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

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\textbf{ABSTRACT}

\textbf{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.

\textbf{Methods:} Cross-sectional analysis of baseline data from 669 participants aged \textgreek{ge} 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.

\textbf{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; \textit{p} = 0.02; OR per 1 SD higher LAR, 1.26; 95 % CI 1.01, 1.57; \textit{p} = 0.04). Sensitivity analyses determined that these findings were driven by the non-obese group (BMI < 30 kg/m\textsuperscript{2}), whereas leptin and LAR were not associated with cognitive impairment in the obese group (BMI \textgreek{ge} 30 kg/m\textsuperscript{2}). Soluble leptin receptor, leptin/soluble leptin receptor ratio, total adiponectin and high-molecular weight adiponectin concentrations were each not associated with impairment.

\textbf{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 (Forny-Germano et al., 2018), and may influence cerebrovascular function and neuroinflammation (Adya et al., 2015; Forny-Germano et al., 2018). Effects of leptin and adiponectin on the pathogenesis of cognitive impairment could thus be
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; Ceza retto 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 Gorksia-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 (Ceza retto 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 11.03 % (Lab 1) and 2.63 % (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 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 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 chi² 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, multivariable 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 (BMI < 30 versus ≥30 kg/m²), and across the total sample tested for effect modification by including interaction terms (adipokine x 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/m² 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 (BMI ≥30 kg/m²) and non-obese participants (BMI < 30 kg/m²; 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 x 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 S5).
Precise range is not shown due to rounding. N = 668. P-value for analyses of variance (ANOVA) or chi² tests.

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

<table>
<thead>
<tr>
<th>Total adiponectin</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>174</td>
<td>167</td>
<td>168</td>
<td>159</td>
</tr>
<tr>
<td>Adiponectin conc.</td>
<td>2.7 – 9.0</td>
<td>9.1 – 12.7</td>
<td>12.8 – 18.0</td>
<td>18.0 – 61.1</td>
</tr>
<tr>
<td>Age, years</td>
<td>71.2</td>
<td>72.4</td>
<td>72.2</td>
<td>72.8</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>70.1</td>
<td>60.5</td>
<td>50.5</td>
<td>42.7</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.1</td>
<td>27.6</td>
<td>27.2</td>
<td>25.2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>68.4</td>
<td>64.1</td>
<td>59.5</td>
<td>53.5</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>28.7</td>
<td>28.1</td>
<td>13.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>25.3</td>
<td>12.6</td>
<td>17.9</td>
<td>17.0</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>4.0</td>
<td>5.6</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Transient ischemic attack, %</td>
<td>4.0</td>
<td>1.8</td>
<td>4.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Cognitive impairment, %</td>
<td>23.0</td>
<td>22.1</td>
<td>24.3</td>
<td>40.2</td>
</tr>
</tbody>
</table>

Precise range is not shown due to rounding. N = 668. P-value for 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 (Pedditizi 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 (Cezairet 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) (Fewliss 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...
HMW, high molecular weight; sOB-R, soluble leptin receptor.

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

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

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Body mass index</th>
<th>Total adiponectin</th>
<th>HMW adiponectin</th>
<th>sOB-R1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>−0.03 (0.44)</td>
<td>0.51 (&lt; 0.001)</td>
<td>−0.07 (0.06)</td>
<td>−0.02 (0.60)</td>
<td>−0.50 (&lt; 0.001)</td>
</tr>
<tr>
<td>sOB-R2</td>
<td>0.09 (0.02)</td>
<td>−0.43 (&lt; 0.001)</td>
<td>0.23 (&lt; 0.001)</td>
<td>0.28 (&lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>HMW adiponectin</td>
<td>0.13 (0.001)</td>
<td>−0.24 (&lt; 0.001)</td>
<td>0.77 (&lt; 0.001)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Total adiponectin2</td>
<td>0.09 (0.02)</td>
<td>−0.24 (&lt; 0.001)</td>
<td>−</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>

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 1n = 644 and 2n = 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.

<table>
<thead>
<tr>
<th>h</th>
<th>Quartiles of plasma concentration</th>
<th>Continuous2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95 % CI) per 1 SD increment</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leptin</td>
<td>sOB-R1</td>
<td>HMW adiponectin</td>
</tr>
<tr>
<td>Model 1</td>
<td>1</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.34 (0.81, 2.20)</td>
<td>1.35 (0.80, 2.28)</td>
<td>0.95 (0.58, 1.54)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.30 (0.77, 2.20)</td>
<td>1.39 (0.80, 2.45)</td>
<td>0.90 (0.55, 1.48)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.58 (1.45, 4.58)</td>
<td>2.86 (1.43, 5.72)</td>
<td>0.83 (0.50, 1.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.007</td>
<td>0.02</td>
<td>0.90</td>
</tr>
<tr>
<td>Model 2</td>
<td>1</td>
<td>1.33 (1.05, 1.69)</td>
<td>0.86 (0.71, 1.04)</td>
<td>0.87 (0.71, 1.06)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.39 (1.03, 1.91)</td>
<td>0.80</td>
<td>0.90 (0.75, 1.07)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.41 (1.01, 1.96)</td>
<td>0.55</td>
<td>1.06 (0.88, 1.27)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.56 (1.13, 2.15)</td>
<td>1.10 (0.90, 1.34)</td>
<td>1.11 (0.93, 1.33)</td>
</tr>
</tbody>
</table>

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 1n = 644 and 2n = 668; analysis of total adiponectin and sOB-R, n = 643.

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.

<table>
<thead>
<tr>
<th>Obese subgroup (BMI ≥ 30 kg/m2)</th>
<th>Non-obese subgroup (BMI &lt; 30 kg/m2)</th>
<th>Pinteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>0.87 (0.60, 1.26)</td>
<td>0.460</td>
</tr>
<tr>
<td>sOB-R1</td>
<td>1.40 (0.76, 2.57)</td>
<td>0.284</td>
</tr>
<tr>
<td>Total adiponectin2</td>
<td>0.85 (0.49, 1.49)</td>
<td>0.570</td>
</tr>
<tr>
<td>HMW adiponectin</td>
<td>1.17 (0.66, 2.06)</td>
<td>0.597</td>
</tr>
<tr>
<td>FLI</td>
<td>0.90 (0.68, 1.19)</td>
<td>0.466</td>
</tr>
<tr>
<td>LAR2</td>
<td>0.95 (0.67, 1.35)</td>
<td>0.761</td>
</tr>
</tbody>
</table>

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, 1n = 142 (21.3 %) in the ‘obese’ group and n = 526 (78.7 %) in the ‘non-obese’ group. All analyses adjusted for 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 lacking (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 & 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 Pharmimage 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.

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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

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disease using a novel enzyme-linked immunosorbent assay to detect HMW adipokine.


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