

RESEARCH ARTICLE

# Nutritional status and structural brain changes in Alzheimer's disease: The NUDAD project

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## Abstract

**Introduction:** Weight loss is associated with higher mortality and progression of cognitive decline, but its associations with magnetic resonance imaging (MRI) changes related to Alzheimer's disease (AD) are unknown.

**Methods:** We included 412 patients from the NUDAD project, comprising 129 with AD dementia, 107 with mild cognitive impairment (MCI), and 176 controls. Associations between nutritional status and MRI measures were analyzed using linear regression, adjusted for age, sex, education, cognitive functioning, and cardiovascular risk factors.

**Results:** Lower body mass index (BMI), fat mass (FM), and fat free mass index were associated with higher medial temporal atrophy (MTA) scores. Lower BMI, FM, and waist circumference were associated with more microbleeds. Stratification by diagnosis showed that the observed associations with microbleeds were only significant in MCI.

**Discussion:** Lower indicators of nutritional status were associated with more MTA and microbleeds, with largest effect sizes in MCI.

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**KEYWORDS**

body mass index, cerebral atrophy, fat free mass, fat mass, malnutrition, microbleeds, mild cognitive impairment, magnetic resonance imaging, nutritional status, white matter hyperintensities

**1 | BACKGROUND**

Changing nutritional status, including weight loss, is already prevalent in early (pre-dementia) stages of Alzheimer's disease (AD).<sup>1,2</sup> A suboptimal nutritional status has been associated with higher mortality and progression of cognitive decline.<sup>3-6</sup> However, it is not clear what the relation is between nutritional status and the neurodegenerative process implicated in AD.

On magnetic resonance imaging (MRI), AD is characterized by cerebral atrophy, including global cortical atrophy (GCA) and medial temporal atrophy (MTA).<sup>7</sup> In particular, MTA is an early marker for AD pathology.<sup>7</sup> Cerebrovascular damage in AD is characterized by white matter hyperintensities (WMH) and microbleeds on MRI.<sup>8</sup> The observation of the latter has been linked to underlying cerebral amyloid angiopathy and AD patients with microbleeds have been shown to have more abnormal concentrations of amyloid beta ( $A\beta$ ) in their cerebrospinal fluid (CSF).<sup>8,9</sup>

In clinical populations of AD and mild cognitive impairment (MCI), studies have shown conflicting results regarding the association between body mass index (BMI) and cerebral atrophy.<sup>10-14</sup> These conflicting findings could be due to differences in study populations, because in some populations cardiovascular risk factors were more prevalent than in others. Alternatively, they could be the consequence of the complex relationship between nutritional status and atrophy, as most of these former studies only evaluated BMI, but nutritional status refers to a broader concept, including parameters such as body composition (ie, fat mass [FM], fat free mass index [FFMI]) and malnutrition as assessed using mini nutritional assessment (MNA). In this study, we aimed to investigate associations among BMI, FM, FFMI, waist circumference, and MNA, as indicators of nutritional status and structural brain changes, including measures of brain atrophy and cerebrovascular pathology, in a memory clinic population with AD dementia, MCI, and controls.

**2 | METHODS****2.1 | Study population**

NUDAD (Nutrition, the Unrecognized Determinant in Alzheimer's Disease) is a prospective cohort study that aims to investigate nutritional determinants in AD dementia and pre-dementia stages, with a clinical follow-up of 3 years.<sup>15</sup> The NUDAD cohort is nested within the Amsterdam Dementia Cohort and consists of patients that visited the Alzheimer Center of the Amsterdam UMC between September 2015 and August 2017, were diagnosed with AD dementia, MCI, or subjective cognitive decline (SCD) and had a Mini-Mental State Examination

(MMSE) score > 16.<sup>16</sup> Here, we present cross-sectional baseline data of the 412 NUDAD participants with available MRI scans, including 129 patients with AD dementia; 107 patients with MCI; and 176 individuals with SCD, who served as controls. Patients underwent standardized dementia screening, including extensive neuropsychological assessment, neurological examination, MRI, lumbar puncture, and laboratory tests.<sup>17</sup> MCI and AD dementia diagnoses were established by consensus in a multidisciplinary meeting according to the National Institute on Aging-Alzheimer's Association criteria.<sup>18,19</sup> As controls, we used subjects with SCD who presented with memory complaints but performed normally on all clinical and cognitive examinations, ie, did not fulfill criteria for MCI, dementia, or psychiatric diagnoses.<sup>17</sup> Informed consent was obtained from all participants and the protocol was approved by the Ethics Committee of the Amsterdam UMC.

Descriptive characteristics included age, sex, educational levels according to the Verhage score (low: 1-3, medium: 4-5, high: 6-7),<sup>20</sup> living situation (independent alone, independent together, or institutionalized), medical history (history of diabetes mellitus, hypertension, hypercholesterolemia, myocardial infarction, or peripheral artery disease—either self-reported or as described in referral letter), smoking status (current, former, never), and alcohol use (in number of consumptions per day). In addition, global cognitive functioning was assessed using the MMSE (scale 0-30).<sup>21</sup> Cardiovascular risk was defined as a cumulative score that increased with one point for the presence of one of the following variables: a self-reported history of diabetes mellitus, hypertension, hypercholesterolemia, or self-reported medication use for any of these conditions; self-reported history of peripheral artery disease or myocardial infarction; or self-reported positive smoking status (current or former smoking).

**2.2 | Indicators of nutritional status**

From measured body height and body weight, BMI,  $\text{kg}/\text{m}^2$  was calculated for all patients. Waist circumference, available in 400 patients, was measured in standing position with a measuring tape at the smallest part between the lowest rib and hip. After multifrequency bioelectrical impedance analysis (50 kHz, Bodystat Quadscan 4000), free fat mass (FFM; kg) was calculated using the Kyle formula, and FM (kg) was calculated by subtracting FFM from total body weight.<sup>22</sup> Subsequently, FFM was divided by squared body height to calculate FFMI ( $\text{kg}/\text{m}^2$ ). Data on FM and FFMI were available for 346 patients. Nutritional status was evaluated in 267 patients using the validated MNA that has a maximum score of 30 points with higher scores indicating a better nutritional status.<sup>23,24</sup> If necessary, study partners assisted patients in completing this questionnaire. Patients scoring lower than 23.5 points are generally regarded as being at risk of

malnutrition and lower than 17 points as malnourished. For the analyses, a modified MNA score was used with a maximum score of 28, in which the question on neuropsychological functioning was omitted to avoid that putative group differences in MNA were driven by diagnosis.<sup>25</sup>

### 2.3 | MRI visual scores

MRI scans were performed on a 3.0T scanner. The MRI protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and gradient echo T2\*-weighted images. A trained neuroradiologist evaluated all scans using visual rating scales. MTA was rated on coronal reconstructions of T1-weighted images on a 5-point rating scale (scores 0–4) that has been previously described by Scheltens et al.<sup>26</sup> MTA was rated on both sides, perpendicular to the long axis of the hippocampus. For the analyses, for each patient an average MTA score was calculated from left and right scores. GCA was quantified on transverse FLAIR images using a 4-point rating scale (scores 0–3) that has been previously described by Pasquier et al.<sup>27</sup> WMHs were assessed on the same sequences using the 4-point Fazekas scale (scores 0–3).<sup>28</sup> Microbleeds were defined as small (up to 10 mm) round hypointense lesions on T2\*-weighted MRI.<sup>29</sup> Microbleeds counts were categorized as follows: no microbleeds, 1 microbleed, 2–4 microbleeds, and  $\geq 5$  microbleeds.

### 2.4 | Amyloid status

Amyloid status determined by either positive emission tomography (PET) or CSF was available for 356 patients (PET  $n = 198$ , CSF  $n = 158$ ). Amyloid PET-scans were made after injection of a tracer dose of either approximately 250 MBq  $\pm$  20% [<sup>18</sup>F]florbetaben (Neuraceq) or approximately 370 MBq [<sup>18</sup>F]florbetapir (Amyvid). Images were assessed for amyloid positivity by an experienced nuclear medicine physician.<sup>30,31</sup> CSF was obtained by lumbar puncture using a 25-gauge needle and collected in 10 mL polypropylene tubes (Sarstedt). Amyloid- $\beta_{1-42}$  ( $A\beta_{42}$ ) concentrations were determined with sandwich enzyme-linked immunosorbent assays (ELISAs; Fujirebio).<sup>32</sup> Patients were classified as having a positive amyloid status, indicative for AD pathology, if they had a either positive amyloid PET scan,<sup>30</sup> or abnormal CSF biomarkers, defined as amyloid- $\beta_{42}$  ( $A\beta_{42}$ ) drift corrected values lower than 813 pg/mL.<sup>33</sup> In total, 187 (52%) patients were classified as amyloid positive.

### 2.5 | Statistical analysis

Differences in descriptive variables, nutritional status parameters, and MRI scores between diagnosis groups were tested using analysis of variance or Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. For ease of comparison, nutritional status parameters were transformed into Z-scores. Linear

### RESEARCH IN CONTEXT

**1** Systematic review: A PubMed search yielded several articles on the relation between body mass index (BMI) and cerebral atrophy.<sup>10–14</sup> These articles showed conflicting results, and only a few of these studies took more in-depth parameters of nutritional status into account.

**2** Interpretation: In our cohort, lower nutritional parameters were associated with more medial temporal atrophy and microbleeds, with largest effect sizes in patients with mild cognitive impairment. Our results extend previous reports by simultaneously evaluating multiple nutritional status parameters in relation to different MRI measures of neurodegenerative and vascular pathology in a clinical AD sample covering the entire cognitive spectrum from cognitively normal to dementia.

**3** Future directions: Our results indicate that worse nutritional status might have a role in the development of AD, either as early consequence of underlying pathology or as an aggravating factor. This should be further studied in intervention studies that focus on optimizing nutritional status in AD.

regression analysis in the total sample was used to evaluate associations between nutritional status parameters and MRI measures in two models: model 1 was adjusted for age, sex, and education (continuous Verhage score); model 2 was adjusted for age, sex, education, MMSE, and cardiovascular risk composite score. Subsequently, we repeated model 2 stratified for diagnosis. Last, we performed a sensitivity analysis for the stratified model 2 including amyloid positive patients only. Significance level was set at  $P < .05$  for all analyses. All statistical analyses were performed with SPSS version 22.0 for Windows and plots were created with RStudio 3.4.2 for Windows using the forestplot package.<sup>34</sup>

## 3 | RESULTS

Patients with MCI and AD dementia were older, had received less education, and had lower MMSE scores than controls (Table 1). There were no differences in sex and living situation. Regarding the nutritional parameters, MCI and AD dementia patients had lower BMI and lower FM than controls. MTA and GCA were most severe in patients with AD dementia, followed by patients with MCI and controls. WMH and microbleed load were most severe in MCI patients compared to controls with AD dementia in between.

Linear regression analyses (Table 2) showed that lower BMI ( $\beta = -0.12$  [ $-0.21, -0.03$ ],  $P < .01$ , model 2), lower FM ( $\beta = -0.11$  [ $-0.20, -0.02$ ],  $P < .05$ , model 2), and lower FFMI ( $\beta = -0.18$  [ $-0.30, -0.06$ ],  $P < .01$ , model 2) were associated with higher MTA scores in both models. In addition, lower FFMI was associated with more GCA ( $\beta = -0.15$  [ $-0.27, -0.03$ ],

**TABLE 1** Population characteristics

Characteristics	Categories	N	Total N = 412	Controls N = 176	MCI N = 107	AD dementia N = 129	P
<i>General</i>							
Sex	Female	412	188 (54.4)	95 (54.0)	67 (62.6)	62 (48.1)	0.082
Age		412	64.6 ± 8.3	60.8 ± 7.6	66.9 ± 7.5 <sup>b</sup>	68.0 ± 7.8 <sup>b</sup>	<.001
Education level	Low	412	27 (6.6)	9 (5.1)	9 (8.4)	9 (7.0)	.012
	Medium		174 (42.2)	59 (33.5)	52 (48.6)	63 (48.8)	
	High		211 (51.2)	108 (61.4)	46 (43.0)	57 (44.2)	
Living situation	Independent, with partner	412	310 (75.2)	129 (72.9)	85 (79.4)	96 (74.4)	.514
	Independent, alone		100 (24.3)	47 (27.1)	21 (19.6)	32 (24.8)	
	Nursing home		2 (0.5)	0 (0.0)	1 (0.9)	1 (0.8)	
MMSE		412	27 [24-29]	29 [27-29]	27 [25-28] <sup>b</sup>	24 [21-26] <sup>bc</sup>	<.001 <sup>a</sup>
Amyloid status	Positive	356	187 (52.5)	34 (23.4)	50 (51.0)	103 (91.2)	<.001
<i>Cardiovascular risk factors</i>							
Smoking status	Smoker	412	55 (13.3)	22 (12.5)	16 (15.0)	17 (13.2)	.938
	Former smoker		154 (37.4)	65 (36.9)	42 (39.3)	47 (36.4)	
	Never		203 (49.3)	89 (50.6)	49 (45.8)	65 (50.4)	
Alcohol use per day		412	1.0 ± 1.3	1.0 ± 1.3	1.1 ± 1.3	0.9 ± 1.2	.553 <sup>a</sup>
Hypertension		412	103 (25.0)	40 (22.7)	31 (29.0)	32 (24.8)	.500
Hypercholesterolemia		412	52 (12.6)	17 (9.7)	14 (13.1)	21 (16.3)	.225
Diabetes mellitus		412	38 (9.2)	13 (7.4)	17 (15.9)	8 (6.2)	.020
Myocardial infarction		412	12 (2.9)	3 (1.7)	5 (4.7)	4 (3.1)	.350
Peripheral artery disease		412	2 (0.5)	2 (1.1)	0 (0.0)	0 (0.0)	.260
<i>Indicators of nutritional status</i>							
BMI		412	25.8 ± 4.1	26.6 ± 4.7	25.3 ± 3.5 <sup>b</sup>	25.0 ± 3.7 <sup>b</sup>	.001
Waist circumference		400	91.3 ± 12.5	92.6 ± 13.5	91.7 ± 11.7	89.1 ± 11.5 <sup>b</sup>	.054
Fat mass		346	25.8 ± 8.2	27.0 ± 8.3	25.3 ± 7.8	24.3 ± 8.1 <sup>b</sup>	.026
Fat free mass		346	52.9 ± 10.5	53.6 ± 11.5	53.4 ± 9.5	51.5 ± 9.8	.256
Fat free mass index		346	17.3 ± 2.4	17.5 ± 2.6	17.2 ± 2.2	17.1 ± 2.1	.282
MNA-modified score		267	25.0 [23.5-25.5]	25.0 [23.5-25.5]	25.0 [23.0-26.0]	25.0 [23.0-26.0]	.052 <sup>a</sup>
<i>MRI markers</i>							
MTA		412	0.90 ± 0.89	0.36 ± 0.51	1.07 ± 0.89 <sup>b</sup>	1.48 ± 0.86 <sup>bc</sup>	<.001 <sup>a</sup>
GCA		412	0.66 ± 0.68	0.31 ± 0.50	0.83 ± 0.69 <sup>b</sup>	0.98 ± 0.67 <sup>b</sup>	<.001 <sup>a</sup>
WMH		411	0.96 ± 0.81	0.69 ± 0.70	1.23 ± 0.89 <sup>b</sup>	1.12 ± 0.76 <sup>b</sup>	<.001 <sup>a</sup>
Microbleeds (≥1)		403	79 (19.6)	24 (13.9)	30 (28.3)	25 (20.2)	.013

Notes: Data are presented as mean ± standard deviation, n (%), or median [interquartile range]. Differences were tested with one-way analysis of variance or Kruskal Wallis tests for continuous variables and chi-square tests for categorical variables. \* =  $P$ -value < .05; <sup>a</sup> = Kruskal-Wallis test; <sup>b</sup> = significantly different from controls upon post-hoc; <sup>c</sup> = significantly different from MCI upon post-hoc.

Abbreviations: BMI = body mass index; GCA = global cortical atrophy; GDS = Geriatric Depression Scale; MMSE = Mini Mental State Examination; MNA = Mini Nutritional Assessment; MRI, magnetic resonance imaging; MTA = medial temporal atrophy; WMH = white matter hyperintensities.

$P < .05$ , model 2). Lower FM ( $\beta$  -0.14 [-0.25, -0.03],  $P < .05$ , model 2) and lower waist circumference ( $\beta$  -0.16 [-0.27, -0.04],  $P < .01$ , model 2) were associated with more microbleeds in both models. Lower BMI was only associated with more microbleeds in model 2 ( $\beta$  -0.11 [-0.21, 0.00],  $P < .05$ ). There were no associations between nutritional parameters and WMH.

Subsequently, we stratified model 2 for diagnosis (Figure 1). Although statistical significance of most associations was lost due to smaller group sizes, effect sizes remained similar. Moreover, associations between nutritional parameters, including lower BMI ( $\beta$  -0.33 [-0.52, -0.13],  $P < .01$ ), FM ( $\beta$  -0.33 [-0.56, -0.11],  $P < .01$ ), FFMI ( $\beta$  -0.44 [-0.72, -0.16],  $P < .01$ ) and waist circumference ( $\beta$  -0.38 [-0.62, -0.13],

**TABLE 2** Associations between nutritional parameters and MRI markers

Determinant	Model 1	Model 2
<b>MTA</b>		
BMI	-0.12 (-0.20; -0.03)*	-0.12 (-0.21; -0.03)*
FM	-0.11 (-0.20; -0.01)*	-0.11 (-0.20; -0.02)*
FFMI	-0.14 (-0.27; -0.02)*	-0.18 (-0.30; -0.06)*
Waist circumference	-0.10 (-0.20; 0.00)	-0.09 (-0.19; 0.01)
MNA-mod score	-0.04 (-0.15; 0.07)	0.00 (-0.11; 0.10)
<b>GCA</b>		
BMI	-0.06 (-0.14; 0.03)	-0.06 (-0.15; 0.02)
FM	-0.04 (-0.13; 0.06)	-0.04 (-0.14; 0.05)
FFMI	-0.12 (-0.25; 0.00)	-0.15 (-0.27; -0.03)*
Waist circumference	-0.01 (-0.11; 0.08)	-0.01 (-0.11; 0.09)
MNA-mod score	-0.10 (-0.20; 0.01)	-0.06 (-0.17; 0.05)
<b>WMH</b>		
BMI	-0.02 (-0.11; 0.07)	-0.05 (-0.15; 0.04)
FM	0.00 (-0.09; 0.10)	-0.04 (-0.14; 0.06)
FFMI	-0.05 (-0.18; 0.08)	-0.08 (-0.21; 0.05)
Waist circumference	0.02 (-0.08; 0.12)	-0.02 (-0.12; 0.09)
MNA-mod score	-0.05 (-0.16; 0.06)	-0.02 (-0.13; 0.09)
<b>Microbleeds</b>		
BMI	-0.09 (-0.19; 0.01)	-0.11 (-0.21; 0.00)*
FM	-0.12 (-0.22; -0.01)*	-0.14 (-0.25; -0.03)*
FFMI	-0.10 (-0.24; 0.04)	-0.11 (-0.25; 0.04)
Waist circumference	-0.14 (-0.25; -0.03)*	-0.16 (-0.27; -0.04)*
MNA-mod score	-0.09 (-0.21; 0.03)	-0.10 (-0.22; 0.03)

Notes: Associations between nutritional parameters and MRI markers are presented as standardized betas with confidence intervals. Model 1 is adjusted for age, sex, and education; model 2 is adjusted for age, sex, education, MMSE, and cardiovascular risk composite score.

\*  $P < .05$ .

Abbreviations: BMI = body mass index; FM, fat mass; FFMI, fat free mass index; GCA = global cortical atrophy; GDS = Geriatric Depression Scale; MMSE = Mini Mental State Examination; MNA = Mini Nutritional Assessment; MRI, magnetic resonance imaging; MTA = medial temporal atrophy; WMH = white matter hyperintensities.

$P < .01$ ) and having more microbleeds were significant in MCI patients. There were no significant associations in AD dementia and controls. There was an association between MNA and WMH in controls ( $\beta$  -0.19 [-0.38, 0.00],  $P < .05$ ), but not in MCI or AD dementia. Associations between lower BMI, FM, FFMI, and waist circumference and higher MTA were largely similar in direction and effect size across diagnosis groups, with somewhat larger effect sizes in patients with MCI.

Finally, we performed a sensitivity analysis for model 2 in the subgroup of 187 patients with positive amyloid status, with a mean age of  $66.5 \pm 7.6$  years, 102 (51.3%) females, 54 (27%) patients with MCI, 104 (52%) patients with AD dementia, and 41 (21%) controls (Table 3). Associations with MTA and GCA became stronger than in the total group. There were no associations between nutritional parameters and

**TABLE 3** Sensitivity analysis in amyloid positive patients

Determinant	Model 1	Model 2
<b>MTA</b>		
BMI	-0.18 (-0.31, -0.05)*	-0.18 (-0.31, -0.05)*
FM	-0.15 (-0.30, -0.01)*	-0.16 (-0.31, -0.02)*
FFMI	-0.18 (-0.36, 0.01)	-0.23 (-0.41, -0.06)*
Waist circumference	-0.15 (-0.31, 0.00)*	-0.15 (-0.30, 0.00)
MNA-mod score	0.02 (-0.14, 0.19)	0.06 (-0.10, 0.21)
<b>GCA</b>		
BMI	-0.11 (-0.25, 0.03)	-0.12 (-0.26, 0.02)
FM	-0.06 (-0.22, 0.09)	-0.08 (-0.24, 0.08)
FFMI	-0.23 (-0.42, -0.03)*	-0.27 (-0.46, -0.08)*
Waist circumference	-0.06 (-0.22, 0.10)	-0.07 (-0.23, 0.09)
MNA-mod score	-0.11 (-0.28, 0.06)	-0.09 (-0.26, 0.08)
<b>WMH</b>		
BMI	-0.06 (-0.20, 0.08)	-0.09 (-0.23, 0.06)
FM	-0.03 (-0.19, 0.12)	-0.08 (-0.24, 0.08)
FFMI	-0.10 (-0.30, 0.09)	-0.12 (-0.32, 0.07)
Waist circumference	0.01 (-0.15, 0.17)	-0.02 (-0.18, 0.14)
MNA-mod score	0.13 (-0.03, 0.30)	0.14 (-0.03, 0.30)
<b>Microbleeds</b>		
BMI	0.02 (-0.13, 0.17)	0.03 (-0.12, 0.19)
FM	-0.04 (-0.21, 0.12)	-0.03 (-0.20, 0.14)
FFMI	0.09 (-0.12, 0.29)	0.12 (-0.08, 0.33)
Waist circumference	-0.09 (-0.26, 0.08)	-0.08 (-0.26, 0.09)
MNA-mod score	-0.01 (-0.19, 0.17)	-0.02 (-0.20, 0.16)

Notes: Associations between nutritional parameters and MRI markers in amyloid positive patients are presented as standardized betas with confidence intervals. Model 1 was adjusted for age, sex, and education; model 2 was adjusted for age, sex, education, MMSE, and cardiovascular risk composite score.

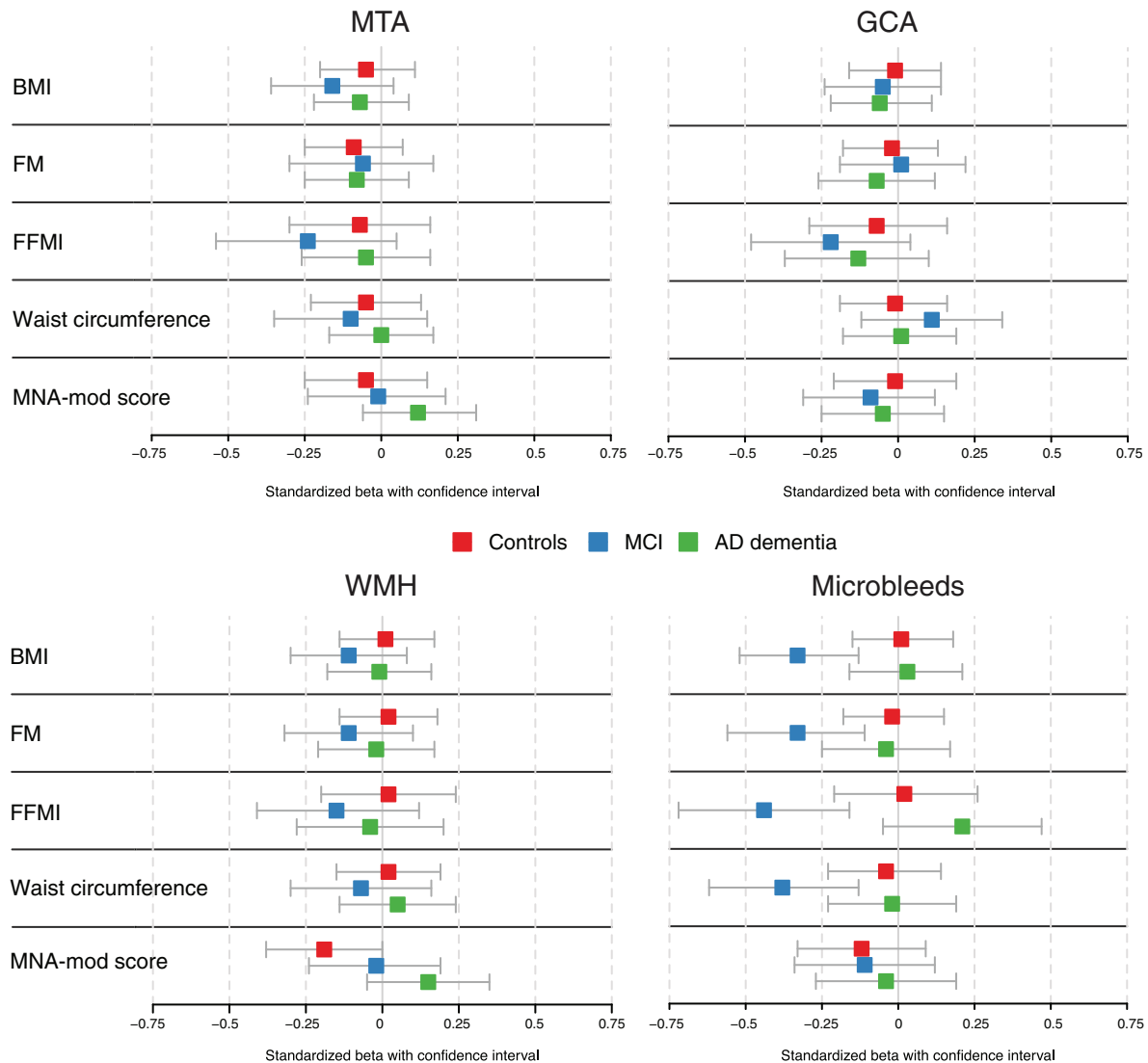
\*  $P < .05$ .

Abbreviations: BMI = body mass index; FM, fat mass; FFMI, fat free mass index; GCA = global cortical atrophy; GDS = Geriatric Depression Scale; MMSE = Mini Mental State Examination; MNA = Mini Nutritional Assessment; MRI, magnetic resonance imaging; MTA = medial temporal atrophy; WMH = white matter hyperintensities.

WMH or microbleeds. After stratification for diagnosis in amyloid positive patients (Figure 2), effect sizes of MTA with nutritional parameters were largest in controls on visual inspection, while effect sizes of WMH and microbleeds with these parameters were largest in MCI.

## 4 | DISCUSSION

The main finding of this study is that lower parameters of nutritional status, including lower BMI, FM, and FFMI, were associated with more severe MTA and more microbleeds. Effect sizes were largest in patients with MCI, although for the associations with MTA significance was lost. Our results extend previous reports by simultaneously evaluating



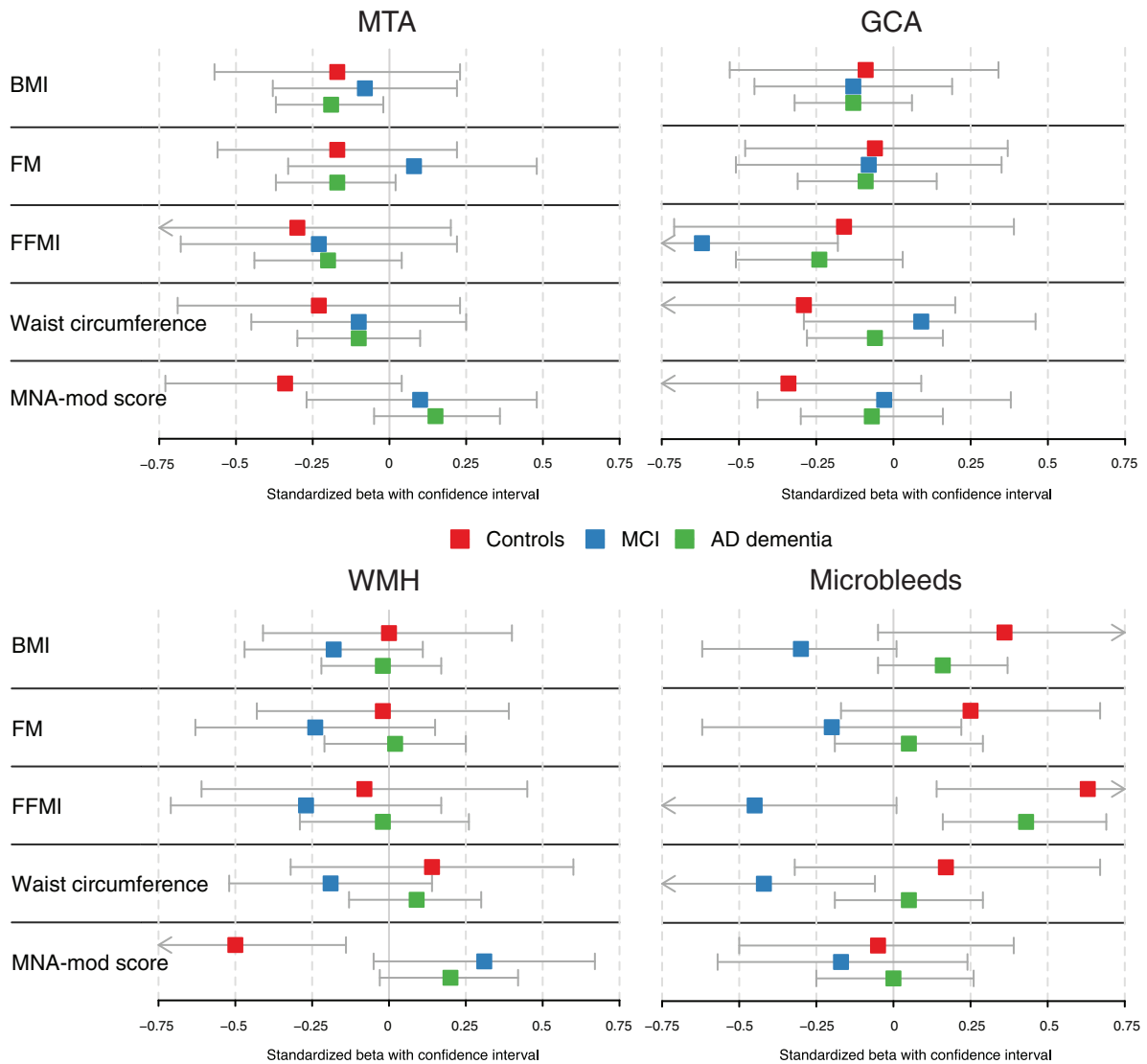
**FIGURE 1** Associations stratified for diagnosis. Forest plots with associations between nutritional parameters and magnetic resonance imaging markers stratified for diagnosis, presented as standardized betas with confidence intervals. BMI, body mass index; FFMI, fat free mass index; FM, fat mass; GCA, global cortical atrophy; GCA, global cortical atrophy; MNA, Mini Nutritional Assessment; MTA, medial temporal atrophy; WMH, white matter hyperintensities

multiple parameters of nutritional status in relation to different MRI measures of neurodegenerative and vascular pathology in a clinical AD sample covering the entire cognitive spectrum of cognitively normal to dementia.

Our findings are in line with two former studies in patients with AD dementia and controls that described associations between lower BMI and more severe MTA,<sup>10</sup> and between lower FFM and higher GCA.<sup>11</sup> By contrast, in two other studies comprising AD and MCI patients, higher BMI was associated with lower total brain or hippocampal volumes.<sup>12,14</sup> However, these studies used a clinical AD diagnosis, while in our study AD diagnosis was confirmed with CSF amyloid in the majority of patients. As such, our cohort probably contains more patients with AD pathology than other studies, which provides the possibility to evaluate the association between nutritional status and AD-related disease processes. In line with this notion, of the four

MRI markers in our analyses, MTA, the most AD specific MRI marker, showed strongest associations in the amyloid positive subgroup. A former study in a geriatric outpatient population described associations between malnutrition, as assessed with MNA, and WMH, but not with MTA.<sup>25</sup> This discrepancy could be due to difference in population, as the former study evaluated a more heterogeneous geriatric population, while our study focused on the clinical spectrum of AD. In line with this notion, we found an association between MNA and WMH in controls only.

In addition, we observed that lower FM and waist circumference were associated with more microbleeds, especially in MCI. Microbleeds are more prevalent in MCI and AD dementia patients and have been related to AD pathology.<sup>8,9</sup> In the sensitivity analysis with amyloid positive MCI patients, the association with waist circumference remained intact, providing further support for the notion that



**FIGURE 2** Associations stratified for diagnosis in amyloid positive patients. Forest plots with associations between nutritional parameters and magnetic resonance imaging markers in amyloid positive patients (N = 187), stratified for diagnosis, presented as standardized betas with confidence intervals. BMI, body mass index; FFMI, fat free mass index; FM, fat mass; GCA, global cortical atrophy; MNA, Mini Nutritional Assessment; MTA, medial temporal atrophy; WMH, white matter hyperintensities

the relationship between nutritional status and microbleeds is AD specific.

This study has several limitations. First, the cross-sectional nature hampers causal interpretation of our findings. Longitudinal studies with repeated imaging and data on, for instance, body weight history are needed to assess if patients with worse nutritional status indeed develop more AD-specific structural brain changes. Second, we used visual MRI scores to quantify brain atrophy and WMH rather than volumetric measurements. Although perhaps somewhat less precise, visual MRI ratings for cerebral atrophy and WMH have nonetheless been shown to be as valid and reliable as volumetric measurements.<sup>35,36</sup> Moreover, these measures have clinical applicability, as they are fairly easy to implement in clinical practice. Strengths of this study include the relatively large clinical cohort that underwent standardized work-up, and availability of AD biomarkers including PET scans and CSF.

Diagnoses were made carefully, and although we can never rule out misdiagnosis, widely accepted diagnostic criteria were used. In addition, we used several parameters of nutritional status, including BMI, FM, FFMI, waist circumference, and MNA. Of note, average BMI of the study population could be considered overweight. Nonetheless, within this sample of patients in the earliest stages of AD, we find that lower nutritional parameters were associated with more MTA and microbleeds. This is in line with the notion that the process of changing nutritional status in AD is a continuous, longer trajectory and that in fact many patients may come from obesity in midlife.<sup>37</sup>

The altered nutritional status in AD could be caused by elevated energy expenditure, lower intake, or malabsorption of nutrients.<sup>38</sup> A mechanism that could explain the associations between lower indicators of nutritional status and MRI measures of AD pathology is a lower availability of important nutrients for maintenance and repair

of brain tissue, such as proteins and fat. In addition, lower levels of specific nutrients required for phospholipid synthesis could result in more synapse loss, ultimately leading to more atrophy. In line with this hypothesis, a recent meta-analysis showed that patients with AD have lower CSF levels of these phospholipid precursors and cofactors such as docosahexaenoic acid (DHA), choline-containing lipid, folate, vitamin B12, vitamin C, and vitamin E.<sup>39</sup>

Alternatively, we cannot rule out reverse causality, in which cerebral atrophy and resulting cognitive decline could have led to lower energy intake, weight loss, and deteriorating nutritional status. However, the observed associations were already present in amyloid positive controls and in patients with MCI. This suggests that the observed relations between nutritional status and structural brain changes are not a mere consequence of cognitive decline but rather a prodrome. To further address the issues of underlying mechanisms and causal directionality regarding lower intake versus change in energy expenditure, future studies should take dietary intake into account.

The associations observed in MCI and controls suggest that an impaired nutritional status has a role in the development of disease, either as early consequence of the underlying pathology or as an aggravating factor. This provides further evidence for the notion that nutrition could also be a target for secondary prevention. This should be further studied in intervention studies that focus on optimizing nutritional status. A recent intervention study, LipiDiDiet, with supplementation that includes precursors and cofactors for phospholipid synthesis, has shown a favorable effect on hippocampal atrophy and functional decline in patients with prodromal AD.<sup>40,41</sup> This underlines the potential benefit of intervening early in the disease process, within the time window where it can still make a difference in terms of neurodegeneration. Whether positive results can also be obtained by intervening on the level of macronutrient intake needs to be elucidated.

Concluding, in our memory clinic cohort, worse nutritional status, indicated by BMI, FM, and FFMI, was associated with more MTA and microbleeds. Our findings indicate that lower nutritional parameters might have a role in the development of AD, either as early consequence of the underlying pathology or as an aggravating factor.

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## CONFLICTS OF INTEREST

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