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Causal Effects Between Blood Pressure Variability and Alzheimer's Disease: A Two-Sample Mendelian Randomization Study

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ABSTRACT

Alzheimer's disease (AD), an escalating global public health concern, demonstrates complex pathogenesis involving both genetic predisposition and vascular components. Blood pressure variability (BPV) has been implicated in neurodegenerative diseases, but its causal relationship with AD remains unclear. This study aims to explore the causal relationship between BPV and AD by applying Mendelian randomization (MR) to genome-wide association study (GWAS) summary data. Genetic instruments were selected from BPV GWAS based on UK Biobank data, ensuring relevance and significance($p < 5 \times 10^{-6}$). Genetic estimates on exposure were obtained from three databases: The The International Genomic of Alzheimer's Project (IGAP); Maternal family history of AD from UK Biobank (MFH-UKBB), and Paternal family history of AD from UK Biobank (PFH-UKBB). Proxy SNPs were manually selected if SNPs were not available in the exposure GWAS. Data harmonization was performed to ensure consistency in effect and reference alleles. Three MR statistical methods were employed to assess causal effects, including inverse variance weighting (IVW) with random or fixed effect, MR-Egger regression, and the Weighted Median Method. Sensitivity analyses to evaluate robustness were also employed. Six SNPs associated with systolic BPV and six SNPs associated with diastolic BPV were included. Significant causal effects of SBPV on AD were found on the PFH-UKBB dataset in all four methods. The odds ratios for AD per 10-unit increment in SBPV were 1.028, 1.015, and 1.015 for MR-Egger, IVW-MR, and weighted median, respectively. In contrast, only IVW methods found significant results for DBPV in the MFH-UKBB dataset. SBPV is a possible causal risk factor for AD, while the evidence for DBPV needs further study. BPV control should be an important treatment target in preventing dementia.

1 | Introduction

Alzheimer's disease (AD), the most prevalent form of dementia, poses a significant global health challenge for aging populations. It impairs daily functioning by affecting memory, attention, perception and communication, placing a heavy burden on families, communities, and healthcare systems [1–3]. By 2050, the number of individuals diagnosed with Alzheimer's is projected to reach 90 million as the population ages [1]. Unfortunately, current pharmacological therapies offer limited effectiveness in managing

symptoms [4, 5], and the efficacy of non-pharmacological interventions remains uncertain. Therefore, identifying modifiable risk factors for AD is essential for prevention.

Hypertension is a well-established risk factor for AD, with research on the association between blood pressure and cognitive decline dating back over 20 years [6]. Recently, attention has shifted to blood pressure variability (BPV) as an independent risk factor for Alzheimer's. The surge of studies in this area has highlighted BPV's potential role, with evidence from both cross-sectional and cohort studies supporting its association with cognitive impairment [7, 8]. Some animal studies suggested that BPV might contribute more significantly to end-organ damage than static blood pressure levels [9]. A meta-analysis of 13 longitudinal studies indicated a relationship between visit-to-visit BPV and both AD and mild cognitive impairment [10]. Different types of BPV—such as 24-h, day-to-day, and visit-to-visit variability—might have unique mechanisms that influence the development of AD [11, 12].

While several studies explored the link between BPV and AD, many were observational and had limitations in establishing causation due to confounding factors. Mendelian randomization (MR) is an emerging statistical method that can help investigate the causal relationships between risk factors and diseases. Since SNPs are naturally assigned to different germ cells during meiosis, like a randomized control study, it avoids the influence of confounders and reverse causation [13]. However, applying MR to BPV is complicated by its reliance on longitudinal assessments rather than single-time measurements. Consequently, genome-wide association studies (GWAS) investigating BPV's genetic architecture remain scarce. To date, few GWAS have explored the genetic determinants of BPV. Early GWAS with limited sample sizes (e.g., $n = 3802$) identified NLGN1 as a potential candidate gene [14], while a more recent UK Biobank study ($n = 9370$) reported additional loci associated with visit-to-visit BPV [15]. Nevertheless, the genetic underpinnings of long-term BPV and its causal relationship with AD pathogenesis remain unresolved.

This study aims to investigate the causal impact of BPV on AD using a two-sample MR analysis. By utilizing summary-level GWAS data, we seek to deepen the understanding of the role of BPV in Alzheimer's pathogenesis and further explore potential therapeutic strategies.

2 | Methods

2.1 | Study Design

This two-sample MR analysis utilized summary-level GWAS data to explore the causal relationship between BPV and AD. This analysis was structured as illustrated in Figure 1.

2.2 | Data Source

Genetic instrument variables, which indeed could be referred to as SNPs, for exposure were selected from a visit-to-visit BPV-related GWAS published in 2022 based on UK Biobank data [15], ensuring that the selected SNPs were contemporary and relevant. Genetic estimates for the outcome were obtained from three databases: The International Genomic of Alzheimer's Project (IGAP) [16]; GWAS, which provided summary data utilizing AD diagnosis as a phenotype; Maternal Family History of AD in the UK Biobank (MFH-UKBB); and Paternal Family History of AD in the UK Biobank (PFH-UKBB). Detailed characteristics of these datasets could be found in Table 1. The IGAP used clinically diagnosed AD, Maternal Family History, and Paternal Family History of AD in the UK Biobank, which were extracted from the questionnaire.

2.3 | Assumptions of MR

The primary assumptions for utilizing an instrumental variable in this analysis are: (1) Association with BPV: The variant must be associated with BPV; (2) no confounder association: the variant should not be linked to any confounders affecting both BPV and dementia; and (3) no alternative pathways: the variant must not influence dementia through pathways other than BPV. Assumptions one and two can be empirically verified through genetic association studies, assumption three requires careful consideration due to potential biases from factors such as linkage disequilibrium and horizontal pleiotropy, which may distort causal inference.

2.4 | Instrumental Variable Selection

To ensure a strong and reliable association between the SNPs and both BPV and AD, we established sufficient significance levels. Genetic instruments were selected based on SNPs achieving suggestive significance ($p < 5 \times 10^{-6}$) in the BPV GWAS. For SNPs that were not identified in the dementia GWAS, proxy SNPs were manually selected within a 5 MB range to maintain statistical power.

In the BPV GWAS, SNPs were filtered based on the following statistical criteria: missing genotype rates (<0.015), minor allele frequency (>0.01), and tests for Hardy–Weinberg equilibrium violations and linkage disequilibrium. Linkage disequilibrium was estimated for all variants within a 5 MB range of the reference SNP, with independent SNPs selected based on a linkage disequilibrium threshold of $r^2 < 0.01$.

To validate our genetic instruments variables, we applied specific exclusion criteria for SNPs: (1) confounding SNPs: to minimize confounding effects, SNPs associated with potential confounders, such as hypertension and arterial stiffness, were excluded using the PhenoScanner GWAS database [17]. (2) Dementia-associated SNPs: SNPs significantly associated with dementia across IGAP GWAS, MFH-UKBB, and PFH-UKBB were removed to avoid inflating causal estimates. (3) Palindromic SNPs: SNPs that were palindromic with an effect allele frequency between 0.4 and 0.7 were excluded to prevent ambiguity in interpretation.

Data harmonization was applied to ensure consistency in effect and reference alleles between the BPV and AD GWAS. Alleles that did not match were adjusted, and the corresponding beta estimates were modified accordingly. A list of genetic instruments is reported in Table 2. We retained six SNPs for SBPV and another six SNPs for DBPV.

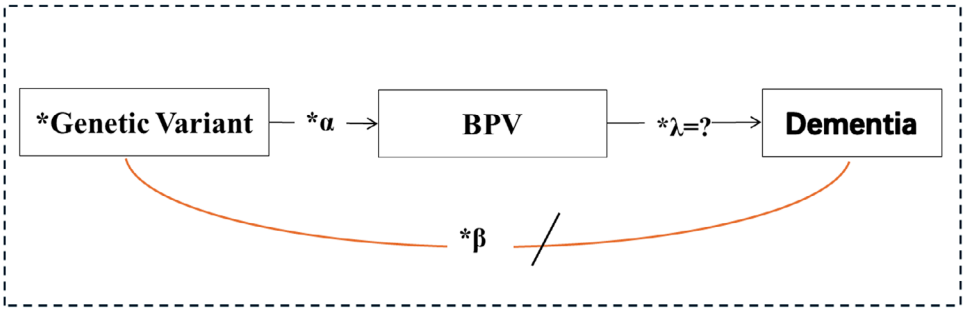

FIGURE 1 | Conceptual framework for SNP identification from genetic variants. *α: the coefficient for the regression of BPV on genetic variants. *γ: the causal effect of BPV on dementia. For a single genetic variant, $\gamma=\alpha/\beta$.

TABLE 1 | Description of four data sources of Alzheimer's disease GWAS.

GWAS databases	Year	Number of SNPs	Sample size	
			Case	Control
The International Genomic of Alzheimer's Project (IGAP)	2013	7 055 881	17 008	37 154
UK Biobank (UKB)	2018	9 851 867	55 803	767 728
Paternal family history			19 255	380 538
Maternal family history			36 548	387 190

TABLE 2 | Instrument genetic variants for BPV and dementia.

CHR	BP	SNP	Effect allele (A1)	Reference allele (A2)	EAF	Locus (gene)	Database
				Systolic BPV			
11	79391059	rs34584627	A	G	0.0944	AP003774.1	UKB+IGAP
3	11090603	rs35696236	C	G	0.1742	SLC6A1	UKB+IGA
7	47047098	rs4720569	C	T	0.3172	AC004901.1; AC004870.4; AC004870.3	UKB+IGA
7	72126227	rs569158324*	G	T	0.1426	TYW1B	UKB
11	64102948	rs574087	G	A	0.3808	CCDC88B	UKB+IGA
7	156411149	rs849074	C	C-G	0.1945	LINC01006	UKB+IGA
				Diastolic BPV			
5	177405145	rs10065231	A	T	0.1793	RP11-1252I4.2	UKB+IGA
15	24322045	rs11630824	T	C	0.0822	PWRN4	UKB+IGA
5	150250368	rs1277463	A	G	0.1096	IRGM	UKB+IGA
4	21105955	rs139184666*	A	C	0.1076	KCNIP4	NA
4	184257252	rs28408355	G	T	0.1001	snoU13	UKB+IGA
3	56246822	rs79211524*	C	T	0.0614	ERC2	NA

Note: rs569158324 is not available in the IGAP dataset, and proxy SNP (rs55891215) was found in other datasets. rs139184666 is not available on the meta dataset; proxy SNP (rs73802496) was found in other datasets. rs79211524 was not available on all four datasets, and a proxy SNP (rs34235403) was found for the meta dataset.
Abbreviation: EAF, effect allele frequency.

2.5 | Statistical Analysis

To enhance the robustness of our findings, we applied three MR statistical methods. First, inverse variance weighting (IVW) estimated the inverse variance-weighted coefficient through a weighted regression of exposure estimates on outcome estimates, with the intercept constrained to zero [18]. The underlying assumption was that all SNPs were valid instruments. Both random and fixed effects methods were employed, for the latter may yield overly precise estimates in the presence of heterogeneity [19]. Second, Mendelian Randomization Egger Regression (MR-Egger), which involved weighted linear regression without constraining the intercept to zero [20]. The intercept represented average pleiotropic effects, and a nonzero intercept indicateed the presence of directional pleiotropy. MR-Egger could provide valid estimates even with invalid instruments and served as a test for overall horizontal pleiotropy [20]. Third, the Weighted Median Method, which estimated the median of the weighted empirical distribution of individual SNP ratio estimates [21]. It offered a consistent effect estimate even when more than 50% of the instruments were invalid, accommodating broader violations of assumptions compared to MR-Egger [21].

To assess the reliability of our causal effect estimates, sensitivity analyses using various MR methods were also conducted: IVW-MR with random effects, IVW-MR with fixed effects, MR-Egger, and weighted median MR. Horizontal pleiotropy was specifically evaluated through the MR-Egger method. To ensure robustness, we excluded proxy SNPs and repeated the analyses on the remaining SNPs. Leave-one-out analysis was performed to test the stability of the results. We also conducted MR analysis using meta GWAS of IGAP and UKB.

The odds ratios (OR) were calculated to evaluate the relationship between BPV and the risk of developing AD. The effect size was expressed as OR with 95% confidence intervals (95% CI), and a significance level was set at $\alpha = 0.05$. An OR greater than 1 indicates an increased risk of AD associated with higher BPV. All data analyses were conducted using R version 4.0.2, employing relevant statistical packages tailored for MR analysis to ensure rigorous and reproducible results.

3 | Results

3.1 | Instrument Variables

Table 2 summarizes the characteristics of the selected SNPs for SBPV and DBPV. For SBPV, five independent SNPs ($r^2 < 0.01$) were chosen as instrument variables for IGAP datasets and six SNPs for the UKBB datasets. Regarding DBPV, four SNPs and one proxy SNP (rs73802496) were chosen for IGAP, PFH-UKB, and MFH-UKB. Four SNPs and one proxy SNP (rs79211524) were selected for the meta dataset. No heterogeneity was detected between those SNPs. The MR-Egger intercepts for all analyses were not significantly different from zero ($p > 0.05$), providing no indication of directional horizontal pleiotropy (Table S1).

3.2 | Associations between SBPV and AD

The effects of SBPV on AD using four datasets are shown in Table 3. Significant causal effects of SBPV on AD were found from the PFH-UKBB dataset in all four methods, with an OR (95% CI) of 1.028 (1.010, 1.046) by MR-Egger, 1.015 (1.005, 1.025) and 1.015 (1.003, 1.027) by the IVW-MR fixed and random effects models respectively, and 1.015 (1.002, 1.028) by the weighted median method, respectively, indicating that 10-unit increment in SBPV increased AD risk by 2.8%.The results were consistent among different methods, as shown in Figure 2. In contrast, the ORs (95% CI) estimated from datasets of IGAP, MFH-UKBB, and meta GWAS were 0.860 (0.556, 1.330), 0.993 (0.983, 1.004), and 0.986 (0.797, 1.220), with no significant results identified.

3.3 | Association between DBPV and AD

The results of DBPV on AD were demonstrated in Table 3. The correlation effect of the SNP between SBPV and DBPV was shown in Figure 3. A marginally significant result was found in the MFH-UKBB dataset using the IVW random effects method, with an OR (95%CI) as 0.983 (0.968, 0.997). However, this result was not significant for other methods in this dataset. Results using datasets of IGAP, PFH-UKB, and meta GWAS did not show significant effect of DBPV on AD.

3.4 | Sensitivity Analysis

Sensitivity analyses were conducted to reduce the impact of proxy SNPs on MR results by discarding them [22]. For SBPV, proxy SNPs were excluded and the other five SNPs were retained. For DBPV, four SNPs were retained from the meta GWAS dataset, which overlaped with four of the five SNPs retained in other datasets. No heterogeneity or pleiotropy was detected across all sensitivity analyses. The results for both SBPV and DBPV are presented in Table S2 and Figure S1, which were consistent with the main analysis. Significant findings were noted for SBPV in the PFH-UKBB dataset, with OR of 1.026 (1.006, 1.048), 1.014 (1.004, 1.024), 1.014 (1.001, 1.028), and 1.015 (1.002, 1.027) for MR-Egger, MR-IVW (random effect), MR-IVW (fixed effect), and MR-weighted methods, respectively. For DBPV, a significant result was only found in the MR-IVW estimation for the MFH-UKBB dataset, with OR of 0.980 (0.963, 0.999) for random effects and 0.980 (0.963, 0.997) for fixed effects. The results for the meta-GWAS of IGAP and UKB were similar to the results of MFH-UKB and were presented in Table S3. The results of Leave-one-out analysis were generally consistent with the main analysis, except for rs35696236. When excluding rs35696236, the result became nonsignificant (Figure S2).

4 | Discussion

The analysis identified significant associations between independent SNPs and both systolic and diastolic BPV. The findings indicated that SBPV may have a significant impact on the risk of developing AD, whereas the influence of DBPV appears to be less clear.

Significant causal effects of SBPV on AD were observed, particularly in the PFH-UKBB dataset, across various methods (MR-Egger, weighted median, IVW-MR). This result indicated that higher SBPV increased the risk of developing AD. The

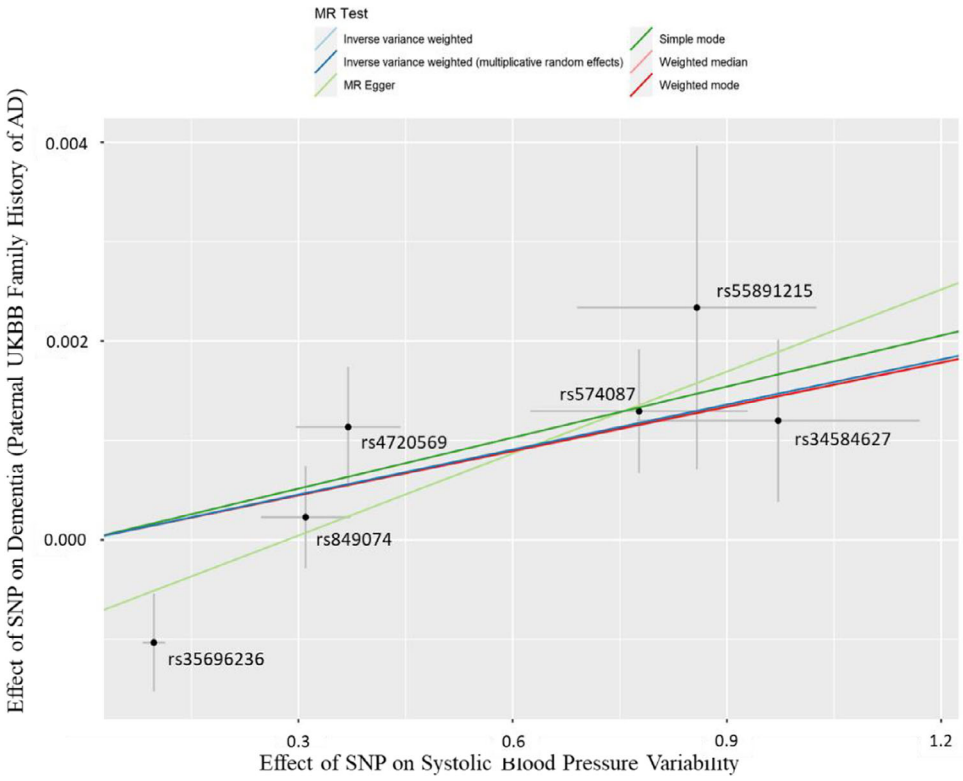

FIGURE 2 | MR analysis of systolic blood pressure variability and Alzheimer's dementia. The dots stand for different SNPs. The slope of the line means the effect of SBPV (per unit increase) on dementia risk.

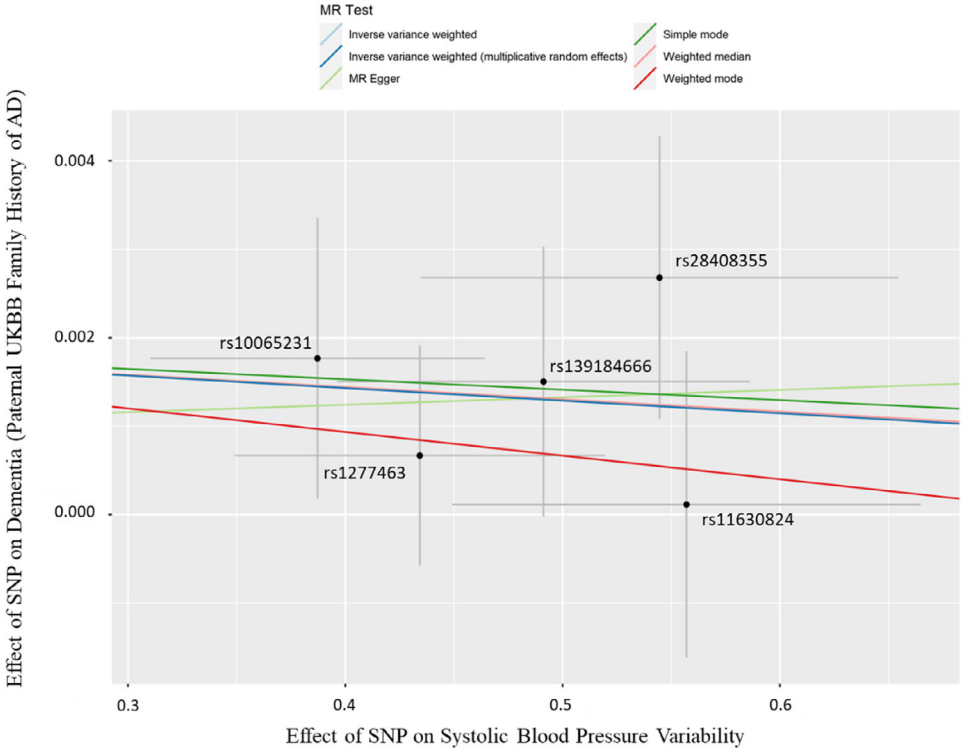

FIGURE 3 | MR analysis of diastolic blood pressure variability and Alzheimer's dementia. The dots stand for different SNPs. The slope of the line means the effect of DBPV (per unit increase) on dementia risk.

TABLE 3 | Summary of the MR analysis of blood pressure variability and dementia.

Databases	IGAP OR (95% CI)	UKB Paternal family history OR (95% CI)	UKB Maternal family history OR (95% CI)
Systolic BPV	(No. of SNP = 5)	(No. of SNP = 6)	
MR Egger	0.615 (0.302, 1.252)	**1.028 (1.010, 1.046)**	0.998 (0.977, 1.020)
IVW (fixed effects)	0.860 (0.615, 1.203)	**1.015 (1.005, 1.025)**	0.993 (0.981, 1.006)
IVW (random effects)	0.860 (0.556, 1.330)	**1.015 (1.003, 1.027)**	0.993 (0.983, 1.004)
Weighted median	0.699 (0.470, 1.041)	**1.015 (1.002, 1.028)**	0.997 (0.981, 1.013)
Diastolic BPV	(No. of SNP = 5)	(No. of SNP = 5)	
MR Egger	0.155 (0.003, 9.051)	1.004 (0.902, 1.118)	0.954 (0.833, 1.094)
IVW (fixed effects)	1.093 (0.645, 1.852)	0.993 (0.979, 1.007)	0.983 (0.966, 1.000)
IVW (random effects)	1.093 (0.756, 1.579)	0.993 (0.984, 1.002)	**0.983 (0.968, 0.997)**
Weighted median	1.118 (0.601, 2.082)	0.993 (0.976, 1.010)	0.986 (0.966, 1.007)

Abbreviations: IGAP, The International Genomic of Alzheimer's Project; UKB, The UK Biobank.

sensitivity analysis also confirmed the robustness of the findings, with no evidence for heterogeneity or pleiotropy. The results were consistent with observational studies [23–25]. A meta-analysis of 16 longitudinal studies to confirm that SBPV is a risk factor for cognitive impairment and dementia [10]. While the results for DBPV were less conclusive, with only a marginally significant result found in the MFH-UKBB dataset. Although no significant associations were identified in other datasets, the sensitivity analysis also demonstrated the reliability of the findings. Per 10-unit increment in DBPV decreased the risk of developing AD by 2%, supported by both IVW random effect and fixed effect models. In 2021, a two-sample MR study was conducted on blood pressure and dementia, but it suggested that high blood pressure is a protective factor for dementia [26], which is contrary to observational results [23].

While this study represents the first MR analysis investigating the causal relationship between BPV and dementia using publicly available GWAS data, several limitations should be acknowledged. First, there is a potential bias since the exposure and outcome GWAS were both derived from the UK Biobank. The overlap rate was calculated and is less than 1%, which indicates to have little influence on the results [27]. Second, the significant association between SBPV and AD was observed only in the PFH-UKBB dataset but was not replicated in other GWAS sources. This inconsistency may stem from the scarcity of large-scale BPV GWAS with longitudinal measurements. To date, only two BPV GWAS exist: an early study (n = 3802) identifying NLGN1 as a candidate gene [14] and a recent UK Biobank analysis (n = 9370) reporting visit-to-visit BPV loci [15]. The limited sample sizes in these BPV GWAS likely cause the power of our instrumental variables, potentially contributing to the observed heterogeneity. Furthermore, while the BPV GWAS utilized in this study included a subgroup analysis of hypertension-free participants, it did not fully adjust for the potential effects of antihypertensive medication, which could introduce residual confounding. Future studies with larger and more diverse BPV GWAS, incorporating detailed medication data, are needed to further confirm the causal association between BPV and AD. Third, our study focused on European-ancestry populations, which limits their generalizability to diverse populations. Future studies should prioritize diverse populations to assess the universality of BPV's causal role in dementia. Furthermore, leave-one-out analysis revealed that the exclusion of rs35696236, located within *SLC6A1*, resulted in a loss of significance. While *SLC6A1* has not been directly implicated in AD by GWAS, transcriptomic evidence suggests a potential link [28], raising concerns about residual horizontal pleiotropy not fully accounted for by MR-Egger. This sensitivity analysis underscores the need for further investigation with larger cohorts and more diverse genetic instruments to mitigate potential bias from individual SNP effects or unmeasured pleiotropy.

This finding adds more evidence for the causal link between BPV and AD, highlighting the potential cognitive benefits of BPV control in older adults. In current clinical settings, stable BPV is not the target of treatment. Although different hypertensive medication varies significantly in BPV control. Consistent home blood pressure monitoring may need more consideration to maintain a stable blood pressure.

5 | Conclusion

SBPV is a possible causal risk factor for AD, while the evidence for DBPV needs further study. BPV control should be an important treatment target in preventing dementia. Clinical treatment strategy should take BPV control into consideration, especially for the sake of dementia prevention.

Author Contributions

Pingping Jia, Kelvin Tsoi contributed to conceptualization, Pingping Jia, Ziyu Hao contributed to methodology, Karen Yiu contributed to software and resources, Pingping Jia, Ziyu Hao, Karen Yiu, and Kelvin Tsoi contributed to validation, investigation, data curation, and visualization. All authors confirmed they have contributed to the original draft writing, review, and editing. Kelvin Tsoi contributes to supervision, project administration, and funding acquisition.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Collaborators GBDD. Global, Regional, and National Burden of Alzheimer's Disease and Other Dementias, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016. *Lancet Neurology* 18, no. 1 (2019): 88–106, https://doi.org/10.1016/S1474-4422(18)30403-4.

2. S. T. Cheng, "Dementia Caregiver Burden: A Research Update and Critical Analysis," *Current Psychiatry Reports* 19, no. 9 (2017): 64, https://doi.org/10.1007/s11920-017-0818-2.

3. R. N. Kalaria, G. E. Maestre, R. Arizaga, et al., "Alzheimer's Disease and Vascular Dementia in Developing Countries: Prevalence, Management, and Risk Factors," *Lancet Neurology* 7, no. 9 (2008): 812–826.

4. S. M. Dyer, S. L. Harrison, K. Laver, et al., "An Overview of Systematic Reviews of Pharmacological and Non-Pharmacological Interventions for the Treatment of Behavioral and Psychological Symptoms of Dementia," *International Psychogeriatrics* 30, no. 3 (2018): 295–309.

5. K. Laver, S. Dyer, C. Whitehead, et al., "Interventions to Delay Functional Decline in People With Dementia: A Systematic Review of Systematic Reviews," *BMJ Open* 6, no. 4 (2016): e010767.

6. I. Skoog, "The Relationship Between Blood Pressure and Dementia: A Review," *Biomedicine & Pharmacotherapy* 51, no. 9 (1997): 367–375, https://doi.org/10.1016/S0753-3322(97)89428-0.

7. M. Tadic, C. Cuspidi, M. Bombelli, et al., "Relationships Between Residual Blood Pressure Variability and Cognitive Function in the General Population of the PAMELA Study," *Journal of Clinical Hypertension* 21, no. 1 (2019): 39–45, http://doi.org/10.1111/jch.13428.

8. C. McDonald, M. S. Pearce, S. R. J. Kerr, et al., "Blood Pressure Variability and Cognitive Decline in Older People: A 5-Year Longitudinal Study," *Journal of Hypertension* 35, no. 1 (2017): 140–147, https://doi.org/10.1097/HJH.0000000000001120.

9. C. Y. Miao, H. H. Xie, L. S. Zhan, and D. F. Su, "Blood Pressure Variability Is More Important Than Blood Pressure Level in Determination of End-Organ Damage in Rats," *Journal of Clinical Hypertension* 24, no. 6 (2006): 1125–1135.

10. P. Jia, H. W. Y. Lee, J. Y. C. Chan, et al., "Long-Term Blood Pressure Variability Increases Risks of Dementia and Cognitive Decline: A Meta-Analysis of Longitudinal Studies," *Hypertension* 78, no. 4 (2021): 996–1004, https://doi.org/10.1161/HYPERTENSIONAHA.121.17788.

11. Y. Ma, P. J. Tully, A. Hofman, et al., "Blood Pressure Variability and Dementia: A State-of-the-Art Review," *American Journal of Hypertension* 33, no. 12 (2020): 1059–1066, http://doi.org/10.1093/ajh/hpaa119.

12. P. M. Rothwell, S. C. Howard, E. Dolan, et al., "Prognostic Significance of Visit-to-Visit Variability, Maximum Systolic Blood Pressure, and Episodic Hypertension," *Lancet* 375, no. 9718 (2010): 895–905, https://doi.org/10.1016/s0140-6736(10)60308-x.

13. D. A. Lawlor, R. M. Harbord, J. A. Sterne, et al., "Mendelian Randomization: Using Genes as Instruments for Making Causal Inferences in Epidemiology," *Statistics in Medicine* 27, no. 8 (2008): 1133–1163, https://doi.org/10.1002/sim.3034.

14. S. Yadav, I. Cotlarciuc, M. S. Khan, et al., "Genome-Wide Analysis of Blood Pressure Variability and Ischemic Stroke," *Stroke: A Journal of Cerebral Circulation* 44, no. 10 (2013): 2703–2709, https://doi.org/10.1161/STROKEAHA.113.002186.

15. P. Jia, N. Zhan, B. K. K. Bat, et al., "The Genetic Architecture of Blood Pressure Variability: A Genome-Wide Association Study of 9370 Participants From UK Biobank," *Journal of Clinical Hypertension (Greenwich, Connecticut)* 24, no. 10 (2022): 1370–1380, https://doi.org/10.1111/jch.14552.

16. J.-C. Lambert, C. A. Ibrahim-Verbaas, D. Harold, et al., "Meta-Analysis of 74,046 Individuals Identifies 11 New Susceptibility Loci for Alzheimer's Disease," *Nature Genetics* 45, no. 12 (2013): 1452–1458.

17. J. R. Staley, J. Blackshaw, M. A. Kamat, et al., "PhenoScanner: A Database of Human Genotype-Phenotype Associations," *Bioinformatics* 32, no. 20 (2016): 3207–3209, https://doi.org/10.1093/bioinformatics/btw373.

18. S. Burgess, A. Butterworth, and S. G. Thompson, "Mendelian Randomization Analysis With Multiple Genetic Variants Using Summarized Data," *Genetic Epidemiology* 37, no. 7 (2013): 658–665, https://doi.org/10.1002/gepi.21758.

19. S. Burgess, J. Bowden, T. Fall, E. Ingelsson, and S. G. Thompson, "Sensitivity Analyses for Robust Causal Inference From Mendelian Randomization Analyses With Multiple Genetic Variant," *Epidemiology (Cambridge, Mass achusetts)* 28, no. 1 (2017): 30.

20. J. Bowden, G. Davey Smith, and S. Burgess, "Mendelian Randomization With Invalid Instruments: Effect Estimation and Bias Detection Through Egger Regression," *International Journal of Epidemiology* 44, no. 2 (2015): 512–525, https://doi.org/10.1093/ije/dyv080.

21. J. Bowden, G. Davey Smith, P. C. Haycock, et al., "Consistent Estimation in Mendelian Randomization With Some Invalid Instruments Using a Weighted Median Estimator," *Genetic Epidemiology* 40, no. 4 (2016): 304–314, https://doi.org/10.1002/gepi.21965.

22. F. P. Hartwig, N. M. Davies, G. Hemani, et al., "Two-Sample Mendelian Randomization: Avoiding the Downsides of a Powerful, Widely Applicable but Potentially Fallible Technique," *International Journal of Epidemiology* 45, no. 6 (2016): 1717–1726, https://doi.org/10.1093/ije/dyx028.

23. D. Hughes, C. Judge, R. Murphy, et al., "Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-Analysis," *JAMA* 323, no. 19 (2020): 1934–1944, https://doi.org/10.1001/jama.2020.4249.

24. S. Theriault, J. Sjaarda, M. Chong, et al., "Identification of Circulating Proteins Associated With Blood Pressure Using Mendelian Randomization," *Circulation: Genomic and Precision Medicine* 13, no. 1 (2020): e002605, https://doi.org/10.1161/CIRCGEN.119.002605.

25. A. Matsumoto, M. Satoh, M. Kikuya, et al., "Day-to-Day Variability in Home Blood Pressure Is Associated With Cognitive Decline: The Ohasama Study," *Hypertension* 63, no. 6 (2014): 1333–1338, https://doi.org/10.1161/HYPERTENSIONAHA.113.01819.

26. W. Sproviero, L. Winchester, D. Newby, et al., "High Blood Pressure and Risk of Dementia: A Two-Sample Mendelian Randomization Study in the UK Biobank," *Biological Psychiatry* 89, no. 8 (2021): 817–824, https://doi.org/10.1016/j.biopsych.2020.12.015.

27. S. Burgess, N. M. Davies, and S. G. Thompson, "Bias Due to Participant Overlap in Two-Sample Mendelian Randomization," *Genetic Epidemiology* 40, no. 7 (2016): 597–608, https://doi.org/10.1002/gepi.21998.

28. N. Sun, L. A. Akay, M. H. Murdock, et al., "Single-Nucleus Multiregion Transcriptomic Analysis of Brain Vasculature in Alzheimer's Disease," *Nature Neuroscience* 26, no. 6 (2023): 970–982, https://doi.org/10.1038/s41593-023-01334-3.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.