



Special Issue: Current evidence and perspectives for hypertension management in Asia

# Hypertensive disorders of pregnancy and the risk of dementia: a systematic review and meta-analysis of cohort studies

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Received: 20 April 2023 / Revised: 16 October 2023 / Accepted: 5 November 2023 / Published online: 1 December 2023  
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## Abstract

This study aimed to investigate the association between hypertensive disorders of pregnancy (HDP) and subsequent risk of dementia using a systematic review and meta-analysis of cohort studies. We searched PubMed and Scopus for eligible studies that investigated the association between HDP and dementia risk. Using the random-effects model, pooled hazard ratio (HR) and 95% confidence interval (CI) of dementia risk in women with HDP were calculated. We applied the  $I^2$  statistic to measure heterogeneity across studies and the test for funnel plot asymmetry to evaluate publication bias. Six cohort studies were eligible: three from the United States, two from Sweden, and one from Denmark. When combined, HDP was associated with the risk of dementia: pooled HR (95% CI) = 1.31 (1.12, 1.53). The heterogeneity across studies was moderate ( $I^2 = 47.3%$ ,  $p$ -heterogeneity = 0.091), but no signs of publication bias were detected. The association of HDP with vascular dementia was stronger than that with Alzheimer's disease: pooled HRs (95% CIs) = 1.66 (1.13, 2.43) and 1.29 (0.97, 1.72), respectively. In conclusion, HDP was associated with a higher risk of dementia and this association was more prominent with vascular dementia.

**Keywords** Hypertensive disorders of pregnancy · Dementia · Meta-analysis · Cohort studies

## Introduction

Alongside aging societies, especially in Western and East-Asian countries, the prevalence and incidence of dementia have been critically increasing [1]. Dementia is characterized by a wide range of cognitive symptoms affecting patients' memory, perception, orientation, judgment, intelligence, and attention [2]. It also has profound societal and financial burdens that affect patients and their relatives,

making it a challenge to healthcare systems [3, 4]. However, a significant proportion of dementia cases can be prevented by managing medical conditions associated with it [5].

Hypertension is among the most significant risk factors for dementia, and controlling blood pressure was shown to preserve cognitive functions and reduce dementia risk [6]. Hypertensive disorders of pregnancy (HDP) include chronic hypertension, gestational hypertension, pre-eclampsia, eclampsia, and HELLP syndrome, a condition characterized by hemolysis, elevated liver enzymes, and low platelets [7]. In addition to being a common complication during pregnancy [7], HDP may confer an increased risk of cognitive decline [8–10]. Vasoactive substances released in HDP may lead to brain edema and consequently

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41440-023-01520-7>.

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## Graphical Abstract

## Hypertensive disorders of pregnancy and the risk of dementia: a systematic review and meta-analysis of cohort studies



This meta-analysis included 6 cohort studies that investigated women from Sweden, Denmark, and the US.



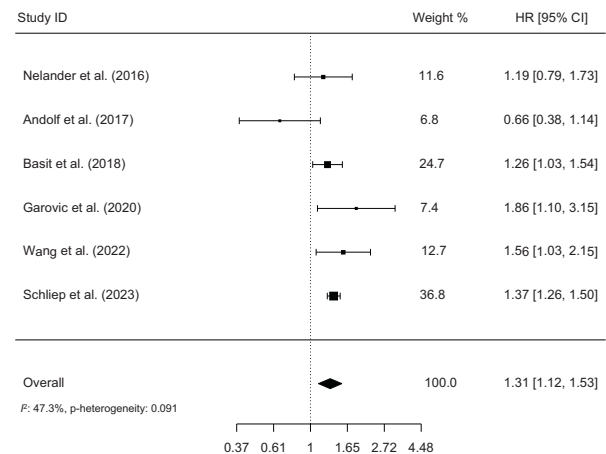
Dementia was diagnosed based on national registries and healthcare records.



The definition of hypertensive disorders of pregnancy (HDP) varied across studies. Typically, HDP includes chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and the HELLP syndrome.



Using the random-effects model, pooled hazard ratio (HR) and 95% confidence interval (CI) of dementia risk for women with HDP were calculated.



**Conclusions:** HDP was associated with a higher risk of dementia. Women with an HDP history should be targeted for dementia screening and preventive intervention.

### Point of view

- **Clinical relevance**  
Hypertensive disorders of pregnancy (HDP) are positively associated with the subsequent risk of dementia.
- **Future directions**  
Investigating the impact of HDP management on dementia prevention should be studied. Elucidating the biological mechanisms explaining the association between HDP and dementia risk is needed as well.
- **Consideration for the Asian population**  
Given the lack of evidence from Asian populations, investigating the association between HDP, as well as other pregnancy complications, with the risk of dementia is warranted.

white matter lesions [11]. These lesions are associated with cognitive decline and dementia progression [12]. Besides, STOX1, a preeclampsia susceptibility gene, can control a conserved pathway in the placenta and brain upregulated in late-onset Alzheimer's disease (AD) [13]. Furthermore, transthyretin, a transport protein in the plasma and cerebrospinal fluid that transmits the thyroid hormone and retinol to the liver, is similarly dysregulated in preeclampsia and AD [14].

Nevertheless, the epidemiological evidence regarding the link between HDP and dementia is marked by inconsistency. While certain studies have observed an elevated risk of dementia in women with HDP [15–18], others have not been able to replicate this finding [19–22]. Furthermore, past meta-analyses have been constrained by the limited number of studies and cases of both HDP and dementia [23–25]. These factors in addition to more recent studies that were not included in previous meta-analyses [17, 18] prompted us to perform an updated meta-analysis to investigate the connection between HDP and the risk of all-cause dementia, vascular dementia, and AD.

### Methods

We reported this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [26]. However, the meta-analysis was not registered in advance with the International Prospective Register of Systematic Reviews (PROSPERO).

### Literature search

AA and MT independently searched PubMed and Scopus databases for potential studies published in English language before the 25th of August 2023 using the following terms: ((Gestational hypertension) OR (Preeclampsia))

AND (Dementia) (Supplementary Table 1). Besides, the reference sections of retrieved studies and relevant review articles were checked for potential studies.

### Eligibility criteria

Our eligibility criteria included: 1) the exposure was HDP or any of its subtypes, 2) the outcome was incident dementia or any of its subtypes, and 3) the study had a cohort design. We did not apply limitations regarding the year of publication. No efforts were made to obtain unpublished data or studies published in a language other than English.

### Data extraction

The following information was extracted from the included studies: the last name of the first author, publication year, place of study, age of participants, the total number of participants, the number of participants with incident dementia, diagnostic methods of HDP and dementia, and covariates included in the most adjusted regression models.

### Risk of bias

AA and MT assessed the risk of bias using the modified Newcastle-Ottawa Quality Assessment Scale in terms of studies' selection, comparability, and outcome [27], with disagreements solved by discussion.

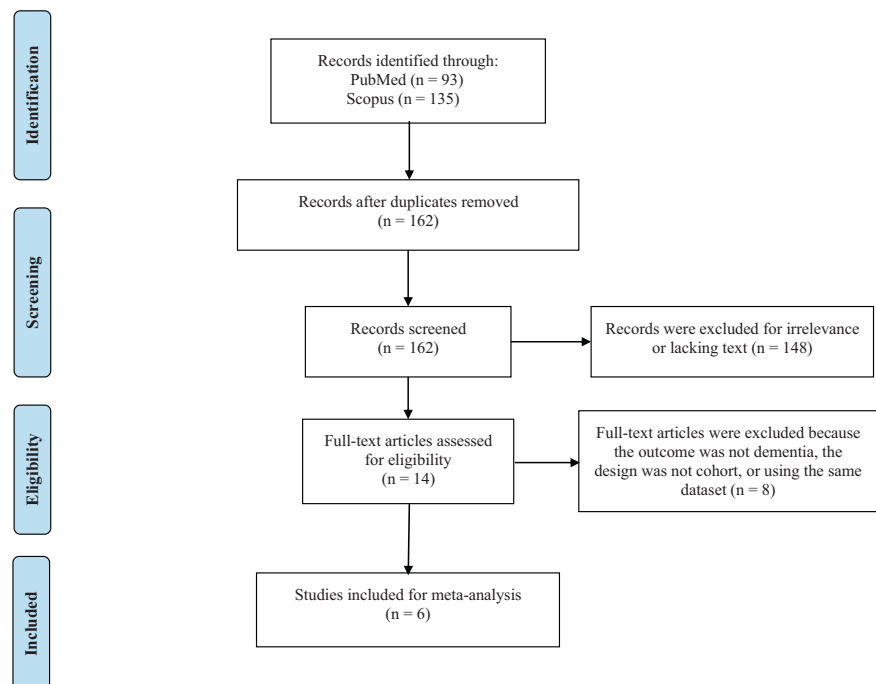
### Statistical analysis

We extracted the hazard ratios (HRs) and their 95% confidence intervals (CIs) of dementia, vascular dementia, and AD in women with HDP history in the most adjusted regression models before calculating the pooled HR (95% CI) using the random-effects model [28]. We also performed the  $I^2$  statistic to evaluate heterogeneity across studies [29] and the test for funnel plot asymmetry to assess publication bias [30]. The R-3.2.0 statistical package (Metafor: Meta-Analysis Package for R) was used for analysis [31].

### Results

First, we removed duplicates, irrelevant records, review articles, studies with designs other than cohort design, and studies that did not assign dementia as an outcome or HDP as an exposure (Fig. 1). We excluded a cohort study that assigned AD mortality as an outcome [32]. We excluded another cohort study that detected only one case of dementia in the preeclampsia group compared to no cases in the normotensive group [9]. Of note, two studies by Andolf et al. assessed similar populations [19, 21]. While the earlier study investigated all forms of HDP separately and together [19], the later study limited the analysis to preeclampsia in one analysis and gestational hypertension in another [21]. Therefore, we decided to include the earlier study [19] in the main meta-analysis and perform sensitivity analyses using the results of the later study [21].

**Fig. 1** PRISMA flow diagram of the study selection process for the meta-analysis



**Table 1** Summary of the studies included in the meta-analysis

Study ID	Population	HDP definition	Dementia diagnosis	Covariates
Nelander et al. [20]	Overall: 3065 Age at inclusion: ≥65 years HDP cases: 419 Follow-up: 10.4 years (mean) Dementia cases: 229 Country: Sweden	Hypertension with/without proteinuria (Self-reported)	National Patient Register (ICD codes) and Cause of Death Register	2, 3, 6
Andolf et al. [19]	Overall: 284,598 Age at birth: ≥13 years HDP cases: 10,769 Follow-up: 35.0 years (max) Dementia cases: 608 non-vascular and 88 vascular Country: Sweden	Hypertension with/without proteinuria, preeclampsia, and eclampsia (Medical Birth Register (ICD codes))	National Patient Register (ICD codes) and Cause of Death Register	1, 3, 5, 7, 8, 11
Basit et al. [15]	Overall: 1,178,005 Age at birth: <45 years (95.4%) HDP cases: 50,068 Follow-up: 21.1 years (median) Dementia cases: 1728 Country: Denmark	Preeclampsia, eclampsia, or HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome (National Patient Register (ICD codes))	National Patient Register (ICD codes)	1, 4, 7, 8, 9, 11
Garovic et al. [16]	Overall: 1713 Age at inclusion: ≥46 years HDP cases: 571 Follow-up: 27.4 years (mean) Dementia cases: 28 Country: United States	Chronic hypertension, gestational hypertension, preeclampsia superimposed on chronic hypertension, preeclampsia, and eclampsia (The Rochester Epidemiology Project medical record)	Inpatient and outpatient visits to Rochester Epidemiology Project -affiliated providers (ICD codes)	1, 2, 5, 6
Wang et al. [18]	Overall: 1249 Age at inclusion: ≥46 years HDP cases: 142 Follow-up: 12 years (mean) Dementia cases: 98 Country: United States	Preeclampsia (Self-reported)	Surveillance DSM IV and NINDS,	1, 2, 3, 4, 5, 6, 7, 8, 10
Schliep et al. (2023)	Overall: 59,668 Age at inclusion: ≥45 years HDP cases: 19,989 Follow-up: 80 years (max) Dementia cases: 2418 Country: United States	Preeclampsia or eclampsia	Death certificates, inpatient hospital records, ambulatory surgery records, or emergency department records.	1, 4

Covariates: 1- age or age at birth, 2- body mass index, 3- marital status, 4- parity, 5- education, 6- smoking, 7- hypertension, 8- diabetes, 9- chronic kidney disease, 10- dyslipidemia, 11- stroke or coronary heart disease

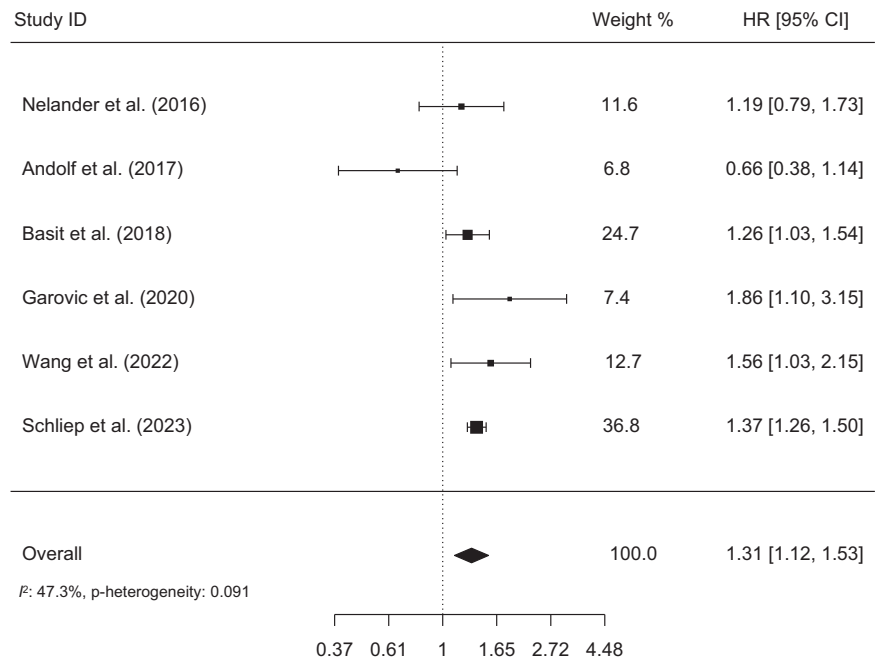
*DSM* Diagnostic and Statistical Manual of Mental Disorders, *ICD* International Classification of Disease, *NINDS* National Institute of Neurological and Communicative Disorders and Stroke

Eventually, six cohort studies were included [15–20]. Of them, three studies were conducted in the United States [16–18], two studies in Sweden [19, 20], and one study in Denmark [15]. The definition of HDP varied across studies: Basit et al. [15]: preeclampsia, eclampsia, and the HELLP syndrome; Garovic et al. [16]: chronic hypertension, gestational hypertension, preeclampsia superimposed on chronic hypertension, preeclampsia, and eclampsia; Schliep et al. [17]: preeclampsia and eclampsia; Wang et al. [18]: preeclampsia; Andolf et al. [19]: hypertension with or without proteinuria, preeclampsia, and eclampsia; and Nelander et al. [20]: hypertension during pregnancy with or without proteinuria. Data about HDP were self-reported in two studies

[18, 20] and were obtained from medical registries in four studies [15–17, 19] (Table 1). No significant risks of bias were detected (Supplementary Table 2).

The weights of the included studies were distributed as follows: Basit et al. [15]: 24.7%; Garovic et al. [16]: 7.4%; Schliep et al. [17]: 36.8%; Wang et al. [18]: 12.7%; Andolf et al. [19]: 6.8%; and Nelander et al. [20]: 11.6%. In the meta-analysis, HDP was positively associated with the risk of dementia: pooled HR (95% CI) = 1.31 (1.12, 1.53). The heterogeneity across studies was moderate ( $I^2 = 47.3%$  and  $p$ -heterogeneity = 0.091) (Fig. 2). No signs of publication bias were identified ( $Z = -0.583$ , and  $p$ -publication bias = 0.560) (Supplementary Fig. 1).

**Fig. 2** Forest plot of the association between hypertensive disorders of pregnancy and the risk of all-cause dementia



Compared to the results of the earlier Andolf et al. study [19] that showed an HR (95% CI) of 0.66 (0.38, 1.14), the HRs (95% CIs) of their later study [21] were 0.98 (0.87, 1.10) for preeclampsia and 1.10 (0.93, 1.29) for gestational hypertension. When we applied the results of preeclampsia or gestational hypertension from the later study instead of HDP results from the earlier study, the pooled HRs (95% CIs) of the meta-analyses did not materially change: 1.28 (1.07, 1.53) and 1.30 (1.16, 1.45), respectively.

The association of HDP with vascular dementia: pooled HR (95% CI) = 1.66 (1.13, 2.43) with ( $I^2 = 28.79\%$  and p-heterogeneity = 0.246) (Fig. 3) was stronger than the corresponding association with AD: pooled HR (95% CI) = 1.29 (0.97, 1.72) with ( $I^2 = 68.1\%$  and p-heterogeneity = 0.044) (Fig. 4).

## Discussion

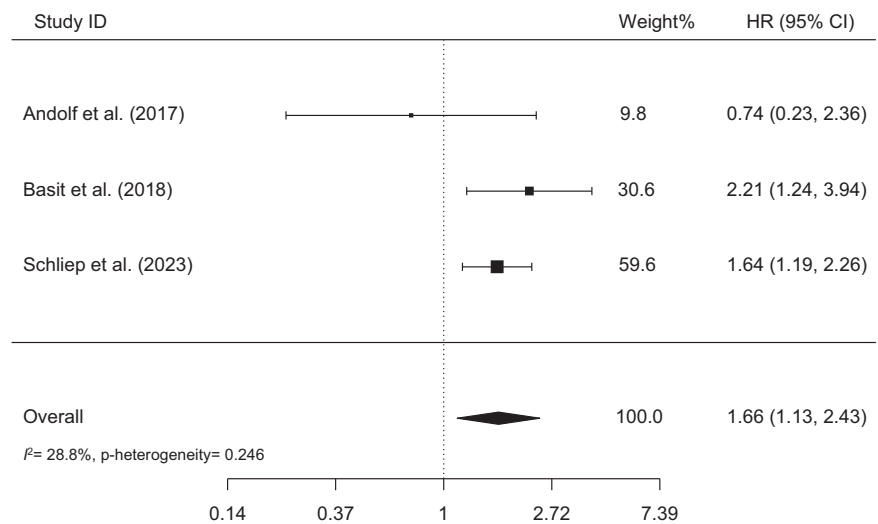
This meta-analysis combined results from six cohort studies and indicated a positive association between HDP and dementia risk, and the association was stronger with vascular dementia.

A few meta-analyses investigated the association between HDP and dementia. One meta-analysis pooled the unadjusted relative risks (RR) of HDP in three studies: 1.34 (1.11, 1.62) [15], 2.00 (1.20, 3.34) [16]), and (1.09 (0.76, 1.57) [20], but failed to find a statistically significant association: pooled RR (95% CI) = 1.37 (0.70, 2.71) [23]. However, the unadjusted RRs (95% CIs), as calculated by the authors of the meta-analysis, suggest that the 95% CI of

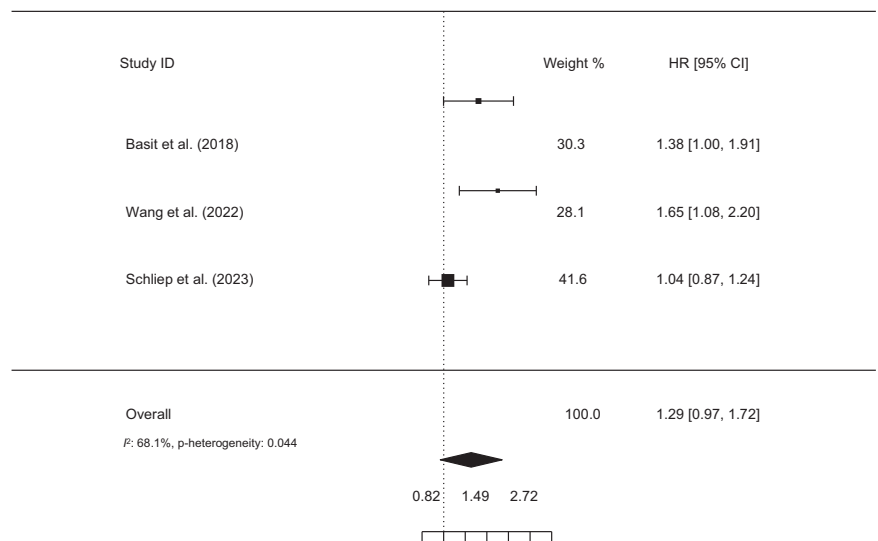
the pooled results should have been much tighter and a statistically significant association between HDP and dementia should have been concluded. Another meta-analysis of two cohort studies [15, 21] showed no association between HDP and dementia risk: HR (95% CI) = 1.08 (0.93, 1.25) [24]. Both meta-analyses were limited by the small number of included studies, making their representativeness questionable. A larger meta-analysis of five cohort studies [9, 15, 20, 21, 32] showed that HDP was significantly associated with the risk of dementia: HR (95% CI) = 1.38 (1.18, 1.61) [25]. However, it included a study assigning AD-attributed mortality as an outcome rather than incident dementia [32] and a study mixing dementia with mild cognitive impairment [9]. Furthermore, more recent studies [16–18] were not included. The three recent studies together contributed to 56.9% of our meta-analysis weight.

Importantly, the association between HDP and dementia can vary by dementia subtype. Previous meta-analyses [24, 25], as well as our meta-analysis, showed a stronger association between HDP and vascular dementia than AD. Additionally, the association between HDP and dementia risk could vary by HDP subtype and severity. Andolf et al. [19] showed that hypertension without proteinuria and preeclampsia without severe features were negatively associated with all-cause and vascular dementia, while hypertension with proteinuria, preeclampsia with severe features, and eclampsia were positively associated with all-cause and vascular dementia. Therefore, future studies should consider stratifying their results by dementia subtypes and HDP subtypes and severity.

**Fig. 3** Forest plot of the association between hypertensive disorders of pregnancy and the risk of vascular dementia



**Fig. 4** Forest plot of the association between hypertensive disorders of pregnancy and the risk of Alzheimer's disease



Of note, it could be speculated that the long-term adverse events associated with HDP, such as chronic hypertension, diabetes mellitus, chronic kidney disease, and stroke [33–35], can mediate the association between HDP and dementia. Mid-life cardiometabolic and mental health factors were shown to explain more than 60% of the association between HDP and subsequent dementia [17].

### Strengths and limitations

One of the main strengths of this meta-analysis is the relatively large numbers of HDP and dementia cases. Besides, the population-based design of the included studies suggests their representativeness for the studied populations. Further, the cohort design of the included studies allowed for a long follow-up period between HDP diagnosis and incident dementia. However, several limitations should be addressed

as well. First, although our meta-analysis included more studies than the previous ones, the number of included studies is small, and even fewer studies assessed the relationship of HDP with vascular dementia and AD. Therefore, the results, especially those of dementia subtypes, should be interpreted with caution. Second, data about dementia and HDP in most studies were collected using registries that could be prone to selection bias [36]. Third, HDP in two studies was self-reported [18, 20], suggesting recall bias. Fourth, since many studies did not adjust their results for potential confounders and essential mid-life cardiometabolic factors, it is difficult to conclude whether HDP independently elevated the risk of dementia or merely unmasked underlying risk factors for dementia. For example, smoking is associated with both HDP and dementia [37, 38]. Fifth, each study defined HDP differently. This could be partly explained by the variations in HDP definitions across

medical societies worldwide [39]. Yet, because of the limited number of studies and the overlap of HDP definitions across them, we could not stratify our meta-analysis by HDP subtypes. Sixth, the investigated women came from Western nations; thus, applying the results to non-Western women should be done cautiously.

## Perspective of Asia

HDP is associated with a higher risk of dementia. However, future studies investigating this association among Asian women are needed.

## Conclusion

In this meta-analysis, HDP was associated with an elevated risk of dementia, especially vascular dementia. Still, more studies are needed to confirm our findings. Future studies should include women from different ethnicities and consider stratifying results by subtypes of HDP and dementia. Additionally, further studies to explain the potential underlying biological links between HDP and dementia are also needed.

## Data availability

All data generated or analyzed during this study were included in this published article.

**Author contributions** All authors made a substantial contribution to this work. Conceptualization (AA and YK), data collection (AA and MT), analysis and manuscript writing (AA), resources (YK), and revision and editing (AA, RK, MT, YS, SN, KS, HK, QG, CM, and YK).

**Funding** This study was supported by the Intramural Research Fund (20-4-9) for the cardiovascular diseases of the National Cerebral and Cardiovascular Center, the JST Grant Number JPMJPF2018, and the Japan Agency for Medical Research and Development (dk0207025).

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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