Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Causal Relationships Between Abdominal Obesity, Type 2 Diabetes, Fasting Insulin, and Cervical Disc Disorders, Osteoporosis, and Rheumatoid Arthritis: A Mendelian Randomization Study

Hanming Tang[1,*], Jie Zhao[2,*], Xuexu Yan[1], Zhiyong Zheng[2], Wenzhe Bai[2], Zhikun Tang[3], Xiaochen Liu[2]

[1]College of First Clinical Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province, 250014, People's Republic of China; [2]Department of Osteoarthropathy, Affiliated Hospital of Shandong Traditional Chinese Medicine University, Jinan, Shandong Province, 250014, People's Republic of China; [3]Department of Cosmetic Dermatology, Affiliated Hospital of Shandong Traditional Chinese Medicine University, Jinan, Shandong Province, 250014, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaochen Liu, Department of osteoarthropathy, Affiliated Hospital of Shandong Traditional Chinese Medicine University, No. 16369, Jingshi Road, Jinan, Shandong Province, 250014, People's Republic of China, Tel +8618753106721, Email lxc18050@163.com; Zhikun Tang, Department of Cosmetic Dermatology, Affiliated Hospital of Shandong Traditional Chinese Medicine University, No. 16369, Jingshi Road, Jinan, Shandong Province, 250014, People's Republic of China, Tel +8613793188565, Email szytzk@163.com

Background: Evidence from prior research indicates a connection between orthopedic diseases and metabolic disorders, including type 2 diabetes (T2D), insulin resistance, and abdominal obesity. However, the causal relationships remain uncertain. This study utilized Mendelian randomization (MR) to investigate the causal effects of abdominal obesity, T2D, and fasting insulin (FI) on cervical disc disorders, osteoporosis (OP), and rheumatoid arthritis (RA).

Methods: Exposure data were sourced from genome-wide association studies (GWAS) for waist-hip ratio (WHR), body mass index (BMI), FI, and T2D with a sample size of 697,734 participants for WHR, 151,013 for BMI, and 62,892 cases with 596,424 controls for FI and T2D. Outcome data were derived from FinnGen, including cervical disc disorders (14,670 cases and 294,770 controls), OP (8,017 cases and 391,037 controls), and RA (13,621 cases and 262,844 controls). Univariate Mendelian randomization (UVMR) was performed using the inverse-variance weighted (IVW), MR-Egger, and weighted median methods. Multivariate Mendelian randomization (MVMR) included BMI as an adjustment. Sensitivity analyses incorporated Cochran's Q test, the MR-Egger intercept test, and leave-one-out analysis.

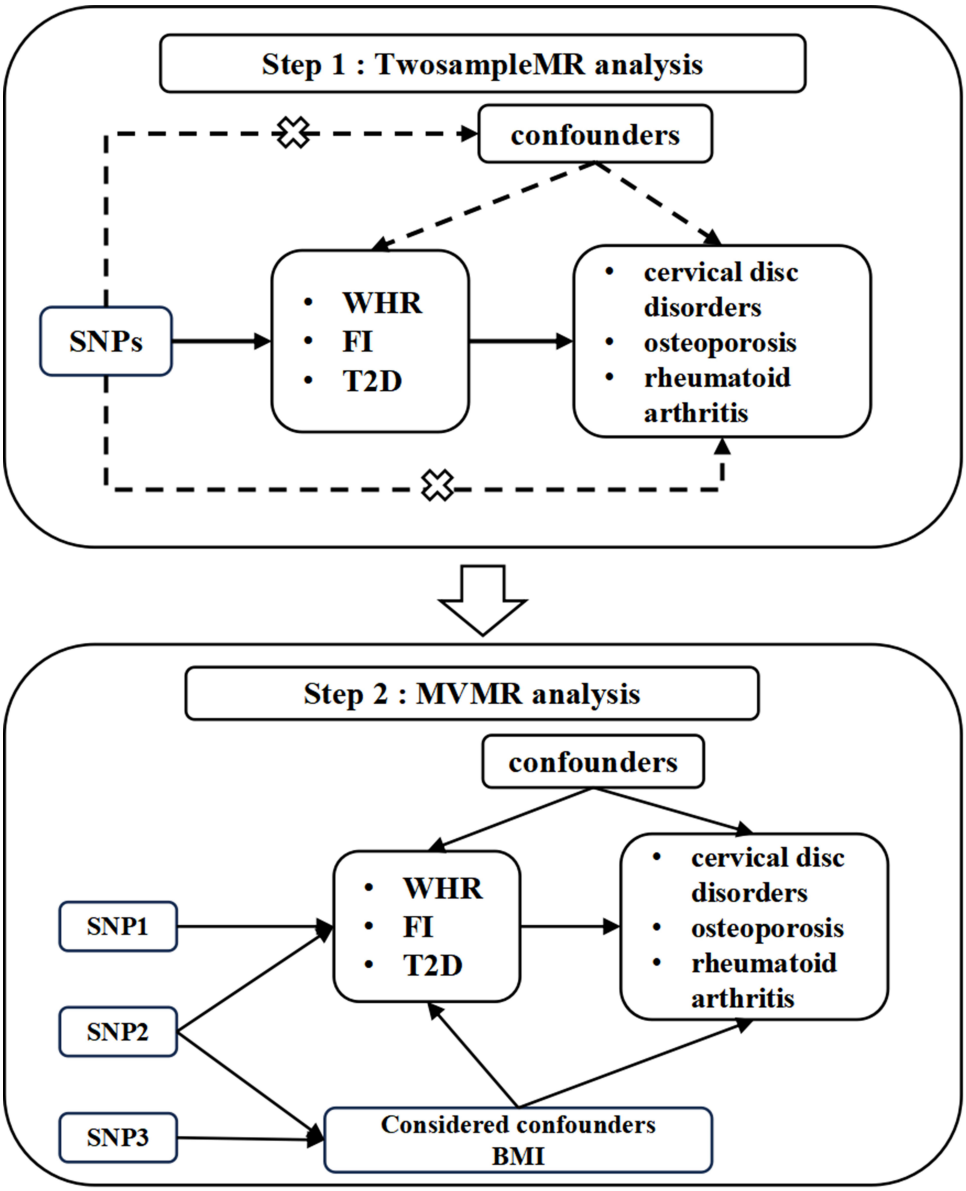
Results: UVMR identified WHR as a risk factor for cervical disc disorders (odds ratio [OR] = 1.147) and RA (OR = 1.260). FI increased the risk of cervical disc disorders (OR = 1.534), while T2D elevated the risk of RA (OR = 1.260) but lowered the risk of OP (OR = 0.925). MVMR confirmed FI's positive association with cervical disc disorders (OR = 1.716), T2D's increased risk for RA (OR = 1.062), and its protective role against OP (OR = 0.912). WHR remained a significant risk factor for RA (OR = 1.203).

Conclusion: Genetically predicted WHR and T2D were associated with an increased risk of RA. Additionally, T2D and FI increased the risk of cervical disc disorders, while T2D was found to have a protective role against OP. These findings provide novel insights into the interplay between metabolic factors and prevalent orthopedic conditions, offering valuable implications for clinical decision-making and targeted disease management strategies.

Keywords: abdominal obesity, cervical disc disorders, fasting insulin, Mendelian randomization, osteoporosis, rheumatoid arthritis, type 2 diabetes

Received: 19 March 2025
Accepted: 16 July 2025
Published: 9 August 2025

Graphical Abstract



Introduction

Abdominal obesity and type 2 diabetes (T2D) are among the most prevalent public health challenges today, serving as significant metabolic contributors and central components of metabolic syndrome.[1] Over the last four decades, the global health landscape has transitioned from having twice as many underweight individuals as those classified as obese to a scenario where the number of obese individuals now exceeds the underweight population. This shift has positioned obesity as a critical global health issue associated with high prevalence and increased mortality rates.[2] Recent estimates indicate that approximately 2 billion people worldwide are overweight or obese, accounting for 30% of the global population.[3] Projections suggest that by 2030, nearly half of the adult population in the United States will be obese, with no state reporting an obesity rate below 35%, and some states nearing 60%.[4]

T2D is one of the most prevalent and severe chronic metabolic diseases worldwide. Shifts in living environments, lifestyles, and dietary habits have contributed to the rise in overweight and obesity, fueling the global T2D epidemic.[5] As

of 2021, more than 500 million individuals worldwide were living with diabetes, with a prevalence rate exceeding 10%, and diabetes-related healthcare costs estimated at $966 billion. By 2045, these figures are expected to increase to 783 million individuals with diabetes and expenditures surpassing $1.054 trillion, creating a substantial burden on both society and families.[6]

Fasting insulin (FI) serves as a key intermediary between obesity and T2D. Increased body fat content has long been recognized as a major pathogenic factor in insulin resistance. In the presence of obesity, insulin resistance and fasting hyperinsulinemia often coexist, even in the absence of hyperglycemia.[7]

Orthopedic diseases, such as cervical disc disorders, osteoporosis (OP), and rheumatoid arthritis (RA), are leading causes of disability globally, placing a significant economic burden on society. Cervical disc disorders, which are prevalent degenerative conditions, are primarily responsible for neck pain and nerve root-related discomfort.[8] OP is a common metabolic disorder characterized by decreased bone mass and altered bone microarchitecture.[9] RA is an autoimmune disease characterized by synovitis, cartilage damage, and bone erosion in peripheral joints.[10] Identifying potential risk and protective factors for orthopedic diseases is crucial for their prevention, particularly those that can be controlled through interventions.

Population-based cross-sectional and cohort studies have demonstrated that abdominal obesity and T2D increase the risk of RA and cervical disc disorders, while T2D may enhance bone mineral density (BMD), acting as a protective factor against OP.[11–13] However, discrepancies in the data persist.[14] Clarifying the causal relationships between metabolic factors and orthopedic diseases is essential for providing valuable insights into clinical treatment. Previous evidence primarily stems from observational studies, and the complex pathogenic factors associated with abdominal obesity and T2D make these studies susceptible to confounding factors, leading to uncertain causal links between metabolic factors and orthopedic diseases. Unlike traditional observational studies, Mendelian randomization (MR) employs genetic variants as instrumental variables (IVs) to assess the association between exposures and outcomes. MR minimizes confounding factors by utilizing single nucleotide polymorphisms (SNPs) which are randomly assigned at conception and are not influenced by environmental or behavioral factors. This approach can effectively eliminate confounding factors and reverse causality, making MR a valuable tool for exploring the associations between complex diseases and their risk factors.[15]

Given the uncertainty regarding the causal impact of metabolic factors on orthopedic diseases, an MR design was applied to evaluate the potential causal relationships. This MR analysis explores the possible causal links between metabolic factors (abdominal obesity, FI, and T2D) and orthopedic conditions including cervical disc disorders, OP, and RA.

Materials and Methods

Study Design

This study utilized genome-wide association studies (GWAS) summary data from public databases for MR analysis to explore the causal relationships between metabolic factors (waist-hip ratio (WHR), FI, and T2D) and orthopedic diseases (OP, cervical disc disorders, and RA). Initially, a two-sample MR approach was utilized, incorporating various GWAS summary datasets to investigate the causal relationships between metabolic factors and the three orthopedic diseases in European populations. Subsequently, body mass index (BMI), as a measure of general obesity, was included as a potential confounder in multivariate Mendelian randomization (MVMR) to account for horizontal pleiotropy. To ensure the validity of the MR analysis, three key principles must be satisfied: (1) a strong correlation between the instrumental variable (IV) and the exposure factor; (2) the IV must be independent of any confounding factors; and (3) the IV should influence the specific disease solely through the exposure factor. This study adhered to the STROBE-MR guidelines to ensure that every step of the Mendelian randomization analysis was conducted appropriately. The specific study design process is illustrated in Figure 1.

Data Sources

Data on BMI and WHR were derived from a large GWAS involving individuals of European ancestry.[16] The study combined data from the Genetic Investigation of Anthropometric Traits (GIANT) consortium (n = 212,248) and the UK Biobank (UKB) (n

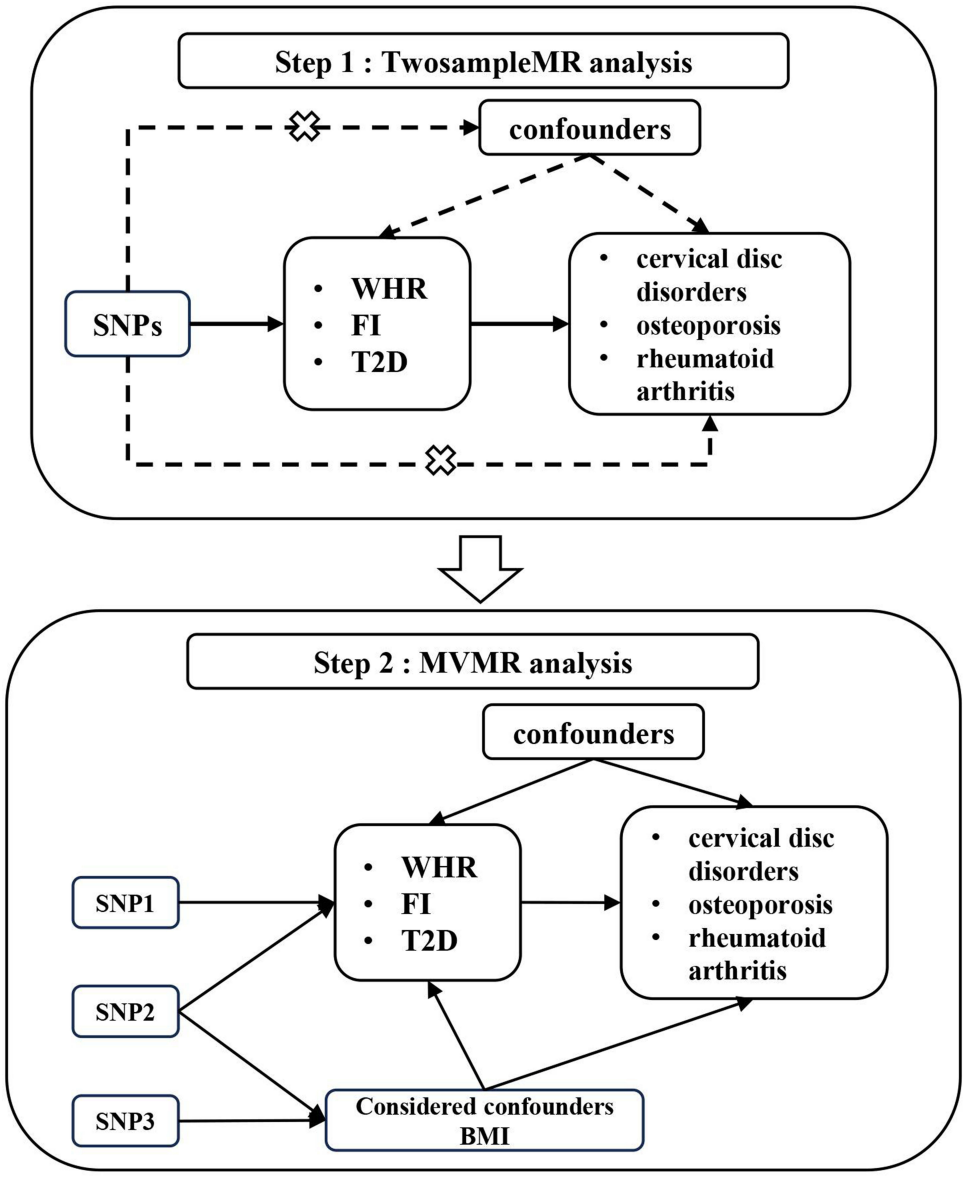


Figure 1 Diagrams illustrating associations examined in this study.
Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism; WHR, waist-hip ratio; FI, fasting insulin; T2D, type 2 diabetes; MVMR, Multivariate Mendelian randomization; BMI, body mass index.

= 485,486), performing a meta-analysis of genome-wide studies. In this GWAS, WHR represented abdominal fat content (abdominal obesity), and BMI served as an indicator of general obesity, comprising a total of 697,734 samples. Data on the FI metabolic phenotype were obtained from the Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC), comprising up to 281,416 non-diabetic individuals of European ancestry, including 151,013 samples.[17] T2D data were sourced from a large-scale GWAS meta-analysis, combining three European-ancestry datasets: the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM), Genetic Epidemiology Research on Aging (GERA), and UKB.[18] This dataset included 62,892 cases and 596,424 controls.

Outcome data were obtained from the latest whole-genome genetic datasets from the Finnish database R10 (https://r10.finngen.fi/), which integrates imputed genotype data generated from both new and legacy samples collected from Finnish biobanks and national health registries dating back to 1969. These data, derived from Finnish residents of European ancestry, included outcomes for OP (8,017 cases and 391,037 controls), cervical disc disorders (14,670 cases and 294,770 controls), and RA (13,621 cases and 262,844 controls) (Table 1).

Table 1 Characteristics of the GWAS Summary Data

Exposures/ Outcomes	Ethnicity	Data Source	Total Sample Size	No. IVs	*P*	*R2*	*F*
Exposures							
WHR	European	10.5281/zenodo.1251813	697,734	316	$P<5.0\times10^{-9}$	0.0330	75.22
FI	European	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90002001-GCST90003000/GCST90002238/	151,013	43	$P<5.0\times10^{-8}$	0.0045	15.85
T2D	European	http://cnsgenomics.com/data.html	62,892 cases, 596,424 controls	139*	$P<5.0\times10^{-8}$	0.2599	1665.14
Outcomes							
Osteoporosis	European	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_M13_OSTEOPOROSIS.gz	8,017 cases, 391,037 controls	-	-	-	-
Cervical disc disorders	European	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_M13_CERVICDISC.gz	14,670 cases, 294,770 controls	-	-	-	-
Rheumatoid arthritis	European	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_M13_RHEUMA.gz	13,621 cases, 262,844 controls	-	-	-	-

Notes: *Selection of IVs: $P<5.0\times10^{-8}$, clumping $R^2<0.01$, window size = 10,000 kb.
Abbreviations: IVs, instrumental variables; WHR, waist hip rate; FI, fasting insulin; T2D, type 2 diabetes mellitus.

Selection of Instrumental Variables

For WHR and FI, the IVs reported in the original literature were directly utilized. This included 316 WHR-related SNPs ($P < 5.0 \times 10^{-9}$) and 43 FI-related SNPs ($P < 5.0 \times 10^{-8}$). For T2D, the genome-wide statistical significance threshold was set at $P < 5.0 \times 10^{-8}$, with parameters set at $R^2 < 0.001$ and kb = 10,000 to mitigate the effects of linkage disequilibrium (LD). SNPs with a minor allele frequency (MAF) of less than 0.01 were excluded. To minimize bias from weak IVs, the F-statistic were used to assess the strength of the association between the IVs and metabolic factors, calculated as: $F=[R^2\times(N-1-K)]/[K\times(1-R^2)]$, where $R^2=\beta^2\times2\times MAF\times(1-MAF)$, β represents the effect size of the genetic variant related to the exposure factor, MAF represents minor allele frequency, R^2 indicates the proportion of exposure explained by genetic variation, N denotes the sample size, and K is the number of genetic variants. An F-statistic greater than 10 is considered indicative of a strong IV, with a higher F-statistic suggesting a lower likelihood of weak IVs.[19,20]

MR Study

The study employed a range of MR techniques, to assess causal relationships, including random or fixed-effects inverse-variance weighted (IVW) analysis, MR-Egger regression, and the weighted median (WM) method. IVW was used as the primary analysis approach. IVW does not account for an intercept term and provides a combined estimate of the causal effect of the exposure on the outcome when the genetic variants satisfy the assumptions of valid IVs.[21] However, IVW results overlook the potential presence of gene-level pleiotropy. Therefore MR-Egger and WM were applied as supplementary methods to verify the validity and consistency of the findings.[22] MR-Egger regression permits pleiotropy for all SNPs, detecting horizontal heterogeneity via intercept testing and providing estimates after adjusting for pleiotropy.[23] WM method weights the causal effect value of each SNP according to its cluster size, yielding a temporary estimate weighted by the most significant SNPs.[24]

A causal estimate is considered significant if the IVW method $P < 0.05$, and the direction is consistent with the MR-Egger and WM results. In the multivariate MVMR analysis, IVW was the primary method. To mitigate data bias from multiple measurements, the Bonferroni correction was applied to adjust the *P*-values. A total of 12 corrections were performed, resulting in a Bonferroni-corrected significance threshold of $\alpha < P/12 = 0.0042$. Therefore, $P < 0.0042$ is regarded as a significant impact, $0.0042 < P < 0.05$ indicates a suggestive association, and $P > 0.05$ suggests no significant effect.

Quality Analysis

To ensure the reliability and stability of the study results, several quality control measures were implemented, including sensitivity analyses, heterogeneity tests, and gene-level pleiotropy assessments. Sensitivity analyses included leave-one-

out analyses, where each IV was excluded individually, and the results of the remaining IVs were recalculated to evaluate their impact on the outcomes. The Cochran Q-test was used to assess heterogeneity among IVs.[25] If the $P > 0.05$ with no evidence of heterogeneity, a fixed-effects IVW model was employed as the primary analysis method. When the $P < 0.05$, indicating significant heterogeneity, a random-effects IVW model was used. MR-Egger regression was utilized to assess horizontal pleiotropy, with a significant deviation of the intercept term from zero indicating the presence of pleiotropy. In these cases, MR-pleiotropy residual sum and outlier (MR-PRESSO) was applied to remove outlier SNPs and eliminate horizontal pleiotropy, after which MR analysis was repeated.[26]

All analyses in this study were conducted using the TwoSampleMR and MVMR packages in R software (version 4.3.1).

Results

Instrumental Variables

Based on the selection criteria for IVs, SNPs for metabolic-related factors were chosen from GWAS data, resulting in 316 SNPs for WHR, 43 for FI, and 139 for T2D. The strength of these IVs was evaluated using the F-statistic. Among the selected SNPs, 13 with an F-statistic < 10, which were significantly associated with FI, were excluded. All remaining SNPs were used for MR analysis. The characteristics of the final selected SNPs are detailed in Supplementary Table S1.

Two-Sample MR Analysis

The MR analysis results suggest a causal relationship between genetically predicted WHR levels and cervical disc disorders, indicating a suggestive association and significant finding. Specifically, each one standard deviation (SD) increase in WHR was associated with a 1.147-fold increased risk of cervical disc disorders (IVW, $p = 0.030$, OR = 1.147, 95% CI: 1.014–1.297) (Figure 2). Similarly, genetically predicted FI levels show a causal relationship with cervical disc disorders, with each one SD increase in FI increasing the risk by 1.534 (IVW, $p = 0.004$, OR = 1.534, 95% CI: 1.145–2.055) (Figure 2), indicating a significant result and suggestive association.

Additionally, genetically predicted T2D levels are causally associated with cervical disc disorders, identifying T2D as a risk factor. Each one SD increase in the Genetic Risk Score (GRS) for T2D raised the risk of cervical disc disorders by

exposure on orthopedic diseases	No.SNPs	OR (95%CI)	P
(a) WHR			
osteoporosis	299	0.915 (0.784-1.067)	0.258
cervical disc disorders	299	1.147 (1.014-1.297)	0.030
rheumatoid arthritis	299	1.260 (1.113-1.426)	<0.001
(b) FI			
osteoporosis	40	0.754 (0.449-1.265)	0.285
cervical disc disorders	40	1.469 (1.034-2.087)	0.032
rheumatoid arthritis	40	0.861 (0.612-1.212)	0.39
(b) FI*			
osteoporosis	29	0.648 (0.356-1.177)	0.154
cervical disc disorders	29	1.534 (1.145-2.055)	0.004
rheumatoid arthritis	29	0.822 (0.542-1.246)	0.356
(c) T2D			
osteoporosis	135	0.925 (0.873-0.981)	0.010
cervical disc disorders	135	1.080 (1.037-1.125)	<0.001
rheumatoid arthritis	135	1.095 (1.000-1.200)	0.051

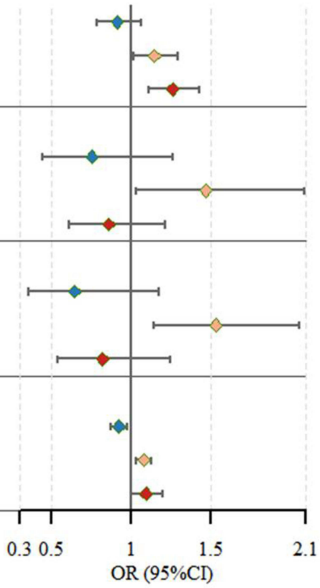


Figure 2 Mendelian randomization association of genetically determined metabolism-related traits with 3 kinds of orthopedic diseases.
Abbreviations: SNP, single nucleotide polymorphism; WHR, waist-hip ratio; FI, fasting insulin; T2D, type 2 diabetes; OR, odds ratio; CI, confidence interval.

1.080 (IVW, $p < 0.001$, OR = 1.080, 95% CI: 1.037–1.125) (Figure 2). This finding is significant and indicates a suggestive association. Genetically predicted WHR levels also show a causal relationship with RA, with each one SD increase in WHR increasing the risk of RA by 1.260 (IVW, $p < 0.001$, OR = 1.260, 95% CI: 1.113–1.426) (Figure 2), signifying a significant result and suggestive association.

Furthermore, genetically predicted T2D levels exhibited a causal relationship with OP, with T2D acting as a protective factor. Each one SD increase in the GRS for T2D reduced the risk of OP by 0.925 (IVW, $p = 0.010$, OR = 0.925, 95% CI: 0.873–0.981) (Figure 2), indicating a significant and suggestive association. Additionally, the analysis of FI-related SNPs (n = 43) without excluding weak IVs reveals a significant causal relationship between genetically predicted FI levels and cervical disc disorders. Each one SD increase in FI raised the risk of cervical disc disorders by 1.469 (IVW, $p = 0.032$, OR = 1.469, 95% CI: 1.034–2.087) (Figure 2), providing further evidence of a significant result and suggestive association. Supplementary Table S2 presents the results of four MR analysis methods, all of which showed consistent Beta directions across the analyses.

MVMR Analysis

In the MVMR analysis, BMI was adjusted as a confounder. After considering the influence of BMI, MVMR was applied to observe the independent effects of exposures on outcomes. The results of the MVMR analysis indicate that the causal relationship between WHR levels and cervical disc disorders disappeared after adjusting for BMI (IVW, $p = 0.107$, OR = 1.118, 95% CI: 0.976–1.281). However, FI levels continued to show a positive causal effect on cervical disc disorders (IVW, $p < 0.001$, OR = 1.716, 95% CI: 1.271–2.317). Similarly, T2D levels maintained a positive causal effect on cervical disc disorders (IVW, $p < 0.001$, OR = 1.092, 95% CI: 1.048–1.137) (Figure 2).

WHR levels continued to show a positive causal effect on RA (IVW, $p = 0.011$, OR = 1.203, 95% CI: 1.044–1.385). T2D levels continued to have a protective effect on OP (IVW, $p < 0.001$, OR = 0.912, 95% CI: 0.867–0.959). Furthermore, after adjusting for BMI, a causal relationship between T2D levels and RA emerged, indicating that T2D is a risk factor for RA. Each unit increase in T2D increased the risk of RA by 1.062 times (IVW, $p = 0.016$, OR = 1.062, 95% CI: 1.012–1.116) (Figure 3 and Supplementary Table S3).

Sensitivity and Pleiotropy Analyses

The MR-Egger intercept tests revealed $P > 0.05$ (Table 2), suggesting no evidence of horizontal pleiotropy between the selected SNPs and outcome factors, confirming the validity of the MR methods for causal inference in this study. Cochran's Q-test for heterogeneity among SNPs showed no significant heterogeneity $p > 0.05$ for FI after excluding weak

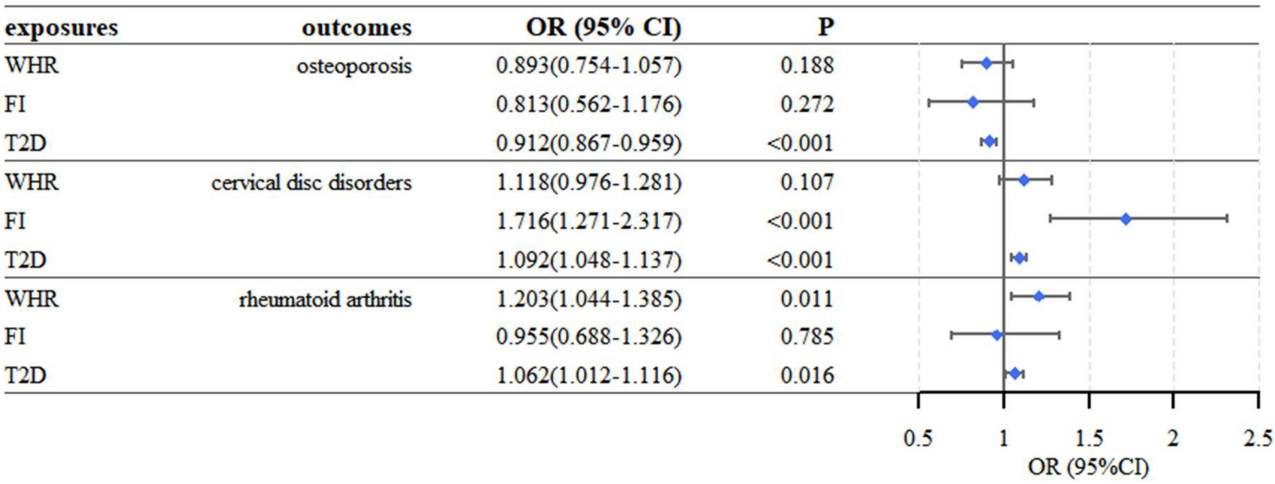


Figure 3 Forest plot for the MVMR adjusted for BMI.
Abbreviations: WHR, waist-hip ratio; FI, fasting insulin; T2D, type 2 diabetes; OR, odds ratio; CI, confidence interval.

https://doi.org/10.2147/JMDH.S529217

Table 2 Sensitivity Analyses with Directional Pleiotropy Test and Heterogeneity Test

Exposures	Outcomes	Weighed Median			MR-Egger			Directional Pleiotropy		Cochran Q-Test	
		OR	95% CI	P	OR	95% CI	P	Egger Intercept	P	Q-Statistic	P
WHR	Osteoporosis	0.836	(0.669–1.044)	0.114	0.742	(0.481–1.145)	0.179	0.0037	0.312	426.69	<0.001
	Cervical disc disorders	1.300	(1.107–1.526)	0.001	1.162	(0.826–1.635)	0.390	−0.0002	0.935	498.37	<0.001
	Rheumatoid arthritis	1.095	(0.896–1.338)	0.380	1.180	(0.836–1.666)	0.350	0.0012	0.690	453.98	<0.001
FI	Osteoporosis	1.174	(0.663–2.080)	0.582	0.587	(0.122–2.839)	0.512	0.0046	0.744	80.48	<0.001
	Cervical disc disorders	1.934	(1.296–2.886)	0.001	2.138	(0.740–6.178)	0.170	−0.0068	0.467	65.89	0.003
	Rheumatoid arthritis	0.795	(0.528–1.197)	0.270	0.673	(0.239–1.894)	0.460	0.0045	0.623	56.67	0.026
FI*	Osteoporosis	1.179	(0.638–2.176)	0.600	0.903	(0.123–6.614)	0.921	−0.0066	0.733	64.53	<0.001
	Cervical disc disorders	2.000	(1.303–3.068)	0.002	2.809	(0.882–8.949)	0.092	−0.0121	0.292	39.49	0.057
	Rheumatoid arthritis	0.755	(0.481–1.184)	0.221	0.686	(0.172–2.742)	0.599	0.0036	0.791	51.05	0.003
T2D	Osteoporosis	0.907	(0.831–0.988)	0.026	0.950	(0.825–1.095)	0.480	−0.0020	0.688	222.93	<0.001
	Cervical disc disorders	1.053	(0.994–1.116)	0.080	1.018	(0.924–1.122)	0.710	0.0045	0.192	186.76	0.001
	Rheumatoid arthritis	0.992	(0.923–1.066)	0.830	1.139	(0.915–1.419)	0.250	−0.0030	0.698	873.83	<0.001

Notes: * Exclude 13 weak instrumental variables (rs77935490, rs17331151, rs11727676, rs9472135, rs2108349, rs972283, rs13258890, rs7903146, rs2845885, rs1351394, rs1402013, rs731839, and rs1206760).
Abbreviations: WHR, waist hip rate; FI, fasting insulin; T2D, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

IVs (Table 2). Consequently, a fixed-effects IVW model was applied for analysis. For other tests showing significant heterogeneity ($P < 0.05$) (Table 2), a random-effects IVW model was employed.

Leave-one-out sensitivity analyses yielded results consistent with the analysis of all included SNPs, with no SNPs significantly influencing causal associations (Supplementary Table S4). These findings confirm stable causal relationships between the three metabolic factors (WHR, FI, and T2D) and the three orthopedic diseases (cervical disc disorders, osteoporosis, and rheumatoid arthritis).

Discussion

This study utilized publicly available GWAS data and employed both Univariate MR (UVMR) and MVMR methods to explore the causal relationships between three metabolic factors (WHR, FI, and T2D) and various orthopedic diseases (OP, cervical disc disorders, and RA). The UVMR results indicated that T2D played a protective role against OP, while WHR, FI, and T2D appeared to be risk factors for cervical disc disorders, and WHR was a risk factor for RA. The findings from the MVMR analysis, which adjusted for BMI as a confounder, indicated that T2D remained protective against OP, while FI and T2D remained risk factors for cervical disc disorders. Notably, the causal relationship between WHR and cervical disc disorders disappeared when accounting for BMI. Additionally, WHR remained a risk factor for RA, but the positive causal relationship between T2D and RA was attenuated after adjusting for BMI.

Cervical disc disorders are common orthopedic diseases caused by degenerative changes in the cervical intervertebral discs, resulting in neck pain and nerve root-related discomfort.[8] This disorder is characterized by a detrimental cycle involving altered cell metabolism, matrix, and biomechanics, ultimately leading to mechanical instability and loss of the shock-absorbing function of the intervertebral discs.[27] Over the past 30 years, the prevalence and disability rates of this disease have significantly increased. By 2015, more than one-third of the global population had experienced neck pain lasting longer than three months.[28]

Most existing literature investigates the relationship between obesity and lumbar diseases, with fewer studies focusing on obesity and cervical diseases, typically using BMI as a measure of obesity levels. However, actual fat distribution varies significantly among individuals, leading to the growing recognition that WHR better reflects fat distribution and central obesity. This makes WHR a more accurate indicator of metabolic status than BMI.[29]

The UVMR results indicate that WHR is a risk factor for cervical disc disorders, while MVMR analysis suggests that this relationship may be attributed to BMI. Sun et al also found that BMI negatively affects the risk of cervical spondylosis in MR studies, demonstrating that general obesity (as indicated by BMI) is a risk factor for cervical

spondylosis (IVW, OR = 1.166, 95% CI: 1.052–1.292, $P = 0.003$).[30] However, observational studies regarding whether obesity causes cervical spondylosis have been inconsistent.

Teraguchi et al used MRI to examine the prevalence and distribution of intervertebral disc degeneration across the entire spine in a small population (n = 975) and identified a significant correlation between obesity (assessed by BMI) and intervertebral disc degeneration in all regions (cervical, thoracic, and lumbar).[11] Sheng et al, however, found no significant association between overweight and obesity (assessed by BMI) and cervical diseases in a cross-sectional sample from the 2014 Medical Expenditure Panel Study (MEPS) (n = 23,048), which is considered representative of the US population.[14] Their study further confirmed the absence of a significant association between obesity and cervical diseases, aligning with the prevailing opinion that no significant relationship exists between obesity and cervical spondylosis. Interestingly, studies on orthopedic diseases in children have shown a high correlation between obesity and neck pain.[31,32] Dianat et al found that children with a BMI below 17.33 were less likely to report neck pain (OR = 0.63, 95% CI: 0.42–0.95), suggesting that lower weight may reduce the risk of neck pain.[33] Azabagic et al found that the most common chronic pain site associated with overweight and obesity (assessed by BMI) was the neck (OR = 1.212), and Krul et al reported a higher frequency of chronic neck pain in overweight or obese children (assessed by BMI) (OR = 2.60; 95% CI: 1.30–5.19).[34,35]

The MVMR results show that after excluding the effect of BMI, BMI-adjusted WHR (WHRadjBMI), which directly measures abdominal fat content and is independent of obesity level, is not associated with cervical disc disorders, consistent with previous observational studies.[14,36] This may be because mechanical factors are the primary pathogenic contributors to disc diseases, and the cervical spine bears less body weight than the lumbar spine, reducing the impact of abdominal obesity on the cervical spine.[37] In children, head weight (indicated by head circumference) is positively correlated with newborn BMI, with the head accounting for 20 to 25% of total body weight at birth, which decreases to 4 to 6% by adulthood.[38] Consequently, children's cervical spines bear greater head weight than those of adults. To more accurately assess local obesity levels in the head and neck region, some scholars have proposed the concept of subcutaneous fat tissue thickness (SFTT) at the cervical level. A retrospective study based on this concept found a close correlation between SFTT at the C3 level and intervertebral disc degeneration, with females having an SFTT > 9.64mm being more likely to develop spinal degeneration, and males showing a similar trend with SFTT > 8.21mm.[39] Unfortunately, GWAS data related to neck circumference or neck fat distribution could not be obtained.

In addition to mechanical factors, significant fat infiltration around the cervical spine creates an inflammatory environment within disc tissues and induces abnormal adipokine production. On one hand, the excessive production of inflammatory factors such as IL-1β, TNF-α, and IL-6 accelerates disc matrix degradation, cell senescence, and cell mortality.[40] On the other hand, adipokines like leptin (primarily produced by white adipose tissue) and resistin (linked to insulin resistance) activate immune regulation and inflammatory signaling pathways within disc tissues, further enhancing the expression of inflammatory factors.[41]

Most existing studies examine the relationship between T2D and lumbar diseases, commonly suggesting that obesity induced by T2D is the primary pathogenic factor.[42] The current study, however, indicates that both T2D and FI are risk factors for cervical disc disorders. The high-glucose environment in patients with T2D accelerates disc degeneration, with advanced glycation end-products (AGEs) associated with diabetes accumulating in the annulus fibrosus, nucleus pulposus, and cartilage endplate, ultimately contributing to disc degeneration independent of obesity.[43] In vitro experiments reveal that elevated blood glucose concentrations inhibit nucleus pulposus cell proliferation and disrupt disc cell homeostasis.[44] Furthermore, since insulin shares structural similarities with Insulin-Like Growth Factor-1 (IGF-1) and IGF-2, hyperinsulinemia may interfere with IGF signaling pathways, accelerating disc degeneration.[45,46]

RA is a chronic inflammatory disease characterized by symmetric synovitis, cartilage damage, and bone erosion in peripheral joints. Its global prevalence ranges from approximately 0.25% to 1.0%, affecting 1 in every 200 individuals. The incidence is 2 to 3 times higher in women than in men, with peak onset occurring between ages 50 and 59.[10,47]

Previous MR studies have confirmed that WHR is a risk factor for RA (OR = 1.41; 95% CI, 1.22–1.62).[48] Similarly, observational studies have shown that abdominal obesity increases the risk of RA compared to general obesity (HR = 1.22, 95% CI: 1.06–1.41), aligning with the UVMR results.[49] When individuals first exhibit symptoms of RA, their immune system may have already been in a state of chronic inflammation for years. Obesity itself is a chronic

inflammatory state, with adipose tissue, particularly visceral fat, promoting the production of various inflammatory factors and adipokines such as IL-1, IL-6, IL-17, TNF-α, interferon-γ, and leptin. This induces systemic inflammation, increases peripheral tissue damage, and triggers autoimmune responses, which may lead to and exacerbate systemic inflammatory conditions, including inflammatory arthritis.[40,41,48] Martin et al proposed new expressions for different body fat distributions: favorable adiposity (FA), which has higher subcutaneous fat but lower visceral fat, and unfavorable adiposity (UFA), characterized by higher subcutaneous and visceral fat.[50] They used MR studies to confirm that both FA and UFA are risk factors for RA, consistent with the UVMR and MVMR results.

T2D and RA share common inflammatory pathological mechanisms. Studies have shown that abnormal glucose metabolism, insulin resistance, and T2D are frequently observed in patients with RA.[51] Zhang et al confirmed through MR studies that RA is a risk factor for T2D (OR = 1.04; 95% CI, 1.02–1.05).[52] However, limited evidence suggests that the risk of RA increases after a T2D diagnosis. Lu et al found that female patients with T2D, especially younger women, had a significantly increased risk of RA (OR = 1.46, 95% CI: 1.24–1.72), while no such association was observed in men.[12] Lahiri et al used data from the European Prospective Investigation of Cancer-Norfolk and the Norfolk Arthritis Register Study (EPIC-2-NOAR Study) and found that T2D (HR = 2.54, 95% CI: 1.26–5.09) and obesity (HR = 2.75, 95% CI: 1.39–5.46) were both associated with an increased risk of inflammatory polyarthritis.[53] This finding provides new insights into the MR research, suggesting that T2D and RA may have a mutual causal relationship.

A high-glucose environment enhances the interaction between thioredoxin-interacting protein (TXNIP) and the NOD-like receptor protein 3 (NLRP3) inflammasome, activating caspase 1 and promoting IL-1β release. Additionally, hyperglycemia directly induces β-cell apoptosis through Fas receptors, further upregulating IL-1β. Synovial fluid of patients with RA contains high levels of IL-1β, which regulates leukocyte recruitment, induces matrix metalloproteinases (MMPs), promotes cartilage degradation, inhibits new matrix synthesis, causes joint damage, and induces bone erosion by stimulating osteoclast differentiation and activation.[51,54] Studies have shown that IL-1 blockers (eg, Anakinra and Canakinumab) can simultaneously improve the progression of both diseases.[55]

OP is a prevalent metabolic disorder characterized by reduced bone mass, altered bone microarchitecture, increased bone fragility, and an elevated risk of fractures. Due to its significant public health impact, it is often referred to as the "silent epidemic of the 21st century".[9] The gold standard for diagnosing OP remains dual-energy X-ray absorptiometry for measuring BMD.

MA et al performed a meta-analysis on the association between T2D and BMD involving 3437 patients with diabetes and 19139 controls.[13] The analysis found significantly higher BMD at the femoral neck, hip, and spine in patients with T2D compared to non-diabetic individuals. However, this study did not include subgroup analyses. Qiu et al conducted a meta-analysis examining the relationship between diabetes and low bone mass, which included 4599 patients with diabetes and 19741 controls.[56] They found no association between T2D and low bone mass, but identified a significant link between type 1 diabetes and low bone density. These results remained consistent in subgroup analyses. Zhou et al utilized data from the US National Health and Nutrition Examination Survey (NHANES) for a cross-sectional study and European GWAS summary statistics for a MR study.[57] They found a positive correlation between fasting glucose levels and BMD at the hip, femoral neck, and first lumbar vertebra (L1) in patients with T2D. Additionally, FI was positively correlated with hip BMD in patients with T2D, who had higher hip BMD than non-diabetic individuals.

Obesity associated with T2D was previously thought to indirectly increased BMD. However, numerous recent MR studies have confirmed a direct protective role of T2D against OP.[58–60] Ma et al demonstrated, through mediated MR analysis, that while BMI increases the risk of OP, this effect is mediated by T2D.[61] The MR results further suggest that T2D acts as a direct protective factor against OP, while FI does not show a significant association with OP, possibly due to the inclusion of non-diabetic individuals in the GWAS. Notably, MR findings suggest FI may be a potential protective factor against OP, though the results were not significant [UVMR: OR = 0.648, P = 0.154; MVMR: OR = 0.813, P = 0.272], which is generally consistent with previous studies. High glucose levels in T2D reduce RANKL levels, inhibiting the RANKL/RANK/OPG pathway, which disrupts osteoclast differentiation and function, thus preventing bone matrix degradation and increasing BMD.[62] Elevated insulin levels in circulation may also contribute to the higher BMD in patients with T2D, as insulin, structurally similar to insulin-like growth factor 1 (IGF-1), can bind to IGF-1 receptors on osteoblasts, facilitating bone anabolic processes.[45]

This study has several limitations. First, the results may not be generalizable to non-European populations, as the GWAS dataset were of European ancestry. Differences in genetics, cultural practices, and lifestyles may influence the observed associations. Future studies should incorporate more diverse cohorts to validate the generalizability of these results across various ethnic and demographic groups. Second, due to limitations within the dataset, we were unable to perform subgroup analyses based on age, sex, or disease severity, which may have provided further insight into differential risk profiles and disease mechanisms. Further subgroup analyses of orthopedic disease datasets could be performed. Third, the complex pathogenesis of abdominal obesity and T2D complicates the complete exclusion of confounding factors, which may account for the variability in results observed across different MR studies.[63] Additional studies incorporating multi-omics data and pathway-specific analyses may better elucidate these relationships and clarify causal mechanisms.

Conclusions

In conclusion, this study suggests that abdominal obesity and T2D are associated with an increased risk of RA, with T2D exhibiting a causal relationship with a heightened risk of cervical disc disorders and a reduced risk of OP. These findings enhance the understanding of the relationships between metabolic factors and common orthopedic diseases, providing valuable insights for clinical practice and disease management.

Data Sharing Statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article.

Ethics Approval

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Affiliated Hospital of Shandong Traditional Chinese Medicine University.

Acknowledgments

All data used in this study were obtained from openly available databases and consortiums. We express our sincere appreciation to them.

Funding

This work was supported by the Shandong Provincial Natural Science Foundation (No. ZR20210H229) and the Science and Technology Plan Projects of Shandong Provincial Administration of Traditional Chinese Medicine (No. 2021Q107).

Disclosure

The authors declare no competing interests in this work.

References

1. Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. Int. *J Mol Sci*. 2024;25(3):1882. doi:10.3390/ijms25031882
2. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism*. 2022;133:155217. doi:10.1016/j.metabol.2022.155217
3. Caballero B. Humans against Obesity: who Will Win? *Adv Nutr*. 2019;10(suppl_1):S4–s9. doi:10.1093/advances/nmy055
4. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. *New Engl J Med*. 2019;381(25):2440–2450. doi:10.1056/NEJMsa1909301
5. Tinajero MG, Malik VS. An Update on the Epidemiology of Type 2 Diabetes: a Global Perspective. *Endocrinol Metab Clinics North Am*. 2021;50(3):337–355. doi:10.1016/j.ecl.2021.05.013
6. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
7. Abdul-Ghani M, DeFronzo RA. Fasting Hyperinsulinemia and Obesity: cause or Effect. *J Clin Endocrinol Metab*. 2023;108(10):e1151–e2. doi:10.1210/clinem/dgad118

8. Qiu Y, Wei X, Tao Y, et al. Causal association of leisure sedentary behavior and cervical spondylosis, sciatica, intervertebral disk disorders, and low back pain: a Mendelian randomization study. *Front Public Health*. 2024;12:1284594. doi:10.3389/fpubh.2024.1284594
9. Aibar-Almazán A, Voltes-Martínez A, Castellote-Caballero Y, Afanador-Restrepo DF, Carcelén-Fraile MDC, López-Ruiz E. Current Status of the Diagnosis and Management of Osteoporosis. *Int J Mol Sci*. 2022;23(16):9465. doi:10.3390/ijms23169465
10. Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. *Lancet*. 2023;402(10416):2019–2033. doi:10.1016/S0140-6736(23)01525-8
11. Ali D, Tencerova M, Figeac F, Kassem M, Jafari A. The pathophysiology of osteoporosis in obesity and type 2 diabetes in aging women and men: the mechanisms and roles of increased bone marrow adiposity. *Front Endocrinol*. 2022;13:981487. doi:10.3389/fendo.2022.981487
12. Lu MC, Yan ST, Yin WY, Koo M, Lai NS. Risk of rheumatoid arthritis in patients with type 2 diabetes: a nationwide population-based case-control study. *PLOS ONE*. 2014;9(7):e101528. doi:10.1371/journal.pone.0101528
13. Ma L, Oei L, Jiang L, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *Eur J Epidemiol*. 2012;27(5):319–332. doi:10.1007/s10654-012-9674-x
14. Sheng B, Feng C, Zhang D, Spitler H, Shi L. Associations between Obesity and Spinal Diseases: a Medical Expenditure Panel Study Analysis. *Int J Environ Res Public Health*. 2017;14(2):183. doi:10.3390/ijerph14020183
15. Tin A, Köttgen A. Mendelian Randomization Analysis as a Tool to Gain Insights into Causes of Diseases: a Primer. J. *Am Soc Nephrol*. 2021;32 (10):2400–2407. doi:10.1681/ASN.2020121760
16. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694649 individuals of European ancestry. *Human Molecular Genetics*. 2019;28(1):166–174. doi:10.1093/hmg/ddy327
17. Chen J, Spracklen CN, Marenne G, et al. The trans-ancestral genomic architecture of glycemic traits. *Nature Genet*. 2021;53(6):840–860. doi:10.1038/s41588-021-00852-9
18. Xue A, Wu Y, Zhu Z, et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. *Nat Commun*. 2018;9(1):2941. doi:10.1038/s41467-018-04951-w
19. Pritchard JK, Przeworski M. Linkage disequilibrium in humans: models and data. *Am J Hum Genet*. 2001;69(1):1–14. doi:10.1086/321275
20. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40(3):755–764. doi:10.1093/ije/dyr036
21. Pagoni P, Dimou NL, Murphy N, Stergiakouli E. Using Mendelian randomisation to assess causality in observational studies. *Evidence Mental Health*. 2019;22(2):67–71. doi:10.1136/ebmental-2019-300085
22. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Geneti Epidemiol*. 2013;37(7):658–665. doi:10.1002/gepi.21758
23. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Human Molecular Genetics*. 2018;27(R2):R195–r208. doi:10.1093/hmg/ddy163
24. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Geneti Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
25. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. *Stat Med*. 2015;34(21):2926–2940. doi:10.1002/sim.6522
26. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife*. 2018;7. doi:10.7554/eLife.34408
27. Vergroesen PP, Kingma I, Emanuel KS, et al. Mechanics and biology in intervertebral disc degeneration: a vicious circle. *Osteoarthritis Cartilage*. 2015;23(7):1057–1070. doi:10.1016/j.joca.2015.03.028
28. Hurwitz EL, Randhawa K, Yu H, Côté P, Haldeman S. The Global Spine Care Initiative: a summary of the global burden of low back and neck pain studies. *Eur Spine J*. 2018;27(Suppl 6):796–801. doi:10.1007/s00586-017-5432-9
29. Åberg F, Färkkilä M, Salomaa V, et al. Waist-Hip ratio is superior to BMI in predicting liver-related outcomes and synergizes with harmful alcohol use. *Communicat Med*. 2023;3(1):119. doi:10.1038/s43856-023-00353-2
30. Sun Y, Jin M, Yu T, Zhang J. Cardiovascular risk factors mediating the protective effect of education on cervical spondylosis risk. *Sci Rep*. 2023;13 (1):936. doi:10.1038/s41598-023-28153-7
31. Singh S, Kumar D, Kumar S. Risk factors in cervical spondylosis. *J Clinl Orthopaedics Trauma*. 2014;5(4):221–226. doi:10.1016/j.jcot.2014.07.007
32. Samal S, Panigrahi P, Dutta A. Social epidemiology of excess weight and central adiposity in older Indians: analysis of Study on global AGEing and adult health (SAGE). *BMJ open*. 2015;5(11):e008608. doi:10.1136/bmjopen-2015-008608
33. Dianat I, Alipour A, Asgari Jafarabadi M. Risk factors for neck and shoulder pain among schoolchildren and adolescents. *J Paediatr Child Health*. 2018;54(1):20–27. doi:10.1111/jpc.13657
34. Azabagic S, Pranjic N. The Site of Musculoskeletal Pain in School Children with Excessive Body Weight and Obesity in Bosnia and Herzegovina. *Materia Socio-Medica*. 2019;31(2):88–92. doi:10.5455/msm.2019.31.88-92
35. Krul M, van der Wouden JC, Schellevis FG, van Suijlekom-Smit LW, Koes BW. Musculoskeletal problems in overweight and obese children. *Ann Family Med*. 2009;7(4):352–356. doi:10.1370/afm.1005
36. Yuan C, Jian Z, Feng S, et al. Do Obesity-Related Traits Affect Prostate Cancer Risk through Serum Testosterone? A Mendelian Randomization Study. *Cancers*. 2023;15(19):4884. doi:10.3390/cancers15194884
37. Gandhi R, Woo KM, Zywiel MG, Rampersaud YR. Metabolic syndrome increases the prevalence of spine osteoarthritis. *Orthopaedic Surg*. 2014;6 (1):23–27. doi:10.1111/os.12093
38. Makhoul IR, Abulhija H, Smolkin T, Shehadeh N, Hochberg Z. Modified anthropometry in prepubertal Israeli children while excluding the head's weight and height. *Acta paediatrica*. 2012;101(11):e496–9. doi:10.1111/j.1651-2227.2012.02792.x
39. Cao J, Sun D, Guo L, Wang R, Liu P. A novel radiological index for the evaluation of cervical posterior subcutaneous fat tissue thickness and cervical spine degeneration: a retrospective study. *Medicine*. 2023;102(29):e34355. doi:10.1097/MD.0000000000034355
40. Francisco V, Pino J, González-Gay M, et al. A new immunometabolic perspective of intervertebral disc degeneration. *Nat Rev Rheumatol*. 2022;18 (1):47–60. doi:10.1038/s41584-021-00713-z
41. Shin JH, Park S, Cho H, Kim JH, Choi H. Adipokine human Resistin promotes obesity-associated inflammatory intervertebral disc degeneration via pro-inflammatory cytokine cascade activation. *Sci Rep*. 2022;12(1):8936. doi:10.1038/s41598-022-12793-2

42. Agius R, Galea R, Fava S. Bone mineral density and intervertebral disc height in type 2 diabetes. *J Diabet Complicat*. 2016;30(4):644–650. doi:10.1016/j.jdiacomp.2016.01.021
43. Yang F, Zhu D, Wang Z, et al. Role of Advanced Glycation End Products in Intervertebral Disc Degeneration: mechanism and Therapeutic Potential. *Oxid Med Cell Longev*. 2022;2022(1):7299005. doi:10.1155/2022/7299005
44. Gorth DJ, Shapiro IM, Risbud MV. Discovery of the drivers of inflammation induced chronic low back pain: from bacteria to diabetes. *Discov Med*. 2015;20(110):177–184.
45. Conte C, Epstein S, Napoli N. Insulin resistance and bone: a biological partnership. *Acta diabetologica*. 2018;55(4):305–314. doi:10.1007/s00592-018-1101-7
46. Lin H, Tian S, Peng Y, et al. IGF Signaling in Intervertebral Disc Health and Disease. *Front Cell Develop Biol*. 2021;9:817099. doi:10.3389/fcell.2021.817099
47. Smith MH, Berman JR. What Is Rheumatoid Arthritis? *JAMA*. 2022;327(12):1194. doi:10.1001/jama.2022.0786
48. Li X, Zhu J, Zhao W, et al. The Causal Effect of Obesity on the Risk of 15 Autoimmune Diseases: a Mendelian Randomization Study. *Obesity Facts*. 2023;16(6):598–605. doi:10.1159/000534468
49. Marchand NE, Sparks JA, Tedeschi SK, et al. Abdominal Obesity in Comparison with General Obesity and Risk of Developing Rheumatoid Arthritis in Women. *J Rheumatol*. 2021;48(2):165–173. doi:10.3899/jrheum.200056
50. Martin S, Tyrrell J, Thomas EL, et al. Disease consequences of higher adiposity uncoupled from its adverse metabolic effects using Mendelian randomisation. *eLife*. 2022;11:1.
51. Di Muzio C, Cipriani P, Ruscitti P. Rheumatoid Arthritis Treatment Options and Type 2 Diabetes: unravelling the Association. *BioDrugs*. 2022;36(6):673–685. doi:10.1007/s40259-022-00561-7
52. Zhang K, Jia Y, Wang R, et al. Rheumatoid arthritis and the risk of major cardiometabolic diseases: a Mendelian randomization study. *Scand J Rheumatol*. 2023;52(4):335–341. doi:10.1080/03009742.2022.2070988
53. Lahiri M, Luben RN, Morgan C, et al. Using lifestyle factors to identify individuals at higher risk of inflammatory polyarthritis (results from the European Prospective Investigation of Cancer-Norfolk and the Norfolk Arthritis Register--the EPIC-2-NOAR Study). *Ann Rheumatic Dis*. 2014;73(1):219–226. doi:10.1136/annrheumdis-2012-202481
54. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci*. 2020;21(17):6275. doi:10.3390/ijms21176275
55. Giacomelli R, Ruscitti P, Alvaro S, et al. IL-1β at the crossroad between rheumatoid arthritis and type 2 diabetes: may we kill two birds with one stone? *Expert Rev Clinical Immunol*. 2016;12(8):849–855. doi:10.1586/1744666X.2016.1168293
56. Qiu J, Li C, Dong Z, Wang J. Is diabetes mellitus a risk factor for low bone density: a systematic review and meta-analysis. *BMC Endocr Disord*. 2021;21(1):65. doi:10.1186/s12902-021-00728-3
57. Zhou H, Li C, Song W, et al. Increasing fasting glucose and fasting insulin associated with elevated bone mineral density-evidence from cross-sectional and MR studies. *Osteoporosis Int*. 2021;32(6):1153–1164. doi:10.1007/s00198-020-05762-w
58. Ahmad OS, Leong A, Miller JA, et al. A Mendelian Randomization Study of the Effect of Type-2 Diabetes and Glycemic Traits on Bone Mineral Density. *J Bone Mineral Res*. 2017;32(5):1072–1081. doi:10.1002/jbmr.3063
59. Huang G, Chen X, Chen Y, et al. Causal relationship between type 2 diabetes mellitus and bone mineral density: a Mendelian randomization study in an East Asian population. *Osteoporosis Int*. 2023;34(10):1719–1727. doi:10.1007/s00198-023-06807-6
60. Cheng L, Wang S, Tang H. Type 2 diabetes mellitus plays a protective role against osteoporosis –Mendelian randomization analysis. *BMC Musculoskel Disorders*. 2023;24(1):444. doi:10.1186/s12891-023-06528-1
61. Ma W, Zhou X, Huang X, Xiong Y. Causal relationship between body mass index, type 2 diabetes and bone mineral density: Mendelian randomization. *PLOS ONE*. 2023;18(10):e0290530. doi:10.1371/journal.pone.0290530
62. Sassi F, Buondonno I, Luppi C, et al. Type 2 diabetes affects bone cells precursors and bone turnover. *BMC Endocr Disord*. 2018;18(1):55. doi:10.1186/s12902-018-0283-x
63. Inamo J, Kochi Y, Takeuchi T. Is type 2 diabetes mellitus an inverse risk factor for the development of rheumatoid arthritis? *J Human Genet*. 2021;66(2):219–223. doi:10.1038/s10038-020-00837-2