Received: 18 October 2024 | Revised: 2 January 2025 | Accepted: 3 January 2025

DOI: 10.1002/trc2.70048

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

The relationship between neurofilament light chain and depressive symptoms according to cognitive status

Federico Bellelli[1,2] | **Jeremy Raffin**[3,4] | **Davide Angioni**[3,4,5] | **Julie Romana**[1,6] | **Maria Soto**[3,4,5] | **Julien Delrieu**[3,4,5] | **Philipe De Souto Barreto**[1,3,4] | **for the MAPT/DSA study group**

[1]Institut du Vieillissement, Gérontopôle de Toulouse, Centre Hospitalo-Universitaire de Toulouse, Toulouse, France

[2]Fellowship in Geriatric and Gerontology, University of Milan, Milan, Italy

[3]IHU HealthAge, La Cité de la Santé, Place Lange, Toulouse, France

[4]CERPOP, Inserm 1295, Toulouse University, INSERM, UPS, Toulouse, France

[5]Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, Toulouse, France

[6]Centre Hospitalo-Universitaire de la Guadeloupe, Route de Chauvel, Guadeloupe, France

Correspondence
Federico Bellelli, Institut du Vieillissement, Gérontopôle de Toulouse, Centre Hospitalo-Universitaire de Toulouse, Toulouse, France.
Email: federicobellelli8@gmail.com

Members of the MAPT/DSA Study Group are listed at the end of the paper

Funding information
Agence Nationale de la Recherche, Grant/Award Number: ANR-23-IAHU-0011; Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009); Pierre Fabre Research Institute; ExonHit Therapeutics SA; Avid Radiopharmaceuticals Inc; University Hospital Center of Toulouse; Association Monegasque pour la Recherche sur la maladie d'Alzheimer (AMPA); INSERM-University of Toulouse III UMR 1095 (CERPOP) Research Unit

Abstract

INTRODUCTION: Although recent studies have suggested a positive association between plasma neurofilament light chain (NfL) and depressive symptoms, the moderating effect of cognitive performance on this relationship remains unclear. The aim of this study was to investigate the association between NfL and depressive symptoms in a population of community-dwelling older adults and to determine whether cognitive status could modify this relationship.

METHODS: This is a secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT), including 512 individuals (60.2% women) with a median age of 76 years (interquartile range [IQR]: 7) and with available data for plasmatic NfL levels. Depressive symptoms and cognitive status were assessed using the 15-item Geriatric Depression Scale (GDS-15) and the Clinical Dementia Rating (CDR) scale, respectively. Multivariable linear regression analyses were conducted to explore the cross-sectional association between GDS-15 (dependent variable) and plasma NfL levels (pg/mL). The interaction between CDR status (binary: 0 or 0.5) and NfL levels in relation to depressive symptoms was also examined, followed by exploratory simple-slope analyses according to CDR status.

RESULTS: No significant association was observed between GDS-15 scores and plasma NfL levels (B = 0.002, standard error [SE] = 0.001, p = 0.08) in the entire sample. Although the CDR–NfL interaction was not significant (B = 0.003, SE = 0.002, p = 0.17), exploratory simple-slope analyses revealed that elevated NfL levels were

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2025 The Author(s). *Alzheimer's & Dementia: Translational Research & Clinical Interventions* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

associated with GDS-15 scores (N = 233, B = 0.004, SE = 0.002, p = 0.03) among individuals with a CDR 0.5, but not among those with a CDR 0 (N = 186, p = 0.81).

DISCUSSION: NfL levels were not significantly associated with GDS-15 in a population of community-dwelling older adults without dementia. Although no significant CDR–NfL interaction was detected, exploratory analyses suggest that plasma NfL might be associated with GDS-15 scores only among people with a CDR 0.5 (indicative of mild cognitive impairment). Further studies with larger sample sizes are needed to elucidate the potential biological differences in depressive symptoms across different cognitive statuses.

KEYWORDS
depressive symptoms, Geriatric Depression Scale, cognition, mild behavioral impairment, mild cognitive impairment, neurofilament light chain, NfL

Highlights

- Plasma neurofilament light (NfL) levels might be associated with 15-Geriatric Depression Scale (GDS-15) scores only among people with Clinical Dementia Rating (CDR) 0.5 (indicative of mild cognitive impairment [MCI]), but not among those with CDR 0 (normal cognition).
- Depressive symptoms arising in the context of cognitive impairment may represent a distinct clinical entity compared to those observed in individuals with normal cognitive functioning.
- Further research with larger sample sizes is needed to elucidate potential biological differences in depressive symptoms across varying cognitive statuses (unimpaired cognition, MCI, and dementia).

1 | BACKGROUND

Depressive symptoms and cognitive impairment are highly prevalent clinical conditions frequently coexisting in older individuals.[1] These conditions not only share multiple risk factors typically associated with aging, such as hypertension,[2,3] diabetes,[2,4] and social isolation,[5,6] but emerging evidence also suggests a bi-directional relationship between them, with each representing a significant risk factor for the other. For instance, older adults with depressive symptoms or depression are at higher risk of developing cognitive impairment.[2,7] At the same time, individuals with cognitive impairment are likely to experience depressive symptoms throughout the course of their illness.[8] Moreover, several studies indicate that depressive symptoms often exhibit neuropathological changes typically associated with cognitive diseases, including amyloid plaques,[9] leukoaraiosis,[10] neuroinflammation,[11] and neurodegeneration.[12]

Neurofilament light chain (NfL) is an exoskeletal protein highly expressed in the cytoplasm of large-caliber myelinated axons, with its levels increasing in both plasma and cerebrospinal fluid in response to neurodegeneration.[13] Previous studies investigating the association between NfL and depression have been focused predominantly on middle-aged individuals[14,15] or those with specific neurological conditions, such as Parkinson's disease,[16] stroke,[17] or multiple sclerosis.[18] In 2024, a large-scale study (n = 3895) involving community-dwelling older adults without specific neurologic diseases, observed that plasmatic NfL levels were cross-sectionally associated with late-life depressive symptoms, as assessed by the Center for Epidemiological Studies Depression Scale (CES-D) and longitudinally linked with a higher risk of developing depressive events over a 7-year follow-up period.[19] However, due to the lack of cognitive assessment in the study, it was not possible to determine whether underlying cognitive status played a role in this association. Given the evidence for common underlying pathological features and the frequent clinical overlap of these conditions, it is plausible that cognitive status influences the potential of neurodegeneration to either trigger or exacerbate depressive symptoms in older adults.

The objective of the study was to investigate the cross-sectional association between neurodegeneration, as indicated by plasma NfL levels and depressive symptoms, assessed using the 15-item Geriatric Depression Scale (GDS-15), in a population of community-dwelling

RESEARCH IN CONTEXT

1. **Systematic review**: The authors conducted a literature review using traditional sources (e.g., PubMed). Although recent studies have suggested a positive association between plasma neurofilament light chain (NfL) levels and depressive symptoms, the moderating effect of cognitive performance on this relationship remains unclear.
2. **Interpretation**: Exploratory analyses suggest that plasma NfL might be associated with Geriatric Depression Scale (GDS)-15 scores only among people with Clinical Dementia Rating (CDR) 0.5 (indicative of mild cognitive impairment [MCI]), but not among those with CDR 0. These findings might suggest that depressive symptoms may arise from different etiological pathways depending on an individual's cognitive performance (e.g., MCI vs normal cognition).
3. **Future directions**: Further longitudinal studies with larger sample sizes are needed to elucidate the potential biological differences in depressive symptoms across varying cognitive statuses (unimpaired cognition, MCI, and dementia). This could have important clinical implications. Specifically, blood biomarkers could assist in guiding diagnostic hypotheses toward behavioral and psychological symptoms in dementia (BPSD) or mild behavioral impairment (MBI) rather than a primary psychiatric disorder. This would facilitate appropriate referrals and support the decision-making process regarding the prescription of antidepressant medications.

older adults without dementia. In addition, the study aimed to examine whether cognitive status (cognitive impairment vs unimpaired cognition) could influence this relationship.

2 | METHODS

2.1 | Study design and participants

This study is a secondary analysis of the Multidomain Alzheimer Prevention Trial (MAPT) (registration: NCT00672685). Briefly, MAPT was a randomized, placebo-controlled trial designed to evaluate the effectiveness of multidomain lifestyle intervention, omega-3 fatty acid supplementation, or their combination, versus placebo in preventing cognitive decline over a 3-year follow-up period. Full details regarding the MAPT have been published previously elsewhere.[20] The study cohort consisted of community-dwelling older adults without a baseline diagnosis of dementia meeting at least one of the following criteria: self-reported memory complaints, slow gait speed (≤0.8 m/s), or limitation in one instrumental activity of daily living.

Considering that secondary analysis on the MAPT indicated no effect of the interventions on improving depressive symptoms,[20] participants from all the four groups were included in our study. The variables of interest were created by matching the GDS-15 and CDR with the timing of plasma NfL measurement (all measurements obtained at the same time-point). Plasmatic NfL levels were evaluated only once, either at the 1-year or 2-year assessment. Of the initial 1679 subjects enrolled in the MAPT, 512 individuals had available data for plasma NfL concentrations. Among them, five subjects were excluded due to missing data on the GDS. Due to the limited presence of individuals with a CDR score indicative of dementia (≥1) in our sample, we decided to focus only on individuals with normal cognition and mild cognitive impairment (MCI). Consequently, three additional subjects with a CDR score of 1 were excluded from the current analysis, resulting in a final count of 505 participants. Ethical approval for the trial protocol was obtained from the Toulouse Ethics Committee and the French Health Authority.

2.2 | Plasma NfL measurement

Plasma NfL levels were assessed either 1 ($n = 465$) or 2 years ($n = 40$) after the start of the trial and stored in ethylenediaminetetraacetic acid (EDTA)–coated tubes. The R-PLEX human Neurofilament L antibody set (F217X-3) with Meso Scale Discovery (MSD) Gold 96-well Small Spot SA SECTOR plates (L45A-1) was utilized to quantify plasma NfL levels (pg/mL). Samples were diluted twofold in Diluent 12 (R50JA-3), assayed in duplicate, and analyzed using an MSD instrument. Blood sampling was performed on the same day as cognitive testing.

2.3 | Assessment of depressive symptoms and cognitive status

Depressive symptoms were assessed using the GDS-15, a validated tool for depression screening.[21] Cognitive status was evaluated using the Clinical Dementia Rating scale Global Score (CDR-GS), which, according to a recent meta-analysis, is effective in distinguish normal cognition and MCI by a criterion of 0.5.[22] Scores of 0 indicated unimpaired cognition, whereas scores of 0.5 were classified as MCI.[22]

2.4 | Statistical analysis

Descriptive statistics were presented in terms of median and interquartile range (IQR) for quantitative variables, whereas frequencies and percentages were utilized for categorical variables.

In order to identify outliers for the plasma NfL variable, we initially normalized its skewed distribution by employing the logarithm of NfL. Subsequently, we excluded five participants with extreme levels, defined as exceeding 3.29 standard deviations (SD) below or above the logarithmic mean.[23] The NfL variable was then back-transformed to its original scale for the regression analyses. Prior to running the

TABLE 1 Characteristics of the population after removing outliers for plasma NfL values.

Characteristics of the population			
No. of subjects	500	MAPT group allocation	
Age, years, *median (IQR)*	76 (7)	Placebo, *n* (%)	131 (26.6%)
Female, *n* (%)	301 (60.2%)	Multidomain intervention, *n* (%)	116 (23.2%)
Plasma NfL level, *median (IQR)*	72.87 (34.50)	Omega-3 supplementation, *n* (%)	124 (24.8%)
GDS-15 score, median (IQR)	3.07 (2.66)	Combined group, *n* (%)	129 (25.8%)
GDS-15 score ≥5, *n* (%)	122 (24.4%)	Cardiovascular risk factors	
MCI, CDR = 0.5, *n* (%)	277 (55.4%)	Dyslipidemia, *n* (%)	164 (32.8%)
Positive plasma Aβ level, *n* (%)	150 (32.1%)	History of CVDs, *n* (%)	131 (26.6%)
Educational level		Diabetes, *n* (%)	168 (34.1%)
Low education, *n* (%)	124 (25.1%)	Hypertension, *n* (%)	201 (40.8%)
Medium education, *n* (%)	168 (34.1%)	BMI (Kg/m^2), *median (IQR)*	25.97 (4.98)
High education, *n* (%)	201 (40.8%)	Creatinine (mg/dL), *median (IQR)*	0.76 (0.24)

Abbreviations: Aβ, amyloid beta; BMI, body mass index; CDR, Clinical Dementia Rating; CVDs, cardiovascular diseases; GDS-15, 15-item Geriatric Depression Scale; IQR, interquartile range; MAPT, Multidomain Alzheimer Preventive Trial; MCI, mild cognitive impairment; N, number of persons; NfL, neurofilament light chain.

regression analyses, a square root transformation was applied on the GDS-15 variable to reduce its skewness and obtain a better distribution of the regression residuals. Then, a multivariable linear regression analysis was conducted to explore the association between the square root of the GDS-15 score (dependent variable) and plasma NfL concentrations (independent continuous variable). A second linear regression model including the interaction between NfL and CDR was employed to evaluate the moderating effect of CDR status on the relationship between NfL levels and the square root of the GDS-15 score (dependent variable). All analyses were adjusted for age, sex, cardiovascular risk factors (hypercholesterolemia, hypertension, diabetes, and cardiovascular disease—defined as having a previous history of stroke, coronary disease, or heart failure), MAPT group allocation, body mass index (BMI),[24] plasmatic creatinine levels,[25] CDR status, plasmatic amyloid status, and educational levels (low, medium, high). Subsequently, exploratory simple-slope analyses were performed to further investigate potential associations between NfL and GDS-15 within each CDR status group (normal cognition vs MCI).[26] The exploratory simple-slope analysis was adjusted for the above-mentioned confounders, except for the CDR status. Statistical analyses were performed with R statistical package Version 2023.12.1+402, with a significance level defined at $p < 0.05$.

3 | RESULTS

The characteristics of the population are presented in Table 1. The participants were equally distributed across the four MAPT groups and the mean age of the sample was 76 (IQR: 7) years.

The results for the associations between NfL and GDS-15 are presented in Table 2. In the overall sample, the GDS-15 score exhibited no significant association with plasmatic NfL levels ($B = 0.002$, standard error [SE] = 0.001, and $p = 0.08$). However, although the interaction between the NfL and CDR status did not reach statistical significance ($B = 0.003$, SE = 0.002, $p = 0.17$), subgroup analysis revealed that among individuals with MCI, elevated NfL levels were associated with higher GDS-15 scores ($N = 233$, $B = 0.004$, SE = 0.002, $p = 0.03$). This association was not evident among individuals with normal cognition ($N = 186$, $B = 0.001$, SE = 0.002, $p = 0.81$) (Figure 1).

4 | DISCUSSION

The main finding of this study is that higher NfL levels were not cross-sectionally associated with higher depressive symptoms in a population of community-dwelling older adults without dementia. However, although the CDR–NfL interaction showed only a trend toward significance, exploratory simple-slope analysis suggests that higher NfL levels may be associated with higher depressive symptoms only in individuals with MCI, whereas no significant associations were found in people with intact cognition. Nevertheless, given the exploratory nature of our analyses, this hypothesis requires confirmation by future research. To our knowledge, this is the first study aimed at evaluating the moderation role of cognitive status on the relationship between plasma NfL and depressive symptoms.

Our findings differ from those of previous studies that reported a significant association between NfL and major depression among young cognitively unimpaired individuals.[14,15] However, our analysis targeted a much older population, where the average NfL concentrations were about 3 times higher compared to those reported in these studies. It is plausible that because neurodegeneration is an age-associated process, the proportion of neurodegeneration attributable to depressive symptoms among older people may not be sufficient to justify significant differences compared to age-matched controls. Moreover, our sample was characterized by only a mild burden of depressive symptoms, which does not rule out the possibility that more

TABLE 2 Association between GDS-15 (square root of the score) and plasma NfL levels (pg/mL).

	Independent variables	Moderator Variable	*n*	*B*	SE	*p* value	Interaction p
Model 1.	*Plasma NfL levels (pg/mL)*		419	0.002	0.001	0.08	
Model 2.	*Plasma NfL levels (pg/mL)*	CDR = 0	186	0.001	0.002	0.81	0.17
	Plasma NfL levels (pg/mL)	CDR = 0.5	233	0.004	0.002	0.03	

Note: Model 1 assesses the association between GDS-15 score and plasma NfL levels alone, whereas Model 2 includes an interaction term to evaluate the combined effect of NfL levels and CDR status on the GDS-15 score.
Abbreviations: B, Beta-coefficient; CDR, Clinical Dementia Rating; GDS-15, 15-item Geriatric Depression Scale; n, number of persons; NfL, neurofilament light chain; SE, standard error.

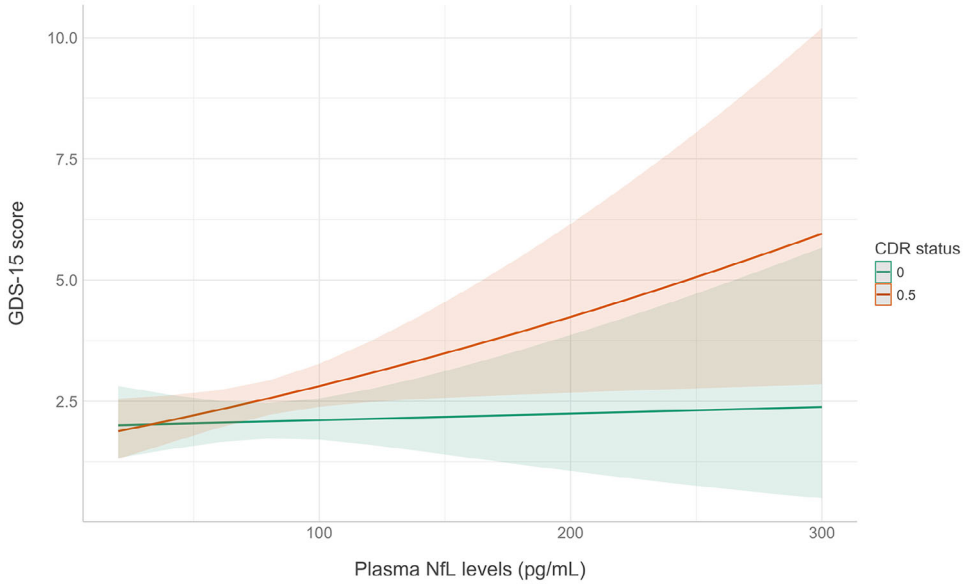

FIGURE 1 Association between GDS-15 score and plasma NfL levels by CDR status. GDS-15, 15-item Geriatric Depression Scale; NfL, neurofilament light chain; CDR, Clinical Dementia Rating.

severe symptoms might be associated with neurodegeneration, even among older people with normal cognition.

Our exploratory analysis suggests that the relationship between neurodegeneration and depressive symptoms may emerge only in the presence of underlying cognitive decline. If confirmed, this finding might indicate that depressive symptoms could originate from distinct etiological pathways depending on an individual's cognitive status. Further larger and longitudinal studies are needed to examine if NfL and other markers of neurodegeneration interact (or not) with cognitive function to determine over time the changes in depressive symptoms as well as incident depression. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), depressive disorders can sometimes be attributed to other medical conditions such as stroke, Parkinson's disease, and traumatic brain injury, which are known to have a clear association and neuroanatomic correlates with depressive symptoms.[27] In addition, the onset of psychiatric symptoms in late life should raise suspicion of an underlying neurodegenerative disease.[28] Therefore, although higher GDS-15 scores may evoke in the first instance a primary mood disorder in individuals with normal cognition, among individuals with MCI (or eventually dementia) these scores may reflect an underlying neurodegenerative disorder rather than a primary psychiatric condition.

In 2016, the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) established criteria for a condition known as mild behavioral impairment (MBI), characterized by behavioral disturbances preceding cognitive decline or concomitant with MCI.[29] Reduced motivation and affective dysregulation, which are among the most commonly affected domains in MBI,[30] include symptoms like apathy, anxiety, dysphoria, or irritability, which may overlap with those typically observed in depressive syndromes in the context of a psychiatric condition. For instance, these symptoms may be addressed by certain questions included in the GDS-15, such as "Have you dropped many of your activities and interests?" or "Do you prefer staying at home rather than going out and doing things?" Therefore, it is plausible that the GDS-15 score among individuals with MCI could reflect the presence of an underlying MBI rather than a primary depressive disorder.

In the future it will be important to further investigate, with longitudinal studies and larger sample sizes, the potential differences in the biology of depressive symptoms according to different cognitive status (unimpaired cognition, MCI, and dementia). Indeed, gaining a better understanding of the relationship between depressive symptoms, neurodegeneration, and cognitive status could open new avenues from a clinical perspective. First, if our hyphothesis is confirmed by future research, elevated NfL levels in older individuals with depressive symptoms and no previous psychiatric history might help in orienting diagnostic hypothesis toward a neurodegenerative disorder rather than a primary psychiatric condition. In this scenario, the evaluation of plasmatic NfL levels might facilitate the early diagnosis of a neurodegenerative disorder in older adults presenting with depressive symptoms and their referral to Memory Clinics, which may be better suited to address their needs. Moreover, being able to distinguish depression from behavioral and psychological symptoms associated with cognitive decline may help in pondering the decision of prescribing antidepressant drugs that might be ineffective in the context of cognitive disorders.[31] Indeed, according to a recent Cochrane review,[31] the beneficial effect of antidepressants over placebo in people with cognitive decline is limited and associated with an increased likelihood of experiencing at least one adverse event within 6–12 weeks.

The study has several strengths. Indeed, it represents one of the first investigations into the association between biomarkers of neurodegeneration and depressive symptoms in a population of community-dwelling older adults without dementia. Furthermore, to our knowledge, it is the first study to evaluate the impact of cognitive function on the relationship between plasma NfL concentrations and depressive symptoms.

However, our study also exhibits some limitations. First, it is a secondary post hoc analysis, and although depressive symptoms (GDS-15 score) were a secondary outcome of the MAPT, the trial was not originally designed to evaluate the combined effect of neurodegeneration and cognitive status in defining depressive symptoms. Moreover, the relatively small sample size may have limited the ability to obtain statistical significance in examining the interaction between plasma NfL levels and CDR status. In addition, the cross-sectional design of the study does not allow for clarification of the temporal relationship between neurodegeneration, cognitive impairment, and depressive symptoms. Further longitudinal studies with larger sample sizes and repeated assessment of the plasmatic NfL levels, GDS-15 score, and CDR scale score are needed to further elucidate this relationship. Finally, because plasma NfL levels were measured ≈1 or 2 years after the start of the MAPT, it remains uncertain whether the intervention may have altered these levels.

In conclusion, in our sample, plasma levels of NfL were not associated with depressive symptoms in the whole population. However, exploratory analysis suggests that higher NfL levels might be associated with higher depressive symptoms only in individuals with MCI, without an association in those with normal cognition. These exploratory data may suggest that depressive symptoms could originate from distinct etiological pathways depending on an individual's cognitive performance. Further studies with larger sample sizes are needed to elucidate the potential biological differences in depressive symptoms across different cognitive statuses.

ACKNOWLEDGMENTS

This work has been developed in the context of the IHU HealthAge, which benefited from funding by the Agence Nationale de la Recherche under the France 2030 program (reference number: ANR-23-IAHU-0011). The Multidomain Alzheimer Preventive Trial (MAPT) was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), ExonHit Therapeutics SA, and Avid Radiopharmaceuticals Inc. The promotion of this study was supported by the University Hospital Center of Toulouse. The data sharing activity was supported by the Association Monegasque pour la Recherche sur la maladie d'Alzheimer (AMPA) and the INSERM-University of Toulouse III UMR 1095 (CERPOP) Research Unit.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human subjects provided written informed consent.

ORCID

Federico Bellelli https://orcid.org/0000-0001-8801-0294

REFERENCES

1. Sun HL, Chen P, Bai W, et al. Depressive Symptoms and Cognitive Function in Older Adults: A Cross-Lagged Network Analysis. *Depress Anxiety*. 2024;2024(1):6166775. doi:10.1155/2024/6166775
2. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6
3. García-Fabela L, Melano-Carranza E, Aguilar-Navarro S, et al. Hypertension as a risk factor for developing depressive symptoms among community-dwelling elders. *Rev Investig Clínica*. 2009;61(4):274-280.
4. Rotella F, Mannucci E. Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. *Diabetes Res Clin Pract*. 2013;99(2):98-104. doi:10.1016/j.diabres.2012.11.022
5. Guarnera J, Yuen E, Macpherson H. The Impact of Loneliness and Social Isolation on Cognitive Aging: A Narrative Review. *J Alzheimers Dis Rep*. 7(1):699-714. doi:10.3233/ADR-230011
6. Holvast F, Burger H, de Waal MMW, van Marwijk HWJ, Comijs HC, Verhaak PFM. Loneliness is associated with poor prognosis in late-life depression: Longitudinal analysis of the Netherlands study of depression in older persons. *J Affect Disord*. 2015;185:1-7. doi:10.1016/j.jad.2015.06.036
7. Shimada H, Park H, Makizako H, Doi T, Lee S, Suzuki T. Depressive symptoms and cognitive performance in older adults. *J Psychiatr Res*. 2014;57:149-156. doi:10.1016/j.jpsychires.2014.06.004
8. Baquero M, Martín N. Depressive symptoms in neurodegenerative diseases. *World J Clin Cases WJCC*. 2015;3(8):682-693. doi:10.12998/wjcc.v3.i8.682
9. Donovan NJ, Locascio JJ, Marshall GA, et al. Longitudinal Association of Amyloid Beta and Anxious-Depressive Symptoms in Cognitively Normal Older Adults. *Am J Psychiatry*. 2018;175(6):530-537. doi:10.1176/appi.ajp.2017.17040442

10. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MMB. Cerebral White Matter Lesions and Depressive Symptoms in Elderly Adults. *Arch Gen Psychiatry*. 2000;57(11):1071-1076. doi:10.1001/archpsyc.57.11.1071
11. Hassamal S. Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. *Front Psychiatry*. 2023;14: 1130989 doi:10.3389/fpsyt.2023.1130989
12. Dotson VM, Davatzikos C, Kraut MA, Resnick SM. Depressive symptoms and brain volumes in older adults: a longitudinal magnetic resonance imaging study. *J Psychiatry Neurosci*. 2009;34(5):367-375.
13. Gaetani L, Blennow K, Calabresi P, Filippo MD, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. *J Neurol Neurosurg Psychiatry*. 2019;90(8):870-881. doi:10.1136/jnnp-2018-320106
14. Bavato F, Cathomas F, Klaus F, et al. Altered neuroaxonal integrity in schizophrenia and major depressive disorder assessed with neurofilament light chain in serum. *J Psychiatr Res*. 2021;140:141-148. doi:10.1016/j.jpsychires.2021.05.072
15. Chen MH, Liu YL, Kuo HW, et al. Neurofilament Light Chain Is a Novel Biomarker for Major Depression and Related Executive Dysfunction. *Int J Neuropsychopharmacol*. 2021;25(2):99-105. doi:10.1093/ijnp/pyab068
16. Urso D, Batzu L, Logroscino G, Ray Chaudhuri K, Pereira JB. Neurofilament light predicts worse nonmotor symptoms and depression in Parkinson's disease. *Neurobiol Dis*. 2023;185:106237. doi:10.1016/j.nbd.2023.106237
17. Zhao H, Mo M, Miao C, et al. Association of serum biomarker neurofilament light concentration with post-stroke depression: A preliminary study. *Gen Hosp Psychiatry*. 2020;64:17-25. doi:10.1016/j.genhosppsych.2020.01.006
18. Tauil CB, Rocha-Lima AD, Ferrari BB, et al. Depression and anxiety disorders in patients with multiple sclerosis: association with neurodegeneration and neurofilaments. *Braz J Med Biol Res Rev Bras Pesqui Medicas E Biol*. 2021;54(3):e10428. doi:10.1590/1414-431x202010428
19. Schuurmans IK, Ghanbari M, Cecil CAM, Ikram MA, Luik AI. Plasma neurofilament light chain in association to late-life depression in the general population. *Psychiatry Clin Neurosci*. 2024;78(2):97-103. doi:10.1111/pcn.13608
20. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol*. 2017;16(5):377-389. doi:10.1016/S1474-4422(17)30040-6
21. Lesher EL, Berryhill JS. Validation of the geriatric depression scale-short form among inpatients. *J Clin Psychol*. 1994;50(2):256-260. doi:10.1002/1097-4679(199403)50:2%3C;256::AID-JCLP2270500218%3E;3.0.CO;2-E
22. Huang HC, Tseng YM, Chen YC, Chen PY, Chiu HY. Diagnostic accuracy of the Clinical Dementia Rating Scale for detecting mild cognitive impairment and dementia: A bivariate meta-analysis. *Int J Geriatr Psychiatry*. 2021;36(2):239-251. doi:10.1002/gps.5436
23. Discovering Statistics Using R. Discovering Statistics. 2017. Accessed June 20, 2024. https://discoveringstatistics.com/books/discovering-statistics-using-r/
24. Manouchehrinia A, Piehl F, Hillert J, et al. Confounding effect of blood volume and body mass index on blood neurofilament light chain levels. *Ann Clin Transl Neurol*. 2020;7(1):139-143. doi:10.1002/acn3.50972
25. Akamine S, Marutani N, Kanayama D, et al. Renal function is associated with blood neurofilament light chain level in older adults. *Sci Rep*. 2020;10(1):20350. doi:10.1038/s41598-020-76990-7
26. Robinson CD, Tomek S, Schumacker RE. Tests of moderation effects: difference in simple slopes versus the interaction term. *Mul Linear Regression Viewpoints*. 2013;39(1):16-24.
27. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. American psychiatric association; 2013.
28. Ismail Z, Gatchel J, Bateman DR, et al. Affective and emotional dysregulation as pre-dementia risk markers: exploring the mild behavioral impairment symptoms of depression, anxiety, irritability, and euphoria. *Int Psychogeriatr*. 2018;30(2):185-196. doi:10.1017/S1041610217001880
29. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement J Alzheimers Assoc*. 2016;12(2):195-202. doi:10.1016/j.jalz.2015.05.017
30. Pan Y, Shea YF, Li S, et al. Prevalence of mild behavioural impairment: a systematic review and meta-analysis. *Psychogeriatr Off J Jpn Psychogeriatr Soc*. 2021;21(1):100-111. doi:10.1111/psyg.12636
31. Dudas R, Malouf R, McCleery J, Dening T. Antidepressants for treating depression in dementia. *Cochrane Database Syst Rev*. 2018;8(8):CD003944. doi:10.1002/14651858.CD003944.pub2

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bellelli F, Raffin J, Angioni D, et al. The relationship between neurofilament light chain and depressive symptoms according to cognitive status. *Alzheimer's Dement*. 2025;11:e70048. https://doi.org/10.1002/trc2.70048

COLLABORATORS

Members of the MAPT/DSA Study Group

MAPT study group: *Principal investigator*: Bruno Vellas (Toulouse); *Coordination*: Sophie Guyonnet (Toulouse); *Project leader*: Isabelle Carrié (Toulouse); *CRA*: Lauréane Brigitte (Toulouse); *Investigators*: Catherine Faisant, Françoise Lala, Julien Delrieu, and Hélène Villars (Toulouse); *Psychologists*: Emeline Combrouze, Carole Badufle, and Audrey Zueras (Toulouse); *Methodology, statistical analysis and data management*: Sandrine Andrieu, Christelle Cantet, and Christophe Morin (Toulouse); and *Multidomain group*: Gabor Abellan Van Kan, Charlotte Dupuy, and Yves Rolland (physical and nutritional components), Céline Caillaud and Pierre-Jean Ousset (cognitive component), and Françoise Lala (preventive consultation) (Toulouse). The cognitive component was designed in collaboration with Sherry Willis from the University of Seattle, and Sylvie Belleville, Brigitte Gilbert, and Francine Fontaine from the University of Montreal. *Co-Investigators in associated centers*: Jean-François Dartigues, Isabelle Marcet, Fleur Delva, Alexandra Foubert, and Sandrine Cerda (Bordeaux); Marie-Noëlle-Cuffi and Corinne Costes (Castres); Olivier Rouaud, Patrick Manckoundia, Valérie Quipourt, Sophie Marilier, and Evelyne Franon (Dijon); Lawrence Bories, Marie-Laure Pader, Marie-France Basset, Bruno Lapoujade, Valérie Faure, Michael Li Yung Tong, Christine Malick-Loiseau, and Evelyne Cazaban-Campistron (Foix); Françoise Desclaux and Colette Blatge (Lavaur); Thierry Dantoine, Cécile Laubarie-Mouret, Isabelle Saulnier, Jean-Pierre Clément, Marie-Agnès

Picat, Laurence Bernard-Bourzeix, Stéphanie Willebois, Iléana Désormais, ad Noëlle Cardinaud (Limoges); Marc Bonnefoy, Pierre Livet, Pascale Rebaudet, Claire Gédéon, Catherine Burdet, and Flavien Terracol (Lyon), Alain Pesce, Stéphanie Roth, Sylvie Chaillou, and Sandrine Louchart (Monaco); Kristel Sudres, Nicolas Lebrun, and Nadège Barro-Belaygues (Montauban); Jacques Touchon, Karim Bennys, Audrey Gabelle, Aurélia Romano, Lynda Touati, Cécilia Marelli, and Cécile Pays (Montpellier); Philippe Robert, Franck Le Duff, Claire Gervais, and Sébastien Gonfrier (Nice); and Yannick Gasnier and Serge Bordes, Danièle Begorre, Christian Carpuat, Khaled Khales, Jean-François Lefebvre, Samira Misbah El Idrissi, Pierre Skolil, and Jean-Pierre Salles (Tarbes). *MRI group*: Carole Dufouil (Bordeaux), Stéphane Lehéricy, Marie Chupin, Jean-François Mangin, and Ali Bouhayia (Paris); Michèle Allard (Bordeaux); Frédéric Ricolfi (Dijon); Dominique Dubois (Foix); Marie Paule Bonceour Martel (Limoges); François Cotton (Lyon); Alain Bonafé (Montpellier); Stéphane Chanalet (Nice); Françoise Hugon (Tarbes); and Fabrice Bonneville, Christophe Cognard, and François Chollet (Toulouse). *PET scan group*: Pierre Payoux, Thierry Voisin, Julien Delrieu, Sophie Peiffer, and Anne Hitzel, (Toulouse); Michèle Allard (Bordeaux); Michel Zanca (Montpellier); Jacques Monteil (Limoges); and Jacques Darcourt (Nice). *Medico-economics group*: Laurent Molinier, Hélène Derumeaux, and Nadège Costa (Toulouse). *Biological sample collection*: Bertrand Perret, Claire Vinel, Sylvie and Caspar-Bauguil (Toulouse). *Safety management*: Pascale Olivier-Abbal.

DSA Group: Sandrine Andrieu, Christelle Cantet, and Nicola Coley (Toulouse).