in CD patients. Previous studies have also shown that the incidence of gastrointestinal symptoms in patients with diabetes is higher than that in the general population. The fasting blood glucose level of patients with gastrointestinal symptoms is significantly higher than that of patients without gastrointestinal symptoms, and diabetes patients with gastrointestinal symptoms have a worse quality of life [23, 24]. Patients with high IR index scores should be given appropriate guidance as early as possible to control them at a lower level. This may be beneficial for lowering the prevalence of CD and optimizing the quality of survival for patients.

Studies of recent years have shown that gut microbiota disorders may be involved in IR by

affecting host metabolism, immunity, and intestinal barrier integrity [25, 26]. The butyric acid-producing bacteria *Faecalibacterium prausnitzii* and *Clostridium leptum* were both negatively correlated with HOMA-IR [27]. Meanwhile, the abundance of *Faecalibacterium prausnitzii* and *Clostridium leptum* was significantly lower in inflammatory bowel disease, which is a common disorder characterized by CD [28-30]. This indicates that butyric acid-producing bacteria are negatively correlated with both CD and HOMA-IR. Additional studies denote that short-chain fatty acids, encompassing acetic acid and butyric acid, may exacerbate both CD and IR through the mediation of 5-hydroxytryptamine (5-HT) [31, 32]. The gut microbiota and its other product, bile acids, form the bile acid-gut microbiota axis. Disruption at either end of this axis may promote the onset of IR [33, 34]. Furthermore, gut microbiota dysbiosis may elevate the permeability of the intestinal mucosa, leading to increased production of inflammatory mediators, including IL-6, which exacerbates IR [35]. Inflammatory mediators like IL-6 and IL-1B affect peristalsis, secretion and reabsorption and may be involved in the pathogenesis of CD [36]. Supplementation with *Bifidobacterium* preparations can reduce gastrointestinal symptoms, alleviate low-level inflammation in individuals with type 2 diabetes, and improve glucose metabolism and IR [37, 38]. From the above, it can be seen that gut microbiota is a critical node in the interaction between CD and IR. The mediators involved in this process include not only short-chain fatty acids, 5-HT, bile acids, and inflammatory mediators, but also numerous other unmentioned factors. Therefore, whether gut microbiota plays a promoting or suppressing role in CD and IR depends on the types, proportions, and relative activity of mediating molecules. In our research, a positive linear correlation between IR and CD is observed. Hence, it can be speculated that IR is primarily related to the gut microbiota and its metabolite derivatives that promote the development of CD.

In addition, the present research revealed sex-specific disparity in the association of METS-IR with the prevalence of CD, with a stronger association observed in women. This may be related to the differences in the synthesis of estrogens and serotonin in the brain, which also involves the functions of gut microbiota and inflammatory mediators [34, 35]. Education partly reflects the socioeconomic status of an individual. Lower education levels indicate limited healthcare access and suboptimal hygiene and health literacy, which may result in delayed medical consultation and reduced compliance. These factors thereby exacerbate IR and increase susceptibility to CD, ultimately leading to variations in the prevalence of CD across education levels.

This study has the following strengths. First, it is the first study to identify a direct association of IR with CD. The study has a clear way of sample acquisition, sufficient sample size, and reliable data sources, which contribute to the reliability of the results. Second, the TyG index, METS-IR, and HOMA-IR are accessible and widely used non-invasive methods. Their relationship with the prevalence of diarrhea is plain to see. Elevated levels of these indices predict a higher prevalence of diarrhea, suggesting that patients with metabolic abnormalities require IR screening and interventions, such as dietary modifications and glucagon-like peptide-1 (GLP-1) agonists. These approaches can guide further diagnostics, therapies, and preventive measures, thereby providing references for clinical practice.

There are certain limitations in this research. First, the data were drawn from NHANES, and most of the participants were of Mexican, Caucasian, and Black ethnicity. Their physical conditions and lifestyles differed greatly from those of Asians. Therefore, the findings need to be corroborated in studies with Asian cohorts. Second, despite adjustment for some confounders, the potential influence of residual confounders cannot be excluded, such as bile acid malabsorption. Third, this is a cross-sectional investigation, which assesses chronic diarrhea and

IR at the same time. Hence, the time series between CD and IR could not be determined, and it does not present any causality. Future prospective cohort studies could integrate bile acid metabolism and the characteristics of gut microbiota to provide robust evidence for a causal association between IR and CD.

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Figure legends

Figure 1 Flow chart of the selection of participants based on NHANES 2005-2010

TG: triglycerides; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; FINS: fasting insulin; PIR: poverty income ratio; BMI: body mass index

Figure 2 RCS analysis (A) The link of HOMA-IR with CD; (B) The link of METS-IR with CD; (C)The link of TyG with CD

Figure 3 (A) The ROC curve of METS-IR scores predicting CD; (B) The ROC curve of TyG index predicting CD; (C) The ROC curve of HOMA-IR scores predicting CD

371 **Table 1** Demographic information of the participants

Characteristic	N	Overall	Non-diarrhea	CD	p-value
Sex	5,606				0.027
Female		2,750(50.08%)	2,497(49.55%)	253(56.63%)	
Male		2,856(49.92%)	2,655(50.45%)	201(43.37%)	
Age	5,606				0.200
<40		2,003(36.94%)	1,875(37.44%)	128(30.79%)	
>60		1,730(23.24%)	1,573(23.19%)	157(23.77%)	
40-60		1,873(39.82%)	1,704(39.37%)	169(45.44%)	
Race	5,606				0.400
Mexican American		993(7.13%)	892(6.99%)	101(8.87%)	
Non-Hispanic Black		1,048(10.14%)	960(10.02%)	88(11.64%)	
Non-Hispanic White		2,902(73.87%)	2,695(74.17%)	207(70.23%)	
Other Hispanic		430(3.81%)	389(3.74%)	41(4.74%)	

Other Race		233(5.04%)	216(5.08%)	17(4.52%)	
Education	5,606				0.004
<High school diploma		1,488(17.19%)	1,308(16.54%)	180(25.20%)	
>High school diploma		2,781(58.63%)	2,608(59.26%)	173(50.84%)	
High school diploma/equivalent		1,337(24.19%)	1,236(24.21%)	101(23.95%)	
Family-PIR	5,606				0.027
<1.3		1,033(12.19%)	910(11.82%)	123(16.74%)	
>3.5		2,404(52.34%)	2,244(53.00%)	160(44.17%)	
1.3-3.5		2,169(35.48%)	1,998(35.18%)	171(39.09%)	
Alcohol consumption	5,606				0.200
No		1,528(22.97%)	1,388(22.65%)	140(26.97%)	
Yes		4,078(77.03%)	3,764(77.35%)	314(73.03%)	
Smoking status	5,606				0.032

Before		1,497(26.02%)	1,380(26.15%)	117(24.40%)	
Never		2,886(50.97%)	2,670(51.42%)	216(45.36%)	
Now		1,223(23.01%)	1,102(22.43%)	121(30.24%)	
Caffeine intake	5,606	128.00(29.00,274.00)	128.00(29.00,274.00)	130.00(36.00,296.00)	0.400
DM	5,606				<0.001
No		4,825(89.94%)	4,470(90.54%)	355(82.64%)	
Yes		781(10.06%)	682(9.46%)	99(17.36%)	
Depression	5,606				<0.001
No		5,181(93.56%)	4,803(94.22%)	378(85.43%)	
Ye		425(6.44%)	349(5.78%)	76(14.57%)	
TyG	5,606	8.63(8.25,9.06)	8.62(8.24,9.04)	8.78(8.41,9.24)	<0.001
HOMA-IR	5,606	2.29(1.38,4.06)	2.26(1.37,4.01)	2.79(1.62,4.97)	<0.001
METS-IR	5,606	2.07(1.89,2.26)	2.06(1.89,2.25)	2.14(1.95,2.34)	<0.001
Fasting plasma glucose (mmol/L)	5,606	5.50(5.11,6.00)	5.50(5.11,5.94)	5.61(5.22,6.27)	0.002

Fasting insulin (uU/mL)	5,606	9.24(5.77,15.42)	9.13(5.71,15.26)	10.41(6.66,18.17)	0.002
Triglyceride (mg/dL)	5,606	112.00(78.00,162.00)	111.00(78.00,160.00)	125.00(88.00,187.00)	<0.001
Direct HDL-C(mg/dL)	5,606	52.00(42.00,64.00)	52.00(42.00,64.00)	49.00(41.00,60.00)	0.009
Body mass index (kg/m^2)	5,606	27.64(24.10,32.19)	27.48(24.05,31.93)	29.29(24.94,34.89)	<0.001

372 DM: diabetes mellitus; PIR: poverty to income ratio; HOMA-IR: Homeostasis Model Assessment of insulin resistance; METS-IR:
373 metabolic score for insulin resistance; HDL-C: high-density lipoprotein cholesterol.

Table 2 Weighted logistic regression analysis of the link of TyG index, the METS-IR score, and the HOMA-IR score with CD

Participants	Model 1		Model 2		Model 3	
	OR (95%CI)	***p*-value**	**OR (95%CI)**	***p*-value**	**OR (95%CI)**	***p*-value**
METS-IR						
Continuous	2.13(1.52, 2.98)	<0.001	2.57(1.74, 3.81)	<0.001	2.00(1.31, 3.06)	0.002
Tertiles						
T1	Ref		Ref		Ref	
T2	1.26(0.86, 1.83)	0.200	1.32(0.91, 1.94)	0.140	1.25(0.84, 1.86)	0.300
T3	1.91(1.43, 2.55)	<0.001	2.18(1.57, 3.03)	<0.001	1.89(1.34, 2.68)	<0.001
TyG						
Continuous	1.47(1.26, 1.73)	<0.001	1.51(1.26, 1.80)	<0.001	1.35(1.12, 1.63)	0.003
Tertiles						
T1	Ref		Ref		Ref	
T2	1.38(0.95, 2.00)	0.087	1.44(0.95, 2.00)	0.065	1.38(0.94, 2.02)	0.100
T3	1.84(1.31, 2.59)	<0.001	1.90(1.31, 2.77)	0.001	1.64(1.11, 2.43)	0.014
HOMA-IR						
Continuous	1.03(1.01, 1.04)	0.006	1.02(1.01, 1.04)	0.010	1.02(1.00, 1.03)	0.036
Tertiles						
T1	Ref		Ref		Ref	
T2	1.36(0.97, 1.90)	0.072	1.34(0.95, 1.87)	0.090	1.35(0.98, 1.86)	0.064
T3	1.67(1.27, 2.20)	<0.001	1.62(1.23, 2.13)	0.001	1.44(1.07, 1.94)	0.017

Note: Model 1 was not adjusted; model 2 was adjusted for age, sex, and race; model 3 was further adjusted for education, poverty-to-income ratio, body mass index, smoking status, alcohol consumption, caffeine intake, history of depression, and history of diabetes mellitus, on the basis of model 2.

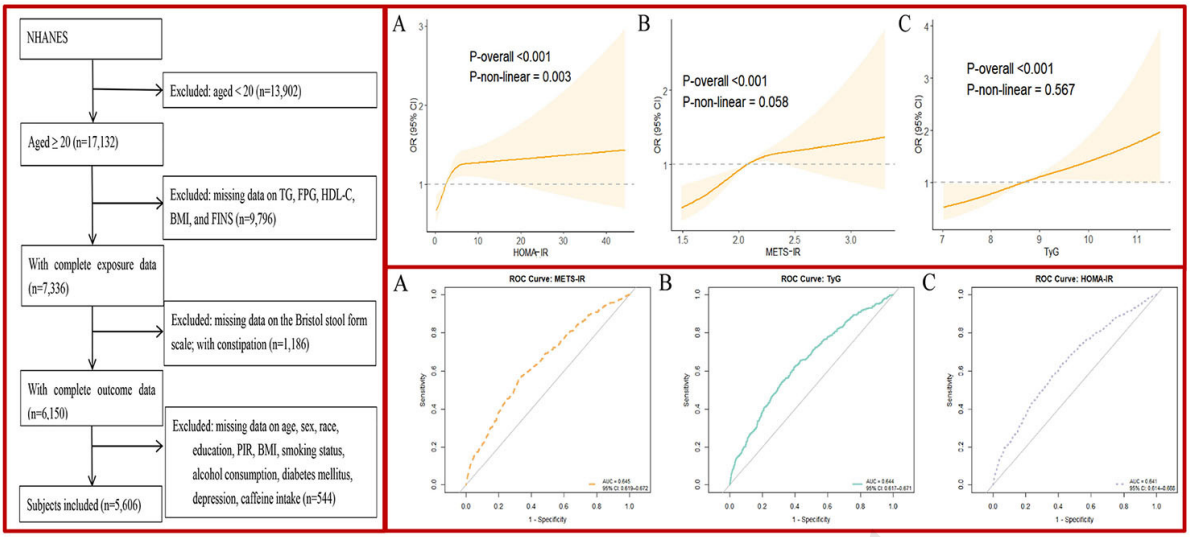
Table 3 Subgroup analyses of the link of METS-IR score, TyG index, and HOMA-IR score with CD

Subgroup	METS-TR			TyG			HOMA-IR		
	OR (95%CI)	*p*-value	*p* for interaction	OR (95%CI)	*p*-value	*p* for interaction	OR (95%CI)	*p*-value	*p* for interaction
Sex			0.016			0.233			0.053
Female	3.63(1.82, 7.27)	<0.001		1.60(1.16, 2.21)	0.006		1.04(1.01,1.08)	0.023	
Male	1.13(0.62,2.08)	0.700		1.16(0.90, 1.49)	0.200		1.00(0.98,1.02)	0.900	
Race			0.341			0.081			0.489
Mexican American	0.62(0.19,2.03)	0.400		0.84(0.48, 1.47)	0.500		1.02(0.961.07)	0.500	
Other Hispanic	9.24(2.63,32.42)	0.002		4.36(2.08, 9.13)	<0.001		0.97(0.96,1.01)	0.300	
Non-Hispanic White	2.01(1.14,3.54)	0.018		1.32(1.01, 1.71)	0.041		1.03(1.00,1.05)	0.036	
Non-Hispanic Black	4.33(1.60,11.8)	0.010		1.62(1.13, 2.34)	0.010		1.03(0.99,1.07)	0.200	
Other race	1.65(0.13,21.4)	0.700		1.10(0.36, 3.34)	0.900		1.09(0.91,1.31)	0.300	
Age			0.362			0.237			0.291
<40	2.84(1.30,6.20	0.010		1.88(1.31, 2.70)	0.001		1.00(0.95,1.05)	>0.900	
40-60	1.63(0.78,3.37)	0.200		1.15(0.83, 1.60)	0.400		1.01(1.00,1.03)	0.093	
>60	2.03(0.92,4.47)	0.080		1.32(0.87, 2.01)	0.200		1.03(0.99,1.08)	0.130	
Poverty to income ratio			0.396			0.242			0.462
<1.3	3.33(1.61,6.90)	0.002		1.48(1.03, 2.12)	0.034		1.01(0.99,1.03)	0.300	
1.3-3.5	1.95(1.19,3.18)	0.009		1.53(1.12, 2.10)	0.009		1.03(1.00,1.07)	0.072	
>3.5	1.48(0.72,3.04)	0.300		1.11(0.84, 1.45)	0.400		1.00(0.97,1.04)	0.800	
Education			0.065			0.030			0.286
<High school diploma	2.12(1.07,4.19)	0.032		1.45(1.05, 2.01)	0.027		1.00(0.98,1.02)	0.700	
High school diploma/equivalent	0.84(0.27,2.60)	0.800		0.85(0.49, 1.47)	0.600		1.02(0.98,1.06)	0.400	
>High school diploma	2.88(1.55,5.37)	0.002		1.55(1.15, 2.10)	0.006		1.04(1.01,1.08)	0.019	
Smoking status			0.692			0.847			0.169
Never	1.78(0.96,3.28)	0.066		1.17(0.84, 1.64)	0.300		1.01(0.98,1.04)	0.500	
Former	2.3(0.96,5.50)	0.061		1.41(0.97, 2.06)	0.072		1.01(0.99,1.029)	0.500	
Current	2.04(1.16,3.58)	0.015		1.51(1.11, 2.05)	0.010		1.06(1.03,1.09)	<0.001	

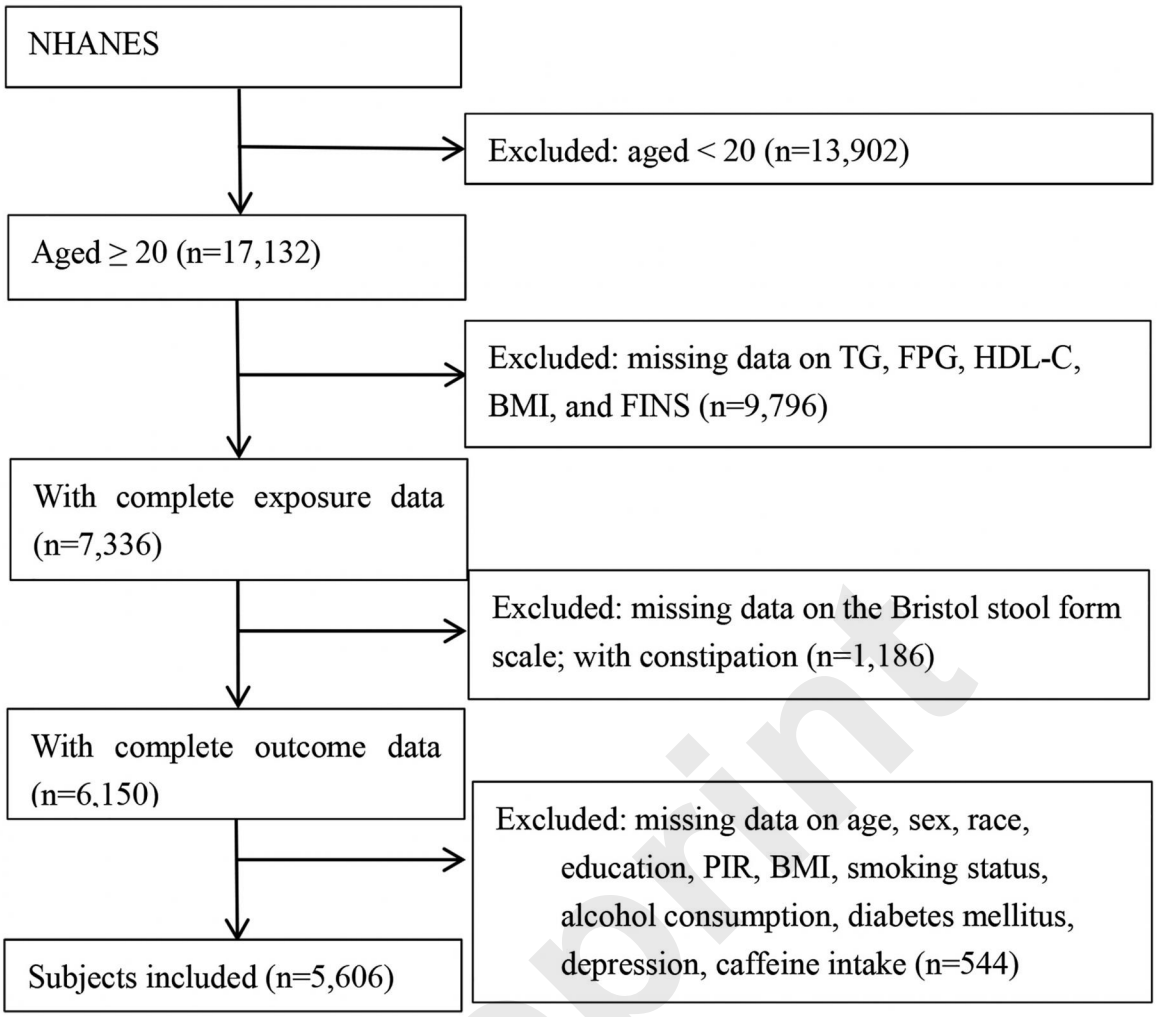
Alcohol consumption			0.004			0.089			0.902
No	4.47(1.95,10.24)	<0.001		1.65(1.09, 2.50)	0.019		1.01(0.98,1.03)	0.700	
Yes	1.62(0.99,2.65)	0.056		1.24(1.00, 1.55)	0.049		1.02(1.00,1.05)	0.079	
Diabetes Mellitus			0.065			0.613			0.503
No	1.81(1.076,3.04)	0.027		1.28(0.98, 1.68)	0.066		1.03(0.99,1.06)	0.120	
Yes	2.61(1.13,6.04)	0.026		1.39(1.00, 1.93)	0.053		1.00(0.98,1.03)	0.800	
Depression			0.409			0.410			0.057
No	2.17(1.35,3.49)	0.002		1.43(1.16, 1.76)	0.002		1.01(1.00,1.03)	0.130	
Yes	1.20(0.39,3.70)	0.700		0.86(0.50, 1.49)	0.600		1.06(1.01,1.11)	0.030	

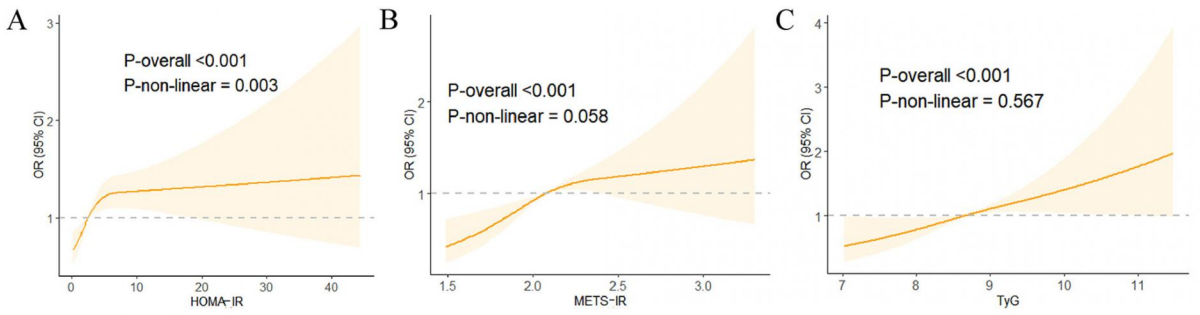
Note: Subgroup analyses were adjusted for age, sex, race, education, poverty-to-income ratio, body mass index, smoking status, alcohol consumption, caffeine intake, depression, and diabetes mellitus.

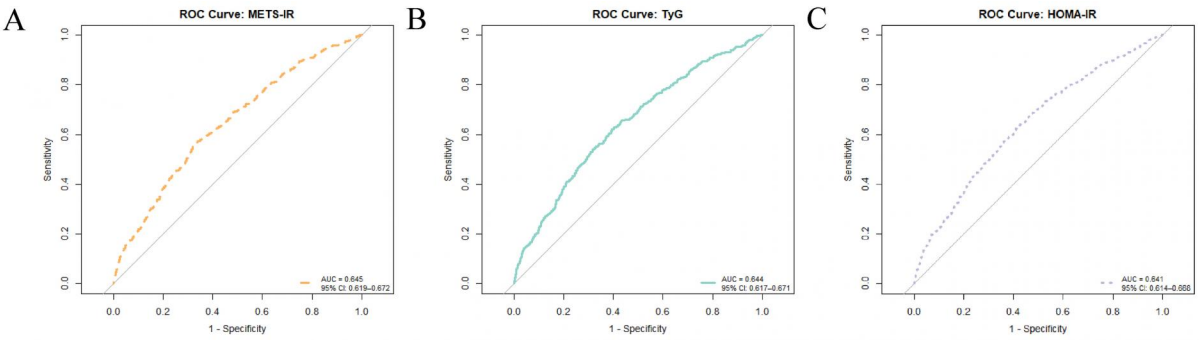
Association of IR with CD



In this cross-sectional investigation,we discovered that HOMA-IR exhibited a nonlinear positive correlation with CD. Separately, both METS-IR and TyG demonstrated significant positive linear correlations with CD after adjustment for key demographic and lifestyle confounders. Furthermore, ROC curve analysis showed that METS-IR score had the strongest diagnostic performance for CD.


NHANES
Excluded: aged < 20 (n=13,902)
Aged ≥ 20 (n=17,132)
Excluded: missing data on TG, FPG, HDL-C, BMI, and FINS (n=9,796)
With complete exposure data (n=7,336)
Excluded: missing data on the Bristol stool form scale; with constipation (n=1,186)
With complete outcome data (n=6,150)
Excluded: missing data on age, sex, race, education, PIR, BMI, smoking status, alcohol consumption, diabetes mellitus, depression, caffeine intake (n=544)
Subjects included (n=5,606)


A
P-overall <0.001
P-non-linear = 0.003
OR (95% CI)
HOMA-IR
B
P-overall <0.001
P-non-linear = 0.058
OR (95% CI)
METS-IR
C
P-overall <0.001
P-non-linear = 0.567
OR (95% CI)
TyG


A
ROC Curve: METS-IR
Sensitivity
1 - Specificity
AUC = 0.645
95% CI: 0.619–0.672
B
ROC Curve: TyG
Sensitivity
1 - Specificity
AUC = 0.644
95% CI: 0.617–0.671
C
ROC Curve: HOMA-IR
Sensitivity
1 - Specificity
AUC = 0.641
95% CI: 0.614–0.668