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Research Article

The Association Between High-Molecular-Weight Adiponectin, Ghrelin and Leptin and Age-Related Cognitive Decline: Results From Longitudinal Aging Study Amsterdam

Merel van Andel, MD,[1,*] Natasja M. van Schoor, PhD,[2] Nicole C. Korten, PhD,[3,4] Hannie C. Comijs, PhD,[4] Annemieke C. Heijboer, PhD,[5,6] and Madeleine L. Drent, MD, PhD[1,7]

[1]Department of Internal Medicine, Endocrine Section, VU University Medical Center, Amsterdam, the Netherlands. [2]Amsterdam Public Health Research Institute, Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands. [3]Department of Old Age Psychiatry, GGZ inGeest, Amsterdam, the Netherlands. [4]Amsterdam Public Health Research Institute, Department of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands. [5]Department of Clinical Chemistry, Endocrine Laboratory, VU University Medical Center, Amsterdam, the Netherlands. [6]Department of Clinical Chemistry, Laboratory of Endocrinology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. [7]Department of Clinical Neuropsychology, VU University, Amsterdam, the Netherlands.

*Address correspondence to: Merel van Andel, MD, Department of Internal Medicine, Endocrine Section, VU University Medical Center, De Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands. E-mail: m.vanandel@amsterdamumc.nl

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Abstract

Background: Age-related cognitive decline has large-scale functional and economic consequences and understanding its' pathophysiological mechanisms is therefore essential. Previous research has suggested associations between hormones adiponectin, ghrelin and leptin and neurodegenerative disease. However, their association with age-related cognitive decline has not been fully described. We examine the association between serum high-molecular-weight (HMW) adiponectin, ghrelin and leptin and age-related cognitive decline in older adults.

Methods: The associations between HMW adiponectin, ghrelin and leptin and the Mini-Mental-State-Examination, Coding task (Coding), 15 Words Test (15WT) and composite Z-score (general cognitive function) were analyzed by means of a sex-stratified multivariable linear regression analysis in a population-based cohort of 898 older adults at baseline and after 3 years of follow-up.

Results: In women, we found a positive association between HMW adiponectin and general cognitive function at baseline (fully adjusted model composite Z-score standardized regression co-efficient beta [β] = .089, p = .025). After 3 years of follow-up, HMW adiponectin was associated with more decline in general cognitive function and information processing speed (fully adjusted model composite Z-score β = −.123, p = .018; Coding β = −.116, p = .027). Ghrelin and leptin were significantly associated with memory in a baseline subgroup analysis of older women. For men, we found no significant associations at baseline or follow-up.

Conclusion: Our results show variable associations between hormones HMW adiponectin, ghrelin and leptin and age-related cognitive decline in women but not in men. As there was no clear trend, all our results should be interpreted with caution.

Keywords: Hormones, Mini-Mental-State-Examination, 15 Words Test, Coding task

Age-related cognitive decline is a phenomenon that befalls all older adults. There is a large variability in the rate of age-related cognitive decline and in each older adult cognitive domains are affected differently. As age-related cognitive decline leads to functional impairments and forms an economic burden on society, it is important to evaluate contributing factors, such that in the future its' impact on the individual and society may be reduced (1).

Adiponectin, ghrelin, and leptin are hormones that have a wide array of individual functions in the human body; amongst others regulating hunger, glucose homeostasis, and satiety. All three hormones have in common that they have receptors in various areas of the brain, such as the hypothalamus and the hippocampus, and all three hormones have been associated with neurodegenerative disease in the past (2–4). Furthermore, all three hormones are influenced by lifestyle changes and, therefore modifiable, making them a potential target to influence age-related cognitive decline (3,5,6).

Leptin has been most extensively studied and there is evidence that leptin protects against age-related cognitive decline (7,8). A number of large studies show a stronger association in women, suggesting a sex-specific association (9,10). Additionally, various studies show significant effect modification by the level of adiposity in both men and women, suggesting that leptin is only associated with less cognitive decline in those with healthy body composition (10,11). It is not fully known which cognitive domain has the strongest association with leptin in age-related cognitive decline, as previous large cohort studies have only performed baseline analysis (12), included cohorts with a non-population based design (13), or have predominantly assessed general cognitive measures (7,10,14).

There are little data available concerning adiponectin and the association with age-related cognitive decline. A large longitudinal cohort study examining risk factors for cardiovascular disease showed no association between baseline adiponectin and decline of Mini-Mental-State-Examination (MMSE) (15). However, various reports have shown that adiponectin is negatively associated with neurodegenerative disease (4,16), this association seems to be stronger in women (17,18). We therefore form the hypothesis that there may also be a sex-specific association between adiponectin and age-related cognitive decline. To the best of our knowledge, there are no population-based cohort studies concerning adiponectin and its' association with specific cognitive domains in older adult.

Adiponectin circulates the blood in multiple isoforms, and in many chronic diseases, high-molecular-weight adiponectin (HMW adiponectin) has a predominant role in pathophysiological mechanisms (6). Although HMW adiponectin has not been demonstrated in cerebrospinal fluid and it is unclear how HMW adiponectin crosses the blood-brain-barrier, HMW adiponectin-specific receptors have been found in the central nervous system (CNS) suggesting that this isoform is biologically active (2,19,20). Only one study is available reporting the association between HMW adiponectin and neurodegenerative disease, in which the authors did not find an association between baseline HMW adiponectin and dementia after 6.9 years of follow-up (21). Receptors for HMW adiponectin have been found in the CNS, it is, therefore, likely that HMW adiponectin is associated with age-related cognitive decline (19).

As for ghrelin, in a cross-sectional study, including 280 older adults, an association with MMSE could not be confirmed (22). Multiple previous small cross-sectional studies discuss the association between ghrelin and the cognitive domain of memory, which report both positive and negative associations (23,24). Longitudinal data concerning the association between ghrelin and age-related cognitive decline is lacking.

To further elucidate the pathophysiology of cognitive aging, we examine the association between HMW adiponectin, ghrelin, and leptin across multiple cognitive domains, in a sex-stratified cohort of community-dwelling Dutch older adults at baseline and after 3 years of follow-up. Based on previous literature, for leptin, we seek to confirm whether there is effect modification by abdominal adiposity on the possible association between leptin and age-related cognitive decline.

Materials and Methods

Study Population

Data was obtained from the Longitudinal Aging Study Amsterdam (LASA), an ongoing population-based cohort study focusing on physical, emotional, cognitive, and social functioning in later life in the Netherlands. LASA consists of a representative sample of the Dutch population, aged 55 years or older. Data collection was initiated in 1992–1993 and consists of 3-yearly general interviews, medical interviews, and blood sampling. First, the main interview was conducted by a trained interviewer at the participants' home. After the interview, a self-report questionnaire was left behind. The medical interview, including clinical measurements, was conducted at the participants' home and the self-report questionnaire was collected on average 11 months later. Within 4 to 6 weeks after the medical interview, fasting blood samples were drawn on location, unless the participant was physically unable to come to the laboratory, in which case blood samples were drawn at home. Sampling and data-collection procedures have been described extensively elsewhere (25,26).

For this study, data and blood sampling from 2008 to 2009 were used as baseline data. Analysis of cognitive function was performed at baseline and after 3 years. At baseline, 1,494 participants took part in the medical interview. Of these, 935 participants had routine blood sampling done. Of the 559 participants who did not have blood sampling done, 351 declined to participate, 70 were not able to come to the laboratory and did not live in an area in which home sampling could be performed, and 6 had died. In 132 cases, there was a "soft refusal" due to a variety of reasons, such as that the participant did not come to the appointment for blood sampling, blood sampling was not successful or the participant declined blood sampling on second thoughts. Participants who did not have blood sampling performed were older, in worse general health, and had worse baseline cognitive function when compared with those who did have blood sampling performed (Supplementary Table S1). In 898 cases, there was surplus blood after routine blood sampling and HMW adiponectin, ghrelin, and leptin were determined. Due to technical issues, a few samples did not return valid results, so the final analysis included 896 participants for HMW adiponectin and leptin, respectively, and 897 participants for ghrelin (Supplementary Figure 1).

At baseline, all cases with a valid result for HMW adiponectin, ghrelin or leptin had one or more valid measurement of cognitive function (n = 898). For 863 cases, all cognitive measures were completed. At follow-up, 803 cases had one or more valid measurement of cognitive function. Of those for whom no follow-up data was available, 41 participants had died, 47 declined to participate, and 7 could not participate due to cognitive or physical disease. At follow-up, for 752 cases, all cognitive measures were completed. Participants with one or more missing values at follow-up were

older, had worse baseline cognitive function and higher levels of HMW adiponectin and leptin when compared with those with a complete dataset at follow-up (Supplementary Table S2).

Ethical approval for the LASA study was given by the Medical Ethical Committee of the VU University Medical Center. All participants provided a written informed consent.

Hormones

Venous blood samples were obtained in 2008–2009 after an overnight fast and subsequently stored at −70°C until analysis. Analyses were performed at the Endocrine Laboratory of the Department of Clinical Chemistry of the VU University Medical Center.

HMW adiponectin was measured using a fully-automated immunoanalyzer (Lumipulse, Fujirebo, Japan, IH7 monoclonal antibodies) with an intra-assay variation of 2.3% and as described in van Andel et al. (27).

Ghrelin was determined using a total ghrelin RIA (Millipore). The lower limit of quantitation is 240 pg/mL. The inter-assay variation of this assay is <7% for the whole concentration range.

Leptin was measured using a radioimmunoassay (RIA) (Millipore, St Charles, MO). The lower limit of quantitation is 0.5 g/L. The inter-assay variation of this assay is <6% for the whole concentration range.

Cognitive Tests

The MMSE, Coding task (Coding), and 15 Words Test (15WT) were performed at baseline and after 3 years of follow-up to assess cognitive function and decline covering different cognitive domains.

The MMSE is a widely used screening tool for cognitive decline (28). It consists of 20 items covering seven cognitive domains (orientation in time, orientation in place, registration of three words, attention and calculation, recall of three words, language, and visual construction). Scoring ranges from 0 to 30 points, higher scores indicate better cognitive functioning (29).

Coding is used to measure information processing speed. Coding used in LASA is an adjusted version of the Alphabet Coding Task-15, in which two sets of two rows of characters are shown to the participant (30). Each character in the top row has a corresponding character in the bottom row. In the test, only the characters of the top row are shown. The participant then has to link the missing character of the bottom row. This is done in three trials of 1 minute. Scores per trial range from 1 to 42.7 points. In LASA, a mean score of three trials was calculated, with a higher mean score indicating a higher information processing speed. As the test was conducted with a verbal response, Coding in LASA mainly measures cognitive speed processes.

The 15WT is used to assess episodic memory. It is the Dutch adaptation of the Auditory Verbal Learning Test (31). Participants are verbally presented with 15 words during five individual trails. After every trial, the participant is asked to recall as many words as possible. After a distraction period of 20 minutes, during which a non-verbal task is performed, the participant is again asked to recall the words he has learned before (retention score). Due to time constraints, the number of trials in LASA was limited to three. Scoring ranges from 0 to 45 points, higher total scores indicate better episodic memory. The retention score represents the percentage of words remembered correctly after the distraction period divided by the highest scoring primary trial.

In addition to the above tests, a composite Z-score for cognitive functioning was computed by transforming the results of the MMSE, Coding, 15WT and 15WT retention score into Z-scores. The composite Z-score was formed by the sum of the individual Z-scores. In case of missing values on one of the cognitive function tests, data were imputed (see statistics).

Covariates

Covariates were defined based on previously published data (7,10,14,17).

Age was the age of the participant on the day of the baseline medical interview. Years in school were derived from the highest achieved level of education. Partner status was defined as "yes" if participants were living with their spouse, irrespective of whether they were married. Alcohol was the number of units of alcohol consumed per week. Smoking was defined as current smoking yes or no.

Waist-hip ratio (WHR) was calculated from the average of two separate measurements of waist and hip circumference. For 17 participants (1.9%), only one measurement of either waist or hip circumference was available; in these cases, one measurement was used.

Comorbidities were self-reported during the medical interview. Eight chronic diseases with a high prevalence in the Dutch population of 55 years and older (>5%) were explicitly inquired after (chronic obstructive pulmonary disease, hypertension, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular accident, rheumatoid arthritis, and cancer). In addition, participants were asked to report any other chronic diseases up to a maximum of two. Total number of medication and use per type was recorded by the interviewer during the medical interview. For diabetes (%), cardiovascular disease (%), and hypertension (%) algorithms were constructed. Participants were recorded as having the disease if they both reported having the disease and were using appropriate medication. All other cases were classified as not having the disease. Comorbidities not included in the algorithms were totaled to form "other comorbidities." Depression was measured with the Center for Epidemiologic Studies Depression Scale (32). The Center for Epidemiologic Studies Depression Scale is a self-report scale designed to measure depressive symptoms in the general population, consisting of 20 items covering depressive symptoms in the past week. Scores range from 0 to 60, higher scores indicate more depressive symptoms. Physical activity was registered per type of activity and amount of time spent per day performing that activity during the 2 weeks before the medical interview. The average amount of minutes spent per day performing physical activity with a Metabolic Equivalent of Task (MET) score of more than three was then calculated for each participant. The results were divided into tertiles.

Creatinine was determined as a routine measurement in fresh blood. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Apolipoprotein E (ApoE) was determined from blood drawn in 1992–1993, 2002–2003, or 2008–2009. Blood samples drawn in 1992–1993 were frozen at −80°C until determination of ApoE phenotypes in 1997–1998. ApoE phenotype was determined by isoelectric focusing of delipidated serum samples, followed by immunoblotting (33). In subsequent years ApoE genotyping was performed. In blood collected in 2002–2003 DNA was extracted from buffy coats, in 2008–2009 DNA was extracted from full blood, samples were frozen at −20°C until ApoE genotyping in 2013. Genotyping was performed by Sanger sequencing. Participants were grouped according to "any ApoE allele e4." For 830 participants, ApoE phenoor genotype was available.

Statistical Analysis

All data were analyzed for men and women separately. Baseline data are expressed as mean and standard deviation or median and interquartile range for non-skewed and skewed variables, respectively. Non-skewed baseline variables were assessed with students *t*-test, skewed with Mann–Whitney U-test. The chi-square test was used to assess significant differences in frequencies. Differences in cognitive function between baseline and follow-up were analyzed using paired *t*-tests.

All cognitive tests were analyzed separately and as composite Z-score in a stepwise multivariable linear regression analysis. At baseline, MMSE was negatively skewed and was therefore transformed by taking the natural log (ln[31-MMSE]) to obtain a near-normal distribution. For the longitudinal analysis, delta scores (follow-up minus baseline) of each individual cognitive test and the composite Z-score were composed. To test for multicollinearity amongst covariates correlation coefficients were calculated. A cutoff point of <0.4 was deemed to exclude multicollinearity. Multicollinearity was only present between total number of medication and cardiovascular disease (%) (correlation coefficient 0.663, $p < .001$). Total number of medication was not included in the final analysis. Multiple imputation of missing values for covariates and outcome variables was performed for all cases where one or more hormones had a valid result (HMW adiponectin $n = 896$, ghrelin $n = 897$, leptin $n = 896$). Multiple imputations were generated using fully conditional specification. In this regression-based model, missing values are estimated with a stepwise imputation model, using the original variables and all filled-in variables from one step as a predictor in all subsequent steps. As 27.17% of our cases had missing values, we created 27 imputed data sets (34).

The linear regression models were constituted of the following steps. Model 1 included simple linear regression. Model 2 additionally corrected for age. Model 3 corrected for age and WHR. The fourth and final model was fully adjusted, additionally correcting for partner status, education, smoking, alcohol, physical activity, depression, diabetes, cardiovascular disease, hypertension, total number of other comorbidities, kidney function, and presence of ApoE-e4 allele. In the longitudinal analysis, we additionally corrected for baseline cognitive function in the fully adjusted model.

To investigate the possibility of effect modification by WHR on the association between leptin and age-related cognitive decline, we added the interaction term leptin × WHR (continuous) to the fully adjusted model analyzing the composite Z-score. As HMW adiponectin, leptin, ghrelin, and cognitive function tests are influenced by age (6), we also tested for the possibility of effect modification by age by adding the interaction term hormone × age (continuous) to the fully adjusted model analyzing the composite Z-score. In case of a significant interaction, 5-year intervals for age were created and the interaction term hormone × age (categorical) was tested again in exploratory analyses to find the most optimal age threshold for stratification. Subsequent analysis of each of the cognitive tests and composite Z-score stratified by optimal age was performed.

As our cohort is population-based, we assessed the impact of participants with likely neurodegenerative disease on the overall results by performing a sensitivity analysis, excluding participants with MMSE < 24.

Statistical analysis was performed using IBM SPSS Statistics version 22. All tests were two-tailed and a *p*-value of <.05 was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics of the cohort are presented in Table 1.

Baseline range for MMSE score was 13–30. At baseline, 35 participants had MMSE score < 24 (3.9%). Thirteen of these scored 23 points (37.14%).

Baseline Analysis

Table 2 presents the results of the multivariable-adjusted linear regression analysis at baseline. In the fully adjusted model, we found only significant associations for women. HMW adiponectin was positively associated with the composite Z-score (standardized regression coefficient beta [β] = .089, $p = .025$). There was a positive trend between HMW adiponectin and information processing speed (β = .082, $p = .061$). In women, age was a suppressor for the association between HMW adiponectin and Coding, 15WT, and composite Z-score, respectively. No significant associations were found for HMW adiponectin and age-related cognitive decline in men in the fully adjusted model.

For women there was a positive association between ghrelin and MMSE (LN[31-MMSE] β = −.110 $p = .015$), 15WT (β = .099, $p = .038$) and composite Z-score (β = .090, $p = .048$) in the unadjusted model, however after correction for age and WHR no significant findings remained. We found no significant associations between ghrelin and cognitive function tests in men.

In the unadjusted model leptin was associated negatively with 15WT (β = −.119, $p = .008$) in men and Coding (β = −.104, $p = .029$), 15WT (β = −.141, $p = .003$) and composite Z-score (β = −.168, $p < .001$) in women. There was a positive association with MMSE (LN[31-MMSE] β = .137, $p = .002$) in women. After correction for age and WHR no significant findings remained.

We found no significant effect modification by WHR on the association between leptin and age-related cognitive decline in either men or women.

After the addition of the interaction term hormone × age, in women, significant effect modification for ghrelin and leptin was found. The optimal cutoff for age-stratified analysis was 65 years for ghrelin and 80 years for leptin ($p < .1$). Age-stratified analysis of ghrelin showed a positive association between ghrelin and memory in participants of 65 years and older (15WT β = .098, $p = .049$ fully adjusted model), which was not seen in those younger than 65 years. Age-stratified analysis of leptin and cognitive function tests showed no significant associations in the fully adjusted model, with the exception of memory, for which we found a negative association between leptin and retention score (β = −.295, $p = .028$) in participants of 80 years and older (Supplementary Table 3). There was no effect modification by age for HMW adiponectin in women or HMW adiponectin, leptin, or ghrelin in men.

Longitudinal Analysis

Table 3 shows the results for the fully adjusted linear regression analysis at follow-up. Significant negative associations in the fully adjusted model were found for women between HMW adiponectin and Coding (β = −.116, $p = .027$) and composite Z-score (β = −.123, $p = .018$), respectively. In men, there was a negative association between HMW adiponectin and Coding in the unadjusted model (β = −.112, $p = .044$), which disappeared after adjustment for age.

Table 1. Baseline Characteristics

	N	Men	*N*	Women	*p*-value
N (%)	414	46.1	484	53.9	.019
Age (y), median (IQR)	414	69.3 (11)	484	70.3 (12.3)	.168
Years in school, mean (*SD*)	414	11 (3.5)	484	9.4 (3.2)	<.001
Partner status / living together (%)	414	341 (82.4)	484	288 (59.5)	<.001
Alcohol (units/wk), median (IQR)	411	7 (18)	484	3 (6.5)	<.001
Smoking (current), (%)	414	65 (15.7)	484	56 (11.6)	.002
WHR	403	1.00 (0.08)	471	0.91 (0.08)	<.001
Diabetes (%)	414	42 (10.1)	484	38 (7.9)	.402
Hypertension (%)	414	115 (27.8)	484	188 (38.8)	.001
Cardiovascular disease (%)	414	142 (34.3)	484	99 (20.5)	<.001
Other comorbidities (*N*), median (IQR)	414	1 (1)	484	1 (1)	<.001
Depression (CES-D), median (IQR)	414	4 (6)	483	6 (8)	<.001
Physical activity (number in highest tertile), (%)	414	140 (33.8)	484	142 (29.3)	.351
eGFR (MDRD, mL/min), mean (*SD*)	413	77 (17)	481	74 (17)	.006
ApoE positive (*N*) (%)	382	119 (31.2)	442	120 (27.1)	.207
Leptin (µg/L), median (IQR)	414	8.4 (8.5)	482	24.2 (20.5)	<.001
HMW adiponectin (µg/mL), median (IQR)	414	3.4 (2.8)	482	5.6 (4.2)	<.001
Ghrelin (ng/L), median (IQR)	414	833 (450)	483	971 (581)	<.001
MMSE, median (IQR)	414	29 (2)	484	28 (2)	.133
Coding (mean of 3 trials), mean (*SD*)	411	26.8 (6.5)	475	27.6 (7.1)	.076
15WT (total of 3 trials), mean (*SD*)	407	18.6 (5.4)	470	20.6 (6.1)	<.001
Retention score, mean (*SD*)[a]	407	65.8 (24.2)	470	71.9 (23.2)	<.001
Composite Z-score, mean (*SD*)[b]	403	−0.29 (2.76)	460	0.42 (2.82)	<.001
Δ MMSE, mean (*SD*)[c]	367	−0.18 (1.92)	435	−0.07 (2.08)	.455
Δ Coding, mean (*SD*)[c]	355	−1.38 (3.33)	410	−1.36 (3.60)	.882
Δ 15WT, mean (*SD*)[c]	348	2.49 (5.14)	401	2.55 (5.23)	.881
Δ Retention score, mean (*SD*)[a,c]	348	6.08 (27.79)	397	1.57 (24.57)	.019
Δ Composite Z-score, mean (*SD*)[b,c]	342	0.13 (1.66)	342	−0.06 (1.67)	.138

Notes: % = percentage, Δ = delta, 15WT = 15 Words Test, ApoE = apolipoprotein E, CES-D = center for epidemiological studies depression scale, coding = coding task, eGFR = estimated glomerular filtration rate, HMW adiponectin = high-molecular-weight adiponectin, IQR = interquartile range, MDRD = modification of diet in renal disease, MMSE = Mini-Mental State Examination, *N* = number, *SD* = standard deviation.

[a]Retention score = percentage score recall / highest of three trails 15WT.

[b]Composite Z-score = total Z-score of baseline cognitive tests (MMSE + coding + 15WT + retention score).

[c]Δ = follow-up cognitive test – baseline cognitive test.

Ghrelin and leptin showed no significant associations with any of the cognitive parameters in any of the tested models. There was no significant effect modification by WHR or age in the longitudinal analysis.

Sensitivity Analysis

Supplementary Tables 4 and 5 show the results for the sensitivity analysis at baseline and after 3 years of follow-up. Overall results were highly similar to the main analysis.

Discussion

In the present study, we examine the association between three hormones and age-related cognitive decline.

HMW Adiponectin

A number of cross-sectional reports have been published showing no association between adiponectin and MMSE in cognitively healthy participants (16,35). This is in agreement with our report; however, in our data, there was a positive association between HMW adiponectin and composite Z-score in women at baseline. The composite Z-score, which is composed of multiple cognitive function tests, may be a more sensitive measure to analyze cognitive decline than the MMSE, which was developed as a simple tool to screen cognitive ability (29). Furthermore, the positive association between HMW adiponectin and general cognitive functioning in women at baseline may be powered by the trend towards an association between HMW adiponectin and processing speed.

To the best of our knowledge, there are no previous longitudinal reports directly comparable to our data. However, a previous report analyzing the association between adiponectin and the Modified MMSE suggested a trend towards an inverse association between baseline adiponectin and general cognitive functioning after 9 years of follow-up (15). Furthermore, a clear association between high baseline adiponectin and the development of neurocognitive disease in women has been described previously (17), which is in line with our data.

It is contradictory that the associations between HMW adiponectin and cognitive function tests in women differ at baseline and follow-up.

In our population-based study, this could, in theory, be due to the influence of results by participants with likely neurodegenerative disease. This was not the case, as sensitivity analyses, including only participants with MMSE ≥ 24, revealed no significant change in results.

A possible theory is that HMW adiponectin has both pro- and anti-inflammatory properties, depending on the etiology and phase of the underlying inflammatory state. In acute inflammatory states

Table 2. Multivariable Baseline Analysis

	Men								Women							
	N = 414								*N* = 482							
	Model 1		Model 2		Model 3		Model 4		Model 1		Model 2		Model 3		Model 4	
HMW Adiponectin (µg/mL)	Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]		Univariable Linear Regression		`+ Age		+ WHR		+ Other Covariates[a]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
MMSE[b]	.082	.093	−.008	.877	.009	.856	−.018	.726	−.009	.842	−.076	.084	−.059	.188	−.049	.276
Coding	**−.169**	**< .001**	−.034	.458	−.056	.220	−.044	.317	.003	.944	**.099**	**.023**	**.094**	**.035**	.082	.061
15WT	−.076	.090	.032	.481	.011	.814	.020	.651	.006	.904	**.091**	**.044**	.072	.116	.038	.410
Retention score[c]	−.092	.065	−.026	.621	−.032	.551	−.043	.430	−.002	.967	.050	.260	.049	.283	.059	.213
Composite Z-score[d]	**−.157**	**.001**	−.013	.792	−.038	.430	−.023	.622	.011	.808	**.115**	**.004**	**.099**	**.016**	**.089**	**.025**
	N = 414								*N* = 483							
	Model 1		Model 2		Model 3		Model 4		Model 1		Model 2		Model 3		Model 4	
Ghrelin (µg/L)	Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]		Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
MMSE[b]	−.064	.195	−.083	.082	−.076	.108	−.071	.145	−.110	.015	−.118	.006	−.108	.013	−.081	.059
Coding	.035	.453	.065	.130	.057	.182	.056	.187	.038	.430	.050	.245	.045	.302	.002	.955
15WT	.044	.335	.066	.124	.058	.177	.065	.131	**.099**	**.038**	**.109**	**.013**	**.097**	**.027**	.064	.152
Retention score[c]	.029	.566	.044	.379	.042	.401	.012	.821	.037	.407	.044	.313	.043	.332	.035	.442
Composite Z-score[d]	.067	.175	**.098**	**.029**	**.089**	**.046**	.078	.076	**.090**	**.048**	**.104**	**.009**	**.092**	**.021**	.055	.151
	N = 414								*N* = 482							
	Model 1		Model 2		Model 3		Model 4		Model 1		Model 2		Model 3		Model 4	
Leptin (µg/L)	Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]		Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
MMSE[b]	.024	.628	.011	.817	−.038	.462	−.048	.400	**.137**	**.002**	**.088**	**.043**	.065	.154	−.013	.785
Coding	−.074	.112	−.055	.201	−.002	.962	.019	.708	**−.104**	**.029**	−.032	.458	−.021	.650	.032	.495
15WT	**−.119**	**.008**	**−.105**	**.014**	−.060	.197	−.010	.848	**−.141**	**.003**	−.079	.081	−.052	.272	.028	.585
Retention score[c]	−.064	.201	−.054	.271	−.050	.357	−.079	.201	**−.104**	**.020**	−.066	.133	−.067	.149	−.027	.601
Composite Z-score[d]	−.088	.072	−.068	.131	−.008	.878	.008	.884	**−.168**	**< .001**	**−.091**	**.023**	−.067	.113	.018	.675

Notes: β = standardized regression coëfficiënt; *p* = *p*- value (associations with *p*- value < .05 are signified in bold).

[a]Education, partner status, alcohol, smoking, %diabetes, %hypertension, %cardiovascular disease, other comorbidities, physical activity, depression, eGFR, ApoE allel.

[b]MMSE = LN (31 – MMSE).

[c]Retention score = percentage delayed recall / highest score of three trials of 15WT.

[d]Composite Z-score = total Z-score of baseline cognitive tests (MMSE + coding + 15WT + retention score).

Table 3. Multivariable Longitudinal Analysis

	Men								Women							
	N = 414								*N* = 482							
	Model 1		Model 2		Model 3		Model 4		Model 1		Model 2		Model 3		Model 4	
HMW Adiponectin (μg/mL)	Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]		Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
ΔMMSE	−.042	.446	−.010	.858	−.010	.864	.008	.879	**−.133**	**.005**	**−.121**	**.013**	**−.107**	**.031**	−.073	.109
ΔCoding	**−.112**	**.044**	−.018	.749	−.022	.701	−.023	.683	**−.165**	**.001**	**−.125**	**.013**	**−.124**	**.016**	**−.116**	**.027**
Δ15WT	−.084	.124	−.005	.935	−5.5[b]	.999	.023	.683	−.066	.177	−.027	.580	−.030	.552	−.003	.955
ΔRetention score[c]	−.037	.481	−.017	.764	−.015	.782	−.026	.575	−.050	.324	−.045	.380	−.046	.385	−.025	.591
ΔComposite Z-score[d]	−.097	.072	−.024	.670	−.019	.738	−.005	.923	**−.177**	**< .001**	**−.151**	**.003**	**−.143**	**.006**	**−.123**	**.018**
	N = 414								*N* = 483							
	Model 1		Model 2		Model 3		Model 4		Model 1		Model 2		Model 3		Model 4	
Ghrelin (μg/L)	Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]		Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
ΔMMSE	−.025	.626	−.018	.723	−.018	.723	.055	.240	.002	.960	.005	.920	.017	.724	.053	.222
ΔCoding	−.017	.746	.003	.947	.002	.968	.026	.617	.037	.443	.043	.361	.048	.314	.020	.675
Δ15WT	.021	.698	.038	.475	.040	.453	.075	.158	−.003	.959	.003	.956	.002	.974	.043	.376
ΔRetention score[c]	.023	.667	.027	.602	.028	.596	.048	.292	−.018	.719	−.017	.733	−.017	.742	−.014	.749
ΔComposite Z-score[d]	.001	.981	.017	.737	.019	.705	.085	.084	−.011	.832	−.006	.900	.003	.960	.015	.761
	N = 414								*N* = 482							
	Model 1		Model 2		Model 3		Model 4		Model 1		Model 2		Model 3		Model 4	
Leptin (μg/L)	Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]		Univariable Linear Regression		+ Age		+ WHR		+ Other Covariates[a]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
ΔMMSE	−.081	.109	−.077	.130	−.094	.097	−.090	.111	.007	.894	.021	.678	−.006	.912	−.019	.706
ΔCoding	−.069	.184	−.056	.270	−.057	.291	−.052	.391	−.055	.295	−.021	.687	−.034	.525	−.009	.883
Δ15WT	−.031	.558	−.020	.705	−.038	.518	−.100	.106	−.009	.862	.023	.647	.029	.592	.021	.695
ΔRetention score[c]	−.042	.406	−.039	.440	−.052	.371	−.083	.127	−.003	.956	.002	.973	−.001	.990	−.016	.748
ΔComposite Z-score[d]	−.089	.081	−.079	.117	−.111	.055	**−.148**	**.014**	−.001	.990	.025	.639	.005	.929	−.014	.801

Notes: β = standardized regression coëfficiënt; *p* = *p*- value (associations with *p*- value < .05 are signified in bold).

[a]Baseline cognitive function test, education, partner status, alcohol, smoking, %diabetes, %hypertension, %cardiovascular disease, other comorbidities, physical activity, depression, eGFR, ApoE allel.

[b]-5.5×10^{-5}.

[c]Retention score = percentage delayed recall / highest score of three trials of 15WT.

[d]Composite Z-score = total Z-score of baseline cognitive tests (MMSE + coding + 15WT + retention score).

such as stroke or myocardial infarction, HMW adiponectin levels are upregulated in an effort to downregulate acute inflammation. In chronic inflammatory states such as diabetes mellitus type 2, adiponectin regulation often becomes dysfunctional and low HMW adiponectin levels are found (6). Neurodegenerative disease can be considered an inflammatory disease and the conflicting associations between HMW adiponectin and age-related cognitive decline at baseline and follow-up may be a reflection of the diverse roles HMW adiponectin has in its' regulation. As we did not measure HMW adiponectin levels at follow-up, this theory remains to be confirmed.

As we find no clear overall trend, it is important to consider the validity of our results.

The lack of a clear trend may be due to technical specifics such as a relatively high baseline cognitive function. Furthermore, a follow-up time of 3 years may be insufficient to show a clear overall trend, especially considering that the change in cognitive function tests at follow-up was relatively small.

However, there are also a number of specific issues that complicate the discussion concerning the association between HMW adiponectin and age-related cognitive decline.

First of all, age-related cognitive decline is a process that takes place in the CNS. Adiponectin levels in the CNS are up to a 1,000-fold lower than in serum (36). Adiponectin in the cerebrospinal fluid is mainly made up of LMW isoforms, suggesting that not HMW but LMW adiponectin is biologically active in the CNS (19). This would not necessarily have to complicate the interpretation of our results, as previous data have suggested that the ratio between the different serum isoforms is a constant rather than a variable, irrespective of underlying disease (27). However, to the best of our knowledge, there is no data available confirming that the ratios between serum HMW adiponectin and CNS adiponectin isoforms correspond to the same degree. Indeed, a cohort study by Une et al. found that participants with Alzheimer's disease and mild cognitive impairment had elevated serum adiponectin levels versus healthy controls, whereas only participants with mild cognitive impairment had significantly elevated CNS adiponectin levels, confirming that one cannot assume that serum adiponectin levels correspond to CNS adiponectin levels when examining age-related cognitive decline (37).

A second complicating factor is the lack of a gold standard in the measurement of adiponectin isoforms. Different assays measure different molecular weights and the nomenclature of which adiponectin isoform is which sometimes overlaps (27). Although we used a well-validated assay in our study, this diagnostic insecurity implies that our—and all previous data—must be interpreted with caution.

Lastly, we find that the association between HMW adiponectin and age-related cognitive decline was significant only in women. Levels of HMW adiponectin in women were significantly higher than in men in our cohort, possibly accounting for the results. In a post hoc analysis, formal testing for effect modification by sex showed no significant results (data not shown), suggesting that our findings may also simply be due to chance.

Ghrelin

Previous evidence for the association between ghrelin and age-related cognitive decline in humans is limited. Cross-sectional analyses have predominantly been performed in small study groups, showing conflicting results, longitudinal data are lacking (22–24).

In our observational population-based study, we found no associations with general cognitive functioning either at baseline or at follow-up, which is in correspondence with previous population-based data (22). To activate its' nutrient-sensing receptor in the brain, ghrelin requires post-translational acylation by the membrane-bound ghrelin *O*-acyl-transferase (3). In murine studies, infusion of acylated ghrelin prevented pathophysiological changes associated with neurodegenerative disease and improved memory performance (38,39). As we measured total ghrelin instead of acylated and deacylated ghrelin separately, this may explain why we found no association between ghrelin and general age-related cognitive decline. Furthermore, a single ghrelin measurement may be insufficient to fully examine the association between ghrelin and age-related cognitive decline as it is influenced by nutrient intake and fasting time and is differentially regulated in normal weight and obese individuals (3).

Of note is that although we found no overall association between ghrelin and age-related cognitive decline, our report did show a significant association specifically between ghrelin and memory at baseline in the subgroup analysis of women of 65 years and older. In murine studies, ghrelin has a positive effect on memory (39). However, both murine data and the lack of previous human data leave us with no explanation as to why we only find this association at baseline in women of 65 years and older. Although it has been previously suggested that ghrelin levels increase with progressive age (40), there is, to the best of our knowledge, no previous data concerning changing ghrelin effects with progressive age. As such, it may be possible that the associations between ghrelin and memory differ in women of 55–65 years of age versus women of 65 years and older; however, the fact that we only find this association in this specific subgroup warrants us to interpret our results with caution.

Leptin

Multiple large longitudinal cohort studies have suggested a positive association between leptin and cognitive measures (7,11,14,41). However, not all data confirm this association (12,42). We too found no overall association between leptin and age-related cognitive decline. Contradictory to previous reports, our analysis revealed no body composition-dependent associations (10,11). The lack of significant associations in our cohort, in the face of multiple previous longitudinal studies that do show significant associations, may be due to the fact that in our cohort baseline cognitive function was relatively high and the change in cognitive function tests was relatively small in comparison to other cohorts with a similar study design (14).

The negative association between baseline leptin and memory in women of 80 years or older may be explained by progressive leptin resistance in the geriatric population (43), however, as we only find a significant association in this specific subgroup, and the association is contrasting to the multiple previous studies showing a protective effect of leptin on age-related cognitive decline, here too we are careful in interpreting our results.

To the best of our knowledge, this is the first report in which the association between three hormones and specific cognitive function domains of age-related cognitive decline are studied in a large population-based cohort both at baseline and after 3 years of follow-up. This is additive to previous data, which has often included smaller study groups, used data from cohorts designed for other purposes or failed to perform analysis both at baseline and at follow-up. Furthermore, previous reports concerning population-based cohorts have often examined pathological cognitive decline or a single cognitive function test rather than multiple cognitive domains. As such, the data from LASA reported

here provide a new insight in the pathophysiology of age-related cognitive decline.

A limitation of our study is that the absolute differences in cognitive function tests after 3 years of follow-up were relatively small, which may explain why we failed to show more statistically significant associations. This is partially due to selection bias, as participants who had blood drawn were on average healthier and had better baseline cognition than those that did not (Supplementary Table S1). This form of selection bias, however, is common in large longitudinal cohort studies and is therefore unlikely to explain differences found between our data and previous reports with a comparable design. Further limitations include that we only measured HMW adiponectin, ghrelin, and leptin at baseline and that we did not specifically include inflammation in our analysis, which influences both the measured hormones and cognitive decline, thus conveying a risk of causation bias (6,44). In some cases, we may not have measured the biologically relevant hormone, for example, serum HMW adiponectin versus CNS LMW adiponectin and acylated versus total ghrelin. Lastly, we performed a relatively large number of statistical tests, and as our results did not show a clear trend, the possibility that the significant associations we find are derived by chance due to multiple testing cannot be ruled out.

Even though our data showed no clear trend and need to be interpreted with caution, we feel future research is warranted. Age-related cognitive decline is a universal phenomenon and the definition of modifiable factors to reduce its' impact on both society and the individual is important. HMW adiponectin, ghrelin, and leptin have all been associated with cognitive function in the past. Furthermore, they are all influenced by lifestyle and, therefore, modifiable (3,5,6). Future research should focus on confirming (or rejecting) our data on the association between HMW adiponectin and age-related cognitive decline. Furthermore, the association between ghrelin and age-related cognitive decline in women aged 65 years and older warrants further research, as despite non-significant results from previous human reports, in our report in this subgroup of older adults ghrelin was associated with memory.

Conclusion

In our cohort study of community-dwelling older adults, we found that at baseline, HMW adiponectin may have a positive association with general cognitive functioning in women. HMW adiponectin may also be associated with a faster rate of general cognitive decline and decline of information processing speed after 3 years of follow-up in women. In men, no significant associations were found. Ghrelin and leptin were not associated with age-related cognitive decline or loss of function of specific cognitive domains in the overall cohort although in women there may be an association with ghrelin and memory in adults of 65 years or older and a negative association with leptin and memory in adults of 80 years or older at baseline. As there was no clear overall trend, all significant associations must be interpreted with caution.

HMW adiponectin, ghrelin, and leptin can all be influenced by simple lifestyle changes (3,5,6). The necessity to further evaluate the association between these hormones and age-related cognitive decline is therefore evident, so that in the future, the burden of age-related cognitive decline on the individual and on society may be reduced. This report suggests that there may be mild associations with age-related cognitive decline, which is additive, especially for HMW adiponectin and ghrelin, for which previous data is lacking.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None reported.

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