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ORIGINAL RESEARCH

Causal Association of Alzheimer's Disease with Low Back Pain: A Mendelian Randomization Study

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Purpose: Previous observational studies have demonstrated that Low back pain (LBP) often coexists with Alzheimer's Disease (AD), however, the causal relationship remains unclear. The purpose of this study is to explore the causal relationship between AD and LBP through Mendelian randomized analysis.

Methods: Instrumental variables (IVs) were derived from the genome-wide association study (GWAS) of AD. Information regarding Instrumental variables (IVs) in LBP was extracted from a GWAS database. MR-Egger, weighted median, inverse variance weighted (IVW)and Weighted mode were used to evaluate the causal effects. Cochran's Q test and MR-Egger intercept were applied to detect the heterogeneity and horizontal pleiotropy, respectively. Outliers were found and remove based on MR-PRESSO analysis to mitigate the effect of horizontal pleiotropy on the results. Deleting each genetic variant applying the leave-one-out analysis can help evaluate the robustness of results. Finally, MR-PRESSO Raw and Outlier-corrected were used to enhance the credibility of the results.

Results: IVW assessment provided strong evidence that AD is positively associated with LBP (Odds Ratio (OR)= 1.046, 95% confidence interval(CI) = 1.023–1.070, $P=5.8\times10^{-5}$). There was no heterogeneity in our study ($p > 0.05$). The results of the pleiotropy test indicated that there was no pleiotropy in our IVW analysis ($p > 0.05$). MR-Egger, Weighted median, Weighted mode analysis results are consistent with our IVW analysis results. There is a genetic relationship between Alzheimer's disease and low back pain.

Conclusion: This study provides evidence for a causal relationship between AD and LBP. It emphasizes the necessity of improving pain management for patients with Alzheimer's disease in clinical practice. However, the data were derived from a European population, which may limit the generalizability of the results to other populations.

Keywords: Alzheimer's disease, causal association, genome-wide association study, low back pain, Mendelian randomization

Introduction

Low back pain (LBP) is a common condition and a leading cause of health function loss worldwide. A comprehensive study carried out across 195 countries evaluated the incidence, prevalence, and disability-adjusted life years for 354 different diseases. The findings revealed that LBP is a primary cause of global productivity loss in 126 of these countries.[1] Furthermore, LBP has consistently been a leading cause of disability over the years in both developed and developing countries, ranking as the sixth leading cause of overall disease burden.[2,3] The incidence of LBP augment with age, ranging from 16.9% to 46.6%.[4] LBP represents a significant chronic health issue that is a leading cause of early retirement among older employees, with a greater impact on workforce departure than the combined effects of cardiovascular diseases, diabetes, hypertension, cancer, respiratory conditions, and asthma.[5,6] LBP can make life and finances very difficult. Because the mechanism of LBP is still unclear, the main focus of treatment is to identify risk factors and reduce symptoms.

Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly and is the single biggest cause of dementia, accounting for 50%–75%.[7] The cardinal features of AD encompass the presence of amyloid plaques and neurofibrillary tangles. Furthermore, neuropil threads, dystrophic neurites, associated astrogliosis, and microglial activation are observed.[8,9] But there is no effective treatment to slow the progression of AD.[10] With the gradual progress of population aging, the incidence of AD is rising every year. This is surprisingly consistent with LBP.[11] Earlier

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observational studies have indicated that AD and LBP often coexist and there is increasing evidence from observational studies that AD is associated with LBP.[12]

A CHARIOT PRO study of 987 participants found that LBP, a safety event, occurred 3% of the time in AD's patients. This suggests that people with AD are more likely than normal to have LBP.[12] Another observational study with 101 participants found that the incidence of back pain was 74% in patients with Parkinson's disease and only 27% in patients without Parkinson's disease. It suggesting that people with Parkinson's disease are more likely to have back pain.[13] Another analysis using genome-wide association data showed no genetic association between LBP and neurodegenerative disease.[14] These inconsistent conclusions may come from a number of confusing reasons, such as different study designs and different populations, and limitations of the data. Due to the sparse and contradictory evidence in existing research, the causal connection between AD and LBP is not yet well understood, and there is a need for further research to gather more persuasive evidence.

The core of Mendelian randomization (MR) is the use of Mendel's second law, which is the law of free combinations. The free combination of genes during meiosis avoids the disturbance of reverse causality and confounding factors. And it has high reliability.[15] MR utilizes genetic variation as instrumental variables (IVs) to address the inherent limitations of observational studies, such as confounding bias, and provides powerful evidence for evaluating causal inferences between exposures and outcomes.MR analysis is akin to a randomized controlled trial (RCT), considered the "gold standard" of medical evidence.[16,17] The present study aimed to examine the causal association of AD and LBP. Due to the poor cognitive and expressive abilities of Alzheimer's disease patients, they often fail to accurately express their pain in a timely manner, which causes certain difficulties for our clinical nursing work. Therefore, it is extremely important to clearly define the specific relationship between Alzheimer's disease and low back pain.

Materials and Methods

Study Design

This MR study utilizes a large-scale summary data set from genome-wide association studies (GWAS). In all of the original genome-wide association studies (GWAS) studies included in this analysis, participants provided informed consent for the use of their genetic and health data. Since this MR study only accessed and analyzed publicly available summary-level statistical data from these GWAS, no additional ethical approval was required for our study. Then we performed a Two-sample MR analysis with GWAS data of AD and FinnGen consortium of LBP. The sensitivity analyses conducted for this study include several methods to ensure the robustness of the MR results. Cochran's Q test is used to assess heterogeneity among the instrumental variables. Leave-one-out analysis is performed to evaluate the influence of individual genetic variants on the overall results. Egger's intercept analysis is employed to detect potential bias due to pleiotropy, where genetic variants might influence the outcome through mechanisms other than the exposure.[18] Additionally, the MR-PRESSO method is used to identify and account for outliers that might distort the results, helping to verify the presence of heterogeneity or pleiotropy in the MR analysis. Subsequent to outlier removal and the assessment of causal relationships, we performed the IVW test for heterogeneity to assess the consistency of the causal effect estimates.[19] As shown in Figure 1, a two-sample MR study must adhere three fundamental assumptions. According to Assumption 1, genetic instruments must be strongly associated with AD. Because SNPs are randomly assigned during pregnancy, Assumption 2 states that the genetic variation in AD should not be confounded by any other factors. Additionally, we performed the IVW analysis to appraise whether there is a causal relationship between AD and potential risk factors for LBP, including BMI and Obesity. Assumption 3 is that the outcome risk (LBP) is strongly influenced by the genetic variation in AD through the AD exposure factor, but not through any other pathways.[20]

Genetic Variants Associated with Alzheimer's Disease

For our study, we used data from a GWAS AD dataset with 398,508 individuals of European ancestry.Details of the data are set out in the Supplementary Table S1. SNPs demonstrating genome-wide significance ($p < 5\times10^{-8}$) were chosen as potential genetic tools. To ensure these SNPs are independent, we pruned them using a 10,000 kb window size with a linkage disequilibrium threshold of r^2 < 0.001. The IVs that were weakly associated with the exposure factors may

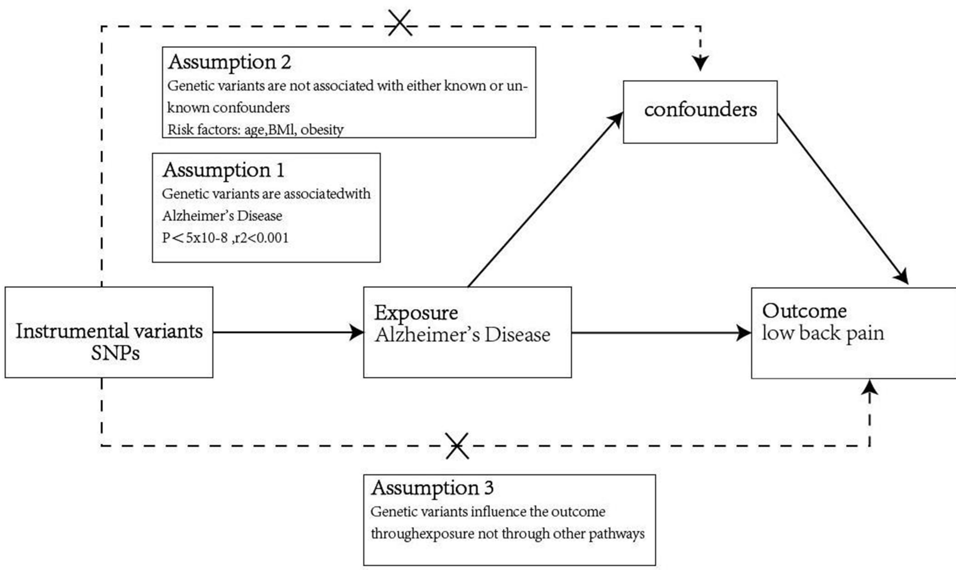

Figure 1 Mendelian randomization estimates from Alzheimer's Disease on Low back pain.

lead to weak instrumental bias. Therefore, the strength of IVs was assessed by the introduction of variance (R2) and F-statistics using the following formulas:[21]

$$R^2 = 2 \times MAF \times (1 - MAF) \times \beta^2$$

$$F = \frac{R^2 \times (N - k - 1)}{k(1 - R^2)}$$

In this equation, R2 is the cumulative explained variance of the selected SNPs during exposure, MAF is the minor allele frequency, β is the effect value, SE is the standard error, k is the number of SNPs used for the final analysis, and N is the sample size.[21] F > 10 suggests a sufficiently strong relationship between IV and exposure such that the outcomes of MR analysis are protected from weak instrumental bias.[21] Finally, data from the outcome database were extracted for collation and merging, followed by effect allele alignment such that the effect values for exposure and outcome correspond to the same effect allele.

GWAS Summary Data for Low Back Pain

The FinnGen Consortium is a large-scale public-private partnership aimed at utilizing data from the Finnish biobank for genomic research. Details of the data are set out in the Supplementary Table S1. This collaboration brings together extensive biological samples and health data from Finland to explore the genetic underpinnings of various diseases. The GWAS summary data for LBP comes from the 10th round of the FinnGen Consortium. The data sources are all from the European population. The genetic message for LBP was obtained from 21,140 cases and 227,388 controls.

Mendelian Randomization Analysis

Extract exposure SNPs from the full GWAS summary data for AD. Then, we perform allele harmonization between the exposure SNPs and the outcome SNPs, and exclude SNPs that have incompatible alleles or are palindromic in their allele frequencies. Speak accurately, there were four steps. In the first step, we get the data we want from the open database. In the second step, SNPS are screened out according to certain conditions. In the third step, SNPs that were significantly associated with the outcome were discarded. In the fourth step, SNPs that were ambiguous or palindromic were excluded. Following these procedures, MR analysis was carried out. Various MR analysis approaches including MR-egger, Weighted median, Inverse-variance weighted (IVW), Weighted mode were performed to estimate the casual effects

between AD and LBP.[22,23] Given that there is no horizontal pleiotropy, we can use IVW regression to obtain an unbiased estimate of the causal effect.[22] Specifically, the IVW was utilized as the main technique for estimating MR effects in this study, and the results are reported as odds ratios (OR) with 95% confidence intervals (95% CI). MR-egger regression is a technique used in MR analysis that focuses on testing for directional pleiotropy, evaluating causal effects, and estimating causal relationships using summary-level genetic data.[20] Although genetic pleiotropy can compromise the core assumptions underlying instrumental variables (IVs), the weighted median estimator offers a more reliable approach for estimating causal effects, even if up to 50% of the message derives from invalid IVs.[24] Both MR-egger regression and the Weighted median estimator offer improvements over the IVW method by providing more robust causal effect estimates. Additionally, methods like the weighted mode are mainly employed to evaluate the stability of MR findings.[18]

Heterogeneity and Horizontal Pleiotropy

The level of pleiotropy of genetic variables is significant because it can significantly affect the results of MR analysis and lead to unstable effect estimates. The level of pleiotropy is primarily evaluated through the MR-egger intercept and MR-PRESSO analysis.[25,26] The former estimates the possibility of pleiotropy by computing the intercept term obtained from linear regression analysis. The F-statistic is computed to assess the strength of the IVs.[27] MR-PRESSO analysis identified potential outliers with horizontal pleiotropy characteristics. By setting the number of permutations to 1000 in the MR-PRESSO analysis, we evaluated the stability of the MR results by comparing the causal relationships before and after the removal of outliers. We used IVW and MR-egger regression to test for heterogeneity and calculated the Q-statistic to quantitatively assess heterogeneity. If heterogeneity was present ($p < 0.05$), the results from the random-effects IVW model were considered predominant; otherwise, the fixed-effects IVW model results were referenced.[25,28] All analyses were performed using the Two Sample MR (version 0.5.11),Mendelian Randomization (version0.8.0),and MR-PRESSO package (1.0) in R Software 4.3.3.

Result

We successfully extracted 30 corresponding AD-related genetic variants from the LBP GWAS database. In our research, the F-statistics range from 29.88 to 1295.25, which is larger than the conventional value of 10, strengthening the reliability of the results. We evaluated the causal relationship between AD and LBP by IVW, MR-Egger regression, and Weighted median. IVW results showed a significant causal relationship between AD and LBP (OR=1.05, 95% CI[1.02, 1.06], $P=5.8\times10^{-5}$). Meanwhile, resemblant risk evaluations were obtained using MR-Egger regression (OR=1.04, 95% CI[1.01, 1.07], $P=6\times10^{-3}$) and Weighted median (OR=1.05, 95% CI[1.02, 1.08], $P=0.03$) (Table 1). The consistency of the three MR Models enhances the reliability of AD in promoting the progression of LBP (Figure 2). In order to fully detect any potential bias in the MR Study, a sensitivity analysis was performed using a complementary approach. The Cochran's Q test shows that there is no heterogeneity (Q value = 163.92, $\boldsymbol{p} < 0.001$). At the same time, egger intercept detection (P=0.76) confirmed that there was no horizontal pleiotropy (intercept=-8×10^{-4}, $\boldsymbol{p}=0.76$). The summary results of pleiotropy and heterogeneity tests are shown in the Table 2. We also performed MR-PRESSO Raw analysis (OR=1.05, 95% CI[1.02, 1.07], $P=3\times10^{-4}$) to enhance the robustness of positive results. In addition, we did MR-PRESSO analysis and found no outliers. Details of the remaining SNPs are set out in the Supplementary Table S2. Leave-one analysis (Figure 3) was employed to

Table 1 Mendelian Randomization From Alzheimer's Disease Concentration on Low Back Pain Experienced

MR Methods	OR	95% CI	P
IVW	1.05	1.02–1.07	5.85E-05
MR Egger	1.04	1.01–1.04	0.006
Weighted median	1.05	1.02–1.08	0.001
Weighted mode	1.05	1.02–1.07	0.001

Abbreviations: MR, mendelian randomization; IVW, inverse variance weighted; OR, odds ratio.

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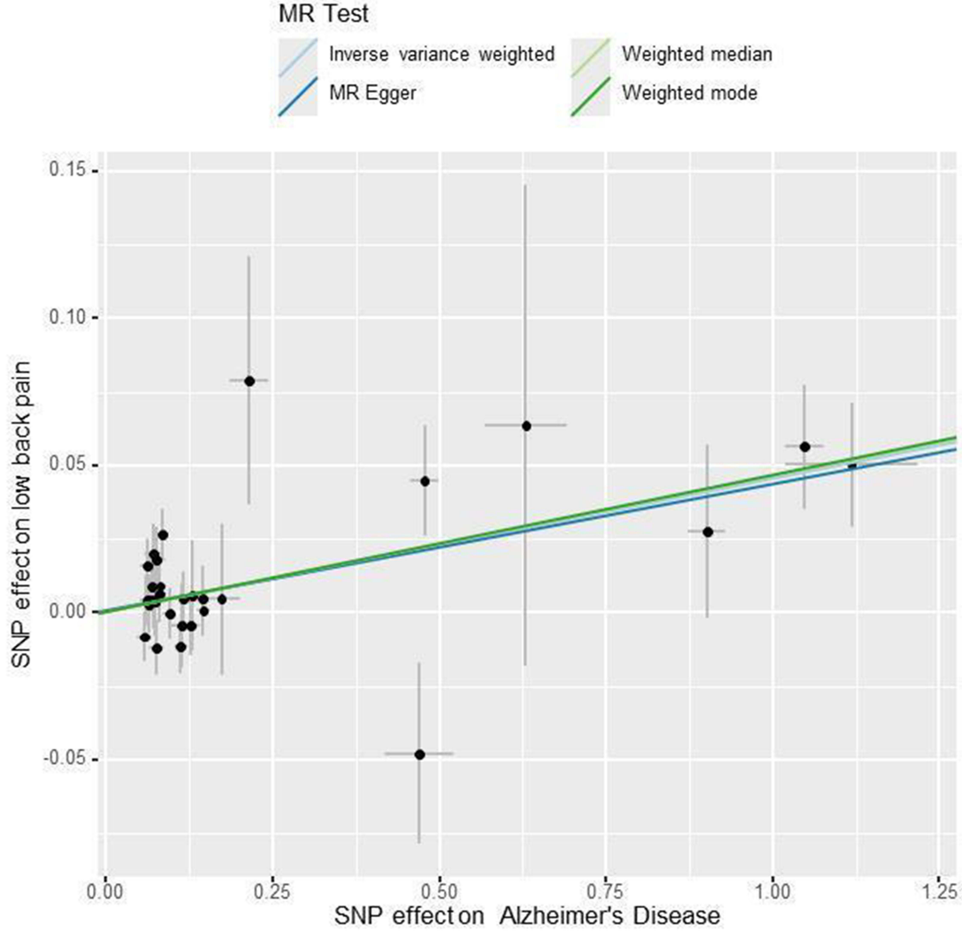

Figure 2 Scatter plot showing the effect of genetic instruments on Alzheimer's Disease on low back pain.

demonstrate the effect of each SNP on the holistic causal estimation. When anyone SNP is excluded, the meta effect of the remaining SNPS does not exceed zero, showing that the results are unchanged and dependable. The funnel plot was presented in Figure 4. There is no reverse causal relationship between AD and LBP. Details of the result are set out in the Supplementary Table S3. In summary, the causal effect of Alzheimer's disease on LBP has not been violated.

Discussion

This is the study to probe causality between AD and LBP using a two-sample Mendelian randomization method, according to large-scale GWAS database. In short, our IVW results strongly suggest that AD has a clear causal relationship with increased risk of LBP.

Table 2 Sensitivity Analysis of Alzheimer's Disease Genetic IVs in GWAS for Low Back Pain

Pleiotropy Test				**Heterogeneity Test**					
MR-egger			**PRESSO**	**MR-egger**			**IVW**		
Intercept	SE	p	p	Q	Q_df	Q_pval	Q	Q_df	Q_pval
0.0008	0.0028	0.7655	<0.001	37.17	28	0.20	37.28	29	0.23

Notes: p ≥ 0.05 represents no significant pleiotropy. Q_pval ≥0.05 represents no significant heterogeneity. IVW, inverse variance weighted.
Abbreviations: MR, mendelian randomization; SE, standard error.

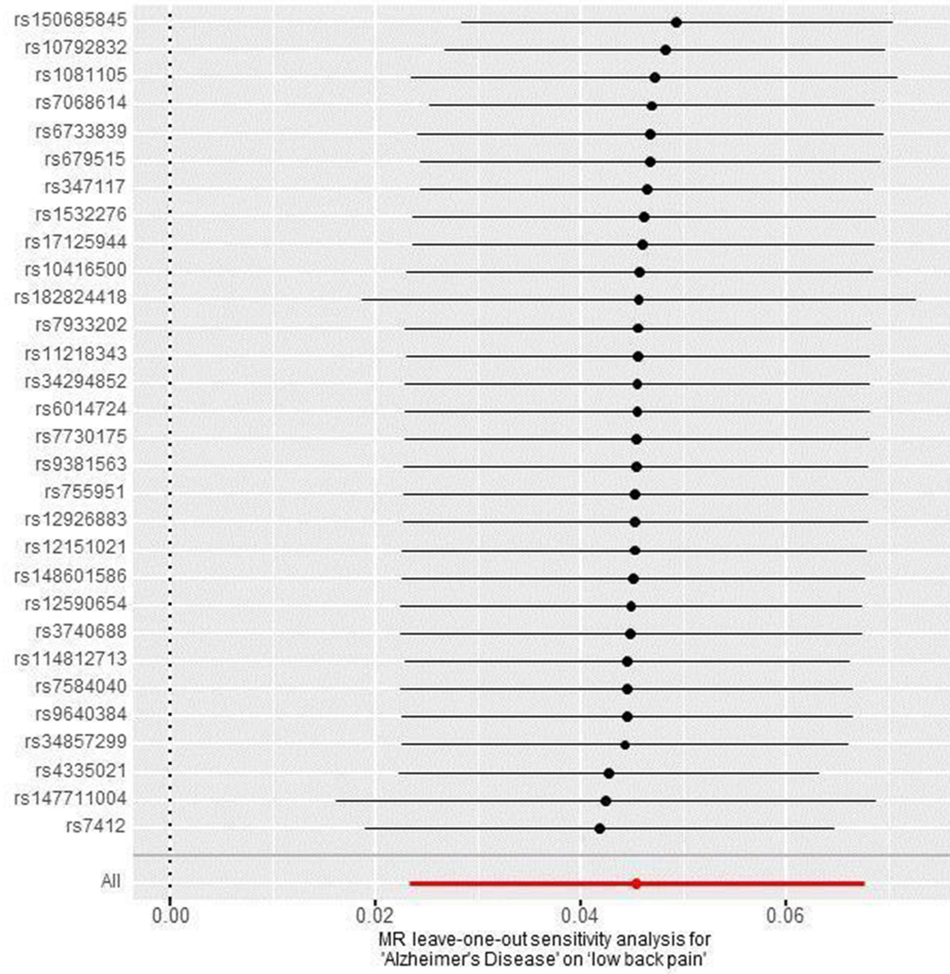

Figure 3 Leave one out of sensitivity tests. Calculate the MR results of the remaining Instrumental Variables (IVs) after removing the IVs one by one.

As the pathophysiological causes are unknown, specific treatments cannot be provided at this time.[29] In an observational study comprising 356,383 participants, it was found that patients with AD were more likely to have pain in more areas (LBP, headache and so on) than those without AD.[30] Another observational study with 123 participants found that patients with Parkinson's disease had a higher incidence of LBP, and the pain was longer and more intense than in other areas.[31] Another analysis using genome-wide association data showed no genetic association between LBP and neurodegenerative disease.[14] The inconsistencies in these conclusions may be due to a number of confusing reasons, such as different study designs and different populations, and limitations of the data. In our study, we used the method of two-sample Mendelian stochastic analysis. In this way, genetic tools can be used to infer causality in potentially causal ways, avoid reverse causality, avoid bias due to confusion, and estimate assumed causality under different conditions. In addition, we performed MR-PRESSO Raw to strengthen the robustness of the results. Additionally, we evaluated potential risk factors and conducted a series of sensitivity analyses to avoid any potential rule violations. Therefore, our results provide a strong conclusion that Alzheimer's disease has a causal relationship with LBP. So far, there is no exact mechanism for how Alzheimer's affects low back pain. Firstly, the high levels of IL-1β, tumor necrosis factor and prostaglandin in patients with Alzheimer's disease cause pain, and the process of pain promotes the further aggregation of inflammatory factors, aggravates the accumulation of Aβ and aggravates cognitive impairment.[32,33] Secondly, AD can cause LBP and other pain in patients with sluggish muscle tone, altered gait, and muscle contracture.[34] The deposition of amyloid-β (Aβ) and hippocampal atrophy are key hallmarks of Alzheimer's disease (AD). Recent studies suggest that Aβ accumulation and hippocampal atrophy may also contribute to chronic pain, which aligns closely with our research findings.[35] Our research has several major advantages. First, the GWAS data sets for

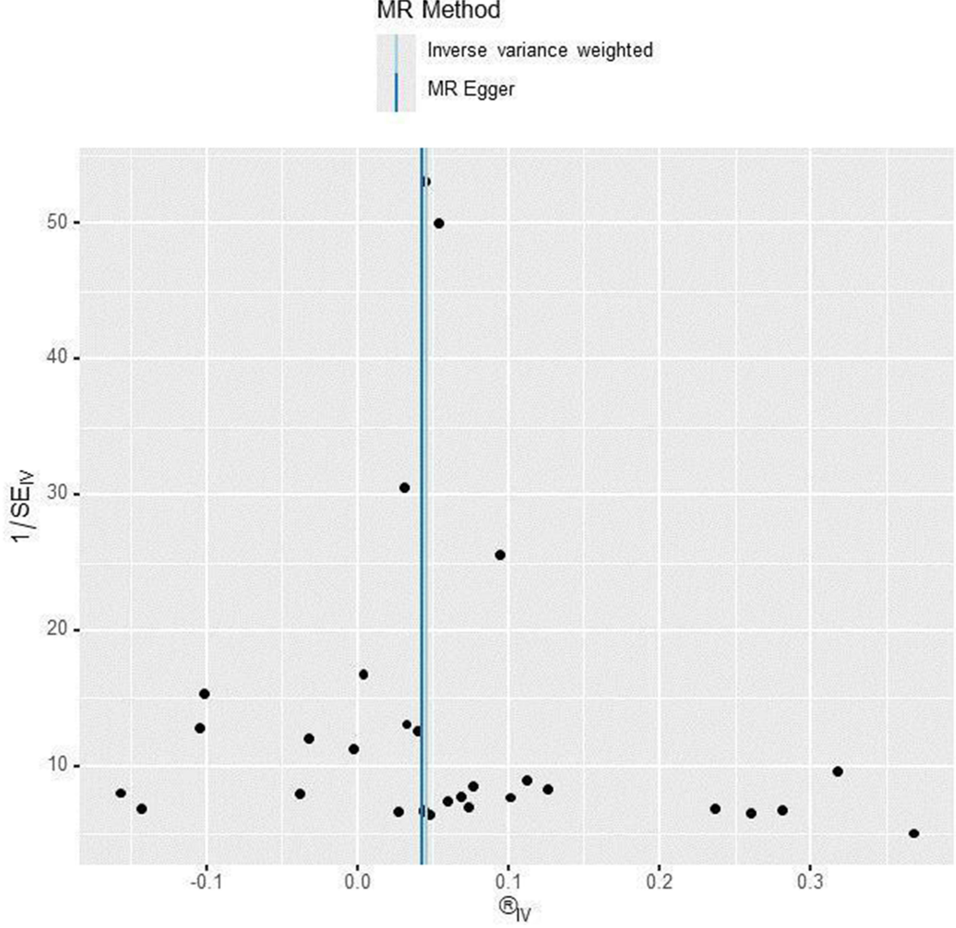

Figure 4 The funnel plot illustrates the relationship between the effect size and precision of each SNP in terms of its association with the Alzheimer's Disease-Low back pain correlation.
Abbreviation: IV, Instrumental Variable.

both LBP and AD genetic IVs come from European populations, which avoids the effect of population stratification. Second, the selected GWAS dataset contains a large number of samples containing millions of detected SNPs, greatly increasing the power of statistical test. Most importantly, in order to assure the robustness of the results, we performed several additional methods to support the stability of the estimates. As our findings suggest, there is a causal relationship between AD and LBP. We should be aware that this study also has some limitations. Firstly, we identified a hypothesized causal relationship between Alzheimer's disease and LBP in European ancestry. Additionally, the data were derived from a European population, which may limit the generalizability of the results to other populations. Future studies are necessary in order to generalize our conclusions to other populations. Secondly, the mechanism which Alzheimer's disease exacerbates LBP in the European population needs to be further validated. Thirdly, we only use statistics at the summary level, so we do not allow for hierarchical analysis.

Conclusion

In our MR Study, there was a causal relationship between AD and LBP in a European population. These findings highlight the necessity of improving pain management in patients with Alzheimer's disease and provide a foundational basis for future clinical practice.

Informed Consent Statement

This MR research utilized only published or publicly available GWAS data. Each participant received ethical approval and informed consent for the respective study, as detailed in the original publication and consortium. Meanwhile, the study was reviewed and approved by the Henan Provincial Ethics Committee.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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