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Association between idiopathic normal pressure hydrocephalus and Alzheimer's disease: a bidirectional Mendelian randomization study

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Observational studies have suggested a bidirectional relationship between idiopathic normal pressure hydrocephalus (iNPH) and Alzheimer's disease (AD). However, the causal association between these two neurodegenerative disorders remains unclear. This study aimed to explore the causal relationship between iNPH and AD using a two-sample bidirectional Mendelian randomization (MR) method. Large-scale genome-wide association studies of iNPH (N_{case} = 767, $N_{control}$ = 375,610) and AD ($N_{case/proxy}$ = 111,326, $N_{control}$ = 677,663) in European individuals were used to screen genetic instruments for MR analysis. Inverse variance-weighted (IVW) method was used as the main analysis, other MR methods and a series of sensitivity analyses were performed to ensure the reliability. In the forward MR analysis, genetic predisposition to iNPH had no effects on the risk of AD development. Likewise, in the reverse MR analysis, AD did not demonstrate a significant causal effect on iNPH. Sensitivity analyses bolstered the reliability of the MR results. Our MR study indicated no genetic evidence supporting a suggestive association between AD and iNPH in either direction, and provided evidence on the dichotomy between true iNPH and neurodegenerative NPH.

Keywords Idiopathic normal pressure hydrocephalus, Alzheimer's disease, Mendelian randomization, Neurodegenerative disorders

Idiopathic normal pressure hydrocephalus (iNPH) and Alzheimer's disease (AD) are both neurodegenerative disorders that share multiple common critical pathologic and clinical features, including amyloid-β (Aβ) aggregates[1,2], impaired glymphatic function[3], and progressive dementia[4,5]. Accumulating evidence indicates that altered cerebrospinal fluid (CSF) dynamics may lead to a vicious cycle of neurological damage in iNPH and AD[6–9]. On the one hand, less clearance and more deposition of Aβ because of compression of the brain in iNPH promotes the progression of AD. On the other hand, the increase in the resistance to CSF outflow due to the deposition of Aβ in the meninges in AD promotes the progression of iNPH. In addition to CSF dynamics, AD and iNPH also share similarities in CSF protein biomarkers. A comprehensive genome-wide meta-analysis of CSF biomarkers for AD identified two genes associated with phosphorylated tau (pTau), which are also linked to lateral ventricular volume. This finding suggests a potential genetic overlap between AD and iNPH[10]. Clinically, AD CSF biomarkers, such as Aβ42, the Aβ42/Aβ40 ratio, and pTau, have been evaluated for their potential to differentiate iNPH from AD and to predict outcomes following shunt surgery in iNPH patients[8,11,12].

A report by the Task Force of the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders (ISHCSF) proposed that iNPH may increase the risk of AD[13]. However, a series of studies have reported different incidence rates (19 – 68%) of AD in iNPH[4,5,14–17]. The discrepancy among these studies could be a result of differences in the types (CSF or brain biopsy) or sources of pathological specimens. Similarly, patients with AD may also have iNPH, but their proportion is reportedly much smaller[3].

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Shunting is the classic surgical management for iNPH. However, given the complex relationship between AD and iNPH, screening suitable patients for shunt surgery is difficult because of the instability of surgical results. According to previous studies, the overlapping stage of the two conditions is likely the key point for shunt surgery[18]. Several studies indicated that shunting is associated with a reduced risk of AD development in patients with early-stage iNPH without AD[19,20]. However, in late-stage iNPH associated with AD, shunting confers no symptomatic relief[5,21–23]. In fact, the available data are far more confusing as it has been reported that the baseline AD pathology may not prognosticate the shunt response[24,25], or that patients with iNPH and AD pathology could also benefit from shunt surgery[26,27]. In addition, several meta-analyses have reached different conclusions regarding the responsiveness of CSF shunting in iNPH, which may be interrupted by AD[28,29].

Given the close relationship between iNPH and AD, it is essential to verify a true causal association between them to clarify the detailed progression or overlap of both diseases, which may be beneficial for the selection of iNPH cases for shunting and for understanding the mechanism of both. However, the bidirectional relationship between iNPH and AD has not yet been fully investigated. Apart from a causal association, it is also likely that the two conditions overlap because of shared common mechanisms (e.g., abnormal CSF dynamics and impaired glymphatic function).

Mendelian randomization (MR) is an analytical method that uses single nucleotide polymorphisms (SNPs) associated with a certain exposure to assess the possible causal relationships between the exposure and outcome[30–32]. It provides a new method to study associations that cannot be achieved by traditional observational studies because of ethical or conditional limitations, in addition to reducing bias from confounding variables apparent in epidemiological studies. We performed two-sample MR analyses to assess the bidirectional causal relationship between iNPH and AD.

Methods

Study design

A bidirectional causal relationship between iNPH and AD was studied by using summary statistics of genome-wide association studies (GWAS) in the European population. Our analyses were based on the following three assumptions: (I) instrumental variables (IVs) are strongly associated with exposures, (II) IVs are independent of any potential confounders, and (III) IVs influence the risk of the outcome only through their effect on the exposure (Fig. 1).

Data sources

The exposure and outcome GWAS summary statistics used in this study did not overlap because they were obtained from two different consortia (Table 1). The GWAS data for iNPH were obtained from the ninth round of the FinnGen research project, released in 2023. The FinnGen is a global research project launched in Finland in 2017 that combines genomic information with digital healthcare data[33]. iNPH was diagnosed using the code G91.2 according to the International Classification of Diseases 10th Revision (ICD-10), and 767 cases of iNPH and 375,610 controls of European ancestry were included.

For AD, we used the latest GWAS meta-analysis dataset of patients with AD and proxy cases (people with a family history of AD) from the European Alzheimer & Dementia Biobank (EADB) consortium[34], which included 111,326 of AD and proxy cases (proxy cases refer to at least one biological relative, like as parents and siblings, affected with dementia either at baseline or follow up) and 677,663 controls.

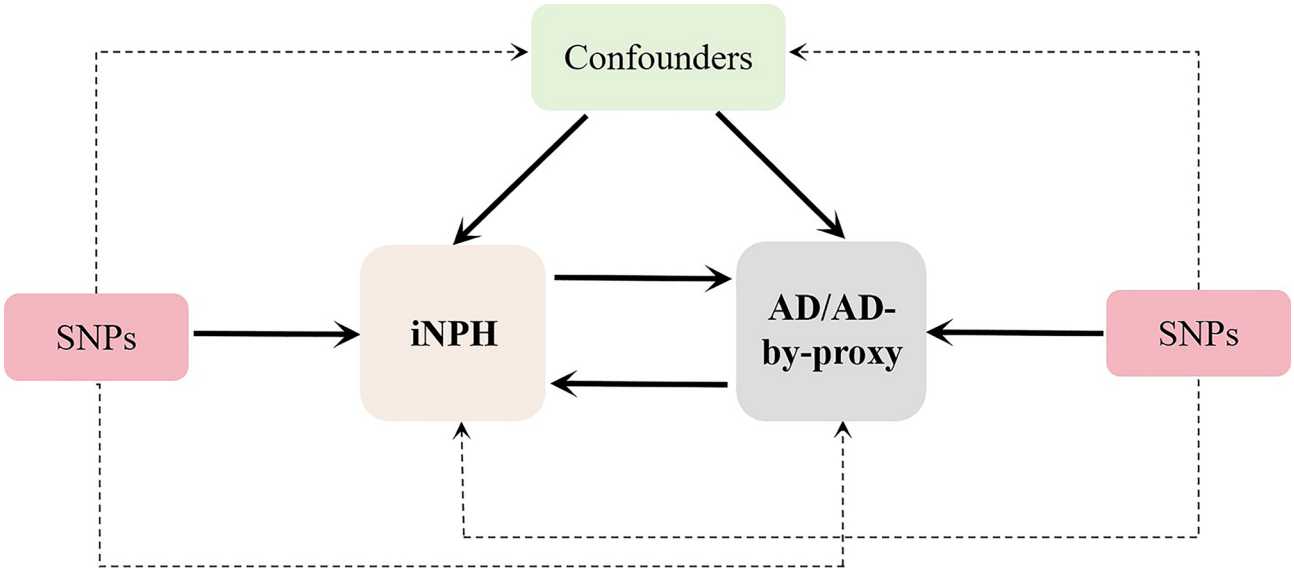

Fig. 1. The three assumptions of this MR analyses. *AD* Alzheimer's disease, *iNPH* idiopathic normal pressure hydrocephalus, *SNPs* single nucleotide polymorphisms.

Variable	Sample size	Reference	GWAS ID	GWAS source	Ancestry
iNPH	767 cases/375,610 controls	NA	G6_HCNP in FinnGen	FinnGen	European
AD/AD-by-proxy	111,326 cases/677,663 controls	Bellenguez C et al	GCST90027158 in GWAS catalog	EADB consortium	European

Table 1. Characteristics of each GWAS summary statistics. *AD* Alzheimer's disease, *EADB* European Alzheimer & Dementia Biobank, *iNPH* idiopathic normal pressure hydrocephalus, *NA* not applicable.

Genetic instruments selection

To identify sufficient SNPs for MR analysis, first SNPs with genome-wide significance ($P < 5 \times 10^{-6}$) were screened to select IVs for iNPH[35]. Then, SNPs were excluded using linkage disequilibrium clumping with a threshold (r^2<0.001 and window size = 10,000 kb) to reduce correlations with other genetic variants and minimize the possibility of IVs directly affecting the outcome[36]. Furthermore, the F-statistic $F = [(N-K-1)/K] \times [R^2/1-R^2]$ (K represents the number of IVs) of each instrument (K = 1) was calculated and filtered according to $F \geq 10$[37]. Subsequently, by using the PhenoScanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/)[38], the association of SNPs with potential confounders was evaluated for the following traits of AD: diabetes, hypertension, obesity, smoking, depression, low educational attainment and physical inactivity[39]. Index SNPs associated with the potential confounders listed above with genome-wide significant associations ($p < 5 \times 10^{-8}$) were removed. Finally, SNPs that were palindromic between the summary statistics of the exposure and outcome were removed by using a harmonization function, and Steiger filtering was used to remove SNPs that showed a stronger association with the outcome than with the exposure[40].

For the AD phenotype, we used the GWAS meta-analysis dataset and genome-wide significance was set to $P < 5 \times 10^{-8}$ due to the larger number of SNPs in AD dataset compared to iNPH dataset. We then applied the same steps as described above for iNPH. Briefly, we removed correlated SNPs using linkage disequilibrium clumping and weak IVs by F-statistic; removed the potential confounders of hypertension, diabetes and stroke for iNPH[41,42], used the harmonise data function to remove palindromic SNPs, and finally applied Steiger filtering.

Statistical analysis

We applied an inverse variance-weighted (IVW) model to estimate the association between iNPH and AD in both directions[43,44]. Given that the IVW method may generate bias in the presence of horizontal pleiotropy[44], sensitivity analyses and other MR methods, such as MR-Egger regression, weighted median, simple mode, and weighted mode, were also implemented to ensure robustness of the results. The MR results were considered meaningful if the IVW model result was significant, and all five MR methods showed effects in the same direction to ensure a more comprehensive interpretation of the statistical results[45,46]. Pleiotropy was estimated using the intercept from MR-Egger regression, and heterogeneity was assessed using Cochran's Q test in the MR-Egger regression and IVW approaches[43]. We also used the MR-PRESSO outlier test to reduce outlier bias by three primary steps: outlier detection, correction of causal effects, and process reiteration[47]. And then leave-one-out analysis attempts to assess whether bias existed due to individual SNPs independently affecting the results[43]. All the analyses were performed by using the TwoSampleMR and MendelianRandomization packages in R version 4.2.1[48].

Results

Instrument selection

For iNPH, 331 index SNPs were extracted from the original summary statistics of GWAS at $P < 5 \times 10^{-6}$. After linkage disequilibrium clumping and weak IV testing, 20 index SNPs were retained. After removing rs4845876 associated with hypertension and rs1182207 associated with diabetes (Supplementary Table 1), 18 index SNPs remained in the group. No palindromic SNPs were identified, and no SNPs with an inverse correlation were discovered by Steiger filtering (from iNPH to AD). Thus, 18 independent genetic instruments were obtained and their associated data are presented in Supplementary Table 2.

For AD, 5637 index SNPs were extracted from the original summary statistics of GWASs at $P < 5 \times 10^{-8}$. Sixty index SNPs were retained after linkage disequilibrium clumping and weak IV testing. Subsequently, two hypertension-associated SNPs (rs11500477 and rs4292) were removed (Supplementary Table 1). Four palindromic SNPs were removed by harmonization, and 54 independent genetic instruments were finally obtained (Supplementary Table 3). No SNPs with an inverse correlation were discovered by Steiger filtering (from the AD to iNPH) (Fig. 2).

Causal relationship between iNPH and AD

Our initial MR analysis demonstrated that a genetic predisposition for iNPH was associated with an increased risk of AD according to the IVW method (odds ratio [OR], 1.022, 95% confidence interval [CI] 1.002 – 1.038; $P = 0.028$) (Figs. 3 and 4A). Furthermore, all the other four MR methods also showed the same direction of the effect, bolstering the reliability of our results (Supplementary Table 4). However, the leave-one-out analysis found that SNP rs11079922 (ABCC3), rs4128399 (PRKAG2), rs6540017 (C16orf95) and rs72677159 (MIS18BP1) had strong influences on the causal estimate for iNPH on AD (Fig. 5). Since the PRKAG2 and C16orf95 have been reported to be associated with AD[10,49], we removed this two SNPs and found the suggestive causal relationship between the iNPH and AD disappeared (OR 1.014, 95% CI 0.997 – 1.032, $P = 0.109$) (Figs. 3 and 4B). In the reverse analysis, there was no significant effect of AD on iNPH (OR 1.044, 95% CI 0.867 – 1.256, $P = 0.651$)

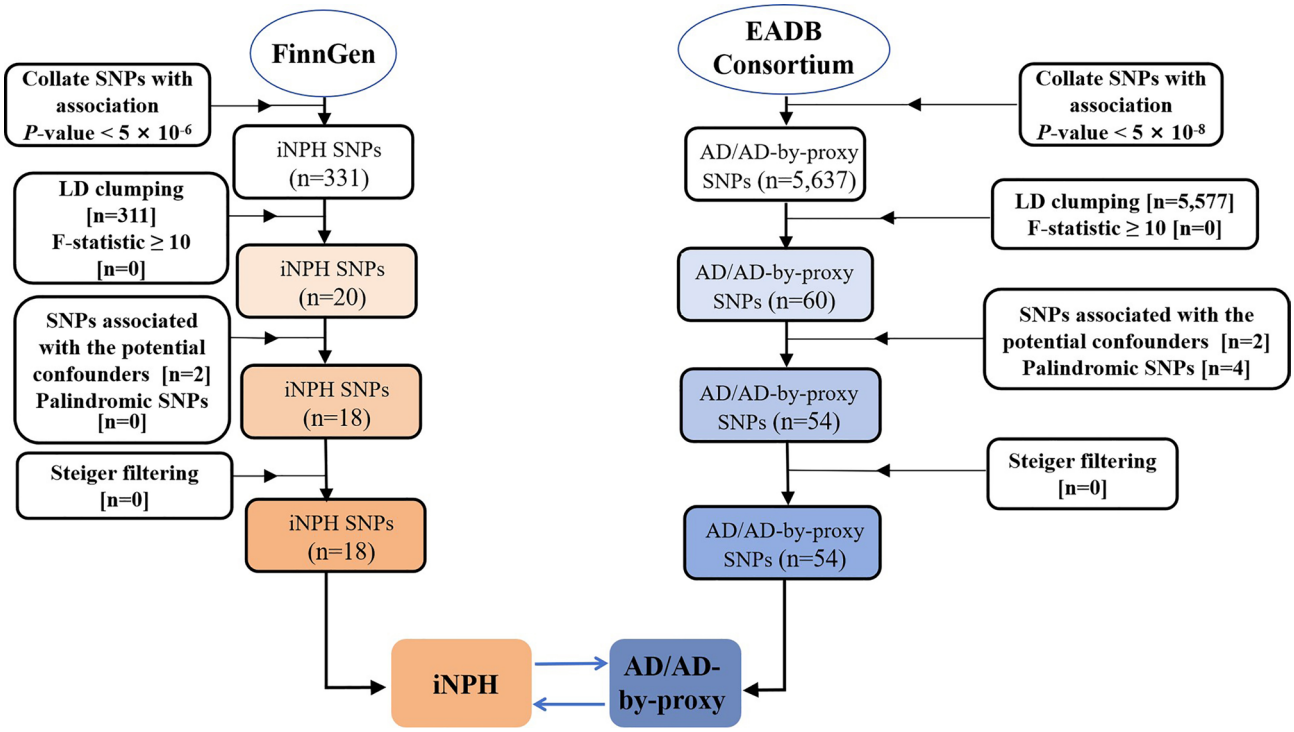

Fig. 2. The process of generating SNPs in this study. Selection of genetic instruments for estimating in iNPH and AD GWAS datasets. The numbers in square brackets represent the number of SNPs removed in each filtering step, and in parentheses represent the number of SNPs remaining after each filtering step. *AD* Alzheimer's disease, *EADB* European Alzheimer & Dementia Biobank, *iNPH* idiopathic normal pressure hydrocephalus, *SNPs* single nucleotide polymorphisms.

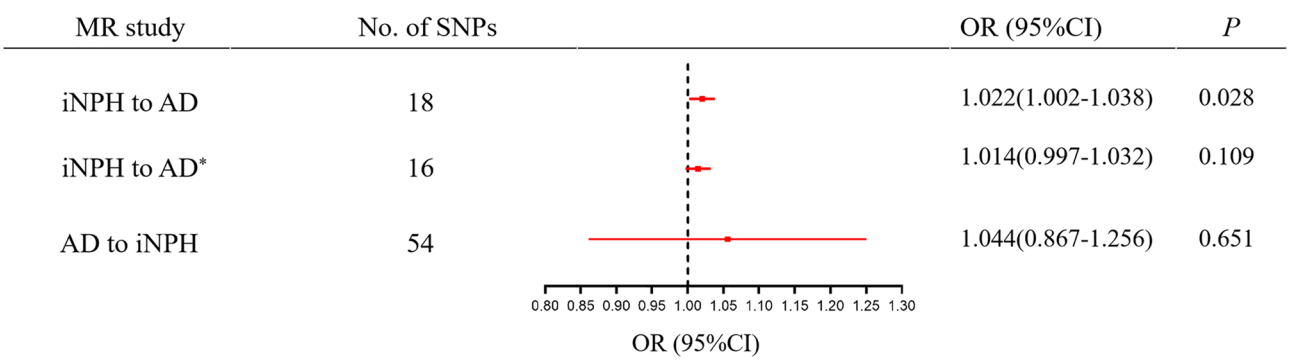

Fig. 3. The causal effect between iNPH and AD. *AD* Alzheimer's disease, *CI* confidence interval, *iNPH* idiopathic normal pressure hydrocephalus, *IVW* inverse variance weighted, *MR* Mendelian randomization, *OR* odds ratio, *SNPs* single nucleotide polymorphisms. Asterisk represents the MR analysis from iNPH to AD after removing rs4128399 (PRKAG2) and rs6540017 (C16orf95).

(Fig. 3). Sensitivity analyses using the Cochran's Q statistic based on the MR-Egger regression and IVW methods demonstrated no evidence of heterogeneity among the screened SNPs. MR-Egger regression showed no evidence of horizontal pleiotropy in any of the MR analyses in our study (Supplementary Table 5).

Discussion

The relationship between iNPH and AD has been controversial for years. iNPH is a neurological disorder characterized by ventricular enlargement without an increase in the intracranial pressure and the clinical triad of gait impairment, urinary incontinence, and cognitive disturbances[50]. It was first described by Hakim and Adams in 1965 and is mostly seen in older individuals[51,52]. As a neurodegenerative disease, AD clinically presents with symptoms similar to those of iNPH. Based on the findings that the incidence of AD in patients with iNPH is greater than that in the general population, AD is considered a common pathological comorbidity of iNPH[53]. Although iNPH is characterized by genetic and pathophysiological mechanisms independent from AD[54], the relationship between the two conditions remains ambiguous, and efforts to identify iNPH and AD through

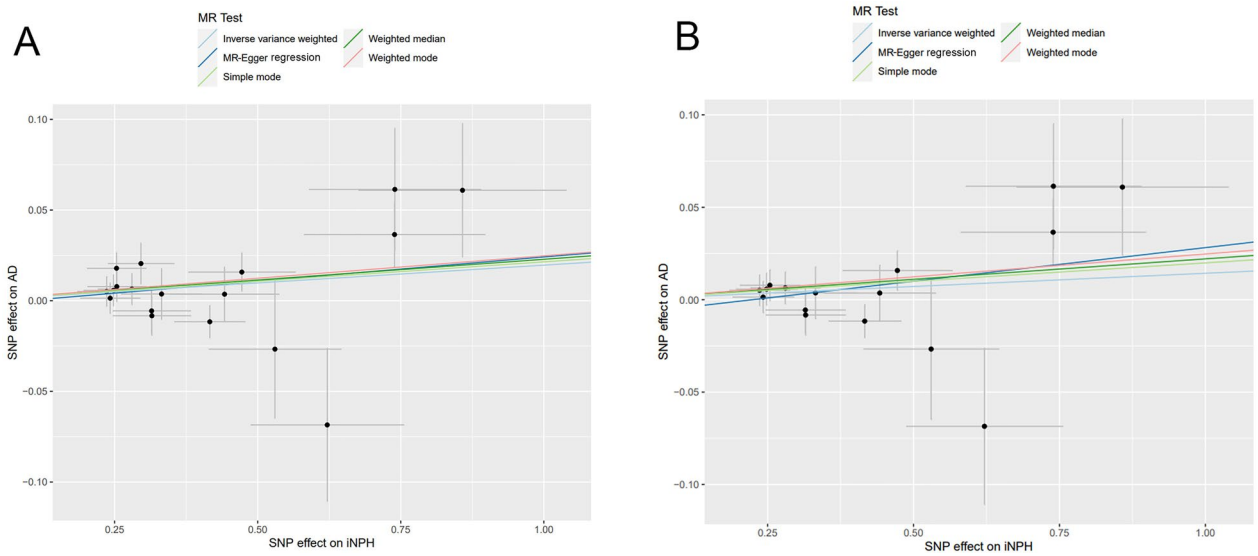

Fig. 4. Scatterplots of SNPs associated with iNPH and AD. (**A**) Scatterplot of SNPs associated with iNPH versus AD. (**B**) Scatterplot of SNPs associated with iNPH versus AD after removing rs4128399 (PRKAG2) and rs6540017 (C16orf95). *AD* Alzheimer's disease, *iNPH* idiopathic normal pressure hydrocephalus, *MR* Mendelian randomization, *SNPs* single nucleotide polymorphisms.

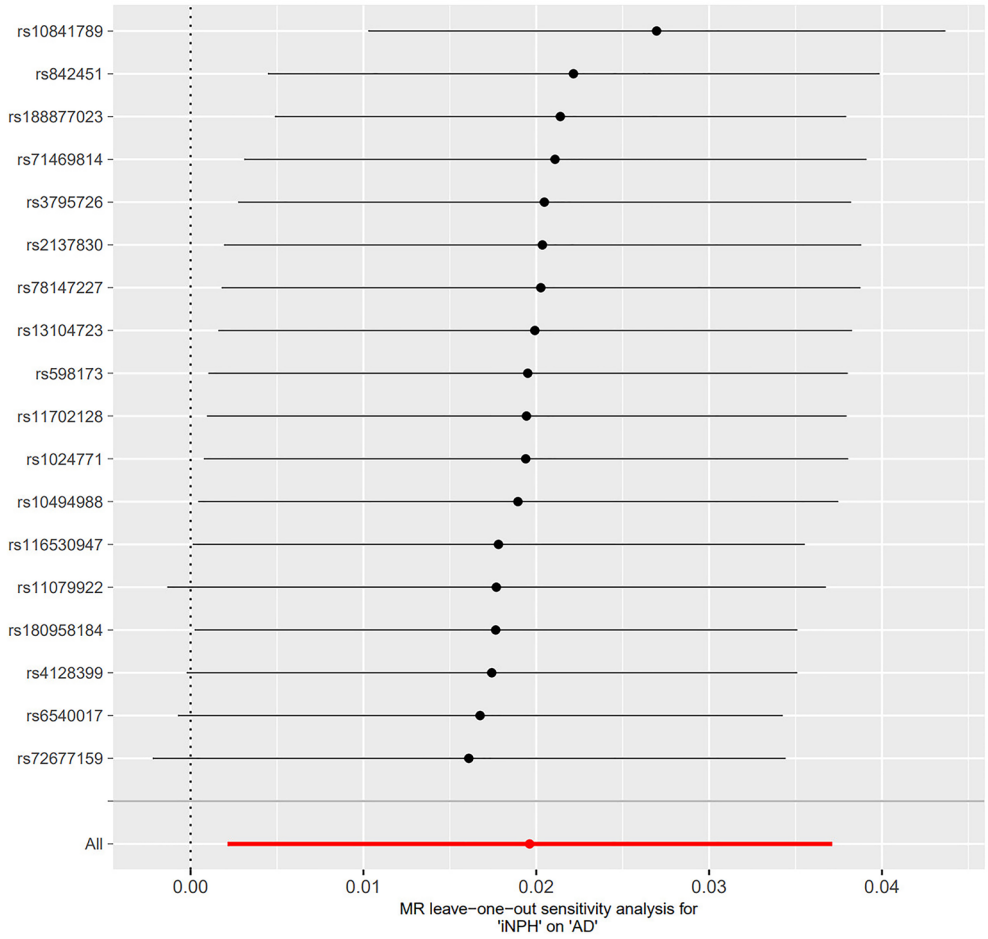

Fig. 5. Leave-one-out analysis of the effect of iNPH on AD. *AD* Alzheimer's disease, *iNPH* idiopathic normal pressure hydrocephalus.

medical imaging, pathology and biochemistry have been ongoing for years[12,55–60]. Gradually, it has been proposed that instead of distinguishing between the two diseases, staging of disease progression in terms of CSF circulation or lymphatic impairment, particularly for iNPH, would be a promising option[3,7]. Thus, the entity of iNPH-AD is gradually receiving increasing attention[5,7,27].

Our initial result demonstrated that iNPH was associated with a higher risk of developing AD. We found that for each 1-standard deviation increase in iNPH, there was a 2.2% increase in the risk of AD. However, the leave-one-out analysis found that SNP rs4128399 (PRKAG2) and rs6540017 (C16orf95) had strong influences on the estimation, and the suggestive causal relationship between the iNPH and AD disappeared after removing the two SNPs. Inversely, no causal effect of AD was observed on iNPH. These outcomes showed that rather than causation, iNPH and AD are more likely to show as two overlapping disease. Currently, the apolipoprotein E (APOE) gene is recognized as the most significant genetic association with AD. However, its role in iNPH appears to be less pronounced. A case–control study has demonstrated that there is no significant difference in the distribution of APOE genotypes between iNPH patients and an age-matched control group[61]. Furthermore, in patients with presumed iNPH, the APOE4 allele does not seem to be a risk factor, although it is associated with the presence of Aβ plaques in frontal cortical biopsies[62,63]. These observational findings may suggest that AD is not a direct cause of iNPH[64], which corroborates our results.

Multiple shared features between iNPH and AD make them more likely to overlap than have a causal association. Abnormal CSF dynamics and impaired glymphatic function are typical characteristics of both diseases. For CSF dynamics, a study assessed the pressure gradient, rotation, and CSF velocity in the Sylvian aqueduct using a special magnetic resonance imaging (MRI) sequence, and showed that patients with iNPH and AD have similar CSF motion profiles characterized by a hyperdynamic state to healthy older individuals owing to decreased compliance of the cerebrospinal cavity[6]. In addition, a preliminary study reported that the pressure gradient is higher in patients with iNPH than in healthy older controls[65]. Based on these observations, we can reasonably speculate that the CSF outflow resistance is increased in both iNPH and AD. However, owing to the small sample size of the above studies, further studies are required to investigate whether the hyperdynamic state of CSF in iNPH and AD is universal.

In terms of impaired glymphatic function, several imaging studies have found impaired glymphatic flux in patients with iNPH compared to healthy controls[66,67]. However, it is difficult to determine the degree of iNPH pathogenesis that attributes to glymphatic impairment. Likewise, the pathological finding of accumulation of Aβ is also observed in AD, which is a result of impaired glymphatic function and clearance of Aβ and tau[68]. Nevertheless, given the complexity of mechanisms underlying the dysfunction of the glymphatic system, the exact phase of disturbance of Aβ clearance due to lymphatic impairment remains elusive[68].

In clinical practice, the main puzzle regarding iNPH is the uncertainty about the effect of shunting in them; therefore, the decision regarding shunt surgery for iNPH is carefully and usually made by a multidisciplinary team consisting of neurologists, neuroradiologists, and neurosurgeons[69]. It appears that the best strategy to ensure that patients with iNPH benefit from shunting is to distinguish true iNPH from neurodegenerative NPH. According to the clinical guidelines, identifying 'possible','probable' and'definite' idiopathic NPH based on the age, imaging features, triad of clinical symptoms, and provocative tests is critical for making a decision regarding shunt surgery[70]. In fact, the slow progression and atypical of natural course of iNPH leads to uncertainly during the diagnosis and treatment[71]. Furthermore, the confounding interference of neurodegenerative diseases such as AD complicates this situation. Based on our results, the overlapping without causation of two diseases means two entities of true iNPH and neurodegenerative NPH could be identified for iNPH patients. The non-overlapping parts would be considered as the true iNPH entity and shunting is usually effective for them. The overlapping parts, however, is the neurodegenerative NPH intermixed with AD. Although the overlapping entity shares multiple pathologic and clinical features with AD, there is no causal relationship between them and shunting is usually ineffective for iNPH due to the interference of AD. For the point of cognitive disturbances, whether in iNPH or AD, the overlapping of two means the tendency that both diseases like to co-occur in a group of older individuals with certain features that are not yet known. In summary, identifying common markers shared between the AD and iNPH is crucial for understanding the pathophysiological mechanisms underlying the overlapping parts, and identifying the true iNPH entity to perform shunt surgery would benefit for the non-overlapping parts.

To the best of our knowledge, this is the first MR study to elucidate the relationship between iNPH and AD. However, our study has some limitations. First, our study population was restricted to a European population, which limits the generalizability of the findings to populations of other races. Second, age is closely associated with both AD and iNPH, and it may serve as an unavoidable confounding factor. Although the datasets used in our study had accounted for the age characteristic, thus reducing the influence of this confounding factor, other approaches, such as multivariable MR, may determine the association between AD and iNPH more accurately. Then, IVW was used as the main approach to estimate this association in the present study. The *P* value of other four MR methods larger than 0.05 was also considered suggestive of an association as long as they showed effects in the same direction with IVW. Although this model suffers from a certain degree of loss of statistical power, its results can still be considered credible. Finally, the number of cases of iNPH is small in our study due to the limitation of public GWAS data, and thus the potential causal relationship between the two may have been obscured.

In conclusions, our current MR findings indicate no genetic evidence on causal effect between iNPH and AD. This study supports the incomplete overlapping relationship between this two neurodegenerative disorders, and provides evidence on the dichotomy between true iNPH and neurodegenerative NPH. It means to identify the true iNPH that do not overlap with AD are worth exploring in future studies because of the importance of selecting suitable patients with iNPH for shunting.

Data availability

All the datasets used in the present study are openly available. Summary statistics of iNPH was downloaded from the ninth round of FinnGen research by phenocode of G6_HCNP. The AD data of European were obtained from the GWAS Catalog under accession number GCST90027158.

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Author contributions

HYJ, LL and GY conceptualized and designed the study. HYJ, CCA and LMT performed data analysis, HYJ and CCA drafted the initial manuscript. GY supervised the study. HHY contributed to critical review and revision

of the manuscript. All authors have approved the final manuscript as submitted and agreed to be accountable for all aspects of this work.

Competing interests
The authors declare no competing interests.

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