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RESEARCH ARTICLE

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The non-causative role of abnormal serum uric acid in intervertebral disc degeneration: A Mendelian randomization study

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Abstract

Background: Intervertebral disc degeneration (IDD) is a common musculoskeletal disorder that contributes significantly to disability and healthcare costs. Serum urate concentration has been implicated in the development of various musculoskeletal conditions. While previous observational studies have suggested an association between the two conditions, it might confound the effect of serum urate concentrations on IDD. This Mendelian randomization (MR) study aimed to investigate the causal relationship between serum urate concentration and IDD.

Methods: We performed a two-sample MR analysis using summary-level data from genome-wide association studies (GWAS) of serum urate concentration ($n =$ 13 585 994 European ancestry) and IDD ($n = 16\,380\,337$ European ancestry). Single nucleotide polymorphisms (SNPs) significantly associated with serum urate concentration ($p < 5 \times 10^{-8}$) were selected as instrumental variables. The associations between genetically predicted serum urate concentration and IDD were estimated using the inverse-variance weighted (IVW) method, with sensitivity analyses employing the weighted median, MR-Egger, and MR-PRESSO approaches to assess the robustness of the findings.

Results: In the primary IVW analysis, genetically predicted serum urate concentration was unrelated associated with IDD (odds ratio [OR] = 1.00, 95% confidence interval (CI): 1.00–1.00, $p = 0.17$)). The results remained consistent across the sensitivity analyses, and no significant directional pleiotropy was detected (MR-Egger intercept: $p = 0.15$).

Conclusions: This MR study provides evidence that there is no causal relationship between serum urate concentration and IDD. It suggests previous observational

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associations may be confounded. Serum urate levels are unlikely to be an important contributor to IDD.

KEYWORDS
genetics, genome-wide association studies, intervertebral disc degeneration, Mendelian randomization, serum urate

1 | INTRODUCTION

Intervertebral disc degeneration (IDD) is a common musculoskeletal disorder that affects a significant proportion of the population, resulting in pain, disability, and reduced quality of life.[1] IDD imposes a significant burden on both individuals and healthcare systems worldwide, making it a critical public health concern. Despite its widespread prevalence, the underlying etiology and pathogenesis of IDD remain incompletely understood. A growing body of evidence suggests that multiple factors, including genetic, environmental, and lifestyle factors contribute to the development and progression of IDD.[2,3]

Abnormal serum uric acid (SUA) levels have been implicated in various metabolic and degenerative disorders, such as gout,[4,5] hypertension,[6] and renal dysfunction.[7] Although the etiology of IDD is multifactorial, recent observational studies have reported potential associations between elevated SUA levels and IDD, suggesting a possible role of SUA in the pathogenesis of IDD[1]. However, these findings may be confounded by various factors, including age, sex, body mass index, and comorbidities.[3]

Observational associations in traditional epidemiological studies are prone to bias, confounding, and reverse causality, and thus findings can be misleading.[8] To overcome this, the Mendelian randomization (MR) is a powerful genetic epidemiological approach that uses genetic variants as instrumental variables (IV) to estimate the causal effect of an exposure on an outcome, thereby minimizing the influence of confounding factors and reverse causation.[9,10] MR studies have been increasingly used in the field of epidemiology to examine the causal effects of modifiable risk factors on disease outcomes.[11] In this study, we employed a Mendelian randomization framework to investigate the potential causal relationship between SUA levels and IDD. We hypothesized that genetically predicted SUA levels are not causally related to IDD.

2 | METHODS

2.1 | Study overview

We conducted a two-sample Mendelian randomization study using summary-level data from genome-wide association studies (GWAS) for SUA and IDD. In adherence with the three fundamental assumptions of MR analysis, (i) the selected IVs demonstrated correlation with the exposure (SUA); (ii) were unrelated to potential confounding factors; and (iii) might influence outcomes (IDD) solely via the exposure (SUA) (Figure 1). All data implemented in this analysis were publicly available, with initial studies providing ethical approval and obtaining written informed consent. We used estimates for the variant association with the exposure and outcome from the largest, most recent genome-wide association studies (GWAS) available for each variable. The exposure dataset was obtained from a large-scale GWAS (UK Biobank, http://www.ukbiobank.ac.uk/) of SUA levels, which included a total of 13 585 994 participants of European ancestry. The outcome dataset was derived from a GWAS (FinnGen, https://www.r8.finngen.fi/en) of IDD, comprising 16 380 337 individuals of European descent8. All data sets used comprised participants of genetically defined European ancestry to obtain a homogeneous large, well-powered sample of both men and women.

2.2 | Selection of genetic instruments

Single nucleotide polymorphisms (SNPs) associated with SUA levels at a genome-wide significance threshold ($p < 5 \times 10^{-8}$) were selected as instrumental variables. To minimize potential pleiotropy, we excluded SNPs that were associated with potential confounders of the SUA-IDD relationship, such as body mass index or renal function.[9] We also excluded SNPs in linkage disequilibrium ($R^2 > 0.01$) to avoid overestimation of the causal effect due to correlated genetic signals10. The final set of genetic instruments comprised 216 independent SNPs.

2.3 | Statistical analysis

All analyses were conducted using the R statistical software (version 4.1.2). We used the MR-Egger regression, weighted median, and inverse variance weighted (IVW) methods to estimate the causal

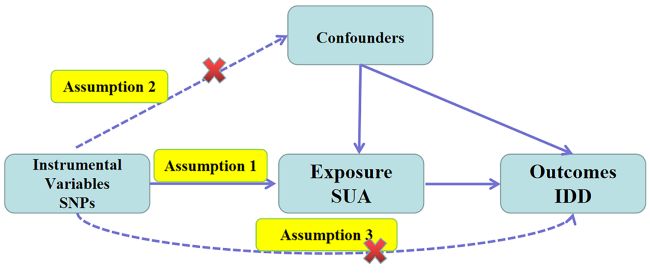

FIGURE 1 Model of the Mendelian randomization analysis.

TABLE 1 The results of MR analysis of SUA on IDD.

Method	Nsnp	b	se	pval	or	95% confidence interval (CI)
Inverse variance weighted	216	−6.00	0.00	0.17	1.00	1.00–1.00
MR egger	216	−8.25	0.00	0.99	1.00	1.00–1.00
Weighted median	216	7.58	0.00	0.89	1.00	1.00–1.00

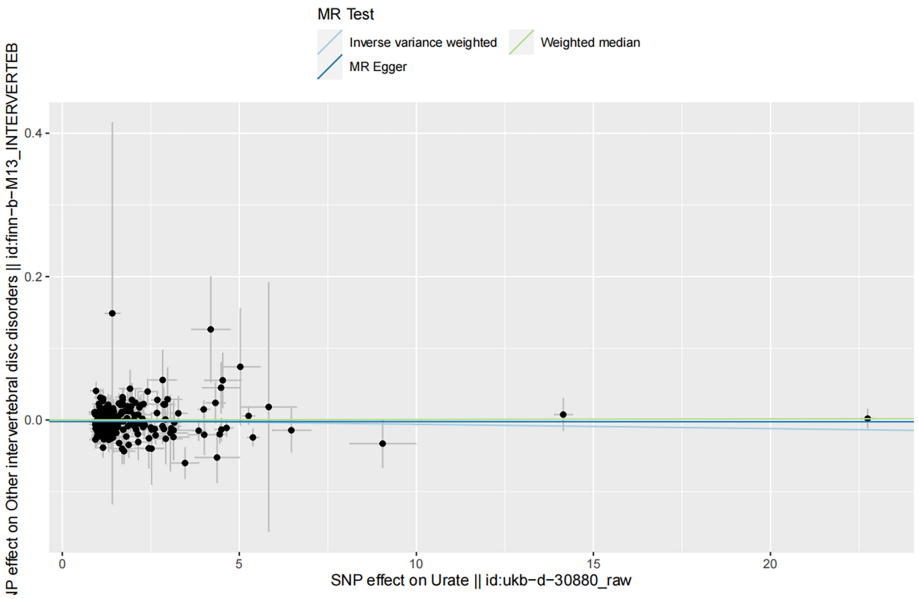

FIGURE 2 Scatter plot of the relationship between SUA and IDD using inverse-variance weighted, MR-Egger, and weighted median. Single-nucleotide polymorphism; ukb-d-30880_row, the GWAS ID of SUA; finn-b-M13_INTERVERTEB, the GWAS ID of IDD.

effect of atherosclerosis on IDD. We employed the inverse-variance weighted (IVW) method as the primary analysis to estimate the causal effect of SUA levels on IDD risk.[11] These analyses were performed using the Mendelian randomization package in R.[12] For genetic instruments of three or lesser, a fixed-effect model was used. For more than three genetic instruments, a multiplicative random-effects model was employed.[13] The Cochran's Q test was used for sensitivity analysis to assess the robustness of the MR assumptions. The MR Egger method was used to assess the presence of directional pleiotropy, which is considered a violation of the MR assumption that all genetic variants only influence the outcome through exposure. Leave-one-out sensitivity analyses were performed using the TwoSampleMR package in R to assess the influence of individual genetic variants on the overall effect estimate.[14] Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) for the causal effect of a one standard deviation increase in genetically predicted SUA levels on IDD risk.

3 | RESULTS

We identified 216 genetic variants (F statistic >10) associated with SUA from the first GWAS dataset that met the inclusion criteria. These variants were used as instrumental variables to estimate the causal effect of atherosclerosis on IDD in the second GWAS dataset. The sample size of the IDD analysis was 16 380 337 individuals of European ancestry.

The complete MR results are provided in Table 1. The causal estimate from IVW was OR = 1 (95% confidence interval (CI): 1.00–1.00, $p = 0.17$). This result indicates that the SUA was not significantly associated with IDD. Additional adjustment for potential confounders including body mass index, cholesterol levels, and C-reactive protein levels did not materially change the results.had no genetic causal relationship with AS. The analysis results of MR Egger and weighted median were consistent with random-effects IVW (Figure 2).

In sensitivity analyses, the results of the sensitivity analyses are consistent with the main analyses and demonstrate the robustness of our findings (Table 2, Figures 3 and 4). The sensitivity analyses using MR-Egger regression method generated consistent results with the IVW analysis, further supporting the robustness of the findings (MR-Egger: $p = 0.00 < 0.05$; IVW: $p = 0.00 < 0.05$). MR-Egger regression and IVW method results showed no heterogeneity between the IVs. The MR-Egger intercept test did not suggest any evidence of directional pleiotropy (intercept = 0, $p = 0.15$). The reliability of the results was further validated by leave-one-out analysis that no significant differences were observed (Figure 4).

In summary, we found no evidence to support a causal effect of serum uric acid on intervertebral disc degeneration or spinal osteophytes using a Mendelian randomization approach. Our results suggest that the observed association between hyperuricemia and disc degeneration in observational studies is likely due to confounding or reverse causation.

TABLE 2 Results of Cochran's Q test and MR-Egger intercept.

Exposure	Id.exposure	Outcome	Id.outcome	Method	Q	Q_df	Q_pval
SUA	ukb-d-30880_row	IDD	finn-b-M13_INTERVERTEB	MR Egger	218.38	214	0.00
SUA	ukb-d-30880_row	IDD	finn-b-M13_INTERVERTEB	IVW	284.09	215	0.00

Abbreviations: IDD, intervertebral disc degeneration; IVW, inverse-variance weighted.

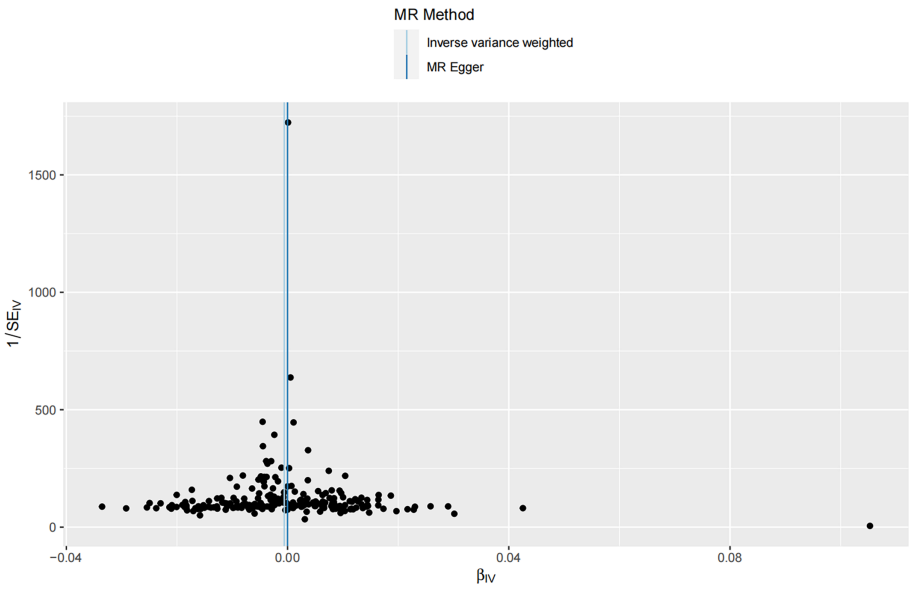

FIGURE 3 Funnel plot MR analysis of SUA on IDD.

4 | DISCUSSION

In this Mendelian randomization study, we aimed to investigate the causal relationship between abnormal serum uric acid levels and IDD. Our findings do not support a causative role of serum uric acid in the development or progression of IDD. Although previous studies have suggested that there may be a link between abnormal serum uric acid and IDD, our findings have failed to find a significant association between these two conditions. Our study utilized genetic variants associated with SUA as instrumental variables to assess the causal effect of abnormal serum uric acid on IDD. We found no significant association between the genetically predicted risk of SUA and IDD, indicating that SUA is unlikely to be a direct causal risk factor for IDD, which makes a positive contribution to the genetic research of IDD.

These results have important implications for the understanding and prevention of IDD. SUA has been proposed as a potential risk factor for IDD due to its potential effects on blood flow[15] and oxidative stress[16] in prior observational studies. Rock[17] reported a high serum uric acid level in IDD tissue would damage the functions of mitochondria and lysosomes and lead to apoptosis. Mavrogonatou and Kletsas[18] found that an excessive UA concentration can affect the cell cycle, cause cell volume changes, and damage DNA. This high level can inhibit PDGF- or IGF-I-mediated DNA synthesis in nucleus pulposus cells, thereby exacerbating IDD.[19] In addition, abnormal serum uric acid will affect the ability of the cartilage endplate to deliver nutrients and oxygen to the IDD.[20] However, our results suggest that there is no causal association between SUA and IDD degeneration. Other factors may play a more significant role in the development of this condition. Further research is needed to identify these factors and to develop effective prevention and treatment strategies for IDD.

It is important to note that our Mendelian randomization analysis assumes that the genetic variants used as instrumental variables are not associated with any confounding factors that may affect the outcome. Our study design employed two-sample Mendelian randomization, which utilizes genetic variants as instrumental variables for the exposure of interest. This method reduces the risk of confounding, reverse causation, and measurement error, thus providing a more robust estimate of the causal effect.[13,21] We used summary-level data from large genome-wide association studies (GWAS) for serum uric acid and IDD, ensuring sufficient statistical power to detect causal effects.[22] Furthermore, the genetic variants used as instrumental variables were strong predictors of serum uric acid levels, as evidenced by the F-statistics well above the threshold of 10.[23]

One potential concern in Mendelian randomization studies is the possibility of horizontal pleiotropy, where genetic variants affect the outcome through pathways other than the exposure.[24,25] However, we performed several sensitivity analyses, including MR-Egger, weighted median, and weighted mode methods, which are robust to horizontal pleiotropy under different assumptions.[26] The results from these analyses were consistent with the main findings, indicating that horizontal pleiotropy is unlikely to have biased our results.

Our study has several limitations. First, the genetic instruments for serum uric acid were derived from a predominantly European

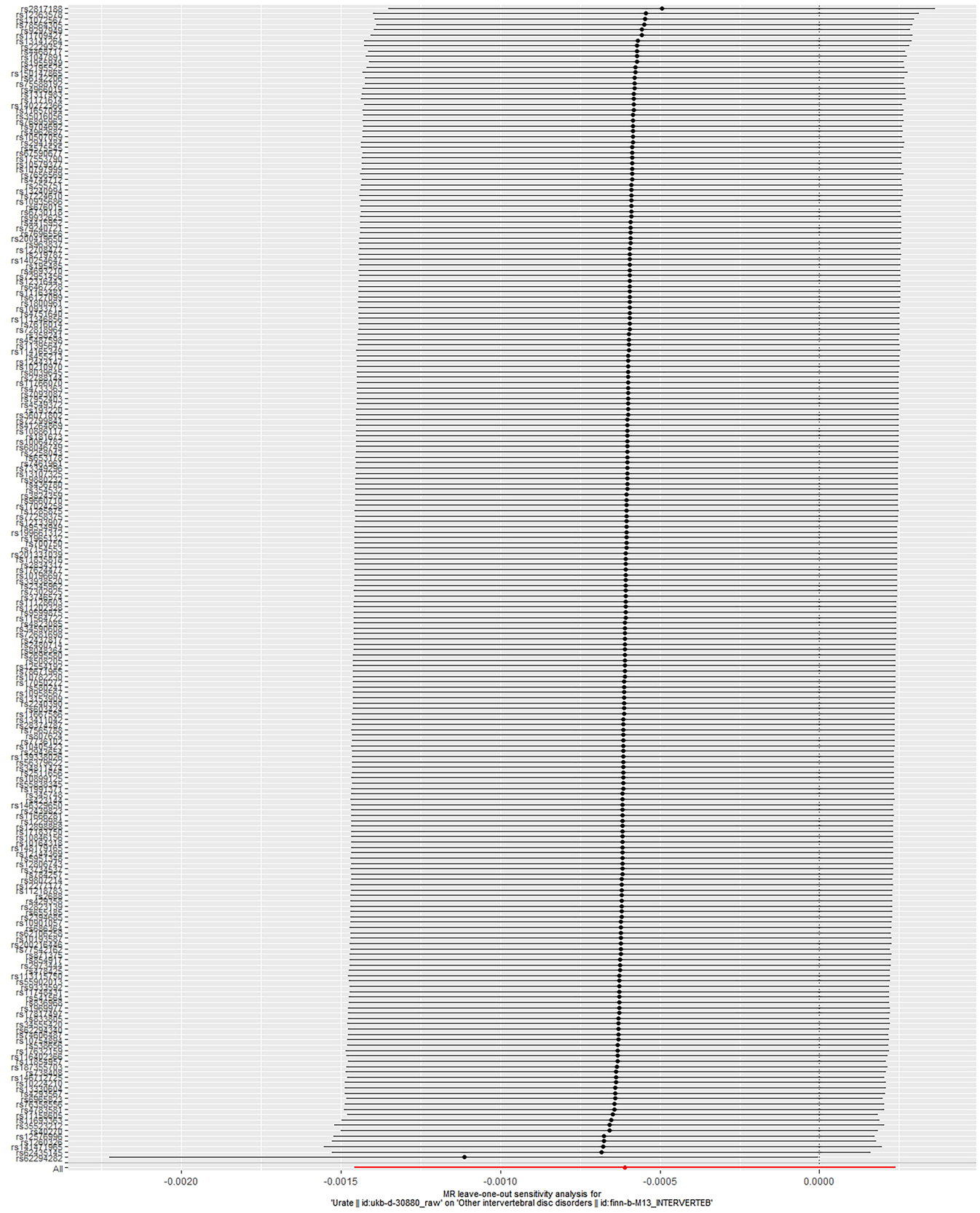

FIGURE. 4 MR leave-one-out sensitivity analysis of SUA on IDD.

population, which raises the possibility of population stratification bias. Second, the GWAS data for IDD were cross-sectional, which precludes the assessment of temporal relationships. As Mendelian randomization relies on the assumption that the genetic variants are related to the exposure before the onset of the outcome, this limitation should be considered when interpreting our results. Lastly,

we cannot rule out the possibility of residual confounding due to linkage disequilibrium between the genetic variants used as instruments and other variants that affect IDD through different pathways. However, given the consistency of our findings across various sensitivity analyses, this seems unlikely to have influenced our results substantially.

In conclusion, our Mendelian randomization study found no evidence to support a direct causal association between abnormal serum uric acid and intervertebral disc degeneration. Further studies are needed to investigate other potential risk factors for IDD and to identify effective preventive measures and treatments for this condition. Our study highlights the importance of utilizing causal inference methods such as Mendelian randomization to investigate the potential causal relationships between risk factors and disease outcomes, which can inform the development of effective prevention and treatment strategies.

AUTHOR CONTRIBUTIONS

Shun-Cong Zhang and Ying Li conceptualized and designed the study. Yong-Xian Li, Li-Ren Wang, and Ling Mo performed data analysis. Yang-Ting Cai wrote the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The genotype and phenotype data are available on application from UK Biobank (http://www.ukbiobank.ac.uk/). Individual cohorts participating in the EGG consortium should be contacted directly as each cohort has different data-access policies. GWAS summary statistics of IDD are available via the EGG website (FinnGen, https://www.r8.finngen.fi/en). Researchers interested in accessing the data are expected to send a reasonable request by sending an e-mail: caiyangting2008@163.com.

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