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Research Article

Do Overweight, Arterial Hypertension and Type 2 Diabetes Worsen Cognitive Impairment in Patients with Alcohol Use Disorders?

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Abstract

Objective: Overweight, Arterial Hypertension (AH) and diabetes are frequently associated with alcohol use disorders. As each of these co-morbidities is independently associated with cognitive impairment, we studied whetherthey could worsen alcohol-related cognitive impairment.

Methods: A retrospective analysis of a clinical database of patients with an alcohol use disorder admitted to an addiction treatment unit of a teaching hospital. Patient weight was classified using WHO recommendations; arterial hypertension and Type 2 diabetes were diagnosed according to the most recent guidelines. Cognitive status was assessed using the MoCA administered on admission and at discharge by trained staff members.

Results: Among the 387 patients included (69.3% male, mean age 50.4), 6.4% suffered from Type II diabetes, AH was present in 22.4% of the sample, and 20.6% were obese (BMI>=30). MoCA scores at admission did not differ as a function of BMI, or AH or Type II diabetes status. At discharge, MoCA scoreshad improved in all subgroups; however, a multivariate analysis showed that they had improved significantly less in the AH group compared to the non-AH group.

Conclusions: Our results confirm the impact of hypertension on cognitive dysfunction, including in patients with severe alcohol use disorders. Monitoring of blood pressure levels is, therefore, an important preventive measure for cognitive dysfunction in these patients.

Keywords: Alcohol use disorder; Cognition; Withdrawal; Arterial hypertension; Diabetes; Overweight

Introduction

Overweight is a chronic inflammatory condition that is associated with Alzheimer's disease, vascular dementia, and brain atrophy [1,2]. The effects of adiposity on cognition have been widely studied, with numerous conclusive observations [3]. For example, in the French VISAT cohort of 2000 middle-aged participants, Cournot et al. [4] showed that a higher Body Mass Index (BMI) predicted lower cognitive scores at five-year follow-up, independent of any confounding factors. Interestingly, the latter study found that cognitive impairments (measured as attention tasks, executive function, and memory) are similar to those observed in patients with Alcohol Use Disorders (AUD).

Cognitive impairment is the most frequent neurologic complication in patients with AUD, with reported prevalence ranging from 50–70% [5,6]. It mostly affects executive functions, along with memory and visuo-spatial abilities [7]. It is now widely-accepted that these alcohol-associated neurological effects might be due to an inflammation process [8]. Alcohol abuse is known to increase bacterial endotoxin lipopolysaccharides, which leads to oxidative stress through excessive production of reactive oxygen species. As a consequence, neuroimmune reactions occur through interactions with factors such as Toll-like receptors and pro-inflammatory cytokines [9]. Therefore, it is reasonable to suspect that any disease associated with a chronic inflammation process such as obesity might also impact cognitive function in AUD patients.

Cognitive impairment might also be mediated, in part at least, by Type II diabetes (T2D), which frequently occurs in overweight subjects. A meta-analysis of studies in the United States and Europe compared obese people with those of normal weight, and found that obese men had a seven-fold, and obese women a 12-fold higher risk of developing T2D [10]. In Europe, 50.9–98.6% of people with T2D are reported to be obese [11]. Meta-analyses also suggest that adults with T2D have negative changes in motor and executive function, processing speed, and verbal and visual memory [12]. A study conducted in a sample of patients aged 40–60 examined brain response to an n-back working memory test, and showed a relationship between task performance and insulin sensitivity [13]. Epidemiological data show a clear association between excessive alcohol use and T2D [14], suggesting that diabetes might also contribute to cognitive impairment in both overweight and AUD patients.

Obesity is known to be a major risk factor for cardiovascular disease, coronary heart disease, heart failure, and hypertension, which together account for about 70% of complications [15]. Arterial

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Hypertension (AH) is now considered to be one of the major risk factors for vascular dementia [16]; notably, Wortmann et al. [17] showed that at least 50% of patients with dementia have cerebral vascular lesions, accompanied by various signs of neurodegeneration. A recent meta-analysis showed that high blood pressure in midlife is linked with poorer cognitive functioning, evidenced in cross-sectional and longitudinal studies [18]. It is well-known that excessive alcohol use increases blood pressure, and that reducing alcohol intakeis consistent with a significant improvement [19]. Taken together, these studies suggest that A His another potential risk factor for cognitive impairment in both overweight and AUD patients.

Heavy drinking does not protect against weight gain. A recent large-scale American study showed that about 20% of those with AUD were overweight [20]. Therefore, it is reasonable to suspect that overweight patients with AUD who are exposed to other risk factors might have more severe cognitive impairment than patients with AUD at normal weight. Although it has been clearly demonstrated that alcohol withdrawal improves cognitive function [6], this improvement might be impaired in overweight AUD patients, due to the risk factors associated with obesity; this could, paradoxically, lead to the suspicion that the patient is still consuming alcohol.

Against this background, the aim of our study was to evaluate the impact of overweight, AH, and/or T2D on cognitive function at admission, and after six weeks of rehabilitation in AUD patients.

Methods and Patients

The study was performed in a hospital-based, substance use rehabilitation center. The present work is retrospective, and is a secondary analysis of data used in Pelletier [6], to which we added 151 patients who were hospitalized in 2019 or 2020, and who met inclusion criteria.

Patients

Inclusion criteria were: AUD according to DSM-5 criteria (American Psychiatric Association, 2013); detoxification of at least seven days; age above 18 years; no alcohol or drug consumption during the hospital stay, checked by regular and random testing; cognitive evaluation at admission and just before discharge; available clinical data regarding a potential history of AH or T2D, and BMI. Exclusion criteria were as follows: severe comorbid neurological or psychiatric disease such as dementia; Alzheimer's disease; psychosis; past history of stroke or coma; encephalopathy; and refusal to participate.

Methods

We recorded the following data: age; sex; marital status (single/in a relationship); education level (≥12 years); professional status (employed or unemployed); alcohol consumption; age at AUD onset; past family history of drug use disorder; tobacco consumption; and cannabis, cocaine and heroin consumption, based on declarative data and urinary tests.

Diagnosis of Factors Studied

Overweight: This was calculated using the patient's BMI (their weight in kg divided by their height in meters squared). We used the 2004 World Health Organization (WHO) classification: group 1, BMI < 18.5; group 2, 18.5≥ BMI<25; group 3, 25 ≥ BMI<30; group 4, BMI>=30.

AH: This included diagnosed patients undergoing treatment for AH at admission. It also included patients in whom an arterial systolic pressure of 140/90 mmHg was recorded, at least three times, after a minimum period of seven days following alcohol withdrawal, as recommended by most guidelines [21].

T2D: In addition to diagnosed patients undergoing treatment, T2D was identified when fasting glycemia was above 1.26 g/l (7.0 mmol) at least two times after a minimum period of seven days following alcohol withdrawal [22].

Cognitive Evaluation

We used version 7.1 of the Montreal Cognitive Assessment (MoCA) provided by the MoCA test organization (http://www.mocatest.org/) for the evaluation at admission, and version 7.2 of the same test at discharge, to avoid memory bias. Both versions were translated into French and administered by experienced occupational therapists or neuropsychologists. All administrators used a similar scoring grid, defined in accordance with proposed guidelines [23]. The test was administered in a quiet room in the morning, and patients had not smoked recently. The MoCA explores eight cognitive domains: visuospatial/executive, naming, memory (not scored), attention (three items scored independently), language (two items scored independently), abstraction, delayed recall, and orientation. Scores were not corrected for education level, and scores ≥ 26 are considered normal [7].

Statistics

We used the *lmer* function in the *lme4* package in *R* [24] and the Maximum Likelihood method to assess how well the data fitted our mixed-effects models [25]. We tested mixed effects because measures for each patient were interdependent, and we needed to adjust our estimates of the model's parameters for "subjects", by adding a random intercept that estimated between-subjects' variance in the mean of the dependent variable. The intercept, the subsequent covariates and their interactions were modeled using fixed effects parameters (unstandardized *B* regression coefficients): *Time* was modeled as a dummy, with admission as the reference (admission=0; after six weeks of rehabilitation=1); *BMI*; *AH* was modeled as a dummy, with no AH as the reference; *T2D* was model as a dummy, with no diabetes as the reference; and education level. Interactions were also modeled as fixed effects. We report values for unstandardized regression coefficients (*B*) to estimate the relationship between the response (i.e., the dependent variable), and both quantitative covariates and dummies. Significance was set at $p \leq .05$.

Results

Socio-Demographic Data

Three hundred and eighty-seven (387) patients were included in the study, divided into 268 men and 119 women, aged 50.4±9.6 years. Most (66.1%) lived alone, a minority (15.6%) were employed, and 16.1% were highly educated. Full socio-demographic characteristics are presented in Table 1. Mean alcohol consumption was high, about 40% had a family history of AUD, over 70% smoked, and about 18% were current cannabis users (Table 1). AH was present in 87 (22.4%) of patients, T2D in 26 (6.7%), and 80 (20.6%) were overweight (Table 1). As the number of patients in group 1 was low (N=12), they were merged into group 2; similarly group 4 (N=8) was merged with

Table 1: Socio-demographic and addiction data.

N		387
Age (years)		50.4±9.6
Sex (%M/%F)		69.3/30.7
Married (%)		33.9
Employed (%)		15.6
Education level (%)		
≤12 y		83.9
>12 y		16.1
Alcohol (g/d)		208±121
Age at AUD onset (%)		33.5±11.4
Family history of AUD		39.2
Active smoker (%)		72.4
Cannabis user (%)		17.8
Other drugs (%)		4.6
Diabetes (%)		6.7
AH (%)		22.4
BMI (%)	<25	49.1
	25>= BMI<30	30.5
	>= 30	20.4

Table 2: MoCA scores at admission (MoCA_A) and discharge (MoCA_D) as a function of BMI group, and AH and T2D status.

BMI group	N	MoCA_A	MoCA_D
1 <25	190	21.8±3.8	24.7±3.5*
2 >= 25 &<30	118	22.0±3.2	24.2±3.8*
3 >= 30	79	22.0±3.7	24.7±3.3*
AH			
No	300	21.9±3.6	24.9±3.2*
Yes	87	22.0±3.6	24.0±3.6*
Diabetes			
No	361	21.9±3.6	24.8±3.3*
Yes	26	22.2±2.8	24.2±3.9*

* p<0.01 vs MoCA_A

group 3, leading to the creation of the following three groups: group 1, BMI <25; group 2, 25≥ BMI<30; and group 3, BMI>=30**.**

Cognitive Status at Admission

A univariate analysis found that MoCA score son admission were not statistically different in the three BMI groups: 21.8±3.8 (group 1); 22.0±3.2 (group 2); and 22.0±3.7 (group 3) (Table 2). Similarly, no significant differences in MoCA scores were observed as a function of the presence of AH compared to normal arterial tension (22.0±3.6 *vs* 21.9±3.6), and T2D compared to no diabetes (22.2±2.8 *vs* 21.9±3.6) (Table 2). While the analysis of education level showed that patients with a high education level had higher MoCA scores than those with a lower education level, here again, there were no significant differences according to BMI group, AH, or T2D status (data not shown).There were also no significant differences in MoCA scores as a function of the duration of alcohol abuse, daily alcohol consumption, smoking status, or family history of alcohol abuse (data not shown).

Table 3: Improvement in MoCA scores as a function of BMI group, and AH and T2D status.

All patients	N	Delta_MoCA
	387	2.8±2.9
BMI group		
1 <25	190	2.7±2.9
2 >= 25 &<30	118	2.7±2.8
3 >= 30	79	2.9±3.0
HTA		
No	300	3.0±2.8
Yes	87	2.0±3.1*
Diabetes		
No	361	2.8±2.8
Yes	26	2.0±3.2

p=0.02 vs absence of HTA

Cognitive Status at Discharge

The analysis found that MoCA scores increased significantly during the hospital stay (Table 2). However,scores at discharge did not differ as a function of BMI group, AH or T2D status, or education level (Table 2).

Improvement in Cognition between Admission and Discharge

The improvement in cognition was assessed as the difference between the patient's MoCA score at discharge minus their score at admission. The analysis found no difference in improvement between the three BMI groups (Table 3), and the result was similar when BMI was considered as a continuous variable (data not shown). Similarly, there was no difference in cognitive improvement as a function of T2D status. However, MoCA improvement was significantly lower among patients with AH compared to those without (2.0±3.1 *vs* 3.0±2.8, $p<0.02$).

Linear Mixed-Effects Models

In order to check whether this difference was a result of chance, we ran a linear mixed model analysis. Our first model showed that the *Time* dummy was significant ($B=2.80$, $p<.001$), and our second model showed that neither the BMI score ($B=.02$, $p=.51$) nor the *BMI* x *Time* interaction ($B=-.01$, $p=.60$) were significant. Our third model showed that the *AH* dummy was not significant ($B=.06$, $p=.88$), but that the *AH* x *Time* interaction was ($B=-.99$, $p=.005$). The fourth model showed that neither the *T2D* dummy ($B=.26$, $p=.71$), nor the *Time x T2D* interaction ($B=-.82$, $p=.17$) were significant. We incorporated all covariates in the fifth model. *Education* level was included as a covariate in this model since it has been shown to be significantly associated with cognitive status. Here, we found significant and positive effects of the *Time* dummy ($B=3.03$, $p<.001$) and *education* ($B=.49$, $p<.001$) on the MoCA score. The *Time* x *AH* interaction remained significant ($B=-1.00$, $p=.005$) (Table 4), and this result showed that the increase in the MoCA score after six weeks of rehabilitation was higher for patients with no AH compared to patients with AH. All remaining predictors were not significant.

Table 4: Parameter values from the fifth mixed-effects model, with the MoCA score as the dependent variable.

Factor	Fixed effects				Random effect (intercept)	
	B	S.E.	C.R.	*p* value	Variance	S.D.
	-	-	-	-	6.30	2.51
Time	3.02	.16	18.25	<.001	-	-
AH	.13	.41	.313	.75	-	-
T2D	−.10	.61	−.165	.87	-	-
BMI	*.05*	*.03*	1.70	.09	-	-
Education	.49	.05	8.79	<.001	-	-
*Time*AH*	−1.00	.35	−2.82	.005	-	-

Note: B=unstandardized Regression coefficient, S.E.=Standard Error, C.R.=critical ratio, S.D.=Standard Deviation, AH= Arterial Hypertension.

Discussion

Increasing life expectancy has led to a search for ways to preserve normal cognitive capacity, and to identify and target those at risk of neurological disorders [26]. The latter notably include obese people and those who consume an excessive amount of alcohol. Obesity, in particular, has become a major contributor to the global burden of chronic disease, specifically among patients who suffer from T2D and AH, as, over the past three and a half decades, its prevalence has nearly doubled worldwide [27]. According to the WHO, more than one billion adults worldwide are now overweight and, of these, it is estimated that about 300 million are obese (please see https://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf, accessed June 8, 2022). Excessive drinking alone accounts for 7.1% and 2.2% of the global burden of disease among males and females, respectively.

As both obesity and AUD are independently associated with cognitive impairment, we hypothesized that the combination of these two factors might lead to more severe impairment. However, our results, based on a large sample of patients, did not validate this hypothesis. At admission, cognitive functioning assessed with the MoCA did not significantly differ according to the patient's BMI group. Moreover, there were no differences in cognitive performance as a function of their AH or T2D status. As our results differ from earlier work, it is reasonable to suspect that they might be biased by one or several confounding factors.

Although a negative association between anthropometric measures of obesity (e.g., BMI, waist circumference) and a number of cognitive domains has been reported [4], a direct effect of obesity on cognition has not been consistently found [13,28]. This may be due to the mediating influence of a number of obesity-associated comorbidities that are known to adversely impact cognitive performance, notably T2D, hypertension, hypercholesterolemia, and insulin resistance [26].

The main difference between our study and earlier work is that our patients were heavy drinkers. Excessive alcohol consumption isa powerful driver of brain injury and the effects are similar to those associated with aging, as reported by Pfefferbaum et al. [29]. The latter authors showed that neuroanatomical changes in AUD patients were similar to those associated with aging, and mostly characterized by cerebral atrophy, specifically in the frontal lobes. Moreover, recent longitudinal data [30] have demonstrated that heavy alcohol consumption accelerates brain aging and that, for a given age group, an alcoholic brain is ten years older than that of a non-alcoholic. Altogether, these data suggest that heavy drinking might exacerbate other causes of cognitive impairment. A supplementary argument in this regard is that the present study found that MoCA scores of cognitive performance significantly improved six weeks after alcohol withdrawal. Earlier work has reported that stopping alcohol is consistent with an improvement in MoCA scores [6]. However, the detailed analysis performed here shows that the presence of AH significantly reduced any cognitive improvement, unlike T2D status and BMI group.

It is now well-known that overweight leads to the appearance of inflamed, dysfunctional adipocytes, which secrete both locally and systemically proinflammatory cytokines [31]. This inflammatory state is presumed to be responsible, at least in part, for cognitive alteration. The results of neuropsychological tests in people with diabetes (especially Type 2) have found mild or moderate cognitive dysfunction [32]. This cognitive decline could be related to inflammatory changes in the brain, as shown in a prospective study [33]. Diabetes is characterized by both insulin resistance, and increased expression of several pro-inflammatory cytokines such as interleukin IL-1, IL-6, and tumor necrosis factor [34]. Moreover, elevated levels of proinflammatory cytokines in the brain of mice correlate with results of behavioral tests [35].

Alcohol-related cognitive dysfunction is thought to be mediated by inflammation. Excessive drinking is associated with an increased level of bacterial endotoxins (mainly lipopolysaccharides), which lead to oxidative stress by increasing the production of reactive oxygen species [36]. The latter damage neurons through interactions with Toll-like receptors and/or pro-inflammatory cytokines [9].

Cognitive impairment in patients with AH is often related to vascular dementia. AH-related cognitive impairment is considered to be due to vessel injuries, such as luminal narrowing, stiffness, and micro-infarction. These wounds have been found to lead to reduced brain perfusion [37] and smaller total, cortical, and hippocampal brain volumes [38]. In addition to vascular injury, inflammation also plays a role in the maintenance of hypertension [39].

Altogether, of the four factors associated with cognitive impairment that are analyzed in this work, three have a mechanism that is related to inflammation, and one is directly linked to vascular injury, and indirectly to inflammation. Inflammation is a reversible process. In overweight patients, a low-calorie or low-fat diet followed for about 12 weeks was found to lead to a significant decrease in C-reactive protein and IL-6, and this was associated with both a weight reduction and an improvement in insulin resistance [40]. Similar results have been observed following bariatric surgery [41].

Drinking cessation is also associated with a reduction in inflammation, which can occur faster. A longitudinal study performed on a sample of 40 AUD patients showed that two weeks after alcohol withdrawal, the percentage of IL-6-producing monocytes had significantly fallen [42]. Moreover, reactive oxygen species are produced during alcohol metabolism by the cytochrome P450IIE1, which is induced by excessive drinking. It has been shown that following cessation, the P450-Alc level rapidly falls, and returns to a normal value as early as the fifth day of abstinence [43].

The reduction in inflammation following alcohol withdrawal might explain the following slight improvement in blood pressure. However, vascular lesions remain unchanged for a long time. In a sample of hypertensive patients, assessed over a successful one-year anti-hypertensive treatment, no significant anatomical modifications were observed [44]. This is consistent with a critical review which claimed that there is no convincing evidence from randomized controlled trials that lowering blood pressure prevents the development of cognitive impairment [45]. Altogether, an alcohol-induced reduction in inflammation appears to be insufficient to improve the patient's cognitive status, as vascular lesions remain unchanged.

The lack of a correlation between cognitive impairment, diabetes and overweight in AUD patients indicates that the effect of alcohol 'overwhelms' other effects related to obesity and diabetes. This could be explained, at least in part, by the very high average alcohol consumption in our population. Nevertheless, it is more likely that there is a direct link between obesity and cognitive disorders, since cognitive functions improve with weight loss, as demonstrated in studies following bariatric surgery [46,47]. Altogether, our results confirm the impact of AH on cognitive dysfunction, including in patients with severe AUD. Monitoring blood pressure is, therefore, an important preventive measure in these patients.

References

1. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol. 2009; 66: 336-42.
2. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Grieve S, et al. Relationship between body mass index and brain volume in healthy adults. Int J Neurosci. 2008; 118: 1582-93.
3. Farruggia MC, Small DM. Effects of adiposity and metabolic dysfunction on cognition: a review. Physiol Behav. 2019; 208: 112578..
4. Cournot MC, Marquié JC, Ansiau D, Martinaud C, Fonds H, Ferrières J, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology. 2006; 67: 1208-14.
5. Copersino ML, Fals-Stewart W, Fitzmaurice G, Schretlen DJ, Sokoloff J, Weiss RD. Rapid cognitive screening of patients with substance use disorders. Exp Clin Psychopharmacol. 2009; 17: 337-44.
6. Pelletier S, Nalpas B, Alarcon R, Rigole H, Perney P. Investigation of Cognitive Improvement in alcohol-dependent inpatients using the Montreal Cognitive Assessment (MoCA) Score. J Addict. 2016; 2016: 1539096.
7. Ewert V, Pelletier S, Alarcon R, Nalpas B, Donnadieu-Rigole H, Trouillet R, et al. Determination of MoCA cutoff score in patients with alcohol use disorders. Alcohol Clin Exp Res. 2018; 42: 403-12.
8. Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. Alcohol Alcohol. 2009; 44: 115-27.
9. Kamal H, Tan GC, Ibrahim SF, Shaikh MF, Mohamed IN, Mohamed RMP, et al. Alcohol use disorder, neurodegeneration, Alzheimer's and Parkinson's disease: interplay between oxidative stress, neuroimmune response and excitotoxicity. Front Cell Neurosci. 2020; 14: 282.
10. Wilding JPH. The importance of weight management in type 2 diabetes mellitus. Int J Clin Pract. 2014; 68: 682-91.
11. Colosia AD, Palencia R, Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. Diabetes Metab Syndr Obes. 2013; 6: 327-38.
12. Palta P, Schneider AL, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. J Int Neuropsychol Soc. 2014; 20: 278-91.
13. Gonzales MM, Tarumi T, Miles SC, Tanaka H, Shah F, Haley AP. Insulin sensitivity as a mediator of the relationship between BMI and working memory-related brain activation. Obesity (Silver Spring). 2010; 18: 2131-7.
14. Babor T, Rehm J, Jernigan D, Vaeth P, Monteiro M et al. Alcohol, diabetes, and public health inthe Americas. Rev Panam Salud Publ. 2012; 32: 151-5.
15. Chrysant SG. Pathophysiology and treatment of obesity-related hypertension. J Clin Hypertens (Greenwich). 2019; 21: 555-9.
16. Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. Hypertension. 2013; 62: 810-7.
17. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimers Res Ther. 2012; 4: 40.
18. Forte G, Casagrande M. Effects of blood pressure on cognitive performance in aging: A systematic review. Brain Sci. 2020; 10: 919.
19. Roerecke M, Kaczorowski J, Tobe SW, Gmel G, Hasan OSM, Rehm J. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. Lancet Public Health. 2017; 2: e108-20.
20. White GE, Richardson GA, Mair C, Courcoulas AP, King WC. Do associations between alcohol use and alcohol use disorder vary by weight status? Results from the national epidemiologic survey on alcohol and related conditions-III. Alcohol Clin Exp Res. 2019; 43: 1498-509.
21. Vischer AS, Burkard T. How should we measure and deal with office blood pressure in 2021? Diagnostics (Basel). 2021; 11: 235.
22. Petersmann A, Müller-Wieland D, Müller UA, Landgraf R, Nauck M, et al. Definition, classification and diagnosis of diabetes mellitus. Exp Clin Endocrinol Diabetes. 2019; 127: S1-7.
23. Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative date for the Montreal Cognitive Assessment in the population-based sample. Neurology. 2011; 77: 1272-5.
24. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
25. Bates D, Maechler M, Bolker B, Walker S. lme4: linear mixed-effects models using Eigen and S4 (R package version 1.0-5); 2013.
26. Dye L, Boyle NB, Champ C, Lawton C. The relationship between obesity and cognitive health and decline. Proc Nutr Soc. 2017; 76: 443-54.
27. Arroyo-Johnson C, Mincey KD. Obesity epidemiology worldwide. Gastroenterol Clin North Am. 2016; 45: 571–579.
28. Boeka AG, Lokken KL. Neuropsychological performance of a clinical sample of extremely obese individuals. Arch Clin Neuropsychol. 2008; 23: 467-74.
29. Pfefferbaum A, Adalsteinsson E, Sullivan EV. Dysmorphology and microstructural degradation of the corpus callosum: interaction of age and alcoholism. Neurobiol Aging. 2006; 27: 994-1009.
30. Sabia S, Elbaz A, Britton A, Bell S, Dugravot A, Shipley M, et al. Alcohol consumption and cognitive decline in early old age. Neurology. 2014; 82: 332-9.
31. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021; 320: C375-91.
32. Moheet A, Mangia S, Seaquist ER. Impact of diabetes on cognitive function and brain structure. Ann N Y Acad Sci. 2015; 1353: 60-71.
33. Marioni RE, Strachan MW, Reynolds RM, Lowe GD, Mitchell RJ, Fowkes FG, et al. Association between raised inflammatory markers and cognitive decline in elderly people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes. 2010; 59: 710-3.
34. Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and cognitive impairment. Curr Diab Rep. 2016; 16: 87.
35. Piatkowska-Chmiel I, Herbet M, Gawronska-Grzywacz M, Ostrowska-Lesko M, Dudka J. The role of molecular and inflammatory indicators in the assessment of cognitive dysfunction in a mouse model of diabetes. Int J Mol Sci. 2021; 22: 3878.

36. Crews FT, Collins MA, Dlugos C, Littleton J, Wilkins L, Neafsey EJ, et al. Alcohol-induced neurodegeneration: when, where and why? Alcohol Clin Exp Res. 2004; 28: 350-64.

37. Alagiakrishnan K, Mah D, Ahmed A, Ezekowitz J () Cognitive decline in heart failure, Heart Fail Rev 2016; 21:661–673.

38. Beauchet O, Celle S, Roche F, Bartha R, alMontero-Odasso al M-O, Allali G et al. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. J Hypertens. 2013; 31: 1502-16.

39. Mikolajczyk TP, Szczepaniak P, Vidler F, Maffia P, Graham GJ, Guzik TJ. Role of inflammatory chemokines in hypertension. Pharmacol Ther. 2021; 223: 107799.

40. Dietrich M, Jialal I. The effect of weight loss on a stable biomarker of inflammation, C-reactive protein. Nutr Rev. 2005; 63: 22-8.

41. Kopp HP, Krzyzanowska K, Möhlig M, Spranger J, Pfeiffer AFH, Schernthaner G. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. Int J Obes (Lond). 2005; 29: 766-71.

42. Donnadieu-Rigole H, Mura T, Portales P, Duroux-Richard I, Bouthier M, Eliaou JF, et al. Effects of alcohol withdrawal on monocyte subset defects in chronic alcohol users. J Leukoc Biol. 2016; 100: 1191-9.

43. Perrot N, Nalpas B, Yang CS, Beaune PH. Modulation of cytochrome P450 isozymes in human liver, by ethanol and drug intake. Eur J Clin Investig. 1989; 19: 549-55.

44. Jennings JR, Mendelson DN, Muldoon MF, Ryan CM, Gianaros PJ, Raz N, et al. Regional grey matter shrinks in hypertensive individuals despite successful lowering of blood pressure. J Hum Hypertens. 2012; 26: 295-305.

45. McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment and dementia in patients without apparent prior cerebrovascular disease. Cochrane Database Syst Rev. 2006; 2: CD004034.

46. Gunstad J, Strain G, Devlin MJ, Wing R, Cohen RA, Paul RH, et al. Improved memory function 12 weeks after bariatric surgery. Surg Obes Relat Dis. 2011; 7: 465-72.

47. Alosco ML, Galioto R, Spitznagel MB, Strain G, Devlin M et al. Cognitive function after bariatric surgery: evidence for improvement 3 years after surgery. Am J Surg. 2014; 207: 870–876.