

RESEARCH

Open Access



# Differential effects of cholesterol levels on cognition according to body mass index in Parkinson's disease

Seong Ho Jeong<sup>1,2</sup>, Seok Jong Chung<sup>3</sup>, Han Soo Yoo<sup>4</sup>, Jin Ho Jung<sup>5</sup>, Jong Sam Baik<sup>1</sup>, Young H. Sohn<sup>2</sup> and Phil Hyu Lee<sup>2,6\*</sup>

## Abstract

**Background** Cholesterol is an essential component of the neuronal cell membrane and is crucial for neuronal function; however, the role of cholesterol levels in Parkinson's disease (PD) is debatable. This study investigated the complex relationship between total cholesterol (TC) levels, body mass index (BMI), and cognition in patients with PD.

**Methods** This study included 321 drug-naïve patients with PD who underwent dopamine transporter (DAT) imaging and baseline neuropsychological tests. Multivariate linear regression and Cox regression models were used to investigate the effect of TC levels on the composite score of each cognitive domain and dementia conversion after adjusting for covariates, respectively. Interaction analyses were performed to examine the interaction effect between TC levels and BMI on baseline cognition and dementia conversion.

**Results** TC levels and cognition showed no significant relationship after adjusting for potential confounders. A significant interaction effect between TC levels and BMI was observed in frontal/executive function and dementia conversion. Further analyses showed that TC levels were positively associated with frontal/executive function in the under-/normal weight group ( $\beta = 0.205$ ,  $p = 0.013$ ), whereas a negative relationship existed between TC levels and frontal/executive function in the obese group ( $\beta = -0.213$ ,  $p = 0.017$ ). Cox regression analyses also showed the differential effects of TC levels on dementia conversion according to BMI (under-/normal weight group: hazard ratio [HR] = 0.550,  $p = 0.013$ ; obese group: HR = 2.085,  $p = 0.014$ ).

**Conclusions** This study suggests a cross-over interaction between TC levels and BMI on cognitive symptoms in PD.

**Keywords** Cholesterol, Body mass index, Parkinson's disease, Cognition, Dementia

\*Correspondence:

Phil Hyu Lee

phlee@yuhs.ac

<sup>1</sup> Department of Neurology, Inje University Sanggye Paik Hospital, Seoul, South Korea

<sup>2</sup> Department of Neurology, Yonsei University College of Medicine, 50 Yonsei-Ro, Seodaemun-Gu, Seoul 03722, South Korea

<sup>3</sup> Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin, South Korea

<sup>4</sup> Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

<sup>5</sup> Department of Neurology, Inje University Busan Paik Hospital, Seoul, South Korea

<sup>6</sup> Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

## Background

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as tremors, rigidity, and bradykinesia [1]. Additionally, cognitive impairment, one of the most common non-motor symptoms in patients with PD, is debilitating and significantly affect patients' and caregivers' quality of life [2].

Cholesterol is a lipid molecule that is essential for the normal functioning of cell membranes and is involved in the production of several important signaling molecules in the brain [3, 4]. Ample evidence has suggested that cholesterol may play a role in the pathogenesis of PD and cognitive decline. Elevated cholesterol levels are associated with an increased risk of cognitive impairment and dementia, including Alzheimer's disease (AD) and vascular dementia [5, 6], whereas the other studies showed contradictory results [7–9]. Similarly, the association between cholesterol levels and cognition in patients with PD has shown conflicting results in several studies. One study showed that elevated plasma low-density lipoprotein (LDL) cholesterol levels were associated with more preserved executive function in PD [10]. Another study showed no significant association between cholesterol levels and cognitive decline in advanced stages of PD [11].

The body mass index (BMI) is an important clinical factor that is related to presynaptic dopaminergic degeneration and cognitive impairment in patients with PD [12–14]. Moreover, BMI is closely associated with cholesterol levels [15, 16], and the effect of cholesterol levels on cognition differs according to BMI in the elderly [17, 18]. Despite the potential importance of cholesterol and BMI in cognitive function, little is known about how these factors interact in patients with PD. Understanding these relationships could help identify novel targets for therapeutic interventions to modulate cognitive function in patients with PD. Therefore, this study aimed to investigate the differential effects of cholesterol levels on baseline and longitudinal cognition according to BMI in patients with PD.

## Methods

### Participants

We reviewed the medical records of 321 consecutive drug-naïve patients with PD who had visited the outpatient clinic for movement disorders at the Severance Hospital between April 2009 and September 2015. PD was diagnosed according to the clinical diagnostic criteria of the United Kingdom PD Society Brain Bank. All patients exhibited nigrostriatal dopamine depletion on [<sup>18</sup>F] N-(3-fluoropropyl)-2 $\beta$ -carbonethoxy-3 $\beta$ -(4-iodophenyl) nortropane positron emission tomography

(<sup>18</sup>F-FP-CIT PET), showing reduced dopamine transporter (DAT) availability in the posterior putamen compared to 26 healthy controls. All patients underwent brain magnetic resonance imaging (MRI) and a detailed baseline neuropsychological study. The severity of parkinsonian motor deficits was assessed using the Unified PD Rating Scale Part III (UPDRS-III) at the initial visit (drug-naïve status). Total cholesterol (TC) levels were measured in blood collected after a 10-h overnight fast. Patients with missing data on the baseline neuropsychological study and TC levels were excluded from the study. The baseline height and weight were measured in all patients at their initial visit and used to calculate the BMI. According to the revised Asia–Pacific BMI criteria of the World Health Organization for western Pacific regions [19], BMI was classified as follows for subgroup analyses: underweight, BMI < 18.5 kg/m<sup>2</sup>; normal weight, BMI  $\geq$  18.5 and < 23 kg/m<sup>2</sup>; overweight, BMI  $\geq$  23 kg/m<sup>2</sup> and < 25 kg/m<sup>2</sup>; and obese, BMI  $\geq$  25 kg/m<sup>2</sup>. We divided the patients with PD into the following three groups: under-/normal weight, BMI < 23 kg/m<sup>2</sup> ( $n$  = 138); overweight, BMI  $\geq$  23 and < 25 kg/m<sup>2</sup> ( $n$  = 102), and obese, BMI  $\geq$  25 kg/m<sup>2</sup> ( $n$  = 81). Underweight participants were pooled with the normal weight group because only 12 patients had a BMI < 18.5 kg/m<sup>2</sup>. All patients were investigated for their medical history and vascular risk factors, including hypertension and diabetes mellitus. We also investigated the types of statins used by the patients (atorvastatin,  $n$  = 58; simvastatin,  $n$  = 10; pitavastatin,  $n$  = 5; fluvastatin,  $n$  = 4; rosuvastatin,  $n$  = 22; and pravastatin,  $n$  = 4). Two movement disorder experts (Y.H.S. and P.H.L.) confirmed levodopa responsiveness and carefully assessed atypical parkinsonism during a mean period of 5.31 years. This study was approved by the institutional review board of Yonsei University College of Medicine (No. 4–2014–0637). Informed consent was waived due to the nature of retrospective study.

### Acquisition and quantitative analyses of <sup>18</sup>F-FP-CIT PET

Image acquisition and quantitative analyses of <sup>18</sup>F-FP-CIT PET data were performed according to the methods reported in our previous study ([Supplementary Methods](#)). Briefly, the striatum was divided into the anterior caudate, posterior caudate, anterior putamen, posterior putamen, ventral putamen, and ventral striatum. Dopamine transporter (DAT) availability of each striatal subregion was defined as (mean standardized uptake value of the striatal subregion volume of interests [VOIs] – mean standardized uptake value of the occipital VOI)/(mean standardized uptake value of the occipital VOI). Because DAT availability in the posterior putamen (DAT-PP) is most severely affected area in patients with PD, DAT activity in this region was included in the data analyses.

### Acquisition of fluid-attenuated inversion recovery (FLAIR) sequence images and grading of the white matter hyperintensities (WMHs)

Of the 321 enrolled patients, 244 (76.01%) underwent brain MRI at Severance Hospital using a 3.0-T scanner (Achieva; Philips Medical System, Best, Netherlands) with a 32-channel receiver array head coil at the initial assessment. Head motion was minimized with restraining foam pads provided by the manufacturer. The imaging protocol included FLAIR images (TR/TE, 9000–10,000/110–125 ms; section thickness, 5 mm; matrix, 256×256). The remaining 77 (23.99%) patients underwent brain MRI including FLAIR sequences at other hospitals before their referral to our hospital. Two neurologists (S.H.J. and S.J.C.) assessed the visual rating scale of WMHs using a semi-quantitative Scheltens scale [20]. The intra- and inter-rater reliabilities of the total WMHs were high (intraclass correlation coefficients=0.984 and 0.966, respectively). If the score was discordant between the raters, the final score was determined by consensus.

### Neuropsychological evaluation

All participants underwent the Seoul Neuropsychological Screening Battery, a standardized neuropsychological battery that contains tests regarding attention/working memory, language, visuospatial function, memory, and frontal/executive function [21]. Standardized *z*-scores were available for all scorable tests based on age- and education-matched norms. We included the following tests: the digit span forward and backward and Stroop color reading test for the attention domain; the Korean version of the Boston Naming Test for the language domain; the copying item of the Rey-Osterrieth Complex Figure Test (RCFT) for the visuospatial domain; immediate recall, 20-min delayed recall, and recognition items of the RCFT and Seoul Verbal Learning Test for the memory domain; and the Controlled Oral Word Association Test for semantic (animal and supermarket) and phonemic fluency for the frontal/executive domain. A lower *z*-score in each test represents worse cognitive performance. A composite score was calculated for each cognitive domain by dividing the sum of *z*-scores by the number of tests. The Korean version of the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-SOB) were used to assess the global cognitive performance.

### Assessment of dementia conversion

Of the 321 patients with PD, 15 were excluded due to changes in the status of statin use. Finally, 306 patients were included in the longitudinal analysis. The participants visited our outpatient clinic every 3–6 months,

and movement disorder experts carefully assessed patients' daily functioning, such as their ability to manage finances, use pieces of equipment, and cope in social situations, through a detailed history obtained from patients and caregivers [12]. In patients with complaints of cognitive decline or evidence of impairments in daily life due to cognitive changes, a detailed neuropsychological battery was subsequently conducted to diagnose Parkinson's disease dementia (PDD) at level II in most patients. PDD was diagnosed using the clinical diagnostic criteria for probable PDD [22] based on the consensus between two neurologists and one neuropsychologist with evidence of abnormal activities of daily living (ADL), judged both clinically and based on instrumental ADL scales, whereas functional disabilities due to parkinsonism were not considered to be an impairment of complex ADL.

### Statistical analysis

To investigate the effect of TC levels per standard deviation (SD), we used individual *z*-transformed values of the TC levels in all analyses. To compare baseline demographic and clinical characteristics according to BMI, one-way analysis of variance with post hoc Bonferroni correction was used for continuous variables, and Pearson's  $\chi^2$  tests or Fisher's exact tests were used for categorical variables. Multivariate linear regression analysis was used to determine the effect of the independent variables on the composite score of each cognitive domain after adjusting for age at symptom onset, sex, years of education, disease duration, hypertension, diabetes mellitus, statin use, DAT-PP, WMHs burden, BMI, and TC levels. We further tested whether there was an interaction effect between BMI and total cholesterol levels on the composite score of each cognitive domain after additional adjustment for the interaction term between BMI and total cholesterol levels. If the interaction term (BMI×TC levels) was significant, further subgroup analyses according to BMI (under-/normal weight, overweight, and obese groups) were performed. False discovery rate (FDR) was used to correct multiple tests for the five cognitive function domains.

Cognitive outcomes were assessed using the Kaplan–Meier survival analysis and Cox regression model for PDD conversion. The time from the onset of motor symptoms to the date of PDD conversion was assessed with Kaplan–Meier estimates in 306 patients with PD who were included in the final longitudinal analysis after categorizing the patients with PD into three groups according to cholesterol levels using a tertile-based approach (1st tertile group [TC levels < 172; *n* = 100], 2nd tertile group [172 ≤ TC levels < 197; *n* = 102], and 3rd tertile group [TC levels ≥ 197; *n* = 104]). The log-rank test was used to compare Kaplan–Meier plots among groups. To assess the

effects of TC levels on PDD conversion, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox regression models while adjusting for age at symptom onset, sex, symptom duration, hypertension, diabetes mellitus, statin use, DAT-PP, WMHs burden, and baseline BMI. We further tested whether there was an interaction effect between BMI and total cholesterol levels on PDD conversion after additional adjustment for the interaction term between BMI and total cholesterol levels. The Bonferroni correction was applied for multiple comparisons of the five cognitive domains. If the interaction term (BMI×TC levels) was significant for the

composite score of the cognitive domain, further subgroup analyses according to BMI (under-/normal weight, overweight, and obese groups) were performed.

Statistical analyses were performed using R software (v.4.0, <http://www.r-project.org/>). Results with  $P < 0.05$  were considered statistically significant.

**Results**

**Baseline demographic and clinical characteristics**

Baseline demographic and clinical characteristics according to BMI group are summarized in Table 1. All clinical variables including age at symptom onset, proportion of

**Table 1** Demographic characteristics in patients with Parkinson's disease

	Under-/normal weight (n = 138)	Overweight (n = 102)	Obese (n = 81)	P value
<b>Demographic characteristics</b>				
Age at symptom onset, years	65.39 ± 8.96	66.60 ± 8.66	65.32 ± 9.24	0.516
Female,	76 (55.07%)	51 (50.00%)	41 (50.62%)	0.693
Years of education, years	9.22 ± 4.50	10.48 ± 4.88	8.67 ± 4.65	0.024 <sup>c</sup>
Symptom duration, months	19.48 ± 17.70	15.88 ± 15.67	13.65 ± 13.04	0.027 <sup>b</sup>
UPDRS-III	24.32 ± 10.66	22.05 ± 8.47	22.07 ± 8.65	0.111
MMSE	26.57 ± 2.62	26.64 ± 2.65	26.36 ± 2.84	0.778
<b>Vascular risk factors</b>				
Hypertension	54 (39.13%)	47 (46.08%)	40 (49.38%)	0.292
Diabetes mellitus	24 (17.39%)	20 (19.61%)	21 (25.93%)	0.310
TC levels	180.74 ± 38.72	184.52 ± 35.18	187.68 ± 37.06	0.398
Statin use	38 (27.54%)	31 (30.39%)	32 (39.51%)	0.176
WMHs burden	11.33 ± 8.75	9.89 ± 7.59	11.04 ± 7.31	0.374
Follow-up duration	5.29 ± 2.28	4.98 ± 2.38	5.77 ± 2.55	0.088
BMI	20.85 ± 1.49	23.91 ± 0.60	27.05 ± 1.71	< 0.001 <sup>a,b,c</sup>
<b>Neuropsychological test</b>				
Attention/working memory	-0.14 ± 0.87	-0.13 ± 0.97	-0.28 ± 0.81	0.458
Language	-0.41 ± 1.12	-0.24 ± 1.13	-0.35 ± 1.16	0.525
Visuospatial	-0.31 ± 1.47	-0.70 ± 2.24	-0.39 ± 1.57	0.215
Memory	-0.36 ± 0.86	-0.31 ± 0.89	-0.29 ± 0.72	0.783
Frontal/executive	-0.33 ± 0.93	-0.25 ± 0.94	-0.46 ± 0.75	0.296
CDR-SOB	1.16 ± 1.35	1.30 ± 1.61	1.22 ± 1.26	0.748
<b>Baseline DAT availability</b>				
Anterior caudate	2.06 ± 0.66	1.98 ± 0.68	2.15 ± 0.63	0.237
Posterior caudate	1.42 ± 0.58	1.30 ± 0.55	1.40 ± 0.52	0.250
Anterior putamen	2.21 ± 0.61	2.17 ± 0.60	2.29 ± 0.59	0.394
Posterior putamen	1.40 ± 0.44	1.38 ± 0.41	1.40 ± 0.45	0.936
Ventral putamen	1.46 ± 0.39	1.45 ± 0.40	1.50 ± 0.40	0.683
Ventral striatum	2.02 ± 0.56	2.04 ± 0.58	2.12 ± 0.57	0.446

Values are expressed as mean ± standard deviation or number (percentage)

BMI body mass index, CDR-SOB Clinical Dementia Rating-Sum of Boxes, DAT dopamine transporter, MMSE Mini-mental status examination, TC total cholesterol, UPDRS-III Unified Parkinson's Disease Rating Scale Part III, WMHs white matter hyperintensities

<sup>a</sup> Significantly different in comparison between the under-/normal weight and overweight groups

<sup>b</sup> Significantly different in comparison between the overweight and obese groups

<sup>c</sup> Significantly different in comparison between the under-/normal weight and obese groups

women, UPDRS-III score, MMSE score, proportion of vascular risk factors including hypertension and diabetes mellitus, TC levels, proportion of statin use prior to PD diagnosis, WMHs burden score, and follow-up duration were comparable across the BMI groups. Years of education were longer in the overweight group than those of the obese group. The symptom duration prior to PD diagnosis was longer in the under-/normal weight group than that of the obese group. There were no differences between the BMI groups in the composite scores of any cognitive domain, including attention/working memory, language, visuospatial, memory, and executive functions, as well as CDR-SOB. Additionally, DAT availability in each striatal subregion was comparable among the BMI groups.

**Relationship between TC levels, BMI, and cognitive function**

There was no significant correlation between the MMSE score and TC levels ( $R=0.08, p=0.149$ ) or BMI ( $R=-0.04, p=0.490$ ). Correlation analysis showed that TC levels were weakly associated with the composite score of frontal/executive function ( $R=0.13, p=0.022$ ), whereas there was no significant relationship between BMI and the composite scores of attention, language, visuospatial, memory, and executive performance (Supplementary Figure S1). However, multivariable linear

regression models showed that neither TC levels nor BMI were associated with the composite score of each cognitive domain after adjusting for covariates (Supplementary Table S1).

**Interaction effect of TC levels and BMI on cognition**

The results of the interaction analysis for each cognitive domain score are presented in Table 2. The interaction term between TC levels and BMI was significant for the frontal/executive function ( $\beta = -0.050$ , standard error [SE]=0.018,  $p=0.006$ , FDR-corrected  $p=0.030$ ) after adjusting for covariates (Table 2). Thus, we examined the relationship between TC levels and frontal/executive function according to the BMI groups. The subgroup analysis showed a significant positive relationship between TC levels and frontal/executive function in the under-/normal weight group ( $R=0.28, p<0.001$ ), whereas TC levels were negatively associated with frontal/executive function in the obese group ( $R=-0.23, p=0.039$ , Fig. 1). However, this association was not significant in the overweight group. In addition, we used regression analysis to examine the opposite relationship between TC levels and frontal/executive functions according to the BMI groups. After adjusting for confounding factors, TC levels were positively associated with frontal/executive function in under-/normal weight group ( $\beta=0.205, SE=0.082, p=0.013$ ) and negatively

**Table 2** Interaction analyses for the association of total cholesterol levels with each cognitive domain

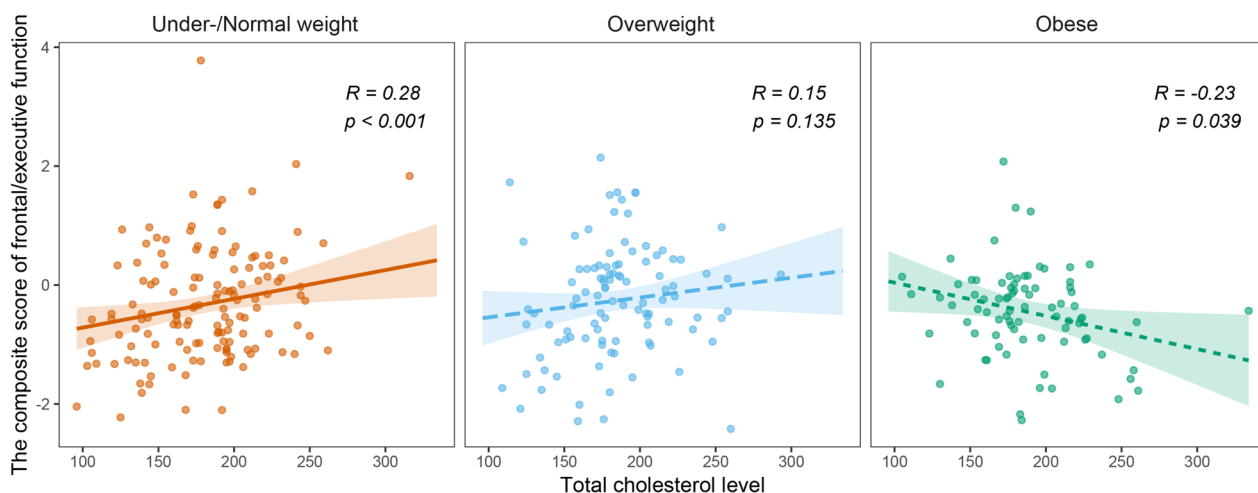
Cognitive domain	Attention/working memory		Language		Visuospatial		Memory		Frontal/executive	
	$\beta$ (SE)	P	$\beta$ (SE)	P	$\beta$ (SE)	P	$\beta$ (SE)	P	$\beta$ (SE)	P
Intercept	-	-	-	-	-	-	-	-	0.413 (0.661)	0.533
Age	-	-	-	-	-	-	-	-	-0.009 (0.006)	0.156
Female	-	-	-	-	-	-	-	-	0.141 (0.106)	0.185
Education	-	-	-	-	-	-	-	-	0.010 (0.011)	0.343
Symptom duration	-	-	-	-	-	-	-	-	-0.001 (0.003)	0.764
Hypertension	-	-	-	-	-	-	-	-	0.085 (0.109)	0.435
Diabetes	-	-	-	-	-	-	-	-	-0.224 (0.127)	0.079
Statin use	-	-	-	-	-	-	-	-	0.022 (0.111)	0.841
DAT-PP										
WMHs burden	-	-	-	-	-	-	-	-	-0.019 (0.007)	0.006
BMI	-	-	-	-	-	-	-	-	-0.011 (0.018)	0.523
TC levels per 1 SD increase	-	-	-	-	-	-	-	-	1.220 (0.426)	0.004
BMI × TC levels	-0.020 (0.018)	0.275	-0.035 (0.022)	0.115	-0.022 (0.038)	0.557	-0.017 (0.017)	0.325	<b>-0.050 (0.018)</b>	<b>0.006</b>

Interaction analyses were performed to investigate the interaction effect between total cholesterol levels and other dependent variables (age at symptom onset, sex, years of education, symptom duration, hypertension, diabetes, statin use, white matter hyperintensities, and BMI) on each cognitive domain. Each interaction analysis was performed after adjusting for age at symptom onset, sex, years of education, symptom duration, the presence of hypertension and diabetes, statin use, white matter hyperintensities, and BMI

$\beta$  regression coefficient, BMI body mass index, DAT-PP dopamine transporter availability in the posterior putamen, SD standard deviation, SE standard error, TC total cholesterol, WMHs white matter hyperintensities

Bold indicates FDR-corrected  $P < 0.05$





**Fig. 1** Scatter plots showing the composite score of frontal/executive function and TC levels according to BMI subgroups. A significant positive relationship is observed between TC levels and frontal/executive functions in the under-/normal weight group (red line), whereas TC levels are negatively associated with frontal/executive functions in the obese group (green line). BMI, body mass index; TC, total cholesterol

associated with frontal/executive function in the obese group ( $\beta = -0.213$ ,  $SE = 0.087$ ,  $p = 0.017$ , Table 3).

**Relationship between TC levels, BMI, and PDD conversion**

Among the 306 patients with PD, 26 (19.7%), 13 (13.5%), and 13 (16.7%) patients in the under-/normal weight, overweight, and obese groups, respectively, developed PDD during the follow-up period. The follow-up duration was  $5.3 \pm 2.3$ ,  $5.0 \pm 2.4$ , and  $5.8 \pm 2.6$  in the under-/normal weight, overweight, and obese groups, respectively.

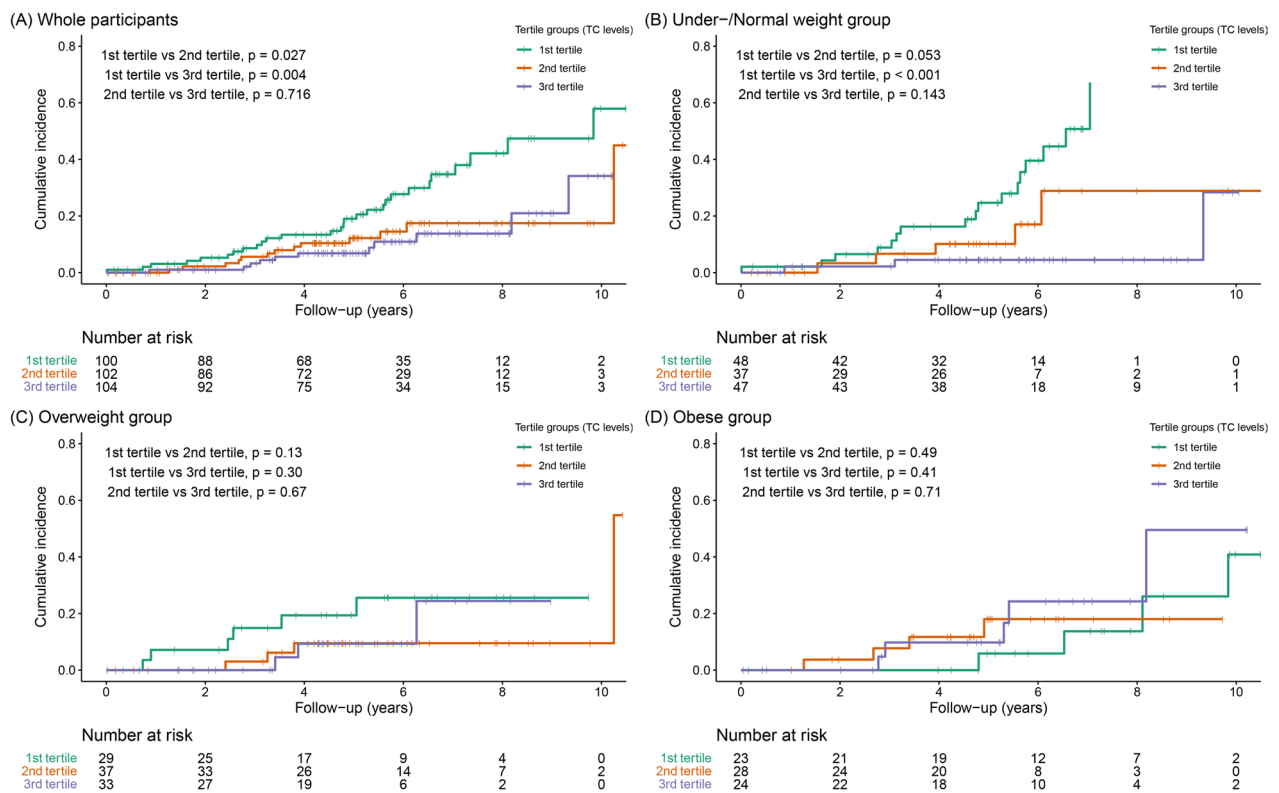
Kaplan–Meier analysis revealed that the 1st tertile group of TC levels had a higher risk of PDD conversion than that of the 2nd and 3rd tertile groups ( $P_{log-rank} = 0.027$  and  $0.004$ , respectively; Fig. 2A). However, the Cox regression model showed that neither TC levels nor BMI predicted PDD conversion after adjusting for confounding factors (Table 4, Model 1). Interaction analysis showed that the interaction term between TC levels and BMI was significant for PDD conversion (Table 4, Model 2). Thus, we further examined the relationship between TC levels

**Table 3** Multivariate linear regression analyses for the association of total cholesterol levels with frontal/executive function according to body mass index

Variables	Under-/normal weight (BMI < 23)		Overweight (23 ≤ BMI < 25)		Obese (BMI > 25)	
	$\beta$ (SE)	P	$\beta$ (SE)	P	$\beta$ (SE)	P
Intercept	-1.088 (1.657)	0.513	5.591 (3.512)	0.115	0.407 (1.599)	0.800
Age	0.002 (0.011)	0.822	-0.024 (0.011)	0.036	-0.009 (0.011)	0.429
Female	0.104 (0.174)	0.550	0.266 (0.199)	0.184	-0.008 (0.191)	0.967
Education	0.012 (0.019)	0.528	0.019 (0.019)	0.333	-0.004 (0.021)	0.835
Symptom duration	0.001 (0.004)	0.802	-0.003 (0.006)	0.649	-0.001 (0.007)	0.930
Hypertension	0.047 (0.188)	0.802	-0.061 (0.199)	0.761	0.356 (0.2)	0.080
Diabetes	-0.37 (0.231)	0.112	-0.159 (0.228)	0.488	-0.19 (0.199)	0.343
Statin use	0.392 (0.195)	0.047	-0.183 (0.208)	0.381	-0.325 (0.186)	0.084
DAT-PP						
WMHs burden	-0.021 (0.01)	0.045	-0.022 (0.013)	0.095	-0.025 (0.014)	0.084
BMI	0.024 (0.058)	0.683	-0.186 (0.143)	0.198	0.003 (0.052)	0.953
TC levels per 1 SD increase	<b>0.205 (0.082)</b>	<b>0.013</b>	0.078 (0.099)	0.436	<b>-0.213 (0.087)</b>	<b>0.017</b>

Multivariate linear regression models were used to investigate the association between total cholesterol levels and cognition, while adjusting for age at symptom onset, sex, years of education, symptom duration, the presence of hypertension and diabetes, statin use, white matter hyperintensities, and BMI

$\beta$  regression coefficient, BMI body mass index, DAT-PP dopamine transporter availability in the posterior putamen, SD standard deviation, SE standard error, TC total cholesterol, WMHs white matter hyperintensities



**Fig. 2** Kaplan–Meier survival curve of PDD conversion. The crosses in the graphs indicate censored data

**Table 4** Cox regression analysis of the effects of total cholesterol levels on dementia conversion

Variables	Model 1 (C-index = 0.791)		Model 2 (C-index = 0.793)	
	HR (95% CI)	P	HR (95% CI)	P
Age at symptom onset	1.063 (1.023–1.105)	0.002	1.068 (1.027–1.111)	0.001
Female	0.381 (0.188–0.771)	0.007	0.367 (0.183–0.736)	0.005
Symptom duration	1.003 (0.984–1.023)	0.736	1.001 (0.981–1.02)	0.958
Education	0.999 (0.933–1.070)	0.973	0.997 (0.931–1.066)	0.919
MMSE score	0.808 (0.710–0.919)	0.001	0.795 (0.695–0.909)	0.001
Hypertension	1.333 (0.725–2.449)	0.355	1.439 (0.782–2.649)	0.242
Diabetes	0.864 (0.442–1.687)	0.668	0.774 (0.392–1.527)	0.459
Statin use	1.513 (0.799–2.866)	0.204	1.489 (0.790–2.807)	0.218
DAT-PP				
WMHs burden	1.025 (0.991–1.061)	0.150	1.025 (0.991–1.061)	0.150
BMI	0.930 (0.837–1.033)	0.177	0.977 (0.872–1.096)	0.696
TC levels per 1 SD increase	0.863 (0.638–1.166)	0.336	0.015 (0.001–0.154)	<0.001
BMI×TC levels	-	-	<b>1.193 (1.081–1.317)</b>	<b>&lt;0.001</b>

Results of Cox regression analyses for PDD conversion after controlling for age at symptom onset, sex, symptom duration, years of education, MMSE scores, the presence of hypertension and diabetes, statin use, WMHs burden, BMI, TC levels, and/or the interaction term of BMI\*TC levels

BMI body mass index, CI confidence interval, DAT-PP dopamine transporter availability in the posterior putamen, HR hazard ratio, MMSE the Mini-Mental state Examination, TC total cholesterol, WMHs white matter hyperintensities

and PDD conversion according to the BMI group. In subgroup analysis according to the BMI groups, Kaplan–Meier analyses showed that 1st tertile group of TC levels had a higher risk of PDD conversion than that of 3rd tertile groups ( $P_{log-rank} < 0.001$ , Fig. 2B) in the under-/normal weight subgroup, whereas the risk of PDD conversion did not differ between the tertile groups of TC levels in the overweight and obese subgroups (Fig. 2C and D). In the Cox regression models, higher TC levels were associated with a lower future risk of PDD conversion in the under-/normal weight group (HR=0.550, 95% CI=0.344–0.880,  $p=0.013$ ) and a higher future risk of PDD conversion in the obese group (HR=2.085, 95% CI=1.160–3.746,  $p=0.014$ ) after adjusting for covariates (Table 5).

**Discussion**

This study investigated the complex relationship among TC levels, BMI, and cognition in drug-naïve patients with PD. The major findings were as follows: (i) baseline cognitive function and longitudinal cognitive outcomes were not associated with baseline TC level and BMI; however, there was a significant interaction effect between TC levels and BMI for frontal/executive function and PDD conversion; (ii) lower TC levels were associated with lower composite scores of frontal/executive function and a higher future risk of PDD conversion in the under-/normal weight group, whereas higher TC levels were associated with poor performance on frontal/executive items and more frequent PDD conversion in the obese group. These findings indicate that the association between TC levels and cognition is moderated by BMI in patients

with PD, suggesting that a cholesterol-lowering strategy could be applied differentially according to BMI.

Clinical studies have demonstrated that individuals with high levels of circulating TC are less likely to develop PD and have better long-term outcomes. [10, 23, 24]. However, high cholesterol levels can worsen the loss of dopaminergic neurons in a PD model [25]. This is because cholesterol facilitates the interaction between oligomeric  $\alpha$ -synuclein and the cell membrane, leading to membrane disruption and cell death. A recent investigation discovered that elevated cholesterol levels have a dual role in PD: they protect against lysosomal membrane permeabilization while also promoting  $\alpha$ -synuclein accumulation [26]. In terms of BMI, although results from several epidemiologic studies are conflicting about the association between BMI and PD risk [27, 28], low BMI or weight loss is associated with dopaminergic neuronal degeneration or cognitive outcomes in patients with PD [12–14]. To date, no study has investigated how BMI and TC levels interact with each other and their effect on cognition in patients with PD.

Although the present study showed a similar relationship between baseline TC levels and frontal/executive function in a simple correlation analysis, this relationship was no longer significant after adjusting for covariates. However, we found a significant interaction between TC levels and BMI for frontal/executive functions, indicating that TC levels differentially affect frontal/executive functions according to BMI. Consistent with the findings from a previous study, further subgroup analyses revealed that higher TC levels were associated with higher composite

**Table 5** Cox regression analysis of the effects of total cholesterol levels on dementia conversion according to body mass index

Variables	Under-/normal weight (C-index=0.816)		Overweight (C-index=0.884)		Obese (C-index=0.86)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at symptom onset	1.044 (0.981–1.110)	0.174	1.122 (1.003–1.256)	0.045	1.155 (1.009–1.322)	0.037
Female	0.206 (0.067–0.630)	0.006	0.263 (0.032–2.15)	0.213	0.171 (0.032–0.916)	0.039
Symptom duration	1.003 (0.975–1.031)	0.85	1.004 (0.969–1.041)	0.813	0.995 (0.933–1.062)	0.882
Education	1.011 (0.902–1.132)	0.856	0.970 (0.816–1.153)	0.727	0.846 (0.689–1.037)	0.107
MMSE score	0.633 (0.504–0.794)	< 0.001	0.907 (0.643–1.279)	0.577	0.912 (0.703–1.184)	0.490
Hypertension	0.718 (0.247–2.089)	0.543	9.886 (1.471–66.428)	0.018	2.497 (0.439–14.211)	0.302
Diabetes	1.229 (0.397–3.805)	0.720	0.076 (0.008–0.774)	0.030	1.370 (0.321–5.850)	0.671
Statin use	1.015 (0.393–2.619)	0.975	2.833 (0.575–13.961)	0.201	0.798 (0.204–3.123)	0.746
DAT-PP						
WMHs burden	1.000 (0.955–1.048)	0.993	1.036 (0.963–1.115)	0.338	1.124 (1.019–1.241)	0.019
BMI	0.867 (0.612–1.230)	0.424	0.981 (0.303–3.181)	0.975	0.947 (0.556–1.613)	0.841
TC levels per 1 SD increase	<b>0.550 (0.344–0.880)</b>	<b>0.013</b>	0.908 (0.399–2.065)	0.818	<b>2.085 (1.160–3.746)</b>	<b>0.014</b>

Results of Cox regression analyses for PDD conversion after controlling for age at symptom onset, sex, symptom duration, years of education, MMSE scores, the presence of hypertension and diabetes, statin use, WMHs burden, BMI, and TC levels

BMI body mass index, CI confidence interval, DAT-PP dopamine transporter availability in the posterior putamen, HR hazard ratio, MMSE the Mini-Mental state Examination, TC total cholesterol, WMHs white matter hyperintensities



scores of frontal/executive function in the under-/normal weight group [10]. In contrast, TC levels were negatively associated with frontal/executive function in the obese group. This result suggests that, although the mechanism remains speculative, TC levels can negatively contribute to cognitive performance in obese patients with PD, similar to the inverse association between TC levels and cognition in young adults reported in previous studies [29, 30].

The longitudinal analysis of PDD conversion showed results similar to those of the cross-sectional analysis. Although TC levels or BMI could not predict PDD conversion in the Cox regression model after adjusting for confounding factors, a significant interaction effect was observed between TC levels and BMI for PDD conversion. In the subgroup analyses, higher TC levels were associated with a lower future risk of PDD conversion in the under-/normal weight group, while higher TC levels were associated with more frequent PDD conversion in the obese group. When examining the association between cholesterol levels and Alzheimer's disease or vascular dementia, previous studies have shown inconsistent results, and this association seems to vary with age at measurement (mid-life [ $<65$  years] or later life [ $\geq 65$  years]) and follow-up duration [31, 32]. In this study, we investigated whether there was a significant interaction between TC levels and each demographic variable, including age, sex, hypertension, diabetes, statin use, and BMI (data not shown), in which only the interaction effect between TC levels and BMI was significant. This is the first study to show that TC levels in patients with PD are associated with baseline cognition and the future risk of dementia conversion in a BMI-dependent manner. Causal relationships could not be assessed in this study, and reverse causation should also be considered. For example, because TC levels are biomarkers of malnutrition [33], patients with PD who have low TC levels in the under-/normal weight group may be malnourished, which subsequently leads to poor cognitive outcome. In addition, a recent study showed that familial patients with PD, particularly those with a glucocerebrosidase (GBA) mutation, have lower cholesterol levels than healthy controls and patients with sporadic PD [34]. Considering the fact that GBA is associated with poor cognitive performance and the risk of PDD [35], poor cognitive outcomes in patients with PD and low TC levels in the under-/normal weight group may be attributed to underlying genetic risk factors [36]. Meanwhile, the relationship between metabolic syndrome and dementia could provide a possible explanation for the opposite association between TC levels and cognitive outcomes in the obese group. Although TC levels are not included in the diagnostic criteria for metabolic syndrome, they

are elevated in patients with metabolic syndrome [37]. Because metabolic syndrome is associated with the risk of AD [38] and TC levels exert an additive effect on the association between obesity and dementia risk [39], high TC levels in the obese PD group may have detrimental effects on cognitive outcome through AD or vascular co-pathology.

Our study had some limitations. First, 24S-hydroxycholesterol and 27S-hydroxycholesterol, which are indicators of brain cholesterol levels, were not analyzed. While this study analyzed TC levels, which correlated well with brain cholesterol content [40], future research using brain cholesterol biomarkers is required to confirm these findings. Second, the study did not have access to data on LDL, high-density lipoprotein cholesterol, and triglyceride levels, which are components of TC; therefore, further research involving larger cohorts is required to determine which fraction of cholesterol affects cognitive symptoms in patients with PD. Third, although the study adjusted for statin use, some degree of under-adjustment may have occurred because of the absence of information on the duration and dosage of statin exposure in this retrospective study. Finally, because this was a single-center study in Korea, the generalization of results is limited by factors such as ethnicity and genetic background.

## Conclusions

In conclusion, our study demonstrated that the relationship between TC levels and cognition in patients with PD was influenced by BMI and differed between subgroups. Lower lipid levels in the under-/normal weight group and higher lipid levels in the obese group were associated with poor performance on frontal/executive items and the higher risk of PDD conversion. These findings suggest that cholesterol-lowering strategy could be applied differentially according to BMI in patients with PD.

## Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
BMI	Body mass index
CDR-SOB	Clinical Dementia Rating-Sum of Boxes
DAT	Dopamine transporter
DAT-PP	Dopamine transporter availability in the posterior putamen
FDR	False discovery rate
FLAIR	Fluid-attenuated inversion recovery
$^{18}\text{F}$ -FP-CIT	$^{18}\text{F}$ N-(3-fluoropropyl)-2 $\beta$ -carbonethoxy-3 $\beta$ -(4-iodophenyl) nortropane
GBA	Glucocerebrosidase
HRs	Hazard ratios
LDL	Low-density lipoprotein
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PET	Positron emission tomography
SD	Standard deviation

SE	Standard error
TC	Total cholesterol
UPDRS-III	Unified Parkinson's Disease Rating Scale Part III
WMHs	White matter hyperintensities

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13195-023-01326-2>.

### Additional file 1: Supplementary Methods. Supplementary Figure S1.

Scatter plots showing the composite score of each cognitive domain and TC levels or BMI. **Supplementary Table S1.** Multivariate linear regression analyses for the association of total cholesterol levels with each cognitive domain.

## Acknowledgements

None.

## Authors' contributions

SHJ drafted the structure of the present work, took care of data analysis, drafted the first version of the work, and revised the following versions critically for important intellectual content. PHL contributed to draft the structure of the present work and revised the first version of the work critically for important intellectual content. All authors had full access to all the data in the study, substantially contributed to the interpretation of data for the present work, revised the work critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SHJ and PHL accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

## Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. RS-2023-00209580) awarded to Seong Ho Jeong. Also, this work was supported by a grant from the Korea Health Technology R&D Project through the Korean Healthy Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HU21C0053) awarded to Phil Hyu Lee.

## Availability of data and materials

Data generated or analyzed during the study are available from the corresponding author by request.

## Declarations

### Ethics approval and consent to participate

This study was approved by the institutional review board of Yonsei University College of Medicine (No. 4–2014–0637). Informed consent was waived due to the nature of retrospective study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

Received: 18 August 2023 Accepted: 5 October 2023

Published online: 31 January 2024

## References

- Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J, Schrag AE, Lang AE. Parkinson disease. *Nat Rev Dis Primers*. 2017;3:17013.

- Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, Weintraub D. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers*. 2021;7(1):47.
- Schroeder F, Jefferson JR, Kier AB, Knittel J, Scallen TJ, Wood WG, Hapala I. Membrane cholesterol dynamics: cholesterol domains and kinetic pools. *Proc Soc Exp Biol Med*. 1991;196(3):235–52.
- Jin U, Park SJ, Park SM. Cholesterol metabolism in the brain and its association with Parkinson's disease. *Exp Neurobiol*. 2019;28(5):554–67.
- Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn Disord*. 2009;28(1):75–80.
- Evans RM, Emsley CL, Gao S, Sahota A, Hall KS, Farlow MR, Hendrie H. Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. *Neurology*. 2000;54(1):240–2.
- Leritz EC, McGlinchey RE, Salat DH, Milberg WP. Elevated levels of serum cholesterol are associated with better performance on tasks of episodic memory. *Metab Brain Dis*. 2016;31(2):465–73.
- Zhou F, Deng W, Ding D, Zhao Q, Liang X, Wang F, Luo J, Zheng L, Guo Q, Hong Z. High low-density lipoprotein cholesterol inversely relates to dementia in community-dwelling older adults: the Shanghai Aging Study. *Front Neurol*. 2018;9:952.
- Mielke MM, Zandi PP, Sjögren M, Gustafson D, Ostling S, Steen B, Skoog I. High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology*. 2005;64(10):1689–95.
- Sterling NW, Lichtenstein M, Lee EY, Lewis MM, Evans A, Eslinger PJ, Du G, Gao X, Chen H, Kong L, et al. Higher plasma LDL-cholesterol is associated with preserved executive and fine motor functions in Parkinson's disease. *Aging Dis*. 2016;7(3):237–45.
- Choe CU, Petersen E, Lezius S, Cheng B, Schulz R, Buhmann C, Pötter-Nerger M, Daum G, Blankenberg S, Gerloff C, et al. Association of lipid levels with motor and cognitive function and decline in advanced Parkinson's disease in the Mark-PD study. *Parkinsonism Relat Disord*. 2021;85:5–10.
- Yoo HS, Chung SJ, Lee PH, Sohn YH, Kang SY. The influence of body mass index at diagnosis on cognitive decline in Parkinson's disease. *J Clin Neurol*. 2019;15(4):517–26.
- Zhang L, Gu LY, Dai S, Zheng R, Jin CY, Fang Y, Yang WY, Tian J, Yin XZ, Zhao GH, et al. Associations of body mass index-metabolic phenotypes with cognitive decline in Parkinson's disease. *Eur Neurol*. 2022;85(1):24–30.
- Lee JJ, Oh JS, Ham JH, Lee DH, Lee I, Sohn YH, Kim JS, Lee PH. Association of body mass index and the depletion of nigrostriatal dopamine in Parkinson's disease. *Neurobiol Aging*. 2016;38:197–204.
- Milyani AA, Al-Agha AE. The effect of body mass index and gender on lipid profile in children and adolescents in Saudi Arabia. *Ann Afr Med*. 2019;18(1):42–6.
- Gostynski M, Gutzwiller F, Kuulasmaa K, Döring A, Ferrario M, Grafnetter D, Pajak A, Project fWHOM. Analysis of the relationship between total cholesterol, age, body mass index among males and females in the WHO MONICA Project. *Int J Obes*. 2004;28(8):1082–90.
- Gergely D, Plózer E, Altbacker A, Perlaki G, Orsi G, Koszegi T, Nagy S, Lucza T, Kovács N, Janszky J, et al. The relationship between serum cholesterol and verbal memory may be influenced by body mass index (BMI) in young healthy women. *Ideggyógy Sz*. 2016;69:177–82.
- Li J, Cao Y, Xiao C. Subgroup analysis of the influence of body mass index on the association between serum lipids and cognitive function in Chinese population. *Lipids Health Dis*. 2020;19(1):130.
- WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157–63.
- Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, Steinling M, Valk J. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci*. 1993;114(1):7–12.
- Ahn HJ, Chin J, Park A, Lee BH, Suh MK, Seo SW, Na DL. Seoul Neuropsychological Screening Battery-dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. *J Korean Med Sci*. 2010;25(7):1071–6.
- Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, et al. Clinical diagnostic

- criteria for dementia associated with Parkinson's disease. *Mov Disord.* 2007;22(12):1689–707. quiz 1837.
23. Huang X, Alonso A, Guo X, Umbach DM, Lichtenstein ML, Ballantyne CM, Mailman RB, Mosley TH, Chen H. Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study. *Mov Disord.* 2015;30(4):552–9.
  24. Huang X, Auinger P, Eberly S, Oakes D, Schwarzschild M, Ascherio A, Mailman R, Chen H, Parkinson Study Group DI. Serum cholesterol and the progression of Parkinson's disease: results from DATATOP. *PLoS One.* 2011;6(8):e22854.
  25. van Maarschalkerweerd A, Vetri V, Vestergaard B. Cholesterol facilitates interactions between  $\alpha$ -synuclein oligomers and charge-neutral membranes. *FEBS Lett.* 2015;589(19 Pt B):2661–7.
  26. Eriksson I, Nath S, Bornefall P, Giraldo AM, Öllinger K. Impact of high cholesterol in a Parkinson's disease model: prevention of lysosomal leakage versus stimulation of  $\alpha$ -synuclein aggregation. *Eur J Cell Biol.* 2017;96(2):99–109.
  27. Noyce AJ, Kia DA, Hemani G, Nicolas A, Price TR, De Pablo-Fernandez E, Haycock PC, Lewis PA, Foltynie T, Davey Smith G, et al. Estimating the causal influence of body mass index on risk of Parkinson disease: a Mendelian randomisation study. *PLoS Med.* 2017;14(6):e1002314.
  28. Hu G, Jousilahti P, Nissinen A, Antikainen R, Kivipelto M, Tuomilehto J. Body mass index and the risk of Parkinson disease. *Neurology.* 2006;67(11):1955–9.
  29. Yaffe K, Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer R, Coker LH, Sidney S. Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation.* 2014;129(15):1560–7.
  30. Iwagami M, Qizilbash N, Gregson J, Douglas I, Johnson M, Pearce N, Evans S, Pocock S. Blood cholesterol and risk of dementia in more than 1.8 million people over two decades: a retrospective cohort study. *Lancet Healthy Longev.* 2021;2(8):e498–506.
  31. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am J Geriatr Psychiatry.* 2008;16(5):343–54.
  32. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. *J Alzheimers Dis.* 2017;56(1):215–28.
  33. Hrnčiarikova D, Hyspler R, Vyroubal P, Klemra P, Hronek M, Zadák Z. Serum lipids and neopterin in urine as new biomarkers of malnutrition and inflammation in the elderly. *Nutrition.* 2009;25(3):303–8.
  34. Macías-García D, Perinán MT, Muñoz-Delgado L, Jimenez-Jaraba MV, Labrador-Espinosa MÁ, Jesús S, Buiza-Rueda D, Méndez-Del Barrio C, Adames-Gómez A, Gómez-Garre P, et al. Serum lipid profile among sporadic and familial forms of Parkinson's disease. *NPJ Parkinsons Dis.* 2021;7(1):59.
  35. Zhang Y, Chen J, Xu C, Feng J, Li J. Effects of glucocerebrosidase gene polymorphisms and mutations on the risk of Parkinson's disease dementia: a meta-analysis. *Neurosci Lett.* 2020;714:134544.
  36. Avisar H, Guardia-Laguarta C, Surface M, Papagiannakis N, Maniati M, Antonellou R, Papadimitriou D, Koros C, Athanassiadou A, Przedborski S, et al. Lipid level alteration in human and cellular models of alpha synuclein mutations. *NPJ Parkinsons Dis.* 2022;8(1):52.
  37. Baez-Duarte BG, Sánchez-Guillén Mdel C, Pérez-Fuentes R, Zamora-Ginez I, Leon-Chavez BA, Revilla-Monsalve C, Islas-Andrade S.  $\beta$ -cell function is associated with metabolic syndrome in Mexican subjects. *Diabetes Metab Syndr Obes.* 2010;3:301–9.
  38. Kim YJ, Kim SM, Jeong DH, Lee SK, Ahn ME, Ryu OH. Associations between metabolic syndrome and type of dementia: analysis based on the National Health Insurance Service database of Gangwon province in South Korea. *Diabetol Metab Syndr.* 2021;13(1):4.
  39. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol.* 2005;62(10):1556–60.
  40. Bretillon L, Lütjohann D, Ståhle L, Widhe T, Bindl L, Eggertsen G, Diczfalussy U, Björkhem I. Plasma levels of 24S-hydroxycholesterol reflect the balance between cerebral production and hepatic metabolism and are inversely related to body surface. *J Lipid Res.* 2000;41(5):840–5.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

