The Journal of Prevention of Alzheimer's Disease 12 (2025) 100086

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

White matter hyperintensity severity modifies gut metabolite association with cognitive outcomes

Naruchorn Kijpaisalratana[a,b,c,d], Chia-Ling Phuah[e,f], Zsuzsanna Ament[a,d], Varun M. Bhave[g], Ana-Lucia Garcia-Guarniz[d], Jonathan Duskin[d], Catharine A. Couch[h], M. Ryan Irvin[h], W. Taylor Kimberly[a,d,g,*], for the Alzheimer's Disease Neuroimaging Initiative[1], and the Alzheimer Disease Metabolomics Consortium[2]

[a] Center for Genomic Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[b] Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[c] Division of Academic Affairs, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[d] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
[e] Departments of Neurology and Neurosurgery, Barrow Neurological Institute, Phoenix, AZ, USA
[f] Barrow Neuro Analytics Center, Barrow Neurological Institute, Phoenix, AZ, USA
[g] Harvard Medical School, Boston, MA, USA
[h] Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA

ARTICLE INFO

Keywords:
Gut metabolite
White matter hyperintensity
Cognitive impairment
Dementia

ABSTRACT

Background: Gut microbiome-associated metabolites and white matter hyperintensities (WMH) are independently associated with cognitive impairment. However, it is unclear if gut metabolites and WMH interact to influence dementia.

Objectives: To examine the association between gut microbial metabolites and cognitive outcomes and assess whether the severity of baseline WMH would impact associations between gut microbial metabolites and cognitive outcomes.

Design: Cross-sectional design. Setting: Cohort of individuals who are clinically normal, mild cognitive impairment, or Alzheimer's Disease in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Participants: A total of 578 participants with available baseline 3.0T 2D-Fluid Attenuation Inversion Recovery (FLAIR) Magnetic Resonance Imaging (MRI) scans and baseline gut microbial metabolite measurement were included in the analysis.

Measurements: Gut metabolite measurements and automated WMH volume estimations were obtained from FLAIR MRI and were used to assess the association and interaction with cognitive impairment.

Results: Of 104 metabolites studied, glycodeoxycholic acid (GDCA) surpassed the false discovery rate and was associated the Alzheimer's Disease Assessment Scale-Cognitive Subscale version 13 (ADAS-Cog13) score ($\beta = 0.12$, 95 % CI = 0.05–0.20, $p = 0.001$) and cognitive impairment determined by mini-mental status exam (MMSE) (OR = 2.11, 95 % CI = 1.41–3.15, $p < 0.001$). GDCA was associated with higher ADAS-Cog13 in participants with low WMH burden ($\beta = 0.21$, 95% CI = 0.10–0.32, $p < 0.001$) but not in participants with high WMH burden ($\beta = 0.04$, 95 % CI = -0.07 to 0.14, $p = 0.48$; interaction $p = 0.02$).

Conclusion: An elevated level of GDCA was associated with worse cognition. WMH severity modified the association between GDCA and cognitive outcomes.

* Corresponding author at: 55 Fruit Street, Lunder 644, Boston, MA 02114 USA.
E-mail address: wtkimberly@mgh.harvard.edu (W.T. Kimberly).

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

[2] Data used in preparation of this article were generated by the Alzheimer's Disease Metabolomics Consortium (ADMC). As such, the investigators within the ADMC provided data but did not participate in analysis or writing of this report. A complete listing of ADMC investigators can be found at: https://sites.duke.edu/adnimetab/team/.

https://doi.org/10.1016/j.tjpad.2025.100086
Received 23 July 2024; Accepted 28 November 2024
Available online 11 February 2025

1. Introduction

The prevalence of dementia continues to increase [1–3] and is predicted to triple by 2050 [1]. Forty percent of dementia worldwide may result from modifiable risk factors [4]. A better understanding of modifiable risk factors that contribute to cognitive impairment is essential for the prevention of dementia.

Increasing evidence points towards a role of gut-brain interactions, which impacts brain health and is linked to neurodegenerative disease [5–9]. The routes of communication between the gut and the brain include several potential mechanisms, including vagus nerve activation and enterochromaffin cell activation, immune-mediated signaling, and gut-derived metabolites [5,10]. Gut microbial metabolites can be classified into 3 types, including diet-derived products, microbial co-metabolites, and intermediary metabolites [10,11]. Both animal and human studies demonstrate associations between the gut microbiota or its metabolites and cognitive impairment, including Alzheimer's disease [5,10,12].

White matter hyperintensities (WMH) are well-characterized imaging features of cerebral small vessel disease (CVSD) [13,14]. They are also a prominent feature in dementia due to both vascular contribution to cognitive impairment and dementia (VCID) [15] and Alzheimer's disease [16,17]. The distinction between Alzheimer's disease and VCID is challenging clinically [18–20]. However, a community-based neuropathological study demonstrated that most elderly individuals had mixed disease [21]. In the setting of known neurodegenerative disease, WMH contribute to cognitive impairment by lowering the threshold for clinical dementia [22]. In addition, WMH may have an additive interaction with Alzheimer's disease pathology [15,23].

Despite independent evidence sugesting associations of both gut metabolites and WMH with cognitive impairment, evidence for potential interaction between gut metabolites and WMH in association with cognitive impairment is lacking. Understanding the interaction between multiple exposures could provide insight into health disparities [24]. For example, evidence suggests that mid-life exposure to vascular risk factors has a stronger impact on cognitive outcomes than late-life exposure [25].

In this study, we aimed to explore the link between gut metabolites, WMH, and cognitive impairment. Several vascular risk factors, such as hypertension, diabetes, and hypercholesterolemia, are risk factors for the development and progression of WMH [19,26,27]. Since metabolite levels can reflect modifiable health behaviors and lifestyles that impact the development of disease [28], understanding the interaction between the metabolites and WMH in association with cognitive impairment could shed light on the appropriate timing of interventions to modify health behaviors that are essential for successful dementia prevention.

The objectives of this study were to determine the association between gut microbial metabolites and cognitive outcomes and assess whether the severity of baseline WMH could impact associations between gut microbial metabolites and cognitive outcomes. In this analysis, we used global and region-based WMH burden derived from etiology-specific WMH topographies [29] to classify the WMH severity into a high vs. low burden. This approach allowed the assessment of whether the WMH burden is an effect modifier in the relationship between gut metabolites and cognitive impairment. We hypothesized that the severity of the WMH would impact the association between gut metabolites and cognitive impairment.

2. Methods

2.1. Study design and population

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/). The ADNI study design has been described elsewhere [30,31]. In brief, participants between the ages of 55 and 90 who spoke English or Spanish fluently and were cognitively normal (CN), had mild cognitive impairment (MCI), or had Alzheimer's disease (AD) without other significant neurological diseases were enrolled. Participants were followed to determine the progression of cognitive impairment using serial measurements of clinical and neuropsychological assessments and biomarkers.

Participants with available baseline 3.0T 2D-FLAIR MRI scans and gut microbial metabolite measurements were included in this study. The ADNI datasets for this study were downloaded in May 2023. Key variables extracted for our analysis include age, years of education, use of antihypertensive, antihyperglycemic, and lipid-lowering medications, smoking, *APOE* genotype, the Alzheimer's Disease Assessment Scale 13-item Cognitive Subscale (ADAS-Cog13), Mini-Mental State Examination (MMSE), metabolite measurements, and cortical standardized uptake value ratio (SUVR) from amyloid positron emission tomography (PET) performed within 12 months of the brain MRI scan.

2.2. Cognitive assessment

Baseline cognitive assessments using the ADAS-Cog13 and MMSE formed the cognitive outcomes in this study. The ADAS-Cog13 score ranges from 0 to 85, with higher scores reflecting worsening cognitive function. Since the ADAS-Cog13 scores did not conform to a normal distribution, the scores were rank-based inverse normal transformed prior to statistical analysis. The MMSE score measures the total number of correct answers with a maximum score of 30, with lower scores reflecting worsening cognitive function. In this study, we identified participants with cognitive impairment by using an MMSE score cut-off of 23 or less [32].

2.3. Image processing for global and region of interest (roi)-based white matter hyperintensities

Automated WMH volume estimations were obtained from FLAIR MRI using a validated convolutional neural network-based segmentation method, as described previously [29]. In brief, standard preprocessing of FLAIR and T1 MRI images, including skull-stripping, co-registration of FLAIR to corresponding T1 images, bias field correction, and intensity harmonization by z-score normalization, were performed using openly available imaging software, including Statistical Parametric Mapping (SPM) and the FMRIB Software Library (FSL) [33]. Voxel-wise WMH probabilistic maps were then calculated by a trained deep neural network [29] using axial FLAIR MRI as input. Finalized WMH maps were co-registered to their corresponding T1-weighted images, spatially aligned, and nonlinearly registered to the ICBM-152 brain template using Advanced Normalization Tools (ANT) [34] and FMRIB's Linear Image Registration Tool (FLIRT). The threshold used for WMH probability maps was ≥ 50 % probability, i.e. the WMH burden was calculated based on the volume of voxels with WMH threshold of ≥0.5. The deep learning network used in our study was previously validated against manual WMH segmentations by experts and the UCD four-tissue segmentation method used by ADNI [29]. The co-registered and standardized individual WMH probability maps were then overlaid on a custom template created for delineating the distribution of five specific WMH spatial topographies, including juxtacortical, deep frontal, periventricular, parietal, and posterior. These topographies were previously identified using data-driven multivariate clustering analysis and demonstrated unique associations with distinct vascular and amyloid CSVD, and AD etiopathologies [29]. We applied this imaging pipeline to the study data to obtain estimations of global and regional WMH volumes within each of the five spatial topographies.

In this study, the total WMH represents the total volume of WMH burden, while the spatial WMH was the relative WMH volume for each region of interest (ROI) or WMH spatial topography adjusted for the total WMH [29]. Values for total and spatial WMH were rank-based inverse normal transformed prior to statistical analysis.

2.4. Amyloid burden parameters

The ^{18}F-florbetapir (FBP) AV45 PET was used to quantify brain amyloid. Details of image acquisition and the processing methods have been described elsewhere [35]. The global Aβ burden was based on a sum of the SUVR of weighted FBP mean uptake in 4 cortical regions, including frontal, lateral temporal, lateral parietal, and cingulate, and normalized to the uptake in the cerebellum. The data for FBP PET analyses in this study were obtained from the ADNI database using the PET scan performed within 1 year of the baseline FLAIR MRI [29]. The SUVR were rank-based inverse normal transformed prior to statistical analysis.

The details of *APOE* genotyping have been described previously [36]. All *APOE* genotype data were subjected to quality control checks, including sex and identity checks. The finalized quality-controlled data was obtained from the ADNI database. The number of *APOE* ε4 alleles was analyzed as a categorical variable [29].

The diagnosis of cerebral amyloid angiopathy (CAA) was performed using T2*-weighted MRIs to assess for presence and number of lobar cerebral microbleeds and cortical superficial siderosis based on the Modified Boston Criteria v1.5 [29,37].

2.5. Metabolite measurements

Gut metabolite data was obtained from the ADNI database. Details of the metabolite measurements are available at https://adni.bitbucket.io/reference/admcgutmetaboliteslong.html. Briefly, fasting serum samples obtained at the baseline visit were used for the extraction of metabolites. Targeted metabolomics profiling of 104 metabolites was performed at the University of Hawaii Cancer Center using an ultra-performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS) system (ACQUITY UPLC-Xevo TQ-S, Waters Corp., Milford, MA). This panel of metabolites is a representative of gut microbial metabolites and bile acids. The peak integration, calibration, and quantification of each metabolite were processed by TMBQ software (v1.0, HMI, Shenzhen, Guandong, China) [38,39]. All values of metabolite levels were logarithmically transformed prior to analysis [38].

2.6. Statistical analyses

Since the objective of this study was to assess the impact of the burden of WMH on the association between metabolites and cognitive outcomes, total WMH volume was dichotomized using the median which corresponds to the Fazekas score of 2 [40,41]. Baseline characteristics of continuous variables were presented as mean ± standard deviation or median with interquartile range based on their distribution. Categorical variables were presented as frequency and percentage. The baseline characteristics between the high and low WMH burden groups were compared using *t*-test, Wilcoxon rank-sum test, and chi-square test for normally distributed continuous, non-normal continuous, and categorical variables, respectively.

First, we identified the gut metabolites associated with cognitive performance as determined by the ADAS-Cog13 score as the primary analysis using linear regression adjusted for age, sex, education, and vascular risk factors, including hypertension, diabetes, hyperlipidemia, and smoking. We also evaluated the association between the gut metabolites and cognitive impairment defined by MMSE using logistic regression with similar adjustment for covariates. Metabolites that surpassed the Benjamini-Hochberg [42] false discovery rate (FDR) of 10 % for 104 tested metabolites were carried forward in the next step.

Next, to determine whether total WMH burden was an effect modifier in the association between candidate gut metabolites and cognitive performance, we examined a metabolite-by-WMH burden interaction in association with the ADAS-Cog13 score in a linear regression adjusted for age, sex, education, hypertension, diabetes, hyperlipidemia, and smoking.

Finally, we assessed whether etiology-associated WMH spatial topographies were an effect modifier in the association between ADAS-Cog13 scores and the gut metabolites for which total WMH burden was an effect modifier. In this analysis, we used a linear regression model adjusted for age, sex, education, hypertension, diabetes, hyperlipidemia, and smoking. We also included the amyloid burden determined by the APOE ε4 genotype and the global Aβ burden from the FBP PET analyses as the covariates in this analysis, as our prior study demonstrated that amyloid burden was associated with different spatial patterns of WMH [29]. All statistical analyzes were performed using STATA version 17.0 (StataCorp, LLC., College Station, TX).

3. Results

3.1. Study population and baseline characteristics

There were 1046 participants with 2D-FLAIR sequences available for WMH analysis [29]. Among these, 578 participants had available gut microbiome metabolite measurements at baseline. The median volume of WMH, which was used as a cut-off point was 12.62 [6.73,22.81] cc. This cut-off value corresponds to the Fazekas score of 2 in prior studies [40,41]. Participants with high WMH burden were older and had fewer years of education, a higher prevalence of hypertension, higher amyloid burden, and higher ADAS-Cog13 scores. The proportion of participants with Alzheimer's disease was also higher in the high WMH burden group (Table 1).

3.2. Gut microbial metabolites and cognitive outcomes

Among 104 metabolites, 18 metabolites were associated with cognitive performance as determined by ADAS-Cog13 scores with a nominal *p-value* <0.05. However, only two bile acids—glycodeoxycholic acid (GDCA) and glycohyodeoxycholic acid (GHDCA)—surpassed the 10 % FDR threshold. Higher levels of both GDCA (β = 0.12, 95 % CI = 0.05–0.20, p = 0.001) and GHDCA (β = 0.12, 95 % CI = 0.05–0.19, p < 0.001) were associated with higher ADAS-Cog13 scores, consistent with worse cognitive performance. We also assessed the associations between the 104 metabolites and cognitive impairment determined by the MMSE [32]. Only GDCA was associated with cognitive impairment and surpassed the FDR threshold (OR = 2.11, 95 % CI = 1.41–3.15, p < 0.001) (Table 2).

3.3. White matter hyperintensity as an effect modifier of the gut microbial metabolites

Since WMH volume has been associated with cognitive function [19,26], we explored whether WMH burden (high versus low) modified the effect of both GDCA and GHDCA on cognition. The association between GDCA and cognitive performance measured by ADAS-Cog13 differed by the severity of the total WMH burden (p for interaction = 0.02). Specifically, GDCA was associated with worsened cognition in participants with low WMH burden (β = 0.21, 95 % CI = 0.10–0.32, p < 0.001) but not in participants with high WMH burden (β = 0.04, 95 % CI = -0.07 to 0.14, p = 0.48). We also performed a sensitivity analysis to determine the significance of the interaction between GDCA and WMH burden in association with cognitive function when WMH burden was treated as a continuous variable (β = -0.08, 95 % CI = -0.15 to -0.003, p = 0.04). This analysis also indicated that increased severity of WMH attenuates the association between GDCA and cognitive function. There were no differential effects in the association between GHDCA and cognitive outcome according to the severity of WMH (p for interaction = 0.66) (Table 3).

Table 1
Baseline characteristics of the study population.

Characteristics	All (n = 578)	Low WMH (289)	High WMH (289)	*p* value
Age, years, mean (SD)	72.56 (7.35)	69.34 (6.7)	75.78 (6.5)	<0.001
Male, N(%)	309 (53.46)	153 (52.94)	156 (53.98)	0.80
Female, N(%)	269 (46.54)	136 (47.06)	133 (46.02)	
Education, years, median [IQR]	16 [14,18]	16 [15,18]	16 [14,18]	0.002
Vascular risk factors, N(%)				
- Hypertension	261 (45.16)	107 (37.02)	154 (53.29)	<0.001
- Diabetes mellitus	60 (10.38)	31 (10.73)	29 (10.03)	0.79
Hyperlipidemia	247 (42.73)	124 (42.91)	123 (42.56)	0.93
- Current smoker	227 (39.27)	105 (36.33)	122 (42.21)	0.15
APOE ε4, N(%)				0.60
- 1 allele	200 (58.13)	95 (32.87)	105 (36.63)	
- 2 alleles	42 (7.27)	20 (6.92)	22 (7.61)	
Amyloid SUVR, median [IQR]	1.11 [1.01,1.34]	1.06 [1.00,1.27]	1.19 [1.02,1.38]	<0.001
Abnormal amyloid PET (SUVR≥1.1), n(%)	290 (51.06)	116 (40.56)	174 (61.70)	<0.001
CAA, N(%)				<0.001
- Probable CAA	59 (10.21)	17 (5.88)	42 (14.53)	
- Possible CAA	124 (21.45)	55 (19.03)	69 (23.88)	
ADAS-Cog 13, median [IQR]	12 [8,18]	11 [7,15.5]	14 [9,20]	<0.001
Total WMH (cc)*, median [IQR]	12.62 [6.73,22.81]	6.73 [4.68,9.54]	22.81 [17.27,33.29]	<0.001
- Juxtacortical	0.03 [0.02,0.07]	0.02 [0.01,0.04]	0.06 [0.03, 0.11]	<0.001
- Parietal	0.08 [0.03,0.15]	0.03 [0.01,0.07]	0.14 [0.09,0.19]	<0.001
- Frontal	0.13 [0.07,0.21]	0.09 [0.05,0.14]	0.18 [0.11,0.29]	<0.001
- Posterior	0.15 [0.08,0.23]	0.13 [0.07,0.19]	0.18 [0.09,0.27]	<0.001
- Periventricular	0.47 [0.36,0.59]	0.52 [0.43,0.64]	0.42 [0.32,0.52]	<0.001
Diagnosis in ADNI, N(%)				0.02
- Cognitively Normal	191 (33.04)	96 (33.22)	95 (32.87)	
- Early Mild Cognitive Impairment	222 (38.41)	124 (42.91)	98 (33.91)	
- Late Mild Cognitive Impairment	124 (21.45)	56 (19.38)	69 (23.53)	
- Alzheimer's Disease	41 (7.09)	13 (4.50)	28 (9.69)	

* Regional WMH are relative WMH adjusted for total WMH

Table 2
Associations between gut metabolites and cognitive outcomes.

Metabolites	ADAS-Cog 13 (n = 578)†		Cognitive impairment (n = 578)‡	
	β (95 %CI)	*p* value	OR= (95 %CI)	*p* value
Glycodeoxycholic Acid	0.12 (0.05–0.20)	0.001*	2.11 (1.41–3.15)	<0.001*
Glycohyodeoxycholic Acid	0.12 (0.05–0.19)	<0.001*	1.60 (1.14–2.24)	0.006
Hippuric Acid	-0.11 (-0.18 to -0.03)	0.007	0.61 (0.41–0.90)	0.01
Apocholic Acid	0.11 (0.03–0.18)	0.007	1.41 (0.96–2.06)	0.08
Deoxycholic Acid	0.09 (0.02–0.17)	0.02	1.67 (1.13–2.46)	0.01
Taurodeoxycholic Acid	0.10 (0.02–0.18)	0.02	1.72 (1.14–2.59)	0.01
3-Oxocholic Acid	0.10 (0.02–0.18)	0.02	1.64 (1.06–2.53)	0.03
Murocholic Acid	0.09 (0.02–0.16)	0.02	1.55 (1.07–2.24)	0.02
Lithocholic Acid 3-Sulfate	0.09 (0.01–0.17)	0.02	1.34 (0.90–2.01)	0.15
Glycolithocholic Acid	0.09 (0.01–0.17)	0.02	1.51 (1.01–2.26)	0.05
p-Cresol Sulfate	0.09 (0.01–0.17)	0.02	1.30 (0.88–1.93)	0.18
L-Tryptophan	-0.09 (-0.18 to -0.01)	0.02	1.02 (0.68–1.53)	0.94
Nordeoxycholic Acid	0.08 (0.01–0.16)	0.03	1.48 (1.02–2.16)	0.04
Gamma-Linoleic Acid	0.09 (0.01–0.16)	0.03	1.10 (0.75–1.63)	0.63
3-Methyl-2-Oxovaleric Acid	-0.09 (-0.17 to -0.01)	0.03	0.79 (0.52–1.20)	0.27
Cholic Acid	-0.09 (-0.17 to -0.01)	0.03	0.87 (0.59–1.30)	0.51
L-Malic Acid	0.09 (0.00–0.17)	0.04	1.19 (0.77–1.82)	0.43
L-Serine	-0.09 (-0.17 to 0.00)	0.04	0.72 (0.47–1.09)	0.12

* Surpassed the Benjamini-Hochberg false discovery rate of 10 % for 104 tests.
† β represents and p values were obtained from linear regressions, and the outcome was the ADAS-Cog 13 score (rank-based inverse normal transformed). Models were corrected for age, sex, education, smoking, hypertension, diabetes, and hyperlipidemia
‡ Odds ratios (OR) and p values were obtained from logistic regressions. Models were corrected for age, sex, education, smoking, hypertension, diabetes, and hyperlipidemia.

Table 3
Total WMH as an effect modifier in the association between metabolite and cognitive performance.

Metabolites	Low WMH*		High WMH*		*p* for interaction
	β (95 %CI)	*p* value	β (95 %CI)	*p* value	
Glycodeoxycholic Acid	0.21 (0.1–0.32)	<0.001	0.04 (-0.07 to 0.14)	0.48	0.02
Glycohyodeoxycholic Acid	0.13 (0.04–0.22)	0.005	0.10 (0.00–0.19)	0.04	0.66

* β represents and p values were obtained from linear regressions. The outcome was the ADAS-Cog 13 score (rank-based inverse normal transformed). Models were corrected for age, sex, education, smoking, and usage of antihypertensive, antidiabetic, and lipid-lowering agents. Models were corrected for age, sex, education, smoking, hypertension, diabetes, and hyperlipidemia. Interaction test was performed in a non-stratified analysis.

Table 4
Association between GDCA and cognitive outcome in different regions of WMH.

	Low WMH*		High WMH*		*p* for interaction
	β (95 %CI)	*p* value	*β* (95 %CI)	*p* value	
Total WMH	0.23 (0.12–0.33)	<0.001	0.03 (-0.07 to 0.13)	0.55	0.014
- Juxtacortical	0.21 (0.10–0.32)	<0.001	0.05 (-0.05 to 0.15)	0.29	0.046
- Parietal	0.21 (0.11–0.32)	<0.001	0.03 (-0.08 to 0.13)	0.65	0.016
- Posterior	0.17 (0.07–0.27)	0.001	0.07 (-0.04 to 0.18)	0.22	0.118
- Frontal	0.11 (0.00–0.21)	0.04	0.12 (0.01–0.22)	0.03	0.923
- Periventricular	0.06 (-0.05 to 0.17)	0.26	0.18 (0.08–0.28)	0.001	0.169

* *β* represents and p values were obtained from linear regressions. The outcome was the ADAS-Cog 13 score (rank-based inverse normal transformed). Models were corrected for age, sex, education, smoking, hypertension, diabetes, hyperlipidemia, APOE ε4 genotype, and amyloid SUVR. Interaction test was performed in a non-stratified analysis.

3.4. White matter hyperintensity spatial patterns modify gdca association with cognition

Next, we examined the effects of regional WMH on the association between GDCA and ADAS-Cog13 in a linear regression model adjusted for age, sex, education, vascular risk factors, APOE ε4 genotype, and brain amyloid burden. We examined associations with five previously identified spatial patterns that reflect different underlying etiologies, including juxtacortical, deep frontal, periventricular, parietal, and posterior WMH [29]. Among these five patterns, the association between GDCA and cognitive outcome differed by the severity of WMH in the juxtacortical (p for interaction = 0.046) and parietal regions (p for interaction = 0.016), two regions associated with CAA and AD pathologies [29]. Accordingly, in a subgroup analysis, GDCA was associated with an increase in ADAS-Cog13 in participants with a low burden of WMH in the juxtacortical ($\beta = 0.21$, 95 % CI = 0.10–0.32, $p < 0.001$) and parietal regions ($\beta = 0.21$, 95 % CI = 0.11–0.32, $p < 0.001$) (Table 4). A sensitivity analysis in a model that excluded amyloid burden (including both APOE ε4 allele status and amyloid SUVR) yielded comparable results to the main findings (Table S1).

4. Discussion

In this study, we identified GDCA as a gut microbial metabolite that is associated with cognitive impairment. We also demonstrated that the severity of global WMH burden modified the association between GDCA and cognitive outcomes. Specifically, GDCA was associated with worse cognition amongst those with a lower burden of WMH. The effect remained significant independent of brain amyloid burden.

Bile acids are an important class of gut microbiota metabolites [43]. They are microbe-host co-metabolites that are synthesized from cholesterol and play an important role in lipid metabolism [10,43]. In prior ADNI studies, alterations in bile acid profiles were found in patients with Alzheimer's disease [38,44]. Lower serum primary bile acids and increased secondary bile acid were observed in patients with Alzheimer's disease compared to cognitively normal participants. Secondary conjugated bile acids, including GDCA, were identified to be associated with higher ADAS-Cog13 scores, reflecting worse cognition. In addition, an increase in the ratio between secondary to primary bile acids was associated with cognitive impairment and predicted the progression of the cognitive impairment [38]. Bile acids were also shown to be associated with neuroimaging and CSF biomarkers related to cognitive impairment. Higher levels of secondary bile acids, including GDCA, and their ratio to the primary bile acids, were associated with a decrease in hippocampal volume, reduction in cortical thickness in several brain regions, and reduction in glucose metabolism. Regarding the amyloid burden, the ratio between GDCA and cholic acid, which is its primary bile acid, was negatively associated with CSF Aβ_{1-42} values and marginally associated with global cortical amyloid load [44]. These findings were in line with our study where we demonstrated the association between GDCA and cognitive impairment as determined by both ADAS-Cog13 scores and MMSE.

GDCA is a glycine-conjugated form of a secondary bile acid, deoxycholic acid (DCA), which is considered a cytotoxic bile acid [38,45]. The cytotoxic effect of DCA results from the disruption of mitochondrial membranes, leading to apoptosis [38,46]. In addition to cytotoxicity, DCA also increases the permeability of the blood-brain barrier and may enter the brain [38,47]. Although the unconjugated form of bile acid, such as DCA, appears to have a more cytotoxic effect than the conjugated form [48], it is likely that the highly toxic DCA is rapidly metabolized to the less toxic form of GDCA, resulting in the detection of its metabolite rather than DCA itself [49]. This cytotoxic effect of DCA could alter brain physiology and play a role in cognitive impairment, though the exact pathophysiology remains to be fully elucidated. [38,47].

WMH is a neuroimaging finding seen in MRI, particularly in the elderly. It represents changes in the water content of the white matter tracts resulting from pathologies such as demyelination, axonal loss, and gliosis [15,19,26]. Chronic hypoxia and ischemia are proposed as the main cause of WMH. Subsequent disruption of the blood-brain barrier resulting from ischemia also leads to the leakage of macromolecules such as albumin and other plasma proteins, leading to microglia and astrocyte activation [15,19]. The association between WMH and cognitive impairment has been demonstrated in several studies [50–52]. This evidence is also supported by a recent meta-analysis, suggesting that WMH is associated with an increased risk of cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer's disease [53]. Cognitive decline in WMH is related to reduced processing speed and executive function [15,19].

Although there is evidence separately connecting bile acids and WMH with cognitive impairment, the relationship between these two risk factors and cognitive function has not been described elsewhere. In this study, we demonstrated that the WMH burden had a differential effect on GDCA in association with cognitive impairment. The impact of secondary bile acids, specifically GDCA, on cognitive impairment was pronounced in participants with a lower burden of WMH. The association remained significant after adjusting for vascular risk factors and amyloid burden. Since different regions of WMH could reflect different underlying pathologies, we also assessed if the regional WMH burden had differential effects on the association between GDCA and cognitive impairment. We adopted 5 spatial WMH patterns identified in our prior study, including juxtacortical, deep frontal, periventricular, parietal, and posterior WMH. These spatial patterns were associated with different etiologies. Brain amyloid burden was associated with juxtacortical and parietal WMH, while risk factors for arteriolosclerosis, including hypertension and diabetes mellitus, were associated with deep frontal WMH. Age was associated with all of the identified spatial patterns. Among these 5 patterns, juxtacortical and parietal WMH were associated with dementia [29]. In this study, we found that the burden of WMH in the juxtacortical and parietal regions had differential effects on the association between GDCA and cognitive impairment. GDCA was associated with poor cognitive outcomes in those with a lower burden

WMH in the juxtacortical and parietal regions. There were no differential effects of WMH burden in other regions.

Our findings suggest that once structural changes become evident through the presence of a significant WMH burden, the association of GDCA on cognition becomes less pronounced. The differential effects of regional WMH burden also support this hypothesis in that once a high WMH burden is present in an area associated with brain amyloid burden and clinical dementia (i.e., the juxtacortical and parietal regions), the GDCA level has less impact on cognitive outcome. This is also supported by a study of the dose-response association between WMH and dementia, in which the association was demonstrated only above moderate severity WMH [53]. The association between GDCA and cognitive impairment in participants with a lower WMH burden identified in our study suggests the potential for early dementia prevention before apparent white matter changes. These highlight the potential of GDCA as the target for intervention for dementia prevention by modifying the GDCA level at the early stage prior to the substantial burden of WMH.

The strengths of this study include the study design of the ADNI cohort, which is a population-based cohort with well-phenotyped characteristics, including cognitive assessments, neuroimaging, and genetic profiles. However, there are some limitations in the study. Due to the observational design of the ADNI study and the cross-sectional analysis, the associations found in this study do not imply a specific directionality in the association or a causal relationship. The ADNI cohort enrolled participants with cognitive impairment predominantly related to amyloid-related pathology, which may limit the generalizability of our findings. Nevertheless, our findings remained significant even after adjustment for the amyloid burden using both the APOE $\varepsilon 4$ genotype and brain amyloid from PET scans. Future prospective studies on the modification of the GDCA level in specific populations, such as those with a lower WMH burden, are warranted to validate the effect of GDCA on cognitive impairment in a prospective study.

5. Conclusions

Appropriate timing of interventions, such as lifestyle modification, is essential for successful prevention of cognitive impairment. In this study, we identified GDCA, a secondary conjugated bile acid, that was associated with cognitive impairment. Using WMH phenotyping, we also demonstrated that the severity of WMH modified the association between GDCA and cognitive impairment. GDCA was associated with worse cognitive outcomes among those with lower total WMH burden, specifically in the juxtacortical and parietal regions. The associations remained unchanged after adjusting for both vascular risk factors and amyloid-related parameters. Our findings suggest that GDCA has a more significant relationship to cognitive impairment in the setting of a lower WMH burden, which highlights the potential role of GDCA in early dementia prevention.

Fundings

This work was supported by the NIH R01 NS099209 (W.T.K.), and the Andrew David Heitman Neurovascular Foundation (A.A.G.G.). C.P. is supported by NIH K23 NS110927, the Charleston Conference for Alzheimer's Disease New Vision Investigator Award, and the Barrow Neurological Foundation. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Ethics approval and consent to participate

Written informed consent, including permission for analysis and data sharing, was obtained from all study participants at the time of enrollment. The original study was approved by the Institutional Review Boards of each participating institution, and the secondary analysis was approved by the Mass General Brigham Institutional Review Board. All human subjects from the ADNI database that met the inclusion criteria were included in this study, irrespective of age, race, gender, and ethnicity. All received data were de-identified.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100086.

References

[1] Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health 2022;7:e105–ee25. doi:10.1016/S2468-2667(21)00249-8.

[2] Catindig J-AS, Venketasubramanian N, Ikram MK, Chen C. Epidemiology of dementia in Asia: insights on prevalence, trends and novel risk factors. J Neurol Sci 2012;321:11–16. doi:10.1016/j.jns.2012.07.023.

[3] Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019. Front Aging Neurosci 2022:14. doi:10.3389/fnagi.2022.937486.

[4] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the LancetCommission. The Lancet 2020;396:413–46. doi:10.1016/S0140-6736(20)30367-6.

[5] Needham BD, Kaddurah-Daouk R, Mazmanian SK. Gut microbial molecules in behavioural and neurodegenerative conditions. Nat Rev Neurosci 2020;21:717–31. doi:10.1038/s41583-020-00381-0.

[6] Kim C-S. Roles of diet-associated gut microbial metabolites on brain health: cell-to-cell interactions between gut bacteria and the Central nervous system. Adv Nutr 2024;15:100136. doi:10.1016/j.advnut.2023.10.008.

[7] Tremlett H, Bauer KC, Appel-Cresswell S, Finlay BB, Waubant E. The gut microbiome in human neurological disease: a review. Ann Neurol 2017;81:369–82. doi:10.1002/ana.24901.

[8] Klingelhoefer L, Reichmann H. Pathogenesis of Parkinson disease–the gut-brain axis and environmental factors. Nat Rev Neurol 2015;11:625–36. doi:10.1038/nrneurol.2015.197.

[9] Dinan TG, Cryan JF. Gut-brain axis in 2016: brain-gut-microbiota axis – mood, metabolism and behaviour. Nat Rev Gastroenterol Hepatol 2017;14:69–70. doi:10.1038/nrgastro.2016.200.

[10] Zhu G, Zhao J, Zhang H, Wang G, Chen W. Gut microbiota and its metabolites: bridge of dietary nutrients and Alzheimer's disease. Adv Nutr 2023;14:819–39. doi:10.1016/j.advnut.2023.04.005.

[11] Zheng X, Cai X, Hao H. Emerging targetome and signalome landscape of gut microbial metabolites. Cell Metab 2022;34:35–58. doi:10.1016/j.cmet.2021.12.011.

[12] Baloni P, Funk CC, Yan J, Yurkovich JT, Kueider-Paisley A, Nho K, et al. Metabolic network analysis reveals altered bile acid synthesis and metabolism in Alzheimer's disease. Cell Rep Med 2020;1:100138. doi:10.1016/j.xcrm.2020.100138.

[13] Rost NS, Etherton M. Cerebral small vessel disease. Continuum (Minneap Minn) 2020;26:332–52. doi:10.1212/con.0000000000000841.
[14] Johansen MC, Gottesman RF, Kral BG, Vaidya D, Yanek LR, Becker LC, et al. Association of coronary artery atherosclerosis with brain white matter hyperintensity. Stroke 2021;52:2594–600. doi:10.1161/strokeaha.120.032674.
[15] Alber J, Alladi S, Bae HJ, Barton DA, Beckett LA, Bell JM, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): knowledge gaps and opportunities. Alzheimers Dement (N Y) 2019;5:107–17. doi:10.1016/j.trci.2019.02.001.
[16] Alosco ML, Sugarman MA, Besser LM, Tripodis Y, Martin B, Palmisano JN, et al. A clinicopathological investigation of white matter hyperintensities and Alzheimer's Disease neuropathology. J Alzheimers Dis 2018;63:1347–60. doi:10.3233/jad-180017.
[17] Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TL, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network. Ann Neurol 2016;79:929–39. doi:10.1002/ana.24647.
[18] Jørgensen IF, Aguayo-Orozco A, Lademann M, Brunak S. Age-stratified longitudinal study of Alzheimer's and vascular dementia patients. Alzheimer's Dementia 2020;16:908–17. doi:10.1002/alz.12091.
[19] Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. Nat Rev Neurol 2015;11:157–65. doi:10.1038/nrneurol.2015.10.
[20] Custodio N, Montesinos R, Lira D, Herrera-Pérez E, Bardales Y, Valeriano-Lorenzo L. Mixed dementia: A review of the evidence. Dement Neuropsychol 2017;11:364–70. doi:10.1590/1980-57642016dn11-040005.
[21] Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. The Lancet 2001;357:169–75. doi:10.1016/S0140-6736(00)03589-3.
[22] Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol 2017;134:171–86. doi:10.1007/s00401-017-1717-7.
[23] Vemuri P, Knopman DS. The role of cerebrovascular disease when there is concomitant Alzheimer disease. Biochim Biophys Acta (BBA) - Mol Basis Dis 2016;1862:952–6. doi:10.1016/j.bbadis.2015.09.013.
[24] Jones NL, Gilman SE, Cheng TL, Drury SS, Hill CV, Geronimus AT. Life course approaches to the causes of health disparities. Am J Public Health 2019;109:S48–55. doi:10.2105/ajph.2018.304738.
[25] Zlokovic BV, Gottesman RF, Bernstein KE, Seshadri S, McKee A, Snyder H, et al. Vascular contributions to cognitive impairment and dementia (VCID): A report from the 2018 National Heart, Lung, and Blood Institute and National Institute of Neurological Disorders and Stroke Workshop. Alzheimers Dement 2020;16:1714–33. doi:10.1002/alz.12157.
[26] Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Assoc 2015;4:001140. doi:10.1161/jaha.114.001140.
[27] Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Malone IB, et al. Associations between vascular risk across adulthood and brain pathology in late life: evidence from a British birth cohort. JAMA Neurol 2020;77:175–83. doi:10.1001/jamaneurol.2019.3774.
[28] Kijpaisalratana N, Ament Z, Patki A, Bhave VM, Jones AC, Couch CA, et al. Plasma metabolites and life's simple 7 in REGARDS. Stroke 2024;55:1191–9. doi:10.1161/strokeaha.123.044714.
[29] Phuah CL, Chen Y, Strain JF, Yechoor N, Laurido-Soto OJ, Ances BM, et al. Association of data-driven white matter hyperintensity spatial signatures with distinct cerebral small vessel disease etiologies. Neurology 2022;99:e2535–47. doi:10.1212/wnl.0000000000201186.
[30] Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, et al. Clinical core of the Alzheimer's disease neuroimaging initiative: progress and plans. Alzheimer's Dementia 2010;6:239–46. doi:10.1016/j.jalz.2010.03.006.
[31] Aisen PS, Petersen RC, Donohue M, Weiner MW. Alzheimer's disease neuroimaging I. Alzheimer's disease neuroimaging initiative 2 clinical core: progress and plans. Alzheimer's Dementia 2015;11:734–9. doi:10.1016/j.jalz.2015.05.005.
[32] Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922–35. doi:10.1111/j.1532-5415.1992.tb01992.x.
[33] Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23(Suppl 1):S208–19. doi:10.1016/j.neuroimage.2004.07.051.
[34] Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal 2008;12:26–41. doi:10.1016/j.media.2007.06.004.
[35] Jagust WJ, Landau SM, Koeppe RA, Reiman EM, Chen K, Mathis CA, et al. The Alzheimer's disease neuroimaging initiative 2 PET Core: 2015. Alzheimers Dement 2015;11:757–71. doi:10.1016/j.jalz.2015.05.001.
[36] Saykin AJ, Shen L, Yao X, Kim S, Nho K, Risacher SL, et al. Genetic studies of quantitative MCI and AD phenotypes in ADNI: progress, opportunities, and plans. Alzheimers Dement 2015;11:792–814. doi:10.1016/j.jalz.2015.05.009.
[37] Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology 2010;74:1346–50. doi:10.1212/WNL.0b013e3181dad605.
[38] MahmoudianDehkordi S, Arnold M, Nho K, Ahmad S, Jia W, Xie G, et al. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease-an emerging role for gut microbiome. Alzheimers Dement 2019;15:76–92. doi:10.1016/j.jalz.2018.07.217.
[39] Xie G, Zhong W, Li H, Li Q, Qiu Y, Zheng X, et al. Alteration of bile acid metabolism in the rat induced by chronic ethanol consumption. FASEB J 2013;27:3583–93. doi:10.1096/fj.13-231860.
[40] van Straaten EC, Fazekas F, Rostrup E, Scheltens P, Schmidt R, Pantoni L, et al. Impact of white matter hyperintensities scoring method on correlations with clinical data: the LADIS study. Stroke 2006;37:836–40. doi:10.1161/01.Str.0000202585.26325.74.
[41] Andere A, Jindal G, Molino J, Collins S, Merck D, Burton T, et al. Volumetric white matter hyperintensity ranges correspond to Fazekas scores on brain MRI. J Stroke Cerebrovasc Dis 2022;31:106333. doi:10.1016/j.jstrokecerebrovasdis.2022.106333.
[42] Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc: Ser B (Method) 1995;57:289–300. doi:10.1111/j.2517-6161.1995.tb02031.x.
[43] Collins SL, Stine JG, Bisanz JE, Okafor CD, Patterson AD. Bile acids and the gut microbiota: metabolic interactions and impacts on disease. Nat Rev Microbiol 2023;21:236–47. doi:10.1038/s41579-022-00805-x.
[44] Nho K, Kueider-Paisley A, MahmoudianDehkordi S, Arnold M, Risacher SL, Louie G, et al. Altered bile acid profile in mild cognitive impairment and Alzheimer's disease: relationship to neuroimaging and CSF biomarkers. Alzheimers Dement 2019;15:232–44. doi:10.1016/j.jalz.2018.08.012.
[45] Ridlon JM, Kang D-J, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. J Lipid Res 2006;47:241–59. doi:10.1194/jlr.R500013-JLR200.
[46] Ignacio Barrasa J, Olmo N, Pérez-Ramos P, Santiago-Gómez A, Lecona E, Turnay J, et al. Deoxycholic and chenodeoxycholic bile acids induce apoptosis via oxidative stress in human colon adenocarcinoma cells. Apoptosis 2011;16:1054–67. doi:10.1007/s10495-011-0633-x.
[47] Quinn M, McMillin M, Galindo C, Frampton G, Pae HY, DeMorrow S. Bile acids permeabilize the blood brain barrier after bile duct ligation in rats via Rac1-dependent mechanisms. Dig Liver Dis 2014;46:527–34. doi:10.1016/j.dld.2014.01.159.
[48] Martinez-Diez MC, Serrano MA, Monte MJ, Marin JJ. Comparison of the effects of bile acids on cell viability and DNA synthesis by rat hepatocytes in primary culture. Biochim Biophys Acta 2000;1500:153–60. doi:10.1016/s0925-4439(99)00099-x.
[49] Oizumi K, Sekine S, Fukagai M, Susukida T, Ito K. Identification of bile acids responsible for inhibiting the bile salt export pump, leading to bile acid accumulation and cell toxicity in rat hepatocytes. J Pharm Sci 2017;106:2412–19. doi:10.1016/j.xphs.2017.05.017.
[50] Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. Neurobiol Aging 2015;36:27–32. doi:10.1016/j.neurobiolaging.2014.07.019.
[51] West NA, Windham BG, Knopman DS, Shibata DK, Coker LH, Mosley TH. Neuroimaging findings in midlife and risk of late-life dementia over 20 years of follow-up. Neurology 2019;92:e917–ee23. doi:10.1212/WNL.0000000000006989.
[52] Burke SL, Hu T, Fava NM, Li T, Rodriguez MJ, Schuldiner KL, et al. Sex differences in the development of mild cognitive impairment and probable Alzheimer's disease as predicted by hippocampal volume or white matter hyperintensities. J Women Aging 2019;31:140–64. doi:10.1080/08952841.2018.1419476.
[53] Hu H-Y, Ou Y-N, Shen X-N, Qu Y, Ma Y-H, Wang Z-T, et al. White matter hyperintensities and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 36 prospective studies. Neurosci Biobehav Rev 2021;120:16–27. doi:10.1016/j.neubiorev.2020.11.007.