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ORIGINAL COMMUNICATION

Association between vascular risk factors and idiopathic normal pressure hydrocephalus: a Mendelian randomization study

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Abstract

Background and objective Patients with idiopathic normal pressure hydrocephalus (iNPH) have a higher prevalence of hypertension and diabetes. However, the causal effects of these vascular risk factors on iNPH remain unclear. This study aimed to explore the causal relationship between vascular risk factors (VRFs) and iNPH.

Methods We conducted the Mendelian randomization (MR) analysis of iNPH. We included nineteen vascular risk factors related to hypertension, diabetes, lipids, obesity, smoking, alcohol consumption, exercise, sleep, and cardiovascular events as exposure factors. We used the inverse-variance weighted method for causal effect estimation and weighted median, maximum likelihood, and MR Egger regression methods for sensitivity analyses.

Results We found that genetically predicting essential hypertension (OR = 1.608 (1.330–1.944), $p = 0.013$) and increased sleep duration (OR = 16.395 (5.624–47.799), $p = 0.009$) were associated with higher odds of iNPH. Type 1 diabetes (OR = 0.869 (0.828–0.913), $p = 0.004$) was associated with lower odds of iNPH. For the other 16 VRFs, there was no evidence that they were significantly associated with iNPH. Sensitivity analyses showed that essential hypertension and type 1 diabetes were significantly associated with iNPH.

Conclusion In our MR study on VRFs and iNPH, we found essential hypertension to be a causal risk factor for iNPH. This suggests that hypertension may be involved in the pathophysiological mechanism of iNPH.

Keywords Idiopathic normal pressure hydrocephalus · Vascular risk factors · Mendelian randomization · Hypertension · Diabetes

Abbreviations

NPH	Normal pressure hydrocephalus
iNPH	Idiopathic normal pressure hydrocephalus
VRF	Vascular risk factor
MR	Mendelian randomization
GWAS	Genome-wide association study
SNP	Single nucleotide polymorphisms
IVW	Inverse-variance weighted
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
RCT	Randomized controlled trial
CSF	Cerebrospinal fluid
ICD	International Classification of Diseases
OR	Odds ratio

Introduction

Normal pressure hydrocephalus (NPH) is a neurological disease characterized by gait disturbance, cognitive impairment, and urinary incontinence [1]. As the population ages, this disease is gaining attention as reversible dementia. Normal pressure hydrocephalus can be divided into idiopathic and secondary according to etiology. The pathophysiology of idiopathic normal pressure hydrocephalus (iNPH) is currently unknown. However, the population of iNPH is mainly the elderly [2, 3], who often have vascular risk factors (VRFs).

From previous case–control studies, hypertension [4–10], diabetes [4–6, 8–11], hyperlipidemia [4], abdominal obesity [4], physical inactivity [4], alcohol use disorder [12], and cardiac and cerebrovascular disease [5] are more common

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in patients with iNPH. Among these VRFs, hypertension is considered to be related to the clinical presentation, imaging, and prognosis of iNPH patients [10, 13]. And a nationwide hospital-based survey found that hypertension was the most common comorbidity in iNPH (40%), followed by diabetes (17.8%) [14]. Therefore, it has been speculated in the past that hypertension may be involved in the mechanism of iNPH, which can increase cerebrospinal fluid (CSF) pressure and pulse pressure, leading to ventriculomegaly [7, 15, 16]. And the ventriculomegaly has now been shown to result from increased CSF pulsatility [17], which is closely regulated by cardiovascular pulsation [18]. In addition, increased blood pressure has been found in mice to reduce the flow of CSF through the perivascular space in the brain, which means a decline in the function of the glymphatic system [19]. The function of the glymphatic system is to facilitate the removal of excess fluid and waste in the central nervous system [20], which has recently been considered one of the pathophysiological mechanisms of iNPH [21, 22]. Moreover, the glymphatic system is closely related to another vascular risk factor: sleep [20]. A previous prospective cohort study found obstructive sleep apnea in 90% (28/31) of patients with iNPH [23]. Sleep apnea is considered to cause iNPH by affecting intracranial venous circulation and glymphatic circulation [24]. In addition to hypertension and sleep apnea, diabetes is also an important vascular factor in iNPH patients. According to a systematic literature review, it occurs more than twice as frequently in iNPH patients as in age-matched controls [11]. And it is considered a risk factor for the development of iNPH along with hypertension and sleep apnea [25]. However, most studies on iNPH and vascular risk factors are observational studies, which cannot directly link the two to observe the impact of vascular risk factors on the occurrence of iNPH. Moreover, the randomized controlled trial (RCT) on iNPH is difficult to implement.

The Mendelian randomization (MR) method is an analysis method based on genetic instrumental variables [26], which can estimate the causal effect of exposure on the outcome. This method directly links exposure to genetic variation, and random segregation of alleles mimics random grouping in RCTs. Therefore, it can theoretically avoid bias from confounding factors between exposures and outcomes.

This study aimed to investigate the causal effect of vascular risk factors on iNPH using Mendelian randomization.

Methods

Study design

In this study, we used the 2-sample MR design to investigate the causal relationships between the 19 VRFs and iNPH. We made the following assumptions for this MR study evaluation: (1) the instrument is associated with the exposure (relevance). (2) There are no confounders of the instrument and the outcome (exchangeability). (3) The instrument has no direct effect on outcome except through exposure (the exclusion restriction).

Instruments

We obtained the GWAS data of the VRFs and used them as exposure factors. The ancestry of all the GWAS data was European. The included exposure factors were essential hypertension [27], secondary hypertension [27], type 1 diabetes (T1DM) [27], type 2 diabetes (T2DM) [27], low-density lipoprotein cholesterol [28], high-density lipoprotein cholesterol [28], triglycerides [28], body mass index [29], smoking initiation [30], cigarettes smoked per day [30], alcohol intake frequency [29], alcohol dependence [27], moderate to vigorous physical activity levels [31], myocardial infraction [32], coronary artery disease [33], stroke [34], sleep apnea [27], insomnia [29], and sleep duration [29]. Among these exposures, diagnostic criteria for disease-related exposures are presented in supplementary table 1. The selected single nucleotide polymorphisms (SNPs) should meet the criteria that genome-wide significance association with each factor was less than 5×10^{-8}. And we clumped the selected SNPs to obtain the SNPs in a threshold of linkage disequilibrium ($r^2 > 0.01$) and a distance of 10000 kb. Later we extracted the SNPs for each exposure factor from the outcome. The effect allele of exposure and outcome datasets were harmonized. Finally, we excluded the SNPs that exit the palindromic sequence.

Data sources for iNPH

The GWAS data of iNPH were obtained from the European cohort: the FinnGen study. The FinnGen study is a global research project that combines genome information with digital health care data [27]. In the FinnGen study round 5, 322 cases defined as NPH and 218,043 controls were included. The endpoint of NPH was defined by the International Classification of Diseases 10th version (ICD-10). The code of NPH in ICD-10 was G91.2.

Statistical analysis

We used the inverse-variance weighted (IVW) method to perform the principal analyses, which combined the SNPs of exposure and the SNPs of the outcome. The Wald ratio (the ratio of genetic association with the outcome to the genetic association with the exposure) was used to estimate the causal effects between exposure and outcome. To test whether the first assumption was satisfied, we calculated

the F statistic for all SNPs using the formula. $F = \text{Beta}^2/\text{SE}^2$. $F > 10$ is considered weak instrument bias is small. And we used the maximum likelihood, the weighted median, and MR Egger regression methods for sensitivity analysis, considering that the IVW method might be affected by pleiotropy. Then MR-PRESSO was used to remove the outlier SNPs, which cause the horizontal pleiotropy. Finally, we searched PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) for all SNPs included in the primary outcome of the analysis, considering potential confounding factors leading to a violation of the second assumption. We included recurrent traits of non-exposed factors as covariates. We then adjusted for covariates with the main outcome using multivariate Mendelian randomization.

All the statistical analyses were performed using R-4.2.1 with R packages. The R packages for analysis included the TwoSampleMR package, MendelianRandomization package, and MR-PRESSO package. For binary exposure factor variables, we used the odds of the exposure factor to estimate its causal effect on the outcome[35]. P value < 0.05 were considered as potential associations.

Data availability

The sources and information of the GWAS data for all exposures and the outcome involved in this study are presented in supplementary table 4. In addition, all the analysis result data are presented in the paper. All the GWAS data were publicly available through the IEU Open GWAS project online [36, 37]. Link: https://gwas.mrcieu.ac.uk/.

Results

The included exposure factors and IVW estimates of their causal effects with iNPH are presented in Table 1. In the IVW analysis, we found that genetically predicting T1DM (OR = 0.869 (0.828–0.913), $p = 0.004$), essential hypertension (OR = 1.608 (1.330–1.944), $p = 0.013$), and sleep duration (OR = 16.395 (5.624–47.799), $p = 0.009$) were associated with iNPH (Fig. 1). No significant associations were observed in the other 16 exposure factors. After combining the other three methods, all except the MR Egger method showed a significant association with iNPH for both type 1 diabetes and essential hypertension (supplementary table 5). For T1DM and essential hypertension, Fig. 2 shows scatterplots of the effect of SNP on exposure and the effect of SNP on the outcome. However, for sleep duration, only the maximum likelihood method showed that it was associated significantly with iNPH (supplementary table 5).

We calculated F statistics for all SNPs used for MR analysis in essential hypertension and type 1 diabetes, and found that they were all > 10 (supplementary table 2; supplementary table 3). In the MR Egger method for the pleiotropy test, potential pleiotropy was only found on body mass index ($p = 0.027$) (Table 1). Using MR-PRESSO for all exposures, we found no significant difference between the results after removing outliers and the original results. And significant heterogeneity was only presented in the IVW method on sleep apnea ($p = 0.049$) (Table 1). Then we adjusted systolic blood pressure, diastolic blood pressure, and taking blood pressure medication with essential hypertension. Multivariate MR analysis showed that essential hypertension was associated with iNPH (OR = 2.195(1.520–3.168), $p = 0.032$) (Fig. 3). In addition, we adjusted for rheumatoid arthritis, autoimmune thyroiditis, and inflammatory bowel disease with type 1 diabetes. Multivariate MR analysis did not show that T1DM was associated with iNPH (OR = 0.841(0.763–0.927), $p = 0.074$).

Discussion

In our MR study on VRFs and iNPH, we found that genetic instruments predicting essential hypertension, and type 1 diabetes were thought to be associated with iNPH. This suggests that they may be vascular factors with a causal effect on iNPH. Essential hypertension increases the risk of iNPH, whereas type 1 diabetes reduces the risk of iNPH. And most sensitivity analyses for essential hypertension and T1DM were consistent with no violation of the MR assumptions. In addition, long sleep duration may be a potential causal risk factor for iNPH. After adjusting for covariates, we found that the causal relationship between essential hypertension and iNPH was attenuated, but still significant. However, after covariate adjustment, there was no significant causal relationship between type 1 diabetes and iNPH. For the other 17 VRFs, there was insufficient evidence for a causal relationship between them and iNPH.

We found that essential hypertension is the only risk factor with a causal effect on iNPH in this study. This suggests that hypertension may be involved in the pathogenesis of iNPH pathophysiology. In previous observational studies, hypertension was often closely associated with ventriculomegaly, which is the primary pathological feature of iNPH. Subsequent studies using monitoring of aqueduct stroke volume [38] confirmed that ventriculomegaly is caused by increased CSF pulsatility, which is regulated by cardiovascular pulsations. This also suggests an association between hypertension and ventriculomegaly to some extent. In addition, we believe that vascular changes caused by hypertension may act to decrease arterial pulsatility, which is a critical process. Furthermore, arterial pulsatility drives the exchange of cerebrospinal fluid and interstitial fluid [39], and decreased exchange indicates impairment of glymphatic system function. A previous study also confirmed

Table 1 An overview of the genetic instruments used in the MR study and the causal relationship between vascular risk factors and idiopathic normal pressure hydrocephalus estimated by the inverse-variance weighted method

Risk factor	SNPs	Used SNPs[a]	Sample	IVW (b/se)	IVW P	IVW het P	Intercept P	MPO P	MMR P
Glucose									
Type 1 diabetes	51	44/51	189,302	−0.140/0.049	0.004**	0.943	0.567	0.941	NA
Type 2 diabetes	36	26/36	202,046	−0.146/0.153	0.339	0.636	0.788	0.654	NA
Hypertension									
Essential hypertension	43	39/43	205,694	0.475/0.190	0.013*	0.409	0.843	0.403	NA
Secondary hypertension[b]	8	7/8	164,147	0.056/0.149	0.706	0.946	0.420	0.941	NA
Lipid									
LDL-C	312	247/312	440,546	−0.239/0.229	0.296	0.152	0.197	0.163	0.706
HDL-C	677	537/677	403,947	0.184/0.174	0.292	0.841	0.465	0.848	0.411
Triglycerides	574	461/574	441,016	−0.124/0.184	0.503	0.500	0.084	0.495	0.457
Fat									
BMI	814	667/814	461,460	−0.019/0.219	0.930	0.355	0.027	0.374	NA
Smoke									
Smoking initiation	106	86/106	632,802	0.072/0.373	0.847	0.605	0.354	0.606	NA
Cigarettes smoked per day	29	25/29	249,752	−0.186/0.409	0.650	0.194	0.837	0.191	NA
Alcohol									
Alcohol intake frequency	117	103/117	462,346	−0.395/0.398	0.320	0.358	0.533	0.344	NA
Alcohol dependence[b]	10	9/10	211,535	0.300/0.293	0.306	0.295	0.144	0.318	NA
Exercise									
MVPA	19	18/19	377,234	1.588/1.513	0.294	0.315	0.123	0.317	NA
Cardiovascular events									
Myocardial infarction	34	25/34	395,795	−0.221/0.183	0.228	0.588	0.066	0.608	NA
Coronary artery disease	86	70/86	547,261	−0.161/0.171	0.344	0.303	0.209	0.307	NA
Stroke	8	6/8	446,696	0.634/0.541	0.241	0.706	0.354	0.720	NA
Sleep									
Sleep apnea	6	6/6	217,955	−0.411/0.618	0.506	0.049	0.385	0.069	NA
Sleeplessness / insomnia	49	39/49	462,341	0.201/1.277	0.875	0.856	0.630	0.872	NA
Sleep duration	77	62/77	460,099	2.797/1.070	0.009**	0.233	0.481	0.245	NA

MR Mendelian randomization, *SNP* single nucleotide polymorphism, *IVW* inverse-variance weighted, *b* Beta, *se* standard error, *het* heterogeneity, *MPO* MR-PRESSO, *MMR* multivariable MR, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *BMI* body mass index, *MVPA* moderate to vigorous physical activity levels, *NA* not available

[a]SNPs used in the present MR analysis

[b]Genome-wide significance of the selected SNPs associated with the factors is less than 5×10^{-6}

*$p < 0.05$

**$p < 0.01$

that hypertension can induce a decrease in the flow of the perivascular space, which may be related to the stiffening of the arterial wall caused by high blood pressure [19]. We think that this decrease in exchange may result in the deposition of toxic substances in the brain that contribute to cognitive impairment in patients with iNPH. The deposition of toxic solutes in the perivascular space may further aggravate the decrease of arterial pulsatility and fall into a vicious circle. Furthermore, decreased arterial pulsatility may be associated with increased aqueduct stroke volume [40, 41], which reflects increased CSF pulsatility consistent with ventriculomegaly. Previously, it was also believed that arterial pulsation restriction, capillary pulsation increase, and intracranial compliance decrease were the origin of hydrodynamic mechanism of chronic hydrocephalus [42]. In addition, increased pulse pressure as a feature of iNPH has also been considered as a possible mechanism involved [42, 43]. This seems to be supported by our findings that diastolic blood pressure also appears to be significantly associated with iNPH (Fig. 3). In addition to changes in arterial pressure, increased intracranial venous pressure can impede CSF absorption through the arachnoid villi and alter intracranial compliance [44]. However, prospective studies on hypertension and iNPH are still lacking. This article provides evidence for a causal effect of hypertension and iNPH. If hypertension has a causal effect on iNPH, the role

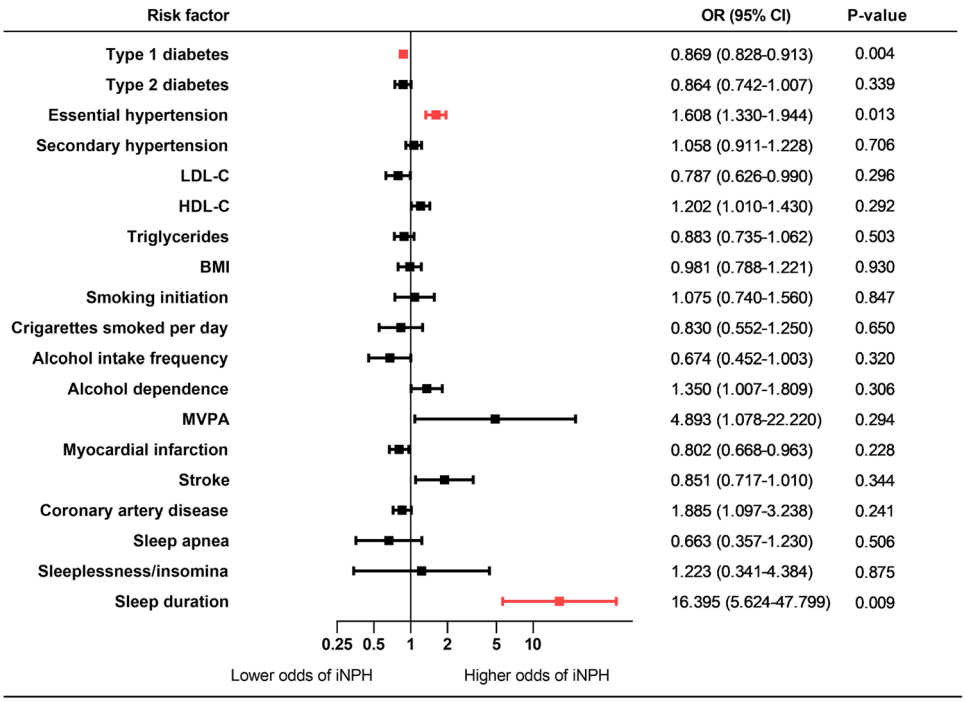

Fig. 1 The association between risk factors and idiopathic normal pressure hydrocephalus (iNPH) using the inverse-variance weighted method. Odds ratios (ORs) represent the association between iNPH and each risk factor. The units of the binary exposure factors are odds: type 1 diabetes; type 2 diabetes; essential hypertension; secondary hypertension; alcohol dependence; myocardial infraction; sleep apnea; sleeplessness/insomnia. The units of the binary exposure factors are logOR: coronary artery disease and stroke. The 1-SD increase is the unit of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, body mass index (BMI), alcohol intake frequency, and moderate to vigorous physical activity levels (MVPA). The unit of smoking initiation is ever smoked regularly compared with never smoked. The unit of cigarettes smoked per day is cigarettes per day

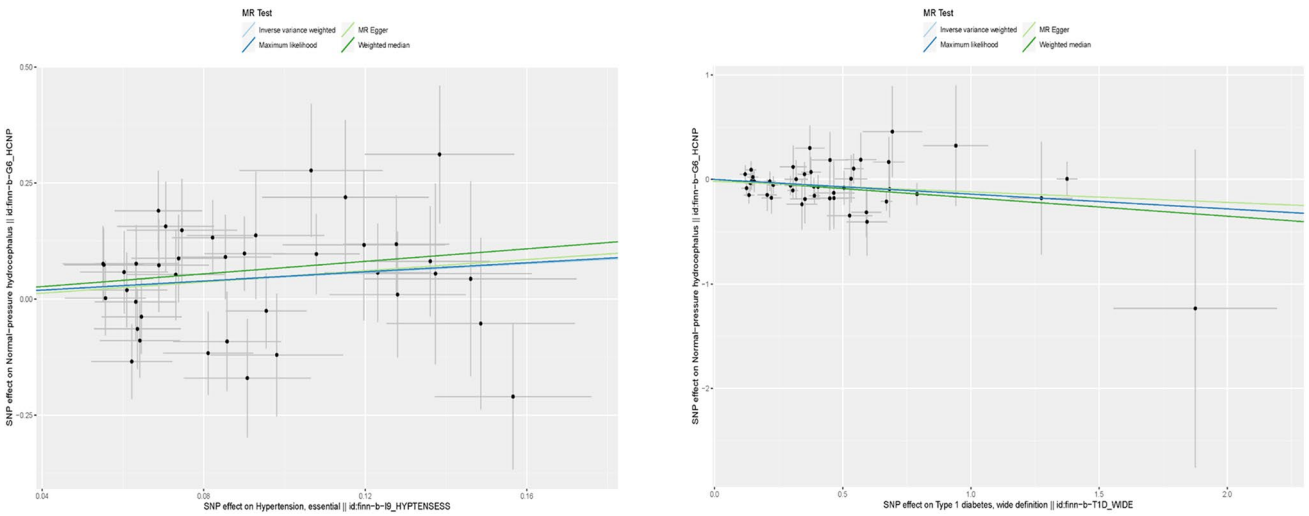

Fig. 2 The causal effects of essential hypertension and type 1 diabetes on idiopathic normal pressure hydrocephalus (iNPH) in scatter plots. On the left is essential hypertension, on the right is type 1 diabetes

of hypertension drugs in patients with iNPH is expected. In addition, of course, we also found that some iNPH patients do not have clinically diagnosed hypertension. In this regard, we believe that hypertension may be a risk factor rather than a decisive factor inducing iNPH. Because some of the iNPH patients are familial iNPH, they are mainly dominated

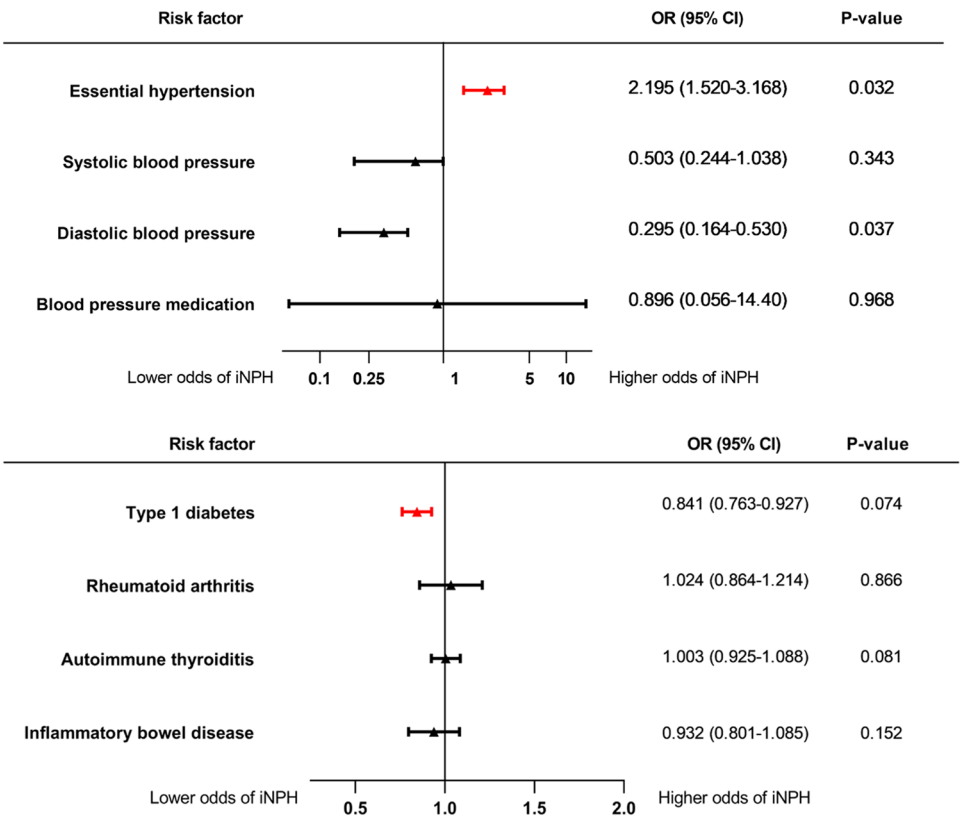

Fig. 3 The figure shows a multivariate Mendelian randomization analysis for essential hypertension and type 1 diabetes. The 1-SD increase is the unit of systolic blood pressure, diastolic blood pressure, and blood pressure medication. The odds of the binary exposure factor is the unit of rheumatoid arthritis, autoimmune thyroiditis, and inflammatory bowel disease

by genetic factors. The link between hypertension and the genetic factors of NPH is also worth considering. In addition, we also considered that the symptoms of iNPH are not specific, and it may be misdiagnosed or overlap with other neurological diseases. And some diseases may have a causal relationship with hypertension, such as vascular dementia, which may bias the results. Therefore, we collected the prevalence of related diseases for the cases of NPH in this study (supplementary table 6). And we consider this bias to be negligible. In addition, secondary hypertension and iNPH are not considered to be related in this study. This may be because secondary hypertension is a secondary diagnosis that can be corrected after the etiology is identified and treated. Therefore, it cannot continuously affect patients like essential hypertension.

Diabetes was discussed separately in this study as T1DM and T2DM. We found that genetically predicting T1DM was associated with iNPH, whereas T2DM was not. Moreover, T1DM appeared to be a causal protective factor for iNPH in this study. We have two explanations for this. First, we concluded that T1DM and iNPH were statistically associated due to survival bias. In the previous studies, most of the studies were on T2DM and iNPH, and there were almost no studies on T1DM and iNPH. The reason is because of the large difference in the age of onset of T1DM and iNPH. The prevalence of iNPH is mainly in the elderly, and in the elderly population, the prevalence of T2DM is remarkably higher than that of T1DM [45]. In the population sample data of our study, the age of onset of T1DM was much younger than that of iNPH (mean age at the first event: 69.76 years old) (supplementary Fig. 1). Compared with the age of iNPH patients, the life expectancy of patients with T1DM is poorer, and they have a high exposure liability to T1DM. In other words, when we select those SNPs that are significantly related to T1DM, the population with higher expression of these SNPs means that they are more susceptible to T1DM. And having T1DM may shorten lifespan, which makes it harder for these populations to reach the age of onset of iNPH. For the protective effect of T1DM, we think that it may be because it is difficult for people with T1DM to reach the age of onset of iNPH. And the causal relationship between T1DM and iNPH dropped dramatically after accounting for other confounding factors. Thus, T1DM presents a pseudo-protective factor effect. Second, we have another conjecture. T1DM is an autoimmune disease, whether there is an association between genetic factors between it and iNPH to present such a result. However, none of the currently known mutated genes that may cause iNPH are associated with susceptibility genes for T1DM. For T2DM, the results of this study showed no causal relationship between it and iNPH. The glymphatic system seems to be considered as the pathway through which T2DM affects iNPH. T2DM has been shown in mice to impair the function of the glymphatic system in the hippocampus and hypothalamus [46],

and impairment of the glymphatic system has also been observed in patients with iNPH [21]. However, impairment of the glymphatic system do not appear to be disease specific in iNPH. The impairment can also be seen in aging and Alzheimer's disease states [47, 48]. The performance of impairment of glymphatic system function is considered to be learning and memory impairment, the reason is that the deposition of amyloid-β and tau protein may be closely related [49, 50]. However, the most prominent symptoms in iNPH patients are abnormal gait and ventriculomegaly rather than cognitive impairment, which are the symptoms mainly improved by shunt therapy. In addition, impairment of glymphatic function may not necessarily be the cause of memory impairment. Therefore, we believe that the relationship between type 2 diabetes, the impairment of glymphatic system, and iNPH may be more manifested in the dementia symptoms of iNPH, rather than directly affecting the pathogenesis of iNPH. Although observational studies have found a high prevalence of type 2 diabetes in iNPH patients, this may be because the elderly with iNPH are already at higher risk of type 2 diabetes. Aging is a non-negligible factor in iNPH. In addition, a previous study suggested that diabetes in iNPH patients may be caused by ventriculomegaly and pituitary dysfunction [11]. In this study, we prefer to believe that T1DM does not play a role in the occurrence of iNPH. However, the risk of diabetes in iNPH patients deserves further study.

Regarding the relationship between sleep and iNPH, we included three exposure factors of sleep apnea, insomnia, and sleep duration in this study. Among these three factors, we only found increased sleep duration as a causal risk factor for iNPH confirmed by the IVW method. Although sleep-disordered breathing was found to be more common in iNPH patients in previous studies, comparisons with age-matched older adults were lacking. The sleep-disordered breathing was considered a risk factor for iNPH more because of the observed impairment of glymphatic function [21], which is responsible for clearing the brain of metabolic waste during sleep. However, the impaired glymphatic function is not only seen in patients with iNPH but also in patients with Alzheimer's disease [48]. A previous MR study on obstructive sleep apnea and Alzheimer's disease also showed no apparent causal relationship between obstructive sleep apnea and Alzheimer's disease [51]. Therefore, we think that there is no causal relationship between sleep apnea and iNPH. And impaired glymphatic function may affect the sleep of iNPH patients. A previous study showed that accumulation of β-amyloid in the brain worsens the sleep–wake cycle [52]. Moreover, Alzheimer's disease had a causal effect on sleep patterns in one MR study [53]. Therefore, we think it may be that patients with iNPH have a higher risk of sleep apnea, both of which are affected by the impaired glymphatic function. Interestingly, however, sleep duration was shown to be associated with iNPH in our study. And in a previous MR study on sleep duration and cognition, sleep duration was considered to have a causal relationship with cognition [54]. Moreover, increased sleep duration was found to be associated with increased perivascular space, suggesting that increased sleep duration may be related to the function of the glymphatic system [55, 56]. However, the causal relationship between sleep duration and impairment of glymphatic system function is unclear. The increase of perivascular spaces may result from increased sleep duration and poor sleep quality, while it is also possible that increased sleep duration is a compensatory mechanism for impaired glymphatic system function. However, the sensitivity analysis of this study did not further support the relationship between increased sleep duration and iNPH, which may be related to the violation of the assumptions caused by confounding factors. Therefore, the causal relationship between increased sleep duration and iNPH may require further study to explore.

This study also has limitations. There are few GWAS data on the outcome of this study. The reason is that there are few current GWAS for NPH available. Moreover, we could not exclude the presence of secondary NPH in the NPH cases studied in the present study. Secondary NPH and idiopathic NPH may differ in the application of conclusions. Therefore, this result may be biased when we emphasize iNPH. The main causes of secondary NPH are subarachnoid hemorrhage, traumatic brain injury, and brain malignancy [57]. We collect the prevalence of related diseases in the cases of NPH in supplementary table 6. In addition, causal relationships explained using genetic instruments have limited precision. We could not avoid bias from all confounding factors. And people need to live to a certain age to be included, which can lead to survivor bias. This bias may have affected the results.

In conclusion, we found hypertension to be a causal risk factor for iNPH in this MR study. This suggests that hypertension may be involved in the pathophysiological mechanism of iNPH. How vascular mechanisms play a role in the pathophysiology of iNPH is worth discussing in future studies. For other VRFs, there was no evidence of a causal relationship between them and iNPH.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-11604-6.

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Author contributions ZD and HW contributed to the study conception and design. Material preparation and data collection were performed by KH, YC, YL, and YR. The analysis was performed by ZD. The initial manuscript was drafted by ZD and HW. All authors read and approved the final manuscript.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval This MR study did not require ethical approval based on the summary data level. All the summary data were obtained from publicly available data sources. No personal information was involved in this study.

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