Psychoneuroendocrinology 103 (2019) 61–66

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Utility of combined inflammatory biomarkers for the identification of cognitive dysfunction in non-diabetic participants of the ELSA-Brasil

Adriana Cezaretto[a], Bianca de Almeida-Pititto[a], Gizelton Pereira Alencar[a], Claudia K. Suemoto[b], Isabela Bensenor[c], Paulo A. Lotufo[c], Sandra R.G. Ferreira[a,*], on the behalf of the ELSA-Brasil researchers[1]

[a] Department of Epidemiology, School of Public Health, University of Sao Paulo, Brazil
[b] Division of Geriatrics, School of Medicine, University of São Paulo, Brazil
[c] Department of Internal Medicine, University of Sao Paulo, Brazil

ARTICLE INFO

Keywords:
Cognitive function
Prediabetes
Subclinical inflammation
Cluster analysis
Dementia
Prevention

ABSTRACT

Introduction: Insulin resistance and low-grade inflammation are pathophysiological mechanisms shared by type 2 diabetes and dementia. A cluster of biomarkers that could help diagnosing cognitive dysfunction prior to the installation of insulin resistance is desirable. This ELSA sub-study examined whether a cluster of selected inflammatory biomarkers was associated with worse cognitive scores in non-diabetic participants.

Methods: A sample of 998 non-diabetic participants of ELSA-Brasil had their cognitive function assessed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), a verbal fluency test and a trail making test. An inflammatory cluster was formed by using the k-means method. ANOVA was used to compare the tertiles of a composite global cognitive z-score with clinical and laboratory variables. Logistic regression modelling with forward stepwise model selection was performed considering cognitive performance as the outcome and the cluster as the independent variable of main interest. Models were stratified by sex and adjusted for age, insulin resistance and other confounders.

Results: The mean age was 45.7 ± 4.9 years and 54.8% were women, who had a higher frequency of university level, healthier behaviors and lower systolic and diastolic blood pressure (BP) levels, fasting plasma glucose, non-HDL cholesterol and E-selectin levels than men. Individuals in the highest tertile of the composite global cognitive z-score were more likely to be women, with university level, and lower mean values of body mass index, BP levels, and HOMA-IR than those in lower tertiles. Using logistic regression model, the cluster category of the highest grade of inflammation showed to be associated with worse cognitive performance in women only.

Conclusion: The association between a cluster of inflammation and worse cognitive performance seems to be useful to identify middle-aged women at risk for cognitive decline, independently of their state of insulin resistance.

1. Introduction

Increased life expectancy has resulted in high morbidity and mortality rates particularly due to cardiometabolic diseases. Despite the decline in cardiovascular mortality rates during the last decades, unhealthy lifestyle that leads to obesity has limited the control of risk factors, especially disturbances of glucose metabolism. A parallel increase in dementia prevalence has been observed, what could be partially explained by pathophysiological links with type 2 diabetes mellitus (DM) (McCrimmon et al., 2012). These diseases are among the top 10 debilitating conditions in a recent report of the global burden of diseases (Group, 2017).

A meta-analysis reported a 60% higher risk of dementia in individuals with type 2 DM compared to non-diabetic ones (Chatterjee et al., 2016). Insulin resistance and low-grade inflammation are mechanisms shared by both type 2 DM and dementia (Kim and Feldman, 2015; Awad et al., 2004; van Himbergen et al., 2012; Willette et al., 2015). Insulin resistance was associated with brain amyloid deposition

* Corresponding author at: Centro de Pesquisa Clínica e Epidemiológica, Hospital Universitário, Universidade de São Paulo, Av. Lineu Prestes 2565, 4ºandar, CEP: 05508-000, São Paulo, SP, Brazil.
E-mail address: sandrafv@usp.br (S.R.G. Ferreira).
[1] see Appendix.

https://doi.org/10.1016/j.psyneuen.2019.01.003
Received 10 October 2018; Received in revised form 23 December 2018; Accepted 3 January 2019

in late middle-aged adults (Willette et al., 2015). Moreover, in Alzheimer's disease, β amyloid deposition leads to glia activation and inflammation, favoring neuronal apoptosis. Resistance to insulin and to insulin growth factor were shown to alter expression and production of amyloid precursor protein, triggering β-amyloid deposition (Matioli and Nitrini, 2015). Insulin receptors are expressed in the central nervous system with elevated density in the hypothalamus, cerebellum, cerebral cortex, olfactory bulb, and hippocampus, which is implicated in the memory regulation (S Roriz-Filho et al., 2009). Therefore, besides being a major abnormality of glucose metabolism, insulin resistance has also been considered a pathway to neuroinflammation related to β amyloid deposition, contributing to cognitive impairment in neurodegenerative diseases.

Several cytokines have been used as circulating biomarkers of inflammation. Elevated production of TNF-α and interleukins (IL) has been described in obesity-related diseases, they were shown to deteriorate insulin signaling (Wieser et al., 2013) and their circulating levels have been associated with increased cardiometabolic risk (Lind, 2003). TNF-α and IL-6 are able to cross the blood brain barrier (BBB) and to affect processes in the central nervous system (Arnoldussen et al., 2014). Animal studies have demonstrated that TNF-α and IL-6 were also produced by glial cells. In humans, association between higher peripheral IL-6 levels and lower hippocampal grey matter volume suggested that this cytokine mediates cognitive decline (Marsland et al., 2015). TNF-α receptors activation in the brain trigger apoptosis (Montgomery and Bowers, 2012; Pickering et al., 2005) and in obese individuals, excessive production of TNF-α was shown to be neurotoxic causing memory and learning deficits (Arnoldussen et al., 2014). Since the BBB is formed by endothelial cells, endothelial dysfunction can affect its functioning and interactions with the brain. E-selectin was considered a marker of endothelial injury and useful to improve cardiovascular risk prediction (de Almeida-Pititto et al., 2016). As far as we know, whether its determination could indicate endothelial dysfunction at the BBB level, favoring neurodegenerative processes has not been investigated.

There is some evidence of sex differences regarding the correlation between immunologic markers and cognitive or neural outcomes. In middle-aged individuals of the Whitehall Study, associations between inflammatory biomarkers and cognition were detected and they were more evident in men than in women (Gimeno et al., 2008). It would be desirable to detect a cluster of biomarkers that could help diagnosing cognitive dysfunction earlier when interventions could be more effective. Cluster analysis of biomarkers seems to be an interesting approach for this purpose (Fraley and Raftery, 1998). Whether analysis of circulating biomarkers in combination would improve the identification of middle-aged individuals at a higher risk of cognitive impairment, prior the installation of insulin resistance, is unknown.

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is appropriate to investigate the hypothesis that cluster of novel biomarkers is associated with cognitive function, prior to clinical feature of insulin resistance. The ELSA-Brasil is a prospective cohort study of civil servants of universities in Brazil that investigates the incidence of type 2 DM and cardiovascular disease and their biological, behavioral, environmental, occupational, psychological and social risk factors (Aquino et al., 2012). The objective of this ELSA sub-study was to examine whether a cluster of selected biomarkers was associated with cognitive scores in non-diabetic participants before old age.

2. Methods

2.1. Participants

This cross-sectional study was conducted with baseline data of the ELSA-Brasil, whose objective and methods were previously reported (Schmidt et al., 2015; Aquino et al., 2012). Briefly, all active or retired employees of six Brazilian cities, aged 35 to 74 years, were eligible for this study. They had an initial interview and then were scheduled for clinical examination and laboratory tests in the research centers. First examinations of 15,105 individuals (54% women) were carried out from August 2008 through December 2010. The present analysis was based on the baseline data from a random sample of 1000 out of 5061 participants of the São Paulo research center included in another sub study aimed to assess the cardiometabolic profile based on non-traditional cardiovascular biomarkers, such as inflammatory and endothelial dysfunction biomarkers. For the current analysis, inclusion criteria were age range of 35 to 54 years and absence of DM and cardiovascular disease. Two individuals were excluded from the final sample because insufficient aliquots were frozen for the analysis of novel biomarkers (Almeida-Pititto et al., 2015). The institutional ethics committee approved the study and written consent was obtained from all participants.

2.2. Cognitive function evaluation

Cognitive function was assessed by three neuropsychological tests: the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) delayed word recall test (Welsh et al., 1991), semantic and phonemic verbal fluency test, and trail making test, version B. A Brazilian version of CERAD including a ten-word list was used to evaluate word-list learning, delayed word list recall, and word-list recognition (Suemoto et al., 2015), in which participants were asked to read 10 words after 3 exposures and 5 min later were asked to record these words. The score was equal to the number of recalled words. The semantic (animal category) and phonemic (letter F) verbal fluency tests were used to assess the language domain, and the score corresponds to the total number of generated words by the participant (Passos et al., 2011). The higher the scores the better cognitive function in those domains. The trail making test was used to evaluate executive function, since it is related to attention, concentration, and psychomotor speed. The score corresponded to the time (in seconds) taken to complete the test. The longer the time taken to complete, the worse the participant's performance. The six subtests can further be used to construct a composite score as an estimate of global cognitive function. A global score was converted into *z*-score using mean value equal zero and standard deviation lower or bigger than one.

2.3. Inflammatory biomarkers

Blood samples were frozen at −80 °C for further determinations of cytokines. Logistics of collection and transportation of biological samples and the organization of the central laboratory in the ELSA-Brasil were previously reported (Fedeli et al., 2013). ELISA was used for the determination of C-reactive protein and E-selectin levels (Dade Behring, Siemens, Marburg, Germany). Interleukin-6 (IL-6), IL-10 and TNF-α were measured using Bio-Plex→ Pro Human Cytokine 4-plex assay panel (Biorad, São Paulo, SP, Brazil). Intra-assay coefficients of variation ranged from 1.8 to 7.2, and inter-assay from 0.9 to 9.1, except for E-selectin (14.4%) (Almeida-Pititto et al., 2015). In order to range the same scale to comparisons, all biomarkers were converted by standard mean distribution, considering mean equal zero and standard deviation equal one.

2.4. Other variables

Physical activity level was assessed using the International Physical Activity Questionnaire (Hallal and Victora, 2004). Body weight and height were measured using calibrated electronic scales and a fixed rigid stadiometer, while individuals wore light clothing without shoes. Body mass index was calculated as weight (in kilograms) divided by squared height (in meters). Waist circumference was measured with an inextensible tape according to the WHO technique. Neck circumference was measured with individuals sitting and looking horizontally, using

an inelastic tape, perpendicular to the long axis of the neck, right under the thyroid cartilage. Blood pressure (BP) was taken three times after a 5-minute rest in the sitting position and the mean of the second and third measurements was used. Presence of hypertension was considered when systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg (or anti-hypertensive treatment). Participants underwent a 2-hour 75-gram oral glucose tolerance test, and American Diabetes Association criteria were used for diagnosing categories of glucose tolerance (Association, A. D., 2010). Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) index (Matthews et al., 1985), and was defined by values > 2.5 (Geloneze et al., 2009).

Plasma glucose was determined by the hexokinase method (ADVIA Chemistry; Siemens, Deerfield, Illinois, USA). Categories of glucose tolerance were defined according to the American Diabetes Association criteria (Association, A. D., 2010); pre-diabetes included individuals with impaired fasting glycemia and impaired glucose tolerance. Insulin was determined by enzyme-linked immunosorbent assay – ELISA (Enzo Life Sciences, Farmingdale, NY, USA). Lipid profile was measured using enzymatic colorimetric assay (ADVIA Chemistry; Siemens, Deerfield, Illinois, USA). LDL-cholesterol was calculated by the Friedewald equation and insulin concentration was determined (Siemens, Tarrytown, USA). When triglyceride concentration was greater than 400 mg/dL, the HDL-cholesterol level was directly measured.

2.5. Statistical analysis

Data were expressed as mean and standard deviation (SD) or frequencies. Student *t*-test was used to compare variables according to sex (or Mann-Whitney U test for non-normal distributed variables). ANOVA with Bonferroni post-hoc test was employed to compare continuous clinical and biochemical variables, and chi-squared test to compare categorical variables, according to global composite cognitive z-score tertiles (or Kruskal-Wallis test for non-normal distributed variables).

The correlation between each two inflammatory markers was initially tested. Except for C-reactive protein, all the four biomarkers (TNF-α, IL-6, IL-10, and E-selectin) were strongly correlated ($p < 0.001$). Then, a cluster was formed using k-means method, in which an algorithm found the partition of K sets (categories) that minimized the distance of each observation to its center (Fraley and Raftery, 1998). Each cluster center was the mean of the observations in that cluster. Partitioning in three categories of the cluster was used and they were ordinated from the lowest to highest "inflammation grade".

Logistic modelling with forward stepwise model selection was performed considering cognitive dysfunction as the outcome (first plus the second tertile of the global cognitive z-score), and the third tertile (higher scores) as the best condition. Cluster entered the models as the independent variable of main interest. Models were stratified by sex and only the one obtained for the female sex is being presented. They were adjusted for age, schooling, physical activity, alcohol use, obesity, hypertension, non-HDL cholesterol levels and insulin resistance index.

Statistical analyses were performed using the STATA version 12, and Statistical Package for Social Sciences, version 19.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The alpha level was set at 0.05.

3. Results

The mean age of the 998 participants was 45.7 ± 4.9 years, and 54.8% were women. The sample had a high level of education, and a higher frequency of women had university level compared to men (Table 1). Moreover, women were less likely to be current smokers and to consume alcohol. They had lower systolic and diastolic BP levels, fasting plasma glucose and non-HDL cholesterol. Comparing global composite cognitive z-scores, mean values differed between sexes (0.21 ± 0.8 *versus* -0.26 ± 1.1, $p < 0.001$, for women and men, respectively).

Stratifying by tertiles of cognitive performance (Table 2), individuals in the highest tertile were more likely to be women, with university level, and have lower mean values of body mass index, abdominal circumference, blood pressure, HOMA-IR and E-selectin than those in lower tertiles.

In crude model of logistic regression, lower values of cognitive scores (first plus second tertiles of global cognitive z-score) were significantly associated with the greater grade of inflammation ($p = 0.016$). When variable sex was included in the model, the significance of this association disappeared, and then analyses were stratified by sex. The association of interest in crude models maintained significant only for women.

Using age-adjusted logistic regression (Table 3, model 1) for the female sex only, the third category of the inflammatory cluster (*i.e.* highest grade of inflammation) showed to be associated with worse

Table 1
Sociodemographic, lifestyle habits, clinical and biochemical data of 998 participants according to sex. Data are described in mean (standard deviation) or frequencies.

	Women n = 547	Men n = 451	P-value
Age (years)	45.8 (4.8)	45.7(5.1)	0.185
University level (%)	51.2 (280)	30.4 (137)	< **0.001**
Current smoker (%)	15.0 (82)	22.6 (102)	**0.002**
Alcohol use (%)	67.5 (369)	75.4 (340)	**0.006**
Physical activity[#] (min/week)	19.3 (97)	23.2 (96)	0.148
Body mass index (kg/m^2)	26.3 (4.2)	26.6 (4.0)	0.283
Abdominal circumference (cm)	83.3 (10.7)	91.3 (10.7)	< **0.001**
Systolic blood pressure (mm/Hg)	112.3 (13.3)	122.6 (14.0)	< **0.001**
Diastolic blood pressure (mmHg)	72.4 (9.6)	78.7 (10.3)	< **0.001**
Fasting plasma glucose (mg/dL)	100.4 (7.4)	105.3 (12.2)	< **0.001**
Non-HDL cholesterol (mg/dL)	148.0 (35.3)	161.3 (36.7)	< **0.001**

[#] Mann-Whitney *U* test.

Table 2
Demographic, lifestyle, clinical data and inflammatory markers of participants according to tertiles of global composite cognitive z-scores. Data are described in mean (standard deviation) or frequencies.

	1st tertile (n = 325)	2nd tertile (n = 324)	3rd tertile (n = 324)	P-value
Interval Interquartiles, mean (min;max) of Cognitive z-scores	−1.10 (-4.2;-0.36)	0.08 (-0.37;0.49)	1.03 (0.50; 2.51)	–
Women (%)	136 (41.8)	178 (54.9)	220 (67.9)	< **0.001**
Age (years)	46.0 (4.9)	45.9 (5.0)	45.4 (4.6)	0.266
University level (%)	82 (25.2)	138 (42.6)	190 (58.6)	< **0.001**
Smokers (%)	68 (20.9)	65 (20.1)	46 (14.2)	0.055
Alcohol use (%)	222 (68.3)	223 (68.8)	250 (77.2)	**0.020**
Physical activity[#](min/week)	13.6 (56.9)	17.9 (55.1)	16.3 (49.6)	0.633
Body mass index (kg/m^2)	26.8 (4.2)	26.4 (4.1)	25.9 (4.1)[b]	**0.042**
Abdominal circumference (cm)	88.6 (11.5)	87.2 (11.4)	84.8 (11.0)[ab]	< **0.001**
Obesity (%)	67 (20.6)	59 (18.2)	58 (17.9)	0.627
Systolic BP (mmHg)	119 (14.4)	117 (14.3)	114 (14.1)[ab]	< **0.001**
Diastolic BP (mmHg)	76 (9.9)	75 (10.9)	73 (10.0)[ab]	< **0.001**
Hypertension (%)	72 (22.2)	77 (23.8)	56 (17.3)	0.109
Non-HDL cholesterol (mg/dL)	154 (37)	156 (37)	151 (34)	0.250
HOMA-IR[#]	2.01 (1.7)	1.87 (1.4)	1.64 (1.2)[a]	**0.006**
C-reactive protein[#](ml/L)	2.81 (4.9)	2.44 (3.0)	2.40 (3.2)	0.294
TNF-α[#] (pg/mL)	37.0 (88.8)	19.1 (36.7)	18.9 (33.8)	0.238
Interleukin-6[#](pg/mL)	21.7 (53.3)	16.3 (15.7)	18.1 (30.0)	0.414
Interleukin-10[#](pg/mL)	8.02 (47.8)	14.0 (76.2)	9.4 (52.9)	0.912
E-selectin[#](ng/mL)	85.8 (54.4)	95.2 (65.8)	80.9 (54.8)[b]	0.021

BP: blood pressure; TNF-α: tumor necrosis factor alpha.
[#] Kruskal-Wallis test and Bonferroni correction.
[a] $p < 0.05$ *versus* tertile 1; [b] $p < 0.05$ *versus* tertile 2.

Table 3
Odds ratio (95% confidence intervals) of the association between cognitive dysfunction (first plus second tertiles of global cognitive z-score) and inflammatory cluster (IL-6 – IL-10 – TNF-α – E-selectin) in women obtained by multiple logistic regression.

	Odds ratio	95% confidence interval	p-value
Model 1			
1st category of cluster (reference)	–	–	–
2nd category	1.07	0.61; 1.91	0.795
3rd category	1.67	1.13; 2.44	**0.009**
Model 2			
1st category of cluster (reference)	–	–	–
2nd category	1.28	0.67; 2.46	0.445
3rd category	1.67	1.07; 2.61	**0.024**

Model 1: adjusted for age.
Model 2: adjusted for age, university level, physical activity, obesity, hypertension, non-HDL-cholesterol, alcohol and medication use, and HOMA-IR.

cognitive function (first plus second tertiles of global cognitive z-score). Such association was maintained in the model 2 in which full adjustment was considered.

4. Discussion

Our main finding supports the hypothesis that a cluster of biomarkers could be useful to identify worse cognitive performance in women at midlife, before the development of DM even before the installation of insulin resistance. We showed that low grade inflammation and endothelial injury were directly associated with worse performance on cognitive tests in participants of the ELSA-Brasil. To our knowledge, cluster analysis addressing this association in middle-aged non-diabetic individuals had not been reported yet. Early identification of individuals at high risk for cognitive impairment is of great interest nowadays considering the urgent need of early biomarkers for dementia.

A large number of substances has been described in association with low grade inflammation – an underlying mechanism of prevalent diseases, such as type 2 DM and dementia (Kim and Feldman, 2015; Awad et al., 2004; van Himbergen et al., 2012; Willette et al., 2015). In our study, we focused on the role of circulating ultrasensitive C-reactive protein, interleukins, TNF-α and E-selectin. The former is the most recognized inflammatory marker used in clinical practice. IL-6 has been linked to altered brain morphology and cognitive decline (Marsland et al., 2015), but effects of IL-10 on neuroinflammation is controversial (Akdis et al., 2011). Animal and cell culture studies showed neuroprotective properties of IL-10 (Grilli et al., 2000), while others found unfavorable effects contributing to β-amyloid accumulation and impaired memory (Chakrabarty et al., 2015; Guillot-Sestier et al., 2015). TNF-α can induce not only insulin resistance (Senn et al., 2002), but also neuronal death and cognitive deficit (Hennessy et al., 2017). In a previous report of our group, E-selectin concentration was considered a marker of endothelial injury (de Almeida-Pititto et al., 2016). In the present analysis, its determination was used as a marker of endothelial dysfunction that could affect BBB and, consequently, predispose to neurodegeneration and cognitive decline (Hughes et al., 2018; Deane et al., 2003). Keeping all these biomarkers actions in mind, our inflammatory cluster was created.

In crude analysis, traditional cardiometabolic risk factors decreased across tertiles of cognitive z-scores, but not non-traditional ones (*i.e.* inflammatory and endothelium biomarkers), except for the HOMA-IR. Interestingly, the cluster of biomarkers, adjusted for several covariables, was significantly associated with the global composite cognitive z-score in women. In a previous study of our group, better cognitive scores in female sex had already been reported (Cezaretto et al., 2018) that is in agreement with studies investigating age- and sex-related cognitive performances, but differs from others (Proust-Lima et al., 2008; van Hooren et al., 2007; Laws et al., 2016). Some investigators who described higher prevalence of Alzheimer disease in women attributed part of such difference to survival bias, since women live longer (Viña and Lloret, 2010). A recent metanalysis did not confirm sex-related differences regarding mild cognitive impairment (Au et al., 2017). Our contrasting results could be attributed to the high proportion of premenopausal participants who also had a better cardiovascular risk profile than men. Moreover, because men in this sample are more likely to be metabolically unhealthy than women, such association could cover up any association of cognition and inflammatory cluster.

The worst category of the cluster showed to be associated with the worst cognitive performance at midlife. The adverse effect of aging in cognitive function is recognized, while schooling is neuroprotective since it is able to elevate cognitive reserve (Katzman, 1993; Gerstorf et al., 2006; Farfel et al., 2013). Our final model was adjusted for the age and schooling, and also for insulin resistance considering its role in the pathogenesis of neurodegenerative diseases. The maintenance of the association of the cluster of biomarkers with the global cognitive z-score could suggest an ability of this approach to detect an early decline in cognitive function in women before old age. A possible explanation could be an enhancement of small impacts of inflammatory and endothelium markers in circulation affecting BBB function. In fact, it was reported that several circulating substances influence the BBB and are capable of increasing brain endothelial permeability and impairing metabolic functions (Abbott et al., 2006).

Our study design impedes to guarantee that our cluster of biomarkers could help in detecting slight decline in cognitive function, independently of insulin resistance, in women at high risk for DM before old age. This possibility is being raised and deserves investigation since it was demonstrated that pathological brain lesions are present several years before dementia diagnosis (Henderson and Rocca, 2012; Serrano-Pozo et al., 2017; Sperling et al., 2014). Alarming projections of people having obesity for this century should motivate the improvement in diagnosis of obesity-related disorders including dementia.

Our study has the limitation of having investigated a specific population at risk for type 2 DM, that avoids extrapolation to the general population. However, it had the strength of having studied a large sample of middle-aged individuals with preserved neurocognitive function. Our approach using cluster of biomarkers in this cross-sectional study should motivate further investigations using prospective designs, since our analysis precludes exploring causality. The ELSA-Brasil cohort is promising to examine the ability of cluster of biomarkers at midlife to predict risk for cognitive decline.

4.1. Conclusion

In conclusion, the cluster of TNF-α, IL-6, IL-10 and E-selectin appeared to be useful to identify middle-aged women at risk for cognitive decline, independently of their state of insulin resistance. This confirmation could help the detection of increased risk for dementia at an early age, when preventive strategies could be more effective. Longitudinal analyses in the cohort of ELSA-Brasil are necessary to investigate the hypothesis raised in the current study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial disclosure

The current work was supported by grant from the São Paulo

Research Foundation (Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP – Protocol 2009/15041-9), also It was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – (Finance Code 001), by fellowship from the National Postdoctoral Program (PNPD-CAPES), Brazil. The ELSA-Brasil baseline study was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology and CNPq- National Research Council) (grants # 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, 01 06 0071.00 RJ).

Authors' contributions

AC participated in the study design, organization of the data, analysis of biomarkers, statistical analysis, interpretation of the results, draft the article. BAP participated in the design of the study, interpretation of the results and review of the article. GPA participated in the all process of statistical analysis and review of the article, CKS participated in the organization of the data about cognition and review of the article. IMB conceived of the ELSA-Brasil study, participated in the interpretation of the results and the review of the article. PAL conceived the ELSA-Brasil study, participated in the interpretation of the results and the review of the article. SRGF conceived the actual study, the design of the study, participated in the interpretation of the results and draft the article. All authors read and approved the final manuscript.

Conflicts of interest

Author's declare no potential conflict of interest relevant to this article.

Acknowledgements

The authors would like to acknowledge the participation of the 15,105 individuals recruited for this study without which this study and those based on the ELSA-Brasil cohort would not have been possible.

Appendix

Estela M. L. Aquino, Eduardo L. A. Mota (Instituto de Saúde Coletiva, Universidade Federal da Bahia, Salvador, Brazil); Sandhi Maria Barreto, Valéria Maria Azeredo Passos (Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil); Dóra Chor, Marilia S. Carvalho (Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil); Isabela M. Bensenor, Paulo A. Lotufo (Faculdade de Medicina, Universidade de São Paulo, Sao Paulo, Brazil); José Geraldo Mill, Maria Del Carmen Molina (Universidade Federal do Espírito Santo, Espírito Santo, Brazil); Bruce B. Duncan, Maria Inês Schmidt (Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil); and Moyses Szklo (Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland).

References

Abbott, N.J., Rönnbäck, L., Hansson, E., 2006. Astrocyte-endothelial interactions at the blood-brain barrier. Nat. Rev. Neurosci. 7, 41–53.

Akdis, M., Burgler, S., Crameri, R., Eiwegger, T., Fujita, H., Gomez, E., Klunker, S., Meyer, N., O'mahony, L., Palomares, O., Rhyner, C., Ouaked, N., Quaked, N., Schaffartzik, A., Van De Veen, W., Zeller, S., Zimmermann, M., Akdis, C.A., 2011. Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. J. Allergy Clin. Immunol. 127 701-21.e1-70.

Almeida-Pititto, B., Ribeiro-Filho, F.F., Lotufo, P.A., Bensenor, I.M., Ferreira, S.R., 2015. Novel biomarkers of cardiometabolic risk are associated with plasma glucose within non-diabetic range. The Brazilian Longitudinal Study of Adult Health - ELSA-Brasil. Diabetes Res. Clin. Pract. 109, 110–116.

Aquino, E.M., Barreto, S.M., Bensenor, I.M., Carvalho, M.S., Chor, D., Duncan, B.B., Lotufo, P.A., Mill, J.G., Molina, M.E.C., Mota, E.L., Passos, V.M., Schmidt, M.I., Szklo, M., 2012. Brazilian longitudinal study of adult health (Elsa-Brasil): objectives and design. Am. J. Epidemiol. 175, 315–324.

Arnoldussen, I.A., Kiliaan, A.J., Gustafson, D.R., 2014. Obesity and dementia: adipokines interact with the brain. Eur. Neuropsychopharmacol. 24, 1982–1999.

Association, A. D, 2010. Diagnosis and classification of diabetes mellitus. Diabetes Care 33 (Suppl 1), S62–9.

Au, B., Dale-Mcgrath, S., Tierney, M.C., 2017. Sex differences in the prevalence and incidence of mild cognitive impairment: a meta-analysis. Ageing Res. Rev. 35, 176–199.

Awad, N., Gagnon, M., Messier, C., 2004. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J. Clin. Exp. Neuropsychol. 26, 1044–1080.

Cezaretto, A., Suemoto, C.K., Bensenor, I., Lotufo, P.A., De Almeida-Pititto, B., Ferreira, S.R.G., Group, E.R., 2018. Association of adiponectin with cognitive function precedes overt diabetes in the brazilian longitudinal study of adult health: elsa. Diabetol. Metab. Syndr. 10, 54.

Chakrabarty, P., Li, A., Ceballos-Diaz, C., Eddy, J.A., Funk, C.C., Moore, B., Dinunno, N., Rosario, A.M., Cruz, P.E., Verbeeck, C., Sacino, A., Nix, S., Janus, C., Price, N.D., Das, P., Golde, T.E., 2015. Il-10 alters immunoproteostasis in App Mice, increasing plaque burden and worsening cognitive behavior. Neuron 85, 519–533.

Chatterjee, S., Peters, S.A., Woodward, M., Mejia Arango, S., Batty, G.D., Beckett, N., Beiser, A., Borenstein, A.R., Crane, P.K., Haan, M., Hassing, L.B., Hayden, K.M., Kiyohara, Y., Larson, E.B., Li, C.Y., Ninomiya, T., Ohara, T., Peters, R., Russ, T.C., Seshadri, S., Strand, B.H., Walker, R., Xu, W., Huxley, R.R., 2016. Type 2 diabetes As a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care 39, 300–307.

De Almeida-Pititto, B., Ribeiro-Filho, F.F., Bittencourt, M.S., Lotufo, P.A., Bensenor, I., Ferreira, S.R., 2016. Usefulness of circulating E-Selectin to early detection of the atherosclerotic process in the brazilian longitudinal study of adult health (Elsa-Brasil). Diabetol. Metab. Syndr. 8, 19.

Deane, R., Du Yan, S., Submamaryan, R.K., Larue, B., Jovanovic, S., Hogg, E., Welch, D., Manness, L., Lin, C., Yu, J., Zhu, H., Ghiso, J., Frangione, B., Stern, A., Schmidt, A.M., Armstrong, D.L., Arnold, B., Liliensiek, B., Nawroth, P., Hofman, F., Kindy, M., Stern, D., Zlokovic, B., 2003. Rage mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nat. Med. 9, 907–913.

Farfel, J.M., Nitrini, R., Suemoto, C.K., Grinberg, L.T., Ferretti, R.E., Leite, R.E., Tampellini, E., Lima, L., Farias, D.S., Neves, R.C., Rodriguez, R.D., Menezes, P.R., Fregni, F., Bennett, D.A., Pasqualucci, C.A., Jacob Filho, W., Group, B.A.B.S., 2013. Very low levels of education and cognitive reserve: a clinicopathologic study. Neurology 81, 650–657.

Fedeli, L.G., Vidigal, P.G., Leite, C.M., Castilhos, C.D., Pimentel, R.A., Maniero, V.C., Mill, J.G., Lotufo, P.A., Pereira, A.C., Bensenor, I.M., 2013. [Logistics of collection and transportation of biological samples and the organization of the central laboratory in the elsa-brasil]. Rev. Saude Publica 47 (Suppl 2), 63–71.

Fraley, C., Raftery, A.E., 1998. How many clusters? Which clustering method? answers via model-based cluster analysis. Comput. J. 41, 578–588.

Geloneze, B., Vasques, A.C., Stabe, C.F., Pareja, J.C., Rosado, L.E., Queiroz, E.C., Tambascia, M.A., Investigators, B., 2009. Homa1-Ir and Homa2-Ir indexes in identifying insulin resistance and metabolic syndrome: brazilian metabolic syndrome study (Brams). Arq. Bras. Endocrinol. Metabol. 53, 281–287.

Gerstorf, D., Herlitz, A., Smith, J., 2006. Stability of sex differences in cognition in advanced old age: the role of education and attrition. J. Gerontol. B Psychol. Sci. Soc. Sci. 61, P245–9.

Gimeno, D., Marmot, M.G., Singh-Manoux, A., 2008. Inflammatory markers and cognitive function in middle-aged adults: the whitehall ii study. Psychoneuroendocrinology 33, 1322–1334.

Grilli, M., Barbieri, I., Basudev, H., Brusa, R., Casati, C., Lozza, G., Ongini, E., 2000. Interleukin-10 modulates neuronal threshold of vulnerability to ischaemic damage. Eur. J. Neurosci. 12, 2265–2272.

Group, G.N.D.C., 2017. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet Neurol. 16, 877–897.

Guillot-Sestier, M.V., Doty, K.R., Gate, D., Rodriguez, J., Leung, B.P., Rezai-Zadeh, K., Town, T., 2015. Il10 deficiency rebalances innate immunity to mitigate alzheimer-like pathology. Neuron 85, 534–548.

Hallal, P.C., Victora, C.G., 2004. Reliability and validity of the international physical activity questionnaire (Ipaq) [Letter]. Med. Sci. Sports Exerc. 36 (3), 556.

Henderson, V.W., Rocca, W.A., 2012. Estrogens And Alzheimer Disease Risk: Is There A Window Of Opportunity? Neurology 79, 1840–1841.

Hennessy, E., Gormley, S., Lopez-Rodriguez, A.B., Murray, C., Cunningham, C., 2017. Systemic Tnf-A produces acute cognitive dysfunction and exaggerated sickness behavior when superimposed upon progressive neurodegeneration. Brain Behav. Immun. 59, 233–244.

Hughes, C.G., Patel, M.B., Brummel, N.E., Thompson, J.L., Mcneil, J.B., Pandharipande, P.P., Jackson, J.C., Chandrasekhar, R., Ware, L.B., Ely, E.W., Girard, T.D., 2018. Relationships between markers of neurologic and endothelial injury during critical illness and long-term cognitive impairment and disability. Intensive Care Med. 44, 345–355.

Katzman, R., 1993. Education and the prevalence of dementia and alzheimer's disease. Neurology 43, 13–20.

Kim, B., Feldman, E.L., 2015. Insulin resistance As a key link for the increased risk of cognitive impairment in the metabolic syndrome. Exp. Mol. Med. 47, E149.

Laws, K.R., Irvine, K., Gale, T.M., 2016. Sex differences in cognitive impairment in alzheimer's disease. World J. Psychiatry 6, 54–65.

Lind, L., 2003. Circulating markers of inflammation and atherosclerosis. Atherosclerosis 169, 203–214.
Marsland, A.L., Gianaros, P.J., Kuan, D.C., Sheu, L.K., Krajina, K., Manuck, S.B., 2015. Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain Behav. Immun. 48, 195–204.
Matioli, M.N.P.S., Nitrini, R., 2015. Mechanisms linking brain insulin resistance to alzheimer's disease. Dement. Neuropsychol. 9, 96–102.
Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28, 412–419.
Mccrimmon, R.J., Ryan, C.M., Frier, B.M., 2012. Diabetes and cognitive dysfunction. Lancet 379, 2291–2299.
Montgomery, S.L., Bowers, W.J., 2012. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. J. Neuroimmune Pharmacol. 7, 42–59.
Passos, V.M., Giatti, L., Barreto, S.M., Figueiredo, R.C., Caramelli, P., Benseñor, I., Da Fonseca, M.E.J., Cade, N.V., Goulart, A.C., Nunes, M.A., Alves, M.G., Da Trindade, A.A., 2011. Verbal fluency tests reliability in a brazilian multicentric study, elsa-brasil. Arq. Neuropsiquiatr. 69, 814–816.
Pickering, M., Cumiskey, D., O'connor, J.J., 2005. Actions of tnf-alpha on glutamatergic synaptic transmission in the central nervous system. Exp. Physiol. 90, 663–670.
Proust-Lima, C., Amieva, H., Letenneur, L., Orgogozo, J.M., Jacqmin-Gadda, H., Dartigues, J.F., 2008. Gender and education impact on brain aging: a general cognitive factor approach. Psychol. Aging 23, 608–620.
S Roriz-Filho, J., Sá-Roriz, T.M., Rosset, I., Camozzato, A.L., Santos, A.C., Chaves, M.L., Moriguti, J.C., Roriz-Cruz, M., 2009. (Pre)Diabetes, brain aging, and cognition. Biochim. Biophys. Acta 1792, 432–443.
Schmidt, M.I., Duncan, B.B., Mill, J.G., Lotufo, P.A., Chor, D., Barreto, S.M., Aquino, E.M., Passos, V.M., Matos, S.M., Molina, M.E.C., Carvalho, M.S., Bensenor, I.M., 2015. Cohort profile: longitudinal study of adult health (Elsa-Brasil). Int. J. Epidemiol. 44, 68–75.
Senn, J.J., Klover, P.J., Nowak, I.A., Mooney, R.A., 2002. Interleukin-6 induces cellular insulin resistance in hepatocytes. Diabetes 51, 3391–3399.
Serrano-Pozo, A., Aldridge, G.M., Zhang, Q., 2017. Four decades of research in alzheimer's disease (1975-2014): a bibliometric and scientometric analysis. J. Alzheimers Dis. 59, 763–783.
Sperling, R., Mormino, E., Johnson, K., 2014. The evolution of preclinical alzheimer's disease: implications for prevention trials. Neuron 84, 608–622.
Suemoto, C.K., Santos, I.S., Bittencourt, M.S., Pereira, A.C., Goulart, A.C., Rundek, T., Passos, V.M., Lotufo, P., Benseñor, I.M., 2015. Subclinical carotid artery atherosclerosis and performance on cognitive tests in middle-aged adults: baseline results from the elsa-brasil. Atherosclerosis 243, 510–515.
Van Himbergen, T.M., Beiser, A.S., Ai, M., Seshadri, S., Otokozawa, S., Au, R., Thongtang, N., Wolf, P.A., Schaefer, E.J., 2012. Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and alzheimer disease: results from the framingham heart study. Arch. Neurol. 69, 594–600.
Van Hooren, S.A., Valentijn, A.M., Bosma, H., Ponds, R.W., Van Boxtel, M.P., Jolles, J., 2007. Cognitive functioning in healthy older adults aged 64-81: a cohort study into the effects of age, sex, and education. Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 14, 40–54.
Viña, J., Lloret, A., 2010. Why women have more alzheimer's disease than men: gender and mitochondrial toxicity of amyloid-beta peptide. J. Alzheimers Dis. 20 (Suppl 2), S527–33.
Welsh, K., Butters, N., Hughes, J., Mohs, R., Heyman, A., 1991. Detection of abnormal memory decline in mild cases of alzheimer's disease using cerad neuropsychological measures. Arch. Neurol. 48, 278–281.
Wieser, V., Moschen, A.R., Tilg, H., 2013. Inflammation, cytokines and insulin resistance: a clinical perspective. Arch Immunol Ther Exp (Warsz) 61, 119–125.
Willette, A.A., Johnson, S.C., Birdsill, A.C., Sager, M.A., Christian, B., Baker, L.D., Craft, S., Oh, J., Statz, E., Hermann, B.P., Jonaitis, E.M., Koscik, R.L., La Rue, A., Asthana, S., Bendlin, B.B., 2015. Insulin resistance predicts brain amyloid deposition in late middle-aged adults. Alzheimers Dement. 11, 504–510 E1.