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Bidirectional Mendelian Randomization Analysis of the Association between Telomere Length and the Risk of Vascular Dementia and Idiopathic Normal Pressure Hydrocephalus

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Abstract: Background: vascular dementia (VaD) and Idiopathic normal pressure hydrocephalus (INPH) are uncommon age-related conditions. Accumulating evidence indicates that progressive telomere shortening contributes to biological aging and is implicated in the pathogenesis of various age-related disorders. Despite growing interest in telomere biology, whether genetically predicted telomere length (TL) causally affects susceptibility to INPH or VaD remains uncertain. This study seeks to elucidate the underlying causality of TL with the risk of INPH and VaD by employing Mendelian randomization (MR) analysis.

Methods: A bidirectional MR was conducted to evaluate the potential causality of TL with the risk of INPH and VaD. Five MR methods were employed for result analysis, with the inverse variance weighted (IVW) method as the main technique. Additionally, various sensitivity analyses were performed to assess the presence of heterogeneity and pleiotropy in the study findings.

Results: In the forward MR analysis, both the IVW analyses suggested an underlying causality, indicating that longer TL may correlate with a reduced incidence of INPH (IVW: OR = 0.44, 95% CI: 0.25–0.77, p = 0.004) and VaD (IVW: OR = 0.31, 95% CI: 0.12–0.82, p = 0.018). No heterogeneity or horizontal pleiotropy was observed. However, reverse MR analysis failed to uncover an underlying causality between INPH, VaD, and TL.

Conclusion: There could be a potential correlation of longer TL with the decreased risk of INPH and VaD within the European population. This research offers fresh perspectives on the association of TL with the risk of INPH and VaD.

Keywords: telomere length; vascular dementia; Mendelian randomization; INPH; GWAS

1. Introduction

Idiopathic normal pressure hydrocephalus (INPH) is featured with unexplained ventricular enlargement, presenting with a combination of bladder dysfunction, gait disorder, and cognitive decline as its primary clinical manifestations, all while exhibiting normal pressure measured by lumbar puncture [1]. Typically observed in individuals aged 60 and above, INPH often has an insidious onset with gradual symptom progression [2]. Shunt surgery can effectively reverse symptoms and improve the condition [3]. The causes and risk factors of INPH remain unknown, though they may be associated with hypertension, diabetes, sleep disorders, neurodegeneration, and cerebrovascular disease [4–7]. The pathogenesis of INPH primarily revolves around abnormal cerebrospinal fluid dynamics, reduced lymphoid clearance rate, and impairment of the blood-brain barrier [8,9].

Vascular dementia (VaD) is a dementia syndrome primarily

caused by cerebrovascular lesions. It is distinguished by amyloid angiopathy, demyelination, white matter lesions, and cerebral infarction [10,11]. VaD stands as the second most prevalent etiology of dementia, with a prevalence rate ranging from 1.26% to 2.40% among individuals over 60 years old. It constitutes approximately 12% to 20% of all dementia cases [12]. VaD frequently coexists with other age-related conditions [13]. Hypertension, along with diabetes, atherosclerosis, hyperhomocysteinemia, coronary artery disease, dyslipidemia, and smoking, represents the primary risk factors for VaD [14].

Telomeres consist of short sequences made up of repeating units of deoxyribonucleic acid, situated at the tips of linear chromosomes in eukaryocytes. With each division of somatic cells, telomeres gradually erode [15]. The maintenance of telomere length and the integrity of telomere-binding proteins are fundamental to telomere protection and play a central role in safeguarding chromosomal stability [16]. Telomere length (TL) is increasingly recognized as a key biomarker reflecting biological aging processes [17,18]. Telomere shortening is linked to a higher risk of mortality [19,20], morbidity from age-related conditions [21], the progression of dementia [22], and overall neurodegenerative conditions [23–27]. A previous study observed no significant variation in TL among patients with Alzheimer's disease (AD), mixed dementia, or VaD relative to healthy controls, highlighting inconsistency in the existing evidence [28]. Nevertheless, the association of TL with the risk of INPH and VaD remains uncertain.

Mendelian randomization (MR) utilizes genetic instrumental variables (IVs) as proxies for modifiable exposures to determine their causal influence on downstream outcomes [29] It establishes a direct connection between exposure and genetic variation, utilizing the random segregation of alleles akin to the randomization in randomized controlled trials. Hence, theoretically, biases stemming from confounding factors between exposure and outcomes can be mitigated. The objective of this study was to assess whether TL exerts a causal effect on the risk of INPH and VaD through MR analysis.

2. Methods

2.1. Study Design

In this research, we conducted a bidirectional MR technique to meticulously investigate the causality of TL on INPH and VaD. For this MR study evaluation, we proceeded based on the next assumptions: (1) the IVs demonstrate strong associations with the exposures; (2) the IVs are required to be free from associations with potential confounding factors; (3) the IVs does not directly influence outcome except by exposure. The diagram of our study design is pictured in Figure 1.

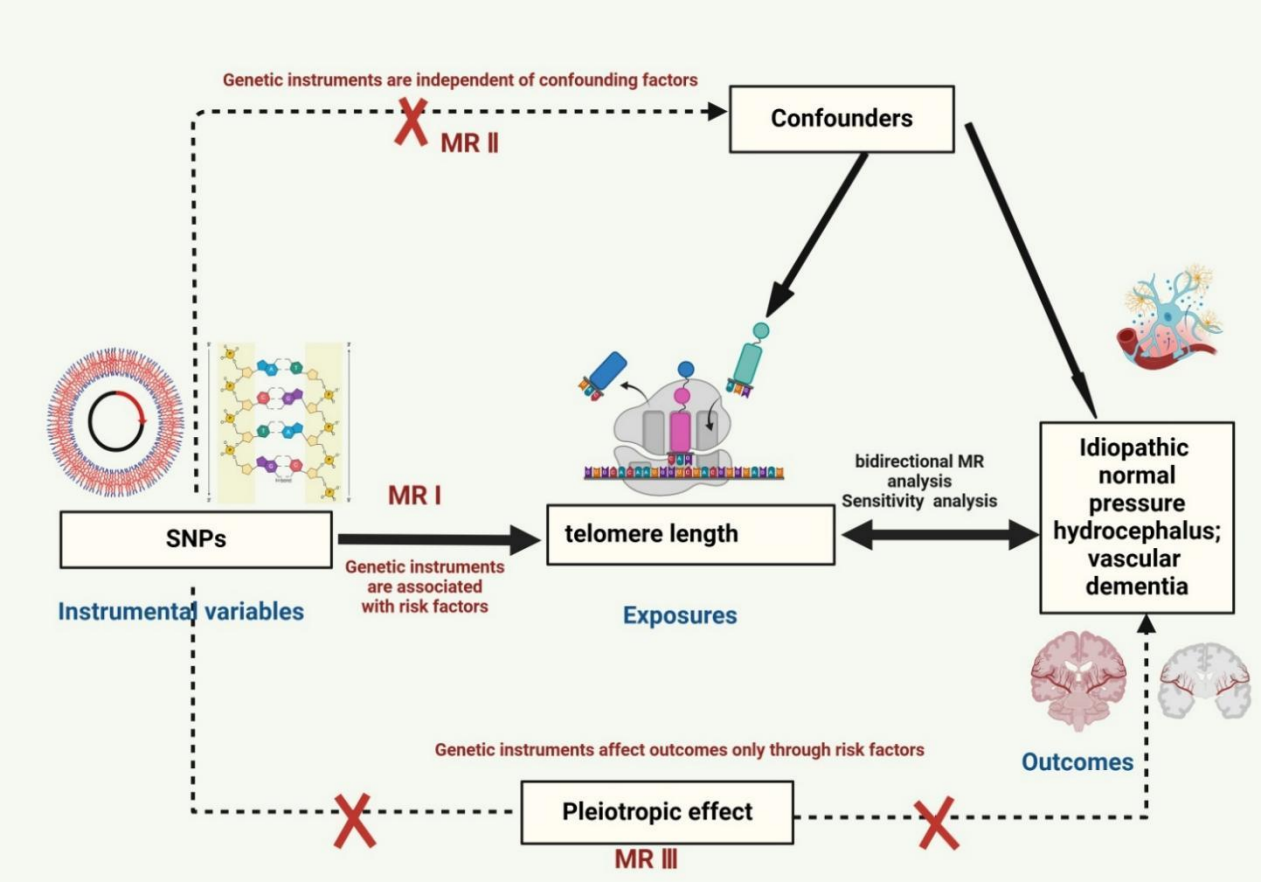

Figure 1. Schematic illustration of the study design. SNPs: single nucleotide polymorphisms. Created with BioRender.com.

2.2. Data Source

Genetic variant data for TL were derived from a large-scale GWAS meta-analysis including 472,174 participants of European descent (ieu-b-4879) [30]. For this study, the GWAS data on INPH comprised 322 INPH cases and 218,043 controls, all of European ancestry. Summary data regarding VaD were collected from the GWAS conducted by the FinnGen biobank, encompassing 98 VaD cases and 211,300 controls of European descent (Table 1). As publicly accessible GWAS summary data were used, this study did not require further ethical approval.

Table 1. Characteristics of genome-wide association study (GWAS) data.

Type	Traits	Source	GWAS ID	Ancestry	Sample size
Exposure	TL	UK Biobank	ieu-b-4879	European	472,174
Outcome	INPH	FinnGen biobank	finn-b-G6_HCNP	European	322 cases/218,043 controls
Outcome	VaD	FinnGen biobank	finn-b-VD_MX	European	98 cases/211,300 controls

TL, telomere length; INPH, Idiopathic normal pressure hydrocephalus; VaD, vascular dementia.

2.3. IVs Selection

IVs linked to TL, INPH, and VaD in GWAS datasets were chosen based on a rigorous set of inclusion criteria. Firstly, the selected SNPs needed to satisfy the requirement that their genome-wide significance association with each factor was below 5 × 10–8. Subsequently, we clustered the chosen SNPs to identify those with a linkage disequilibrium threshold ($r2 > 0.01$) and located within a distance of 10,000 kb. Thereafter, we isolated the SNPs linked to each exposure of interest within the outcome dataset to ensure alignment of genetic instruments. We then harmonized the effect alleles between the exposure and outcome datasets to ensure consistent allele orientation. Palindromic SNPs that could not be reliably aligned were excluded. Instrumental variable strength was evaluated using the F statistic, and SNPs with an F value < 10 were discarded to avoid weak instrument bias [31] (Supplement Table 1). For a comprehensive overview of all IVs utilized in this study, please refer to Supplement Table 2.

Table 2. MR sensitivity analysis results.

Exposures	Outcomes	Analytical method	Q	Q_pval	egger_intercept_P	MR-PRESSO_P
TL	INPH	MR Egger	224.40	0.134		
		IVW	226.10	0.127	0.218	0.127
TL	VaD	MR Egger	198.70	0.553		
		IVW	200.07	0.545	0.243	0.546

TL, telomere length; INPH, Idiopathic normal pressure hydrocephalus; VaD, vascular dementia.

2.4. Statistical Analysis

For the primary analyses, we employed the inverse-variance weighted (IVW) framework, which provides the most efficient estimates under the assumption that all instruments are valid. Additionally, we employed weighted model, weighted median, the simple model, and the MR-Egger as complementary techniques. To assess the satisfaction of the initial assumption, we computed the F-statistic for all SNPs utilizing the provided formula. An F statistic greater than 10 indicates a small bias due to weak instrument effect. The robustness of the causal estimates was examined through a series of sensitivity analyses, including leave-one-out analysis, heterogeneity and pleiotropy assessments, and the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test [32]. Heterogeneity was evaluated employing Cochran's Q statistic, where *p*-values exceeding 0.05 suggest no heterogeneity [33]. Directional pleiotropy was examined through MR-Egger intercept analysis, with a *p*-value above 0.05 indicating no pleiotropy [34]. The MR-PRESSO approach was adopted to test and eliminate outliers that could potentially influence the findings [32]. Additionally, a leave-one-out analysis was performed by sequentially removing each SNP to evaluate the stability of the findings [35]. Consistency in the remaining results, without significant alterations, indicates a

stable and reliable causal relationship. Eventually, we utilized PhenoScanner (http://www.phenoscanner.medsci.cam.ac.uk/) to investigate all SNPs involved in the principal outcome analysis, aiming to identify underlying confounding factors that may violate the second assumption [36].

The statistical analyses were conducted utilizing R-4.3.2, utilizing a range of R packages including MendelianRandomization, MR-PRESSO, and TwoSampleMR. In cases where the exposure variable was binary, we employed the odds of exposure to quantify its causal impact on the outcome. Associations were deemed statistically significant when the *p*-value was less than 0.05.

3. Results

3.1. The results of forward MR analysis

We performed an extensive analysis utilizing data from FinnGen on INPH and VaD to evaluate the causality between TL and the onset of INPH and VaD (Figure 2). The IVW estimate revealed that higher TL was related to a reduced risk of developing INPH (IVW: OR = 0.44, 95% CI: 0.25–0.77, p = 0.004), as well as VaD (IVW: OR = 0.31, 95% CI: 0.12–0.82, p = 0.018). To further explore the correlation of TL with INPH and VaD, we performed sensitivity analysis, which indicated no heterogeneity and pleiotropy (Figures 3,4).

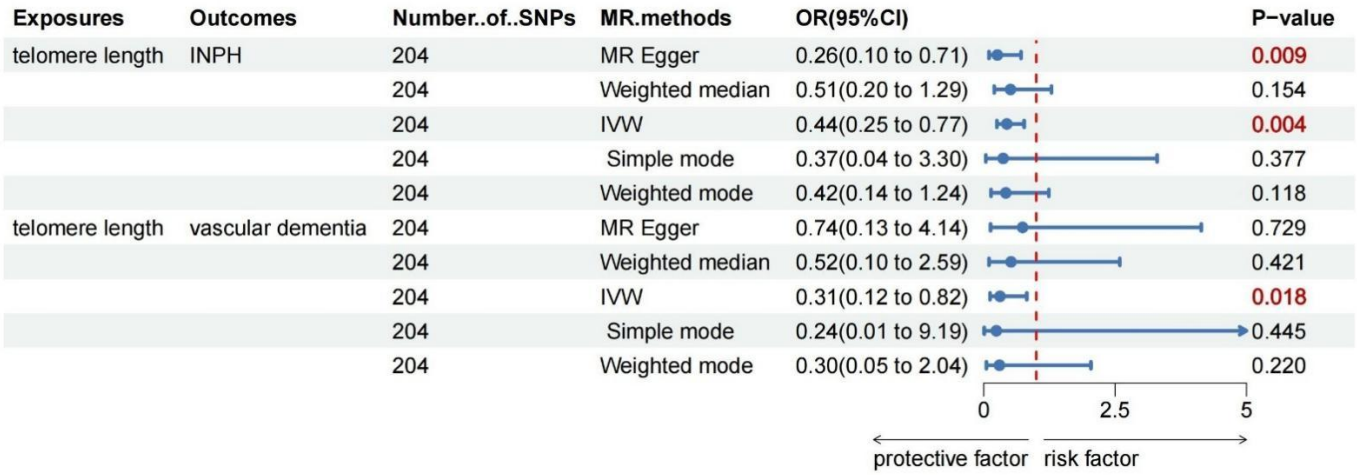

Figure 2. Forest plots showing the causal estimates of TL on INPH and VaD with IVW. INPH, Idiopathic normal pressure hydrocephalus; VaD, vascular dementia; OR, odds ratio; IVW, inverse-variance weighted; CI, confidence interval.

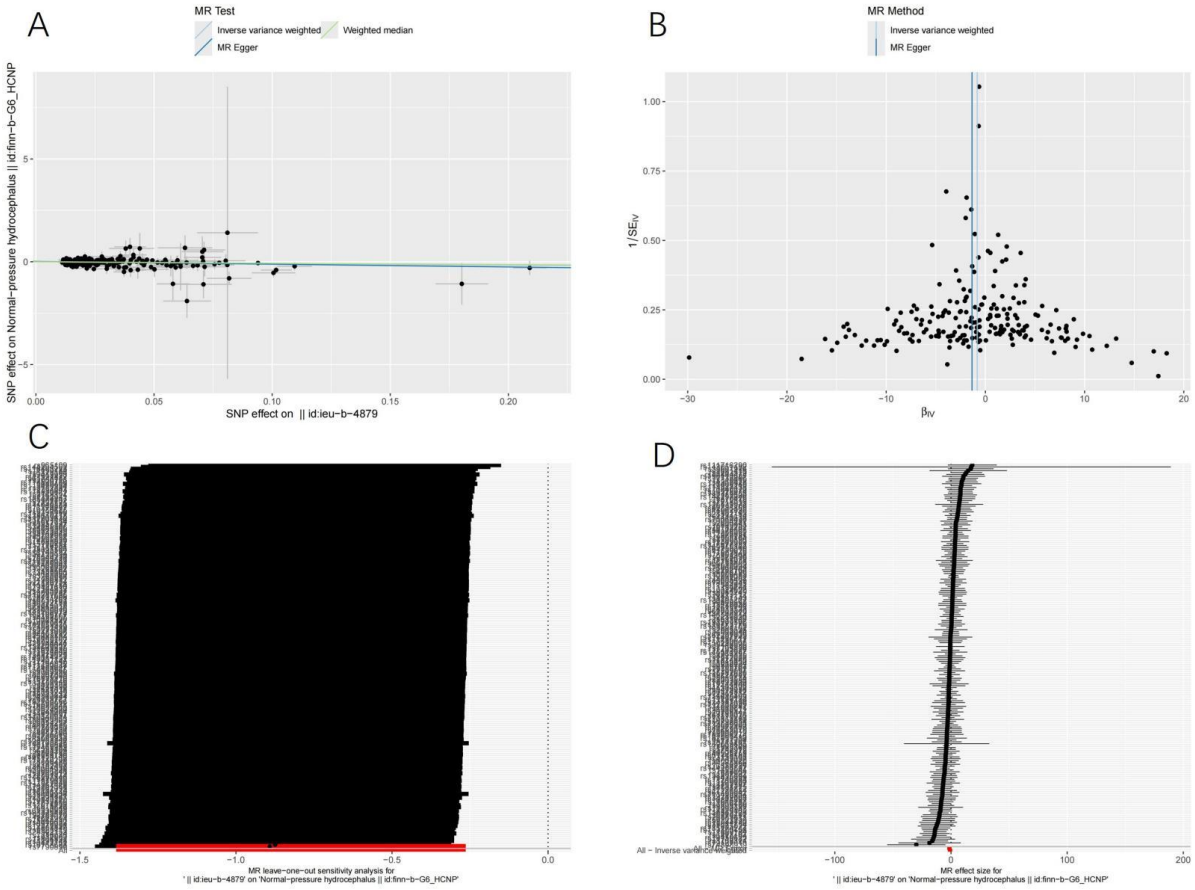

Figure 3. Scatter (A), Funnel (B), leave-one-out (C), and forest (D) plot illustrating the distribution of individual ratio estimates of TL with INPH as the outcome.

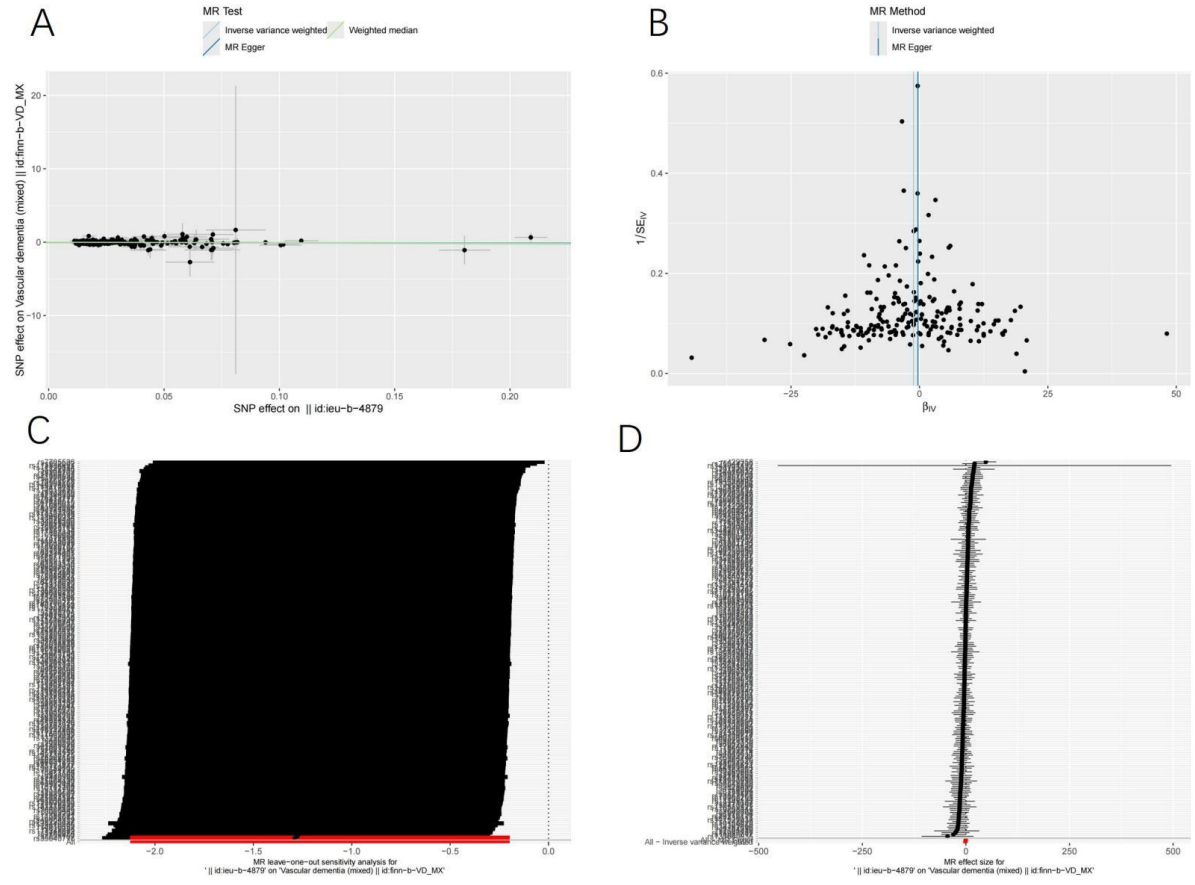

Figure 4. Scatter (A), Funnel (B), leave-one-out (C), and forest (D) plot illustrating the distribution of individual ratio estimates of TL with VaD as the outcome.

3.2. The results of reverse MR analysis

The reverse MR analysis suggests no causality between INPH (IVW: OR = 1.000, 95% CI: 0.997–1.003, $p = 0.912$) and TL. Similarly, the results of the reverse MR analysis indicate a lack of adequate evidence to support a causality between VaD and TL. This assertion is reinforced by the IVW approach (IVW: OR = 1.003, 95% CI: 0.998–1.008, $p = 0.249$).

4. Discussion

INPH and VaD represent significant global challenges, and our study pioneers the use of MR to explore the correlation between TL and both conditions. Our findings uncover a substantial causal connection between TL and INPH as well as VaD, suggesting that individuals with shorter telomeres face an elevated risk of developing these conditions. Nevertheless, the results from the reverse MR analysis suggest that there is no substantial causality of INPH and VaD with TL.

Dementia primarily manifests as cognitive function impairment, resulting in a notable decline in daily functioning, social engagement, and work capacity for affected individuals. INPH stands out as the foremost type of reversible dementia, while VaD ranks as the second most common form after AD. Typically, these conditions manifest in individuals aged 60 and above, and with the aging population, the incidence of INPH and VaD is on the rise. Consequently, pinpointing specific biomarkers associated with INPH and VaD becomes imperative for accurate diagnosis and effective prevention strategies against these conditions.

While there's a lack of existing literature exploring the correlation between INPH and TL, it's commonly acknowledged that advanced age poses a risk factor for INPH. Moreover, the confirmed causal link between TL and neurodegeneration adds depth to this understanding. Notably, INPH exhibits some overlapping pathological features with neurodegenerative disorders like AD [37]. Key pathological features of INPH include the buildup of cerebral metabolic waste and amyloid-β (Aβ) plaques, accompanied by aberrant localization of AQP4 and perivascular reactive astrogliosis [38,39]. Given that glial cells—most notably microglia—represent the only adult CNS cell population with appreciable mitotic potential, they are inherently prone to telomere attrition [40]. Research indicates that in AD patients, telomere shortening may induce aging of microglia, consequently exacerbating Aβ accumulation [41]. Additionally, TL plays a pivotal role in brain structure and neurodevelopment [42]. Studies indicate that reactivation of telomerase can reverse brain tissue degeneration in elderly telomerase-deficient mice [43]. Additionally, TL has also been linked to cardiovascular disease risk, with vascular risk factors identified as significant contributors to INPH [44,45]. These factors may be related to increased cognitive decline, tau pathology, and amyloid burden in patient with INPH [46,47]. Hence, we hypothesize that telomere shortening could elevate the risk of INPH through multiple pathways, including heightened vascular risk, increased aggregation of microglia, exacerbated accumulation of Aβ, and aggravated brain tissue degeneration.

Considerable research has examined the relationship between telomere length (TL) and dementia, particularly focusing on vascular dementia (VaD), which represents the second most prevalent dementia subtype [48–50]. Nonetheless, the precise causal relationship between VaD and TL remains uncertain. Pathological features of VaD encompass lacunar infarction, cortical and subcortical microinfarction, arteriolar sclerosis, diffuse white matter alterations, brain atrophy, and focal brain degeneration [51]. Prior research has established an association between TL and lacunar infarction, brain atrophy, diminished white matter, and premature vascular brain injury [42,52–55]. Telomere attrition has been implicated in heightened vulnerability to multiple cardiovascular and cerebrovascular conditions and is concurrently associated with key metabolic and vascular risk factors, including hypertension and diabetes [56–59]. Furthermore, telomere shortening may contribute to blood-brain barrier disruption and instigate neuroinflammatory responses [60]. This cascade of events could potentially underlie the mechanism driving the onset and progression of VaD mediated by TL.

However, we do recognize some limitations in our research. Firstly, the samples of INPH and VaD cases might be inadequate, which could introduce bias into the research. Secondly, since the GWAS data utilized in this study are derived from European populations, it warrants further investigation to ascertain whether the findings can be extrapolated to other ethnicities. In addition, we recognize the distinct genetic architecture of the Finnish population and acknowledge that variations in ancestral background may alter LD structure, thereby influencing the robustness of our Mendelian randomization results. Lastly, despite employing multiple sensitivity analysis techniques to bolster the strength of our results, we acknowledge that these factors may still exert some influence on the findings.

Building on these findings, future research should not only elucidate the biological mechanisms linking telomere shortening to INPH and VaD but also leverage artificial intelligence (AI) to enhance risk prediction and early diagnosis. State-of-the-art AI methodologies, especially deep learning and

machine learning, can integrate large-scale genomic, neuroimaging, and clinical datasets to capture complex, nonlinear associations that may be missed by conventional statistical methods. Incorporating TL with multimodal biomarkers, including MRI-derived features, cerebrospinal fluid proteins, and vascular imaging data, may enable AI-driven models to achieve more refined disease stratification and individualized risk prediction. Such integrative frameworks have the potential to accelerate the identification of high-risk populations, inform preventive strategies, and optimize therapeutic decision-making for INPH and VaD.

5. Conclusion

To sum up, our research indicates an underlying inverse correlation of TL with the risk of INPH and VaD through bidirectional MR analysis. TL could serve as a particular biomarker for both INPH and VaD, holding significant clinical implications for their diagnosis and prevention.

Supplementary Materials: Supplement Table 1: F-Value; Supplement Table 2: Instrument variables.

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Statement of Ethics: Ethical approval and consent are not required for this study in accordance with local or national guidelines.

Data Availability Statement: We have annotated the article with the source of all original data, please contact the original authors for access if needed. The results of this study can be obtained by contacting the corresponding author.

Conflicts of Interest: The authors declare that they have no competing interests.

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