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The Association of Plasma Leptin, Soluble Leptin Receptor and Total and High-Molecular Weight Adiponectin With the Risk of Perioperative Neurocognitive Disorders

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ABSTRACT

Background: *Perioperative neurocognitive disorders (NCD) are poorly characterized in terms of their risk factor profiles. Leptin and adiponectin are adipose-tissue-derived hormones with a role in inflammation and atherosclerosis whose function in perioperative NCD is unclear. Here, we used a cohort of older adults to examine the association of preoperative plasma concentrations of these biomarkers with the risk of perioperative NCD.* ***Methods:*** *Prospective analysis of 768 participants aged ≥ 65 years of the BioCog study. Blood was collected before surgery for measurement of plasma total and high-molecular-weight (hmw) adiponectin, leptin, and soluble leptin receptor (sOB-R). The free leptin index (FLI, leptin:sOB-R) was calculated. Postoperative delirium (POD) was assessed twice daily until postoperative day 7/discharge. Five hundred twenty-six patients (68.5%) returned for 3-month follow-up and provided data on postoperative cognitive dysfunction (POCD). POCD was defined as a decline on six neuropsychological tests that exceeded that of a nonsurgical control group. Logistic regression analyses examined the associations of each exposure with POD and POCD risk, in separate models adjusted for age, sex, fasting, surgery*

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type, and body mass index (BMI). ***Results:*** *Of 768 patients, 152 (19.8%) developed POD. Of 526 attendants of the follow-up, 54 (10.3%) had developed POCD. Leptin, sOB-R, and total and hmw adiponectin were each not associated with POD. For POCD, we observed reduced risk in patients in FLI quartile 4 compared with quartile 1 (odds ratio, 0.26; 95% CI 0.08, 0.89). Sensitivity analyses for the outcome POD revealed statistically significant interaction terms of sOB-R and total adiponectin with obesity (BMI≥30kg/m^2 versus BMI<30kg/m^2). For the outcome POCD, a higher sOB-R was associated with an increased risk in the obese subgroup (odds ratio, 4.00; 95% CI 1.01, 15.86).* ***Conclusions:*** *We did not find consistent evidence for the role of leptin, its receptor, and total and hmw adiponectin in POD and POCD risk. Future research should be used to support or refute our findings and to fully characterize any differences in the associations of these hormones with POD/POCD between obese and nonobese individuals.* (Am J Geriatr Psychiatry 2024; 32:1119−1129)

Highlights

- **What is the primary question addressed by this study?**
  In the largest study on the topic to date, we examined preoperative adipokine concentrations in circulation and the risks of postoperative delirium (POD) and cognitive dysfunction (POCD).
- **What is the main finding of this study?**
  Lower free leptin was associated with an increased risk of POD during the hospital stay, although due to a large number of statistical analyses, we cannot rule out an influence of type I error.
- **What is the meaning of the finding?**
  We present preliminary evidence for low leptin as a potential risk factor for POD.

INTRODUCTION

Exposure to surgery often comes with a substantial risk of developing perioperative neurocognitive disorders (NCD), particularly in older age. Over 20% of surgical patients can be affected by postoperative delirium (POD) during the first few days after surgery.[1] POD is characterized by acute onset of symptoms such as apathy or confusion. Postoperative cognitive dysfunction (POCD) may develop after POD, but may also occur independently.[2] Neuropsychological impairment in cognitive domains such as memory or processing speed with new onset after surgery is characteristic of POCD, which is typically transient but can persist for months to years. For instance, 10%−25% of patients have POCD at 3 to 6-month follow-up.[3] POD and POCD both affect the quality of life of patients and their caregivers[4−6] and may be associated with health hazards including increased dementia risk[7,8] and premature mortality.[9,10] A fuller understanding of the conditions including their preoperative risk factor profiles, which could deliver insight into their etiologies[1,11] and could aid risk stratification of patients, is needed.

Following a surge in interest in perioperative NCD,[12,13] we now have evidence to suggest that parameters indicative of systemic metabolic dysfunction may be a risk factor.[14,15] Several studies have suggested that obesity for instance may be linked to perioperative NCD, and leptin and adiponectin are strong candidate mediators of this relationship. They are adipokines secreted by adipocytes and primarily function to sustain metabolic homeostasis.[16−19] Leptin − which circulates at levels dependent on adipose tissue mass[20] − is a promotor of atherosclerosis, endothelial dysfunction, and inflammation; whereas adiponectin − circulating inversely to adipose tissue mass[21] − has positive effects on vascular health,

inflammation, and insulin sensitivity.[18,19] These effects appear to extend to the brain, where leptin and adiponectin (having crossed the blood-brain-barrier[22,23]) influence cerebrovascular function and neuroinflammatory processes.[23,24] For leptin in particular, in addition to its detrimental effects, beneficial effects on neurological function have been described.[25] The evidence from population-based cohorts examining the association of leptin and adiponectin concentrations with cognitive function has been mixed.[26–40] In the context of surgery, we deem it plausible that patients with raised leptin or reduced adiponectin concentrations are vulnerable to the effects of surgery on the brain and are at increased risk of perioperative NCD as a result. To date, only two studies have been published in this context, but they have been limited by small sample sizes and a lack of consideration of potential confounding factors such as body weight-related parameters.[41,42] An analysis in a large, well-characterized surgical cohort is needed.

We have recently shown in a cross-sectional analysis of a subset of patients participating in the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study that a higher preoperative leptin concentration was associated with a reduced cognitive function preoperatively.[43] Nonobese participants (body mass index, BMI<30kg/m^2) were identified as drivers of that association. For adiponectin, no association was found.[43] Here, in a prospective analysis of the cohort, we aimed to quantify the associations of preoperative concentrations of leptin, its soluble receptor, and total and high-molecular-weight (hmw) adiponectin with the risk of POD during the first seven postoperative days and the risk of POCD at 3-month follow-up. Sensitivity analyses determined any potential differences in obese versus nonobese patients.

MATERIALS AND METHODS

Study Design

Prospective analysis of data from the BioCog cohort.[44] 933 surgical patients had been recruited in study centers in Berlin, Germany, and Utrecht, the Netherlands. Inclusion criteria included, among others: ≥ 65 years old, scheduled for elective surgery, and Mini Mental State Examination, MMSE ≥ 24.[45] Patients were followed up after surgery during the hospital stay and were reinvited after 3 months.

Clinical Assessment

At preoperative assessment, sociodemographic data and medical history on hypertension, diabetes, coronary heart disease (CHD), transient ischemic attack (TIA), and stroke were collected. A combination of self-report and clinical records was used for this purpose. Height and weight were measured to calculate BMI. Obesity was defined as a BMI ≥ 30 kg/m^2; underweight was defined as a BMI<18.5kg/m^2.[46]

Adipokine Measurement

Blood was collected on the day of surgery in a supine position before incision. Plasma was stored at a centralized biobank for later measurement of concentrations of leptin, soluble leptin receptor (sOB-R), total adiponectin, and hmw adiponectin using commercial ELISA kits.[43] Leptin and sOB-R were measured at two different laboratories, but lab allocation was not related to exposure, outcome, study site, or any potential confounding factor. Interassay coefficients of variation (CV) and intra-assay CV were less than 15% for each biomarker. Measurements that were below or above the limits of quantification were set as the respective lower or upper limit of quantification (leptin, n = 28; sOB-R,n = 6; hmw adiponectin, n = 1 among our analysis sample). We additionally calculated the leptin-adiponectin ratio (LAR) as an exposure to reflect their antagonistic effects.[47] The leptin/sOB-R ratio (free leptin index, FLI) was derived as an index of free, unbound leptin in circulation, which functions as a measure of leptin resistance.[48] We thus had a total of six exposure variables.

Postoperative Delirium (POD)

POD was assessed twice daily between the day of surgery and postoperative day 7 or hospital discharge, whichever came first, by trained study physicians/medical students, and in accordance with DSM-5 based on these criteria: 1) greater than or equal to 2 cumulative points on the Nursing Delirium Screening Scale (Nu-DESC); 2) positive Confusion Assessment Method (CAM) score; 3) positive CAM for the Intensive Care Unit (CAM-ICU); 4) patient

chart includes descriptions of delirium (e.g., confused, agitated, antipsychotics given for POD).

Postoperative Cognitive Dysfunction (POCD)

Patients performed six age-sensitive neuropsychological tests during the days before surgery. Four were from the CANTAB® battery (Verbal Recognition Memory; Paired Associates Learning; Spatial Span; Simple Reaction Time); two were conventional (Trail-Making Test; Grooved Pegboard). POCD was defined using ISPOCD criteria. Specifically, patients' change in scores was compared with the change in scores of a nonsurgical control group of over 65-year-olds.[49]

Datasets for Analysis and Handling of Missing Data

Due to late introduction of blood collection into the study protocol, of the initial N = 933 cohort, 768 patients had complete data on leptin, hmw adiponectin, and POD and served as an analysis sample for the outcome POD (our prior cross-sectional analysis was limited to 669 patients because it had required complete data on all preoperative cognitive tests[43]). Analyses revealed that the n = 768 analysis sample did not differ on sociodemographics or clinical parameters from those n = 165 who could not be included (data not shown). Among our n = 768 analysis sample, data on total adiponectin were missing for n = 1 and on sOB-R for n = 28. For patients with missing data on diabetes, hypertension, CHD, TIA, or stroke, the respective condition was assumed to be absent (of n = 768, diabetes, n = 12, 1.6%; hypertension, n = 13, 1.7%; CHD, n = 18, 2.3%; TIA, n = 21, 2.7%; stroke = 17, 2.2%). Missing data on anesthesia duration (n = 12, 1.6%) were replaced by median duration (204 minutes), and surgical site (n = 17, 2.2%), by the most common site (peripheral surgery). Of the 768 patients in the analysis sample, 526 (68.5%) returned 3 months later, had complete cognitive data, and were thus included in the analysis of the outcome POCD.

Statistical Analysis

Among the full N = 768 analysis sample, patients were divided into quartiles based on the distribution of each adipokine. Next, sociodemographic and clinical characteristics were compared across quartiles of biomarker exposures using analyses of variance (ANOVA) for continuous variables and chi^2 tests for categorical variables. Similarly, to our previous analysis,[43] we examined the associations among the biomarkers and of each with age and BMI were determined using Spearman rank correlation analyses.

Multiple logistic regression determined the association of quartiles 2, 3 and 4 of each biomarker (versus quartile 1) and each one standard deviation higher biomarker concentration with the risk of POD and POCD respectively. Additionally, for the quartile analyses, a trend across quartiles was assessed using the Wald chi^2 statistic. Model 1 adjusted for the potential confounding factors age, sex, surgery type, fasting status, and (for analyses of leptin, sOB-R, LAR, FLI) for analysis lab. In model 2, we additionally adjusted for BMI as another strong potential confounder. In model 3, we added the potential intermediaries diabetes, hypertension, CHD, TIA, and stroke. In model 4, anesthesia duration as another potential intermediary was additionally controlled for. To test for nonlinearity we added quadratic terms to the respective model 4. In post hoc analyses, we repeated any statistically significant models 4, 1) with the exclusion of underweight patients, and 2) for the outcome POCD with adjustment for POD.

In sensitivity analyses, we repeated model 2 and model 4 stratified by obesity status (BMI<30 versus $\geq$30kg/m^2). Across the total sample, we tested for effect modification by including interaction terms (exposure x BMI).

In a post hoc analysis of achieved power (two-tailed), we determined that we had a 88.7% power to detect associations between a biomarker and POD risk among our N = 768 study sample, assuming that a standard deviation higher biomarker concentration was associated with a 25% POD risk whereas a mean biomarker concentration was associated with a 20% risk.

RESULTS

Sample Characteristics

Patients in the full N = 768 analysis sample had a mean age of 72 years (see Supplemental Table S1). Reasons for loss to follow-up by 3 months included death and a lack of interest. Those n = 526 patients who returned 3 months later and had complete cognitive data (a prerequisite for inclusion in the analysis of POCD) were more likely to be male, to be free of

diabetes and free of hypertension, had a shorter anesthesia duration and higher preoperative MMSE scores as compared with those n = 242 patients who did not return for follow-up and/or had incomplete cognitive data (see Supplemental Table S1).

Correlations Among Preoperative Leptin and Adiponectin Biomarkers and Their Correlations With Covariates

As previously reported based on a smaller sample size,[43] leptin was positively correlated with BMI; whereas sOB-R, total adiponectin, and hmw adiponectin were inversely correlated with BMI (see Supplemental Table S2). Leptin was inversely related to sOB-R and weakly inversely related to total adiponectin and hmw adiponectin. There was a positive correlation between total adiponectin and hmw adiponectin. For covariate structures according to quartiles, see Supplemental Table S3–S6.

POD and POCD

Of 768 patients, 152 (19.8%) developed POD. Of 526 attendants of the 3-month follow-up, 54 (10.3%) had POCD. POD and POCD were not associated with one another ($chi^2(1, 526) = 1.39$; $p = 0.24$).

Preoperative Leptin and Adiponectin, and POD Risk

Preoperative concentrations of leptin, sOB-R, total adiponectin, hmw adiponectin, and FLI and LAR were not associated with POD (Table 1). We found statistically significant interactions of BMI with sOB-R and total adiponectin, suggesting that the associations with POD differ by the BMI of the patient; however, the stratum-specific associations were not statistically significant (Supplemental Table S7). Adjustment for the potential intermediaries vascular risk factors, vascular disease, and anesthesia duration did not alter these results (Table 2; Supplemental Table S8). Exclusion of 11 underweight patients produced almost identical results (data not shown).

Preoperative Leptin and Adiponectin, and POCD Risk

In a model adjusting for the potential confounding factors age, sex, fasting, surgery type, and BMI (model 2), leptin, sOB-R, total adiponectin, hmw adiponectin, and LAR were not significantly associated with POCD risk (Table 3). Patients in the highest FLI quartile were at a reduced risk compared with the lowest FLI quartile which served as a reference group. However, the trend across all four FLI quartiles as

TABLE 1. Adjusted Odds and 95% CI of POD for Quartiles of Adipokine Concentration, and for Continuous Adipokine Concentration

		Quartiles of Plasma Concentration					Continuously[a]	
		I	II	III	IV	P_{trend}	OR (95% CI) Per 1 SD Increment	P_{OR}
Leptin	Model 1	1.0 (Ref)	0.86 (0.52, 1.43)	0.71 (0.41, 1.23)	0.90 (0.49, 1.64)	0.65	1.04 (0.84, 1.29)	0.73
	Model 2	1.0 (Ref)	0.82 (0.49, 1.39)	0.66 (0.36, 1.20)	0.79 (0.38, 1.64)	0.58	1.03 (0.80, 1.34)	0.81
sOB-R [1]	Model 1	1.0 (Ref)	0.66 (0.38, 1.13)	0.71 (0.41, 1.21)	0.78 (0.46, 1.31)	0.45	1.03 (0.86, 1.23)	0.73
	Model 2	1.0 (Ref)	0.65 (0.38, 1.14)	0.71 (0.41, 1.23)	0.78 (0.44, 1.38)	0.46	1.05 (0.87, 1.26)	0.64
Total adiponectin[2]	Model 1	1.0 (Ref)	0.86 (0.51, 1.46)	0.87 (0.52, 1.47)	0.90 (0.53, 1.52)	0.94	1.01 (0.84, 1.22)	0.89
	Model 2	1.0 (Ref)	0.87 (0.51, 1.47)	0.88 (0.52, 1.48)	0.92 (0.53, 1.58)	0.95	1.03 (0.85, 1.24)	0.79
HMW adiponectin	Model 1	1.0 (Ref)	1.29 (0.77, 2.16)	1.17 (0.69, 1.99)	0.87 (0.50, 1.51)	0.48	0.98 (0.81, 1.18)	0.83
	Model 2	1.0 (Ref)	1.29 (0.77, 2.17)	1.18 (0.69, 2.02)	0.88 (0.50, 1.56)	0.50	0.99 (0.81, 1.20)	0.91
FLI[1]	Model 1	1.0 (Ref)	0.88 (0.53, 1.48)	0.87 (0.50, 1.51)	1.00 (0.56, 1.81)	0.92	1.09 (0.91, 1.32)	0.34
	Model 2	1.0 (Ref)	0.87 (0.51, 1.47)	0.85 (0.47, 1.52)	0.95 (0.46, 1.94)	0.92	1.10 (0.90, 1.35)	0.35
LAR[2]	Model 1	1.0 (Ref)	0.71 (0.43, 1.18)	0.64 (0.38, 1.08)	0.74 (0.44, 1.25)	0.35	1.06 (0.87, 1.29)	0.55
	Model 2	1.0 (Ref)	0.67 (0.40, 1.12)	0.58 (0.33, 1.00)	0.62 (0.34, 1.14)	0.22	1.07 (0.84, 1.34)	0.59

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 = 768, except [1]n = 740 and [2]n = 767.

Logistic regression analyses. p-value for trend (two-sided) across quartiles is based on the Wald chi^2 statistic (df = 1).

Model 1: adjusted for age, sex, fasting, surgery type (and for leptin, sOB-R, FLI, LAR additionally for analysis lab). Model 2: Model 1+body mass index.

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

TABLE 2. Influence of Potential Intermediaries on Relationship of Adipokine Concentrations With POD

		Quartiles of Plasma Concentration					Continuously[a]	
		I	II	III	IV	P_{trend}	OR (95% CI) Per 1 SD Increment	P_{OR}
Leptin	Model 3	1.0 (Ref)	0.82 (0.48, 1.40)	0.66 (0.36, 1.21)	0.75 (0.36, 1.57)	0.62	1.00 (0.77, 1.30)	0.99
	Model 4	1.0 (Ref)	0.84 (0.49, 1.46)	0.68 (0.37, 1.27)	0.82 (0.39, 1.75)	0.67	1.05 (0.84, 1.36)	0.74
sOB-R[1]	Model 3	1.0 (Ref)	0.68 (0.39, 1.19)	0.73 (0.42, 1.28)	0.79 (0.44, 1.42)	0.56	1.06 (0.88, 1.28)	0.56
	Model 4	1.0 (Ref)	0.82 (0.46, 1.46)	0.88 (0.49, 1.57)	0.93 (0.51, 1.68)	0.92	1.07 (0.88, 1.30)	0.50
Total adiponectin[2]	Model 3	1.0 (Ref)	0.93 (0.55, 1.59)	0.93 (0.54, 1.57)	0.97 (0.56, 1.68)	0.99	1.05 (0.87, 1.28)	0.61
	Model 4	1.0 (Ref)	0.89 (0.52, 1.54)	0.84 (0.49, 1.45)	0.79 (0.45, 1.40)	0.87	0.94 (0.76, 1.16)	0.56
HMW adiponectin	Model 3	1.0 (Ref)	1.40 (0.83, 2.38)	1.34 (0.77, 2.33)	0.96 (0.54, 1.73)	0.39	1.02 (0.84, 1.24)	0.85
	Model 4	1.0 (Ref)	1.42 (0.82, 2.45)	1.28 (0.72, 2.27)	0.99 (0.54, 1.79)	0.46	1.02 (0.84, 1.25)	0.83
FLI[1]	Model 3	1.0 (Ref)	0.89 (0.52, 1.51)	0.84 (0.47, 1.51)	0.93 (0.45, 1.89)	0.94	1.08 (0.87, 1.33)	0.49
	Model 4	1.0 (Ref)	0.92 (0.53, 1.60)	0.79 (0.43, 1.45)	0.88 (0.42, 1.83)	0.90	1.10 (0.89, 1.36)	0.37
LAR[2]	Model 3	1.0 (Ref)	0.70 (0.41, 1.18)	0.58 (0.33, 1.01)	0.61 (0.33, 1.12)	0.24	1.02 (0.81, 1.30)	0.85
	Model 4	1.0 (Ref)	0.80 (0.46, 1.38)	0.73 (0.41, 1.29)	0.79 (0.42, 1.50)	0.73	1.07 (0.85, 1.37)	0.55

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 = 768, except [1]n = 740 and [2]n = 767.

Logistic regression analyses. p-value for trend (two-sided) across quartiles is based on the Wald chi^2 statistic (df = 1).

Model 3: Model 2+diabetes, hypertension, stroke, transient ischemic attack, coronary heart disease Model 4: Model 3+anesthesia duration

[a] Adipokines were standardized for these analyses, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine concentration. Adding adipokine squared into the respective Model 4 led to the following results for quadratic terms: leptin^2: Wald chi ^{2} 0.58 (df = 1), p = 0.44; sOB-R^2: Wald chi ^{2} 0.26 (df = 1), p = 0.61; total adiponectin^2: Wald chi ^{2} 0.29 (df = 1), p = 0.59; HMW adiponectin^2: Wald chi ^{2} 1.11 (df = 1), p = 0.29; FLI^2: Wald chi ^{2} 0.49 (df = 1) p = 0.49; LAR^2 Wald chi ^{2} 0.04 (df = 1), p = 0.85.

well as the effect estimate of the continuous analysis of FLI were each not statistically significant (Table 3).

In sensitivity analyses, for the obese subgroup (BMI≥30kg/m^2), each 1 SD increase in sOB-R concentration was associated with a 4-fold increased POCD risk, although the confidence interval was notably large (Supplemental Table S9; for unadjusted descriptive data, see Supplemental Figure S2). No associations were observed in the nonobese subgroup (BMI<30kg/m^2) and interaction terms were not statistically significant (Supplemental Table S9).

To determine the role of potential intermediaries in the relationships observed in model 2, we adjusted for vascular risk factors, diagnosed vascular disease, and anesthesia duration. The reduced POCD risk for FLI quartile 4 versus quartile 1 remained statistically significant in this step (Table 4). The finding on sOB-R and POCD risk in the obese subgroup (BMI≥30kg/m^2) also remained statistically significant (model 4; Supplemental Table S10).

Post hoc adjustment for POD did not change the results on FLI across the total sample (FLI quartile 4 versus 1, model 4, OR 0.24; 95% CI 0.07, 0.82; Wald chi^2 = 5.05; df = 1; p = 0.025; trend across quartiles Wald chi^2 = 5.83, df = 3, p_{trend} = 0.12) or on sOB-R in the obese subgroup (OR 5.50; 95% CI 1.15, 26.36; Wald chi^2 = 4.55; df = 1; p = 0.033).

The remaining preoperative exposures were each not associated with POCD in any of the models across the full sample and subgroup analyses (Tables 3–4, Supplemental Tables S9 and S10). We repeated the analyses of the total sample and the nonobese subgroup (BMI<30kg/m^2) with the exclusion of five underweight patients with close to identical results (data not shown).

DISCUSSION

Principal Findings

In a large cohort of older surgical patients, despite a substantial statistical power, we found no evidence for an association of preoperative leptin, its soluble receptor, or total and hmw adiponectin with the risk of POD during the hospital stay. Sensitivity analyses indicated that the associations of sOB-R and total adiponectin with POD risk differed according to patients' BMI with statistically nonsignificant trends for a reduced POD risk with higher sOB-R and higher total adiponectin concentrations which were limited to the obese subgroup (BMI≥30kg/m^2). For the outcome of POCD at 3 months, patients in the highest FLI quartile had a lower POCD risk as compared

TABLE 3. Adjusted Odds and 95% CI of POCD for Quartiles of Adipokine Concentration, and for Continuous Adipokine Concentration

		Quartiles of Plasma Concentration					Continuously[a]	
		I	II	III	IV	P_{trend}	OR (95% CI) Per 1 SD Increment	P_{OR}
Leptin	Model 1	1.0 (Ref)	0.86 (0.34, 2.16)	1.32 (0.56, 3.13)	0.94 (0.35, 2.52)	0.72	1.11 (0.82, 1.52)	0.50
	Model 2	1.0 (Ref)	0.57 (0.22, 1.52)	0.73 (0.28, 1.90)	0.35 (0.11, 1.17)	0.28	0.86 (0.59, 1.27)	0.45
sOB-R [1]	Model 1	1.0 (Ref)	1.19 (0.51, 2.75)	1.32 (0.57, 3.09)	0.79 (0.31, 2.05)	0.69	0.99 (0.73, 1.34)	0.93
	Model 2	1.0 (Ref)	1.38 (0.58, 3.28)	1.65 (0.68, 4.00)	1.28 (0.44, 3.72)	0.73	1.09 (0.81, 1.48)	0.57
Total adiponectin[2]	Model 1	1.0 (Ref)	1.21 (0.54, 2.74)	1.04 (0.46, 2.36)	0.84 (0.35, 2.03)	0.86	0.87 (0.62, 1.20)	0.39
	Model 2	1.0 (Ref)	1.27 (0.56, 2.88)	1.10 (0.48, 2.52)	1.04 (0.42, 2.56)	0.94	0.94 (0.67, 1.33)	0.74
HMW adiponectin	Model 1	1.0 (Ref)	1.68 (0.73, 3.89)	1.98 (0.86, 4.57)	0.64 (0.24, 1.74)	**0.047**	0.81 (0.59, 1.11)	0.19
	Model 2	1.0 (Ref)	1.69 (0.73, 3.92)	2.14 (0.92, 4.98)	0.75 (0.27, 2.07)	0.068	0.87 (0.63, 1.21)	0.40
FLI[1]	Model 1	1.0 (Ref)	0.72 (0.28, 1.83)	1.11 (0.48, 2.57)	0.75 (0.29, 1.98)	0.68	0.99 (0.72, 1.36)	0.96
	Model 2	1.0 (Ref)	0.50 (0.19, 1.32)	0.62 (0.24, 1.58)	**0.26 (0.08, 0.89)**	0.14	0.80 (0.51, 1.23)	0.31
LAR[2]	Model 1	1.0 (Ref)	1.56 (0.53, 3.93)	2.19 (0.94, 5.12)	1.55 (0.62, 3.91)	0.34	1.07 (0.78, 1.47)	0.66
	Model 2	1.0 (Ref)	1.24 (0.48, 3.22)	1.61 (0.65, 3.99)	0.94 (0.33, 2.74)	0.51	0.82 (0.55, 1.22)	0.33

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 = 526, except [1]n = 503 and [2]n = 525.

Logistic regression analyses. p-value for trend (two-sided) across quartiles is based on the Wald chi[2] statistic (df = 1).

Model 1: adjusted for age, sex, fasting, surgery type (and for leptin, sOB-R, FLI, LAR additionally for analysis lab). Model 2: Model 1+body mass index.

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

with patients in the lowest FLI quartile. Sensitivity analyses additionally revealed an association of higher sOB-R with an increased POCD risk that was limited to the obese subgroup.

The aforementioned statistically significant findings were independent of the potential confounding factors of age, sex, fasting, surgery type and BMI, and also of vascular risk, vascular disease, anesthesia duration throughout, showing that these factors likely did not function as mediators. The results on POCD at 3 months were additionally independent of POD, indicating no contribution of POD to the finding. However, all of the aforementioned statistically significant findings were often of limited effect size,

TABLE 4. Influence of Potential Intermediaries on Relationship of Adipokine Concentrations With POCD

		Quartiles of Plasma Concentration					Continuously[3]	
		I	II	III	IV	P_{trend}	OR (95% CI) Per 1 SD Increment	P_{OR}
Leptin	Model 3	1.0 (Ref)	0.56 (0.21, 1.50)	0.72 (0.27, 1.88)	0.34 (0.10, 1.14)	0.27	0.86 (0.58, 1.28)	0.46
	Model 4	1.0 (Ref)	0.56 (0.21, 1.49)	0.71 (0.27, 1.86)	0.33 (0.10, 1.13)	0.26	0.86 (0.58, 1.27)	0.44
sOB-R[1]	Model 3	1.0 (Ref)	1.36 (0.57, 3.26)	1.64 (0.68, 3.99)	1.28 (0.44, 3.74)	0.74	1.09 (0.80, 1.47)	0.59
	Model 4	1.0 (Ref)	1.35 (0.56, 3.24)	1.63 (0.67, 3.98)	1.28 (0.44, 3.77)	0.72	1.10 (0.80, 1.51)	0.55
Total adiponectin[2]	Model 3	1.0 (Ref)	1.25 (0.55, 2.87)	1.08 (0.47, 2.49)	1.01 (0.40, 2.53)	0.95	0.94 (0.66, 1.30)	0.70
	Model 4	1.0 (Ref)	1.26 (0.55, 2.88)	1.10 (0.48, 2.54)	1.04 (0.42, 2.62)	0.95	0.95 (0.67, 1.35)	0.78
HMW adiponectin	Model 3	1.0 (Ref)	1.68 (0.72, 3.96)	2.11 (0.89, 4.98)	0.73 (0.26, 2.04)	0.069	0.86 (0.61, 1.20)	0.37
	Model 4	1.0 (Ref)	1.68 (0.72, 3.96)	2.15 (0.91, 5.08)	0.72 (0.27, 2.04)	0.064	0.86 (0.61, 1.20)	0.36
FLI[1]	Model 3	1.0 (Ref)	0.49 (0.18, 1.31)	0.61 (0.24, 1.58)	**0.26 (0.08, 0.88)**	0.14	0.80 (0.52, 1.25)	0.33
	Model 4	1.0 (Ref)	0.48 (0.18, 1.28)	0.60 (0.23, 1.55)	**0.25 (0.07, 0.87)**	0.13	0.80 (0.51, 1.25)	0.32
LAR[2]	Model 3	1.0 (Ref)	1.25 (0.48, 3.26)	1.60 (0.64, 3.99)	0.95 (0.32, 2.76)	0.52	0.82 (0.54, 1.23)	0.33
	Model 4	1.0 (Ref)	1.19 (0.45, 3.15)	1.52 (0.60, 3.84)	0.88 (0.30, 2.65)	0.54	0.81 (0.54, 1.22)	0.31

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 = 526, except [1]n = 503 and [2]n = 525.

Logistic regression analyses. p-value for trend (two-sided) across quartiles is based on the Wald chi[2] statistic (df = 1).

Model 3: Model 2+diabetes, hypertension, stroke, transient ischemic attack, coronary heart disease Model 4: Model 3+anesthesia duration

[a] Adipokines were standardized for these analyses, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine concentration. Adding adipokine squared into the respective Model 4 led to the following results for quadratic terms: leptin[2]: Wald chi [2] 2.26 (df = 1), p = 0.13; sOB-R[2]: Wald chi [2] 0.05 (df = 1), p = 0.82; total adiponectin[2]: Wald chi [2] 1.56 (df = 1), p = 0.21; HMW adiponectin[2]: Wald chi [2] 0.19 (df = 1), p = 0.66; FLI[2]: Wald chi [2] 0.64 (df = 1), p = 0.43; LAR[2]: Wald chi [2] 1.85 (df = 1), p = 0.17.

often came with large confidence intervals, and will have been affected by a considerable risk of type I statistical error, and should thus only be considered preliminary.

Comparison With Other Studies: Leptin, sOB-R, Total and hmw Adiponectin and POD

In spite of leptin as a promoter of atherosclerotic and proinflammatory processes,[50] a higher concentration has been implicated as protective in the context of delirium. The only study on leptin and POD found an association of lower preoperative leptin concentrations with an increased POD risk among 186 hip fracture surgery patients.[41] In one Chinese study of delirium in the ICU, patients with lower leptin concentrations at admission were at increased risk,[51] and in a Colombian case-control study, patients with delirium had higher leptin concentrations compared with those without delirium.[52]

Because none of those studies had controlled for BMI, such observations could reflect lower leptin concentrations as a correlate of a lower BMI and, relatedly, the presence of frailty as established risk factors for POD[53,54] (which together with a *higher* BMI as a risk factor for POCD[14,15] further strengthens POD and POCD as distinct syndromes). In all of those prior studies, BMI itself was unrelated to POD/delirium, but the clinical presentation of their study samples (characterized by multimorbidity,[52] severe diseases requiring ICU stay[51] and advanced age combined with hip fracture surgery which could be suggestive of frailty[41]) could have contributed nonetheless by introducing a residual confounding to the association of leptin with POD. On the other hand, the beneficial effects of leptin on neurological function, which could outweigh its detrimental effects on inflammatory/atherosclerotic processes, may also account for those observations.[25]

Here, in the first strategic analysis of leptin, sOB-R, and a derived index, we found no evidence to support associations of leptin parameters with POD in either direction. However, we found preliminary evidence for an interaction effect of sOB-R x BMI on POD risk. This may suggest a differential role of sOB-R according to BMI, which should be investigated in detail in further cohort studies.

To the best of our knowledge, this is the first study on total and hmw adiponectin and POD. We found no associations across the total sample as well as in subgroup analyses according to obesity. We did observe however an interaction effect of total adiponectin x BMI on POD risk. This again may point to a differential role of adiponectin in POD risk according to BMI.

Comparison With Other Studies: Leptin, sOB-R, Total and hmw Adipinectin and POCD

No study to date has apparently addressed leptin parameters and POCD. Here, patients with a higher degree of leptin resistance had a lower POCD risk as compared with patients with a lower leptin resistance. In our prior cross-sectional analysis, we had not found an association of FLI with preoperative cognitive function but had observed an association of a higher leptin concentration with a lower preoperative cognitive function.[43] However, these disparate findings likely reflect inherent differences between the two cognitive outcomes examined in the present and our prior analysis[43]: preoperative cognitive function describes a snapshot of ability whereas POCD accounts for preoperative cognitive function and describes a decline in function over time.

Additionally, in the present analysis, among the obese subgroup, we found evidence for an association of higher concentrations of circulating, free sOB-R with an increased POCD risk. No prior study had applied stratification by obesity status so this finding warrants assessment in further cohorts. A single previous study had addressed adiponectin and POCD and had reported no association of preoperative concentrations with POCD at 7 days in univariate analysis.[42] Whereas in that study, statistical power was limited, we too did not find any consistent results on total or hmw adiponectin and POCD at 3 months despite a greater statistical power.

Strengths and Limitations

We used data from a large cohort with comprehensive clinical characterization of patients. The strength of the correlations of adipokines with BMI was in a similar magnitude as in other studies,[29,55,56] suggesting that laboratory measurement error does not explain our null results. We controlled for potential confounding factors and approached underlying mechanisms through adjustment for potential mediating factors in hierarchical model building. With a

close relationship of BMI with adipokines, our sensitivity analyses according to obesity status are also an asset of our study. Some limitations must be considered. Single-time measurement of biomarkers may not have properly captured long-term exposure. However, adiponectin and leptin measurements show high reliability over long periods.[57,58] We performed a large number of statistical analyses, though the six exposure variables were index variables (FLI, LAR) or essentially measures of the same compounds (for leptin, leptin and sOB-R; for adiponectin, total and hmw adiponectin) and we applied hierarchical model building combining the use of quartile analyses with the use of the exposures as continuous measures, so that these were strictly speaking not all separate analyses. Nonetheless, even with a conservative approach to p-value adjustment, the statistically significant associations reported in this study would not have survived which needs to be considered in its interpretation. We used single imputation to replace missing data on covariates whereas more complex imputation strategies may be preferable. However, imputation was only performed on covariates rather than our exposures/ outcomes and missing data was relatively rare so we expect minimal influence of this factor on our results. Finally, our study may have been affected by selection bias, whereas a comparison of patients returning for follow-up with those who did not reveal only minor differences in parameters known to be central in adipokines and cognitive aging, such as age and BMI.

Conclusion

We found only limited evidence for a role of preoperative concentrations of leptin, its receptor, and total and hmw adiponectin in the risk of POD and POCD. Interestingly, our observations may point to a differential role for these compounds for obese versus nonobese individuals, which warrants detailed evaluation.

STATEMENT OF ETHICS

All assessments complied with the Declaration of Helsinki. The BioCog study protocol was reviewed and approved by the ethics committees on human research at Charité University Medicine Berlin and UMC Utrecht (approval number EA2/092/14). Participants provided full written informed consent upon enrolment and were able to withdraw consent at any time, without providing reasons and without penalty.

TRIAL REGISTRATION

The BioCog study is registered on clinicaltrials.gov (NCT02265263).

DISCLOSURES

This work was supported by the European Union, Seventh Framework Programme (FP7/2007−2013), under grant agreement no. HEALTH−F2−2014−602461 BioCog (Biomarker Development for Postoperative Cognitive Impairment in the Elderly): www.biocog.eu. 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.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meeting.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2024.03.015.

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