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Original Article

Pregnancy hypertension is associated with higher p-tau217 in healthy midlife women

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ABSTRACT

Introduction: There is very limited knowledge on the relationship between pregnancy hypertension and the occurrence of pre-clinical Alzheimer's disease (AD).
Methods: Community-dwelling midlife women without dementia were enrolled from well-woman clinics of the National University Hospital, Singapore. Sociodemographic parameters and history of pregnancy hypertension were obtained. Cognition was assessed using the Montreal Cognitive Assessment-Basic tool. Fasted blood samples were stored for batched analysis of renal function, APOE genotyping and p-tau217 levels using Simoa® ALZpath p-tau217 Advantage PLUS (Quanterix, MA, USA). General linear modelling was used to examine the association between pregnancy hypertension and p-tau217.
Results: Among 743 women (mean age 62.9 ± 6.0; range: 50.7 to 76.6 years) enrolled, 68 (9.2%) reported pregnancy hypertension. General linear modelling showed that an older age [mean difference: 0.002 (95% CI: 0.001, 0.003)], mild cognitive impairment [0.016 (0.001, 0.032)], lower BMI [0.068 (0.027, 0.109)], eGFR<60 mL/min/1.73 m^2 [0.132 (0.072, 0.193)] and the *APOE4* carrier genotype [0.038 (0.018, 0.058)] were independently associated with higher serum p-tau217 levels. History of pregnancy hypertension remained significantly associated with subsequent higher serum p-tau217 [0.040 (0.013, 0.067)], after adjustment for age, mild cognitive impairment, hypertension, BMI, renal function, and *APOE4* genotype status.
Discussion: Pregnancy hypertension was associated with AD pathology with mean differences similar to high risk APOE4 carrier genotypes. Information on pregnancy hypertension could help physicians to identify women who might benefit from early p-tau217 screening for Alzheimer's disease, allowing for early clinical intervention.

1. Introduction

Women have approximately twice the incidence of Alzheimer's disease compared to men, and most people living with dementia are women [1]. Although selective survival may account for a portion of sex differences in dementia incidence [2], simulations indicate that biological differences could contribute up to 20 % higher risk in women [3]. Although not unanimous [4], limited epidemiological evidence suggests a link between pregnancy hypertension and later development of Alzheimer's disease, with a meta-analysis indicating a 40 % to 92 % higher risk among women with pregnancy hypertension, compared to those without [5,6]. A population study from Utah indicated that pregnancy hypertension and its severe manifestation, pre-eclampsia, was associated with 3.44-fold excess risk for mortality from Alzheimer disease, greater than that observed for diabetes, ischemic heart disease, and stroke [7].

Despite pregnancy hypertension and Alzheimer's disease having no common clinical features, striking parallels exist in their pathogenesis [8]. The urine of women with pre-eclampsia have been noted to contain amyloid-like aggregates, reminiscent of the protein conformational

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disorders noted in Alzheimer's and prion disease [9,10]. Defective clearance of aggregation of misfolded proteins, including the amyloid beta peptide (Aβ), have been reported [8,11]. Cerebrospinal fluid levels of Aβ peptides and tau protein concentrations were observed to be higher in women who developed severe pregnancy hypertension [12,13]. The pre-eclampsia susceptibility gene STOX1 is abundantly expressed in the brain and is involved in Aβ protein precursor processing and Alzheimer's disease, suggesting a conserved pathway for protein processing shared between the placenta and the brain [14].

In recent years, elevated blood-based phosphorylated-tau217 (p-tau217) has been shown to reflect abnormal amyloid and tau positron emission tomography burden [15,16]. P-tau217 correlated with neurodegeneration in Alzheimer's disease, and targeting p-tau217 with immunotherapy ameliorated murine tauopathy [17]. The cost-effective and accessible blood-based biomarker, p-tau217, correlated with post-mortem Alzheimer's disease pathology, differentiated Alzheimer's disease from other types of dementia, and predicted future progression from normal cognition and mild cognitive impairment (MCI) to Alzheimer's disease [18,19]. There is only a very limited knowledge on the relationship between pregnancy hypertension and the occurrence of AD pathology decades later in midlife. We postulate that women with a history of pregnancy hypertension would have higher serum p-tau217 levels and increased risk for Alzheimer's Disease.

In this study, we measured serum p-tau217 to examine the relationship between pregnancy hypertension and subsequent development of AD pathology in community dwelling midlife women without dementia.

2. Methods

2.1. Study setting and population

Between February 2021 and June 2024, women from the Integrated Women's Health Program were contacted via phone calls, emails, and text messages to attend a follow-up visit 6.8 years after their baseline visit in 2014 to 2016 [20]. Eligibility criteria at baseline included an age range of 45 to 69 years, being of Chinese, Malay and Indian ethnicities, and having no diagnosis of life-threatening or terminal illnesses. Participants were recruited from four well-women clinics at the National University Hospital (NUH), Singapore. This study utilized cross-sectional data from the 2021 to 2024 follow-up visit and was approved by the Domain Specific Review Board of the National Healthcare Group, Singapore (Reference number: 2020/00,201). All participants provided written informed consent.

2.2. Outcome: serum p-tau217

Blood (30 ml) was drawn following an overnight fast at the study visit and processed within 6 h of collection. The blood was first left at room temperature to clot for 30 min to an hour. Next, the tubes were centrifuged at 3000x*g* in 4 °C, before the serum was aliquoted and stored at −80 °C for analyses.

Serum p-tau217 was analyzed using the Simoa® ALZpath p-tau217 Advantage PLUS (Quanterix, MA, USA). This digital immunoassay for the quantitative determination of p-tau217 has been validated as a serum biomarker of AD comparable with CSF biomarkers and correlating highly with PET imaging [16], and is one of two commercially available p-tau217 assays found to have similarly high diagnostic performance [21]. The assay was performed by analysts from the Agency for Science, Technology and Research, Singapore Immunology Network Multiplex Analysis of Proteins platform, who were blinded to clinical backgrounds of the samples. Median centric normalization was used to normalize each plate to a common median to reduce plate to plate variations. The functional lower limit of p-tau217 quantification was 0.00978 pg/mL. All samples were within the limit of quantification range, although 6 samples were excluded due to sample matrix issues preventing data collection. The intra- and inter-assay coefficients of variation were 0.12–6.85 % and 8.65 % for p-tau 217.

2.3. Exposure: hypertension during pregnancy

Pregnancy hypertension was self-reported using the question: "Did you develop high blood pressure during your pregnancy?" Participants who answered *yes* were considered to have the condition. Participants who reported pregnancy hypertension were subsequently re-contacted by phone to obtain additional data including dates of each pregnancy, number of pregnancies with hypertension, and hospital admissions. Latency period between pregnancy hypertension and p-tau217 testing was calculated by subtracting age at first hypertensive pregnancy from age at follow-up.

2.4. Covariates

Demographic characteristics, including age, ethnicity (Chinese, Malay, Indian), and highest education attainment (no formal or primary, secondary or post-secondary, university) were self-reported via a questionnaire. Reproductive information such as gestational diabetes (yes, no), breastfeeding status (yes, no), and parity (nulliparous, parous) were also self-reported.

MCI was ascertained using the 30-question Montreal Cognitive Assessment-Basic (MoCA-B), a tool with high sensitivity and specificity for detecting MCI in patients who are performing in the normal range on the widely used Mini-Mental State Examination [22]. The assessment was administered by trained and certified study coordinators. MOCA-B evaluated six cognitive domains, including executive functioning, memory, orientation, language, attention and visual perception with a maximum (best) score of 30. A cut-off score of $\leq$25 gave high sensitivity (86 %) and specificity (86 %) in detecting individuals with MCI [22].

Blood pressure was measured thrice using the OMRON IntelliSense (HEM-7211), in a seated position, with one-minute intervals between each measurement. Participants were instructed to bring all medications and supplements consumed in the past two weeks to the study visit, and study coordinators recorded their dosage and frequency [20]. Hypertension was defined as having an average systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, use of anti-hypertensive medication, or a self-reported physician diagnosis. Height and weight were measured once, and twice, respectively using the SECA 769 Electronic Measuring Station, with footwear removed and pockets emptied. Body mass index (BMI) was calculated as weight divided by average height squared and categorized into underweight ($<$18.5 kg/m^2), healthy weight (18.5–22.9 kg/m^2), overweight (23.0–27.49 kg/m^2), and obese ($\geq$27.5 kg/m^2) according to Asian standards [23].

Serum creatinine was quantified using the Alinity C Creatinine (Enzymatic) Reagent kit (Abbott Laboratories, USA) at NUH's Referral Laboratory, accredited by the Joint Commission International. Renal function was assessed using the estimated glomerular filtration rate (eGFR), which was calculated using the CKD-EPI 2021 equation [24]. Values were categorized into $\geq$90 mL/min/1.73 m^2, 60–89 mL/min/1.73 m^2, and $<$60 mL/min/1.73 m^2, in accordance with clinical practice guidelines [25,26]. No participant had readings $<$15 mL/min/1.73 m^2. Genetic testing was conducted to phenotype apolipoprotein ε2 (*APOE2*), ε3 (*APOE3*), and ε4 alleles (*APOE4*), as previously described [27]. To examine the contribution of ε4 alleles on p-tau217 levels, participants with one or two ε4 alleles were grouped together.

2.5. Statistical analysis

Descriptive statistics were used to examine the relationship between characteristics and pregnancy hypertension using the independent samples *t*-test or Pearson's chi-square test. Univariate associations

between participant characteristics and serum p-tau217 levels were evaluated using general linear modelling for continuous variables (such as age) or the independent samples *t*-test or one-way analysis of variance (ANOVA) for categorical variables (such as pregnancy hypertension, ethnicity, or highest education attainment). The results were presented as mean difference and 95 % confidence intervals (CI) or mean and standard deviation (SD).

General linear modelling was used to examine the association between pregnancy hypertension and p-tau217 levels. Variables known to be associated with Alzheimer's disease *a-priori* [28–30] or had a univariate result of $p < 0.10$ in Table 2 were added as covariates into the same model. Covariates included age, MCI, hypertension, BMI, renal function, and *APOE4* genetic status. Time since pregnancy was not included as a covariate due to small numbers.

All results were analyzed using IBM SPSS statistics software (version 29.0; IBM Corp., Armonk, NY) and GraphPad Prism (version 10.0; GraphPad software, Boston, MA). A two-sided p-value<0.05 indicated statistical significance.

3. RESULTS

Among 998 participants enrolled at the 6.8-year follow-up visit, 255 with missing p-tau217 ($n = 108$) and/or pregnancy hypertension data ($n = 147$) were excluded, resulting in an analytical sample of 743 (Fig. 1). The mean age of study participants was 62.9 ± 6.0 years (range: 50.7 to 76.6 years). The majority were of Chinese ethnicity (82.3 %) and had at least secondary education (87.7 %) (Table 1). 58.5 % were overweight or obese, 48.0 % had hypertensive disease at midlife, 42.3 % had MCI (MOCA scores ≤25), 22.0 % had reduced renal function (eGFR <90 mL/min/1.73 m^2) and 16.7 % were carriers of the high risk *APOE4* genotype.

3.1. Characteristics of women by the exposure variable, pregnancy hypertension (Table 1)

Among 743 women, 68 (9.2 %) reported pregnancy hypertension. Women with a history of pregnancy hypertension were more likely to report gestational diabetes (Table 1). In contrast, ethnicity, educational attainment, breastfeeding and parity were not associated with pregnancy hypertension. Some decades later in midlife, participants with a history of pregnancy hypertension were more likely to have higher body mass index, hypertensive disease and poorer renal function. Pregnancy hypertension was not associated with MCI or *APOE4* genotype.

Women with pregnancy hypertension were recontacted and the characteristics of those pregnancy episodes were shown in **Supplementary Table**. Mean age at onset for pregnancy hypertension was 29.3 ± 5.6 years, and mean latency period between pregnancy and p-tau analysis was 32.1 ± 8.3 years. 28.2 % of pregnancy hypertension cases occurred more than once, 27.3 % required admission to hospital, and about three quarters of pregnancies with hypertension occurred in the 1st pregnancy (74.4 %).

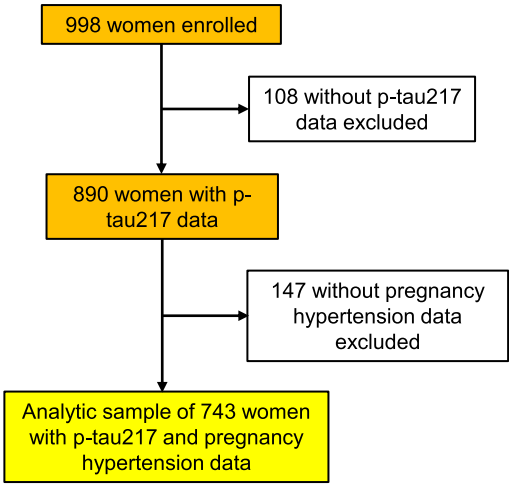

Fig. 1. Participant flow chart.

Table 1
Participant characteristics by pregnancy hypertension status ($n = 743$).

Characteristics	N (%) Mean ± SD or n (%)	Pregnancy hypertension		P-value
		Yes ($n = 68$, 9.2 %)	No ($n = 675$, 90.8 %)	
Age, years	743 (100.0)	62.6 ± 5.9	62.9 ± 6.0	0.668
Ethnicity				0.092
Chinese	591 (82.3)	48 (8.1)	543 (91.9)	
Malay	47 (6.5)	6 (12.8)	41 (87.2)	
Indian	80 (11.1)	12 (15.0)	68 (85.0)	
Highest education attainment				0.117
No formal or primary	90 (12.3)	4 (4.4)	86 (95.6)	
Secondary or post-secondary	501 (68.5)	53 (10.6)	448 (89.4)	
University	140 (19.2)	10 (7.1)	130 (92.9)	
Gestational diabetes				<0.001
Yes	93 (12.7)	18 (19.4)	75 (80.6)	
No	641 (87.3)	48 (7.5)	593 (92.5)	
Breastfed				0.284
Yes	517 (71.3)	44 (8.5)	473 (91.5)	
No	208 (28.7)	23 (11.1)	185 (88.9)	
Parity				0.684
Nulliparous	16 (2.2)	1 (6.3)	15 (93.8)	
Parous	727 (97.8)	67 (9.2)	660 (90.8)	
Mild cognitive impairment				0.175
Yes	314 (42.3)	34 (10.8)	280 (89.2)	
No	429 (57.7)	34 (7.9)	395 (92.1)	
Hypertension				<0.001
Yes	355 (48.0)	53 (14.9)	302 (85.1)	
No	384 (52.0)	14 (3.6)	370 (96.4)	
Body mass index, kg/m^2				<0.001
<18.5	27 (3.6)	0 (0.0)	27 (100.0)	
18.5–23.0	281 (37.9)	21 (7.5)	260 (92.5)	
>23.0–27.4	270 (36.4)	15 (5.6)	255 (94.4)	
≥27.5	164 (22.1)	32 (19.5)	132 (80.5)	
Renal function (eGFR)				0.008
<60	12 (1.6)	4 (33.3)	8 (66.7)	
60–89	151 (20.4)	10 (6.6)	141 (93.4)	
≥90	578 (78.0)	54 (9.3)	524 (90.7)	
APOE4 genotype				0.638
Carriers	124 (16.7)	10 (8.1)	114 (91.9)	
Non-carriers	617 (83.3)	58 (9.4)	559 (90.6)	

Results were analyzed using the independent samples *t*-test or Pearson's chi-square test and presented as mean ± SD or frequencies and percentages, n (%). Missing data accounted for 0.1 % to 3.4 % of the overall data.

3.2. Unadjusted risk factors for AD pathology in midlife (Table 2)

Univariate analysis indicated that pregnancy hypertension was associated with a trend towards higher serum p-tau217 ($p = 0.085$) (Table 2). Boxplots were generated to examine the distribution of serum p-tau217 levels of the participants with pregnancy hypertension ($n = 68$), and those without ($n = 675$) (Fig. 2). For subjects with pregnancy hypertension, the 25th percentile was 0.21 pg/ml, 50th percentile was 0.24 pg/ml and the 75th percentile was 0.31 pg/ml, whilst corresponding values for women without pregnancy hypertension were 0.21, 0.24, and 0.28 pg/ml respectively. Mean values for p-tau217 in women with pregnancy hypertension were 0.30 pg/ml compared to 0.26 pg/ml for those without.

Table 2
Participant characteristics by serum p-tau217 levels ($n = 743$).

Characteristics	P-tau217 (pg/ml)		
	N (%)	Mean difference (95 % CI) or mean ± SD	P-value
Age, years	743 (100.0)	0.003 (0.002, 0.005)	<0.001
Ethnicity			0.702
Chinese	591 (82.3)	0.26 ± 0.12	
Malay	47 (6.5)	0.25 ± 0.08	
Indian	80 (11.1)	0.26 ± 0.08	
Highest education attainment			0.489
No formal or primary	90 (12.3)	0.28 ± 0.13	
Secondary or post-secondary	501 (68.5)	0.26 ± 0.11	
University	140 (19.2)	0.26 ± 0.11	
Gestational diabetes			0.583
Yes	93 (12.7)	0.27 ± 0.10	
No	641 (87.3)	0.26 ± 0.11	
Pregnancy hypertension			0.085
Yes	68 (9.2)	0.30 ± 0.19	
No	675 (90.8)	0.26 ± 0.10	
Breastfed			0.188
Yes	517 (71.3)	0.26 ± 0.10	
No	208 (28.7)	0.27 ± 0.13	
Parity			0.381
Nulliparous	16 (2.2)	0.29 ± 0.10	
Parous	727 (97.8)	0.26 ± 0.11	
Mild cognitive impairment			0.004
Yes	314 (42.3)	0.28 ± 0.14	
No	429 (57.7)	0.25 ± 0.07	
Hypertension			0.009
Yes	355 (48.0)	0.27 ± 0.13	
No	384 (52.0)	0.25 ± 0.09	
Body mass index, kg/m^2			0.004
<18.5	27 (3.6)	0.33 ± 0.18	
18.5–23.0	281 (37.9)	0.27 ± 0.11	
>23.0–27.4	270 (36.4)	0.25 ± 0.10	
≥27.5	164 (22.1)	0.26 ± 0.09	
Renal function (eGFR)			<0.001
<60	12 (1.6)	0.42 ± 0.18	
60–89	151 (20.4)	0.28 ± 0.11	
≥90	578 (78.0)	0.25 ± 0.11	
APOE4 genotype			0.004
Carriers	124 (16.7)	0.29 ± 0.13	
Non-carriers	617 (83.3)	0.26 ± 0.10	

Results were analyzed using the general linear model, independent samples *t*-test or one-way ANOVA and presented as mean difference (95 % CI) or mean ± SD. Missing data accounted for 0.1 % to 3.4 % of the overall data.

In unadjusted analyses, contemporaneous factors associated with higher serum p-tau217 levels were older age, MCI, hypertension, *lower* body mass index, poorer renal function, and the *APOE4* genotype (Table 2). Ethnicity, educational attainment, gestational diabetes, breastfeeding and parity were not associated with serum p-tau217 levels.

3.3. General linear modelling for independent factors associated with p-tau217 (Fig. 3)

Fig. 3 shows independent factors associated with higher p-tau217 levels. General linear modelling showed that an older age [mean difference: 0.002 (95 % CI: 0.001, 0.003)], MCI [0.016 (0.001, 0.032)], lower BMI (<18.5 kg/m^2) [0.068 (0.027, 0.109)], and eGFR<60 mL/min/1.73 m^2 [0.132 (0.072, 0.193)] were independently associated with higher serum p-tau217 levels. Subjects with *APOE4* carrier genotype had higher serum p-tau217 levels [0.038 (0.018, 0.058)]. History of pregnancy hypertension was significantly associated with subsequent higher serum p-tau217 [0.040 (0.013, 0.067)], after adjustment for age, MCI, hypertension, BMI, renal function, and *APOE4* genotype status (Fig. 3).

4. Discussion

We report that in community dwelling midlife women without dementia, a history of pregnancy hypertension increased risk for AD pathology many decades later. Higher serum p-tau217 levels were still observed in women with pregnancy hypertension after adjustment for age, MCI, hypertension, BMI, renal function, and *APOE4* carrier status. Our findings merit consideration that a history of hypertensive disorders in pregnancy is a potential risk factor for Alzheimer's disease.

To our knowledge, this is the first investigation into the relationship between the history of pregnancy hypertension and AD pathology many decades later. Pregnancy hypertension is a multisystemic disorder unmasked by the gravid state. Starting with hypertension in the second half of pregnancy, the disease progresses to pre-eclampsia and eclampsia, resulting in greater risk for the subsequent development of hypertension, ischemic heart disease, stroke, and dementia [31]. Cerebral blood velocity responses can be altered in women with a history of preeclampsia, linking impairments in cerebrovascular regulation to the structural and functional changes in the brain [32].

Although cardiovascular disease, ministrokes and reduced cerebrovascular blood flow are recognized pathogenic mechanisms for Alzheimer's disease [33], it has been postulated that disorders of pregnancy hypertension may contribute more directly to AD pathology in the brain [34]. Tau hyperphosphorylation has been observed in animal models of preeclampsia and may be early etiological drivers for both pregnancy hypertension and pre-clinical Alzheimer's disease [35]. Cis p-tau, an early etiological driver and blood biomarker in pre-clinical Alzheimer's have been reported to be higher in the placenta and serum of pre-eclampsia patients [35]. Concentrations for p-tau181 in cerebro-spinal fluid obtained following regional anesthesia during pregnancy were higher in subjects with severe pregnancy hypertension compared to those with normal blood pressure [36]. Women with pre-eclampsia demonstrated 2.18-fold higher plasma concentrations of neurofilament light chain, 2.17-fold higher tau and 2.77-fold higher glial fibrillary acidic protein compared to women with normotensive pregnancies [37]. These diverse lines of evidence suggest abnormalities of protein processing in preeclampsia that may increase risk for

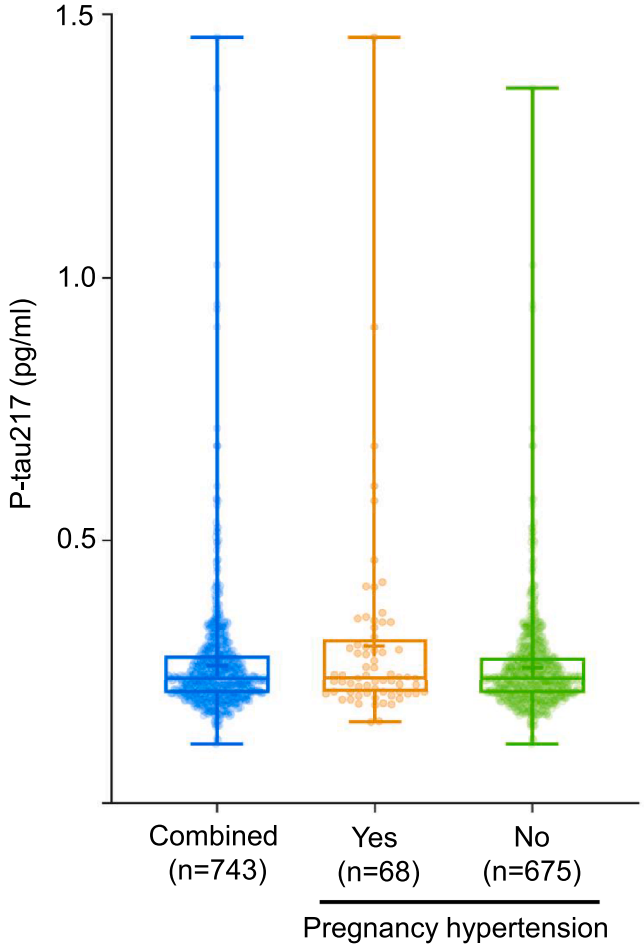

Fig. 2. Serum p-tau217 levels in the total cohort (n = 743), and in participants with (n = 68) and without pregnancy hypertension (n = 675). Boxplots reflect the minimum value, 25th, 50th, 75th percentiles, and maximum value. $^{+}$indicates the mean values in each of the three groups.

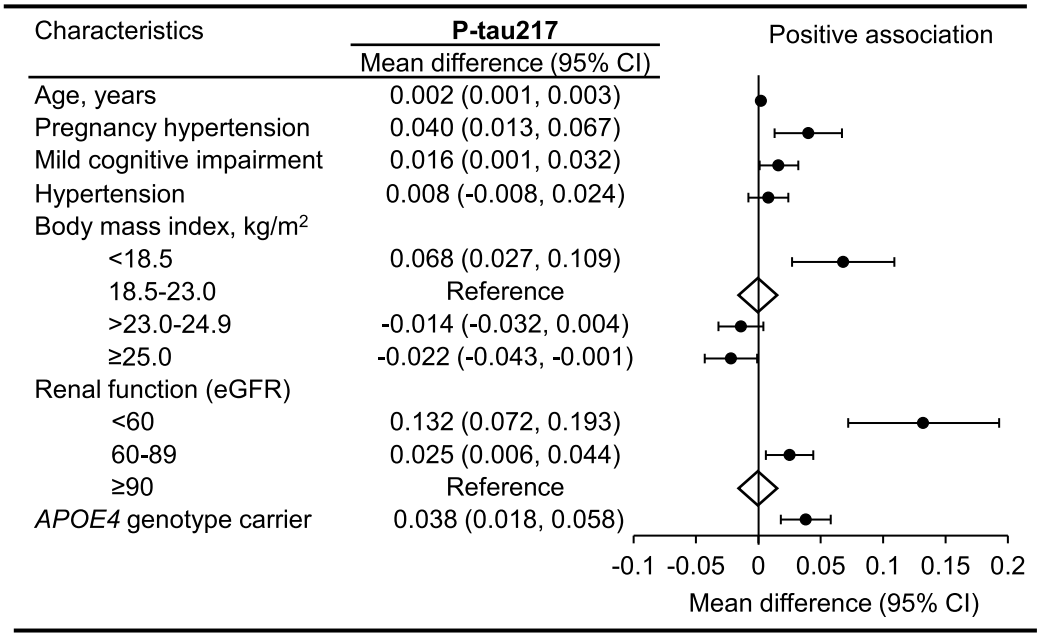

Fig. 3. General linear modelling showing the association between pregnancy hypertension and p-tau217 levels. Forest plot depicts the mean difference in p-tau217 (pg/ml) after mutual adjustment for age, MCI, hypertension, BMI, renal function, and *APOE4* genotype status in the same model. Results are presented as mean difference (95 % CI).

Alzheimer's disease in later life.

MCI is conceptualized as a transitional stage between normal aging and dementia. The MoCA-B tool, an instrument with good test–retest reliability and internal consistency [22], indicated a MCI prevalence of 42.3 % in our cohort of midlife women (mean age 62.9 ± 6.0 years), consistent with 36.2 % for subjects ≥55 years from a large Chinese study using MOCA [38]. Although a portion of these cases with MCI may be due to cerebral small vessel disease [39], our study suggests that Alzheimer's pathology contributes to MCI. Anticipating increased Alzheimer's disease risk will allow women with a history of pregnancy hypertension to receive additional support, early intervention, and close monitoring.

Our study needs to be interpreted considering several limitations. Firstly, pregnancy history was self-reported, which might be prone to recall bias since the events had a latency period of 32.1 years on average. Nevertheless, a study on low-birth-weight babies indicated 96.5 % sensitivity for pregnancy hypertension recall compared to that documented in obstetric case records [40]. Next, about 40 % of our cohort had MCI, which might have influenced reporting of pregnancy events. To address this, we have accounted for MCI as a covariate in adjusted analyses. We found that pregnancy hypertension was significantly associated with p-tau217 levels, independent of MCI. Thirdly, the cross-sectional design of this study makes it difficult to determine causality or temporality, although from a biological standpoint, pregnancy hypertension would naturally precede AD pathology. Fourth, although we have adjusted for current hypertension, MCI, renal function and *APOE4* carrier status; subjects with pregnancy hypertension may have other co-morbid conditions or residual confounders not considered in this study that increase risk for Alzheimer's disease. Fifth, the latency period (time since pregnancy) was not included as a covariate due to small numbers. Finally, our single center study identified only a relatively small number of subjects with pregnancy hypertension, which limit generalizability to other populations. There is a need to replicate our findings in other cohorts.

A key strength of this study was the use of a serum p-tau217 immunoassay that has been validated to accurately identify Alzheimer's disease, comparable with results using cerebral spinal fluid biomarkers and superior to brain atrophy assessments, with reproducible cut-offs across cohorts that can detect longitudinal changes at the preclinical stage [16,41,42]. Furthermore, key confounders such as age, MCI, hypertension, BMI, renal function, *APOE4* genotype, were accurately and rigorously quantified. If our findings are validated in other populations, one key implication is that obstetricians and primary care physicians should pay more attention to pregnancy hypertension as a risk factor for Alzheimer's Disease and brain health.

5. Conclusion

In summary, pregnancy hypertension was associated with AD pathology with mean differences similar to high risk *APOE4* carrier genotypes. Premature placental aging underlies early-onset preeclampsia [43] and pregnancy may be a stress factor that unmasks a latent inability to clear misfolded Aβ amyloid proteins, resulting in deposition of protein aggregates in the placenta and brain [44]. Abnormal dysregulation of protein homeostasis may be common to the development of both pregnancy hypertension and Alzheimer's disease [44]. Information on history of preeclampsia could help physicians to identify women who might benefit from early p-tau217 screening for Alzheimer's disease, allowing for early clinical intervention [35].

Author contributions

Prof. Yong has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Yong, Wong, Chong, Chen. *Acquisition, analysis, or interpretation of data:* Yong, Wong, Tan, Shen, Thia. *Drafting of the manuscript:* Yong, Wong, Shen. *Critical review of the manuscript for important intellectual content:* Yong, Wong, Tan, Shen, Chong, Chen. *Statistical analysis:* Wong, Shen, Thia. *Obtained funding:* Yong. *Administrative, technical, or material support:* Wong, Tan. *Supervision:* Yong, Chen.

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DATA sharing statement

Data cannot be shared publicly because of ethical-legal considerations and consent was not sought from study participants for public data sharing. However, data is available from the corresponding author for researchers who meet the criteria for access to confidential data at obgyel@nus.edu.sg.

Declaration of generative AI

We declare that no generative AI and AI-assisted technologies were used in this manuscript.

CRediT authorship contribution statement

Eu-Leong Yong: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Beverly Wen Xin Wong:** Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Conceptualization. **Darren Yuen Zhang Tan:** Writing – review & editing, Project administration, Formal analysis. **Liang Shen:** Writing – review & editing, Writing – original draft, Formal analysis. **Benecia Wan Qing Thia:** Formal analysis. **Joyce Ruifen Chong:** Writing – review & editing, Conceptualization. **Christopher Li-Hsian Chen:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100316.

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