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RESEARCH ARTICLE

Body weight changes and longitudinal associations with cognitive decline among community-dwelling older adults

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Abstract

Introduction: We aim to investigate the longitudinal associations between changes in body weight (BW) and declines in cognitive function and risk of mild cognitive impairment (MCI)/dementia among cognitively normal individuals 65 years or older.

Methods: Data from the Age Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study) including 2620 participants, were examined using multiple logistic regression models. Cognitive function included speed of processing (SP), executive function (EF), and memory function (MF). Changes in BW were classified as; weight loss (WL), weight gain (WG), and stable weight (SW).

Results: Mean follow-up time was 5.2 years and 61.3% were stable weight. Participants who experienced WL (13.4%) were significantly more likely to have declines in MF and SP compared to the SW group. Weight changes were not associated with EF. WL was associated with a higher risk of MCI, while WG (25.3%) was associated with a higher dementia risk, when compared to SW.

Discussion: Significant BW changes in older adulthood may indicate impending changes in cognitive function.

KEYWORDS
APOE ε4, body weight changes, cognitive function, dementia, executive function, memory function, mild cognitive impairment, nutrition, speed of processing

1 | INTRODUCTION

The increase int the aging populations around the world comes with a burden of neuropsychological disorders including mild cognitive impairment (MCI) and dementia, which are multi-factorial disorders that are determined by an interplay of environmental factors and genetic susceptibility.[1] Older age remains the strongest risk factor for dementia, although many modifiable risk factors have been suggested

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was searched using relevant sources such as Google Scholar and PubMed. Identified papers concerning body weight and changes in cognitive function were cited appropriately.
2. **Interpretation**: Our study showed that participants who lost body weight during the follow-up period had lower cognitive function after follow-up compared to weight-stable or weight-gaining participants and that consequently these participants had a higher risk of developing mild cognitive impairment (MCI). Weight gain had an association with increased risk for dementia compared to weight-stable participants.
3. **Future direction**: The design of future prevention trials on dementia should consider body weight changes among older adults as a marker for cognitive changes. Future intervention studies should address the question whether keeping body weight stable during older adulthood helps to maintain cognitive function and decreases the risk of MCI and dementia.

by observational studies[2] as estimated to account for at least 30% of dementia occurrence. These risk factors include a variety of life-style related factors, for example, physical activity (PA), body mass index (BMI), and nutrition.[1–6]

Although prior studies have associated BMI with cognitive function and dementia, results have been conflicting due to variability in study design[7] and whether BMI is measured in mid-life or late-life.[8,9] Some studies showed that high mid-life BMI is associated with a risk of developing dementia,[9] but conversely, the same is true for low BMI when measured in late-life.[8] However, according to a recent meta-analysis, current available evidence does not support a clear association between overweight/obesity and incident dementia in old age.[10]

Fewer studies are available on changes in body weight and cognitive function during old adulthood. It has been shown that weight loss is associated with the risk of dementia[11]; it has also been suggested that weight loss is rather a consequence of the preclinical phase of dementia and this suggests a reverse causation between weight loss and dementia. However, associations between cognitive function and weight loss as well as weight gain are less clear.

The mechanism relating weight loss to cognition are not fully understood but recent studies have suggested that apathy, anxiety, depression, and irritability among dementia and MCI cases affect appetite.[12] However, it is also conceivable that weight loss could accelerate brain atrophy before the onset of MCI or dementia.[11]

Weight loss coming from an inadequate dietary intake eventually leads to deficiency in critical nutrients,[13] making nutrition important in these associations. Another consideration is whether body weight changes are associated with cognition via known or suggested risk factors for dementia; for example, vitamin D has been suggested to be associated with cognitive decline[14] as well as apolipoprotein E (*APOE*) ε4.[15,16]

To gain more knowledge on the relation between cognitive function and body weight, we conducted this analysis based on data from the longitudinal Age Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study). The aim of this study was to (1) investigate the longitudinal associations between changes in late-life body weight and declines in cognitive function and risk of MCI/dementia in community-dwelling older adults with normal cognitive function at baseline. Further adding to the novelty of this study, we considered potential confounding of physical activity, nutritional factors, and *APOE* ε4 when examining the associations between changes in body weight and cognitive function.

2 | METHODS

2.1 | Study population and study design

The current longitudinal analysis is based on data from the AGES-Reykjavik Study (N = 5764), which examined risk factors for diseases in old age, including environmental factors, genetic susceptibility, and their interactions. Briefly the AGES-Reykjavik (AGES I) Study was enrolled in 2002 to 2006 as a continuation of the population-based Reykjavik Study (RS) in Iceland, initiated in 1967, including men and women born in 1907 to 1935 and living in the Reykjavik area.[17] Detailed baseline information has been described in the AGES study paper.[18] Between 2007 and 2011, all surviving AGES I participants (58%, N = 3316) returned for a 5-year follow-up visit (AGES II). The current study included participants who were cognitively normal at baseline and had relevant follow-up examination including cognitive tests and BMI. The study was approved by the National Bioethics Committee in Iceland (approval VSN-00-063), the Data Protection Authority, and by the National Institute on Aging Intramural Institutional Review Board. Written informed consent was obtained from all participants.

2.2 | Anthropometrics

Weight and height were measured and BMI was calculated as kg/m^2. Participants were categorized as underweight (baseline BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), and obese (BMI ≥30.0). Using the weight variables (baseline and follow-up), participants were further categorized into weight stable, weight gain, and weight loss if they had lost or gained ≥5% weight during follow-up as is considered clinically relevant weight changes.[19]

2.3 | Cognitive function assessment

Assessment of cognitive function included eight tests, both at baseline and follow-up, focusing on three cognitive domains, that is, memory, processing speed, and executive function.

For each of the domains, a composite score was constructed based on a theoretical grouping of the tests and by converting raw scores into standardized z scores reflecting the distribution within the study sample as previously described.[20] The inter-rater reliability for all tests was excellent (Spearman correlation coefficients range 0.96 to 0.99).[21] The memory composite measure included the immediate and delayed-recall portions of a modified version of the California Verbal Learning Test.[22] The processing speed composite measure included the Digit Symbol Substitution Test,[23] the Figure Comparison Test,[24] and the Stroop Test[25] Part I (reading) and Part II (color naming). The executive function composite measure included the Digits Backward Test[23] and the Stroop Test, Part III (word-color interference). The three domains of memory, processing speed, and executive function composite measures were each used as a continuous variable.

2.4 | Mild cognitive impairment

The diagnoses of MCI were done by a panel of specialists. The criterion was having deficits in memory or one other domain of cognitive function or deficits in at least two cognitive domains without being severe enough to cross the threshold for dementia and without loss of instrumental activities of daily living. Cognitive performance on a given domain was evaluated with scoring <−1.5 SD below a cut-point determined from the distribution of scores in a cohort subsample.[19]

2.5 | Dementia

Assessment of cognitive function was done following a three-step protocol to identify subjects with dementia. First, the Digit Symbol Substitution test[23] and the Mini-Mental State Examination (MMSE)[26] were administered to the total sample. Participants who scored 23 or lower on the MMSE or had a raw score of 17 or lower on the Digit Symbol Substitution test were administered a second diagnostic cognitive test battery. Participants who scored 8 or more on Trails B,[27] which was the ratio of time taken for "Trails B/Trails A," or had lower than total score of 19 for the four immediate recall trials of the Rey Auditory Verbal Learning[28] went on to a third step. This step included a neurological test and a proxy interview regarding medical history, social, cognitive, and daily functioning changes of the participant.

A consensus diagnosis of dementia made by a team composed of a geriatrician, neurologist, neuropsychologist, and a neuroradiologist was made according to international guidelines from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.[29]

2.6 | Covariates

2.6.1 | Baseline demographic data

Participants were asked about their age, gender, and current marital status categorized as married, widowed, divorced, or single. Education was categorized into four levels: primary, secondary, college, and university.

2.6.2 | Blood pressure

Blood pressure (mm Hg) was measured in a recumbent position using mercury sphygmomanometer and a large cuff on the right arm (with a few exceptions) after participants had rested for 5 minutes.

2.6.3 | Lifestyle and nutritional data

The accredited Icelandic Heart Associations laboratory performed 25-hydroxy vitamin D (25OHD) measurements in batch using unfrozen serum samples and the Liaison chemiluminescence immunoassay (DiaSorin Inc, Stillwater, Minnesota). Existing serum 25OHD levels were then standardized according to the international Vitamin D Standardization Program as described previously.[20]

Leisure time physical activity (PA) was assessed by a self-reported questionnaire and categorized into (1) none, (2) ≤3 hours per week, or (3) > 3 hours per week. Smoking status was evaluated as ever versus never smoker. Alcohol consumption was evaluated as currently consuming versus not consuming.

2.6.4 | Medication use and *APOE* ε4 genotype

Participants were instructed in advance to bring all medication they had used during the preceding 2 weeks before the clinic visit and were categorized into ≤4 medications versus ≥5 medications. *APOE* ε4 alleles were genotyped on a subsample of 2113 people using standard methods.[30] The basic characteristics of this subsample did not differ from those of the remaining sample. Participants were considered *APOE* ε4 positive if they carried ε3/4 and ε4/4 genotype; otherwise if they carried ε2/2, ε2/3, and ε3/3 they were considered *APOE* ε4 noncarriers.

2.7 | Analytical sample

From the original sample size of 5764 in the provided data base, 3316 participants completed the follow-up measurements. Participants with an MCI (n = 204) or dementia diagnosis (n = 47) at baseline and participants having incomplete data (n = 445) were excluded from the present analysis. From the remaining sample, 2620 participants had a complete data set of relevant variables and were thus included into the present study.

2.8 | Statistical analysis

Statistical analyses were carried out using IBM SPSS version 22.0 (SPSS, Chicago, IL, USA). Demographic, anthropometric, lifestyle and nutritional data, medication use, and *APOE* ε4 genotype variables were used to describe baseline characteristics of the participants (Table 1) according to body weight change categories. We used the chi-square

TABLE 1 Demographic and health characteristics according to weight groups among AGES-Reykjavik participants (N = 2620)

	Weight loss (n = 352, 13.4%) Mean ± SD	Weight gain (n = 665, 25.3%) Mean ± SD	No weight change (n = 1603, 61.3%) Mean ± SD	P *
Demographic data				
Age (years)	75.14 ± 4.69	73.46 ± 4.36	74.15 ± 4.53	<.001
Male (%)	33.4	36.7	43.4	<.001
Female (%)	66.6	63.3	56.6	
Education-primary (%)	16.9	22.7	17.1	.161
Married (%)	61.5	57.9	68.5	.001
Lifestyle data				
Physical inactivity (%)	33.3	31.2	28	.020
Alcohol-no (%)	30.1	33.1	27.7	.340
Smoke-yes (%)	8.1	11.8	7.3	.026
Anthropometric data				
BMI (kg/m2)	27.93 ± 4.47	26.97 ± 4.27	27.16 ± 4.05	<.001
Body fat (%)	30.5 ± 7.44	29.30 ± 7.94	28.77 ± 7.62	<.001
SBP (mm Hg)	142.1 ± 20.51	140.2 ± 20.11	142.4 ± 19.14	.171
DBP (mm Hg)	73.1 ± 9.18	74.8 ± 9.13	74.60 ± 9.37	.002
Laboratory data				
25OHD (nmol/L)	56.01 ± 16.94	55.39 ± 18.92	60.13 ± 17.11	<.001
Neuropsychological data				
Memory (z-score)	0.140 ± 0.882	0.242 ± 0.888	0.195 ± 0.854	.204
Executive (z-score)	0.080 ± 0.702	0.097 ± 0.744	0.164 ± 0.722	.035
Speed (z-score)	0.192 ± 0.664	0.146 ± 0.688	0.204 ± 0.667	.36
Medication/APOE ε4				
APOE ε4 allele carriers (%)	0.8	1.8	1.7	.28
Medications >5 (number)	35.6	33.9	30.9	.09

*Table represents baseline data. **Chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables were to test for statistical differences. SD, standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; 25OHD, 25 hydroxy-vitamin D; APOE, apolipoprotein E

test for categorical variables and analysis of variance (ANOVA) for continuous variables to test for statistical differences.

To calculate longitudinal associations between changes in body weight and the three domains of cognitive function (Tables 2-4), univariate general linear models (GLMs) were applied controlling for various confounders. For each outcome variable the following three-step model was applied: model 1 adjusted for age, gender, and baseline cognitive function; model 2 additionally adjusted for 25OHD, baseline BMI, and PA; and model 3 additionally adjusted for marital status, smoking, education, *APOE* ε4, and medication use. Results from the GLM are presented as parameter estimates showing unstandardized B, 95% CI, and *P*-value.

To calculate whether changes in body weight predict the onset of MCI or dementia (Tables 5 and 6), regression analyses were applied controlling for various confounders as outlined for GLM above.

The level of statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Baseline

Baseline characteristics of the participants categorized by weight changes during follow-up can be seen in Table 1. Most of the baseline characteristics among participants were significantly different between the three categories. Participants in the weight gain group had the lowest vitamin D levels, had higher frequency of smoking, and fewer were married. Participants in the weight gain/loss group had lower proportion of physical activity.

3.2 | Follow-up

During a mean follow-up of 5.2 years, 352 participants (13.4%) lost weight, 665 (25.3%) gained weight, and 1603 (61.3%) were weight stable.

TABLE 2 Associations[a] between weight-change categories and memory function among AGES-Reykjavik participants (N = 2620)[b]

	Model 1				Model 2				Model 3			
Parameter	**B**	**95% CI**		***P***	**B**	**95% CI**		***P***	**B**	**95% CI**		***P***
Intercept	2.246	1.808	2.685	<.001	2.154	1.647	2.662	<.001	2.105	1.509	2.702	<.001
Weight loss[c]	**−0.115**	**−0.177**	**−0.054**	**<.001**	**−0.114**	**−0.176**	**−0.053**	**<.001**	**−0.114**	**−0.176**	**−0.052**	**<.001**
Weight gain[c]	**0.008**	**−.070**	**0.086**	**.838**	**0.010**	**−0.068**	**0.089**	**.799**	**0.016**	**−0.063**	**0.094**	**.696**
Baseline of dependent variable	0.713	0.681	0.745	<.001	0.712	0.680	0.744	.000	0.707	−0.229	−0.109	<.001
Male[d]	−0.147	-0.202	−0.093	<.001	−0.147	−0.203	−0.091	<.001	−0.169	−0.236	−0.117	<.001
Age (years)	−0.032	−0.038	−0.026	<.001	−0.032	−0.038	−0.026	<.001	−0.032	−0.038	−0.026	<.001
25OHD (nmol/L)					0.001	−0.001	0.002	.493	0.001	−0.001	0.002	.575
BMI (kg/m2)					0.001	−0.005	0.007	.731	0.001	−0.005	0.008	.718
Physical activity = none[e]					0.013	−0.071	0.097	.761	0.022	−0.062	0.107	.604
Physical activity ≤3 h/week[3]					0.038	−0.039	0.114	.331	0.041	−0.035	0.118	.291
Married[f]									0.049	−0.068	0.165	.412
Widowed[f]									0.032	−0.092	0.155	.613
Divorced[f]									−0.032	−0.186	0.123	.686
Smoking-no[g]									0.04	−0.056	0.137	.411
Education- primary[h]									−0.074	−0.174	0.026	.146
Education-secondary[h]									−0.065	−0.149	0.018	.125
Education-college[h]									−0.075	−0.173	0.022	.128
APOE_ε4									−0.01	−0.219	0.199	.926
Medication use < 5[i]									0.038	−0.018	0.094	.182

[a]Based on univariate GLM with a mean 5.2 years of follow-up.
[b]Excluded: participants with dementia and mild cognitive impairment at baseline. **Model 1**: age, gender, and baseline cognitive function. **Model 2**: additionally 25OHD, body mass index, and physical activity. **Model 3**: additionally marital status, smoking, education, apolipoprotein E, and medication use.
[c]Compared to weight stable.
[d]Compared to female.
[e]Compared to PA > 3 h/wk.
[f]Compared to single.
[g]Compared to smoking-yes.
[h]Compared to university.
[i]Compared to medication use ≥5.

In these categories 91 (12.6%), 23 (6.2%), and 125 (7.4%) participants, respectively, were diagnosed with MCI and 42 (5.8%), 30 (8%), and 64 (3.8%) participants, respectively, were diagnosed with dementia.

Baseline BMI categories (underweight, normal weight, overweight, obese) were not related to cognitive function or MCI/dementia at the end of follow-up.

Tables 2–4 show the longitudinal associations between weight change categories and cognitive function based on GLM. Weight loss was associated with a lower memory function and lower speed of processing after follow-up when compared to weight stable. As shown in models 1 to 3, correction for baseline cognitive function and BMI, demographic factors, lifestyle, and medication and *APOE* ε4 variables did only marginally change these results. However, weight loss was not associated with executive function.

Tables 5 and 6 show that weight change categories were associated with the development of MCI and dementia during follow-up based on logistic regression. Weight loss was associated with a higher likelihood of MCI when compared to weight stable. Further, weight gain was associated with a higher dementia risk when compared to weight stable. Similar to the GLM results shown above, the correction for baseline BMI, demographic factors, and lifestyle as well as medication and *APOE* ε4 variables did only marginally change these results.

Inclusion of *APOE* ε4 and 25OHD as covariates did not change the results (tables 2-6). Nutritional factors related to vitamin D levels, that is, cod liver oil consumption and consumption of fatty fish, did not have significant associations with any of the cognitive function domains (nutritional resulst (cod liver oil and fatty fish) are not represented in tables as indicated in text (Not shown in table). However, results regarding APOE4 and 25 OH D can be seen in tables 2-6.) and

TABLE 3 Associations[a] between weight change categories and speed of processing among AGES-Reykjavík participants (N = 2620)[a]

	Model 1				Model 2				Model 3			
Parameter	**B**	**95% CI**		***P***	**B**	**95% CI**		***P***	**B**	**95% CI**		***P***
Intercept	1.413	1.049	1.776	<.001	1.506	1.082	1.931	<.001	1.365	0.873	1.856	<.001
Weight loss[b]	**−0.116**	**−0.166**	**−0.066**	**<.001**	**−0.111**	**−0.161**	**−0.060**	**<.001**	**−0.113**	**−0.163**	**−0.062**	**<.001**
Weight gain[b]	**−0.036**	**−0.100**	**0.028**	**.272**	**−0.035**	**−0.099**	**0.029**	**.289**	**−0.035**	**−0.099**	**0.030**	**.289**
Baseline of dependent variable	0.945	0.912	0.977	<.001	0.941	0.908	0.973	<.001	0.930	.894	0.965	<.001
Male[c]	−0.081	−0.124	−0.038	<.001	−0.085	−0.129	−0.041	<.001	−0.098	−0.145	−0.050	<.001
Age (years)	−0.022	−0.027	−0.017	<.001	−0.022	−0.027	−0.018	<.001	−0.024	−0.029	−0.018	<.001
25OHD (nmol/L)					0.001	−0.001	0.002	.374	0.001	−0.001	0.002	.45
BMI (kg/m2)					−0.003	−0.008	0.002	.219	−0.004	−0.009	0.001	.121
Physical activity = none[d]					−0.009	−0.078	0.059	.790	−0.002	−0.071	0.067	.946
Physical activity ≤3 h/week[3]					0.007	−0.055	0.070	.818	0.008	−0.054	0.071	.794
Married[e]									0.036	−0.059	0.131	.456
Widowed[e]									0.034	−0.067	0.134	.514
Divorced[e]									−0.002	−0.128	0.124	.975
Smoking-no[f]									0.066	−0.013	0.145	.102
Education-primary[g]									−0.046	−0.129	0.038	.284
Education- secondary[g]									−0.054	−0.123	0.015	.125
Education- college[g]									−0.026	−0.105	0.053	.520
APOE_ε4									0.219	0.049	0.390	.012
Medication use <5[h]									−0.015	−0.061	0.030	.505

[a]Based on univariate GLM with mean 5.2 years follow-up **Excluded: participants with dementia and mild cognitive impairment at baseline. **Model 1**: age, gender, and baseline cognitive function. **Model 2**: additionally 25OHD, body mass index, and physical activity. **Model 3**: additionally marital status, smoking, education, apolipoprotein E,and medication use.
[b]Compared to weight stable.
[c]Compared to female.
[d]Compared to PA >3 h/wk.
[e]Compared to single.
[f]Compared to smoking-yes.
[g]Compared to university.
[h]Compared to medication use ≥5.

therefore did not alter the associations between body weight changes and cognitive function.

4 | DISCUSSION

This large longitudinal study investigated the associations between body weight changes and cognitive function among community-dwelling older adults who had normal cognitive function at baseline. We found that participants who lost weight during the follow-up period had lower cognitive function after follow-up compared to weight-stable or weight-gaining participants. We also found that these participants had a higher risk of developing MCI. Furthermore, our study suggests that participants who gained weight during follow-up were at an increased risk for dementia compared to weight-stable participants. BMI categories themselves were neither related to cognitive function nor to risk of MCI or dementia.

Because the risk of reverse causation can distort the relationship between dementia and weight loss, the current study exclusively included participants with normal cognitive function at baseline, which reduces this risk. The associations between body weight changes and cognitive function we found agree with several previous studies on this topic.[1–6] When comparing results from different studies, it has to be considered that longitudinal studies concerning body weight, BMI, and cognitive function use various techniques measuring cognitive abilities with different endpoints ranging from MCI to dementia. In addition, studies enroll participants of different age groups and it has been shown that, for example, high BMI can be both detrimental as well as protective for a given health outcome depending on the participant's age.[31–33]

TABLE 4 Associations[a] between weight change categories and executive function among AGES-Reykjavík participants (N = 2620)[a]

	Model 1				Model 2				Model 3			
Parameter	**B**	**95% CI**		***P***	**B**	**95% CI**		***P***	**B**	**95% CI**		***P***
Intercept	0.790	0.378	1.202	<.001	0.917	0.436	1.398	<.001	1.144	0.583	1.706	<.001
Weight loss[b]	**−0.030**	**−0.089**	**0.028**	**.311**	**−0.024**	**−0.083**	**0.035**	**.417**	**−0.029**	**−0.088**	**0.030**	**.336**
Weight gain[b]	**−0.029**	**−0.104**	**0.045**	**.444**	**−0.028**	**-0.103**	**0.047**	**.458**	**−0.025**	**−0.099**	**0.050**	**.521**
Baseline of dependent variable	0.660	0.625	.694	<.001	0.656	0.622	0.691	<.001	0.632	0.596	0.668	<.001
Male[c]	−0.105	−0.155	−0.055	<.001	−0.108	−0.159	−0.057	<0.001	−0.135	−0.189	−0.080	<.001
Age (years)	−0.013	−0.019	−0.008	<.001	−0.013	−0.018	−0.007	<0.001	−0.013	−0.019	−0.008	<.001
25OHD (nmol/L)					0.000	−0.001	0.002	0.571	0.000	−0.001	0.002	.753
BMI (kg/m2)					−0.004	−0.010	0.002	0.161	−0.004	−0.010	0.003	.257
Physical activity = none[d]					−0.022	−0.102	0.058	0.586	−0.003	−0.083	0.077	.941
Physical activity ≤3 h/wk[3]					0.018	−0.055	0.091	0.634	0.023	−0.049	0.096	.527
Married[e]									−0.024	−0.134	0.087	.676
Widowed[e]									−0.003	−0.120	0.114	.957
Divorced[e]									−0.049	−0.196	0.097	.509
Smoking-no[f]									0.075	−0.017	0.166	.109
Education-primary[g]									−0.218	−0.314	−0.122	<.001
Education-secondary[g]									−0.139	−0.219	−0.059	.001
Education- college[g]									−0.092	−0.184	0.001	.051
APOE_ε4									−0.138	−0.336	0.061	.175
Medication use <5[h]									0.038	−0.015	0.090	.165

[a]Based on univariate GLM with mean 5.2-years follow-up. **Excluded: participants with dementia and mild cognitive impairment at baseline. **Model 1**: age, gender, and baseline cognitive function. **Model 2**: additionally 25OHD, body mass index, and physical activity. **Model 3**: additionally marital status, smoking, education, apolipoprotein E, and medication use.
[b]Compared to weight stable.
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[g]Compared to university.
[h]Compared to medication use ≥5.

In the present study, weight loss was associated with faster cognitive decline for memory and speed of processing when compared to weight-stable or weight-gaining participants. Of interest, intentional weight loss in obese/overweight adults has been reported to be associated with improvements in performance across various cognitive domains,[34] which might further be related to significant reduction in metabolic syndrome.[35] However, in a recently published cohort study among community-dwelling older adults, weight loss predicted higher cognitive decline over a 5-year follow-up, independently of baseline BMI.[36]

Furthermore, it has been reported that both weight loss and weight gain were associated with poor cognitive performance in middle-aged and older women compared with women with stable weight after 7 years of follow-up.[37]

In our study, weight loss during the study period was associated with a 61% higher risk of MCI diagnosis. This is in agreement with a large prospective longitudinal cohort study from the United States in which weight loss was associated with a higher risk of incident MCI independent from BMI.[38] Similar results were reported in old adults from an African study with 10 years of follow-up.[39]

Contrary to our expectations, we found that weight gain during follow-up was associated with a greatly increased risk of dementia. In contrast, two cohort studies from the United States reported weight loss to be associated with a higher risk of incident dementia,[36,40] whereas weight gain did not have any significant associations.[36] No information is available in published literature linking weight gain with dementia risk, although there are several studies published having linked obesity to dementia risk.[41,42] However, according to a recent meta-analysis, current available evidence does not support an association between overweight/obesity and incident dementia in old age.[10] There are many studies available that link BMI categories with cognitive function, MCI, and dementia.[33,43,44] In the present study,

TABLE 5 Body weight change categories and risk of development of MCI among AGES-Reykjavik participants (N = 2620)[a]

	Model 1				Model 2				Model 3			
Parameter	**OR**	**95% CI**		***P***	**OR**	**95% CI**		***P***	**OR**	**95% CI**		***P***
Weight loss[b]	**1.590**	**1.141**	**2.216**	**.006**	**1.526**	**1.092**	**2.133**	**.013**	**1.613**	**1.145**	**2.271**	**.006**
Weight gain[b]	**1.048**	**0.633**	**1.736**	**.855**	**1.004**	**0.605**	**1.667**	**.987**	**0.951**	**0.566**	**1.597**	**.849**
Male[c]	0.663	0.489	0.900	.008	0.626	0.459	0.855	.003	0.449	0.319	0.632	<.001
Age (years)	1.142	1.106	1.178	<.001	1.143	1.106	1.179	<.001	1.137	1.097	1.177	<.001
25OHD (nmol/L)					0.990	0.981	1.000	.042	0.992	0.983	1.001	.097
BMI (kg/m2)					1.009	0.972	1.048	.636	1.000	0.961	1.040	.994
Physical activity = none[d]					1.194	0.723	1.972	.485	1.027	0.613	1.721	.920
Physical activity ≤3 h/wk[3]					1.051	0.654	1.689	.838	1.017	0.625	1.654	.946
Married[e]									1.227	0.565	2.665	.606
Widowed[e]									1.464	0.661	3.242	.347
Divorced[e]									1.862	0.724	4.790	.197
Smoking-no[f]									0.660	0.385	1.129	.129
Education-primary[g]									8.499	3.729	19.373	<.001
Education-secondary[g]									4.719	2.133	10.438	<.001
Education-college[g]									1.909	0.762	4.780	.167
APOE_ε4									0.776	0.228	2.641	.685
Medication use <5[h]									0.688	0.502	0.945	.021

[a]Based on logistic regression with mean 5.2 years follow-up. **Excluded: participants with dementia and mild cognitive impairment at baseline. **Model 1**: age, gender, and baseline cognitive function. **Model 2**: additionally 25OHD, body mass index, and physical activity. **Model 3**: additionally marital status, smoking, education, apolipoprotein E, and medication use.
[b]Compared to weight stable.
[c]Compared to female.
[d]Compared to PA >3 h/wk.
[e]Compared to single.
[f]Compared to smoking-yes.
[g]Compared to university.
[h]Compared to medication use ≥5.
OR, odds ratio.

BMI categories were not related to cognitive decline, MCI, or dementia diagnosis. It has to be considered that of our study population, actually few were underweight (n = 22), which excludes the possibility of a meaningful statistical analysis. On the other hand, our study shows that body weight change is an important predictor of future cognitive function independent of BMI category.

There are several plausible explanations as to how body weight changes can be associated with cognitive function. However, they fail to explain our findings entirely because body weight stability has been associated with an intact social environment and might in general reflect good health in an older adult. Weight loss on the other hand might be an early sign of deteriorating health. Although body fat is associated with increased levels of leptin,[45] which might act as protective factor for cognition in old age,[46] weight gain in older adulthood can also be associated with sedentary lifestyle and physical inactivity.

In fact, the distribution of body fat might be crucial to understand the inconclusive associations between obesity and dementia.[47] In the present study, we cannot distinguish between visceral and subcutaneous fat in the weight gain group, but previous studies have shown an association between visceral adipose tissue (rather than subcutaneous adipose tissue) and microstructural brain tissue damages as well as poorer brain connectivity.[47,48] In this perspective it is appropriate to discuss a study by Spauwen et al. (2017), which is a cross-sectional study using data from AGES-Reykjavik, showing that a higher amount of subcutaneous fat was negatively associated with the risk of dementia at baseline.[49] Thus visceral fat might be a driving force in these associations between weight gain and dementia.

Previous studies have shown that type 2 diabetes increases the risk of dementia[21], therefore, we considered type 2 diabetes in additional analyses. Our results showed that the association between weight changes and cognitive function/MCI/dementia was unchanged when controlling for type 2 diabetes.

Physical activity has been shown to have positive implications for various health-related outcomes among older adults,[50–52] including

TABLE 6 Body weight change categories and risk of development of dementia among AGES-Reykjavik participants (N = 2620)[a]

	Model 1				Model 2				Model 3			
Parameter	**OR**	**95% CI**		***P***	**OR**	**95% CI**		***P***	**OR**	**95% CI**		***P***
Weight loss[b]	**1.094**	**0.625**	**1.915**	**.752**	**1.028**	**0.584**	**1.810**	**.911**	**1.076**	**0.607**	**1.909**	**.802**
Weight gain[b]	**2.797**	**1.585**	**4.935**	**<.001**	**2.663**	**1.504**	**4.716**	**<.001**	**2.697**	**1.511**	**4.815**	**.001**
Male[c]	0.996	0.622	1.593	.986	0.945	0.586	1.525	.818	0.787	0.468	1.322	.366
Age (years)	1.183	1.129	1.239	<.001	1.181	1.126	1.237	<.001	1.182	1.124	1.244	<.001
25OHD (nmol/L)					0.990	0.977	1.004	.165	0.991	0.977	1.005	.203
BMI (kg/m^2)					0.997	0.943	1.055	.924	0.993	0.937	1.053	.814
Physical activity = none[d]					1.420	0.654	3.084	.376	1.245	0.564	2.748	.588
Physical activity ≤3 h/wk[3]					0.996	0.468	2.120	.991	0.995	0.463	2.139	.989
Married[e]									0.537	0.245	1.177	.120
Widowed[e]									0.399	.0171	0.927	.033
Divorced[e]									0.308	0.078	1.214	.092
Smoking-no[f]									0.769	0.332	1.784	.541
Education- primary[g]									5.188	1.726	15.593	.003
Education-secondary[g]									2.405	0.824	7.016	.108
Education-college[g]									2.459	0.783	7.723	.123
APOE_ε4									0.564	0.124	2.577	.460
Medication use <5[h]									0.933	0.573	1.518	.780

[a]Based on logistic regression with mean 5.2-years follow-up. **Excluded: participants with dementia and mild cognitive impairment at baseline. **Model 1**: age, gender, and baseline cognitive function. **Model 2**: additionally 25OHD, body mass index, and physical activity. **Model 3**: additionally marital status. smoking, education, apolipoprotein E, and medication use.
[b]Compared to weight stable.
[c]Compared to female.
[d]Compared to PA > 3 h/wk.
[e]Compared to single.
[f]Compared to smoking-yes.
[g]Compared to university.
[h]Compared to medication use ≥5. OR, odds ratio.

brain health.[4,53] As shown in Table 1, the proportion of physical inactivity among the weight gain group was high, or 31%. Additional calculations (not shown in table) stratifying by physical activity levels showed that the weight gain associations were driven mainly by participants who did not engage in any physical activity. Weight-gaining participants reporting no participation in physical activity had a 3.8 higher odds for dementia compared to weight stable participants (odds ratio [OR]: 3.8, $P = .03$). This further confirms the protective effects of physical activity among this group of older adults.

This study has limitations, since it cannot explain what contributes to the weight loss of the older adult, weather it is voluntary or involuntary. We suggest that losing weight because of inadequate caloric intake or as a part of disease progression might be the negative factor in these associations. Future intervention studies should address the question of whether keeping body weight stable during older adulthood helps to maintain cognitive function and decreases risk of MCI and dementia.

In addition, because dementia is a hyper term, representing a broad array of brain diseases, we could not distinguish between common subgroups like AD and vascular dementia, thereby limiting precise interpretation of weight changes among older adults.

It is a strength of our longitudinal study that it included a large number of participants who underwent detailed examinations at baseline and at follow-up of the study.

In the present statistical analyses, we included several potential confounders. The extensive statistical correction only marginally changed results in the GLM and logistic regression models. Unexpectedly, physical activity and nutritional factors were not significantly associated with any of the cognitive function domains or risk of dementia/MCI diagnosis in the final analysis and therefore did not confound the observed associations between body weight changes and cognitive function. Furthermore, *APOE ε4*, although being significantly related to cognitive function in our study, did not change the observed associations between body weight change and cognitive outcomes.

5 | CONCLUSION

Our study showed that participants who lost body weight during the follow-up period had lower cognitive function after follow-up compared to weight-stable or weight-gaining participants, and consequently these participants had a higher risk of developing MCI. In contrast to our expectations, we found that participants who gained weight during follow-up were at an increased risk for dementia compared to weight-stable participants. Level of BMI categories themselves were neither related to cognitive function nor to risk of MCI or dementia.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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