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The role of Tau, amyloid-β and neuroinflammation in the association between cognition and white matter hyperintensities in a southeast Asian cohort

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STRUCTURED ABSTRACT

Background: Elevated Glial Fibrillary Acidic Protein (GFAP) is associated with increased Phosphorylated Tau 181 (pTau181) induced neurodegeneration in Alzheimer's Disease.
Objective: However, the role of GFAP and pTau181 in vascular/mixed dementias requires elucidation within the Southeast Asian context, where their burden is considerable.
Design: Population based cross-sectional study.
Setting: Biomarkers and Cognition Study, Singapore (BIOCIS).
Participants: Baseline data from $n = 583$ (40.3 % male), non-demented but at risk, Southeast Asian community participants, were included in this analysis. All participants displayed cognitive symptoms on the Subjective Memory Complaints Questionnaire, although they may or may not have objective cognitive deficits and did not meet the criteria for dementia as per the DSM – 5.
Methods: Neuropsychological assessments for executive function evaluation, volumetric White Matter Hyperintensities (WMH) measurement and plasma biomarker expression, were determined in non-demented but at risk, Southeast Asian research participants. Partial correlation analysis demonstrated variable associations. Simple moderation analysis revealed the ability for plasma biomarkers to influence the relationship between executive function and WMH.
Results: WMH burden positively correlated to Neurofilament-Light (NfL) and pTau181. Executive function and processing speed negatively correlated to WMH burden. GFAP positively correlated to pTau181 and negatively correlated to executive function. NfL, GFAP, pTau181, and Amyloid beta 42/Amyloid beta 40 (Aβ42/Aβ40) ratio independently moderated, the relationship between executive function/processing speed and WMH burden.
Conclusion: Inflammatory mechanisms represented by GFAP were linked to tau pathology and WMH and also moderated the association between WMH on cognitive performance.

1. Introduction

Cerebral Small Vessel Disease (CSVD) is an umbrella term that takes into account any damage (transient or irreversible) of the small cerebrovasculature, giving rise to cerebral ischemia and associated hypoperfusion events, which progressively culminate in white matter hyperintensities (WMH) and silent stroke development [1–3]. Epidemiologically CSVD affects 80 % of elderly individuals above the age of

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60, globally [2,4,5]. Amongst Asians, CSVD burden is increasingly prevalent with advancing age, vascular risk factors and deteriorating global cognition [6–8]. Within the Asian context, WMH has been demonstrated to be of higher prevalence (WMH: 28.1 % at 61 – 70 years of age and 65.2 % at $\geq$ 81 years of age) as compared to Amyloid beta (Aβ) positivity (Aβ Positivity: 20 % at 70 years of age and 40 % at 90 years of age) within cognitively normal subjects [6,7,9]. These findings suggests that vascular disease and associated cognitive impairment/-dementia syndromes, are more profound within Asian populations, as compared to their western counterparts where amyloid positivity has higher prevalence as compared with WMH burden [10–12].

Astrocytes are major neuroregulatory cells with a prime focus in cellular events that encapsulate the cerebrovasculature and are essential for neuronal homeostasis, metabolic support, cerebral blood flow regulation, maintenance of the blood-brain-barrier and synaptic function [13,14]. With natural aging, injuries and disease associated neurovascular insults, astrocytes adopt an altered reactive phenotype by undergoing hypertrophy - where they become potent contributors of cytokine induced inflammatory processes, associated pathological clearance and tissue repair [14]. The upregulation of the cytoskeletal intermediate filament, Glial Fibrillary Acidic Protein (GFAP) is a consequence of reactive astrocytes. Production of GFAP may result from reactive gliosis which may occur due to either protective or detrimental neuroinflammatory circumstances, wherein prolonged reactive gliosis may contribute to neurodegeneration resulting from a loss in neuroprotective effects [14–16].

Astrocyte reactivity is a critical neuroinflammatory feature of various neurodegenerative disorders, including Alzheimer's disease (AD) and other neurodegenerative conditions [14]. In the postmortem brains of the cognitively unimpaired, astrocyte reactivity is a common clinical manifestation and together with amyloid beta (Aβ) plaques, mark early pathological anomalies of AD [17]. WMH volume has demonstrated associations with global and domain specific cognitive dysfunction and are associated with an increased risk of mild cognitive impairment (MCI) and dementia (Alzheimer's, Vascular and all cause) [18–20]. Specifically, posterior WMH accumulation (eg. periventricular) has been found to be associated with amyloid burden and could therefore be a secondary consequence to AD, whereas frontal WMH accumulation had more vascular causes [21,22]. Increasing plasma GFAP has associations with volumetric WMH in incident dementia as well as in amyloid positivity, with known associations with cognition [23–25]. Evidence from preclinical dementia patients indicates that astrocyte reactivity is a critical feature accompanying Aβ induced phosphorylation of Tau [17]. Increasing plasma pTau181 demonstrates associations with volumetric WMH in prodromal AD, with a decrease in global and domain specific (executive function, episodic memory, visuospatial function and semantic fluency) cognition observed [26].

An outstanding question is the biomarker associated contributions to the pathophysiology of vascular and mixed type presentation of cognitive impairment within the Southeast Asian context, where their burden is considerable [6,27,28]. Therefore, the objective of this cross-sectional study was to examine the specific associations between plasma GFAP, Aβ and pTau181 and WMH, a surrogate marker of CSVD and executive function in community dwelling non-demented, Southeast Asians, at risk of dementia [7].

2. Methods

2.1. Study participants

This cross-sectional study used baseline data from 583, non-demented but at risk, Southeast Asian community participants, who were recruited into the Biomarker and Cognition Study (BIOCIS), an ongoing longitudinal study, at the Dementia Research Centre (Singapore) [8]. Kindly view Leow et al. 2024 for detailed information on the study cohort [8] . Key BIOCIS inclusion criteria include participants aged between 30 and 95 years of age, who are English/-Mandarin literate and have a presence of a subtle cognitive concern [8]. All participants must have displayed cognitive symptoms on the Subjective Memory Complaints Questionnaire [29]. They may or may not have had objective cognitive deficits and did not meet criteria for dementia as per the DSM - 5 [30]. Key BIOCIS exclusion criteria include illiteracy, diagnosis of a major neurological, psychiatric, or systemic disease [8]. Informed consent was obtained from all participants and all methods and procedures employed in this study were in accordance with ethical guidelines [8]. This study was conducted in accordance with the declaration of Helsinki, together with local clinical research regulations and University Institutional Review Board (IRB) regulations and was granted IRB approval (NTU-IRB-2021–1036) [8].

2.2. Cognitive assessment tools

Neuropsychological assessments, evaluating the cognitive domains of executive function and processing speed were administered by trained research psychologists. Executive function test included the Trail Making Test B, Colour Trails 2 and Digit Span Backwards. Processing speed tests included the Colour Trails 1 and Symbol Digit Modalities. Upon administration, all cumulative test scores were converted and presented as composite Z scores [31]. The computation of Z-scores involved the subtraction of normative mean as derived from 70 cognitively normal research participants, from raw test scores (for the cognitive tests as described), followed by the division of that mean by the normative standard deviation. For time-based assessments, the resulting Z-scores were multiplied by −1 to account for the inverse scoring. Domain specific Z scores involved averaging the relevant test Z scores to form a composite Z score.

2.3. Sample processing

Blood samples were drawn via venepuncture by trained phlebotomists into ethylenediaminetetraacetic acid (EDTA) vacutainers and left standing at ambient temperature for 30 min, prior to processing. Upon processing, the blood samples were centrifuged at 2000 g for a duration of 10 min at 4 °C, and blood plasma was aliquoted accordingly and stored at –80 °C.

2.4. Biochemical analysis

Plasma biomarkers (Neurofilament Light – NfL, Glial Fibrillary Acidic Protein - GFAP, Amyloid beta - Aβ40, Amyloid beta 42 - Aβ42, Phosphorylated Tau 181 - pTau181) were quantified using Quanterix's Single Molecule Array (Simoa) platform. The following kits - Neurology 4-PlexE (NfL, GFAP, Aβ40, Aβ42) and pTau181 Advantage V2.1 kits, were used to perform the expression analysis on the HD-X Analyzer (Quanterix, Billerica, MA, USA), in accordance with manufacturer's protocol and instructions.

2.5. Neuroimaging analysis

MRI scanning was performed on the 3T Prisma Fit System platform (Siemens, Erlangen, Germany). T1-weighted Magnetization Prepared Rapid Gradient Echo and T2-Fluid Attenuated Inversion Recovery images were obtained [32]. Independent visual ratings to quantify WMH lesions based on the modified Fazekas scale (0 to 12) were conducted, where a score of 0 to 4 was defined as absent to mild cerebrovascular disease (CVD) and a score of 5 to 12 was defined as moderate to severe CVD (as detailed in [27,33]). Image processing was carried out using the Statistical Parametric Mapping (SPM 12 – https://www.fil.ion.ucl.ac.uk/spm/) based Computational Anatomy Toolbox (CAT – https://dbm.neuro.uni-jena.de/cat12/) and Lesion Segmentation Toolbox (LST version 2.0.15) for the extraction of binary WMH lesion belief maps using the automated lesion prediction algorithm (as detailed in [32]).

Total WMH lesion volume was obtained using the exact values of interest option within the Lesion Segmentation Toolbox and normalized using total intracranial volume (as detailed in [32]). This ratio was log transformed for use in statistical analysis (as detailed in [32]).

2.6. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 29.0, Armonk, NY, IBM Corp) and Microsoft Excel for Microsoft 365 (Version 2404, Redmond, Washington, US, Microsoft). Means and associated proportions were calculated for all variables. A partial correlation analysis (controlled for confounders Age, Gender and Education) was used to demonstrate correlative associations between two variables. Bivariate relationship combinations involving - log transformed White Matter Hyperintensities/Intracranial Volume (WMH/TIV ratio) with Cognition (Executive Function and Processing Speed) and log transformed plasma biomarkers (NfL, pTau181, Aβ42/Aβ40 and GFAP), were examined by partial correlation. A moderation analysis was performed using the PROCESS Macro model version 4.2, by *Hayes* for SPSS, to determine if log biomarkers NfL, pTau181, Aβ 42/Aβ40 and GFAP moderated the relationship between cognition and log WMH/TIV ratio, via linear regression analysis with the inclusion of interaction terms (log WMH/TIV ratio X log biomarker), within the whole study cohort and stratified study cohort in accordance with amyloid (Aβ42/Aβ40 ≤ 0.05) and vascular burden (Modified Fazekas ≥ 5) [34]. P-value of $P < 0.05$ were considered statistically significant. Any association with a P-value of $P > 0.05$ but less than 0.1, were referred to as trending associations.

3. Results

3.1. Demographics and clinical characteristics

The mean, age for the 583 participants was 60.55 (±SD 10.27) years and education was 14.40 (±SD 3.54) years, with 40.3 % of the study cohort belonging to the male gender. Within the study cohort, 23.67 % were amyloid positive and 44.05 % had high vascular burden with moderate to severe WMH burden. Notably, in participants <50 years, 64.89 % (n = 61) demonstrated WMH burden of Fazekas grade 1 severity (mild burden) and 10.64 % (n = 10) demonstrated WMH burden of Fazekas grade 2 severity (moderate burden). The mean global cognitive measures (MoCA and VCAT) and percentage of the cohort with Diabetes Mellitus, Hypertension and Hyperlipidaemia are as presented in Table 1.

Table 1
Cohort demographics and clinical characteristics (n = 583).

Demographics and Clinical Characteristics (n = 583)	Mean±SD
Demographics and Vascular Risk Factors	
Age, years (Mean±SD)	60.55 ± 10.27
Education, years (Mean ± SD)	14.40 ± 3.54
Gender - male (%)	n = 235 /583 (40.31)
Diabetes Mellitus (%)	n = 81 /583 (13.89)
Hypertension (%)	n = 143 /583 (24.53)
Hyperlipidaemia (%)	n = 244 /583 (41.85)
Systolic Blood Pressure, mmhg (Mean ± SD)	126.89 ± 18.48
Diastolic Blood Pressure, mmhg (Mean ± SD)	78.04 ± 11.36
Total Cholesterol, mmol/L (Mean ± SD)	5.35 ± 1.08
High Density Lipoprotein Cholesterol, mmol/L (Mean ± SD)	1.68 ± 0.43
Low Density Lipoprotein Cholesterol, mmol/L (Mean ± SD)	3.14 ± 0.90
Cholesterol/High Density Lipoprotein ratio, mmol/L (Mean ± SD)	3.35 ± 0.90
Triglycerides, mmol/L (Mean ± SD)	1.17 ± 0.61
Fasting Glucose, mmol/L(Mean ± SD)	5.23 ± 1.11
Glycated Hemoglobin, A1C (%)	5.92 ± 0.70
Plasma Biomarkers	
Neurofilament Light, mean concentration, pg/ml (Mean ± SD)	15.12 ± 9.48
Neurofilament Light, Log (Mean ± SD)	1.12 ± 0.23
Amyloid Beta 42, mean concentration, pg/ml (Mean ± SD)	5.14 ± 2.00
Amyloid Beta 42, Log (Mean ± SD)	0.68 ± 0.18
Amyloid Beta 40, mean concentration, pg/ml (Mean ± SD)	79.27 ± 24.78
Amyloid Beta 40, Log (Mean ± SD)	1.87 ± 0.16
Glial Fibrillary Acidic Protein, mean concentration, pg/ml (Mean ± SD)	87.65 ± 45.65
Glial Fibrillary Acidic Protein, Log (Mean ± SD)	1.89 ± 0.21
Phosphorylated Tau181, mean concentration, pg/ml (Mean ± SD)	18.40 ± 7.99
Phosphorylated Tau181, Log (Mean ± SD)	1.23 ± 0.16
Amyloid Beta 42/Amyloid Beta 40, Ratio (Mean ± SD), Amyloid positive, ≤0.05,n, (%)	0.07 ± 0.353, n = 138/583 (23.67)
Amyloid Beta 42/Amyloid Beta 40, Ratio, Log (Mean ± SD)	−1.2 ± 0.12
Cognitive Characteristics	
Montreal Cognitive Assessment - Adjusted for Age	25.5 ± 2.62
Visual Cognitive Assessment Test	26.46 ± 2.92
Episodic Memory, Z Score (Mean ± SD)	−0.40 ± 0.84
Executive Function, Z Score (Mean ± SD)	−0.58 ± 1.21
Processing Speed, Z Score (Mean ± SD)	−0.29 ± 0.89
Visuospatial Abilities, Z Score (Mean ± SD)	−0.27 ± 0.91
Language Z Score, Score (Mean ± SD)	−0.37 ± 1.33
Neuroimaging Measures	
Modified Fazekas White Matter Hyperintensities Scale, Score (Mean ± SD), Fazekas 5 and above, n, (%)	4.24 ± 2.82, n = 237/538 (44.05)
White Matter Hyperintensities Volume / Total Intracranial Volume, Ratio (Mean ± SD)	0.0016 ± 0.0023
White Matter Hyperintensities Volume / Total Intracranial Volume, Ratio, Log (Mean ± SD)	−2.97 ± 0.36

3.2. WMH burden positively correlates with plasma NfL and pTau

WMH burden as determined by log transformed WMH/TIV ratio, was significantly positively correlated to plasma NfL (Table 2, $R = 0.150$, p-value = ≤ 0.001) and pTau181 (Table 2, $R = 0.107$, p-value = ≤ 0.01). WMH burden did not demonstrate any association with plasma GFAP (Table 2, $R = 0.036$, p-value = 0.389) and plasma Aβ42/Aβ40 ratio (Table 2, $R = -0.055$, p-value = 0.184).

3.3. WMH burden negatively correlates with cognitive measures

Executive function is significantly negatively correlated to WMH/TIV ratio (Table 2, $R = -0.089$, p-value = <0.05). Processing speed did not demonstrate any association with WMH/TIV ratio (Table 2, $R = -0.060$, p-value = 0.150).

3.4. Influence of GFAP on pTau181, WMH burden and cognition

Plasma GFAP is significantly positively correlated to pTau181 (Table 2, $R = 0.142$, p-value = ≤ 0.001, Fig. 1D) and NfL (Table 2, $R = 0.342$, p-value = ≤ 0.0001, Fig. 1A) and significantly negatively correlated to executive function (Table 2, $R = -0.098$, p-value = < 0.05) and processing speed (Table 2, $R = -0.083$, p-value = < 0.05). Plasma NfL was significantly positively correlated with pTau181 (Table 2, $R = 0.320$, p-value = ≤ 0.0001, Fig. 1B), negatively correlated with Aβ42/Aβ40 ratio (Table 2, $R = -0.087$, p-value = < 0.05, Fig. 1C) and demonstrated a negative correlative trend with executive function (Table 2, $R = -0.077$, p-value = 0.063). Plasma pTau181 was significantly negatively correlated with processing speed (Table 2, $R = -0.104$, p-value = < 0.05), and demonstrated a negative correlative trend with executive function (Table 2, $R = -0.074$, p-value = 0.075) and Aβ42/Aβ40 ratio (Table 2, $R = -0.077$, p-value = 0.065, Fig. 1F). All bivariate associations between blood-based biomarkers, WMH burden and cognition are detailed in Table 2.

Table 2
Partial Correlations, respective p-values (asterisks) and r values are presented, $n = 583$ (Controlled for Age, Education and Gender).

	WMH / TIV	Executive Function	Processing Speed	NfL	GFAP	pTau 181	Aβ42 / Aβ40
WMH / TIV	1.000						
Executive Function	* −0.089	1.000					
Processing Speed	ns (0.150) −0.060	**** 0.547	1.000				
NfL	*** 0.150	ns (0.063, trending) −0.077	ns (0.282) −0.045	1.000			
GFAP	ns (0.389) 0.036	* −0. 098	* −0.083	**** 0.342, Fig 1A	1.000		
pTau181	** 0.107	ns (0.075, trending), −0.074,	* −0.104	**** 0.320, Fig 1B	*** 0.142, Fig 1D	1.000	
Aβ42 / Aβ40	ns (0.184), −0.055	ns (0.240), 0.049	ns (0.284), 0.045	* −0.087, Fig 1C	ns (0.179), 0.056, Fig 1E	ns (0.065, trending), −0.077, Fig 1F	1.000

Legend. p-value: ns ($P > 0.05$), * ($P < 0.05$), ** ($P \leq 0.01$), *** ($P \leq 0.001$), **** ($P \leq 0.0001$). Any association with a P-value of $P > 0.05$ but less than 0.1, were referred to as a trending association.

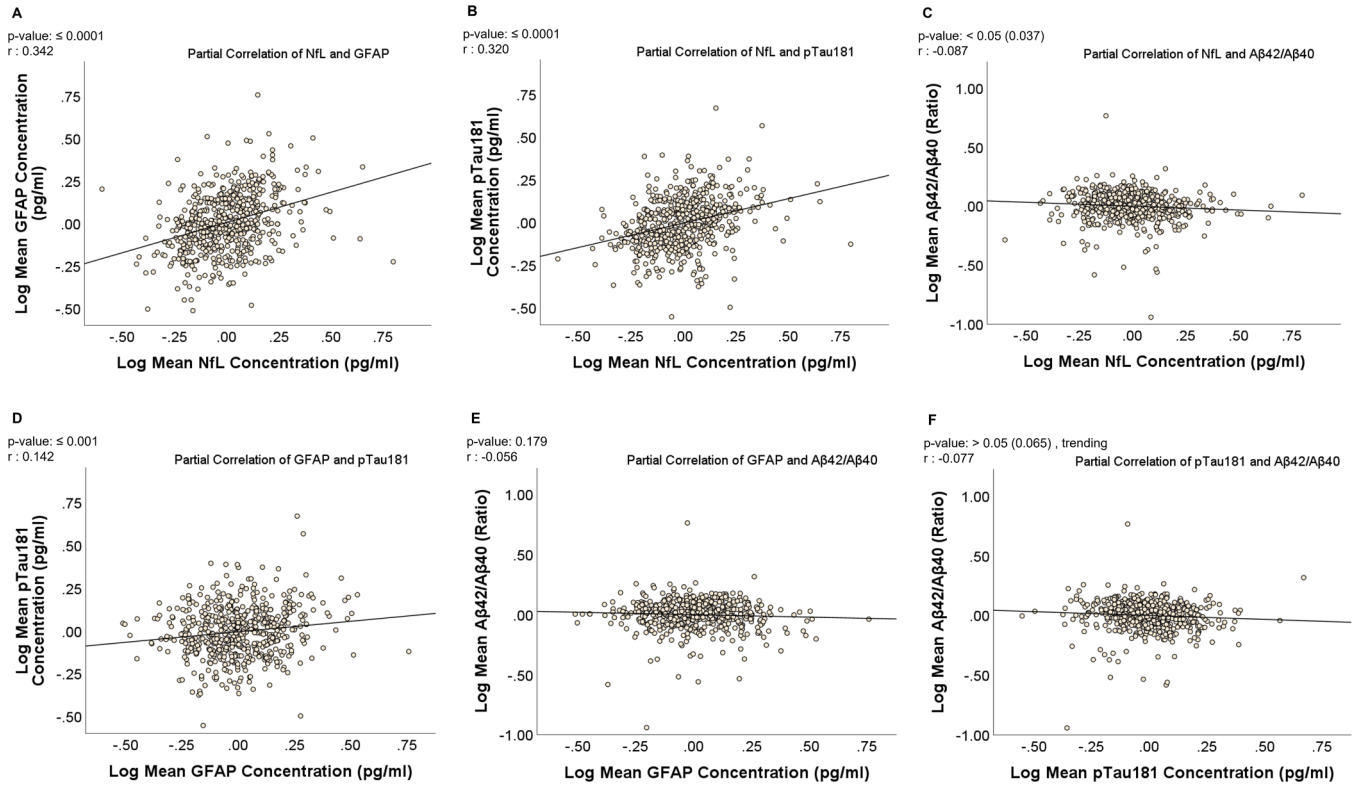

Fig. 1. Plasma biomarkers demonstrate significant correlative associations. Figures A to F depict scatter plots of the partial correlations (controlled for Age, Education and Gender) of the respective correlations. p-value: ns ($P > 0.05$), * ($P < 0.05$), ** ($P \leq 0.01$), *** ($P \leq 0.001$), **** ($P \leq 0.0001$). Any association with a P-value of $P > 0.05$ but less than 0.1, were referred to as a trending association.

3.5. Plasma biomarkers moderate the relationship between executive function/ processing speed and WMH burden

Simple moderation analysis reveals the moderating effects of various pathological markers on the relationship between WMH burden and measures of executive function. Increasing WMH burden relates to deteriorating executive function, with increasing plasma NfL (Fig. 2A, p-value = ≤ 0.001), increasing GFAP (Fig. 2B, p-value = ≤ 0.01) and increasing pTau181 (Fig. 2C, p-value = ≤ 0.001), and lower plasma Aβ42/Aβ40 ratio (Fig. 2D, p-value = < 0.05 (0.031)), lower ratio suggesting higher amyloid-β burden), respectively. Increasing WMH burden relates to deteriorating information processing speed, with increasing plasma NfL (Fig. 3A, p-value = ≤ 0.001) and pTau181 (Fig. 3B, p-value = < 0.05 (0.013)) and lower plasma Aβ42/Aβ40 ratio (Fig. 3C, p-value = < 0.05 (0.022)), respectively. These effects remain unchanged even after controlling for diagnosis.

3.6. Plasma biomarkers moderate the relationship between executive function/ processing speed and WMH burden, when stratified according to amyloid and vascular burden

Upon stratification of the study cohort according to amyloid and vascular burden, moderation analysis was performed, and results reveal that NfL was a key moderator in the relationship between WMH and executive function/processing speed across all groups while pTau181 was a key moderator between WMH and executive function in amyloid

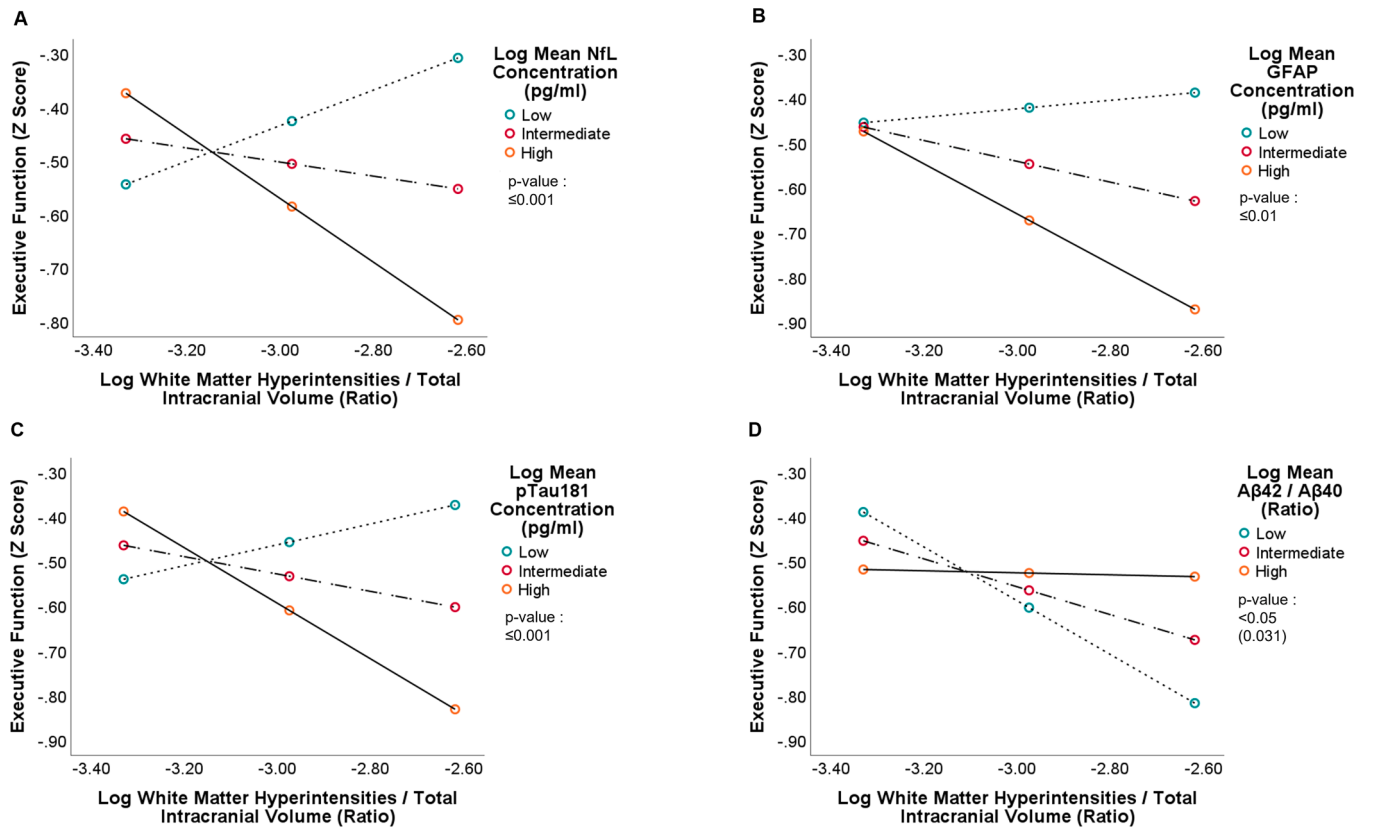

Fig. 2. Plasma biomarkers independently influence the relationship between Executive Function and WMH burden. Significant positive moderation effect with NfL (A), GFAP (B), pTau181 (C) and Aβ40/Aβ42 (D) [low Aβ40/Aβ42 indicates higher amyloid load]. P - values indicate the interaction terms (log WMH/TIV ratio X biomarker). These effects remain unchanged even after controlling diagnosis.

positive groups only (Table 3).

4. Discussion

This cross-sectional study evaluated the correlative associations between plasma biomarkers (pTau181, GFAP and Aβ42/Aβ40), WMH burden and cognition, in a non-demented but at risk, Southeast Asian cohort. Our findings demonstrate NfL and pTau181 to be significantly increased with higher WMH burden. Executive function scores were significantly lower, while information processing speed scores demonstrated a lower correlative trend with higher WMH burden. The GFAP biomarker of astrogliosis was found to be significantly increased with higher levels of pTau181 and with lower executive function as well as processing speed scores. We also demonstrate the relationship between WMH burden and executive function to be positively moderated by NfL, pTau181, GFAP and Aβ42/Aβ40. The relationship between WMH burden and processing speed was positively moderated by NfL, pTau181 and Aβ42/Aβ40. Upon stratification of the study cohort according to amyloid and vascular burden, the relationship between WMH burden and executive function/processing was moderated by NfL across all subgroups whereas the relationship between executive function and WMH was moderated by pTau181 in amyloid positivity only.

Plasma NfL has been previously demonstrated to be significantly increased with increasing WMH burden, in line with our findings (Table 2)[35]. Upon axonal damage/injury; NfL gets released into the extracellular space and is resultantly increased in biofluids [36]. Axonal damage has been found to be key to the acute development of WMH, preceding white matter hypoperfusion induced demyelination due to oligodendrocyte death, which is key to chronic WMH propagation [37, 38]. Interestingly, systemic inflammatory profiles have associations with WMH [39]. Systemic inflammation has also been found to be related to axonal damage as represented by a predicted increase in NfL [40]. Therefore, resultant axonal damage, neuroinflammatory mechanisms and perfusion dynamics could therefore explain the increase of NfL with higher WMH, in our cohort.

Our findings demonstrate that plasma pTau181 is significantly increased with high WMH burden in line with literature (Table 2) [26, 41]. In its hyperphosphorylated state, pathologic Tau induced neurofibrillary tangles (together with Amyloid pathology) are known to impair axonal transport, influence axonal homeostasis and thereby induce axonal degeneration [42]. Degenerative white matter changes as a consequence of hyperphosphorylated Tau has been found to lead to WMH pathology [43–45]. Furthermore, neuroinflammatory mechanisms which have known associations with WMH are potent exacerbators of Tau pathology and further aggravate downstream inflammatory responses [39,46,47]. Therefore, resultant axonal degeneration and an interplay of neuroinflammatory responses could explain the association of higher pTau181 with higher WMH, in our cohort.

Plasma GFAP has been demonstrated to be significantly increased with increasing WMH burden, however this is not in line with our findings (Table 2) [23]. Nevertheless, the observed increase in GFAP as reported by Shir et al., was found to be driven by amyloid pathology [23]. This emphasizes the possibility of an indirect effect of GFAP on WMH burden, within out cohort. Plasma biomarkers revealed significant correlative associations, whereby plasma NfL was significantly increased with increasing GFAP and pTau181 (Table 2, Fig. 1A and 1B). This suggests that the presence of astrocyte reactivity (which can be triggered by Amyloid, Tau and further vascular consequences, besides its numerous homeostatic functions) is a likely contributor to neurodegeneration in our cohort [48,49]. Based on work by Garwood et al. and Bellaver et al., there is evidence suggesting that the propagation of Tau is a subsequent event following astrocyte reactivity [17,50]. This is

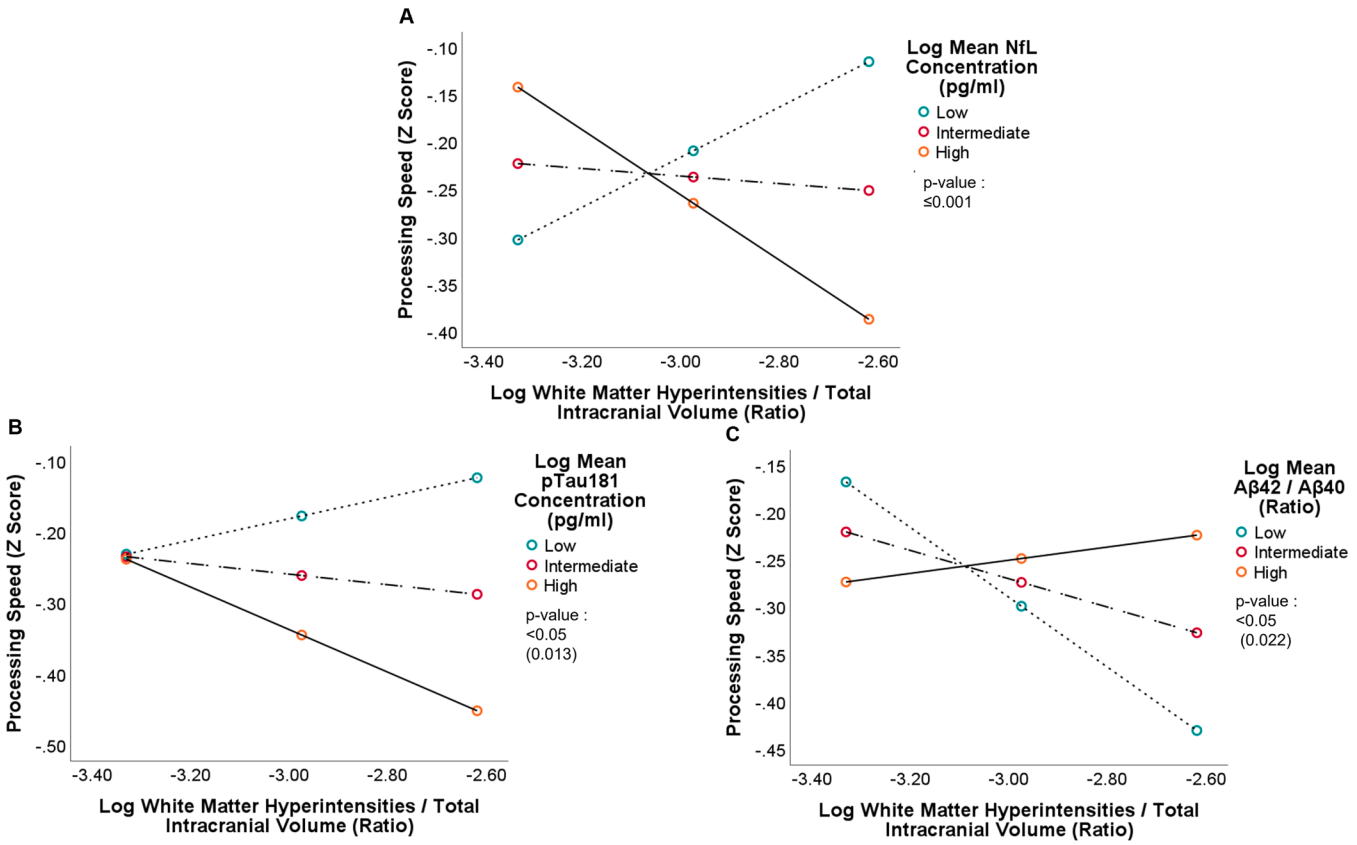

Fig. 3. Plasma biomarkers independently influence the relationship between Information Processing Speed and WMH burden. Significant positive moderation effect with NfL (A) pTau181 (B) and Aβ40/Aβ42 (C) [low Aβ40/Aβ42 indicates higher amyloid load]. P - values indicate the interaction terms (log WMH/TIV ratio X biomarker). These effects remain unchanged even after controlling diagnosis.

Table 3
Moderation subgroup analysis in research participants stratified according to amyloid and vascular burden, respective p-values are presented, $n = 583$ (Controlled for Age, Education and Gender).

Biomarker moderation of relationship between WMH and cognition (Controlled for Age, Education and Gender)		A-V-: Low Amyloid, Low Vascular Load ($n = 278$)	$A + V$-: High Amyloid, Low Vascular Load ($n = 68$)	A-V+: Low Amyloid, High Vascular Load ($n = 167$)	$A + V$+: High Amyloid, High Vascular Load ($n = 70$)
Executive Function	**WMH / TIV X NfL**	$p = 0.025$*	$p = 0.014$*	$p = 0.093$, trending	$p = 0.039$*
	WMH / TIV X GFAP	$p = 0.149$	$p = 0.882$	$p = 0.118$	$p = 0.715$
	WMH / TIV X pTau181	$p = 0.168$	$p = 0.036$*	$p = 0.072$, trending	$p = 0.646$
Processing Speed	**WMH / TIV X NfL**	$p = 0.191$	$p = 0.021$*	$p = 0.641$	$p = 0.033$*
	WMH / TIV X GFAP	$p = 0.709$	$p = 0.343$	$p = 0.867$	$p = 0.846$
	WMH / TIV X pTau181	$p = 0.445$	$p = 0.210$	$p = 0.544$	$p = 0.863$

Legend. p-value: * Significant moderation effects. Any association with a P-value of $P > 0.05$ but less than 0.1, were referred to as a trending association.

in line with our findings wherein GFAP was found to be significantly increased with increasing pTau181 (Table 2, Fig. 1D). pTau181 continued to demonstrate an increasing trend with decreasing Aβ42/Aβ40, in line with literature (Table 2, Fig. 1F) [51]. This emphasizes the presence of amyloid dependent and independent (vascular induced) activation of the astrocyte reactivity phenomenon within our cohort. When a correlative association between GFAP and Aβ42/Aβ40 was assessed, albeit an increase in GFAP was observed with decreasing Aβ42/Aβ40 ratio, this increase was insignificant likely due to the mixed pathological phenotypic presentation observed within our cohort.

The ability for plasma biomarkers to independently moderate effects between executive function (Executive Function and Processing Speed) and volumetric WMH were assessed (Figs. 2 and 3). Increasing plasma NfL has known associations with decreasing global cognition, executive function, processing speed and increasing WMH burden respectively [35,41,52–54]. This could explain its positive influence on the relationship between executive function/processing speed and volumetric WMH in our cohort (Fig. 2A and 3A, Table 3). Increasing plasma GFAP has known associations with decreasing global cognition, executive function and processing speed and increasing WMH burden respectively [23,54,55]. This could explain its positive influence on the relationship between executive function and volumetric WMH in our non demented but at-risk cohort (Fig. 2B). Increasing pTau181 has known associations with increasing WMH burden and decreasing global and domain specific cognition (except processing speed) in prodromal AD [26,41,54]. This could explain its positive influence on the relationship between executive function and volumetric WMH in our non demented but at-risk cohort (Fig. 2C, Table 3). Furthermore, pTau181 associated influence on the relationship between processing speed and volumetric WMH has yet to be reported (Fig. 3B). Decreasing plasma Aβ42/Aβ40 has known associations with cognitive decline, decrease processing speed and

increasing WMH burden respectively [5,53,54,56]. This could explain its positive influence on the relationship between processing speed and volumetric WMH in our cohort (Fig. 3C). Furthermore, Aβ42/Aβ40 associated influence on the relationship between executive function and volumetric WMH has yet to be reported (Fig. 2D). Holistically, plasma NfL, GFAP, pTau181 and Aβ42/A40's ability to moderate the relationship between cognitive measures (Executive Function/Processing Speed) and WMH indicate a convergence at the ability for systemic neuroinflammatory processes to influence the magnitude of WMH development and its degenerative effects on executive function. To the best of our knowledge, this study is the first to report the ability for plasma biomarkers to significantly influence the relationship between cognitive performance and volumetric WMH, in individuals who are not demented but at risk of developing dementia.

This cross – sectional study has several strengths and limitations. Strengths of this study include evaluation of a cohort having early-stage cognitive impairment, which allows early disease contributory alterations to be identified. Other strengths include the availability of neuroimaging and comprehensive blood biomarker panels as well as the relatively large sample size. Nevertheless, this study also has some limitations; whereby albeit significant, the moderation effects were small, which is likely a result of the early pathological stage of the study cohort. The cross-sectional and observational nature of our community-based study has inherent limitations in drawing causal inferences and generalizability of our findings to clinical outcomes. Our analyses also may have missed controlling for potential confounders such as baseline systemic inflammation status or other unmeasured variables which also impact the generalizability of our findings. A longitudinal follow up is thus necessary to further study this moderation effect and evaluate causality, which will be addressed once longitudinal data becomes available. Additionally, the influence of genetics (eg. APOE4 burden which is considerably lower in Southeast Asians) and polymorphic (eg. NOTCH3) effects on the relationship between plasma biomarkers, cognition and WMH burden, has yet to be explored in this context and are being planned [8,57,58]. Furthermore, WMH are a comorbidity and not a primary pathology of Alzheimer's dementia and thus the contribution of other cerebrovascular disease markers and vascular risk factors on primary dementia pathology will need to be addressed in future studies. In conclusion, findings from this study indicate that neuroinflammatory mediators play an important role in dementia pathology in Southeast Asians - the pathobiology could be a result of early upstream astrocyte mediated modulation of Blood-Brain Barrier permeability and resultant perfusion dynamics, and its impact on Aβ clearance. pTau181 facilitated events are likely downstream effects of GFAP induced astrocyte reactivity, irrespective of amyloidosis. Further mechanistic validation in a more stratified cohort, with longitudinal data is necessary and in progress.

Author contributions

G.K.S and A.V developed and designed the study, conducted experimental design and execution, data acquisition and associated data analyses and prepared the manuscript and figures; J.L contributed to sample collection, processing, the execution of the biochemical analyses experiments and data analyses of the cognitive assessment data; F.Z.Z and S.X.Y contributed to sample collection, processing and the execution of the biochemical analyses experiments; P.T, F.P.L.H.E, S.X.Y, S.G, L.Y. J, L.S.Y and G.B contributed to the acquisition and analyses of the cognitive assessment data; R.B.S.M.S and Q.B contributed to the acquisition and analyses of the neuroimaging data; N.K developed and designed the study, acquired funding, conducted experimental design and data analyses and prepared the manuscript and figures, as well as performed the final review of the manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors have nothing to declare. No generative AI and AI-assisted technologies were used in the writing process.

CRediT authorship contribution statement

Gurveen Kaur Sandhu: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ashwati Vipin:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jacklyn Leonardo:** Project administration, Methodology, Investigation, Formal analysis, Data curation. **Fatin Zahra Zailan:** Project administration, Investigation, Data curation. **Pricilia Tanoto:** Project administration, Methodology, Investigation, Formal analysis, Data curation. **Faith Phemie Hui En Lee:** Project administration, Investigation, Formal analysis, Data curation. **Xin Ying Sim:** Project administration, Investigation, Formal analysis, Data curation. **Smriti Ghildiyal:** Project administration, Investigation, Formal analysis, Data curation. **Yi Jin Leow:** Project administration, Investigation, Formal analysis, Data curation. **Shan Yao Liew:** Project administration, Investigation, Formal analysis, Data curation. **Gursimar Bhalla:** Project administration, Investigation, Formal analysis, Data curation. **Rasyiqah Binte Shaik Mohamed Salim:** Project administration, Investigation, Formal analysis, Data curation. **Bocheng Qiu:** Project administration, Investigation, Formal analysis, Data curation. **Nagaendran Kandiah:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Conflict of interest statement

The authors declare no competing interest. The authors have nothing to disclose.

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