**Clinical Research Article**

# Causal association of obesity and chronic pain mediated by educational attainment and smoking: a mediation Mendelian randomization study

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**ABSTRACT**

**Background:** Obesity and chronic pain are related in both directions, according to earlier observational research. This research aimed to analyze the causal association between obesity and chronic pain at the genetic level, as well as to assess whether common factors mediate this relationship.

**Methods:** This study used bidirectional two sample Mendelian randomization (MR) technique to analyze the association between obesity and chronic pain. Obesity's summary genome-wide association data were obtained from European ancestry groups, as measured by body mass index (BMI), waist-to-hip ratio, waist circumference (WC), and hip circumference (HC), genome-wide association study data for chronic pain also came from the UK population, including chronic pain at three different sites (back, hip, and headache), chronic widespread pain (CWP), and multisite chronic pain (MCP). Secondly, a two-step MR and multivariate MR investigation was performed to evaluate the mediating effects of several proposed confounders.

**Results:** The authors discovered a link between chronic pain and obesity. More specifically, a sensitivity analysis was done to confirm the associations between greater BMI, WC, and HC with an increased risk of CWP and MCP. Importantly, the intermediate MR results suggest that education levels and smoking initiation may mediate the causal relationship between BMI on CWP, with a mediation effect of 23.08% and 15.38%, respectively.

**Conclusions:** The authors' findings demonstrate that the importance of education and smoking in understanding chronic pain's pathogenesis, which is important for the primary prevention and prognosis of chronic pain.

**Keywords:** Chronic Pain; Educational Status; Genome-Wide Association Study; Mendelian Randomization Analysis; Mediation Analysis; Obesity; Smoking.

## INTRODUCTION

Obesity is a complex global problem with far-reaching impact and is the core issue of global health. It affects approximately 33% of the world's population and has become an important public health issue of global con-

cern [1]. The heritability of obesity is 50–70 [2]. When a person's body mass index (BMI) is greater than 30 kg/m$^2$, they are defined as obese [3]. Chronic pain is often defined as pain persisting for over three months, and is another important global health issue that affects most populations [4]. According to statistical data, approximately 20% to 40% of adults globally experience chronic pain conditions [5], and they have an average of three pain sites [6], including cancer-related pain, lower back pain, and myofascial pain [7]. Chronic widespread pain (CWP) and multisite chronic pain (MCP) are both common phenotypes of chronic pain and are widely present in obese people [8]. CWP denotes widespread pain affecting at least four-fifths of the body or three or more body quadrants, which are delineated by the upper, lower, left, and right sections, as well as the central axis bones, including the neck, back, chest, and abdomen. The worldwide prevalence of CWP in the general population is 10%–15% [9]. MCP refers to the number of chronic pain sites, patients with more than three chronic pain sites had longer pain duration than patients with fewer than three chronic pain sites [10]. In the current treatment regimen for chronic pain, opioids are now one of the best ways to treat moderate to serious pain [7]; However, opioids such as fentanyl and its derivatives have led to the serious consequences of the "opioid crisis" [11,12]. Therefore, it is essential to evaluate the possible risk factors of chronic pain and to study chronic pain management measures.

Obesity and chronic pain often happen at the same time [13]; compared with people of normal weight, those who are overweight have a significantly higher incidence of persistent pain, as high as 40% [14]. At present, the relationship between obesity and pain has become an important research area, nevertheless the mechanism of action remains unknown. The common mechanism of pain is the biological-psycho-social factor model, which posits that pain arises from the interplay of psychological, social, and biological aspects. In terms of the impact of obesity on pain, adipokines in obese patients are beneficial for promoting the production of inflammatory factors such as interleukin (IL)-2 [15], IL-6 [16], and IL-1β [17]. In addition, obesity also increases the load on joints such as lower limbs and spine. These factors may be influencing the level of pain and the number of pain sites [18]. At present, the body anxiety and deformed aesthetic, which are common in the society, aggravate the pain of obese people through the psycho-social mechanism. The pain experience is not only the result of physiological effects, but also social pressure and psychological conditions affect the pain experience of patients [19]. Among the

effects of pain on obesity, a "fear-avoidance model" proposes that the frequency of physical activity of pain patients decreases significantly under the influence of pain, which increases the risk of obesity [9]. However, studies on obesity and chronic pain are mainly observational [20]. Confounding variables, such as harmful behaviors like smoking and drinking, neurological and mental diseases like sadness and anxiety, and social lifestyles like education level, may readily alter observational study outcomes and observation processes. Therefore, in addition to studying the association between obesity and various chronic pain phenotypes, further investigation is needed to examine possible mediating factors, and it is conceivable that education level and negative behaviors (such as smoking) may be potential mediating factors between the two.

Mendelian randomization (MR) is a strategy for conducting genetic cause-and-effect studies on disease exposure and outcomes using genome-wide association study (GWAS) data. In MR analysis, single nucleotide polymorphisms (SNPs) are employed as instrumental variable (IVs). Instrumental variables related to exposure factors are screened. The causal link between instrumental factors and outcomes to deduce the link between exposure and results is investigated [21]. Genetic differences are believed to be randomly assigned prior to birth, rendering them mostly independent of environmental factors and established well before the beginning of sickness, hence reducing residual bias and reverse causality problems that limit traditional observational studies [22]. Although chronic pain conditions can be multifactorial and co-occur with overweight or obesity, few studies have examined the association at the genetic level. To examine the association between obesity and chronic pain at the genetic level, and to explore the potential mediators that may exist in the association, using a bidirectional MR method, this study assessed the causal link between obesity, assessed by BMI, waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR), and multiple phenotypes of chronic pain. To clarify the potential procedure, a two-step MR for mediation analysis was used, followed by multivariate MR (MVMR) to assess the mediating effects of common risk factors such as alcohol consumption and education level.
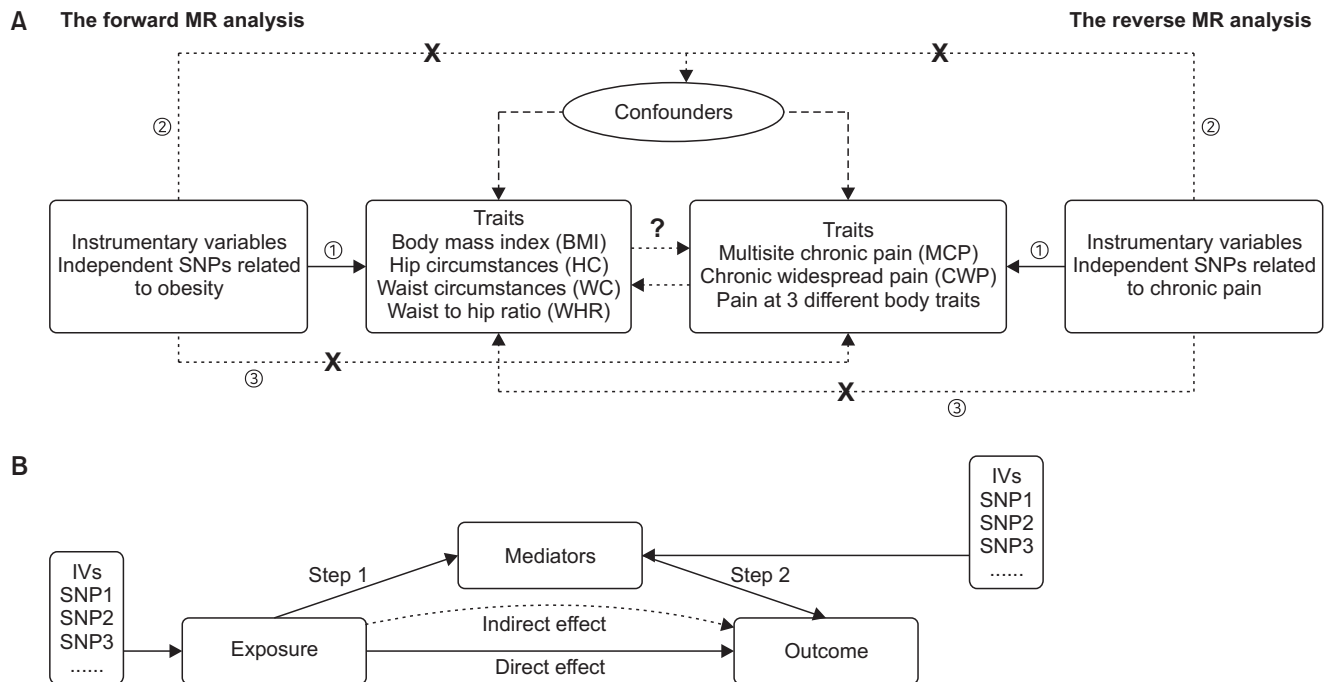
**Fig. 1.** (A) Schematic diagram of three assumptions for MR in this study: (i) Relevance: genetic variant is associated with the exposure; (ii) Independence: genetic variant is not related to any confounding factors of the exposure-outcome association and (iii) Exclusion restriction: genetic variant does not affect outcome except through its potential effect on the exposure. (B) Two-step MR analysis framework. Step 1 estimated the causal effect of the exposure on the potential mediators, and step 2 assessed the causal effect of the mediators on outcome. 'Direct effect' indicates the effect of exposure on outcome after adjusting for the mediator. 'Indirect effect' indicates the effect of exposure on outcome through the mediator. MR: Mendelian randomization, SNPs: single nucleotide polymorphisms, IVs: instrumental variables.

## MATERIALS AND METHODS

### 1. Study design

**Fig. 1** presents a detailed flow map of the study design. Firstly, a two-sample bidirectional MR was performed between obesity proxies and chronic pain phenotypes using the current comprehensive GWAS for individuals of European descent. The authors next assessed mediators between obesity and chronic pain using two-step MR and MVMR. The study was designed to meet each of the requirements in the STROBE-MR Checklist [23].

### 2. Study population

The comprehensive exposure data employed in the MR analysis were obtained from consolidated GWAS findings. The genetic information related to BMI characteristics originated from the extensive Genetic Investigation of Anthropometric Traits (GIANT) Consortium (https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files), encompassing

152,893 European individuals and 2,477,659 SNPS. According to numerous investigations by the GIANT Consortium, genetic differences in WC (N = 232,101), HC (N = 127,997), and WHR characteristics (N = 212,244) also came from this consortium.

In addition, the data of outcome were obtained using aggregated statistical data on MCP and CWP collected from GWAS' extensive biobank database (UK Biobank Consortium). The data for MCP comes from a cohort study of 387,469 people. The data for CWP (6,914 patients and 242,929 controls) come from Rahman et al.'s study [24]. The MCP phenotype is the number of painful sites in seven different body sites where the pain lasted for at least three months, on a scale of 0 to 7. CWP refers to systemic pain, including pain in the knees, shoulders, buttocks, and back for more than three months, as well as fibromyalgia [24]. The present study also included three other pain phenotypes, with headache data sourced from a UK Biobank study on headache genetic variation, which included 98,704 cases and 363,153 controls. The data on hip pain (52,087 patients and 409,770 controls) and back pain (118,471 patients and 343,386 controls) were also

sourced from the UK Biobank GWAS meta-analysis.

Potential mediators that may mediate the association between BMI [25] and chronic pain were explored in this study, including alcohol intake frequency, smoking initiation, physical inactivity, years of schooling and major depressive disorder. The data of these variables were derived from publicly accessible GWASs. **Supplementary Table 1** provides detailed information and sources for the GWAS data utilized in the authors' studies.

### 3. Selection of genetic instruments

A genome-wide threshold of $5 \times 10^{-8}$ was applied to select SNPs. If there were no SNPs available, the exposure-outcome connection was not investigated. SNPs with substantial linkage disequilibrium ($r^2 > 0.001$ or aggregate windows under 10 Mb) were eliminated [23]. The $F$-statistic is a measure of instrument strength. It is related to the proportion of variance in the phenotype explained by the genetic variants ($R^2$), sample size ($n$) and number of instruments ($k$) by the formula $F = \left( \frac{n-k-1}{K} \right) \left( \frac{R^2}{1-R^2} \right)$. In order to remove the weak instrumental variables, the F-value of each SNP were calculated using the formula, and when the F-value was less than 10, the instrumental variable was considered as a weak instrumental variable [26]. This research only included SNPs with F-values over 10.

### 4. Two-sample bidirectional MR

MR analysis is predicated on three fundamental assumptions: (1) SNPs identified as IVs are substantially related with exposure; (2) SNPs selected as IVs are not associated with confounders of the connection between exposures and outcomes; and (3) SNPs solely influence health outcomes through exposures. The positive results of this study were determined mainly by the inverse variance weighted (IVW) method. In statistics, IVW is a method of aggregating two or more random variables to minimize the variance of the weighted average, the IVW method utilized a meta-analysis approach along with Wald estimates for each SNP, and use the reciprocal of outcome variance as the weight to fit and summarize. Compared with the IVW method, the MR-Egger method considers the intercept term as an influential factor. When the regression intercept of the MR-Egger method is not zero, it indicates that the instrumental variables included in the study have multiple effects. The weighted median (WM) method produces the median of the data after the effects of each individual instrumental variable are sorted by weight. This method can still obtain valid statistical

results when up to 50% of the instrumental variables are invalid [27,28]. Sensitivity analysis was carried out in strict accordance with STROBE MR Guidelines to ensure the robustness of the study results. Cochran's Q test was initially utilized to identify heterogeneity, further assessing the impact of heterogeneity on causal differences. The Cochran's Q test is a non-parametric statistical test that determines if there is a difference in percentage between various relevant categories. Secondly, multi-efficiency testing was carried out utilizing MR Egger regression analysis, The average pleiotropy effect of the genetic variants in the study may account for the intercept in the MR Egger analysis. The IVW method yields reliable estimates of causal effects when the mean pleiotropy impact is zero. So, by looking at the MR Egger analysis's intercept, one may evaluate the reliability of the instrumental variable assumptions. A non-zero intercept suggests that the IVW estimate is biased. MR-PRESSO was used in this investigation to remove outliers and to detect and rectify horizontal pleiotropy. This method enables the calculation of the distance between the fitted line and each SNP that was obtained after SNP elimination. Horizontal pleiotropy increases as the distance is increased. Finally, the leave-one-out approach was utilized to determine if a single SNP may introduce significant drivers and biases into the summary.

### 5. Mediation analysis

Based on two-step MR analysis [29], this study analyzed the mediating role of smoking initiation, alcohol consumption, years of schooling, and depression on BMI in the occurrence of CWP. The standard error was calculated using the delta method [30], and the product of coefficients method was used to estimate the indirect effect [31]. Subsequently, the authors used MVMR to further evaluate the role of mediating factors in BMI and MCP, as well as BMI and CWP.

### 6. Statistical analysis

Both the bidirectional MR analysis and the intermediate Mendelian analysis in this study were carried out using R software (version 4.1.3), which includes the "Two Sample MR" package and the "MR PRESSO" package.
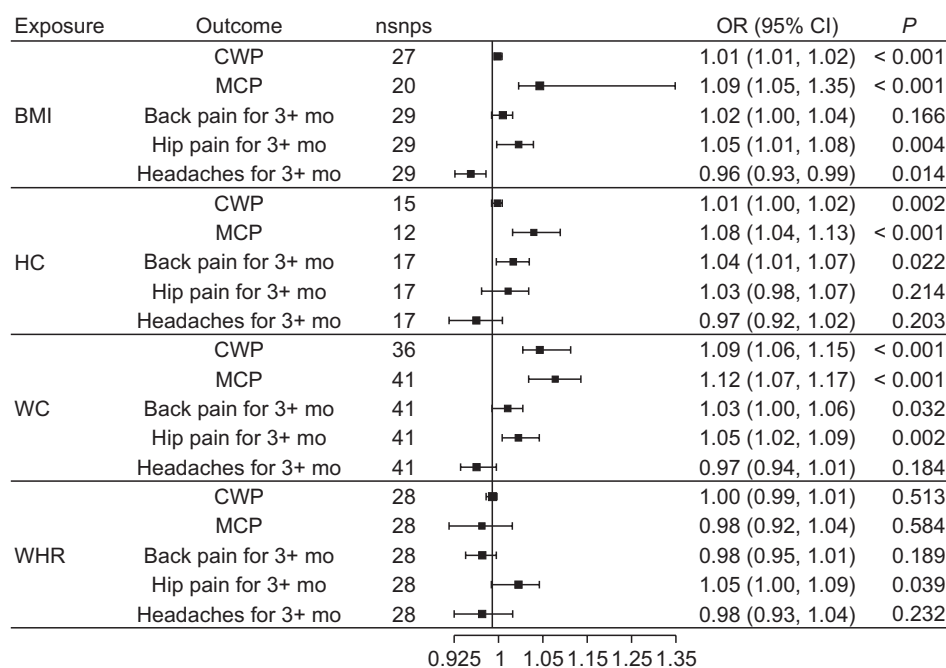
| Exposure | Outcome | nsnps | | OR (95% CI) | P |
|---|---|---|---|---|---|
| | CWP | 27 | | 1.01 (1.01, 1.02) | < 0.001 |
| | MCP | 20 | | 1.09 (1.05, 1.35) | < 0.001 |
| BMI | Back pain for 3+ mo | 29 | | 1.02 (1.00, 1.04) | 0.166 |
| | Hip pain for 3+ mo | 29 | | 1.05 (1.01, 1.08) | 0.004 |
| | Headaches for 3+ mo | 29 | | 0.96 (0.93, 0.99) | 0.014 |
| | CWP | 15 | | 1.01 (1.00, 1.02) | 0.002 |
| | MCP | 12 | | 1.08 (1.04, 1.13) | < 0.001 |
| HC | Back pain for 3+ mo | 17 | | 1.04 (1.01, 1.07) | 0.022 |
| | Hip pain for 3+ mo | 17 | | 1.03 (0.98, 1.07) | 0.214 |
| | Headaches for 3+ mo | 17 | | 0.97 (0.92, 1.02) | 0.203 |
| | CWP | 36 | | 1.09 (1.06, 1.15) | < 0.001 |
| | MCP | 41 | | 1.12 (1.07, 1.17) | < 0.001 |
| WC | Back pain for 3+ mo | 41 | | 1.03 (1.00, 1.06) | 0.032 |
| | Hip pain for 3+ mo | 41 | | 1.05 (1.02, 1.09) | 0.002 |
| | Headaches for 3+ mo | 41 | | 0.97 (0.94, 1.01) | 0.184 |
| | CWP | 28 | | 1.00 (0.99, 1.01) | 0.513 |
| | MCP | 28 | | 0.98 (0.92, 1.04) | 0.584 |
| WHR | Back pain for 3+ mo | 28 | | 0.98 (0.95, 1.01) | 0.189 |
| | Hip pain for 3+ mo | 28 | | 1.05 (1.00, 1.09) | 0.039 |
| | Headaches for 3+ mo | 28 | | 0.98 (0.93, 1.04) | 0.232 |

0.925  1  1.05 1.15 1.25 1.35

**Fig. 2.** Forest plots summarizing the causal effects of obesity on chronic pain. OR: odds ratio, CI: confidence interval, BMI: body mass index, HC: hip circumstance, WC: waist circumstance, WHR: waist to hip ratio, CWP: chronic widespread pain, MCP: multisite chronic pain.

# RESULTS

## 1. Genetic instruments

All SNPs selected by the authors according to the screening criteria are in the **Supplementary Tables 2–10**. After a very demanding screening step, it was found that all SNPS in this study had F-values greater than 10, indicating that all instrumental variables used in this study were valid.

## 2. The causal effect of obesity on chronic pain

**Fig. 2** shows a link between genetic susceptibility to obesity, as measured by four obesity features, and five unique chronic pain phenotypes. Significantly, these relationships remained significant after the consideration of repeated comparisons. A hereditary predilection for obesity has been linked to a higher frequency of chronic pain on all kinds of pain phenotypes, including CWP, MCP, back pain, and hip pain. The consistency of MR estimates across multiple methodologies (such as weighted model, WM, and MR-Egger) makes these causal linkages more valid, as detailed in **Supplementary Table 11**. In sensitivity studies, all MR-Egger intercept tests for MR analysis exceeded 0.05. The Cochran Q-test found no significant heterogeneity in any relevant correlations (all $P > 0.05$). The outcome of leave-one-out analysis indicating that no single SNP affected causal estimates (**Supplementary Fig. 1**).

## 3. The causal effect of various chronic pain phenotypes on obesity

Reverse MR analysis was performed using the genetic susceptibility to chronic pain as an exposure to examine its possible causative impact on chronic pain. A robust association was identified between the genetic susceptibility of MCP and HC (odds ratio [OR] = 1.32, 95% confidence interval [CI] = 1.14–1.52, $P < 0.001$), WC (OR = 1.25, 95% CI = 1.12–1.39, $P < 0.001$), as detailed in **Supplementary Table 12**. Nevertheless, there is little proof to substantiate a causal link between chronic pain and other obesity-related factors. MCP and CWP show directional agreement in MR estimation of obesity proxy markers using various approaches (**Supplementary Table 13**). Moreover, the MR-Egger intercept tests revealed no substantial pleiotropy (see **Supplementary Table 14**). The outcome of leave-one-out analysis indicating that no single SNP affected causal estimates (**Supplementary Fig. 2**).

**Table 1.** Causal effect of BMI on chronic pain in multivariable Mendelian randomization analyses

| Outcome | Mediators adjusted | OR (95% CI) | P value |
|---------|--------------------|-----------| --------|
| MCP | Smoking initiation | 1.11 (1.06, 1.16) | < 0.001 |
| | Alcohol intake frequency | 1.12 (1.05, 1.20) | < 0.001 |
| | Years of schooling | 0.81 (0.68, 0.96) | 0.015 |
| | All mediators | 1.01 (0.96, 1.06) | 0.752 |
| CWP | Smoking initiation | 1.01 (1.00, 1.02) | < 0.001 |
| | Years of schooling | 0.97 (0.95, 0.99) | 0.004 |
| | Major depressive disorder | 1.01 (0.99, 1.02) | 0.139 |
| | All mediators | 1.01 (1.00, 1.02) | 0.007 |

BMI: body mass index, OR: odds ratio, CI: confidence interval, MCP: multisite chronic pain, CWP: chronic widespread pain.
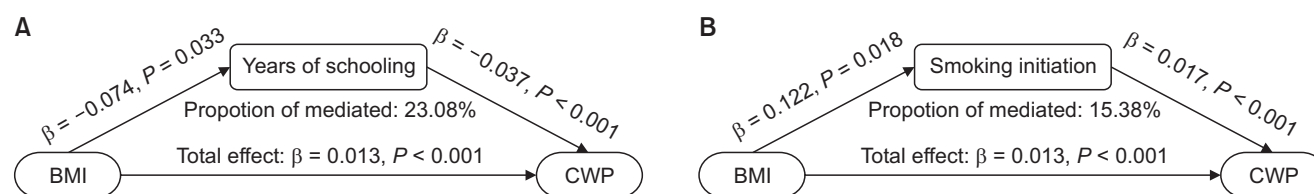


**Fig. 3.** (A) Mediation analysis of the causal effect of BMI on CWP *via* years of schooling. (B) Mediation analysis of the causal effect of BMI on CWP *via* smoking initiation. BMI: body mass index, CWP: chronic widespread pain.

## 4. Mediation MR analysis

The two-step MR and MVMR were then used for a mediation MR investigation. **Supplementary Table 15** displays the mediation MR analysis findings. In two-step MR, the results demonstrated that genetic predisposition to both BMI and MCP correlated with increased smoking initiation, frequency of alcohol consumption, and education attainments. In addition, education, initiation of smoking, and risk of depression also mediated the association between BMI and CWP. As is shown in **Table 1**, in MVMR, after considering smoking initiation, frequency of alcohol consumption, years of schooling, and all mediators, the adverse effect of obesity on MCP disappeared. After considering smoking initiation, years of schooling, major depression and all mediators, the adverse effects of genetic predisposition to obesity on CWP remain. After examination by two MR methods, it was concluded that years of schooling and smoking initiation are reliable mediators of the association between BMI and CWP. In the causal link between BMI and CWP, the mediating effects of smoking initiation and years of schooling were 15.38% and 23.08%, respectively (**Fig. 3**).

## DISCUSSION

In order to determine whether there is a correlation and the degree of correlation between obesity proxy indicators and various types of chronic pain, the authors conducted a comprehensive analysis, employing large-scale pooled GWAS data. BMI, WC, and HC all had a positive correlation with CWP and MCP, WC had a positive correlation with hip pain; and WHR was significantly correlated with hip pain. In reverse MR, a possible causal connection between higher MCP and HC/WC was discovered. In the connection between BMI and CWP, smoking and years of schooling had mediation effects of 15.38% and 23.08%, respectively.

Many earlier studies had shown that obesity or extreme weight might be related to persistent pain. A cross-sectional study in Spain found that 37% of 436 CWP patients were obese (BMI ≥ 30 kg/m²) [32]. Furthermore, research by Çakit et al. [33] and Vincent et al. [27] found that fat people experience more pain than non-obese patients. Similarly, in experiments, weight management has been demonstrated to dramatically reduce pain intensity in people with chronic pain [28] and reduce the number of pain sites [34]. Additionally, individuals experience cephalalgia and back pain differently, and the underlying causes can vary as well [35,36], making it difficult to establish a consistent cause-and-effect connection with

fat. Overall, these findings further solidify the causal link between obesity and chronic pain at a genetic level.

Our reverse MR study investigated the influence of several chronic pain phenotypes on indicators of obesity. In reverse MR analyses of CWP across a number of obesity characteristics, GWAS for CWP revealed just three genome-wide significant variations, limiting the capacity to undertake robust genic techniques. An iterative analysis was executed using a succession of $P$ valued thresholds: $5 \times 10^{-8}$, $5 \times 10^{-7}$, and $1 \times 10^{-6}$. Finally, the authors discovered that the analytic results were consistent across multiple thresholds, with no significant connection between CWP and distinct obesity phenotypes. It is intriguing that the authors found that an elevated risk of WC and HC was associated with genetic vulnerability to MCP, implying that as the WC and HC increased, the number of chronic pain sites also increased. These findings show that chronic pain causes not just physical suffering but may also contribute to obesity. This study's findings are comparable with prior observational studies [10], which found that chronic pain is independently associated with obesity. Chronic pain can lead to obesity as a result of a lack of physical exercise or the use of food as an opioid-mediated analgesic. However, no significant effects of additional pain phenotypes on BMI were found, owing to restricted instrumental factors and larger statistical variability [37]. Future study might benefit from looking at the impact of additional site-specific pain on obesity.

Four common characteristics, namely smoking, alcohol intake, education level, and depression, were identified as mediating factors between BMI and CWP/MCP, using two-step MR analysis. Following MVMR verification, the mediating effect of smoking and education persisted in the casual link of BMI and CWP. The effects of these mediating variables are similar to earlier observational studies [38], which indicated that obesity is related to smoking and increases the risk and duration of smoking. Smoking has also been linked to a variety of pain conditions, including headaches, lower back pain, and diabetic problems [39]. Smoking is also linked to the rate and intensity of pain onset [40]. Obesity-induced loss in academic performance has an impact on education, manifesting itself primarily in two ways. Obese people's cerebral blood flow and velocity diminish physiologically [41], causing harm to the cerebral blood supply and brain oxygen supply levels. Brain hypoxia causes sluggish thinking, delayed reaction, tiredness, and inattention throughout the learning process, all of which have a negative impact on academic achievement. In today's culture, there is concern about body image and distorted aesthetics, and

fat youngsters are more likely to be isolated from peers as well as discriminated against and ridiculed by social groups. Long-term isolation and unfavorable appraisal will harm children's self-esteem and increase their likelihood of experiencing negative emotions such as sadness and anxiety compared to children of normal weight [42], impacting their academic performance. Finally, it has an impact on educational attainment. Another study found a relationship between education level and chronic pain. The most educated people had an 80% lower chance of experiencing chronic pain than the least educated people, according to a 12-year study of 20,000 adults over the age of 51. People with graduate degrees experience one-fourth the agony of individuals who did not graduate from high school [43]. All of these imply that educational achievement and habitual smoking have a mediation role in the causal link between obesity and chronic pain. This introduces a novel idea for the primary prevention of chronic pain.

The authors' main finding, which has public health implications and can guide clinical therapy, is that obesity and chronic pain have a two-way causal connection. This means that controlling obesity can help prevent the occurrence of chronic pain, reduce the severity of chronic pain, speed up the onset, and shorten the course of the disease, and the use of drugs to control chronic pain can also control pain patients' weight, thereby preventing the occurrence of some obesity-related chronic diseases such as diabetes and hypertension. Second, it was discovered that smoking and education were important factors in the primary prevention of chronic pain, which might induce overweight and obese persons to adopt a healthy lifestyle, quit smoking, and avoid alcohol use. While assisting obese individuals, particularly children, in losing weight in a healthy manner, medical personnel should also advocate for the use of social media and school education to promote a healthy body image, reduce body-related anxiety, educate children about positive perceptions of body image, and provide psychological counseling for obese children. This approach can help them learn happily while maintaining mental health, leading to improved academic performance and overall educational outcomes. Taken together, these findings offer important insights on lowering the prevalence of chronic pain and enhancing the well-being of chronic pain sufferers.

Chronic pain impacts over 20% of the global population, and its economic costs exceed those of HIV/AIDS, cardiovascular disease, and cancer combined. The majority of research on chronic pain has concentrated on symptoms and therapies, with little emphasis on the ge-

netic basis of chronic pain. There are several phenotypes of chronic pain, and currently only a few phenotypes have been studied for their genetic mechanisms. As a result, the causal link between obesity and headaches, low back pain, hip pain, CWP, and MCP was evaluated. Another novel aspect of this work is the use of a two-way MR design, which significantly reduced the inaccuracy caused by confounding and reverse causation. The authors performed a rigorous assessment to ensure that their work met the three main assumptions in MR analysis. The GWAS data sets used all had substantial sample sizes, which increased the study's reliability and validity. To account for racial prejudice, participation was restricted to people of European heritage. The authors also employed MR-Egger and MR-PRESSO to rule out any pleiotropy in MR analysis. Furthermore, common life and social components were evaluated using two-step MR and MVMR, and potential mediating factors between BMI and CWP were discovered, improving understanding of the mechanism and giving evidentiary support for primary preventive and treatment methods.

Obviously, there are some limitations in this study. First, the research limited the scope of application for the results by only including those of European background. Second, the processes behind chronic pain are varied and diverse. Despite the efforts to cover as many pain phenotypes as possible, the study's list of chronic pain phenotypes remains incomplete. Finally, the factors included in the mediation analysis were all potential factors suggested by observational studies to be associated with obesity and chronic pain, however, unexamined variables in observational studies may have affected the relationships identified in the research. Given the complexity and diversity of possible variables, more study is required to confirm and generalize this study's findings using larger data sets and more varied populations.

Our study found a bidirectional causal relationship between obesity and chronic pain. In addition, there were mediating factors between chronic pain and obesity, including smoking and educational attainment. This means that chronic pain can be prevented and managed with the support of public health initiatives.

## DATA AVAILABILITY

The datasets supporting the finding of this study are available from the corresponding author upon reasonable request.

## ACKNOWLEDGMENTS

## CONFLICT OF INTEREST

## FUNDING

## AUTHOR CONTRIBUTIONS

YS Lyu and Q Yu designed the article and drafted the manuscript; YS Lyu, QX Lu, Y Liu, MT Xie conducted data collection, data analysis and chart correction, and all other authors made contributions to the manuscript's development, including manuscript reviewing, editing, and submission.

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## SUPPLEMENTARY MATERIALS

Supplementary materials can be found *via* https://doi.org/10.3344/kjp.24331.

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