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ORIGINAL RESEARCH

Metabolic Syndrome and Low Back Pain: Evidence from Cross-Sectional and Mendelian Randomization Analysis

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Background: Metabolic syndrome (MetS) and low back pain (LBP) are major health concerns, but their relationship remains unclear. Components of MetS, such as abdominal obesity and hypertension, may contribute to musculoskeletal degeneration. This study investigated the association and causality between MetS and LBP.

Methods: We analyzed 5,523 adults (≥20 years) from NHANES 1999–2004 with complete MetS and LBP data. MetS was defined using National Cholesterol Education Program's Adult Treatment Panel III (ATPIII), International Diabetes Federation (IDF), and "modified World Health Organization (mWHO) criteria". Weighted logistic regression and stratified analyses assessed associations. Mediation analysis examined the role of C-reactive protein (CRP), and Mendelian randomization (MR) using GWAS summary statistics tested causal effects of MetS components on LBP.

Results: MetS prevalence was higher in participants with LBP (IDF: 41.0% vs 34.4%; ATPIII: 31.6% vs 25.8%; mWHO: 25.6% vs 21.2%). Fully adjusted models confirmed significant associations: IDF (OR = 1.27; 95% CI: 1.06–1.53), ATPIII (OR = 1.26; 95% CI: 1.05–1.50), mWHO (OR = 1.21; 95% CI: 1.03–1.42). CRP did not mediate these associations. MR analysis supported causal effects of hypertension (OR = 2.34; 95% CI: 1.38–3.97; FDR p = 0.002) and waist circumference (OR = 1.45; 95% CI: 1.34–1.57; FDR p < 0.001) on LBP, while other MetS components showed no causal links.

Conclusion: MetS is associated with LBP across multiple definitions, with genetic evidence implicating abdominal obesity and hypertension. Improving metabolic health may be a promising strategy to reduce LBP burden.

Keywords: metabolic syndrome, low back pain, mendelian randomization, NHANES, epidemiology

Introduction

Metabolic syndrome (MetS), also known as Reaven's syndrome, Syndrome X, or insulin resistance syndrome, refers to a cluster of interrelated metabolic abnormalities.[1] Its core features include abdominal obesity, hyperglycemia, insulin resistance, dyslipidemia, and hypertension.[2,3] In recent years, the global prevalence of MetS has been rising steadily, especially in developing countries and among younger populations, with estimated prevalence ranging from 20% to 40% across different demographic groups.[4,5] Among the elderly, MetS is one of the most common chronic conditions, significantly increasing the risk of cardiovascular diseases, type 2 diabetes, and all-cause mortality.[6,7]

Low back pain (LBP) is one of the most prevalent musculoskeletal disorders worldwide, with increasing incidence and disease burden year by year. According to the Global Burden of Disease Study, LBP is the leading cause of disability globally.[8,9] Its prevalence has grown by over 50% since 1990, now affecting more than 450 million people.[10]

Despite the high prevalence of both MetS and LBP, the association between them remains underexplored. Some studies suggest that obesity, insulin resistance, physical inactivity, and chronic inflammation may serve as potential mechanisms linking MetS and LBP.[11–13] However, existing findings are inconsistent. For instance, Teraguchi et al

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reported that MetS was significantly associated with intervertebral disc degeneration (IVDD) in the cervical, thoracic, and lumbar spine.[14] Conversely, a large-scale study conducted among Japanese adults found a significant association between MetS and LBP only in women, with no clear correlation observed in men.[15] Interestingly, a study by Huang et al based on the China Health and Retirement Longitudinal Study found that MetS was associated with a lower risk of LBP in cross-sectional analyses, while no significant association was observed in longitudinal analyses.[16] The inconsistent findings may be explained by two main factors. First, low back pain (LBP) is a highly heterogeneous symptom, and its definitions in epidemiological studies vary considerably—encompassing point prevalence, 12-month prevalence, lifetime prevalence, or professionally diagnosed LBP, often with differing severity and disability thresholds. Such measurement variability introduces significant heterogeneity and potential misclassification bias. Second, differing diagnostic criteria for metabolic syndrome (MetS)—such as those from ATP III, IDF, and mWHO—may lead to variations in the observed strength of associations. Inconsistent evidence, combined with diverse diagnostic standards and a lack of studies assessing causality, constitutes a major knowledge gap in understanding the relationship between metabolic health and low back pain.

Most current evidence on MetS and LBP comes from observational studies (cross-sectional or longitudinal), which are inherently limited by confounding (eg, from physical inactivity, socioeconomic status, analgesic use, or depression) and reverse causality. To overcome these constraints and probe the direction of causality, we implemented a Mendelian randomization (MR) approach. Additionally, by applying three major diagnostic criteria (ATP III, IDF, and mWHO), this study aims to evaluate the consistency of the MetS-LBP association across different definitions, offering new metabolic perspectives for managing low back pain.[17–20]

Methods

NHANES Study Design and Data Source

The National Health and Nutrition Examination Survey (NHANES) is a large-scale, nationally representative, continuous health survey conducted jointly by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS).[21] NHANES employs a multistage, stratified probability sampling design to ensure national representativeness of the US civilian, non-institutionalized population. The study protocol was approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent. All data utilized in this study are publicly available at https://www.cdc.gov/nchs/nhanes.

Study Population

We utilized data from three consecutive NHANES cycles: 1999–2000, 2001–2002, and 2003–2004. Participants aged ≥20 years were eligible for inclusion if they had complete data on components of metabolic syndrome (eg, waist circumference, blood pressure, fasting triglycerides, fasting glucose, fasting insulin) and information related to low back pain (LBP). Exclusion criteria included missing values for the aforementioned variables, missing or zero sample weights, or failure to meet NHANES analytic requirements. Detailed inclusion and exclusion procedures are illustrated in Figure 1. After applying these criteria, a total of 5,523 participants were included in the final analytic sample. Participants were categorized into two groups based on the presence or absence of LBP: the LBP group (n = 2,113) and the non-LBP group (n = 3,410).

Definition of Metabolic Syndrome

Metabolic syndrome (MetS) was defined using three internationally recognized criteria:

ATPIII Criteria

MetS was diagnosed when 3 or more of the following 5 components were present: (1) waist circumference ≥102 cm for men or ≥88 cm for women; (2) elevated triglycerides: ≥150 mg/dL; (3) reduced high-density lipoprotein cholesterol (HDL-C): <40 mg/dL for men or <50 mg/dL for women; (4) elevated blood pressure: systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or current use of antihypertensive medication; (5) elevated fasting glucose: ≥110 mg/dL or current use of antidiabetic medication:[22,23]

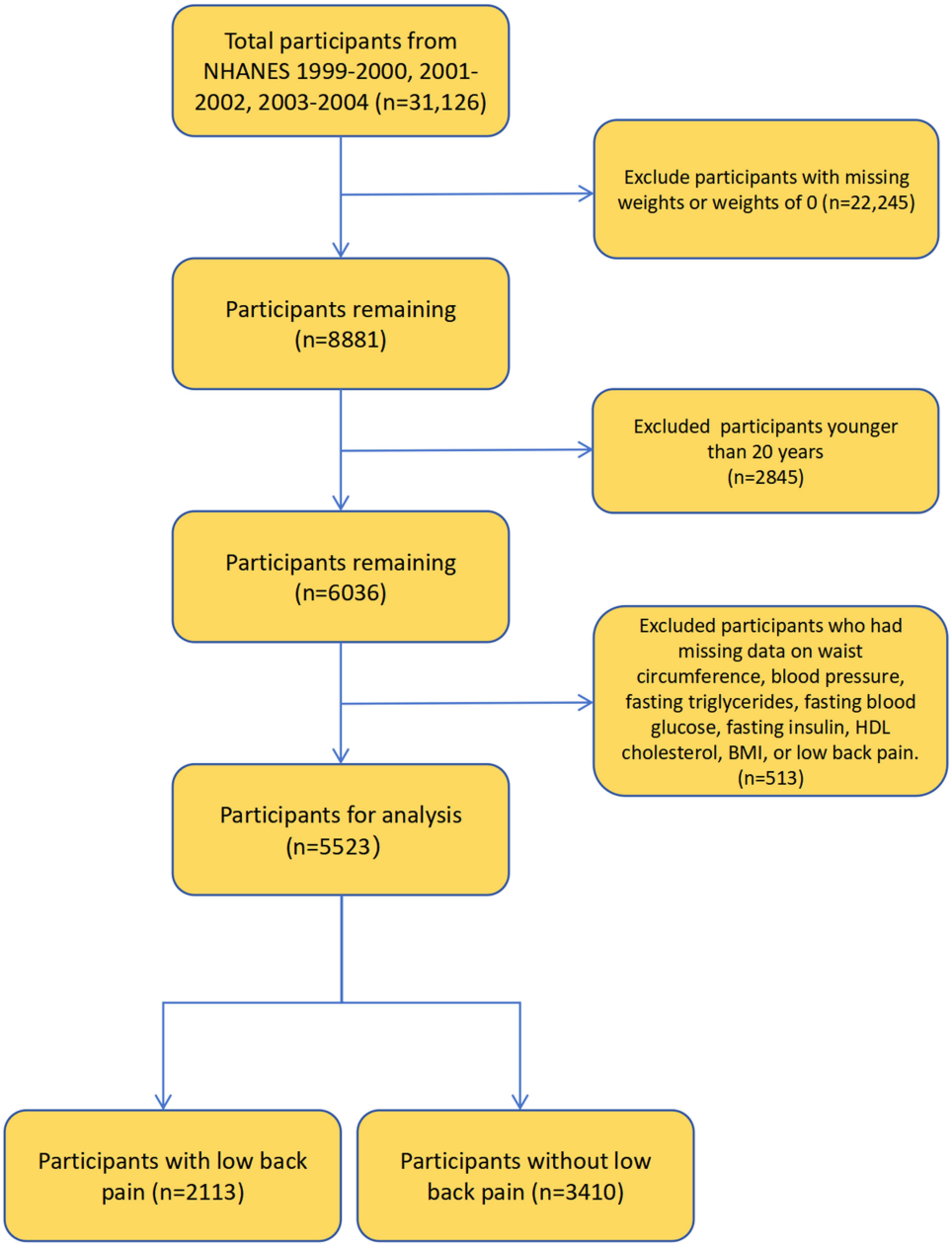

Figure 1 Flowchart of Participant Inclusion in the NHANES 1999–2004 Analysis.

IDF Criteria

MetS was defined by the presence of central obesity plus 2 or more of the following components: (1) triglycerides ≥150 mg/dL; (2) reduced HDL-C: <40 mg/dL in men, <50 mg/dL in women; (3) elevated blood pressure: systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or use of antihypertensive therapy; (4) fasting glucose ≥110 mg/dL or current use of glucose-lowering medications.[24]

For the application of the IDF ethnicity-specific criteria, we mapped the NHANES race/ethnicity categories to the established IDF classifications as follows:

1. Non-Hispanic White → Europid (Waist Circumference [WC] ≥94 cm for men, ≥80 cm for women).
2. Non-Hispanic Black → Sub-Saharan African (WC ≥94 cm for men, ≥80 cm for women).
3. Mexican American and Other Hispanic → South/Central American (WC ≥90 cm for men, ≥80 cm for women).

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4. Other Race (Including Non-Hispanic Asian) → Asian (WC ≥90 cm for men, ≥80 cm for women). The "Other Race" category in NHANES is heterogeneous, including individuals of Asian descent, Native Americans, and those reporting multiple races. Given that Asians have lower thresholds for visceral adiposity and constitute a significant portion of this group, we cautiously applied the Asian-specific cutoffs (90/80 cm) to the entire "Other Race" group.

mWHO Criteria

MetS was defined as the presence of diabetes, impaired glucose tolerance, impaired fasting glucose, or insulin resistance, plus 2 or more of the following: (1) elevated blood pressure: systolic ≥140 mm Hg or diastolic ≥90 mm Hg, or antihypertensive therapy; (2) triglycerides ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women; (3) central obesity: waist-to-hip ratio >0.90 in men or >0.85 in women, and/or BMI >30 kg/m^2; (4) microalbuminuria: urinary albumin excretion rate ≥20 μg/min or albumin-to-creatinine ratio ≥20 mg/g.[17,25]

Due to the lack of oral glucose tolerance test (OGTT), waist-to-hip ratio, and urinary albumin excretion rate data in the NHANES 1999–2004 cycles, we made the following modifications: IGT was not considered; Central obesity was defined solely as BMI >30 kg/m^2; Microalbuminuria was defined as an ACR ≥20 mg/g. Insulin resistance was defined as the upper quartile of the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR ≥2.68), calculated as: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L) / 22.5.[26]

Detailed variable descriptions can be found at https://www.cdc.gov/nchs/.

Definition of Low Back Pain (LBP)

Low back pain (LBP) was defined based on the self-reported symptom captured in the questionnaire item MCQ070. Participants were asked: "[During the past 3 months], did {you/SP} have low back pain?" Participants who responded "Yes" were classified as LBP-positive.[27]

Covariates

Covariate data were collected via structured self-reported questionnaires. Information was obtained on age, sex, race/ethnicity, educational attainment, household income, marital status, smoking history, alcohol consumption, and history of chronic cardiovascular diseases (CVD).Race was categorized into five groups: Mexican American, non-Hispanic White, other Hispanic, non-Hispanic Black, and other races.[28] Educational level was classified into three categories: below High school, high school, and above High school.[28] Poverty-income ratio (PIR) was calculated by dividing household income by the US federal poverty threshold for the corresponding survey year. PIR was then grouped into low, middle, and high categories to reflect relative socioeconomic status.[29,30] Marital status was categorized as never married, previously married, or married/living with partner.[31] Smoking status was defined as never, former, or current smoker.[28] Participants were classified as having CVD if they answered "yes" to any physician diagnosis of angina, coronary heart disease, myocardial infarction, stroke, or congestive heart failure.[19] Missing values among covariates were addressed using multiple imputation (MI) via the mice package in R. Imputation models were tailored to variable type: multinomial logistic regression for categorical variables with ≥3 categories, binary logistic regression for dichotomous variables, and predictive mean matching for continuous variables. Auxiliary variables were included to improve imputation accuracy. The predictor matrix was adjusted to allow all variables to inform each other. Five imputed datasets were generated with 10 iterations each. The differences in features before and after imputation regarding the proportion of missing information can be found in the Supplementary Table 1.

NHANES Data Analysis

This study was based on data from the National Health and Nutrition Examination Survey (NHANES), which uses a complex, multistage probability sampling design to ensure national representativeness of the US civilian, noninstitutionalized population. All analyses accounted for NHANES-provided sample weights to produce nationally representative estimates. In accordance with NHANES analytic guidelines, combined weights were calculated for the 1999–2004 survey cycles. For participants from the 1999–2002 cycles, the 6-year sample weight (WTSAF6YR) was calculated as: WTSAF6YR = (2/3) × WTSAF4YR.For participants from the 2003–2004 cycle, the weight was calculated as: WTSAF6YR = (1/3) × WTSAF2YR.[32]

All statistical analyses were conducted using R version 4.4.1, with the survey package used to account for the complex sampling design of NHANES. Continuous variables were summarized as weighted medians with interquartile ranges (IQRs), and categorical variables were presented as unweighted counts with survey-weighted percentages. Group comparisons were performed using weighted Pearson χ^2-tests for categorical variables and weighted Kruskal–Wallis tests for continuous variables. The weighted prevalence of MetS—defined according to the ATPIII, IDF, and mWHO—was estimated for the overall population, and separately for participants with and without low back pain (LBP). Prevalence was also stratified by age groups (21–40, 41–60, and >60 years). To assess the association between MetS and LBP, weighted χ^2-tests were first used for preliminary comparisons. Then, three weighted logistic regression models were constructed using the survey design: Model 1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity, income, educational attainment, and marital status; Model 3: additionally adjusted for smoking status, alcohol intake, cardiovascular disease history, and C-reactive protein (CRP) level. To examine the robustness of the associations, stratified analyses were conducted by age, sex, race/ethnicity, income, educational level, and CVD status. Potential mediation by CRP in the association between MetS and LBP was further explored using a regression-based mediation analysis via the mediation package in R. The average causal mediation effect (ACME), average direct effect (ADE), and total effect were estimated using 1000 bootstrap replications, and 95% confidence intervals were computed. Finally, the five individual MetS components defined by ATPIII (central obesity, hypertension, elevated fasting glucose, hypertriglyceridemia, and low HDL cholesterol) were each examined in separate weighted multivariable logistic regression models adjusted for the covariates in Model 3, to evaluate their independent associations with LBP.

Mendelian Randomization Design and Data Sources

To further explore the causal relationship between individual components of metabolic syndrome (MetS) and low back pain (LBP), we conducted a Mendelian randomization (MR) analysis. MR is a widely used approach that leverages genetic variants as instrumental variables (IVs) to infer the causal effect of an exposure on an outcome in observational settings.[33] For a valid MR design, three core assumptions must be satisfied:[34] (1) Relevance: The genetic instruments must be strongly associated with the exposure; (2) Independence: The instruments should be independent of confounders that may bias the exposure–outcome relationship; (3) Exclusion Restriction: The instruments must influence the outcome only through their effect on the exposure, with no direct or pleiotropic pathways. Genome-wide association study (GWAS) summary statistics for MetS components (based on ATP III criteria) and for LBP were extracted from publicly available large scale datasets. Detailed information regarding the data sources and selection of genetic instruments is provided in Supplementary Table 2.

Selection of Instrumental Variables (IVs)

Instrumental variables (IVs) were selected based on the following criteria: First, single nucleotide polymorphisms (SNPs) were required to reach genome-wide significance ($P < 5 \times 10^{-8}$) for their association with the exposure. Second, SNPs were subjected to linkage disequilibrium (LD) pruning to ensure independence, using a window size of 10,000 kb and an LD threshold of $r^2 < 0.001$. We performed LD clumping using the 1000G EUR reference panel and used proxies ($r^2 \geq 0.8$) when lead SNPs were missing in the outcome GWAS. To reduce potential bias from weak instruments, we calculated the F-statistic for each SNP using the following formula:[35] $F = /R^2 \times (N - K - 1)] / [K \times (1 - R^2)]$.Where: R^2 represents the proportion of variance in the exposure explained by the SNPs, K is the number of SNPs used as instruments, N is the total sample size.[36] SNPs with F-statistics < 10 were considered weak instruments and were excluded from the analysis.[37]

Mendelian Randomization Analysis

In this study, we employed multiple Mendelian randomization (MR) methods to comprehensively assess the causal relationship between exposures and the outcome. The following five approaches were applied: Inverse Variance Weighted (IVW), MR Egger, Weighted Median, Simple Mode, Weighted Mode. Causal estimates were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Among these methods, IVW served as the primary analytical approach, which combines the Wald ratios of individual SNPs in a meta-analysis framework. Under the assumption that all genetic variants are valid instrumental variables, the IVW method can provide an unbiased estimate of the

causal effect.[38] To correct for multiple testing and control the false discovery rate (FDR), Benjamini–Hochberg correction was applied to the IVW p-values across five exposures. FDR-adjusted p-values < 0.05 were considered statistically significant. We assessed heterogeneity using Cochran's Q test. When significant heterogeneity was detected ($p < 0.05$), results from a random-effects IVW model were reported; otherwise, a fixed-effects IVW model was used.[39] Horizontal pleiotropy was evaluated using the MR-Egger intercept test. An intercept p-value > 0.05 was interpreted as no evidence of directional pleiotropy.[40] For SNPs potentially exhibiting pleiotropy, we applied MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) to detect and correct for outliers and horizontal pleiotropy[41] Leave-one-out analysis was conducted to assess the influence of individual SNPs on the overall MR estimate. Forest plots, scatter plots, and funnel plots were generated to visually assess the causal relationships and the contribution of individual SNPs. All MR analyses were performed in R version 4.4.1, statistical significance was defined as $p \leq 0.05$.

Results

Characteristics of NHANES Participants

A total of 5523 participants were included in the study, of whom 2113 reported having low back pain (LBP) and 3410 did not. Baseline characteristics by LBP status are presented in Table 1. Compared with participants without LBP, those with LBP were more likely to be female, aged 41–60 years, and non-Hispanic White. They also had lower income and

Table 1 Participant Characteristics by Low Back Pain Status

Characteristic	Low Back Pain			P value
	Overall, N = 5523	No, N = 3410	Yes, N = 2113	
Age (years)				0.007
20-40	2,089 (38%)	1,301 (38%)	788 (37%)	
41-60	1,675 (30%)	985 (29%)	690 (33%)	
>60	1,759 (32%)	1,124 (33%)	635 (30%)	
Gender				0.005
Female	2,852 (52%)	1,710 (50%)	1,142 (54%)	
Male	2,671 (48%)	1,700 (50%)	971 (46%)	
Race				<0.001
Mexican American	1,312 (24%)	860 (25%)	452 (21%)	
Other Hispanic	227 (4.1%)	125 (3.7%)	102 (4.8%)	
Non-Hispanic White	2,857 (52%)	1,688 (50%)	1,169 (55%)	
Non-Hispanic Black	944 (17%)	621 (18%)	323 (15%)	
Other Race	183 (3.3%)	116 (3.4%)	67 (3.2%)	
Income				<0.001
High	2,272 (41%)	1,469 (43%)	803 (38%)	
Low	944 (17%)	523 (15%)	421 (20%)	
Middle	2,307 (42%)	1,418 (42%)	889 (42%)	
Education				<0.001
Below High school	1,725 (31%)	1,028 (30%)	697 (33%)	
High school	1,283 (23%)	754 (22%)	529 (25%)	
Above High school	2,515 (46%)	1,628 (48%)	887 (42%)	
Marital status				<0.001
Never married	831 (15%)	571 (17%)	260 (12%)	
Previously married	1,118 (20%)	655 (19%)	463 (22%)	
Married/Living with partner	3,574 (65%)	2,184 (64%)	1,390 (66%)	
CVD				<0.001
No	4,991 (90%)	3,134 (92%)	1,857 (88%)	
Yes	532 (9.6%)	276 (8.1%)	256 (12%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Low Back Pain			P value
	Overall, N = 5523	No, N = 3410	Yes, N = 2113	
Smoking status				<0.001
Never	2,833 (51%)	1,842 (54%)	991 (47%)	
Former	1,504 (27%)	920 (27%)	584 (28%)	
Current	1,186 (21%)	648 (19%)	538 (25%)	
Alcohol intake				0.002
None	1,729 (31%)	1,085 (32%)	644 (30%)	
Occasional	1,393 (25%)	890 (26%)	503 (24%)	
Moderate	1,871 (34%)	1,146 (34%)	725 (34%)	
Heavy	530 (9.6%)	289 (8.5%)	241 (11%)	
CRP (mg/dL)	0.24 (0.10, 0.52)	0.23 (0.09, 0.49)	0.26 (0.11, 0.56)	<0.001
ACR	6.40 (4.16, 12.50)	6.39 (4.16, 12.78)	6.43 (4.16, 12.06)	0.749
HOMA-IR	2.25 (1.45, 3.70)	2.20 (1.42, 3.55)	2.33 (1.48, 3.94)	<0.001
Triglyceride (mg/dL)	121.00 (84.00, 179.00)	118.00 (82.00, 176.00)	125.00 (88.00, 185.00)	<0.001
HDL-Cholesterol (mg/dL)	49.00 (41.00, 62.00)	50.00 (42.00, 62.00)	49.00 (41.00, 61.00)	0.070
Fasting glucose (mmol/L)	5.34 (4.96, 5.83)	5.33 (4.95, 5.82)	5.37 (4.97, 5.83)	0.141
Insulin (μU/mL)	9.31 (6.27, 14.47)	9.09 (6.17, 13.93)	9.64 (6.45, 15.07)	<0.001
WC (cm)	96.40 (86.70, 106.20)	95.50 (86.00, 105.20)	97.70 (88.20, 107.80)	<0.001
Height (cm)	167.30 (160.30, 175.00)	167.20 (160.30, 174.90)	167.30 (160.30, 175.10)	0.730
BMI (kg/m^2)	27.33 (24.08, 31.30)	27.01 (23.90, 30.84)	27.93 (24.41, 32.07)	<0.001
MetS (ATPIII)				0.001
No	3,807 (69%)	2,405 (71%)	1,402 (66%)	
Yes	1,716 (31%)	1,005 (29%)	711 (34%)	
MetS (IDF)				0.001
No	3,285 (59%)	2,086 (61%)	1,199 (57%)	
Yes	2,238 (41%)	1,324 (39%)	914 (43%)	
MetS (mWHO)				0.014
No	4,102 (74%)	2,572 (75%)	1,530 (72%)	
Yes	1,421 (26%)	838 (25%)	583 (28%)	

Notes: Median (IQR) for continuous variables; n (%) for categorical variables. Pearson's χ^2 for categorical; Kruskal–Wallis test for continuous. Data presented as median (interquartile range) for continuous variables; number (percentage) for categorical variables. P-values calculated using Pearson's χ^2-test for categorical variables and Kruskal–Wallis test for continuous variables.

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; MetS, metabolic syndrome; ATPIII, Adult Treatment Panel III; IDF, International Diabetes Federation; mWHO, modified World Health Organization; CVD, cardiovascular disease; CRP, C-reactive protein; ACR, albumin-to-creatinine ratio; WC, waist circumference; BMI, body mass index.

educational attainment, higher rates of smoking and heavy alcohol use, and a higher prevalence of cardiovascular disease (all $P < 0.05$).In addition, participants with LBP had significantly higher levels of inflammatory and metabolic biomarkers, including C-reactive protein (CRP), homeostatic model assessment of insulin resistance (HOMA-IR), triglycerides, insulin, waist circumference, and body mass index (BMI) (all $P < 0.05$). The prevalence of metabolic syndrome (MetS) was also consistently higher in the LBP group across all three diagnostic criteria (Figure 2). There were no significant differences between groups in albumin-to-creatinine ratio (ACR), high-density lipoprotein cholesterol (HDL-C), fasting glucose, or height.

Prevalence of Metabolic Syndrome

In the overall study population, the prevalence of metabolic syndrome (MetS) was highest using the IDF definition (37.0%), followed by ATPIII (28.1%) and mWHO (23.0%) criteria. This pattern remained consistent when stratified by LBP status, with all three definitions showing significantly higher MetS prevalence among participants with LBP compared to those without (all $P < 0.001$). Age-stratified analysis further revealed a clear increasing trend in MetS prevalence with advancing age. In both the 21–40 and 41–60 year age groups, participants with LBP had significantly

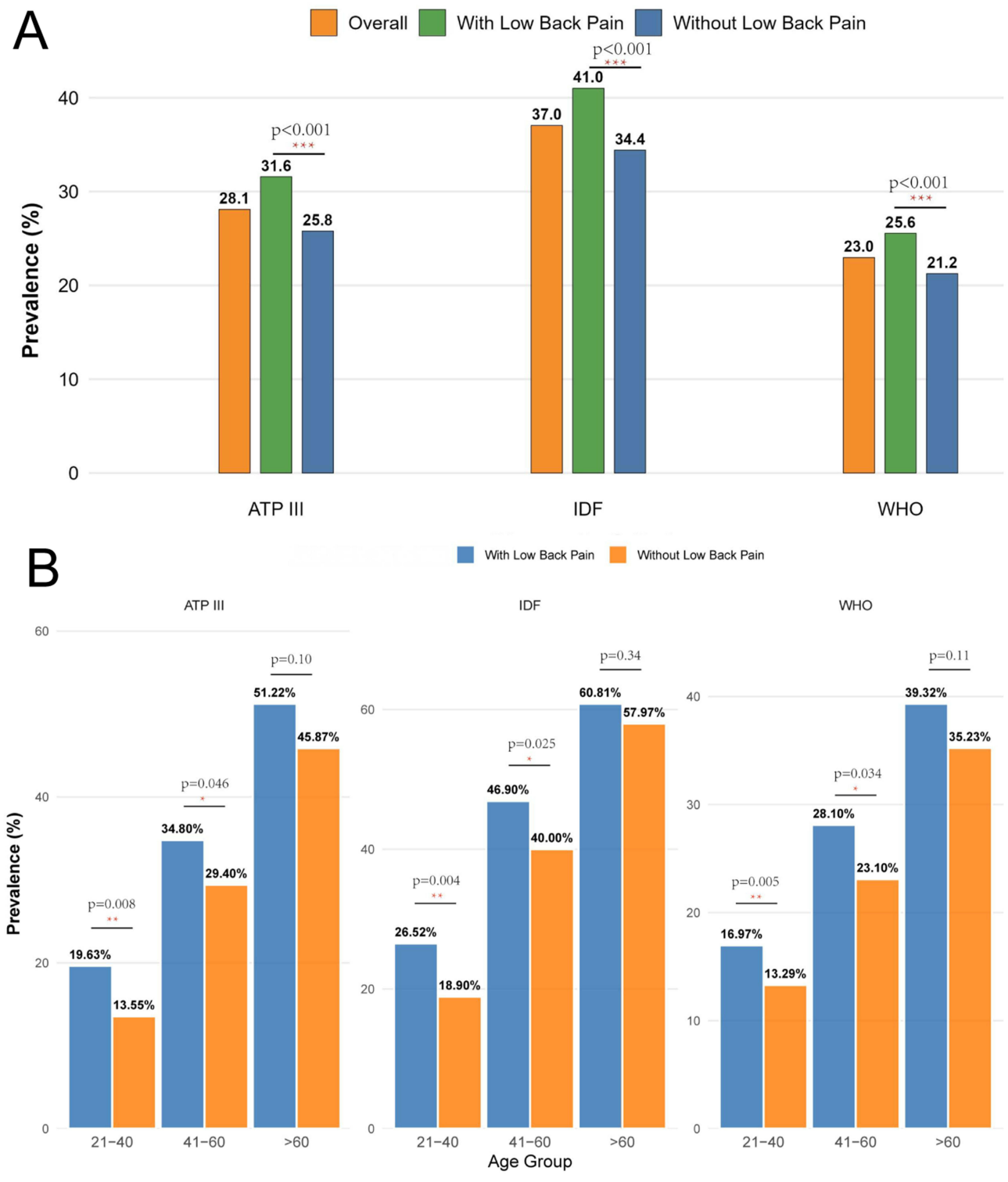

Figure 2 Prevalence of Metabolic Syndrome Across Different Population Subgroups.
Notes: (**A**) Prevalence of MetS in the total population, LBP group, and non-LBP group. (**B**) Age-stratified prevalence of MetS across three diagnostic criteria MetS was defined based on IDF, ATPIII, and WHO criteria. ***P<0.001; **P<0.01; *P<0.05.

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higher MetS prevalence than those without LBP (P < 0.05). However, among individuals aged >60 years, although MetS prevalence remained numerically higher in the LBP group, the difference was not statistically significant (Figure 2).

Association Between Metabolic Syndrome and Low Back Pain

Weighted χ^2-tests indicated a statistically significant association between MetS and low back pain (LBP) across all three diagnostic definitions: ATPIII (F = 13.194, P < 0.001), IDF (F = 12.064, P =.001), and mWHO (F = 12.797, P < 0.001). Weighted logistic regression analyses demonstrated that MetS was significantly associated with LBP in all models—unadjusted, partially adjusted, and fully adjusted—regardless of the diagnostic criteria used (all P < 0.05; Table 2).In the unadjusted model, the ATPIII definition showed the strongest association with LBP (OR = 1.328; 95% CI, 1.134–1.555). After full adjustment for covariates, the strength of association was slightly attenuated, with the highest odds observed under the IDF definition (OR = 1.273; 95% CI, 1.059–1.531), followed by ATPIII (OR = 1.257; 95% CI, 1.054–1.499) and mWHO (OR = 1.208; 95% CI, 1.027–1.421).

Stratified Analyses

Stratified analyses by age, sex, race/ethnicity, income level, educational attainment, and cardiovascular disease (CVD) status demonstrated consistent positive associations between MetS and LBP across most subgroups, suggesting the robustness of the observed relationship (Figure 3).Tests for interaction revealed no statistically significant interactions between MetS and any of the stratification variables (P >0.05), indicating that the association between MetS and LBP was not significantly modified by these covariates.

Forest plot showing odds ratios (ORs) for the association between metabolic syndrome and low back pain across subgroups stratified by age, sex, race/ethnicity, income, education level, and cardiovascular disease history. (A) ATPIII; (B) IDF; (C) mWHO.

Mediation Analysis

As shown in Table 3, the total effect of MetS on LBP was statistically significant under all three diagnostic definitions (all P < 0.05), with the strongest effect observed using the IDF definition (estimate = 0.045; P = 0.002).However, the average causal mediation effect (ACME) through C-reactive protein (CRP) was not statistically significant under any of the definitions (all P > 0.05), suggesting that CRP did not mediate the association between MetS and LBP.

Association Between MetS Components and Low Back Pain

Multivariable survey-weighted logistic regression revealed that abdominal obesity and hypertension were significantly associated with an increased risk of low back pain (LBP) (Table 4), while no significant associations were observed for the other MetS components (all p > 0.05).

In the Mendelian randomization (MR) analysis, genetic instruments for each MetS component are listed in Supplementary Table 3. The IVW method indicated that genetically predicted hypertension significantly increased the risk of LBP (OR = 2.34, 95% CI: 1.38–3.97, FDR-adjusted p = 0.002; Figure 4). This relationship was visualized in Scatter plots (Supplementary Figure 1). Funnel plots (Supplementary Figure 2) and leave-one-out sensitivity analysis (Supplementary Figure 3) supported the robustness of the findings. Alternative MR approaches, except MR-Egger, also

Table 2 Cross-Sectional Association Between Metabolic Syndrome and Low Back Pain Based on Three Diagnostic Criteria

Exposures	Model 1 OR (95% CI)	P	Model 2 OR (95% CI)	P	Model 3 OR (95% CI)	P
ATP III	1.328 (1.134–1.555)	<0.001	1.264 (1.069–1.494)	0.007	1.257 (1.054–1.499)	0.013
IDF	1.324 (1.125–1.559)	0.001	1.277 (1.067–1.529)	0.009	1.273 (1.059–1.531)	0.012
mWHO	1.272 (1.111–1.458)	<0.001	1.223 (1.049–1.425)	0.011	1.208 (1.027–1.421)	0.024

Abbreviations: ATPIII, Adult Treatment Panel III; IDF, International Diabetes Federation; mWHO, modified World Health Organization.

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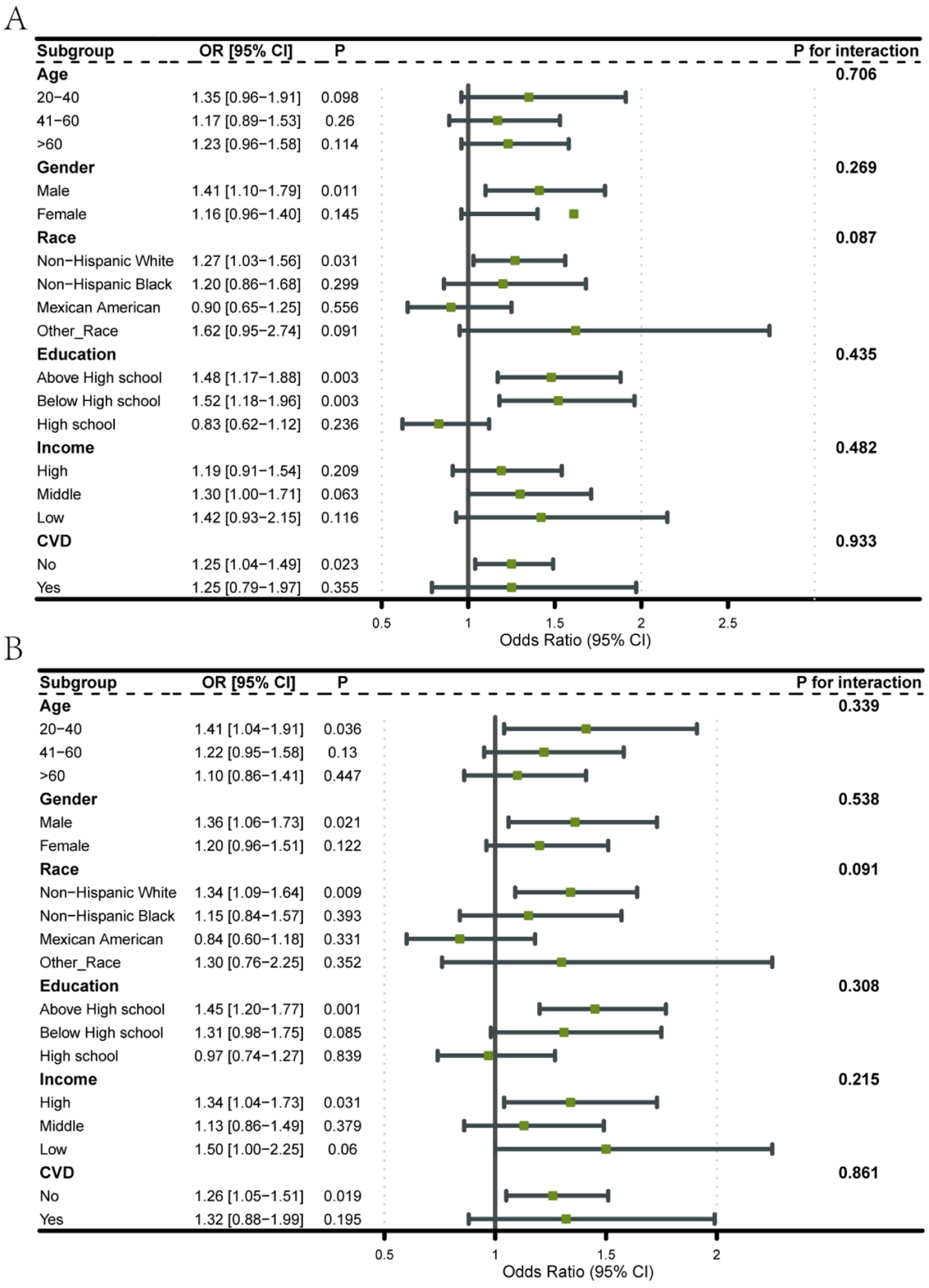

Figure 3 Continued.

C

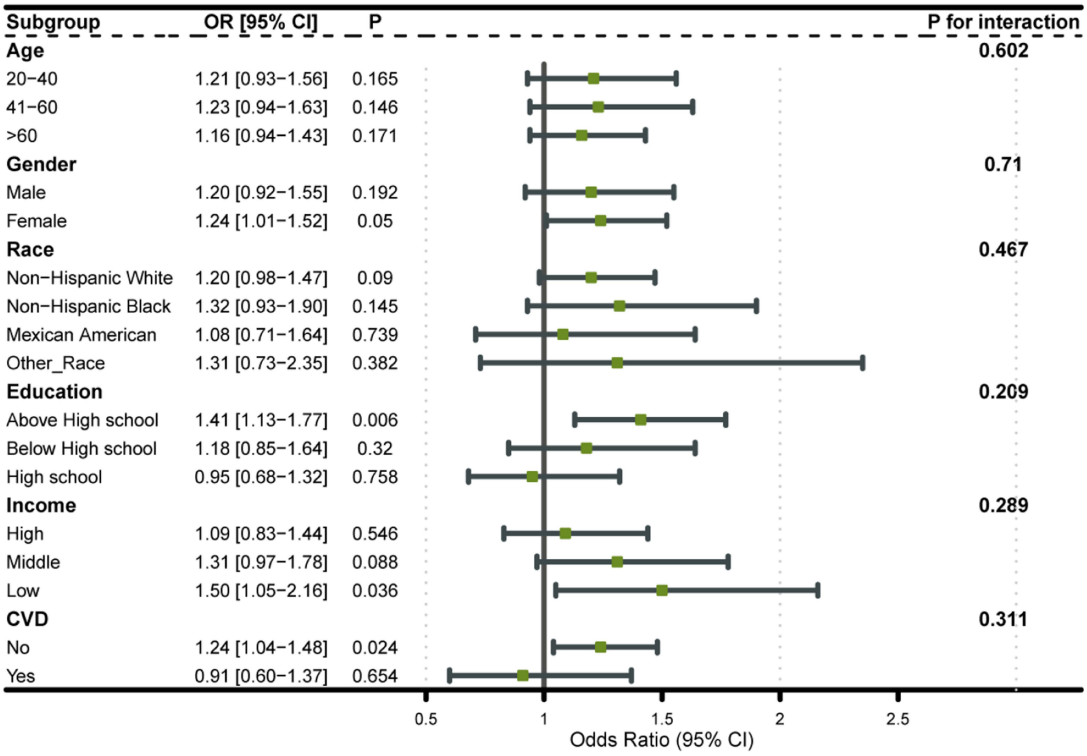

Figure 3 Subgroup Analyses of the Association Between Metabolic Syndrome and Low Back Pain.
Notes: (**A**) ATP III; (**B**) IDF; (**C**) mWHO.

supported this association, although their p-values did not reach statistical significance (Supplementary Table 4). Cochran's Q test indicated potential heterogeneity. MR-Egger regression detected evidence of horizontal pleiotropy (Supplementary Table 5). MR-PRESSO identified one outlier SNP potentially contributing to pleiotropy (Supplementary Table 6); however, after outlier correction, the association between hypertension and LBP remained significant (OR = 2.22, 95% CI: 1.35–3.64, p = 0.002).

For waist circumference, IVW analysis also revealed a significant causal association with LBP (OR = 1.45, 95% CI: 1.34–1.57, FDR-adjusted p < 0.001; see Figure 4), and the association was consistently supported by all four alternative MR methods (all p < 0.05; Supplementary Table 4).Cochran's Q test indicated potential heterogeneity, but MR-Egger did not detect evidence of pleiotropy (Supplementary Table 5).

For the remaining MetS components, no statistically significant causal effects on LBP were observed after FDR correction (Figure 4).

Table 3 Mediation Effect of C-Reactive Protein in the Association Between Metabolic Syndrome and Low Back Pain

Effect	ATPIII		IDF		mWHO	
	Estimate (95%CI)	P	Estimate (95%CI)	P	Estimate (95%CI)	P
Total Effect	0.043 (0.015,0.072)	0.004	0.045 (0.017,0.074)	0.002	0.032 (0.002,0.062)	0.044
Direct Effect (ADE)	0.041 (0.012,0.070)	0.006	0.043 (0.015, 0.072	0.008	0.029 (−0.000,0.060)	0.052
Indirect Effect (ACME)	0.002 (−0.001,0.005)	0.130	0.002 (−0.001,0.005)	0.112	0.002 (−0.000,0.006)	0.098
Proportion Mediated (%)	4.8 (−1.6, 17.9)	0.134	4.4 (−1.3, 16.2)	0.114	7.0 (−5.5, 48.9)	0.142

Abbreviations: ATPIII, Adult Treatment Panel III; IDF, International Diabetes Federation; mWHO, modified World Health Organization.

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Table 4 Association Between Individual Components of Metabolic Syndrome (ATP III Criteria) and Low Back Pain

Variable	OR (95% CI)	P_Value	FDR P_Value
Abdominal obesity	1.26 (1.07–1.49)	0.008	0.040
Hypertension	1.22 (1.04–1.42)	0.014	0.035
High fasting glucose	1.15 (0.96–1.39)	0.13	0.217
Hypertriglyceridemia	1.13 (0.93–1.38)	0.206	0.258
Low HDL cholesterol	1.03 (0.89–1.20)	0.665	0.665

Discussion

In this study, we explored the association between metabolic syndrome (MetS) and low back pain (LBP) using a large-scale cross-sectional dataset combined with Mendelian randomization (MR) analysis. Our findings revealed a significant and consistent association between MetS and LBP across three major diagnostic definitions (ATPIII, IDF, and mWHO), and the associations remained consistent after controlling for multiple confounding variables. Specifically, the fully adjusted odds ratios (ORs) for LBP among individuals with MetS ranged from approximately 1.21 to 1.27 across the

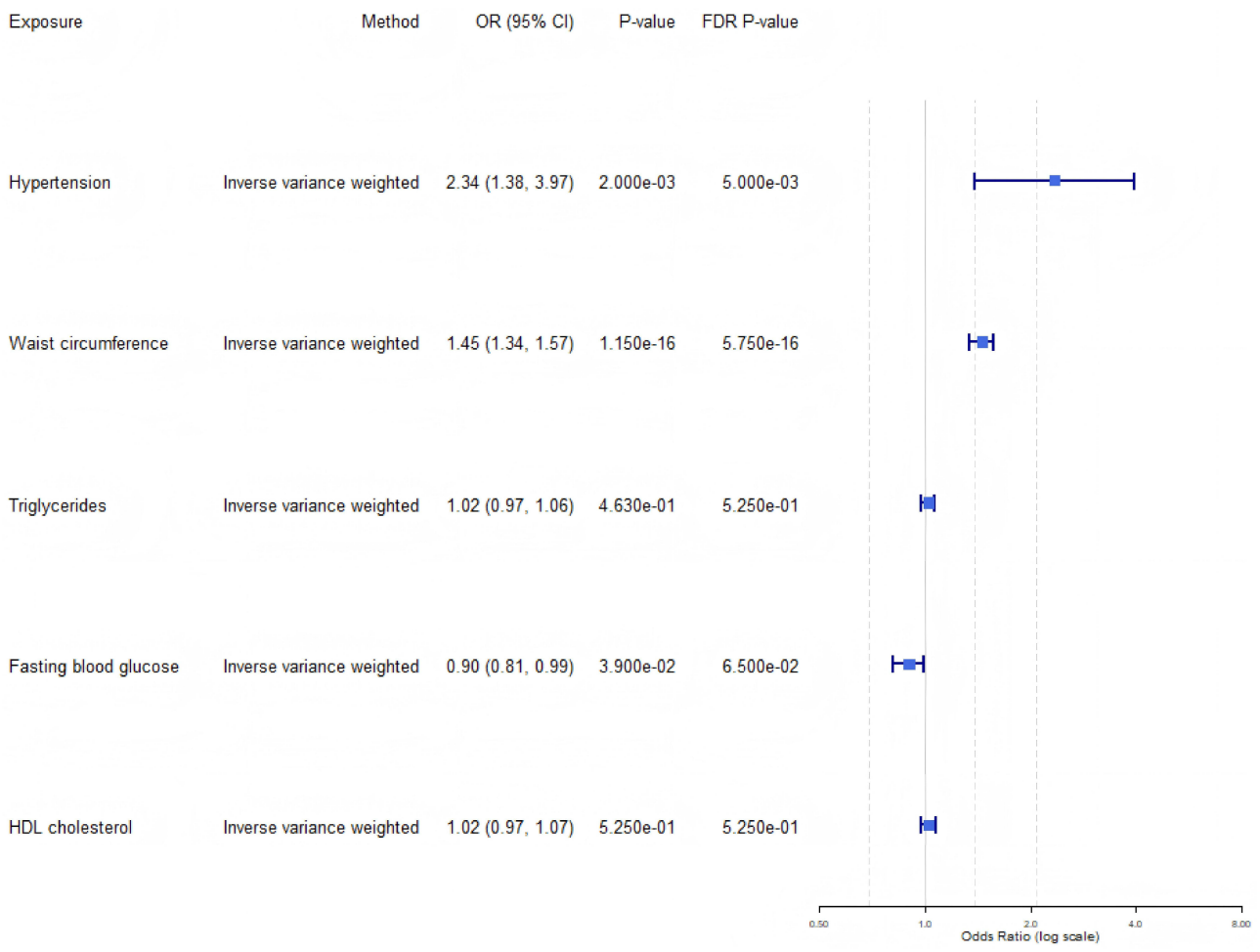

Figure 4 Forest Plot of Mendelian Randomization Estimates for the Association Between Metabolic Syndrome Components and Low Back Pain.

three definitions. Notably, MetS was more prevalent among individuals with LBP compared to those without, and this pattern held under all diagnostic definitions.

The prevalence of MetS varied substantially by diagnostic criteria, with the IDF definition producing the highest estimates, followed by ATPIII and mWHO. These differences likely reflect the criteria's inclusiveness: the IDF definition mandates central obesity using ethnicity-specific waist circumference cutoffs, thereby identifying more cases—particularly in populations with higher central adiposity.[18] In contrast, the mWHO definition requires evidence of insulin resistance or related metabolic impairment, along with data elements such as waist-to-hip ratio and urinary albumin excretion, which were unavailable in NHANES and likely led to underestimation. These discrepancies highlight that the choice of diagnostic criteria not only influences prevalence estimates but also affects the measured strength of association with outcomes like LBP.[17]

Additionally, we observed a progressive increase in MetS prevalence with advancing age, consistent with existing literature.[7] This trend may be attributed to age-related visceral fat accumulation, increased insulin resistance, and the growing burden of cardiovascular risk factors—all core features of MetS.[6] Among individuals aged 21–60, MetS was significantly more common in those with LBP than without, indicating a stronger association in younger and middle-aged adults. However, this difference was not statistically significant in those aged 60 or older, possibly because both MetS and LBP become nearly ubiquitous in older populations, blurring between-group differences. Moreover, in the elderly, LBP is frequently multifactorial and influenced by age-related spinal degeneration, osteoporosis, and sarcopenia, which may overshadow the contribution of metabolic factors.[9]

The findings of this study offer novel insights into the relationship between metabolic syndrome (MetS) and low back pain (LBP). The consistent associations observed in our cross-sectional analysis and the causal support from our MR findings for hypertension and waist circumference suggest three major interconnected pathophysiological pathways linking MetS components to LBP: I. Vascular-Disc Microcirculation: Hypertension, a well-known risk factor for atherosclerosis, may promote vascular degeneration in the microcirculation supplying the intervertebral discs (IVDs). This impairment of nutrient and waste exchange is a critical factor in accelerating IVD degeneration, thereby increasing the risk of LBP.[42,43] Our finding that hypertension is both significantly associated with LBP (observational) and causally linked (MR) provides strong support for this vascular mechanism. II. Adiposity and Biomechanics: Abdominal obesity, indexed by waist circumference, reflects increased visceral and subcutaneous adipose tissue accumulation. This physical burden imposes greater biomechanical stress and altered load distribution on the lumbar spine, contributing directly to spinal and intervertebral disc degeneration.[44] The consistent positive association (cross-sectional) and confirmed causal effect (MR) of waist circumference strongly support this biomechanical pathway. III. Adipose-Cytokine Neuroinflammation: Beyond mechanical load, adipose tissue (prominently reflected by waist circumference) is an active endocrine organ that secretes various pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[45] These cytokines can lead to neuroinflammation and central sensitization, thereby enhancing the intensity and persistence of LBP.[46,47] This systemic inflammatory and neurogenic pathway likely co-exists with the biomechanical pathway, originating from the same adiposity component.

However, some MR analyses indicated the presence of heterogeneity through Cochran's Q test or showed evidence of directional pleiotropy via the MR-Egger intercept test. Consequently, we employed a random-effects IVW model and conducted sensitivity analyses using robust estimation methods, including MR-Egger, weighted median, and MR-PRESSO. Based on these approaches, our MR findings provide strong supporting evidence for a causal relationship between hypertension, abdominal obesity, and low back pain, though the results should be interpreted with caution.

It is noteworthy that C-reactive protein (CRP), a widely recognized systemic inflammatory marker, is typically elevated in individuals with metabolic syndrome and has been implicated in the pathophysiology of chronic pain conditions.[48] However, in our exploratory, cross-sectional, and survey-weighted mediation analysis, CRP did not significantly mediate the association between MetS and low back pain (LBP). This finding suggests that while systemic inflammation may be involved, its mediating role might be masked by other factors, such as localized inflammation, structural degeneration, or biomechanical stress. It is possible that CRP, as a nonspecific general marker, lacks the specificity to capture localized inflammatory responses in the spine or paraspinal tissues.

Limitations

Despite the important findings, this study has several limitations that should be acknowledged. First, the NHANES dataset is cross-sectional in nature, which limits our ability to establish causal relationships between MetS and low back pain (LBP).

Although Mendelian randomization (MR) was employed to strengthen causal inference, the findings should still be interpreted with caution. Second, due to the limited availability of LBP-related data in NHANES, we included only survey cycles from 1999 to 2004. As a result, the findings may not fully capture more recent trends in the prevalence and characteristics of MetS and LBP. Third, the absence of key variables in the NHANES database—such as oral glucose tolerance test (OGTT) results, waist-to-hip ratio, and urinary albumin excretion rate—may have led to misclassification or underestimation of MetS prevalence under the "modified WHO criteria", potentially attenuating observed associations between MetS and LBP. Fourth, the mediation analysis focused solely on C-reactive protein (CRP) as a proxy for systemic inflammation. Other potentially relevant inflammatory markers—such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)—could not be assessed due to lack of available data. Fifth, this study did not perform multivariable Mendelian randomization (MVMR) to account for generalized adiposity factors (eg, BMI or waist circumference) when assessing the independent causal effects of other MetS components (eg, triglycerides, HDL-C, glucose, and blood pressure). This is a crucial area for future research to precisely delineate independent metabolic pathways. Finally, the diagnosis of LBP was based on self-reported physician confirmation, which may be subject to recall bias or reporting bias, potentially affecting classification accuracy.

Conclusion

In summary, this study provides strong evidence—through both large-scale cross-sectional analysis and Mendelian randomization—that metabolic syndrome (MetS) is significantly associated with low back pain (LBP). Notably, hypertension and abdominal obesity emerged as key causal components contributing to this relationship. These findings suggest that Aggressive blood pressure control and waist-focused weight reduction may plausibly reduce the LBP burden; pragmatic trials embedding metabolic optimization into LBP care are warranted. Future studies are warranted to further elucidate the underlying biological mechanisms, which may guide more effective, metabolically informed therapeutic approaches for musculoskeletal pain disorders.

Abbreviation

MetS, Metabolic Syndrome; LBP, Low Back Pain; ATPIII, Adult Treatment Panel III; IDF, International Diabetes Federation; mWHO, Modified World Health Organization; MR, Mendelian Randomization; GWAS, Genome-Wide Association Study; SNP, Single-Nucleotide Polymorphism; NHANES, National Health and Nutrition Examination Survey; OR, Odds Ratio; CI, Confidence Interval; CRP, C-Reactive Protein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; CVD, Cardiovascular Disease; BMI, Body Mass Index; PIR, Poverty Income Ratio; ACR, Albumin-to-Creatinine Ratio; MI, Multiple Imputation; IV, Instrumental Variable; FDR, False Discovery Rate.

Data Sharing Statement

All the datasets presented in this study are publicly available on the official website of the NHANES (https://wwwn.cdc.gov/nchs/nhanes).

Ethics Statement

The requirement for ethical approval for this study was waived by the Institutional Review Board of Qilu Hospital of Shandong University because the data were obtained from the NHANES. This study employs publicly accessible data that has been lawfully acquired and satisfies the criteria for exemption from review as outlined in the ethical review protocols for life sciences and medical research involving human subjects.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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