Original Article

Journal of Geriatric Psychiatry and Neurology
2022, Vol. 35(3) 434–441

DOI: 10.1177/08919887211016068
journals.sagepub.com/home/jgp
SAGE

Plasma β-Amyloid in Mild Behavioural Impairment – Neuropsychiatric Symptoms on the Alzheimer's Continuum

Ruxin Miao[1,2], Hung-Yu Chen, PhD[1,3], Sascha Gill, MSc[1,2,3], James Naude[1], Eric E. Smith, MD, MPH[1,2,3], and Zahinoor Ismail, MD[1,2,3,4], for the Alzheimer's Disease Neuroimaging Initiative

Abstract

Introduction: Simple markers are required to recognize older adults at higher risk for neurodegenerative disease. Mild behavioural impairment (MBI) and plasma β-amyloid (Aβ) have been independently implicated in the development of incident cognitive decline and dementia. Here we studied the associations between MBI and plasma $A\beta_{42}/A\beta_{40}$. **Methods:** Participants with normal cognition (n = 86) or mild cognitive impairment (n = 53) were selected from the Alzheimer's Disease Neuroimaging Initiative. MBI scores were derived from Neuropsychiatric Inventory items. Plasma $A\beta_{42}/A\beta_{40}$ ratios were assayed using mass spectrometry. Linear regressions were fitted to assess the association between MBI total score as well as MBI domain scores with plasma $A\beta_{42}/A\beta_{40}$. **Results:** Lower plasma $A\beta_{42}/A\beta_{40}$ was associated with higher MBI total score ($p = 0.04$) and greater affective dysregulation ($p = 0.04$), but not with impaired drive/motivation ($p = 0.095$) or impulse dyscontrol ($p = 0.29$) MBI domains. **Conclusion:** In persons with normal cognition or mild cognitive impairment, MBI was associated with low plasma $A\beta_{42}/A\beta_{40}$. Incorporating MBI into case detection may help capture preclinical and prodromal Alzheimer's disease.

Keywords

Alzheimer's disease, mild behavioural impairment, beta-amyloid, neuropsychiatric symptoms

Background

Alzheimer's disease (AD) is a neurodegenerative condition characterized by abnormal β-amyloid (Aβ) and tau aggregation into plaques and tangles, resulting in cerebral dysfunction.[1] A clinical diagnosis of dementia is established by the presence of functional decline, at which point neuronal loss and AD pathology are extensive and likely irremediable. AD clinical trials have failed to identify disease-modifying treatments, hindered in part by poor recruitment and retention of early phase disease.[2,3] One unifying goal in dementia research is to recognize high-risk individuals in the preclinical and prodromal stages of AD, not only to provide timely intervention but to target recruitment for future research. Simple markers for risk are required.[4]

Although cognitive changes and functional decline are the hallmarks of AD progression, non-cognitive markers are also associated with incident dementia.[5] Of these markers, neuropsychiatric symptoms (NPS) are simple and inexpensive to determine and can be captured at scale. Mild behavioural impairment (MBI) is a validated neurobehavioural syndrome characterized by the later-life emergence of persistent NPS[6] as an at-risk state for incident cognitive decline and dementia, and the initial manifestation of dementia for some.[7-10] While research has been reliant on detailed neuropsychological testing, CSF biomarkers, and PET imaging in the early detection of dementia, these markers are labour-intensive and expensive, which limits scalability. Plasma biomarkers could also satisfy the need for a cost-effective, minimally invasive approach to quantify early AD risk and to correlate with non-cognitive markers such as MBI as an initial screen.

A growing body of work has demonstrated the efficacy of plasma biomarkers in the evaluation of early neurodegeneration.[11-13] Plasma $A\beta_{42}/A\beta_{40}$ ratio is a promising AD biomarker

[1] Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
[2] Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[3] Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada
[4] Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

Received 1/3/2021. Received revised 3/26/2021. Accepted 4/6/2021.

Corresponding Author:
Zahinoor Ismail, 3280 Hospital Drive NW, TRW Building 1st Floor Calgary, AB, T2 N 4Z6, Canada.
Email: ismailz@ucalgary.ca

that predicts cerebral amyloid and AD pathology in at-risk individuals.[14] Little research has explored the association between MBI and plasma biomarkers,[15] and to our knowledge, none with plasma amyloid. Here we assessed plasma Aβ associations with MBI. Informed by recent evidence on the association between MBI and amyloid PET,[16] we hypothesized that MBI symptomatology would be associated with lower plasma $A\beta_{42}/A\beta_{40}$, signifying increased amyloid burden in the brain.

Methods

Study Population

Alzheimer's disease neuroimaging initiative (ADNI). Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). ADNI is currently in its 4th iteration at the time of writing. All data used in this study were accessed from ADNI before October 19th, 2020.

Participants

Participants were between 55-90 years of age (inclusive) and spoke either English or Spanish. They were accompanied by study partners. Informed consent was obtained from all participants before study enrollment. We selected participants with MMSE scores between 24-30 (inclusive). Exclusion criteria in ADNI included concurrent neuropsychiatric diagnoses such as clinically significant depression, psychosis, or non-Alzheimer's neurological disorders.

Measures

Clinical variables. Age, sex, and education were included to assess for potential associations with plasma $A\beta_{42}/A\beta_{40}$. Cognitive status (normal cognition [NC] or mild cognitive impairment [MCI]) was determined at the initial visit based on ADNI criteria (https://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf).

Neuropsychiatric variables. In ADNI, NPS were assessed using the ten NPS domains of the Neuropsychiatric Inventory (NPI), excluding the neurovegetative domains of sleep and appetite changes.[17] Based on a published algorithm,[18] NPI items were used to derive the five MBI domains: decreased drive/motivation (NPI apathy/indifference); affective dysregulation (NPI depression, anxiety, elation/euphoria); impulse dyscontrol (NPI agitation/aggression, irritability, aberrant motor behaviour); social inappropriateness (NPI disinhibition); and abnormal thoughts/perception (NPI delusions, hallucinations). For example, participants were considered to have affective dysregulation if they had either depression, anxiety, or elation/euphoria as assessed by the NPI. MBI domain scores were calculated as the product of domain frequency (range of 0 to 4) and severity (range of 0 to 3). Scores across the five transformed MBI domains were added to generate a total MBI score (theoretical range of 0 to 60). Domains were scored as zero if all domain symptoms were absent. Conversely, participants had MBI domain scores above zero if they had a minimum of one NPI symptom within that specific domain.

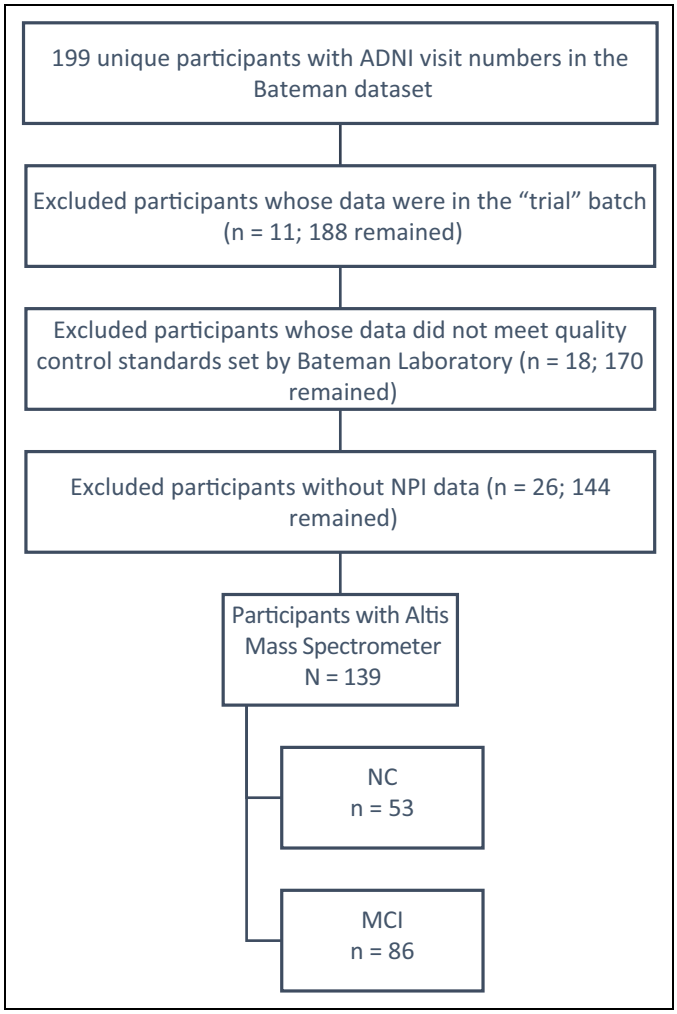

Figure 1. Flowchart showing how the sample populations were obtained from the ADNI cohort.

Biomarkers. Analysis of plasma $A\beta_{42}$ and $A\beta_{40}$ was completed by the Bateman Laboratory using the Thermo Scientific TSQ Altis Triple Quadrupole Mass Spectrometer, described elsewhere.[19]

Sample

Participants with available plasma amyloid were selected. NC and MCI participants with NPI data and plasma $A\beta_{42}/A\beta_{40}$ measurements were included in the final analysis (N = 139).

Table 1. Sample Characteristics.

Characteristics	Overall N = 139	NC n = 86	MCI n = 53
Age (mean, SD)	72.4 (7.6)	73.9 (6.3)	70.1 (6.5)
Female sex, (n, %)	71 (51.8)	45 (52.3)	26 (49.1)
Race: White (n, %)	129 (92.8)	79 (91.9)	50 (94.3)
Race: Black (n, %)	7 (5.0)	5 (5.8)	2 (3.8)
Race: Asian (n, %)	3 (2.2)	2 (2.3)	1 (1.9)
Ethnicity: Hispanic/ Latino (n, %)	2 (1.4)	2 (2.3)	0 (0)
Education years, (median, Q1-Q3)	17 (15-18)	17 (15-18)	17 (16-18)
MBI total score (mean, Q1-Q3)	0.54 (0 -1)	0.41 (0-0)	0.75 (0 -1)
Any MBI symptoms (%)	39 (28.1)	20 (23.3)	19 (35.8)
Affective dysregulation domain score (mean, Q1-Q3)	0.22 (0-0)	0.14 (0-0)	0.36 (0 -1)
Drive/motivation domain score (mean, Q1-Q3)	0.058 (0-0)	0.047 (0-0)	0.075 (0-0)
Impulse dyscontrol domain score (mean, Q1-Q3)	0.22 (0-0)	0.20 (0-0)	0.26 (0-0)
$A\beta_{42}/A\beta_{40}$ (mean, SD)	0.123 (0.0133)	0.122 (0.0131)	0.124 (0.0136)

Table 2. The Association Between Mild Behavioural Impairment (MBI) and Plasma $A\beta_{42}/A\beta_{40}$.

	Unstandardized coefficients		
	Estimate	Std. Error	Pr (> |t|)
(Intercept)	1.58×10^{-1}	1.51×10-2	<0.001*
Age (per year)	-2.02×10^{-3}	9.68×10^{-4}	0.003*
Male sex	3.42×10^{-4}	4.56×10^{-4}	0.328
Education (per year)	-2.23×10^{-3}	2.27×10^{-3}	0.455
MCI versus NC	1.58×10^{-1}	1.51×10^{-2}	0.478
MBI total score (per additional point)	-2.02×10^{-3}	9.68×10^{-4}	0.039*

*Significant p values <0.05.

Table 3. The Association Between Mild Behavioural Impairment Domains and Plasma $A\beta_{42}/A\beta_{40}$.

	Unstandardized coefficients‡		
	Estimate	Std. Error	Pr (> |t|)
MBI (Affect)	-4.62×10^{-3}	2.23×10^{-3}	0.041*
MBI (Apathy)	-6.36×10^{-3}	3.78×10^{-3}	0.095
MBI (Impulse Dyscontrol)	-2.03×10^{-3}	1.93×10^{-3}	0.294

‡Coefficients derived from separate models and adjusted for age, sex, education and baseline cognitive status (NC or MCI).
*Significant p values <0.05.

A detailed flowchart of how the final sample was obtained is shown in Figure 1.

Statistical Analysis

Statistical analysis was performed using R (version 3.6.2). Linear regressions were fitted to assess the association between MBI total score as well as MBI domain scores with the outcome variable, plasma $A\beta_{42}/A\beta_{40}$. The domain scores included the following: affective dysregulation, drive/motivation, and impulse dyscontrol. Abnormal thoughts/perception and social inappropriateness were low frequency domains in this sample, precluding analysis. The models controlled for participants' age, sex, education, and diagnostic status (NC or MCI). Due to low numbers of non-White and non-Hispanic/ Latino participants, race and ethnicity could not be incorporated into our models.

Results

Sample characteristics, including basic demographic information such as age, sex, race, ethnicity, and education, are shown in **Table 1**. A total of 139 participants were included in the analysis, with 86 in the NC group, and 53 in the MCI group.

Linear regressions revealed that a higher MBI total score was associated with decreased plasma $A\beta_{42}/A\beta_{40}$ ($p = 0.04$) (Table 2). An association with age was also observed such that older patients had lower $A\beta_{42}/A\beta_{40}$ ($p = 0.003$). Other variables, including sex, education, and baseline diagnosis of MCI versus NC, were not associated with plasma $A\beta_{42}/A\beta_{40}$. Further analyses of MBI domains showed a significant relationship between higher MBI affective dysregulation and lower plasma $A\beta_{42}/A\beta_{40}$ ($p = 0.04$) (Table 3). However, neither decreased motivation (Table 3; $p = 0.095$) nor higher impulse dyscontrol (Table 3; $p = 0.29$) were associated with lower plasma $A\beta_{42}/A\beta_{40}$.

Discussion

In a sample of 139 participants with NC and MCI, those with greater MBI burden had significantly lower plasma $A\beta_{42}/A\beta_{40}$. Looking at MBI domains, decreased plasma $A\beta_{42}/A\beta_{40}$ was significantly associated with greater MBI affective dysregulation, but not MBI decreased motivation or impulse dyscontrol. To our knowledge, this study is the first to demonstrate the relationship between MBI and plasma $A\beta_{42}/A\beta_{40}$.

Amyloid plaques, particularly $A\beta_{42}$, have been implicated in the pathogenesis of AD.[1] Plasma $A\beta_{42}/A\beta_{40}$ has shown promise in supporting the diagnosis of AD,[20-22] and has better diagnostic accuracy than plasma $A\beta_{42}$ or $A\beta_{40}$ alone.[14,23] Further, plasma $A\beta_{42}/A\beta_{40}$ has predictive value for abnormal amyloid density in the brain[11-13] and can work in conjunction with other plasma AD markers to detect brain atrophy and risk of clinical progression to dementia in NC and MCI populations.[13] Plasma $A\beta_{42}$ and $A\beta_{40}$ concentrations increase significantly

with age,[1] consistent with our finding that age was a significant covariable in the regression models. However, the predictive performance of $A\beta_{42}/A\beta_{40}$ is not influenced by age.[14] Newer research has identified high levels of plasma Aβ at baseline as a risk factor for future neurodegeneration in NC populations. These studies have also implicated decreasing plasma $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ in early AD progression.[24,25] Thus, a declining $A\beta_{42}/A\beta_{40}$ ratio may portend the development of clinical dementia symptoms. Overall, plasma $A\beta_{42}/A\beta_{40}$ appears to be an appropriate biomarker for the screening of pre-dementia states.

NPS are present in both preclinical and prodromal disease. In our sample, MBI symptoms were present in 39/139 (28.1%) participants. In a population-based cohort, using a similar methodology for NPI score transformation as ours, NPS were present at rates of 30.8% in NC and 47.1% in subjective cognitive decline (SCD).[18] According to one systematic review, NPS are also common in prodromal AD at 35-85%.[26] The emergence of NPS in older adults can herald cognitive decline in both NC[8] and MCI.[27] In a study of 2769 National Alzheimer's Coordinating Center participants with a Clinical Dementia Rating (CDR) of 0 at baseline, 23.1% with MBI developed cognitive and functional decline to a CDR > 0 at 3-year follow-up.[8] While the risk of progression from MCI to dementia is around 10-15% at baseline,[28] this incidence jumps to 25% in the context of NPS.[29] MBI provides a validated approach to NPS characterization in at-risk older adults.[30] Prevalence of MBI varies depending on the setting and approach to MBI case ascertainment. In a psychiatric outpatient clinic, MBI prevalence was as low as 3.5%[9] using chart review, whereas prevalence was higher at 5.8% in SCD[31] and 14.2% in MCI[32] in a primary care setting using the MBI checklist (MBI-C).[30] A sample of memory clinic patients had a high MBI prevalence of 76.5% in SCD and 85.3% in MCI,[33] determined using the NPI-Q.[34] Using the same methodology as the present study, community-based population estimates of MBI varied according to cognitive status, from 43.1% in at-risk NC to 48.9% in MCI.[18] Overall, prevalence estimates using the MBI-C are lower than those using the NPI.[31,32] Nonetheless, MBI is associated with cognitive decline throughout the AD continuum, including faster progression in NC[7] and greater incidence of dementia.[9,10] MBI also confers a greater risk of progression to dementia than MCI without MBI.[35]

MBI has several biological correlates, which the literature is just beginning to explore. Known associations exist between MBI and biological markers of AD, including Aβ-positron emission tomography (PET),[16] cerebrospinal fluid (CSF) tau and tau-PET,[36,37] white matter atrophy,[38,39] grey matter atrophy,[40,41] plasma neurofilament light (NfL),[15] and AD risk gene loci.[42,43] The current study extends the literature on the biological basis of MBI. MBI captures the neurobehavioural symptomatology of early phase disease as evidenced by its inverse relationship with plasma $A\beta_{42}/A\beta_{40}$. Our data corroborate the use of MBI as a sensitive instrument for tracking pre-dementia states. There were no significant differences in plasma $A\beta_{42}/A\beta_{40}$ between NC and MCI groups. This supports the utility of MBI in identifying at-risk individuals regardless of baseline cognitive status (NC or MCI), and suggests that for some individuals, MBI may be more sensitive to early Aβ changes than cognition. Importantly, MBI is incorporated into the National Institute on Aging and Alzheimer's Association (NIA-AA) clinical staging for AD. Specifically, individuals can be placed in stage 2 AD based on neurobehavioural symptoms alone, in the absence of cognitive decline. These "mild neurobehavioural changes" should have a clearly defined recent onset, which persist and cannot be explained by life events alone.[44] Our data further support the NIA-AA clinical staging by linking neurobehavioural symptoms with Alzheimer's proteinopathies.

Although the connection between $A\beta_{42}/A\beta_{40}$ and cognitive decline is well-established, relatively less is known about AD biomarkers and their role in the neuropsychiatric sequelae of disease. In this study, affective dysregulation was the only MBI domain significantly associated with decreased plasma $A\beta_{42}/A\beta_{40}$. MBI affective dysregulation consists of NPI depression, anxiety, and elation/euphoria, and relates to changes in regulating emotional tone as a consequence of the structural and functional changes associated with AD.[6] The association between AD biomarkers and anxiety is supported in the literature, with three studies showing a relationship between decreased CSF $A\beta_{42}$ and anxiety.[45-47] The relationship between Aβ and depression is more uncertain. Some studies identified no relationship between decreased CSF $A\beta_{42}$ and increased depression in samples of mixed cognitive status;[45,46,48] others revealed interactions with mood disturbance in NC[47,49] and chronic subsyndromal depressive symptoms in MCI.[50] Plasma Aβ levels have been associated with depression, such that higher baseline plasma $A\beta_{42}$ was a predictor for first depressive episode in NC older adults, and progression to AD at 5 years.[51] Higher baseline $A\beta_{40}$ was also associated with depressive symptoms in the context of dementia at 11-year follow-up.[52] In a longitudinal study of cognitively normal older adults with no mood symptoms or mild depression at baseline, worsening depressive symptoms over 2-7 years were significantly associated with cognitive decline, and this effect was moderated by the presence of cortical amyloid on PET imaging.[53] However, amyloid deposition was less severe in older adults with concurrent major depression than in older adults without depression.[54] In NC samples, it appears that the pathophysiology of dementia differs in MBI (as characterized by the later-life onset of persistent NPS) versus in pre-existing psychiatric conditions. Although the data are equivocal, if there is a true acceleration of cognitive decline in older adults with emergent depression and concurrent amyloid burden, treatment of depressive symptoms might offer an opportunity to delay the progression of dementia symptoms.[53]

We found a trend toward an association between lower plasma $A\beta_{42}/A\beta_{40}$ and MBI decreased motivation. MBI decreased drive/motivation, as denoted by NPI apathy/indifference, may have a tenuous association with amyloid biomarkers in the literature. The relationship between lower CSF $A\beta_{42}$ and apathy was seen in one study[45] but not in several others.[46,47,55]

However, new work demonstrated a significant association between Aβ-PET and MBI decreased motivation.[37] As well, another study determined that new-onset apathy, agitation, and irritability predicted faster progression from MCI to AD.[56] A systematic review and meta-analysis determined that the most common NPS in AD is apathy (49%), followed by depression (42%) and aggression (40%).[57] Considering the high prevalence of MBI decreased motivation in dementia, it is unsurprising that the association between $A\beta_{42}/A\beta_{40}$ and apathy trended towards significance in this small sample.

Finally, domain analysis revealed no association between plasma $A\beta_{42}/A\beta_{40}$ and MBI impulse dyscontrol. There have been several studies related to the domain of MBI impulse dyscontrol, which is comprised of NPI agitation/aggression, irritability, and aberrant motor behaviour. One review found a consistent relationship between CSF AD biomarkers ($A\beta_{42}$, t-tau, and p-tau) and agitation/aggression in a mixed population of MCI and AD, with no other NPS correlates.[55] In contrast, another review paper investigating CSF $A\beta_{42}$ and agitation/aggression in AD did not demonstrate a clear association.[58] In summary, the association between $A\beta_{42}$ and MBI impulse dyscontrol-related NPS is inconsistent and somewhat surprising given the natural history of impulse dyscontrol symptoms in the evolution of dementia. Several longitudinal studies have identified emergent impulse dyscontrol symptoms among the earliest behavioural changes associated with incident cognitive decline and dementia.[28,59,60] Two studies found that impulse dyscontrol symptoms were comparable to hippocampal atrophy for prognostication of cognitive decline and dementia,[39,61] associated with both grey and white matter changes in advance of dementia.[38] Thus, the link between AD biomarkers and MBI domains can be challenging to interpret, and further investigation is required to explore these relationships.

Limitations and Future Directions

Our study has some limitations. MBI total score was extrapolated from composite scores on corresponding NPI items. The MBI-C is the case ascertainment instrument developed to capture MBI in accordance with the International Society to Advance Alzheimer's Research and Treatment - Alzheimer's Association MBI criteria.[30] The MBI-C captures emergent and persistent NPS over a period of 6 months or greater, whereas NPI addresses a point estimate of NPS over a 1-month period. Despite the established algorithm of transformation of NPI items to MBI domains, point estimates of NPS are more susceptible to the inclusion of reactive or transient NPS, decreasing specificity and potentially inflating MBI prevalence.[18,33]Thus, the approach in this analysis approximates MBI, with the time frame, domain composition, and uncertainty regarding the natural history of symptoms potentially contributing to imprecision in the estimates. Additionally, the size of the sample may have been a limiting factor for domain analyses, as lower frequency domains may not have been well represented enough to generate stable models of estimates or associations. With our current screening measures, it can be difficult to distinguish between chronic and recurrent psychiatric conditions in late life, versus new-onset neuropsychiatric symptoms in the context of neurodegeneration. Thus, ADNI exclusion criteria around pre-existing psychiatric illnesses may preclude the participation of some older adults with MBI if the pre-existing symptoms are of relatively recent onset. Therefore, our ADNI sample might not be fully representative of MBI. Finally, the NPI was developed for and validated in a clinical AD population, and though it has since been used extensively in MCI, its ability to evaluate NPS in NC is not as well defined.

To elucidate the relationship between MBI and plasma biomarkers of AD, future studies should more precisely measure NPS. The MBI-C would allow for a standardized approach to documenting NPS in pre-dementia populations,[30] which may increase the specificity and yield of NPS domain analyses. Unfortunately, our data for NPS were limited to a single time-point due to linkage with the plasma biomarker analyses. Previous studies have successfully used NPS captured at two time points to approximate the persistence criterion of MBI,[8,61] and subsequent studies could use this approach if MBI-C data are not available. It would be valuable to track the natural history of MBI as it relates to longitudinal changes in plasma $A\beta_{42}/A\beta_{40}$. Our study suggests that MBI predicts early Aβ pathology regardless of baseline cognitive status (NC or MCI), and thus potentially in advance of substantial cognitive changes. This merits replication in future analyses. Finally, 129/139 study participants were White, limiting generalizability of these findings to other racial or ethnocultural groups. Studies in more diverse populations are required.

Conclusion

Our study provides evidence for the biological association between MBI and plasma $A\beta_{42}/A\beta_{40}$, a validated marker of brain beta-amyloid.[25] Therefore, MBI may have utility as an accessible case ascertainment approach in AD clinical trial recruitment. More research is required to delineate the patterns of association between AD biomarkers and MBI symptoms over time.

Authors' Note

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

Acknowledgements

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.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: ZI is supported by the Canadian Institutes of Health Research and the Canadian Consortium for Neurodegeneration in Aging.

ORCID iDs

Ruxin Miao https://orcid.org/0000-0002-7308-3797
Hung-Yu Chen https://orcid.org/0000-0001-8562-2113
Zahinoor Ismail https://orcid.org/0000-0002-5529-3731

References

1. Molinuevo JL, Ayton S, Batrla R, Bednar MM, Bittner T, Cummings J. *Current State of Alzheimer's Fluid Biomarkers*. Springer Berlin Heidelberg; 2018.
2. Gauthier S, Albert M, Fox N, et al. Why has therapy development for dementia failed in the last two decades? *Alzheimer's Dement*. 2016;12(1):60-64. doi:10.1016/j.jalz.2015.12.003
3. Mortby ME, Black SE, Gauthier S, et al. Dementia clinical trial implications of mild behavioral impairment. *Int Psychogeriatrics*. 2018;30(2):171-175. doi:10.1017/S1041610218000042
4. Montero-Odasso M, Ismail Z, Camicioli R.Alzheimer disease, biomarkers, and clinical symptoms - Quo Vadis? *JAMA Neurol*. 2020;77(3):393-394. doi:10.1001/jamaneurol.2019.4959
5. Montero-Odasso M, Pieruccini-Faria F, Ismail Z, et al. CCCDTD5 recommendations on early non cognitive markers of dementia: A Canadian consensus. *Alzheimer's Dement (New York, N Y)*. 2020;6(1):e12068. doi:10.1002/trc2.12068
6. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's Dement*. 2016;12(2):195-202. doi:10.1016/j.jalz.2015.05.017
7. Creese B, Brooker H, Ismail Z, et al. Mild Behavioral Impairment as a Marker of Cognitive Decline in Cognitively Normal Older Adults. *Am J Geriatr Psychiatry*. 2019;27(8):823-834. doi:10.1016/j.jagp.2019.01.215
8. Ismail Z, Mcgirr A, Gill S, Hu S, Forkert, Smith EE. Mild behavioral impairment and subjective cognitive decline predict cognitive and functional decline. *J Alzheimer's Dis*. 2021;80(1):459-469.
9. Matsuoka T, Ismail Z, Narumoto J. Prevalence of mild behavioral impairment and risk of dementia in a psychiatric outpatient clinic. *J Alzheimer's Dis*. 2019;70(2):503-511. doi:10.3233/JAD-190278
10. Taragano FE, Allegri RF, Heisecke SL, et al. Risk of Conversion to Dementia in a Mild Behavioral Impairment Group Compared to a Psychiatric Group and to a Mild Cognitive Impairment Group. *J Alzheimer's Dis*. 2018;62(1):227-238. doi:10.3233/JAD-170632
11. Fandos N, Pérez-Grijalba V, Pesini P, et al. Plasma amyloid β 42/40 ratios as biomarkers for amyloid β cerebral deposition in cognitively normal individuals. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2017;8:179-187. doi:10.1016/j.dadm.2017.07.004
12. Schindler SE, Bollinger JG, Ovod V, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology*. 2019;93(17): E1647-E1659. doi:10.1212/WNL.0000000000008081
13. Shen X, Li J, Wang H, et al. Plasma amyloid, tau, and neurodegeneration biomarker profiles predict Alzheimer's disease pathology and clinical progression in older adults without dementia. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2020;12(1):1-11. doi:10.1002/dad2.12104
14. Vergallo A, Mégret L, Lista S, et al. Plasma amyloid β 40/42 ratio predicts cerebral amyloidosis in cognitively normal individuals at risk for Alzheimer's disease. *Alzheimer's Dement*. 2019;15(6):764-775. doi:10.1016/j.jalz.2019.03.009
15. Naude JP, Gill S, Hu S, et al. Plasma Neurofilament Light: A Marker of Neurodegeneration in Mild Behavioral Impairment. *J Alzheimer's Dis*. 2020;76(3):1017-1027. doi:10.3233/JAD-200011
16. Lussier FZ, Pascoal TA, Chamoun M, et al. Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. *Alzheimer's Dement*. 2020;16(1):192-199. doi:10.1002/alz.12007
17. Cummings JL. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology*. 1997;48(5 SUPPL. 6):10S-6S. doi:10.1212/wnl.48.5_suppl_6.10 s
18. Mortby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. *Int Psychogeriatrics*. 2018;30(2):221-232. doi:10.1017/S1041610217001909
19. Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimer's Dement*. 2017;13(8):841-849. doi:10.1016/j.jalz.2017.06.2266
20. Blennow K, Meyer G, Hansson O, et al. Evolution of Aβ42 and Aβ40 levels and Aβ42/Aβ40 ratio in plasma during progression

of Alzheimer's disease: A multicenter assessment. *J Nutr Heal Aging*. 2009;13(3):205-208. doi:10.1007/s12603-009-0059-0

21. Kim HJ, Park KW, Kim TE, et al. Elevation of the plasma Aβ40/Aβ42 ratio as a diagnostic marker of sporadic early-onset Alzheimer's disease. *J Alzheimer's Dis*. 2015;48(4):1043-1050. doi:10.3233/JAD-143018
22. Waragai M, Yoshida M, Mizoi M, et al. Increased protein-conjugated acrolein and amyloid-β40/42 ratio in plasma of patients with mild cognitive impairment and Alzheimer's disease. *J Alzheimer's Dis*. 2012;32(1):33-41. doi:10.3233/JAD-2012-120253
23. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. *Alzheimer's Res Ther*. 2019;11(1):1-15. doi:10.1186/s13195-019-0485-0
24. Mayeux R, Schupf N.Blood-based biomarkers for Alzheimer's disease: Plasma Aβ40 and Aβ42, and genetic variants. *Neurobiol Aging*. 2011;32(SUPPL. 1): S10. doi:10.1016/j.neurobiolaging.2011.09.004
25. van Oijen M, Hofman A, Soares HD, Koudstaal PJ, Breteler MM. Plasma Aβ1-40 and Aβ1-42 and the risk of dementia: a prospective case-cohort study. *Lancet Neurol*. 2006;5(8):655-660. doi:10.1016/S1474-4422(06)70501-4
26. Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. *J Alzheimer's Dis*. 2009;18(1):11-30. doi:10.3233/JAD-2009-1120
27. Ismail Z, Mortby ME. *Cognitive and Neuropsychiatric Screening Tests in Older Adults*. In: Springer; 2017:343-368. doi:10.1007/978-981-10-2414-6_16
28. Geda YE, Roberts RO, Mielke MM, et al. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: A population-based study. *Am J Psychiatry*. 2014;171(5):572-581. doi:10.1176/appi.ajp.2014.13060821
29. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and alzheimer disease. *Am J Geriatr Psychiatry*. 2013;21(7):685-695. doi:10.1016/j.jagp.2013.01.006
30. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *J Alzheimer's Dis*. 2017;56(3):929-938. doi:10.3233/JAD-160979
31. Mallo SC, Ismail Z, Pereiro AX, et al. Assessing mild behavioral impairment with the mild behavioral impairment checklist in people with subjective cognitive decline. *Int Psychogeriatrics*. 2019;31(2):231-239. doi:10.1017/S1041610218000698
32. Mallo SC, Ismail Z, Pereiro AX, et al. Assessing Mild Behavioral Impairment with the Mild Behavioral Impairment-Checklist in People with Mild Cognitive Impairment. *J Alzheimers Dis*. 2018;66(1):83-95. doi:10.3233/JAD-180131
33. Sheikh F, Ismail Z, Mortby ME, et al. Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden. *Int Psychogeriatrics*. 2018;30(2):233-244. doi:10.1017/S1041610217001510
34. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233-239. doi:10.1176/jnp.12.2.233
35. Taragano FE, Allegri RF, Krupitzki H, et al. Mild behavioral impairment and risk of dementia: A prospective cohort study of 358 patients. *J Clin Psychiatry*. 2009;70(4):584-592. doi:10.4088/JCP.08m04181
36. Johansson M, Stomrud E, Insel PS, et al. Mild behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. *Transl Psychiatry*. 2021;11(1):76. doi:10.1038/s41398-021-01206-z
37. Lussier FZ, Pascoal TA, Therriault J, et al. Mild behavioral impairment is associated with beta-amyloid and tau across the alzheimer's disease spectrum. In: *Journal of Cerebral Blood Flow and Metabolism*. Vol 39. Sage Publications Inc; 2019:158-159.
38. Gill S, Wang M, Forkert ND, MacMaster FP, Smith EE, Ismail Z. Diffusion Tensor Imaging in pre-dementia risk states: white matter atrophy findings in Mild Behavioral Impairment (P5.1-025). *Neurology*. 2019;92(15 Supplement).
39. Gill S, Wang M, Mouches P, et al. Neural Correlates of the Impulse Dyscontrol Domain of Mild Behavioral Impairment. *Int J Geriatr Psychiatry*. 2021.
40. Matuskova V, Ismail Z, Nikolai T, Markova H, Cechova K, Laczó J, et al. Mild behavioral impairment is associated with atrophy of entorhinal cortex and hippocampus in a memory clinic cohort. *Front Aging Neurosci*. 2021;13:236.
41. Yoon EJ, Ismail Z, Hanganu A, et al. Mild behavioral impairment is linked to worse cognition and brain atrophy in Parkinson disease. *Neurology*. 2019;93(8): e766-e777. doi:10.1212/WNL.0000000000007968
42. Andrews SJ, Ismail Z, Anstey KJ, Mortby M. Association of Alzheimer's genetic loci with mild behavioral impairment. *Am J Med Genet Part B Neuropsychiatr Genet*. 2018;177(8):727-735. doi:10.1002/ajmg.b.32684
43. Creese B, Arathimos R, Brooker H, et al. Genetic risk for Alzheimer's disease, cognition, and mild behavioral impairment in healthy older adults. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2021;13(1):e12164. doi:10.1002/dad2.12164
44. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
45. Banning LCP, Ramakers IHGB, Köhler S, et al. The association between biomarkers and neuropsychiatric symptoms across the Alzheimer's disease spectrum. *Am J Geriatr Psychiatry*. 2020;28(7):735-744. doi:10.1016/j.jagp.2020.01.012
46. Ramakers IHGB, Verhey FRJ, Scheltens P, et al. Anxiety is related to Alzheimer cerebrospinal fluid markers in subjects with mild cognitive impairment. *Psychol Med*. 2013;43(5):911-920. doi:10.1017/S0033291712001870
47. Sannemann L, Schild A-K, Altenstein S, et al. Neuropsychiatric symptoms in at-risk groups for AD dementia and their association with worry and AD biomarkers—results from the DELCODE study. *Alzheimers Res Ther*. 2020;12(1):131. doi:10.1186/s13195-020-00701-7

48. Kramberger MG, Jelic V, Kåreholt I, et al. Cerebrospinal Fluid Alzheimer Markers in Depressed Elderly Subjects with and without Alzheimer's Disease. *Dement Geriatr Cogn Dis Extra*. 2012; 2(1):48-56. doi:10.1159/000334644
49. Babulal GM, Ghoshal N, Head D, et al. Mood Changes in Cognitively Normal Older Adults are Linked to Alzheimer Disease Biomarker Levels. *Am J Geriatr Psychiatry*. 2016;24(11): 1095-1104. doi:10.1016/j.jagp.2016.04.004
50. Gonzales MM, Insel PS, Nelson C, et al. Chronic depressive symptomatology and CSF amyloid beta and tau levels in mild cognitive impairment. *Int J Geriatr Psychiatry*. 2018;33(10): 1305-1311. doi:10.1002/gps.4926
51. Blasko I, Kemmler G, Jungwirth S, et al. Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer disease. *Am J Geriatr Psychiatry*. 2010;18(11):973-982. doi:10.1097/JGP.0b013e3181df48be
52. Direk N, Schrijvers EMC, de Bruijn RFAG, et al. Plasma amyloid β, depression, and dementia in community-dwelling elderly. *J Psychiatr Res*. 2013;47(4):479-485. doi:10.1016/j.jpsychires.2012.12.008
53. Gatchel JR, Rabin JS, Buckley RF, et al. Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. *JAMA Netw Open*. 2019;2(8):198964. doi:10.1001/jamanetworkopen.2019.8964
54. Mackin RS, Insel PS, Landau S, et al. Late-life depression is associated with reduced cortical amyloid burden: findings from the Alzheimer's disease neuroimaging initiative depression project. *Biol Psychiatry*. 2021;89(8):757-765. Published online July 2020. doi:10.1016/j.biopsych.2020.06.017
55. Showraki A, Murari G, Ismail Z, et al. Cerebrospinal Fluid Correlates of Neuropsychiatric Symptoms in Patients with Alzheimer's Disease/Mild Cognitive Impairment: A Systematic Review. *J Alzheimer's Dis*. 2019;71(2):477-501. doi:10.3233/JAD-190365
56. Goukasian N, Hwang KS, Romero T, et al. Association of brain amyloidosis with the incidence and frequency of neuropsychiatric symptoms in ADNI: A multisite observational cohort study. *BMJ Open*. 2019;9(12):31947. doi:10.1136/bmjopen-2019-031947
57. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*. 2016;190:264-271. doi:10.1016/j.jad.2015.09.069
58. Ruthirakuhan M, Lanctôt KL, Di Scipio M, Ahmed M, Herrmann N.Biomarkers of agitation and aggression in Alzheimer's disease: a systematic review. *Alzheimer's Dement*. 2018;14(10): 1344-1376. doi:10.1016/j.jalz.2018.04.013
59. Wise EA, Rosenberg PB, Lyketsos CG, Leoutsakos JM. Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2019;11:333-339. doi:10.1016/j.dadm.2019.02.006
60. Masters MC, Morris JC, Roe CM. "Noncognitive" symptoms of early Alzheimer disease: A longitudinal analysis. *Neurology*. 2015;84(6):617-622. doi:10.1212/WNL.0000000000001238
61. Gill S, Mouches P, Hu S, et al. Using machine learning to predict dementia from neuropsychiatric symptom and neuroimaging data. *J Alzheimer's Dis*. 2020;75(1):277-288. doi:10.3233/jad-191169