



Plasma leptin, but not adiponectin, is associated with cognitive impairment in older adults

Insa Feinkohl^{a,*}, Jürgen Janke^a, Arjen J.C. Slooter^b, Georg Winterer^c, Claudia Spies^c, Tobias Pischon^{a,c,d}

^a Molecular Epidemiology Research Group, Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Robert-Rössle Str. 10, D-13092 Berlin, Germany

^b Department of Intensive Care Medicine, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Universiteitsweg 98, 3584 CG Utrecht, the Netherlands

^c Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Charitéplatz 1, D-10117 Berlin, Germany

^d MDC/BIH Biobank, Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), and Berlin Institute of Health (BIH), Robert-Rössle Str. 10, D-13092 Berlin, Germany

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ABSTRACT

Background: Leptin and adiponectin are adipose-tissue derived hormones primarily involved in glucose, lipid, and energy metabolism, inflammation, and atherosclerosis. Both adipokines may cross the blood-brain barrier but evidence on their roles in cognitive impairment is limited and conflicting. Here, we determined associations of plasma adipokine concentration with cognitive impairment in older adults.

Methods: Cross-sectional analysis of baseline data from 669 participants aged ≥ 65 years of the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study were recruited 2014–2017 at study sites in Berlin, Germany and Utrecht, the Netherlands. Cognitive impairment was defined as the lowest tertile of a cognitive summary score derived from six neuropsychological tests.

Results: After adjustment for age, sex, fasting, BMI, diabetes, hypertension, cerebrovascular disease, and coronary heart disease, higher leptin concentrations and a higher leptin/adiponectin ratio (LAR) were associated with a higher odds of cognitive impairment (OR per 1 SD higher leptin concentration, 1.33; 95 % CI 1.05, 1.69; $p = 0.02$; OR per 1 SD higher LAR, 1.26; 95 % CI 1.01, 1.57; $p = 0.04$). Sensitivity analyses determined that these findings were driven by the non-obese group ($BMI < 30 \text{ kg/m}^2$), whereas leptin and LAR were not associated with cognitive impairment in the obese group ($BMI \geq 30 \text{ kg/m}^2$). Soluble leptin receptor, leptin/soluble leptin receptor ratio, total adiponectin and high-molecular weight adiponectin concentrations were each not associated with impairment.

Conclusions: With leptin as a known promoter of atherosclerosis and inflammation, our findings point to a pathogenic role of leptin in age-related cognitive impairment that may be limited to non-obese individuals and warrants further investigation.

1. Introduction

The adipokines leptin and adiponectin are secreted by adipocytes and contribute to metabolic homeostasis (Grassmann et al., 2017; Lopez-Jaramillo et al., 2014; Nimptsch et al., 2019; Stern et al., 2016) but have opposing effects on vascular function and inflammation. Leptin (which circulates at levels proportional to adipose tissue mass and is thus a signal for adiposity (McGuire and Ishii, 2016)) promotes atherosclerosis, endothelial dysfunction and inflammation. In contrast,

adiponectin (which circulates at levels inverse to adipose tissue mass (Aleksandrova et al., 2018)) has vascular health-promoting, anti-inflammatory and insulin-sensitizing properties (Grassmann et al., 2017; Nimptsch et al., 2019). Both adipokines may cross the blood-brain barrier (BBB) (Adya et al., 2015; Bloemer et al., 2018) (though the evidence on adiponectin is conflicting (Forný-Germano et al., 2018)), and may influence cerebrovascular function and neuroinflammation (Adya et al., 2015; Forný-Germano et al., 2018). Effects of leptin and adiponectin on the pathogenesis of cognitive impairment could thus be

* Corresponding author at: Max-Delbrueck Center for Molecular Medicine (MDC), Robert-Roessle-Str. 10, D-13092 Berlin, Germany.

E-mail address: insa.feinkohl@mdc-berlin.de (I. Feinkohl).

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expected. Nonetheless, epidemiological investigations on their associations with cognition are often limited by small sample size and a focus on patient populations (Gustafson et al., 2015; Labad et al., 2012), children (Buck et al., 2019; Li et al., 2019) or younger adults (Bove et al., 2013) and they have produced mixed results (e.g., Albala et al., 2016; Bednarska-Makaruk et al., 2017; Bove et al., 2013; Cezaretto et al., 2018; Gilbert et al., 2018; Gunstad et al., 2008; Gustafson et al., 2012, 2015; Holden et al., 2009; Kitagawa et al., 2016; Labad et al., 2012; Lieb et al., 2009; Oania and McEvoy, 2015; Sang et al., 2018; Warren et al., 2012). For instance, reports of an inverse relationship of leptin concentration with cognitive function (Gunstad et al., 2008; Gustafson et al., 2015; Labad et al., 2012; Gorska-Ciebiada et al., 2016) are contrasted with studies implicating higher leptin concentration or higher leptin bioavailability (indicated by lower levels of its soluble receptor, sOB-R; (Gruzdeva et al., 2019)) in reducing cognitive risk (Albala et al., 2016; Gilbert et al., 2018; Holden et al., 2009; Khemka et al., 2014; Lieb et al., 2009; Yin et al., 2018) as well as null results (Bednarska-Makaruk et al., 2017). Similarly, whereas some reported a positive correlation of adiponectin with cognitive test performance (Cezaretto et al., 2018; Teixeira et al., 2013), others found a higher adiponectin concentration in patients with dementia compared with healthy or less severely impaired controls (Bednarska-Makaruk et al., 2017; Gilbert et al., 2018; Khemka et al., 2014) or inverse associations with cognitive function (Sanz et al., 2019).

Of note, adiponectin occurs in trimer, hexamer, and multimeric (high-molecular weight, HMW) form of which the latter appears to be biologically particularly active (Aso et al., 2006). Only a few studies have measured HMW adiponectin (Arnoldussen et al., 2018; Gustafson et al., 2015; Kitagawa et al., 2016) but surprisingly found no association with cognition despite the fact that adiponectin-induced improvement in cerebrovascular function and neuroinflammation would likely depend on the biological activity of the compound. Clarification of the roles of total versus HMW adiponectin in cognition is therefore needed.

Here, our goal was to determine the associations of leptin and its receptor, and of total and HMW adiponectin with cognitive impairment in a large sample of older adults. To operationalize the antagonistic effects of leptin and adiponectin, we additionally calculated the leptin/adiponectin ratio as an 'atherosclerotic index' that has previously been shown to correlate with metabolic health (Finucane et al., 2009) and health outcomes (Park et al., 2013) as well as the leptin/sOB-R ratio as an index of free, unbound leptin in circulation (Herrick et al., 2016).

2. Materials and methods

2.1. Study design

We used a cross-sectional study design based on data from the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study, an observational study on post-operative cognitive impairment. The full study protocol has been reported elsewhere (Winterer et al., 2018). In brief, BioCog recruited 1033 participants in Berlin, Germany, and Utrecht, the Netherlands, who were ≥ 65 years old, scheduled for elective surgery of any type (expected duration ≥ 60 min), were Caucasian, free of clinical dementia (Mini Mental State Examination, MMSE ≥ 24 (Folstein et al., 1975)), and had no history of neuropsychiatric disease or addiction disorder. Only baseline data collected during the days before surgery were used.

2.2. Ethical consideration

The BioCog study has full institutional ethical approval at Charité Universitätsmedizin Berlin (EA2/092/14) and UMC Utrecht (No. 14-469), and is registered on clinicaltrials.gov (NCT02265263). Assessments complied with the Declaration of Helsinki and participants provided informed consent.

2.3. Clinical assessment

Sociodemographic data and medical history including history of hypertension, diabetes, coronary heart disease (CHD), transient ischemic attack (TIA) and stroke were ascertained using a combination of self-report and clinical records. Current smoking and level of education were self-reported. Height and weight were measured to derive body mass index (BMI). Obesity was defined as BMI ≥ 30 kg/m². Underweight was defined as BMI < 18.5 kg/m² (NCD Risk Factor Collaboration, 2016).

2.4. Adipokine measurement

Blood was collected on the day of surgery in a supine position, following an overnight fast and before incision, and was centrifuged after 30–40 min at room temperature at 2500 x g for 10 min to obtain serum. Plasma was collected into ethylenediaminetetraacetic acid (EDTA) tubes which were placed on a rocking mixer for at least 30 s for anticoagulation and was centrifuged at 2500 x g for 10 min. Samples were frozen at -80 °C, and following a single thaw/refreeze cycle, were shipped from a central coordinating lab to analysis laboratories for measurement of leptin and receptor (sOB-R) and of total adiponectin and HMW adiponectin from plasma. For logistical reasons, leptin and sOB-R were measured at two laboratories (37 % of samples at Lab 1; 63 % at Lab 2). Allocation of samples to labs was unrelated to study site, outcome or any other potentially confounding factor. The first sets of samples arriving at the central lab were allocated to Lab 1 and later samples to Lab 2. Both labs used identical ELISA kits (BioVendor GmbH, catalogue # RD191001100 for leptin; catalogue # RD194002100 for sOB-R). Total and HMW adiponectin were measured at a single laboratory (Lab 2) using a kit manufactured by Alpco (Salem, USA; catalogue # 47-ADPHU-E01). Assays were performed according to the manufacturers' protocols. Mean intra-assay coefficients of variation (CV) for pool plasma (controls) were 6.43 % for total adiponectin and 7.41 % for HMW adiponectin; inter-assay CV were 12.51 % and 14.09 % respectively. Mean intra-assay CV were 3.39 % (Lab 1) and 2.45 % (Lab 2) for leptin, and 4.81 % (Lab 1) and 3.63 % (Lab 2) for sOB-R. Inter-assay CVs were 11.03 % (Lab 1) and 2.63 % (Lab 2) for leptin and 4.76 % (Lab 1) and 4.28 % (Lab 2) for sOB-R. Measurements which were below or above the limits of quantification were set as the respective lower or upper limit of quantification (leptin, n = 22; sOB-R, n = 6; HMW adiponectin, n = 1 across both labs). For a small number of samples, Lab 2 additionally produced values that were outside of the limits of quantification (leptin, n = 22; total adiponectin, n = 2; sOB-R, n = 1). These were included as those measured values for the purpose of this analysis. We derived the leptin/adiponectin ratio (LAR) and the leptin/sOB-R ratio (free leptin index; FLI). Additionally, plasma C-reactive protein (CRP) and interleukin-6 (IL-6) were measured.

2.5. Cognitive examination

Participants performed six age-sensitive neuropsychological tests tapping the domains of processing speed, executive function and verbal and non-verbal memory during the days before surgery. Four tests (Paired Associates Learning; Verbal Recognition Memory; Spatial Span; Simple Reaction Time) were from the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition Ltd.) and two were conventional tests (Grooved Pegboard; Trail-Making Test-B). From performance on those six tests, the latent 'g' factor was calculated as an index of participants' global cognitive ability (Spearman, 1904) as reported in detail elsewhere (Feinkohl et al., 2019). Use of g is advantageous, because it reflects only the variance shared by all six cognitive tests; thus it is immune to test-specific measurement error and so interpretations of analyses based on g may have higher reliability compared with analyses of observed test scores (Penke and Deary, 2010). G is a standardized score with mean 0 and standard deviation 1

in the total sample. Here, we defined cognitive impairment as the lowest g tertile. We have previously cross-validated this definition of cognitive impairment with the more commonly used cognitive screening instrument Mini-Mental State Examination (MMSE) (Folstein et al., 1975) by showing that MMSE scores were lower in the lowest g tertile compared with the upper tertiles (Feinkohl et al., 2019).

2.6. Statistical analysis

669 participants had complete data on sociodemographic and cognitive parameters, and on leptin and HMW adiponectin, and provided our analysis sample. Data on total adiponectin were missing for $n = 1$ and on sOB-R for $n = 25$ participants.

Participants were divided into quartiles based on the distribution of each adipokine. Characteristics were compared across quartiles using analyses of variance (ANOVA) for continuous variables and χ^2 tests for categorical variables. The associations of each adipokine with one another and with age and BMI were examined in univariate Spearman rank correlation analyses.

Multiple logistic regression analyses determined the association of quartiles of each adipokine with the odds of cognitive impairment using the lowest quartile as the reference category. In addition, we estimated the odds ratio associated with a 1 standard deviation higher adipokine concentration on a continuous scale. In the respective first model (Model 1) we adjusted for age, sex, fasting status and (for analyses of leptin, sOB-R, LAR, FLI) for analysis lab. Model 2 additionally adjusted for BMI, diabetes, hypertension, CHD, TIA and stroke. To test for non-linearity, we subsequently added quadratic terms to the multivariable models (Model 2) of adipokines as continuous parameters. Finally, multivariate models (Model 2) of continuous adipokines were repeated with additional adjustment for CRP, IL-6, education and smoking, and, separately, with exclusion of underweight participants. For those adipokine exposures with statistically significant results in Model 2, multiple linear regression analyses additionally explored their associations with scores on the six individual cognitive tests used to generate g.

In post-hoc analyses, we repeated all multivariable models (Model 2) associating continuous adipokines with odds of cognitive impairment stratified by obesity status ($\text{BMI} < 30$ versus $\geq 30 \text{ kg/m}^2$), and across the total sample tested for effect modification by including interaction terms (adipokine \times BMI). In cases where information was missing on a covariate, we assigned the respective covariate as 'absent' (hypertension, $n = 13$; diabetes, $n = 13$; stroke, $n = 16$; CHD, $n = 18$; TIA, $n = 19$; smoking $n = 16$). Missing data on CRP were replaced by the median of the distribution ($n = 6$). Missing data on education were not imputed ($n = 53$). Data on all remaining variables were complete.

3. Results

3.1. Sample characteristics

Participants were aged between 65 and 90 years (mean 72.2 ± 4.9 years) and ten participants were not fasted. Those with high leptin concentrations as compared to those with low concentrations had higher BMI, were more likely to have a history of hypertension and diabetes, and less likely to be male and to have a history of CHD (Table 1). Participants with high as compared to those with low adiponectin concentrations had a lower BMI, were older, less likely to be male, and less likely to have a history of hypertension, diabetes, and CHD (Table 2). The covariate structure according to quartiles of sOB-R and HMW adiponectin is shown in Supplemental Tables S1 and S2.

In correlation analyses, leptin concentrations were positively correlated to BMI and inversely associated with sOB-R (Table 3). sOB-R was inversely correlated to BMI, modestly positively correlated with total and HMW adiponectin, and weakly positively correlated with age. Total and HMW adiponectin were inversely correlated with BMI and weakly positively associated with age. Total adiponectin was highly

correlated with HMW adiponectin.

3.2. Adipokines and cognitive impairment

In multiple logistic regression analyses, we found that higher quartiles of leptin and higher quartiles of LAR were each associated with higher odds of cognitive impairment (Table 4). The association for leptin but not for LAR remained following multivariable adjustment (Model 2). For instance, participants in the highest quartile of leptin concentration were at 2.9-fold increased odds of impairment relative to the lowest quartile (OR 2.86; 95 % CI 1.43, 5.72). Quartiles of sOB-R, total and HMW adiponectin, and FLI were unrelated to cognitive impairment throughout (Table 4).

Next we assessed the adipokines as continuous parameters in further multiple logistic regression analyses. Higher leptin concentration and higher LAR were each associated with increased odds of cognitive impairment (Table 4). Each standard deviation higher leptin and each standard deviation higher LAR were associated with 1.30-fold (OR 1.30; 95 % CI 1.07, 1.57) and 1.28-fold (OR 1.28; 95 % CI 1.07, 1.54) increased odds of cognitive impairment, respectively, with age, sex, fasting and analysis lab controlled for. In absolute numbers, each 1 ng/mL higher leptin concentration was associated with a 0.9 % higher odds of impairment (OR 1.01; 95 % CI 1.00, 1.02). These results were unchanged following multivariable adjustment in Model 2 (for leptin, OR per 1 standard deviation increment 1.33, 95 % CI 1.05, 1.69; for LAR, OR per 1 standard deviation increment in LAR 1.26, 95 % CI 1.01, 1.57). Addition of quadratic terms did not produce statistically significant estimates (quadratic term for leptin, $P = 0.11$; quadratic term for LAR, $P = 0.41$) indicating that non-linearity did not underlie the aforementioned associations. Quadratic terms for all of the remaining adipokines were also statistically non-significant (sOB-R, $P = 0.54$; total adiponectin, $P = 0.10$; HMW adiponectin, $P = 0.12$; FLI, $P = 0.07$).

Addition of CRP, IL-6, education and smoking into the respective Model 2, or exclusion of seven underweight participants, did not change any of the results (data not shown). Associations of leptin and LAR with cognitive impairment appeared to be driven by the timed tests of processing speed and executive function (Simple Reaction Time, Grooved Pegboard, Trail-Making Test-B), as trends were observed for higher leptin and higher LAR associated with slower performance on these tests (Supplemental Table S3).

3.3. Sensitivity analyses

BMI was not associated with cognitive impairment in any of the multivariable models presented above and in Table 5 (data not shown; all $P > 0.20$) and in analyses controlling only for age and sex (OR per 1 kg/m^2 increment 1.03; 95 % CI 0.99, 1.07; $P = 0.16$), but due to its close relationship with adipokine concentrations we explored a potential interaction of adipokines with BMI in determining odds of cognitive impairment. As a first step, the respective Model 2 with adipokines as continuous parameters were repeated separately for obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) and non-obese participants ($\text{BMI} < 30 \text{ kg/m}^2$; Table 5). In the non-obese group, higher leptin (OR per 1 standard deviation increment 2.09, 95 % CI 1.44, 3.02), higher LAR (OR per 1 standard deviation increment 1.72, 95 % CI 1.23, 2.41), lower sOB-R (OR per 1 standard deviation reduction 1.28, 95 % CI 1.01, 1.61) and higher FLI (OR per standard deviation increment 1.54, 95 % CI 1.03, 2.30) were each associated with higher odds of cognitive impairment. There were no findings for the obese group (all $P > 0.20$; Table 5). As a second step, we repeated the analyses across the total sample with addition of adipokine \times BMI interaction terms. Differential relationships with cognitive impairment according to BMI were indicated by interaction terms for leptin (multivariable-adjusted $P = 0.002$), LAR (multivariable-adjusted $P = 0.03$) and FLI (multivariable-adjusted $P = 0.05$; Table 5).

Table 1
Characteristics of total study sample and by quartiles of leptin.

	Total sample	Leptin				P-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
N	669	166	164	174	165	
Leptin concentration, range, ng/mL	0.2–159.9	0.2 – 5.7	5.8 – 13.4	13.4 – 30.6	30.7 – 159.9	
Age, years, mean	72.2	72.7	71.9	72.2	71.8	0.33
Male sex, %	58.3 %	84.3	62.2	52.3	34.5	< 0.001
Body mass index, kg/m ² , mean	27.0	24.2	26.6	27.3	30.1	< 0.001
Hypertension, %	61.6	55.4	56.7	58.6	75.8	< 0.001
Diabetes, %	20.2	13.3	20.7	17.8	29.1	0.003
Coronary heart disease, %	18.4	25.3	18.9	14.9	14.5	0.04
Stroke, %	4.8	4.8	4.9	5.2	4.2	0.98
Transient ischemic attack, %	3.3	4.2	3.0	2.3	3.6	0.78
Cognitive impairment, %	33.3	22.0	23.4	23.8	30.2	0.06

Precise range is not shown due to rounding. N = 669. P-value for comparison among leptin quartiles in analyses of variance (ANOVA) or chi² tests.

4. Discussion

We found in a sample of older adults that higher levels of total (bound and unbound) leptin and a higher leptin/adiponectin ratio (LAR) were each associated with higher odds of being cognitively impaired. The associations were independent of sociodemographics, vascular risk factors, macrovascular disease and inflammation as well as BMI. Neither total nor HMW adiponectin alone were associated with impairment. Our data overall suggest that higher leptin concentrations are related to a higher odds of cognitive impairment, while they do not support the hypothesis that adiponectin concentrations are related to this outcome.

Metabolic dysregulation and obesity are candidate risk factors for age-related cognitive impairment (Peditizi et al., 2016; Van den Berg et al., 2009), but fewer studies have evaluated adipokine concentrations as potential contributors to the relationship.

Previous investigations had reported a higher level of adiponectin as a correlate of higher cognitive function in middle-aged (Cezaretto et al., 2018) and older adults (Teixeira et al., 2013) and lower adiponectin in patients with mild cognitive impairment or Alzheimer's disease (AD) compared with controls (Teixeira et al., 2013; Gorska-Ciebiada et al., 2016). In direct contrast, others implied higher adiponectin as associated with presence of cognitive impairment (Bednarska-Makaruk et al., 2017; Gilbert et al., 2018; Khemka et al., 2014; Sanz et al., 2019; Wennberg et al., 2016). Here, we found no relationship of adiponectin with cognition even with minimal adjustment and are thus unable to resolve this inconsistency.

Higher circulating leptin had previously been associated with a reduced cognitive risk in a number of epidemiological investigations (Gilbert et al., 2018; Holden et al., 2009; Johnston et al., 2014; Khemka et al., 2014; Lieb et al., 2009; Littlejohns et al., 2015; Zeki Al Hazzouri

et al., 2013; Yin et al., 2018). Such reports appear counterintuitive in the face of leptin as a promoter of atherosclerosis, endothelial dysfunction and inflammation, but can be explained by an additional role of leptin as a cognitive enhancer. Leptin receptors are expressed in several regions of the brain, where it not only acts as a satiety signal (Banks et al., 2006; Letra et al., 2014), but is also involved in neurogenesis and brain growth (Banks et al., 2006), the clearance of beta amyloid (a neuropathological hallmark of Alzheimer's disease) (Fewlass et al., 2004), and in hippocampal synaptic plasticity (Forny-Germano et al., 2018; McGregor and Harvey, 2018).

Yet, in our analysis, and in several other studies of older adults, higher leptin was associated with cognitive impairment (Gorska-Ciebiada et al., 2016; Gunstad et al., 2008; Labad et al., 2012). For instance, in male participants of the Edinburgh Type 2 Diabetes Study (ET2DS) after controlling for a range of covariates including age, BMI, waist-hip ratio, estimated pre-morbid cognitive ability, inflammation, vascular risk factors and macrovascular disease, higher plasma leptin was associated with a lower global cognitive function and with a poorer performance on a verbal fluency test and the Trail-Making Test-B as a measure of processing speed and executive function (Labad et al., 2012). Here, we observed a trend for poorer performance on this test as associated with higher leptin concentration albeit the trend fell short of statistical significance and was of smaller effect size compared with ET2DS results. In any event, associations of higher leptin with cognitive impairment are corroborated by reports of associations of higher leptin concentration with brain atrophy (Rajagopalan et al., 2013) and may reflect the aforementioned beneficial effects of leptin on brain function being outweighed by its effects on atherosclerosis, endothelial dysfunction and inflammation (Forny-Germano et al., 2018). Although in our analysis the association of leptin with cognitive impairment remained after adjustment for CRP and IL-6, speaking against mediation

Table 2
Characteristics of study participants by quartiles of total adiponectin.

	Total adiponectin				P-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
N	174	167	168	159	
Adiponectin concentration, range, ng/μL	2.7 – 9.0	9.1 – 12.7	12.8 – 18.0	18.0 – 61.1	
Age, years, mean	71.2	72.4	72.2	72.8	0.02
Male sex, %	70.1	60.5	54.2	47.2	< 0.001
Body mass index, kg/m ² , mean	28.1	27.6	27.2	25.2	< 0.001
Hypertension, %	68.4	64.1	59.5	53.5	0.04
Diabetes, %	28.7	28.1	13.7	9.4	< 0.001
Coronary heart disease, %	25.3	12.6	17.9	17.0	0.02
Stroke, %	4.0	6.6	4.2	4.4	0.66
Transient ischemic attack, %	4.0	1.8	4.2	3.1	0.60
Cognitive impairment, %	23.0	22.1	24.3	40.2	0.12

Precise range is not shown due to rounding. N = 668. P-value for analyses of variance (ANOVA) or chi² tests.

Table 3
Correlations among adipokines and of adipokines with age and body mass index.

	Age	Body mass index	Total adiponectin ²	HMW adiponectin	sOB-R ¹
Leptin	−0.03 (0.44)	0.51 (< 0.001)	−0.07 (0.06)	−0.02 (0.60)	−0.50 (< 0.001)
sOB-R ¹	0.09 (0.02)	−0.43 (< 0.001)	0.23 (< 0.001)	0.28 (< 0.001)	–
HMW adiponectin	0.13 (0.001)	−0.24 (< 0.001)	0.77 (< 0.001)	–	–
Total adiponectin ²	0.09 (0.02)	−0.24 (< 0.001)	–	–	–

HMW, high molecular weight; sOB-R, soluble leptin receptor.

Values are Spearman rank correlation coefficients (*P*-values). Analysis *n* = 669, except ¹*n* = 644 and ²*n* = 668; analysis of total adiponectin and sOB-R, *n* = 643.

Table 4
Adjusted odds and 95 % CI of cognitive impairment for quartiles of adipokine concentration, and for continuous adipokine concentration.

h		Quartiles of plasma concentration					Continuously ³	
		I	II	III	IV	<i>P</i> _{trend}	OR (95 % CI) per 1 SD increment	<i>P</i> _{OR}
Leptin	Model 1	1.0 (Ref)	1.34 (0.81, 2.20)	1.30 (0.77, 2.20)	2.58 (1.45, 4.58)	0.007	1.30 (1.07, 1.57)	0.009
	Model 2	1.0 (Ref)	1.35 (0.80, 2.28)	1.39 (0.80, 2.45)	2.86 (1.43, 5.72)	0.02	1.33 (1.05, 1.69)	0.02
sOB-R ¹	Model 1	1.0 (Ref)	0.95 (0.58, 1.54)	0.90 (0.55, 1.48)	0.83 (0.50, 1.37)	0.90	0.86 (0.71, 1.04)	0.12
	Model 2	1.0 (Ref)	0.94 (0.57, 1.54)	0.91 (0.54, 1.53)	0.85 (0.49, 1.49)	0.95	0.87 (0.71, 1.06)	0.17
Total adiponectin ²	Model 1	1.0 (Ref)	0.98 (0.61, 1.56)	0.82 (0.51, 1.32)	0.88 (0.54, 1.42)	0.83	0.90 (0.75, 1.07)	0.21
	Model 2	1.0 (Ref)	0.97 (0.60, 1.56)	0.91 (0.56, 1.49)	1.05 (0.63, 1.75)	0.95	0.95 (0.79, 1.15)	0.61
HMW adiponectin	Model 1	1.0 (Ref)	0.67 (0.42, 1.07)	0.62 (0.39, 1.01)	0.76 (0.47, 1.24)	0.22	0.98 (0.82, 1.16)	0.80
	Model 2	1.0 (Ref)	0.69 (0.42, 1.11)	0.72 (0.44, 1.19)	0.95 (0.57, 1.59)	0.31	1.06 (0.88, 1.27)	0.55
FLI ¹	Model 1	1.0 (Ref)	1.30 (0.79, 2.14)	1.30 (0.77, 2.20)	1.83 (1.05, 3.19)	0.21	1.11 (0.93, 1.33)	0.24
	Model 2	1.0 (Ref)	1.32 (0.78, 2.22)	1.35 (0.77, 2.39)	1.93 (0.98, 3.81)	0.30	1.10 (0.90, 1.34)	0.37
LAR ²	Model 1	1.0 (Ref)	0.94 (0.57, 1.53)	1.14 (0.69, 1.89)	1.86 (1.10, 3.16)	0.04	1.28 (1.07, 1.54)	0.008
	Model 2	1.0 (Ref)	0.88 (0.53, 1.47)	1.10 (0.63, 1.91)	1.76 (0.93, 3.33)	0.10	1.26 (1.01, 1.57)	0.04

BMI, body mass index; CI, confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; SD, standard deviation; sOB-R, leptin receptor.

Analysis *n* = 669, except ¹*n* = 644 and ²*n* = 668.

p-value for trend (two-sided) across quartiles is based on the median adipokine concentrations within quartiles, used as a continuous variable and analyzed using the Wald chi² statistic.

Model 1: adjusted for age, sex, fasting (and for leptin, sOB-R, FLI, LAR additionally for analysis lab).

Model 2: Model 1 + body mass index, diabetes, hypertension, stroke, transient ischemic attack, coronary heart disease.

³adipokines were standardized for these analyses, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine concentration.

of the relationship by inflammation, these markers were measured in peripheral blood and so may not have captured the degree of leptin-induced neuroinflammation in our participants. Macrovascular disease as another potential causal intermediate also did not contribute to the relationship though we measured only symptomatic macrovascular disease; thus subclinical atherosclerosis remains a potential mediator. Finally, cognitive reserve is a determinant both of leptin (Labad et al., 2012) and cognitive ability in older age (Opdebeeck et al., 2016), and an important potential confounder as a result. Here, we showed that the

associations of leptin with cognitive impairment was independent of education as a proxy of cognitive reserve thus corroborating potential causal effects.

Several previous studies found that (in those cases, inverse) associations of leptin with 5- to 8-year cognitive risk were limited to non-obese (BMI < 30 kg/m²) (Lieb et al., 2009) or non-overweight/obese individuals (BMI < 25 kg/m²) (Zeki Al Hazzouri et al., 2013). Due to this and the close relationship of leptin and adiponectin with BMI, we not only controlled for BMI but had additionally included interaction

Table 5
Adjusted odds and 95 % CI of cognitive impairment stratified by obesity status, and results for adipokine x BMI interaction terms across total sample.

	Obese subgroup (BMI ≥ 30 kg/m ²)		Non-obese subgroup (BMI < 30 kg/m ²)		<i>P</i> _{Interaction}
	OR (95 % CI) per 1 SD increment	<i>P</i> -value	OR (95 % CI) per 1 SD increment	<i>P</i> -value	
Leptin	0.87 (0.60, 1.26)	0.460	2.09 (1.44, 3.02)	< 0.001	0.002
sOB-R ¹	1.40 (0.76, 2.57)	0.284	0.78 (0.62, 0.99)	0.04	0.60
Total adiponectin ²	0.85 (0.49, 1.49)	0.570	0.96 (0.78, 1.17)	0.65	0.30
HMW adiponectin	1.17 (0.66, 2.06)	0.597	1.04 (0.86, 1.27)	0.67	0.30
FLI ¹	0.90 (0.68, 1.19)	0.466	1.54 (1.03, 2.30)	0.03	0.05
LAR ²	0.95 (0.67, 1.35)	0.761	1.72 (1.23, 2.41)	0.002	0.03

BMI, body mass index; CI, confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; sOB-R, leptin receptor.

Analysis *n* = 669. Of these, *n* = 142 (21.1 %) in the 'obese' group and *n* = 527 (78.8 %) in the 'non-obese' group.

¹Analysis *n* = 644. Of these, *n* = 137 (21.3 %) in the 'obese' group and *n* = 507 (78.7 %) in the 'non-obese' group.

²Analysis *n* = 668. Of these, 142 (21.3 %) in the 'obese' group and *n* = 526 (78.7 %) in the 'non-obese' group.

All analyses adjusted for age, sex, fasting (and for leptin, sOB-R, FLI, LAR additionally for analysis lab), body mass index, diabetes, hypertension, stroke, transient ischemic attack, coronary heart disease.

Adipokines were standardized, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine.

Interaction terms from analysis of (adipokine x body mass index) in separate logistic regression models of each adipokine and cognitive impairment in total sample.

terms and also stratified analyses by obesity status. Associations of leptin with cognitive impairment were restricted to non-obese individuals (BMI < 30 kg/m²), which further supports our interpretation of leptin as a direct promoter of cognitive impairment: leptin transport from circulation across the BBB is in fact compromised in obesity (Banks et al., 2006), which can account for obesity failing to induce satiety despite high circulating leptin (Banks et al., 2006) as well as for an attenuation of correlations of CSF with plasma leptin in obese relative to non-obese individuals (Johnston et al., 2014). We assume that in our sample participants in the non-obese group were exposed to a steadily increasing cognitive risk with higher circulating (and therefore brain) leptin concentration, whereas for obese individuals circulating leptin did not reflect leptin concentration in the brain, leading to null findings for that group. Alternatively, analyses of the obese group may have been limited by reduced statistical power due to low participant number, though on inspection of effect estimates combined with the statistical significance of the interaction terms, we deem this possibility unlikely. We urge readers to interpret the results from these subgroup analyses with caution nonetheless. Of note, BMI itself was unrelated to cognitive impairment in our analysis and in a previous investigation of a subsample of this cohort (Feinkohl et al., 2019) so that a recent report of leptin as a mediator of the relationship of higher BMI with lower cognitive function (Smith et al., 2019) was not supported by our data.

Irrespective of the role of leptin in the pathogenesis of cognitive impairment, we have demonstrated that it has potential as a biomarker of cognitive impairment and could be used for risk stratification of older adults. Measurement of total (bound and unbound) leptin appears to suffice for this purpose. Combined measurement with levels of its receptor or adiponectin did not add any valuable additional information over and above leptin.

4.1. Strengths and limitations

Our study has several strengths. We used a large sample of older adults who were all free of clinical dementia and defined cognitive impairment from performance on a large battery of cognitive tests using principal component analysis to account for measurement error. Yet, a number of limitations should be considered. Because we defined 'cognitive impairment' relative to the sample, we are unable to generalize our findings to clinically relevant cognitive outcomes such as dementia. Given that blood-based diagnostic biomarkers of dementia are lacked (Feinkohl et al., 2020; Hampel et al., 2010), further research is needed in that direction. We used a cross-sectional design and included only participants of the BioCog cohort who had complete data on adipokines and cognition. This will have introduced a selection bias; the analysis sample was unlikely representative of the full BioCog cohort. Because participants were scheduled for surgery within a few days of providing these data, our sample was presumably of a relatively low health status and unlikely representative of the general older population. At the same time, the surgical nature of the sample is also an asset to our study, because it allowed recruitment of patients who would otherwise not be enrolled into a study that required active travel to a study site. Leptin and sOB-R were measured in two different labs and although we controlled our analysis for this factor, residual confounding by analysis lab is a possibility. An influence by unmeasured variables too cannot be ruled out. We ran a large number of statistical analyses thus increasing the risk of Type I error.

4.2. Future directions

Further research is needed to tease out the beneficial versus detrimental effects of leptin on brain function. Separate investigation of obese and non-obese groups, or, in sufficiently large samples, of underweight, normal weight, overweight and obese groups is advisable. Long-term prospective studies could further account for reverse causality of prodromal dementia impacting on adipose tissue mass and,

consequently, adipokine levels, which may also in part drive reports of reduced cognitive risk in high-leptin individuals in older age. Here, we used a surgical patient sample. Whether the association of higher leptin concentration with higher odds of cognitive impairment before surgery extends to an increased risk of post-operative cognitive dysfunction (POCD) remain to be explored.

5. Conclusion

In one of the largest studies on adipokine concentration and cognition performed to date, higher plasma leptin concentrations were associated with increased odds of cognitive impairment and independently of sociodemographics, vascular risk factors, macrovascular disease, inflammation, as well as BMI. Underlying mechanisms warrant further assessment.

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CRediT authorship contribution statement

Insa Feinkohl: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Jürgen Janke:** Investigation, Methodology, Writing - review & editing. **Arjen J.C. Slooter:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Georg Winterer:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Claudia Spies:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Tobias Pischon:** Resources, Conceptualization, Funding acquisition, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

GW is coordinator of the BioCog consortium and is chief executive of the company Pharmaimage Biomarker Solutions GmbH (<http://www.pi-pharmaimage.com>). Among other academic and private partners, the company is a partner of the BioCog study. CD, AS and TP are project leaders in BioCog. IF, JJ, AS, CS and TP declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2020.104783>.

References

- Adya, R., Tan, B.K., Randevara, H.S., 2015. Differential effects of leptin and adiponectin in endothelial angiogenesis. *J. Diabetes Res.* 2015, 648239. <https://doi.org/10.1155/2015/648239>.
- Albala, C., Angel, B., Lera, L., Sanchez, H., Marquez, C., Fuentes, P., 2016. Low leptin availability as a risk factor for dementia in Chilean older people. *Dement. Geriatr. Cogn. Dis. Extra* 6 (2), 295–302. <https://doi.org/10.1159/000447447>.
- Aleksandrova, K., Mozaffarian, D., Pischon, T., 2018. Addressing the perfect storm: biomarkers in obesity and pathophysiology of cardiometabolic risk. *Clin. Chem.* 64 (1), 142–153. <https://doi.org/10.1373/clinchem.2017.275172>.
- Arnoldussen, I.A.C., Sundh, V., Backman, K., Kern, S., Ostling, S., Blennow, K., et al., 2018. A 10-year follow-up of adiposity and dementia in Swedish adults aged 70 years and older. *J. Alzheimers Dis.* 63 (4), 1325–1335. <https://doi.org/10.3233/jad-180099>.
- Aso, Y., Yamamoto, R., Wakabayashi, S., Uchida, T., Takayanagi, K., Takebayashi, K., et al., 2006. Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery

- disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. *Diabetes* 55 (7), 1954–1960. <https://doi.org/10.2337/db05-1525>.
- Banks, W.A., Farr, S.A., Morley, J.E., 2006. The effects of high fat diets on the blood-brain barrier transport of leptin: failure or adaptation? *Physiol. Behav.* 88 (3), 244–248. <https://doi.org/10.1016/j.physbeh.2006.05.037>.
- Bednarska-Makaruk, M., Graban, A., Wisniewska, A., Lojkowska, W., Bochynska, A., Gugala-Iwaniuk, M., et al., 2017. Association of adiponectin, leptin and resistin with inflammatory markers and obesity in dementia. *Biogerontology* 18 (4), 561–580. <https://doi.org/10.1007/s10522-017-9701-0>.
- Bloemer, J., Pinky, P.D., Govindarajulu, M., Hong, H., Judd, R., Amin, R.H., et al., 2018. Role of adiponectin in central nervous system disorders. *Neural Plast.* 2018, 4593530. <https://doi.org/10.1155/2018/4593530>.
- Bove, R.M., Brick, D.J., Healy, B.C., Mancuso, S.M., Gerweck, A.V., Bredella, M.A., et al., 2013. Metabolic and endocrine correlates of cognitive function in healthy young women. *Obesity (Silver Spring)* 21 (7), 1343–1349. <https://doi.org/10.1002/oby.20212>.
- Buck, C.O., Eliot, M.N., Kelsey, K.T., Chen, A., Kalkward, H., Lamphear, B.P., Braun, J.M., 2019. Neonatal adipocytokines and longitudinal patterns of childhood growth. *Obesity (Silver Spring)* 27 (8), 1323–1330.
- Cezaretto, A., Suemoto, C.K., Bensenor, I., Lotufo, P.A., de Almeida-Pittito, B., Ferreira, S.R.G., 2018. Association of adiponectin with cognitive function precedes overt diabetes in the Brazilian Longitudinal Study of Adult Health: ELISA. *Diabetol. Metab. Syndr.* 10, 54. <https://doi.org/10.1186/s13098-018-0354-1>.
- Feinkohl, I., Janke, J., Hadzidiakos, D., Slioter, A., Winterer, G., Spies, C., Pischon, T., 2019. Associations of the metabolic syndrome and its components with cognitive impairment in older adults. *BMC Geriatr.* 19 (1), 77. <https://doi.org/10.1186/s12877-019-1073-7>.
- Feinkohl, I., Schipke, C.G., Kruppa, J., Menne, F., Winterer, G., Pischon, T., Peters, O., 2020. Plasma amyloid concentration in Alzheimer's disease: performance of a high-throughput amyloid assay in distinguishing Alzheimer's disease cases from controls. *J. Alzheimer Dis.* 74 (4), 1285–1294.
- Fewlass, D.C., Noboa, K., Pi-Sunyer, F.X., Johnston, J.M., Yan, S.D., Tezapsidis, N., 2004. Obesity-related leptin regulates Alzheimer's abeta. *FASEB J.* 18 (15), 1870–1878. <https://doi.org/10.1096/fj.04-2572com>.
- Finucane, F.M., Luan, J., Wareham, N.J., Sharp, S.J., O'Rahilly, S., Balkau, B., et al., 2009. Correlation of the leptin:adiponectin ratio with measures of insulin resistance in non-diabetic individuals. *Diabetologia* 52 (11), 2345–2349. <https://doi.org/10.1007/s00125-009-1508-3>.
- Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198.
- Forný-Germano, L., De Felice, F.G., Vieira, M., 2018. The role of leptin and adiponectin in obesity-associated cognitive decline and Alzheimer's disease. *Front. Neurosci.* 12, 1027. <https://doi.org/10.3389/fnins.2018.01027>.
- Gilbert, T., Roche, S., Blond, E., Bar, J.Y., Drai, J., Cuerq, C., et al., 2018. Association between peripheral leptin and adiponectin levels and cognitive decline in patients with neurocognitive disorders ≥ 65 years. *J. Alzheimers Dis.* 66 (3), 1255–1264. <https://doi.org/10.3233/jad-180533>.
- Gorska-Ciebiada, M., Saryusz-Wolska, M., Borkowska, A., Ciebiada, M., Loba, J., 2016. Adiponectin, leptin and IL-1 beta in elderly diabetic patients with mild cognitive impairment. *Metab. Brain Dis.* 31 (2), 257–266. <https://doi.org/10.1007/s10111-015-9739-0>.
- Grassmann, S., Wirsching, J., Eichmann, F., Aleksandrova, K., 2017. Association between peripheral adipokines and inflammation markers: a systematic review and meta-analysis. *Obesity Silver Spring (Silver Spring)* 25 (10), 1776–1785. <https://doi.org/10.1002/oby.21945>.
- Gruzdeva, O., Borodkina, D., Uchasova, E., Dyleva, Y., Barbarash, O., 2019. Leptin resistance: underlying mechanisms and diagnosis. *Diabetes Metab. Syndr. Obes.* 12, 191–198. <https://doi.org/10.2147/dms.o.s182406>.
- Gunstad, J., Spitznagel, M.B., Keary, T.A., Glickman, E., Alexander, T., Karrer, J., et al., 2008. Serum leptin levels are associated with cognitive function in older adults. *Brain Res.* 1230, 233–236. <https://doi.org/10.1016/j.brainres.2008.07.045>.
- Gustafson, D., R., Backman, K., Lissner, L., Carlsson, L., Waern, M., Ostling, S., et al., 2012. Leptin and dementia over 32 years: the prospective population study of women. *Alzheimers Dement.* 8 (4), 272–277. <https://doi.org/10.1016/j.jalz.2011.05.2411>.
- Gustafson, D.R., Mielke, M.M., Keating, S.A., Holman, S., Minkoff, H., Crystal, H.A., 2015. Leptin, adiponectin and cognition in middle-aged HIV-infected and uninfected women. The Brooklyn women's interagency HIV study. *J. Gerontol. Geriatr. Res.* 4 (5). <https://doi.org/10.4172/2167-7182.1000240>.
- Hampel, H., Shen, Y., Walsh, D.M., Aisen, P., Shaw, L.M., Zetterberg, H., et al., 2010. Biological markers of amyloid beta-related mechanisms in Alzheimer's disease. *Exp. Neurol.* 223 (2), 334–346. <https://doi.org/10.1016/j.expneurol.2009.09.024>.
- Herrick, J.E., Panza, G.S., Golli, J.M., 2016. Leptin, leptin soluble receptor, and the free leptin index following a diet and physical activity lifestyle intervention in obese males and females. *J. Obes.* 2016, 8375828. <https://doi.org/10.1155/2016/8375828>.
- Holden, K.F., Lindquist, K., Tykavsky, F.A., Rosano, C., Harris, T.B., Yaffe, K., 2009. Serum leptin level and cognition in the elderly: findings from the Health ABC Study. *Neurobiol. Aging* 30 (9), 1483–1489. <https://doi.org/10.1016/j.neurobiolaging.2007.11.024>.
- Johnston, J.M., Hu, W.T., Fardo, D.W., Greco, S.J., Perry, G., Montine, T.J., et al., 2014. Low plasma leptin in cognitively impaired ADNI subjects: gender differences and diagnostic and therapeutic potential. *Curr. Alzheimer Res.* 11 (2), 165–174.
- Khemka, V., K., Bagchi, D., Bandyopadhyay, K., Bir, A., Chattopadhyay, M., Biswas, A., et al., 2014. Altered serum levels of adipokines and insulin in probable Alzheimer's disease. *J. Alzheimers Dis.* 41 (2), 525–533. <https://doi.org/10.3233/jad-140006>.
- Kitagawa, K., Miwa, K., Okazaki, S., Sakaguchi, M., Mochizuki, H., 2016. Serum high-molecular-weight adiponectin level and incident dementia in patients with vascular risk factors. *Eur. J. Neurol.* 23 (3), 641–647. <https://doi.org/10.1111/ene.12915>.
- Labad, J., Price, J.F., Strachan, M.W., Deary, I.J., Seckl, J.R., Sattar, N., Reynolds, R.M., 2012. Serum leptin and cognitive function in people with type 2 diabetes. *Neurobiol. Aging* 33 (12), 2938–2941. <https://doi.org/10.1016/j.neurobiolaging.2012.02.026>.
- Letra, L., Santana, I., Seica, R., 2014. Obesity as a risk factor for Alzheimer's disease: the role of adipocytokines. *Metab. Brain Dis.* 29 (3), 563–568. <https://doi.org/10.1007/s11011-014-9501-z>.
- Li, N., Arbuckle, T.E., G., M., Lanphear, B.P., Boivin, M., Chen, A., et al., 2019. Associations of cord blood leptin and adiponectin with children's cognitive abilities. *Psychoneuroendocrinology* 99, 257–264.
- Lieb, W., Beiser, A.S., Vasan, R.S., Tan, Z.S., Au, R., Harris, T.B., et al., 2009. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. *Jama* 302 (23), 2565–2572. <https://doi.org/10.1001/jama.2009.1836>.
- Littlejohns, T.J., Kos, K., Henley, W.E., Cherubini, A., Ferrucci, L., Lang, I.A., et al., 2015. Serum leptin and risk of cognitive decline in elderly Italians. *J. Alzheimer Dis.* 44, 1231–1239.
- Lopez-Jaramillo, P., Gomez-Arbelaiz, D., Lopez-Lopez, J., Lopez-Lopez, C., Martinez-Ortega, J., Gomez-Rodriguez, A., Triana-Cubillos, S., 2014. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. *Horm. Mol. Biol. Clin. Investig.* 18 (1), 37–45. <https://doi.org/10.1515/hmbci-2013-0053>.
- McGregor, G., Harvey, J., 2018. Food for thought: leptin regulation of hippocampal function and its role in Alzheimer's disease. *Neuropharmacology* 136 (Pt B), 298–306. <https://doi.org/10.1016/j.neuropharm.2017.09.038>.
- McGuire, M.J., Ishii, M., 2016. Leptin dysfunction and Alzheimer's disease: evidence from cellular, animal, and human studies. *Cell. Mol. Neurobiol.* 36 (2), 203–217. <https://doi.org/10.1007/s10571-015-0282-7>.
- NCD Risk Factor Collaboration, 2016. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* 387, 1377–1396.
- Nimptsch, K., Konigorski, S., Pischon, T., 2019. Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine. *Metabolism*. <https://doi.org/10.1016/j.metabol.2018.12.006>.
- Oania, R., McEvoy, L.K., 2015. Plasma leptin levels are not predictive of dementia in patients with mild cognitive impairment. *Age Ageing* 44 (1), 53–58. <https://doi.org/10.1093/ageing/afu160>.
- Opdebeeck, C., Martyr, A., Clare, L., 2016. Cognitive reserve and cognitive function in healthy older people: a meta-analysis. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 23 (1), 40–60. <https://doi.org/10.1080/13825585.2015.1041450>.
- Park, J.T., Yoo, T.H., Kim, J.K., Oh, H.J., Kim, S.J., Yoo, D.E., et al., 2013. Leptin/adiponectin ratio is an independent predictor of mortality in nondiabetic peritoneal dialysis patients. *Perit. Dial. Int.* 33 (1), 67–74. <https://doi.org/10.3747/pdi.2011.00066>.
- Pedditizi, E., Peters, R., Beckett, N., 2016. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. *Age Ageing* 45 (1), 14–21. <https://doi.org/10.1093/ageing/afv151>.
- Penke, L., Deary, I.J., 2010. Some guidelines for structural equation modelling in cognitive neuroscience: the case of Charlton et al.'s study on white matter integrity and cognitive ageing. *Neurobiol. Aging* 31, 1656–1660.
- Rajagopalan, P., Toga, A.W., Jack, C.R., Weiner, M.W., Thompson, P.M., 2013. Fat-mass-related hormone, plasma leptin, predicts brain volumes in the elderly. *Neuroreport* 24 (2), 58–62. <https://doi.org/10.1097/WNR.0b013e32835c5254>.
- Sang, Y.M., Wang, L.J., Mao, H.X., Lou, X.Y., Zhu, Y.J., 2018. The association of short-term memory and cognitive impairment with ghrelin, leptin, and cortisol levels in non-diabetic and diabetic elderly individuals. *Acta Diabetol.* <https://doi.org/10.1007/s00592-018-1111-5>.
- Sanz, B., Arrieta, H., Hervas, G., Rezola-Pardo, C., Ruiz-Litago, F., Iturburu, M., et al., 2019. Serum adiponectin is associated with body composition and cognitive and psychological status in older adults living in long-term nursing homes. *Exp. Gerontol.* 121, 1–9.
- Smith, P.J., Mabe, S., Sherwood, A., Babyak, M.A., Dorauswamy, P.M., Welsh-Bohmer, K.A., et al., 2019. Association between insulin resistance, plasma leptin and neurocognition in vascular cognitive impairment. *J. Alzheimer Dis.* 71 (3), 921–929.
- Spearman, C., 1904. 'General intelligence', objectively determined and measured. *Am. J. Psychol.* 15, 201–292.
- Stern, J.H., Rutkowski, J.M., Scherer, P.E., 2016. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. *Cell Metab.* 23 (5), 770–784. <https://doi.org/10.1016/j.cmet.2016.04.011>.
- Teixeira, A.L., Diniz, B.S., Campos, A.C., Miranda, A.S., Rocha, N.P., Talib, L.L., et al., 2013. Decreased levels of circulating adiponectin in mild cognitive impairment and Alzheimer's disease. *Neuromolecular Med.* 15, 115–121.
- Van den Berg, E., Kloppenborg, R.P., Kessels, R.P.C., Kappelle, L.J., Biessels, G.J., 2009. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. *Biochimica et Biophysica Acta* 1792, 470–481.
- Warren, M.W., Hynan, L.S., Weiner, M.F., 2012. Lipids and adipokines as risk factors for Alzheimer's disease. *J. Alzheimers Dis.* 29 (1), 151–157. <https://doi.org/10.3233/jad-2012-111385>.
- Wennberg, A.M., Gustafson, D., Hagen, C.E., Roberts, R.O., Knopman, D., Jack, C., et al., 2016. Serum adiponectin levels, neuroimaging, and cognition in the mayo clinic study of aging. *J. Alzheimers Dis.* 53 (2), 573–581. <https://doi.org/10.3233/jad-151201>.

- Winterer, G., Androsova, G., Bender, O., Boraschi, D., Borchers, F., Dschietzig, T.B., et al., 2018. Personalized risk prediction of postoperative cognitive impairment - rationale for the EU-funded BioCog project. *Eur. Psychiatry*. <https://doi.org/10.1016/j.eurpsy.2017.10.004>.
- Yin, H., Tian, S., Huang, R., Cai, R., Guo, D., Lin, H., et al., 2018. Low plasma leptin and high soluble leptin receptor levels are associated with mild cognitive impairment in type 2 diabetic patients. *Front. Aging Neurosci.* 10, 132. <https://doi.org/10.3389/fnagi.2018.00132>.
- Zeki Al Hazzouri, A., Stone, K.L., Haan, M.N., Yaffe, K., 2013. Leptin, mild cognitive impairment, and dementia among elderly women. *J. Gerontol. A Biol. Sci. Med. Sci.* 68 (2), 175–180. <https://doi.org/10.1093/gerona/gls155>.