Observational Study

Medicine

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# Causal association between smoke and the risk of chronic knee pain

## A Mendelian randomization study

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**Abstract**

A plethora of research has identified a comorbid association between smoke and an elevated risk of knee pain. Despite these findings, the causal link between genetically influenced smoke and the risk of knee pain remains to be elucidated. Considering this knowledge gap, we undertook a Mendelian randomization (MR) study to delineate the potential causal relationship. The instrumental variables were derived from genome-wide association studies (GWAS). We procured summary statistics for ever smoked from a GWAS dataset (280,508 cases and 180,558 controls, dataset: ukb-b-20261) to represent the exposure. The outcome was determined by GWAS data for knee pain for 3+ months, encompassing 76,910 cases and 20,979 controls (dataset: ukb-b-8906). The primary MR method employed was the inverse-variance weighted approach. Assessments for pleiotropy and heterogeneity were conducted utilizing the MR pleiotropy residual sum and outlier test, the MR-Egger intercept test, the leave-one-out analysis, and the Cochran *Q* test. There was a statistically significant genetic causal effect of smoke on the increased risk of knee pain (odds ratio = 1.08, 95% confidence interval = 1.01–1.16, $P = .014$]. Cochran *Q* statistic showed no heterogeneity (*Q* $P = .66$). The leave-one-out analysis chart, the global test *P* value in MR-pleiotropy residual sum, and outlier revealed no significant pleiotropy (global test $P = 0.53$). The intercept *P* value in MR-Egger revealed no significant pleiotropy (intercept $P = 0.66$). Our MR study showed no pleiotropy or heterogeneity. The findings from our study point toward an association between genetic predisposition to smoke and the incidence of knee pain. This genetic association underscores the clinical relevance of our findings, indicating that interventions aimed at smoking cessation could be particularly beneficial for those individuals who are predisposed to smoking or are at risk of developing knee pain.

**Abbreviations:** GWAS = genome-wide association studies, IV = instrumental variable, MR = Mendelian randomization, SNP = single-nucleotide polymorphism.

**Keywords:** chronic pain, genetic susceptibility, knee pain, Mendelian randomization, smoke

## 1. Introduction

Tobacco use is a well-documented health hazard. Paradoxically, there is evidence suggesting that smoking may have some positive impacts on knee osteoarthritis.[1] As knee osteoarthritis is a leading cause of chronic discomfort and impairment in the elderly,[2] it is imperative to comprehend the factors that influence its onset and escalation to develop effective preventative measures. Empirical research examining the link between smoking and knee osteoarthritis has produced inconsistent findings,[3–5] with some studies indicating that smoking might offer a protective effect against the evolution of structural abnormalities observable through radiography, including reduced joint space, cartilage degeneration, and osteophyte formation,[3,5] as well as against the advancement to total knee arthroplasty.[4]

Considering this unmet need, leveraging genetic insights to deepen our understanding of the link between smoking and knee osteoarthritis, including that of the knee, presents a rational strategy. Mendelian randomization (MR) offers a robust epidemiological tool for establishing causality. In the MR paradigm, single-nucleotide polymorphisms (SNPs) that exhibit a strong relationship with the exposure of interest – smoking in this case – are utilized as instrumental variables (IVs) for analysis.[6] This approach is particularly advantageous as it circumvents biases related to reverse causation and confounding factors that often plague traditional observational studies.[7] The extensive datasets yielded by genome-wide

*The authors have no funding and conflicts of interest to disclose.*

*The datasets generated during and/or analyzed during the current study are publicly available.*

*Supplemental Digital Content is available for this article.*

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*How to cite this article: Xu Z, Chen G, Xie D, Yan X, Li S. Causal association between smoke and the risk of chronic knee pain: A Mendelian randomization study. Medicine 2025;104:18(e42331).*

*Received: 8 August 2024 / Received in final form: 19 December 2024 / Accepted: 16 April 2025*

*http://dx.doi.org/10.1097/MD.0000000000042331*

association studies (GWAS), accessible to the public, lay a substantial statistical foundation for the utilization of these IVs.[8] In the context of knee pain, applying MR to assess the impact of smoking could unveil novel preventive and therapeutic opportunities. By discerning the causal pathways, we may tailor smoking cessation programs and pain management strategies to improve the quality of life for those afflicted with knee pain.

## 2. Methods

### 2.1. MR design and data source

A schematic representation of the MR design is depicted in Figure 1. This framework utilized genetic variants as IVs to investigate the potential association between smoke and the risk of developing knee pain. The aggregation of genetic variant data was derived from GWAS and was predicated on 3 foundational assumptions[9]: significantly associated with smoke; not linked to confounders that affect the relationship between smoke and knee pain; a direct effect on the outcome via the exposure of interest, rather than through intermediary factors.

Details of the GWAS used in our analysis are shown in Table 1. All data were openly available and ethically approved in the original studies. We selected summary statistics for ever smoked from a GWAS dataset (280,508 cases and 180,558 controls, dataset: ukb-b-20261) to represent the exposure. The outcome was determined by GWAS data for knee pain for 3+ months, encompassing 76,910 cases and 20,979 controls (dataset: ukb-b-8906).

In MR studies, ethical approval is often waived because these studies use existing, de-identified genetic data without direct intervention or increased risk to participants. In addition, these studies aim to understand causal relationships rather than directly influencing clinical practice, which may exempt them from ethical review.

### 2.2. Selection of IVs

We extracted significant SNPs that met the genome-wide significance threshold ($P < 5 \times 10^{-8}$) from the ever smoked GWAS. The SNPs in linkage disequilibrium ($r^2 < 0.001$ within a 10 Mb window) were excluded. We removed the IVs with an $F$ statistic < 10 to decrease the weak instrument bias.[10] The formula for calculating the $F$ statistic and $R^2$ is:

$$F = R^2 \div \left(1 - R^2\right) \times (N - 2).$$

$$R^2 = 2 \times \text{beta}^2 \times \text{MAF} \times (1 - \text{MAF}).$$

Palindromic variants were deliberately excluded from our analysis. Adhering to these stringent criteria, we ultimately identified and selected 39 SNPs associated with smoke. The comprehensive characteristics of these extracted SNPs are delineated in Table S1, Supplemental Digital Content, https://links.lww.com/MD/O831.

### 2.3. Statistical analysis

To ascertain the robustness and validity of our findings, we employed a suite of MR methodologies. The inverse-variance weighted method stood out as a pivotal and potent approach, amalgamating the effects of individual SNPs.[11] The weighted median method delivered congruent outcomes under the premise that the proportion of invalid variants did not exceed the 50% threshold.[12] In addition, the weighted model method offered a suitable assessment of the genetic associations.[13] A $P$ value for the intercept in the MR-Egger regression < 0.05 or a global test $P$ value in the MR pleiotropy residual sum and outlier (MR-PRESSO) < 0.05 was interpreted as suggestive of potential pleiotropy.[14,15] Cochran $Q$ statistic was utilized to identify heterogeneity among the SNP effects.[16] Furthermore, the leave-one-out analysis was conducted to pinpoint any SNPs exerting a disproportionate influence on the results.[16] The flowchart of our MR study is shown in Figure 2.

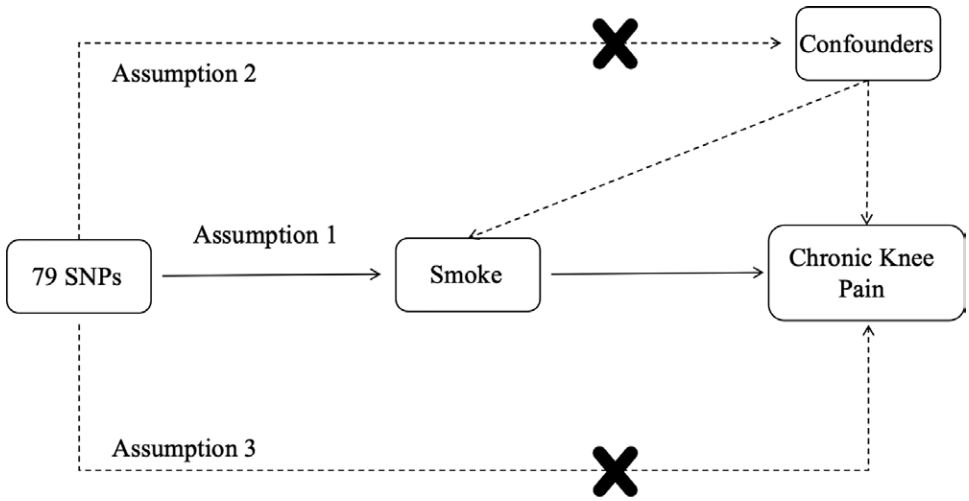


**Figure 1.** An overview of the design of our MR analysis. Dashed lines indicate causal associations that would go against the assumptions of MR. MR = Mendelian randomization, SNP = single-nucleotide polymorphism.

**Table 1**

**Details of the GWAS used in the MR analysis.**

| Traits | Dataset | Used as | *n* Cases | *n* Controls | Number of SNPs |
|---|---|---|---|---|---|
| Smoke | ukb-b-20261 | Exposure | 280,508 | 180,558 | 9,851,867 |
| Knee pain | ukb-b-8906 | Outcome | 76,910 | 20,979 | 9,851,867 |

GWAS = genome-wide association studies, MR = Mendelian randomization, SNP = single-nucleotide polymorphism.

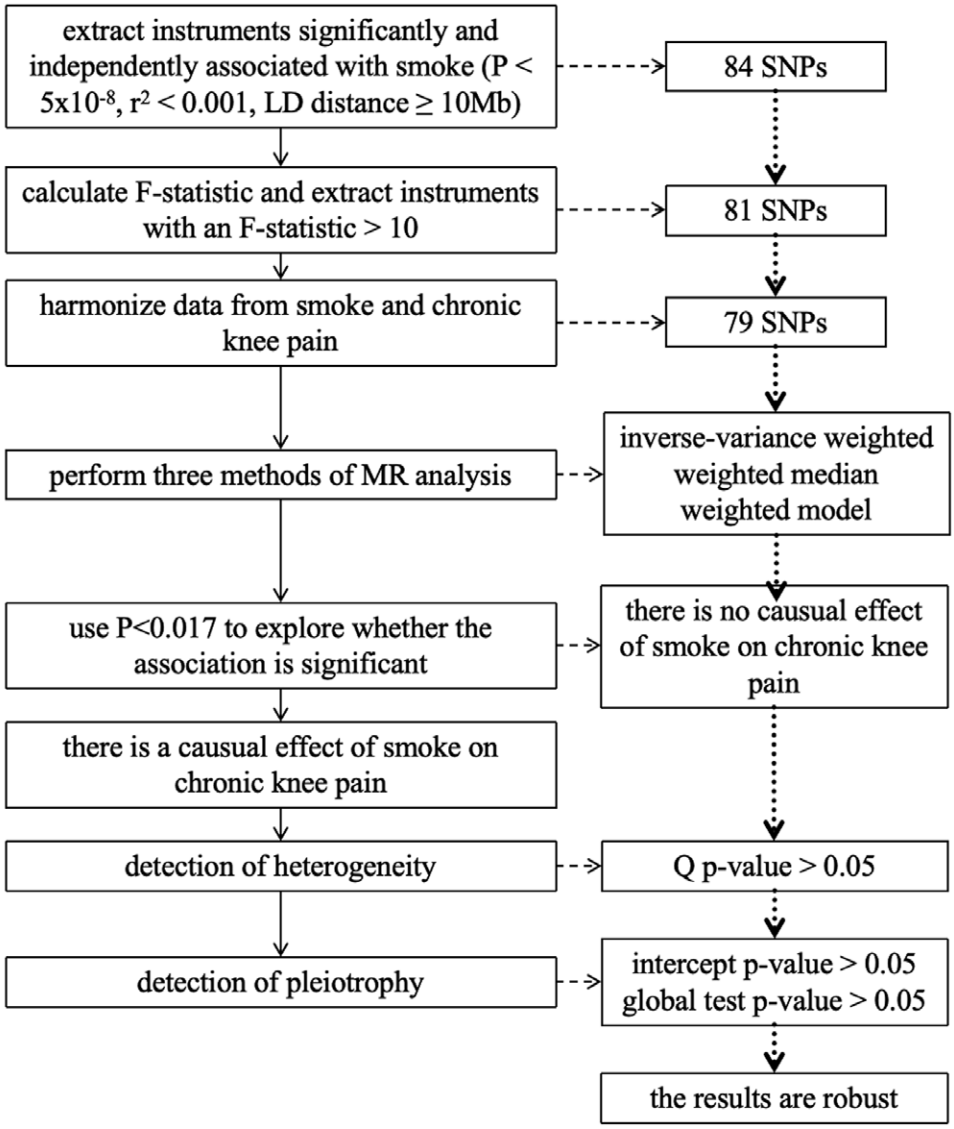


**Figure 2.** The flowchart of our MR study. LD = linkage disequilibrium, MR = Mendelian randomization, SNP = single-nucleotide polymorphism.

The R version 4.2.2 with the "Two-Sample MR" and "MR-PRESSO" packages was used to perform all statistical analyses.[16] We adjusted the significance *P* value for the association to .017 using the Bonferroni method.

## 3. Results

### 3.1. Causal effect of smoke on knee pain

The specific outcomes of the MR analysis are delineated in Table 2 and illustrated in Figure 3. The MR analysis did not uncover a statistically significant genetic causal influence of smoke on the heightened risk of knee pain, with an odds ratio of 1.08 and a 95% confidence interval ranging from 1.01 to 1.16, culminating in a *P* value of .014. Conversely, the Cochran *Q* statistic, a measure of heterogeneity, yielded a *P* value of .66, indicating a significant variability among the genetic estimates. Further examination through the leave-one-out analysis and the global test within the MR-PRESSO did not detect any notable pleiotropy, as evidenced by a global test *P* value of 0.66. The MR-Egger intercept test pointed toward the presence of pleiotropy, with no significant intercept *P* value of 0.53. The graphical representation of our MR analysis is depicted in Figure 4.

**Table 2**

**Details of the causal association between smoke and knee pain performed by MR.**

| Exposure | Smoke | | |
|---|---|---|---|
| Outcome | Knee pain | | |
| Methods | IVW | Weighted median | Weighted mode |
| nSNPs | 79 | 79 | 79 |
| OR (95% CI) | 1.08 (1.01–1.16) | 1.03 (0.93–1.13) | 0.91 (0.74–1.13) |
| *P* | .014 | .60 | .42 |
| Q *P* value | | .66 | |
| Intercept *P* value | | .53 | |
| Global test *P* value | | .66 | |

CI = confidence interval, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, SNP = single-nucleotide polymorphism.

## 4. Discussion

Our MR study provides intriguing evidence for a causal association between genetic predisposition to smoking and the risk of knee osteoarthritis. Utilizing a robust epidemiological approach, our findings suggest that smoking may contribute to the development of knee pain, potentially through pathways

that are yet to be fully elucidated. The observed association between smoking and knee pain is biologically plausible, given the known impact of smoking on inflammation and oxidative stress, both of which are implicated in the pathogenesis of knee osteoarthritis.[17–19] Furthermore, smoking is known to impair bone health and tissue repair mechanisms, which could indirectly contribute to the degeneration observed in knee osteoarthritis.[20–22]

Our study extends previous research by employing MR, a method that leverages genetic variants as IVs to infer causality. This approach is advantageous as it circumvents many of the biases inherent in traditional observational studies, such as reverse causation and confounding. The use of GWAS data in our MR analysis strengthens our findings by providing a large and diverse sample size, enhancing the generalizability and reliability of the results. Our MR study lies in its potential to inform preventive measures and personalized medicine. Understanding the genetic underpinnings of smoking behavior and its downstream effects on knee health can guide targeted interventions.

However, our study is not without limitations. The primary limitation is the potential for pleiotropy, where the genetic

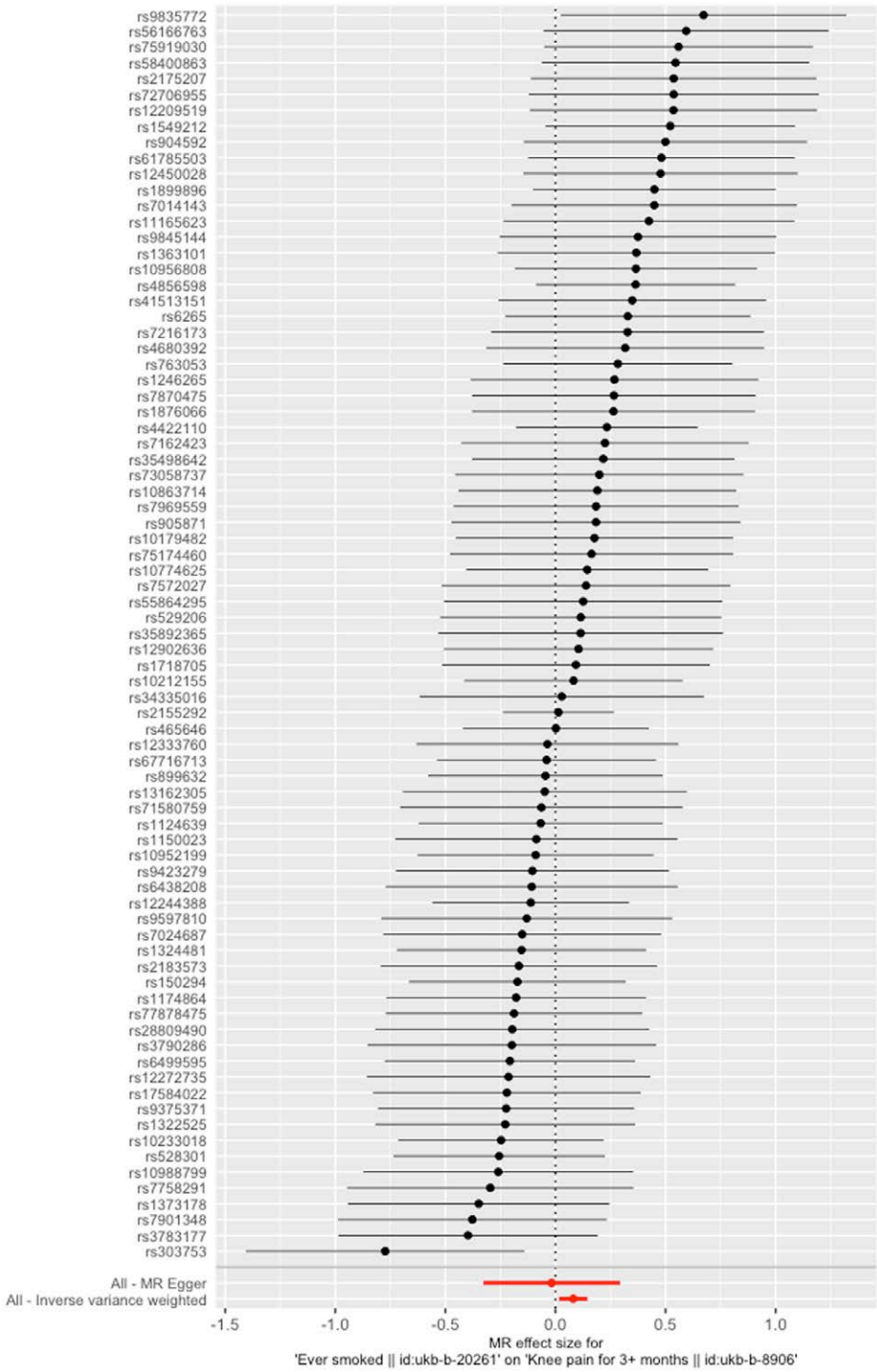


**Figure 3.** The results of the association between smoke and chronic knee pain risk. MR = Mendelian randomization.

variants associated with smoking may also be associated with other factors that influence knee pain. Although our sensitivity analyses did not detect significant pleiotropy, we cannot completely exclude this possibility. In addition, the generalizability of our findings may be limited due to the predominantly European ancestry of the GWAS data used. Future studies employing MR in more diverse populations are needed to confirm our findings. Another consideration is the multifactorial nature of knee pain. While our study points toward a potential causal role of smoking, it is likely that a combination of genetic, environmental, and behavioral factors contributes to the development and severity of knee pain. Future research should aim to explore these interactions and identify potential mediating factors.

## 5. Conclusions

In conclusion, our MR study provided evidence suggesting a causal relationship between a genetic propensity to smoke and the risk of developing chronic knee pain. This genetic association underscores the clinical relevance of our findings, indicating that interventions aimed at smoking cessation could be particularly beneficial for those individuals who are predisposed

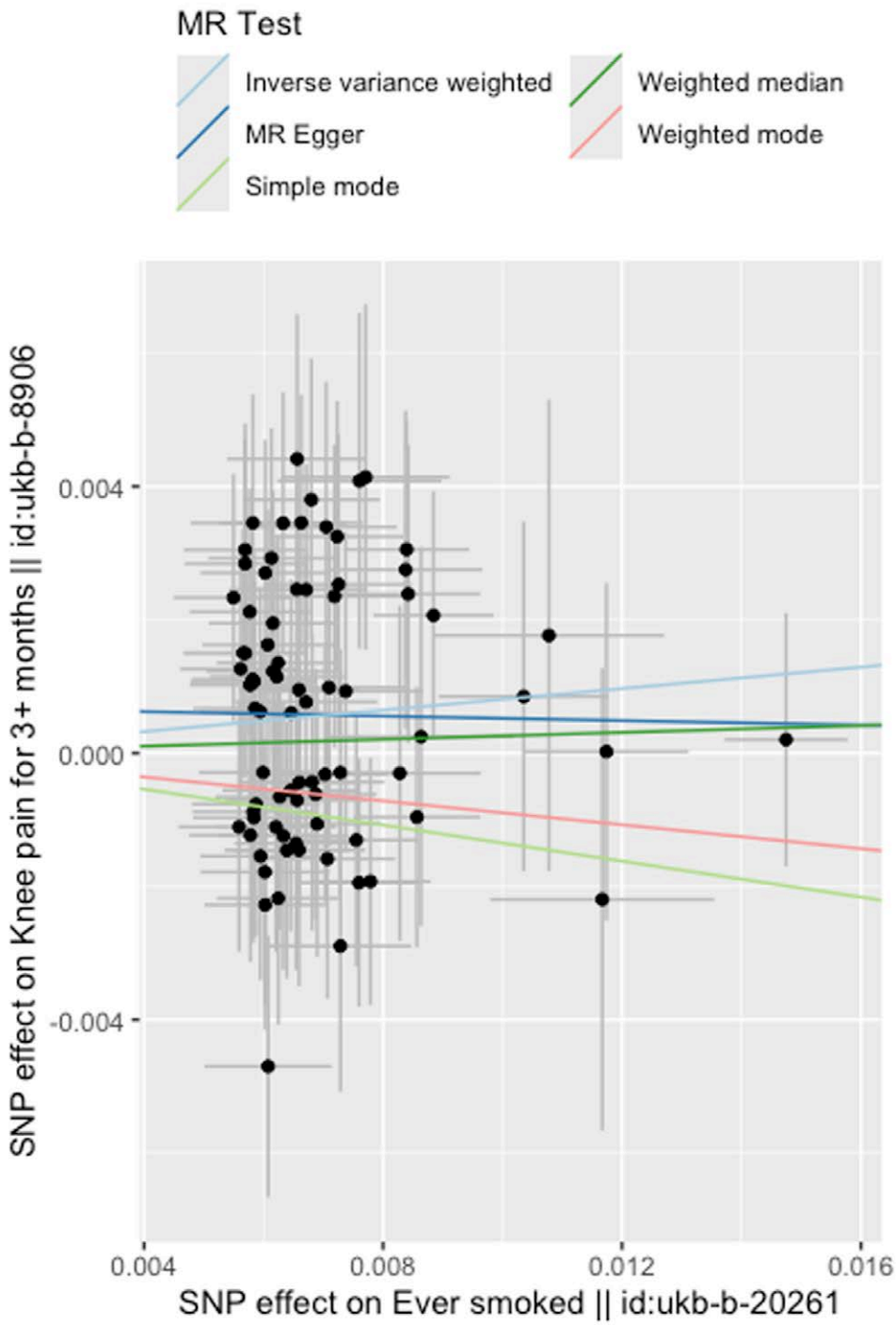


**Figure 4.** Scatter plot of the causal effect of smoke on the risk of chronic knee pain. MR = Mendelian randomization, SNP = single-nucleotide polymorphism.

to smoking or are at risk of developing knee pain. However, further research is warranted to elucidate the precise biological mechanisms at play and to devise more effective preventive and therapeutic strategies.

## Acknowledgments

We appreciate the FinnGen consortium and the IEU GWAS for making the summary datasets of instrumental variables available to the public.

## Author contributions

**Data curation:** Zhouliang Xu, Daofen Xie, Xiaoyan Yan.
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**Visualization:** Ganlu Chen, Daofen Xie.
**Conceptualization:** Shuangyue Li.
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