Larissa Fortunato Araújo

“CURSO DE VIDA E FUNÇÃO COGNITIVA NA VIDA ADULTA: ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL), 2008-2010”

Universidade Federal de Minas Gerais
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RESUMO

Introdução: Evidências indicam que o declínio cognitivo com o envelhecimento é resultado de um processo patológico que se inicia por volta dos 45 anos de idade. Com o crescente envelhecimento populacional brasileiro, as doenças neurodegenerativas tem se tornado cada vez mais um problema de saúde pública por estarem relacionadas a maior dependência e mortalidade nessa população. O estudo de marcadores de risco que afetam o desempenho cognitivo ao longo do curso de vida é de grande importância para subsidiar ações e políticas públicas que prolonguem o início do declínio cognitivo e promovam o envelhecimento saudável. Neste campo, destacam-se os estudos de marcadores socioeconômicos, nutricionais e de saúde cardiovascular, incluindo modos de vida e alimentação.

Objetivos: A presente tese tem cinco objetivos, a saber: 1)Estimar o efeito independente da baixa escolaridade materna, baixo peso ao nascer e menores comprimentos da perna e do tronco no pior desempenho dos testes de função cognitiva em adultos; 2)Analisar o efeito acumulado da baixa escolaridade materna e dos marcadores nutricionais de desnutrição pregressa no pior desempenho nos testes de função cognitiva em adultos; 3)Explorar o efeito independente da baixa escolaridade materna, menor comprimento de tronco e alto risco para doenças cardiovasculares em 10 anos por meio do Framingham Risk Score no pior desempenho cognitivo global em adultos; 4)Verificar se efeito acumulado de piores condições socioeconômicas e nutricionais no decorrer da vida, bem como do alto risco para doenças cardiovasculares em 10 anos por meio do Framingham Risk Score estão associados ao pior desempenho cognitivo global e em diferentes domínios da função cognitiva em adultos; 5) Analisar a

relação do consumo de café nos últimos 12 meses com o desempenho cognitivo global e em diferentes domínios da função cognitiva em adultos e idosos; e 6) Estimar a quantidade de consumo de café por dia que estaria relacionado ao melhor desempenho cognitivo global e em diferentes domínios da função cognitiva em adultos e idosos.

Metodologia: A amostra deste estudo é proveniente da linha de base do Estudo Longitudinal de Saúde do Adulto, composta por 15.105 adultos e idosos, servidores públicos em universidades federais e centros de pesquisa, localizados em seis estados brasileiros: Minas Gerais, São Paulo, Rio de Janeiro, Espírito Santo, Bahia e Rio Grande do Sul. Três artigos foram desenvolvidos, no primeiro artigo, as variáveis resposta foram o desempenho em três diferentes testes de função cognitiva categorizados em uma variável binária que comparou o pior decil com os demais decis. Em uma população de adultos (35-64 anos), por meio de regressão logística múltipla estimou a chance de estar no pior decil de desempenho cognitivo ao ser exposto aos seguintes marcadores de condições socioeconômicas e nutricionais de curso de vida: baixa escolaridade materna, baixo peso ao nascer e menores comprimentos de perna e tronco. No segundo artigo, por meio de regressão linear múltipla, foi investigado se a exposição a condições socioeconômicas (baixa escolaridade materna) e nutricionais (menores comprimentos de tronco) desfavoráveis no decorrer da vida e a alto risco para doenças cardiovasculares, estimado por meio do Score de Framingham para o risco de doenças cardiovasculares em 10 anos, estariam associados ao pior desempenho cognitivo global e em três diferentes testes de função cognitiva na vida adulta (35-64 anos). O terceiro artigo estimou por meio de regressão linear múltipla e modelo linear generalizado se o café em categorias de consumo nos últimos 12 meses estaria

relacionado ao melhor desempenho cognitivo global e em diferentes domínios cognitivos em adultos e idosos (35-74 anos).

Resultados: No primeiro artigo, após mutuo ajuste pelas variáveis de exposição de interesse, observamos que a baixa escolaridade materna esteve associada com um gradiente de dose-resposta a maior chance de pior desempenho em todos os testes de função cognitiva. O baixo peso ao nascer esteve associado a maior chance de pior desempenho no teste de trilha B, já o comprimento do tronco com o teste de fluência verbal semântica e fonêmica, e de trilha B. O comprimento da perna não esteve associado a nenhum teste de função cognitiva. As associações observadas não foram modificadas pela escolaridade atual do participante. No artigo dois, a baixa escolaridade materna, menor comprimento de tronco e alto risco para doenças cardiovasculares estimado por meio do Score de Framingham, estiveram associados ao pior desempenho cognitivo global e nos testes de aprendizado, retenção e reconhecimento de palavras, no teste de fluência verbal semântica e fonêmica e no teste de trilha B em adultos. No artigo três após ajuste pelas condições socioeconômicas, demográficas e de saúde atual, o consumo de maior número de xícaras de café por dia nos últimos 12 meses anteriores a realização dos testes cognitivos esteve associado ao melhor desempenho nos testes de aprendizado, retenção e reconhecimento de palavras, e pior desempenho no teste de trilha B em adultos e idosos.

Conclusões: O presente estudo encontrou que a exposição a condições socioeconômicas e nutricionais desfavoráveis no início da vida, representada pela baixa escolaridade materna, baixo peso ao nascer e menor comprimento de tronco, foram associados de forma independente com um pior desempenho nos testes de memória

semântica, aprendizado, atenção, controle executivo e linguagem em uma coorte de adultos brasileiros. Nossos resultados sugerem que a escolaridade atual atenua, mas não remove completamente a associação entre piores condições socioeconômicas e nutricionais durante a infância e adolescência e o pior desempenho cognitivo, especialmente no controle executivo. Os resultados encontrados neste estudo são consistentes aos publicados na literatura demonstrando a importância das condições socioeconômicas e nutricionais no início da vida, bem como do risco de doenças cardiovasculares no desempenho cognitivo em adultos. Uma compreensão extensiva dos determinantes sociais e de saúde na cognição requer atenção as exposições desfavoráveis a saúde no decorrer da vida, com especial foco em certos períodos (como na infância, adolescência e início da vida adula) e ao seu efeito acumulado. O consumo de até 4 xícaras de café por dia esteve associado a um melhor desempenho cognitivo relacionado a memória e preveniria o pior desempenho na função executiva em adultos e idosos, mesmo após ajuste pelas variáveis de confusão que poderiam estar associados a um mecanismo de causalidade reversa. Intervenções sociais, nutricionais e materiais em todo o ciclo de vida, e especialmente durante o início da vida, podem impactar substancialmente no envelhecimento saudável.

Palavras-chave: Escolaridade materna, peso ao nascer, comprimento de perna, cumprimento de tronco, risco de doença cardiovascular, consumo de café, ELSA-Brasil, escolaridade, função cognitiva, envelhecimento.

ABSTRACT

Introduction: Recently, evidence suggests that cognitive decline in aging is the result of a pathological process that begins around 45 years of age. By the aging of Brazilian population, the burden of neurological disease has influence on public health because it is related to high dependency and mortality in this population. The study of how socioeconomics, nutritional exposures and the cardiovascular risk disease in later life influences on cognitive performance in adults is relevant. The knowledge of risk factors of life course on cognition allows guiding for which stage of life preventive measures will prolong the onset of cognitive decline with aging. It is also relevant the study of food that have a larger consumption from the population, such as coffee, which has bioactive components that can also contribute to preventing cognitive decline.

Objectives: The objectives of this thesis are threefold: 1) to estimate the independent effect of low maternal educational attainment, low birth weight and smaller leg and trunk lengths in poor performance on cognitive function tests in adults; 2) analyze the cumulative effect of low maternal educational attainment and nutritional markers of malnutrition in poor performance on cognitive function tests in adults; 3) explore the independent effect of low maternal educational attainment, smaller trunk length and the higher cardiovascular risk disease in 10 years by the Framingham Risk Score on poor global cognition in adults; 4) to investigate the cumulative effects of worse socioeconomic and nutritional conditions throughout life, and the higher risk for cardiovascular disease in 10 years by the Framingham Risk Score are associated with poor global cognition and different domains of cognitive function in adults; and 5) analyze the relationship of coffee consumption in the last 12 months with global

cognition and different domains of cognitive function in adults and elderly; and 6) to estimate the amount of coffee consumption per day that would be related to better global cognitive performance and in different domains of cognitive function in adults and elderly.

Methodology: The sample of this study is from the baseline of the Brazilian Longitudinal Study of Adult Health, comprised of 15,105 adults and elderly, government employees from universities and research centers located in six Brazilian states: Minas Gerais, São Paulo, Rio de Janeiro, Espírito Santo, Bahia and Rio Grande do Sul. Three papers were developed, in the first article, the response variables were three different tests of cognitive function categorized into a binary variable which the worst decile was compared with the others. By multiple logistic regression in a adulthood population (35-64 years old), we estimated the chance of being in the worst decile of cognitive performance when exposed to the following markers of socioeconomics and nutritional conditions of life course, such as lower maternal education, lower birth weight, and smaller leg and trunk lengths. In the second article by multiple linear regression, we explored whether participants that were exposed to unfavorable socioeconomic (lower maternal education) and nutritional (smaller trunk lengths) conditions throughout life, and higher cardiovascular risk disease measured by Framingham Risk Score is associated with worse performance on global cognition and on three different tests of cognitive function in adulthood (35-64 years old). The third article, we estimated by multiple linear regression and generalized linear model if coffee in categories of consumption was associated with better performance on global cognition and also on various tests of cognitive function in adults and elderly (35-74 years old).

Results: In the first article, after mutual adjustments with all variables of exposure, we found that lower maternal educational attainment was associated with a dose-response gradient with higher chance of poor performance on all cognitive function tests. Low birth weight was associated with a higher chance of poor performance in trail-making test version B, also the trunk length in the phonemic verbal fluency tests and trail-making test version B. The leg length was not associated with any cognitive function test. The associations observed were not modified by the current educational level of the participant. The second article, the cumulative effect of lower maternal educational attainment, smaller trunk length and higher cardiovascular risk disease, was associated with worse performance on global cognition and also on learning, recall and word recognition tests, semantic and phonemic verbal fluency tests, and the trail-making test version B in adulthood. The third article, after adjustments for current socioeconomic, demographic and health conditions, higher consumption of coffee cups per day in the last 12 months was associated with better performance in learning, recall and word recognition tests and worse performance trail-making test version B in adults and elderly.

Conclusions: The present study found that exposure to unfavorable socioeconomic and nutritional conditions in early life, represented by lower maternal educational attainment, lower birth weight and smaller trunk lengths has an independent and negative effect on semantic memory, learning, attention, executive control and language in a cohort of Brazilian adults. Our results suggest that the current educational attainment mitigates but does not completely remove the association between poor socioeconomics and nutritional conditions during childhood and adolescence and worse cognitive performance, especially in executive control. The results of this study are

consistent with published studies demonstrating the importance of socioeconomic and nutritional conditions in early life, as well as the cardiovascular risk diseases estimated by the Framingham Risk Score on cognitive performance in adulthood. An extensive understanding of the social determinants of health and cognitive functioning in aging, requires attention to unfavorable exposures to health throughout life, with particular focus on certain periods (as in childhood, adolescence and early adulthood life), as well as the knowledge of cumulative effect. The coffee consumption until 4 cups per day may have a protective neurodegenerative effect on memory and also prevents the detrimental effect on executive function in adults and elderly, even after adjustment for confounding variables that might be associated with a mechanism of reverse causality. Social, nutrition and materials interventions throughout the life cycle, especially during early life can have a substantial impact in reducing and/or delay in cognitive decline in aging.

Keywords: life course epidemiology, maternal education, low birth weight, leg length, trunk length, cardiovascular risk, coffee consumption, education, ELSA-Brasil, cohort study and cognitive function, ageing

APRESENTAÇÃO

1. APRESENTAÇÃO

Este volume trata-se de uma tese de doutorado desenvolvida no Programa de Pós Graduação em Saúde Pública na área de Concentração em Epidemiologia da Universidade Federal de Minas Gerais (PPGSP-UFMG). Esta tese insere-se na linha de pesquisa de epidemiologia das doenças e agravos não transmissíveis do Grupo de Pesquisa GERMINAL- Grupo de Pesquisa em Doenças Crônicas e Ocupacionais. O estudo apresentado faz parte do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil). O ELSA-Brasil é um estudo prospectivo multicêntrico, desenvolvido por instituições de ensino superior e pesquisa, em seis estados brasileiros: Minas Gerais, São Paulo, Rio de Janeiro, Espírito Santo, Bahia e Rio Grande do Sul. Os principais objetivos do ELSA-Brasil são: investigar a incidência e a progressão do diabetes e das doenças cardiovasculares; e examinar os fatores biológicos, comportamentais, ambientais, ocupacionais, psicológicos e sociais relacionados a essas doenças e suas complicações, buscando compor um modelo causal que contemple suas inter-relações.[1]

Esta tese analisa dados provenientes de 15.105 participantes da linha de base do ELSA-Brasil (2008-2010), e é apresentada sob a forma de três artigos científicos que tiveram por objetivo investigar se fatores adversos do curso de vida estão associados ao desempenho em testes de função cognitiva em adultos e idosos brasileiros. A aplicação de uma perspectiva de curso de vida no estudo da cognição na vida adulta tem implicações para intervenções em saúde pública, e futuras pesquisas que objetivam desvendar os mecanismos causais e prevenir o declínio cognitivo.

[1]Aquino EML, Barreto SM, Bensenor IM, et al. ELSA-Brasil (Brazilian Longitudinal Study of Adult Health): objectives and design. Am J Epidemiol. 2012; 175(4):315-24.

CONSIDERAÇÕES INICIAIS

2. CONSIDERAÇÕES INICIAIS

A epidemiologia do curso de vida objetiva investigar o efeito de períodos da vida, bem como o efeito acumulado e a interação de processos biológicos, sociais e psicossociais[2] no desenvolvimento de doenças na vida adulta. Assim, a herança genética juntamente com exposições intrauterinas, infância, adolescência, e início da fase adulta podem influenciar a saúde do indivíduo no envelhecimento[3]. A proposta da metodologia do curso de vida é construir e testar modelos teóricos que postulam caminhos ligando exposições em diferentes momentos, sendo explicitamente necessário considerar um ordenamento temporal e suas inter-relações ocasionando resultados na saúde[4].

2.1 Perfil sócio demográfico no decorrer da vida e função cognitiva na vida adulta:

O declínio cognitivo representa umas das maiores cargas de doenças e é associado com baixa independência[5], deterioração na qualidade de vida e maior risco de morte prematura[6]. A associação entre a baixa posição socioeconômica no decorrer da vida e o pior desempenho cognitivo na idade adulta e terceira idade[7,8] direcionam medidas de saúde pública para a importância das inequidades em saúde e suas consequências no longo prazo.[9,10] Evidências sugerem uma forte associação entre

[2] Kuh D, Ben-Shlomo Y. A life course approach to chronic Disease epidemiology. Oxford: Oxford University Press, 1997.
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condições socioeconômicas na idade adulta, a escolaridade em particular, e a função cognitiva[11,12,13]. Parte dessas associações tem sido cada vez mais atribuída às condições socioeconômicas prevalentes no início da vida[14].

Há evidências robustas do efeito de condições socioeconômicas adversas no desenvolvimento cognitivo na infância e adolescência[15,16], que inclui exposições maternas durante a gestação, deficiências nutricionais, problemas de saúde, práticas parenterais, falta de estímulo mental e pobreza[17,18]. Tais condições são especialmente importantes para a função cognitiva porque a mesma se desenvolve substancialmente na infância, apresentando pouca variação durante a meia-idade[19,20]. Os anos iniciais da vida são cruciais para o desenvolvimento do cérebro, sendo concebível que ineficiências cognitivas podem se agravar com o envelhecimento[21]. Crianças de famílias com baixo perfil socioeconômico apresentaram pior desenvolvimento cognitivo do que crianças de famílias com alto perfil socioeconômico[22] e pior habilidade de fala nos primeiros cinco anos de vida[23]. Além disso, crianças nascidas em ambientes com baixo perfil

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socioeconômico geralmente tem menores oportunidades educacionais e são menos expostas à aprendizagem e a ambientes estimulantes[24,25].

Ademais, a condição socioeconômica na infância tende a influenciar as oportunidades no decorrer da vida, levando ao acúmulo de desvantagens sociais com o avançar da idade[26]. Em particular, condições desfavoráveis no início da vida parecem afetar o desenvolvimento cognitivo em todo o curso da vida[27]. Desvantagens socioeconômicas na infância restringem as oportunidades educacionais, que por sua vez limitam as opções de trabalho e podem afetar negativamente as trajetórias econômicas, acarretando em persistência e até aumento dessas inequidades[28]. Há indício de que a escolaridade materna está mais fortemente associada ao desempenho cognitivo na fase adulta do que os marcadores sociais paternos[29]. Essas relações são complexas, mas acredita-se que a posição socioeconômica dos pais influencia o desenvolvimento cognitivo dos filhos por meio do acesso aos recursos materiais e do estímulo intelectual ligado principalmente a escolaridade materna[30]. Assim, o estudo do perfil socioeconômico utilizando uma abordagem de curso de vida é fundamental para compreender como as iniquidades sociais influenciam a função cognitiva na vida adulta[31,32].

[24] Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: Conceptual models, empirical challenges and interdisciplinary perspectives. International Journal of Epidemiology. 2002; 31:285-293.
[25] Fernald LC, Neufeld LM, Barton LR, Schnaas L, Rivera J, Gertler GJ. Parallel deficits in linear growth and mental development in low-income Mexican infants in the second year of life. Public Health Nutrition. 2006; 9:178-186.
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[30] Kaplan GA, Turrell G, Lynch JW, Everson SA, Helkala EL, Salonen JT. Childhood socioeconomic position and cognitive function in adulthood. International Journal of Epidemiology. 2001; 30:256-263.
[31] Kaplan GA, Turrell G, Lynch JW, Everson SA, Helkala EL, Salonen JT. Childhood socioeconomic position and cognitive function in adulthood. International Journal of Epidemiology. 2001; 30:256-263.
[32] Turrell G, Lynch JW, Kaplan GA, Everson SA, Helkala EL, Kauhanen J, Salonen JT. Socioeconomic position across the life course and cognitive function in late middle age. Journals of Gerontology. Series B, Psychological Sciences and Social Sciences. 2002; 57(1):43-51.

2.2 Peso ao nascer e função cognitiva na vida adulta:

A fase fetal é considerada um período crítico durante o qual certas exposições podem causar alterações na estrutura dos órgãos e nas funções metabólicas. Dessa forma, influências genéticas e ambientais podem levar a mudanças permanentes no desenvolvimento do feto, resultando em baixo peso ao nascer, e uma predisposição para doenças crônicas na vida adulta. O mecanismo desta relação envolve a desnutrição fetal durante períodos críticos de rápida divisão celular, podendo impactar de forma permanente vários órgãos[33,34]. Assim, a desnutrição intrauterina pode afetar o desenvolvimento cerebral[35], que explicaria a relação entre o peso ao nascer e a função cognitiva.

Além do baixo peso ao nascer, a redução do crescimento na infância também pode ser considerada preditora de resultados adversos de saúde no decorrer da vida[36,37,38,39]. O ambiente no entorno do indivíduo também é importante para o desenvolvimento da função cognitiva. O nível educacional[40,41], área de residência[42], a ocupação dos pais e o tamanho da família na infância[43] têm sido identificados como fatores associados com baixo desempenho cognitivo. Uma possível explicação é que um ambiente adverso no estágio precoce da vida, afeta a maturação do cérebro, e pode

[33] Barker DJP. Maternal nutrition, fetal nutrition, and disease in later life. Nutrition. 1997; 13:807–13
[34] Barker DJP. Mothers, babies and disease in later life. London: BMJ Publishing Group, 1994.
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[43] Moceri VM, Kukull WA, Emmanuel I, et al. Using census data and birth certificates to reconstruct the early-life socioeconomic environment and the relation to the development of Alzheimer's disease. Epidemiology. 2002; 12:383–389.

aumentar a vulnerabilidade da função cognitiva. As dimensões da estrutura esquelética são consideradas *proxy* de informações potencialmente importantes do ambiente da infância e se mantém estáveis ao longo da vida.

Evidências sugerem que o baixo peso ao nascer ou bebês com crescimento intrauterino retardado tendem a apresentar pior desempenho cognitivo no envelhecimento[44]. Em estudos de coorte foram observadas associações entre baixo peso ao nascer e a pior desempenho na função cognitiva com o envelhecimento[45,46,47,48]. Um potencial fator de confusão da associação entre peso ao nascer e a função cognitiva é a idade gestacional: sem esta informação, muitos estudos têm sido incapazes de distinguir a influência do baixo peso ao nascer causado pela prematuridade daquela causada pela restrição do crescimento intrauterino[49,50]. Portanto, ao investigar influências do início da vida sobre o desenvolvimento cognitivo, é importante considerar a combinação de peso ao nascer e idade gestacional[51].

O baixo peso ao nascer foi associado com menor pontuação em testes de função cognitiva aos 8 anos de idade[52], e na idade de 17-18 em recrutas para o exército[53,54]. A relação entre peso ao nascer e a função cognitiva também foi verificada na vida adulta[55], sugerindo uma mediação com a cognição aos oito anos de idade. Porém, em outro

[44] Drillien CM. The incidence of mental and physical handicaps in school age children of very low birth weight. II. Pediatrics. 1967;39:238–47.
[45] Richards M, Hardy R,Kuh D, Wadsworth ME. Birth weight and cognitive function in the British 1946 birth cohort: longitudinal population based study. BMJ. 2001; 322:199–203.
[46] Sorensen HT, Sabroe S, Olsen J, et al. Birth weight and cognitive function in young adult life: historical cohort study. BMJ. 1997; 316:747.
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[48] Martyn CN, Gale CR, Sayer AA, Fall C. Growth in utero and cognitive function in adult life: follow up study of people born between 1920 and 1943. BMJ. 1996; 312:1393–6.
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[53] Sorensen HT, Sabroe S, Olsen J, et al. Birth weight and cognitive function in young adult life: historical cohort study. BMJ. 1997; 315:401-3.
[54] Seidman DS, Laor A, Gale R, et al. Birth weight and intellectual performance in late adolescence. Obstet Gynecol. 1992; 79:543–6.
[55] Richards M, Hardy R,Kuh D, Wadsworth ME. Birth weight and cognitive function in the British 1946 birth cohort: longitudinal population based study. BMJ. 2001; 322:199–203.

estudo com adultos mais velhos (com idade média de 60,9 anos), não se observou uma associação significativa entre peso ao nascer e a função cognitiva (após remover o efeito da idade e da classe social)[56]. Entretanto, uma revisão de literatura concluiu que a restrição no crescimento intrauterino teve pouco efeito sobre a função cognitiva na infância ou na adolescência, mas foi um substituto útil para a privação social[57]. Martyn e colaboradores (1996) sugerem que o crescimento fetal é menos importante do que fatores genéticos e as influências ambientais pós-natais para determinar o desempenho cognitivo na idade adulta[58].

2.3 Comprimentos de perna e tronco e função cognitiva na vida adulta:

Nas duas últimas décadas, vem crescendo o interesse dos epidemiologistas em estudar a altura em adultos[59,60] e sua relação com as doenças crônicas. A altura é influenciada por fatores genéticos e ambientais durante o crescimento pré-natal, infância e puberdade. Por isto, ela tem sido utilizada como *proxy* de condições de saúde no início da vida, desvantagem socioeconômica, deficiência nutricional e estresse psicossocial[61].

Os fatores socioeconômicos estão associados com a altura na idade adulta[62,63,64,65]. A fome e as doenças infecciosas podem influenciar o crescimento e,

[56] Martyn CN, Gale CR, Sayer AA, Fall C. Growth in utero and cognitive function in adult life: follow up study of people born between 1920 and 1943. BMJ. 1996; 312:1393–6.
[57] Hack M. Effects of intrauterine growth retardation on mental performance and behavior, outcomes during adolescence and adulthood. Eur J Clin Nutr. 1998; 52(1):65–S70.
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historicamente, tais fatores provavelmente causam a maioria das diferenças de altura entre as camadas mais pobres e mais ricas da população. O crescente enriquecimento em muitas sociedades levou a uma drástica redução da fome e das doenças infecciosas e aumento da estatura média da população[66]. Porém, os resultados acumulados da desvantagem social e material durante a vida fetal e infância podem ser responsáveis por uma parte substancial das diferenças de altura entre os vários grupos da sociedade[67].

O comprimento da perna na idade adulta pode ser um marcador útil de influências ambientais na primeira infância, uma vez que este é o período de mais rápido crescimento. Assim, a amamentação no peito, uma dieta adequada até os cinco anos de idade, e boas condições sociais no início da vida são associados com maiores comprimentos de perna. O comprimento do tronco, porém apresenta forte associação com fatores que afetam a criança por período mais longo que se inicia na infância e vai até a puberdade. E ambos estão associados com comprometimento na saúde[68].

Há mais de um século, Porter (1892) em seus estudos observou que estudantes mais altos apresentavam melhor desempenho acadêmico que os mais baixos[69]. Desde então, estudos têm mostrado uma associação positiva entre a altura para a idade, a capacidade cognitiva e os resultados educacionais[70,71]. O retardo no crescimento é um indicador de desnutrição crônica que permanece como importante problema de saúde pública em lactentes e crianças jovens na maioria dos países em desenvolvimento[72,73].

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[66] Padez C. Stature and stature distribution in Portuguese male adults 1904–1998: the role of environmental factors. Am J Human Biol. 2002;14:39–49.
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Case e Paxson (2008) observaram que crianças saudáveis e bem nutridas foram significativamente mais prováveis de atingirem a capacidade total da altura e o potencial cognitivo na vida adulta.[74] Estudos sobre o declínio cognitivo tem observado uma associação entre fatores ambientais na infância e a função cognitiva na idade adulta[75,76]. Assim, menores estaturas são preditivas de pior performance cognitiva e/ou Doença de Alzheimer (DA)[77,78]. O baixo desempenho cognitivo na idade adulta é associado com exposições no decorrer da infância que refletem o baixo perfil socioeconômico, como por exemplo, residir na zona rural, ocupação paterna com trabalhos manuais e famílias com maior número de filhos[79,80]. Assim, tem sido proposto que a etiologia da demência pode ser considerada a partir de exposições no decorrer da vida, em que fatores genéticos e ambientais interagem para desenvolvimento da demência no envelhecimento[81].

2.4 Fatores de risco para doenças cardiovasculares e função cognitiva na vida adulta:

No início dos anos 90 estudos epidemiológicos começaram a sugerir que as doenças cardiovasculares estariam associadas ao desenvolvimento da doença de

[74] Case A, Paxson C. Height, health, and cognitive function at older ages. American Economic Review, 2008; 98: 463–467.
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Alzheimer[82]. Posteriormente, houve evidências de que fatores de risco para as doenças cardiovasculares compartilhavam o mesmo caminho patológico para o desenvolvimento de demências vasculares e da doença de Alzheimer[83,84]. Existem poucos estudos na literatura que investigam os determinantes do declínio cognitivo, por meio da relação entre as doenças cardiovasculares e a função cognitiva no início da vida adulta[85,86].

Evidências científicas suportam a relação entre os fatores de risco para doenças cardiovasculares e a deficiência cognitiva em idosos[87]. Esses fatores incluem aterosclerose, hipertensão, dislipidemia e diabetes[88,89]. Vários estudos também sugerem que o elevado risco para doenças cardiovasculares levam para o início e rápida progressão de demências[90,91]. Embora a precisa relação temporal entre os fatores de risco cardiovasculares e subsequente demência ainda não está completamente estabelecida. Estudos anteriores indicam que elevados níveis de colesterol e a presença de hipertensão arterial no decorrer da vida são associados com aumento do risco para doença de Alzheimer[92,93]. Associações entre modificáveis fatores de risco cardiovascular e dano cognitivo no envelhecimento são importantes para a saúde pública porque indicam que as estratégias de prevenção primária que visem a redução

[82] de la Torre JC. Cardiovascular Risk Factors Promote Brain Hypoperfusion Leading to Cognitive Decline and Dementia. Cardiovascular Psychiatry and Neurology. 2012. doi:10.1155/2012/367516.
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[91] Sakurai H, Hanyu H, Sato T, Kanetaka H, Shimizu S, Hirao K, et al. Vascular risk factors and progression in Alzheimer's disease. Geriatr Gerontol Int. 2011; 11:211–214.
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do risco cardiovascular podem, por sua vez, também retardar o aparecimento ou diminuir a carga causada pela demência[94,95].

Alguns estudos apontam para um efeito negativo dos fatores de risco modificáveis, como obesidade e tabagismo, no desempenho cognitivo de adultos[96,97]. Elias e colaboradores (2004) observaram que adultos jovens podem ser vulneráveis da mesma maneira que adultos idosos para os efeitos danosos da hipertensão na cognição. Há evidência de que o efeito negativo dos fatores de risco para as doenças cardiovasculares na performance cognitiva não se restringem apenas aos idosos[98]. Elevados níveis de pressão arterial, colesterol e glicemia tem associação com fenótipos do envelhecimento, incluindo pior função cognitiva[99] e demência[100]. Essa relação longitudinal tem sido explorada mais extensivamente com foco na terceira idade[101]. Estudos observacionais sugerem que os fatores de risco para doenças cardiovasculares podem ser passíveis de intervenção precoce, prevenindo o dano cognitivo[102,103]. Porém, ensaios clínicos evidenciam que o tratamento da hipertensão, dislipidemia, e do diabetes, por exemplo, tiveram resultados contraditórios na função cognitiva no envelhecimento[104,105].

[94] Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. Arch Neurol. 2009; 66:1210 –1215.
[95] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011; 10:819–828.
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Beason e colaboradores (2012)[106]observaram um fraco efeito dos fatores de risco para as doenças cardiovasculares na função cognitiva em 97 adultos e idosos saudáveis. Entretanto, Kaffashian e colaboradores (2011)[107]observaram que um perfil adverso para doença cardiovascular pode estar relacionado com baixo desempenho cognitivo em servidores civis. Porém, essas associações não podem ser extrapoladas para adultos com idade inferior a 50 anos, já que os dois estudos não incluíram adultos jovens. No estudo de Whitmer e colaboradores (2005) foi observado que múltiplos fatores de risco para doenças cardiovasculares na vida adulta são independente de sexo, idade, raça e educação e substancialmente aumentam o risco de demência em idosos. Aqueles que possuem simultaneamente colesterol alto, hipertensão, diabetes e sendo tabagistas tiveram o dobro do risco de desenvolver demência comparado com quem não apresentava nenhum desses fatores de risco[108]. O score de risco para demência desenvolvido por Kivipelto e colaboradores (2005) também evidenciam o efeito de múltiplos fatores de risco para doenças cardiovasculares em adultos e o futuro risco de demência[109].

Existe um inverso gradiente na associação entre as condições socioeconômicas e as doenças cardiovasculares em muitos países em desenvolvimento, onde a posição socioeconômica em adultos é mensurada pela educação, ocupação e renda[110,111]. A evidência é bastante consistente de que a posição socioeconômica na infância (mensurada pela escolaridade e ocupação dos pais) também é inversamente associada com os fatores de risco para as doenças cardiovasculares, incluindo tabagismo, diabetes,

[106] Beason-Held LL, Thambisetty M, Deib G, Sojkova J, Landman BA, PhD; Zonderman A, Ferrucci L, Kraut MA, MD, Resnick SM. Baseline Cardiovascular Risk Predicts Subsequent Changes in Resting Brain Function. Stroke. 2012; 43:1542-1547.
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alta pressão sanguínea, colesterol e para as mulheres, obesidade[112,113,114]. Para melhor entender como a posição socioeconômica pode influenciar nas doenças cardiovasculares, é importante conhecer as condições socioeconômicas no decorrer da vida[115,116].

A exposição a circunstâncias socioeconômicas são diferentes no decorrer da vida e cada período tem influência no curso das doenças crônicas. Em estudos de caso-controle[117] e utilizando registro de óbitos[118,119], observaram que o efeito acumulado da posição socioeconômica é inversamente associado com as doenças cardiovasculares. Em uma revisão sistemática foi observado uma associação inversa entre as condições socioeconômicas na infância com o risco de doença cardiovascular em 31 dos 40 estudos analisados[120].

O mecanismo em que os fatores de risco para as doenças cardiovasculares influenciam na função cognitiva em adultos jovens ainda não estão estabelecidos. O efeito acumulado do alto risco para doenças cardiovasculares pode aumentar o risco de isquemia subclínica e causar dano cerebrovascular, especialmente de natureza subcortical. Estudos longitudinais com ressonância magnética em idosos demostram que os fatores de risco para doenças cardiovasculares podem acelerar o risco para mudanças na estrutura do cérebro, incluindo atrofia e infarto[121,122,123], e danos nas

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regiões subcorticais do cérebro podem levar um pior desempenho na função executiva[124].

2.6 Consumo de café e função cognitiva na vida adulta:

Evidências sugerem que o acúmulo progressivo do dano oxidativo no cérebro com o envelhecimento pode levar a perda cognitiva[125,126]. Nos últimos anos, baseado na possível ligação entre o dano oxidativo e o declínio cognitivo, há um crescente interesse em estudar componentes bioativos da dieta que podem atrasar ou impedir o dano celular. O café, uma bebida amplamente consumida, tem sido estudado como um alimento capaz de produzir efeitos fisiológicos ou metabólicos no organismo humano, levando o corpo a se adaptar as adversidades ambientais. Estudos têm demostrado que a cafeína, um dos principais constituintes de café, induz um grande espectro de respostas celulares e farmacológicas no sistema nervoso central com estímulo da atividade motora[127], melhoria do desempenho cognitivo[128], ansiedade e distúrbios do sono[129,130], e atividade antioxidante[131].

Além da cafeína, o café contém inúmeras outras substâncias, como polímeros fenólicos, ácidos clorogênicos, lipídeos e terpenos que possuem efeito

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antioxidante[132,133], anticancerígeno[134], antimicrobiano[135], e atividades de neuroproteção[136,137]. Evidências sugerem que há uma ligação entre o consumo crônico de café/cafeína e melhor desempenho cognitivo[138,139]. A cafeína possui efeitos agudos sobre o estado de alerta, humor e atenção[140], além de efeitos positivos em longo prazo[141], incluindo a manutenção da função cognitiva na velhice[142,143,144].

Existe uma relação dose-gradiente da cafeína no funcionamento do cérebro[145], incluindo na prevenção de lesões na substância branca e/ou lesões isquêmicas microvasculares [146]. Um potencial mecanismo para o efeito neuroprotetor de longo prazo da cafeína envolve o bloqueio dos receptores A_1 e A_{2a} da adenosina[147], o que pode reduzir os danos causados pela β-amilóide, um peptídeo tóxico que se acumula no cérebro sendo associado à doença de Alzheimer (DA)[148]. Outro mecanismo protetor da cafeína é melhorar a resistência insulínica[149], reduzindo o risco de diabetes[150], sendo o

[132] Cho ES, Jang YJ, Hwang MK, Kang NJ, Lee K, Lee HJ. Attenuation of oxidative neuronal cell death by coffee phenolic phytochemicals. Mutat Res 2009; 661:18–24.
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diabetes um forte fator de risco para o dano cognitivo. A resistência à insulina em pessoas com diabetes tipo 2 tem sido também associada com diminuição da degradação amiloide-β[151]. Estudos experimentais com ratos observaram que tanto a cafeína, como os antagonistas do receptor de adenosina A_1 e A_{2a} podem prevenir a β-amilóide de induzir danos cognitivos [152].

Um estudo recente sugere que a cafeína pode também reverter os danos cognitivos e diminuir os níveis cerebrais de amiloide-β em camundongos idosos com DA[153]. A administração crônica da cafeína em modelos experimentais mostrou ter efeitos neuroprotetores na hipóxia e isquemia, também relacionados com a ação da cafeína como antagonista do receptor de adenosina[154]. Além disso, o efeito do café também pode ser atribuído à sua capacidade antioxidante ao circular no sangue[155]. O polifenol mais abundante no café é o ácido clorogénico (o éster do ácido cafeico associado ao ácido quínico) provável responsável por uma parte importante do efeito antioxidante do café[156]. Embora os fatores de risco vasculares sejam importantes para o desenvolvimento de demência/DA[157], o efeito do café sobre os fatores de risco vasculares e suas consequências na cognição ainda não está estabelecido.

Em um estudo prospectivo com 10 anos de seguimento, com uma amostra de homens idosos, Van Gelder e colaboradores[158] observaram que um consumo de três xícaras de café (cerca de 300 mg de cafeína) por dia foi associado a um retardo do

[151] Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE .Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Ver 1999; 51:83-133.
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declínio cognitivo. Mais recentemente, mulheres que tiveram um maior consumo de café por um período de quatro anos apresentaram menor declínio cognitivo do que aquelas que consumiam menor quantidade ou não faziam uso de café[159]. Além disso, o consumo crônico do café foi associado a uma redução de 65% no risco para DA[160]. O estudo epidemiológico mais consistente que mensurou associação entre a cafeína e DA foi conduzido por Maia e de Mendonça[161]. Estes autores relataram que pacientes com DA possuíam um consumo menor de cafeína durante os 20 anos anteriores ao diagnóstico da DA, em comparação com indivíduos da mesma idade sem DA. Pelas razões apontadas acima, tem crescido o número de estudos sobre a possibilidade da cafeína/café melhorar o processamento de informação nos idosos, bem como em adultos jovens[162].

[159] Ritchie K, Carri`ere I, de Mendonc¸a A, Portet F, Dartigues J, Rouaud O, Barberger-Gateau P, Ancelin M (2007) The neuroprotective effects of caffeine: a prospective population study (the Three City Study). Neurology 2007; 69: 536-545.
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OBJETIVO

3. OBJETIVO

3.1 Objetivo Geral

Investigar se a exposição a condições adversas ao longo da vida mensuradas pela baixa escolaridade materna, marcadores antropométricos de deficiência nutricional pregressa, risco para doenças cardiovasculares em 10 anos, além do consumo de café nos últimos 12 meses influenciam no desempenho dos testes de função cognitiva em participantes do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil).

3.2 Objetivos específicos

- Estimar o efeito independente da baixa escolaridade materna, baixo peso ao nascer e menores comprimentos da perna e do tronco no pior desempenho dos testes de função cognitiva em adultos.
- Analisar o efeito acumulado da baixa escolaridade materna e dos marcadores nutricionais de desnutrição pregressa no pior desempenho nos testes de função cognitiva em adultos.
- Explorar o efeito independente da baixa escolaridade materna, do menor comprimento de tronco e alto risco para doenças cardiovasculares em 10 anos no pior desempenho cognitivo global em adultos.
- Verificar se efeito acumulado de piores condições socioeconômicas e nutricionais no decorrer da vida, bem como o alto risco para doenças

cardiovasculares em 10 anos estão associados ao pior desempenho cognitivo global e em diferentes domínios da função cognitiva em adultos.

- Analisar a relação do consumo de café nos últimos 12 meses com o desempenho cognitivo global e em diferentes domínios da função cognitiva em adultos e idosos.
- Estimar a quantidade de consumo de café por dia que estaria relacionado ao melhor desempenho cognitivo global e em diferentes domínios da função cognitiva em adultos e idosos.

ARTIGOS ORIGINAIS

4.0 ARTIGOS ORIGINAIS

4.1 Artigo Original 1

Araújo LF, Giatti L, Chor D, Passos VMA, Barreto SM: Maternal education, anthropometric markers of malnutrition and cognitive function (ELSA-Brasil). BMC Public Health 2014, 14:673.

"Maternal Education, Anthropometric Markers of Malnutrition and Cognitive Function (ELSA-Brasil)"

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Abstract

Background: The early exposure to poor social and nutritional conditions may influence cognitive function during adult age. However, the relative impact of these factors has not yet been established and they can vary during the course of life. **Methods:** Analysis of data from 12,997 participants (35-64 years) of the baseline exams (2008-2010) of the Longitudinal Study of Adult Health (ELSA-Brasil), a cohort of Brazilian civil servants. Four cognitive tests were applied: learning, recall and word recognition; semantic and phonemic verbal fluency; trail-making test version B. The markers of early nutritional and social conditions were maternal educational level, birth weight, and length of trunk and leg. The presence of independent association between every early marker and the poor performance in each cognitive test was investigated by multiple logistic regression, after mutual adjustment and considering the effects of gender, age and participant`s schooling level. The cut off for poor performance was the worst age-specific percentile of the final score distribution for each test. **Results:** After full adjustments, lower maternal education increased the chances of poor performance in all cognitive tests, with a dose-response gradient; low birth-weight was related to poor performance in the trail-making test B (OR=1.63, 95%IC=1.29-2.06); and greater trunk length decreased the chances of poor performance in the semantic and phonemic verbal fluency (OR= 0.96, 95%IC= 0.94-0.97) and in the trail-making test B (OR=0.94, 95%IC=0.92-0.95). Leg length was not associated with any of the tests examined. The associations found were not modified by the educational attainment of the participants. **Conclusions:** Early exposure to adverse social and nutritional conditions appear detrimental to semantic memory, learning, concentration, executive control and language among adults, independent of adulthood educational achievement.

Key-worlds: maternal education; nutritional markers; life course; cognitive function.

Background

Lifetime cognitive development results from a combination of normative and non-normative processes that affect cerebral function (Sliwinski *et al*., 2003). Normative ageing is associated with better cognitive abilities during early adulthood, followed by a period of relative cognitive stability during adulthood and cognitive decline with advanced age. Non-normative ageing refers to effects that go beyond the normative process and result in rapid cognitive decline, even before a disease such as Alzheimer's is diagnosed (Steinerman *et al*., 2010). Investigating the factors that influence cognitive function during adulthood is essential in order to understand these two ageing processes.

Children from families with low socioeconomic position (SEP) have much greater chances of worse health and psychological well-being, as well of impaired cognitive and emotional development throughout the lifespan (Hackman *et al*., 2010). Many indicators of SEP in the childhood have been linked to poor cognitive outcomes among adult and older individuals (Singh-Manoux *et al*., 2005; Hazzouri *et al.*, 2011; Brunner, 2005). Kaplan et al. (2001) observed that children of mothers with higher levels of education had better cognitive function during adulthood. Lower socioeconomic status during childhood was independently associated with worse semantic memory and increased rate of cognitive decline in later life among an ethnically diverse cohort in the US (Melrose *et al*., 2008). The influence of lifetime SEP on cognitive ageing is particularly important to low and middle income countries due to the enduring and profound social inequalities as well the high prevalence of poverty that prevails in most of these societies.

Victora et al. (2008) showed that maternal and child malnutrition during the first year of life can cause irreversible damages, including shorter adult height, lower

educational level and reduced adult income, and lower birth weight of offspring. Early life factors, such as low birth weight and/or growth problems during childhood and puberty seem also to have adverse effects on cognitive function in adulthood (Kaplan *et al.*, 2001; Monk *et al*., 2013; Torche *et al*., 2011; Mak *et al*., 2006). Lower adult height, which can indicate bad nutritional conditions during childhood, has been associated with worse cognitive function in adults (Abbott *et al*., 1998; Schnaider *et al*., 2005; Case, Paxson, 2008).

There is considerable debate concerning the mechanisms by which adverse SEP and nutritional conditions during early life stages influences cognitive function later in life (Glymour, Manly, 2008). Hackman et al. (2010) listed three potential mechanisms underlying the effects of SEP's on neurocognitive development: prenatal factors, parental care and cognitive stimulation. The prenatal period is a sensitive time during which intrauterine exposures can alter the course of development with enduring effects on the offspring. Review of findings from clinical, epidemiologic, and basic science research indicates that poor maternal diet and psychosocial distress during pregnancy can significantly affect children's future neurodevelopment, especially memory related (Monk *et al*., 2013). Low SEP is associated with parental irritability, depression and anxiety and can compromise the parent– child interactions (Farah *et al*., 2008). In a longitudinal study, parental care in early childhood predicted better declarative memory and smaller hippocampal volume in low SEP adolescents, independent of cognitive stimulation and maternal intelligence (Farah *et al*., 2008).

Epigenetic theory postulates that the mismatch between the maternally programmed behaviors of the offspring, and the actual environment in which he develops, may create disadvantages that increase the offspring susceptibility to health problems in adulthood, including those related to stress response, memory, and

cognitive capacity (Wilson *et al*., 2009). Cognitive stimulation during childhood is very important to boost academic and professional achievement, which are strong predictors of cognitive function in adulthood (Kaplan *et al*., 2001; Bloom *et al*., 2010). Differences in the quality and quantity of schooling is one plausible mechanism for the differences in cognitive function related to SEP, but a review on this subject showed that achievements in formal education cannot, on their own, account for all of the variance in cognition and brain development attributable to SEP (Hackman, Farah, 2009).

Low- and medium-income countries (LMIC) are facing an accelerated ageing process (Lupu *et al*., 2012), and cognitive impairment has become a growing public health problem. Currently, large numbers of people with dementia live in LMIC and rapid increases are predicted in the near future (Ferri *el al.*, 2005). However, few studies have examined the long lasting effects of early life SEP and nutritional conditions on cognitive ageing in these countries (Torche, Echevarrıa, 2011; Maurer, 2010; McEniry, 2013). Despite recent socioeconomic improvements, the greater exposure to adverse conditions during pregnancy and childhood of most Brazilians in the 20th century makes Brazilians quite different from populations of high-income countries. Thus, even a small effect of an exposure to early adverse SEP on adult cognitive function is likely to have greater impact on the Brazilian population as a whole, due to the higher prevalence of such adversities in the country.

The present study investigates whether the exposure to adverse socioeconomic and nutritional conditions early in life influences cognitive function in adulthood, using the baseline data from the Longitudinal Study of Adult Health (ELSA-Brasil).

Methods

The ELSA-Brasil is a prospective multicenter study with 15,105 active and retired civil servants of higher education and research institutions in six Brazilian states. A detailed description of the baseline study has been published elsewhere (Aquino *et al.*, 2012; Schmidt *et al*., 2014)

This study uses data regarding all the adults (35-64 years old) who undertook cognitive tests in the baseline study (2008-2010). Since intrinsic aspects of ageing and certain clinical conditions affect cognitive function, participants aged 65 years or more and those who reported previous diagnosis of stroke and/or who were using neuroleptics, anticonvulsants, anticholinesterase or antiparkinsonian drugs did not participate in the present analysis. We also excluded participants who had reading difficulties and those who took the learning, recall and word recognition tests using figures instead of words.

From 12,997 eligible participants, 12,988 took the learning, recall and word recognition test (99.9%), 12,953 the semantic and phonemic verbal fluency tests (99.7%) and 12,399 the trail-making test B (95.4%). All participants had their standing and sitting height measured; 10,707 knew their birth weight and were term birth (86.9%), and 12,742 reported their mothers' educational level (98.0%).

Response variables

The response variables were the final scores obtained in the following cognitive function tests:

1) The **learning, recall and word recognition tests** of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Bertolucci *et al*., 1998) validated for the

elderly Brazilian population, were used to evaluate declarative memory. We used the simple sum of the scores of these three tests.

2) The **semantic (animal category) and phonemic (letter F) verbal fluency tests,** which are also part of the CERAD's (Bertolucci *et al*., 1998) group of tests, were used to evaluate semantic declarative memory and language. The score corresponds to the total number of correct animal names and words beginning with the letter "F" given by the participant. Initially, the semantic verbal fluency (animals) and the phonemic verbal fluency (letter F) tests were analyzed separately, but there were no differences in the direction and magnitude of the associations found. For this reason, they were after analyzed together and we considered the simple sum of the scores of both tests.

3) The **trail-making test** evaluates executive function, which is related to attention, concentration and psychomotor speed (Lezak *et al*., 2004). The Trail-making test version A was used as a training test by the participants. The score corresponded to the time (in seconds) taken to complete trail-making test version B. In this article, we will refer to the trail-making test version B such as trail-making test B.

The reliability of these tests varied from moderate, for the learning and word recall test (Kappa= 0.56; 0.33-0.79), to very good, for the trail-making test B (Kappa=0.91; 0.87-0.95) (Batista *et al*., 2013).

The present study did not use predefined cut-off points, as they are not available for healthy and functional adults. The final score obtained in each test was categorized using age-specific deciles based on 5-year age intervals (35-39, 40-44, 45-49, 50-54, 55-59, 60-64). The individuals located in the first decile of the learning, recall and word recognition tests and of the semantic and phonemic verbal fluency tests and those located in the tenth decile of the trail-making test B were regarded as having poor test performance. The age-specific cut-off points that defined poor performance in each test

were presented in the Table 1.

Table 1. Age-specific cut-off points that represented poor performance in the learning, recall and word recognition tests, semantic and phonemic verbal fluency tests and trail-making test B among adults' participants of the ELSA-Brasil (2008-2010)

	Learning, recall and word recognition (n=12,988)	**Semantic and phonemic verbal fluency (n=12,953)**	**Trail-making test B (n=12,399)**
Age (years)	**Up to (no. of words)**	**Up to (no. of words)**	**Above (duration in seconds)**
35-39	34	24	129
40-44	32	23	153
45-49	31	22	175
50-54	30	20	225
55-59	28	19	256
60-64	28	19	266

Explanatory variables of interest

The level of maternal educational attainment was assessed by the question, "What is your mother's educational level?" and the answers grouped into four categories: high school or more (≥11 years of school), complete elementary school (≥8 and <11 years of school); did not finish elementary school (<8 years of school); and never attended school. The birth weight was obtained by the question: "According to the information you have, what was your birth weight?" and a weight inferior to 2.5 kg was classified as being low birth weight. The participants who reported premature birth were not included in this analysis, because prematurity affects not only birth weight but also can compromise growth development beyond birth weight.

Since leg length and trunk length are influenced by nutritional conditions in different phases of a child development, we used both measures to investigate the relationship between nutritional conditions in early life and cognitive function in adulthood (Wadsworth *et al*., 2002). Leg and trunk length (in centimeters) were ascertained by combining the standing and the sitting heights. Trunk length was

obtained by subtracting the height of the bench (46 cm) used to measure the sitting height from the total sitting height. Leg length was obtained by subtracting the trunk length from the standing height. In order to avoid multicolinearity with age, for the regression analysis we created centered variables for leg and trunk length by means of subtracting each individual measure of leg and trunk lengths from their gender-specific means. The centered leg and trunk length were entered as continuous variables in the analysis.

Adjusting variables

The following variables were considered as potential confounders in the analyses: gender, age (continuous in the multivariate analyses) and current educational level (undergraduate school, high school, elementary school, incomplete elementary school). Income per capita was not included as a control variable due to its high correlation with educational attainment (Spearman's rho= 0.69).

Statistical analysis

The associations between the covariates and each response variable were estimated by the chi-square test (categorical variables) and by the t test for means (continuous variables) using a significance level of $p<0.05$. The magnitude of the associations were estimated by the odds ratio (OR) and its 95% confidence interval, obtained by logistic regression.

The spearman correlation coefficients regarding the explanatory variables of interest were weak, except for the one concerning leg and trunk lengths, which was moderate (data not shown). We tested for possible multicollinearity between the

variables included in the final multivariate model by calculating the variance inflation factor (VIF).

Due to the high percentage (13.1%) of missing information on birth weight, we performed the multiple imputation procedure by logistic regression to correct for this loss of information, using the following variables in the estimation of missing data: gender, age, education, leg and trunk lengths, and maternal education. We assumed that missing data on birth weight was not because of any specific variable for which information was lost. Each missing information was imputed twenty times, given its binary nature and the large amount of missing data. A complete data analysis was performed on each imputed data set, and their final results were combined according to the rule of Rubin (1987) (Rubim, 1987). The imputation was performed using the package MICE (Buren, Groothuis-Oudshoorn, 2011) of the R software version 3.0.1. The birth weight was imputed for the participants with term birth, and the imputed variable was used only in the analysis by logistic regression.

We guided the multivariate analysis by the life-course approach, which hypothesizes that the health in adulthood is affected by the complex interplay of social and biological factors during pregnancy, infancy and childhood (Kuh, Ben-Shlomo, 1997). A fully adjusted OR for the association between every explanatory variable of interest (maternal education, low birth weight, trunk and leg lengths) and poor performance in each of the cognitive tests was obtained by multivariate logistic regression analysis. Firstly, we estimated the crude OR for each exposure of interest (Model 0), then we adjusted the crude OR that were statistically significant for age, gender and participant`s schooling level (Model 1). Afterwards, we further adjusted the OR for the other exposures of interest (Model 2), whenever they were also associated with the response variable at the level of $p<0.05$ in Model 1. We retained in the final

model all the variables that remained statistically associated with the response variable ($p<0.05$) after all the adjustments. In order to test for possible heterogeneity in the effect of every variable of interest according to the educational attainment of the participant we created and added interaction terms to the final model, retaining the ones that were statistically significant. The goodness of fit of the final models was assessed by the Hosmer & Lemeshow test. The analysis was performed using Stata 12.0 (Stata Corporation, College Station, USA).

Ethical aspects

All participants signed a free and informed consent form. The study was approved by the National Committee of Ethics in Research (approval nº 976/2006).

Results

Among the 12,997 participants, 54.8% were women, 25.2% were between the age of 35 and 44 years, 44.0% between 45 and 54 years, and 30.8% between 55 and 64 years. Most of the participants (52.7%) had undergraduate education, 36.5% had completed graduate school, and 4.4% had not finished elementary school. The majority of the participants' mothers did not complete elementary school (56.2%) and 24.4% had high school or more. The frequency of low birth weight was 5.5% (Table 2).

The mean leg length was 82.34 cm (SE=0.06) for men and 75.32 cm (SE=0.05) for women. The mean trunk length was 90.17 cm (SE=0.05) for men and 84.06 cm (SE=0.04) for women.

Table 2. Socio-demographic characteristics and birth weight of participants of the ELSA-Brasil (2008-2010)

Variables	**N**	**%**
Gender		
Male	5,880	45.2
Female	7,117	54.8
Age (years)		
34-39	1,133	8.7
40-44	2,145	16.5
45-49	3,006	23.1
50-54	2,716	20.9
55-59	2,430	18.7
60-64	1,567	12.1
Educational attainment		
Undergraduate school or more	6,851	52.7
High school	4,743	36.5
Elementary school	826	6.4
Incomplete elementary school	577	4.4
Maternal education		
High school or more	3,112	24.4
Elementary school	2,471	19.4
Incomplete Elementary school	5,492	43.1
Never attended school	1,667	13.1
Missing	255	2.0
Birth-weight (Kg)		
≥2.5	10,115	94.5
<2.5	592	5.5
Missing	1,621	13.1

The prevalence of poor performance in all cognitive tests was more frequent among men and reduced as the educational level of the participant increased ($p<0.001$ in all tests). The frequency of poor performance was also more frequent as maternal education decreased and it was greater among participants who reported low birth weight ($p<0.001$ in all tests) (Table 3). Overall, the greater leg and trunk lengths, lower the chance of poor performance in the semantic and phonemic fluency and trail-making test B ($p<0,001$). The association between leg and trunk length and poor outcome in the learning, recall and word recognition test was statistically significant among men ($p=0.016$), but borderline among women ($p<0.054$) (Table 4).

Table 3. Prevalence of poor performance in the learning, recall and word recognition tests, semantic and phonemic verbal fluency tests and trail-making test B, according to socio-demographic characteristics and birth weight among adults (35-64 years-old) participants of the ELSA-Brasil (2008-2010)

Explanatory variable	**Learning, recall word recognition (%)**	**Semantic and phonemic verbal fluency (%)**	**Trail-making test B (%)**
Gender			
Male	16.8	13.0	11.6
Female	7.4	9.5	8.6
Educational attainment			
Under Graduate school or more	5.4	3.1	2.0
High school	15.1	14.6	14.7
Elementary school	25.9	34.7	31.8
Incomplete elementary school	37.7	43.6	51.7
Maternal education			
High school or more	6.3	3.8	2.4
Elementary school	8.2	8.4	6.9
Incomplete Elementary school	12.3	12.0	10.5
Never went to school	22.2	23.3	26.5
Birth-weight (Kg)			
$\geq$2.5	10.8	9.7	8.5
<2.5	14.9	14.5	17.9

Chi-squared test with $p<0.001$ in all tests.

Table 4. Poor performance in the learning, recall word recognition tests, semantic and phonemic verbal fluency tests, and trail-making test B, according to the leg and trunk lengths among adult men and women (35 to 64 years of age) participating in the ELSA-Brasil (2008-2010)

Explanatory variable	Learning, recall word recognition (N= 12,980)		Semantic and phonemic verbal fluency (N= 12,945)		Trail-making test B (N=12,392)	
	Poor Performance		Poor Performance		Poor Performance	
	Yes Mean (SE)	No Mean (SE)	Yes Mean (SE)	No Mean (SE)	Yes Mean (SE)	No Mean (SE)
Leg length (cm)						
Men	82.02 (0.14)*	82.40 (0.07)	81.56 (0.17)	82.45 (0.06)	81.72 (0.18)	82.49 (0.07)
Women	74.98 (0.17) (a)	75.35 (0.05)	74.79 (0.16)	75.38 (0.05)	74.82 (0.17)	75.40 (0.06)
Trunk length (cm)						
Men	89.54 (0.12)	90.31 (0.05)	88.80 (0.14)	90.39 (0.05)	88.47 (0.14)	90.52 (0.05)
Women	83.19 (0.15)	84.13 (0.04)	82.71 (0.14)	84.20 (0.04)	82.60 (0.14)	84.27 (0.04)

T test with $p<0.001$ in all tests. (a)Was not significant. *$0.01<p< 0.05$

In the logistic regression analysis (Table 5), after considering the effect of gender, age and individual's educational attainment (Model 1), lower maternal education remained associated with poor performance in all cognitive function tests. Low birth-weight continued to be associated with poor performance in the trail-making test B (OR=1.73, 95%IC=1.37-2.18). Leg length did not remain associated with poor performance in any of the cognitive tests examined. The OR for the association between leg length and poor outcome in the semantic and the phonemic verbal fluency test was borderline ($p<0.057$). Greater trunk length decreased the chance of poor performance in the semantic and phonemic verbal fluency test (OR=0.95, 95%IC=0.93-0.96) and in the trail-making test B (OR=0.93, 95%IC=0.91-0.94). The associations between trunk length and poor performance in learning recall and word recognition test became borderline ($p<0.053$). In all of the previous analysis, the associations were slightly weaker after considering the effect of the socio-demographic variables.

In Model 2 (Table 5), after full adjustment, low maternal educational level remained associated with higher chances of having a poor performance in all cognitive tests. Low birth weight only remained associated with poor performance in the trail making test B (OR=1.63, 95%IC=1.29-2.06). Greater trunk length persisted associated with lower chances of poor outcome in the semantic and phonemic verbal fluency tests (OR=0.96, 95%IC=0.94= 0.97) and in the trail-making test B (OR=0.94, 95%IC=0.92-0.95). Leg length did not remain statistically associated with poor performance in any of the cognitive tests examined. There was no statistically significant interaction between any of the explanatory variables in final models and the educational achievement of the participants. The variance inflation factor of the final models ranged from 1.71 to 3.23. The Hosmer & Lemeshow test indicated good fitting of all final models (p-values range from 0.11 to 0.84).

Table 5. Crude and adjusted *Odds Ratios* for poor performance in the learning, recall, word recognition tests, semantic and phonemic verbal fluency tests and trail-making test B, according to maternal education, low birth-weight, leg and trunk lengths among men and women (35 to 64 years of age) participating in the ELSA-Brasil (2008-2010)

Cognitive function test	**Learning, recall and word recognition**			**Semantic and phonemic verbal fluency**			**Trail-making test B**		
Explanatory variable	**Crude OR (CI-95%)**	**Model 1 (CI-95%)**	**Model 2 N=12,734 (CI-95%)**	**Crude OR (CI-95%)**	**Model 1 (CI-95%)**	**Model 2 N=12,694 (CI-95%)**	**Crude OR (CI-95%)**	**Model 1 (CI-95%)**	**Model 2 N=11,547 (CI-95%)**
Maternal education									
High school or more	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elementary school	1.32 (1.08, 1.62)**	1.02 (0.83, 1.27)	1.02 (0.83, 1.27)	2.34 (1.86, 2.95)**	1.48 (1.16, 1.89)**	1.42 (1.12, 1.82)**	3.02 (2.29, 4.00)**	1.80 (1.35, 2.41)**	1.72 (1.27, 2.33)**
Incomplete Elementary school	2.11 (1.79, 2.49)**	1.36 (1.13, 1.62)**	1.36 (1.13, 1.62)**	3.46 (2.83, 4.25)**	1.64 (1.32, 2.03)**	1.58 (1.27, 1.95)**	4.76 (3.72, 6.09)**	2.07 (1.59, 2.69)**	1.95 (1.48, 2.56)**
Never went to school	4.23 (3.51, 5.08)**	1.89 (1.53, 2.34)**	1.89 (1.53, 2.34)**	7.76 (6.24, 9.64)**	2.17 (1.70, 2.78)**	2.02 (1.58, 2.58)**	14.60 (11.28, 18.90)**	3.89 (2.93, 5.16)**	3.53 (2.63, 4.75)**
Birth-weight (Kg)									
≥2.5	1.00	1.00	-	1.00	1.00	-	1.00	1.00	1.00
<2.5	1.34 (1.08, 1.67)**	1.07 (0.85, 1.35)		1.55 (1.25, 1.92)**	1.13(0.90, 1.43)		2.20 (1.79, 2.71)**	1.73 (1.37, 2.18)**	1.63 (1.29, 2.06)**
Centered leg length (cm)	0.98 (0.97, 0.99)**	1.00 (0.99, 1.01)	-	0.96 (0.95, 0.97)**	0.99 (0.97, 1.00)	-	0.97 (0.95, 0.98)**	0.99 (0.98, 1.01)	-
Centered trunk length (cm)	0.94 (0.93, 0.96)**	0.98 (0.97, 1.00)	-	0.89 (0.88, 0.91)**	0.95 (0.93, 0.96)**	0.96 (0.94, 0.97)**	0.87 (0.86, 0.88)**	0.93 (0.91, 0.94)**	0.94 (0.92, 0.95)**

Model 1: Variables adjusted for gender, age and educational attainment of the participants. Model 2: Variable(s) that remained statistically associated after adjustment for all the variables in Model 1 plus the other explanatory variables in the table. *$0.01<p< 0.05$ and **$p<0.01$

Discussion

In this cohort of Brazilian public servants, we found that poor performance in all cognitive function tests was associated with lower maternal educational attainment. We also verified that participants with adverse nutritional markers at birth and during childhood exhibited higher chances of poor outcomes in the semantic and phonemic verbal fluency and in the executive function tests. We found no indication that the educational attainment of the participants modified the associations found.

Longitudinal studies among adults have shown strong associations between early socioeconomic factors and cognitive function (Zhao *et al*., 2005), in special between better socioeconomic conditions and better cognitive performance and slower age-related decline in cognitive performance (Anstey *et al*., 2001; Turrell *et al*., 2002). However, it is still not clear which specific domains of adult cognition are associated with early socioeconomic conditions and to what extent current socioeconomic conditions, especially education, can mitigate or overcome the effects of early socioeconomic adversity that were found in this and earlier studies. Evidences suggest that childhood socioeconomic status is particularly important to performances on language and executive function tests (Hackman, Farah, 2009).

Our findings support previous ones, which indicate that the influence of maternal education on cognitive function tend to persist during adulthood after considering the formal education of the participants. Similar association was found in a cohort of men between the age of 50 and 64 years (Kaplan *et al*., 2001). Results from the Aging, Demographics and Memory Study (Rogers *et al*., 2009) suggested that, after adjusting for paternal education, exposure to low maternal schooling doubled the risk of cognitive impairment, even for the elderly.

Maternal education is associated with better health and nutritional conditions during pregnancy and after birth (Shmueli *et al*., 1999; Victora *et al*., 1992), which indirectly predicts better health and development throughout life (Victora *et al*., 2008). Higher maternal education also relates to better learning environments in childhood, more intellectual stimulation and greater mentorship quality, which, in turn, can lead to higher educational attainment and better cognitive performance (Dubow *et al*., 2009; Jefferson *et al*., 2011; Byford *et al*., 2011). Among the participants in this study, maternal schooling was moderately correlated with the individual's educational level (Spearman's rho= 0.43, data not shown).

Executive functions refer to the cognitive processes that are necessary for concentration, working memory, behavioral regulation and academic performance (Clair-Thompson, Gathercole, 2006). In the present study, the magnitude of the association between low birth weight and poor performance in the trail-making test B decreased after controlling for the effects of participant educational level, which suggests that educational attainment throughout life may mitigate the negative effects of low birth weight on adult executive function. In the Helsinki Birth Cohort, low birth weight and smaller head circumference were associated with poorer cognitive ability among men with an average age of 67.9 years and with a decline in cognitive ability after the age of 20.1 years (Raikkonen *et al*., 2013).

Adult leg length is a marker of environmental and nutritional conditions during early childhood, a period of faster leg growth. In contrast, trunk length is a marker of factors taking place after early infancy and before puberty, when the trunk growth more rapidly (Bogin, Varela-Silva, 2010, Wadsworth *et al*., 2002). A birth cohort study in Brazil showed that leg and trunk length contribute almost equally to differences in overall height, and that both biological and socioeconomic variables strongly influence

determinants of height, though socioeconomic factors appear to be more important in early growth (Gigante *et al*., 2009).

Growth considered as the reflection of genetics, childhood nutrition, and childhood medical illness, appears to provide a milieu upon which cognitive ageing occurs (Melrose *et al*., 2013). Many epidemiological studies reported on the association between shorter adult height and poor cognition in adults (Abbott *et al*., 1998; Case, Paxson, 2008; Maurer, 2010; Quan *et al*., 2013; Laitala *et al*., 2011), but few studies have examined the separate contributions of the trunk and the lower limb.

In the present study, leg length was not associated with poor performance in any of the cognitive function tests. Increased trunk length, on the other hand, reduced the chances of poor performance in the semantic and phonemic verbal fluency tests and in the trail-making test B. That is, after adjusting for social and demographic factors, maternal education and birth weight (Model 2), there were more subjects with poor cognitive performance among participants with shorter trunk length than among those with lengthier trunks.

Heys et al. (2009) observed a stronger effect of the trunk length than the leg length on cognition, suggesting that early childhood growth might be less important than later childhood development, or its effect on adult cognition more difficult to be overcome. However, a study of community residents in Korean aged 65 years and more found that only limb length (but not trunk length) was associated with dementia/cognitive impairment, after adjustment for age and education (Abbott *et al*., 1998). Research with healthy populations indicates that the environment is a more powerful force influencing height and body proportions than genes (Raikkonen *et al.*, 2013), and that parental heights have stronger influence on leg than trunk length (Li *et al.*, 2007). However, as we have no information on parental height, we cannot discard

the possibility of a common genetic pathway underlying both trunk growth and poor cognition in the present study.

Our results may have important implications for the Brazilian population because a sizeable fraction of the adults and elderly in the country were born from mothers with low level of education and experienced socioeconomic hardship during childhood and adolescence. More than 50% of the Brazilians were illiterate in the 1940s and 1950s, and more than one-third of the population was still illiterate in the 1970s (Barros *et al*., 2002). In the 1970s, 54% of the Brazilians lived below the poverty line (per capita monthly income below US$90) and 18.6% of the children under 5 years old were malnourished (Monteiro *et al*., 1992). Thus, Brazil will continue to have cohorts of adults and elders exposed raised by mothers with low educational attainment or who faced nutritional scarcity in childhood for many decades to come. Thus, even small effects of such exposures are of great importance to public health.

ELSA-Brasil is a longitudinal study that will evaluate cognitive function in Brazilian adults. The longitudinal design will enable the measurement of changes in cognitive function during the follow-up visits and to examine whether maternal education, birth weight, leg and trunk lengths predict cognitive decline. Despite the cross-sectional nature of these analyses, there is no doubt that the indicators of early socioeconomic position examined precede the measures of cognitive function.

The prevalence of the exposures examined in the present study is likely to differ from that found in the Brazilian population as a whole, because the ELSA-Brasil cohort is not representative of the country population, does not include the unemployed and has a much higher percentage of people with university degree. However, the social and regional diversity of the ELSA-Brasil cohort is large enough to allow the investigation of important inequities in health in Brazil (Santos *et al*., 2014; Mueller *et al*., 2014),

such as the ones examined in this work. As extensively debated recently, sampling representativeness is necessary when we aim to estimate the prevalence of a condition in a given population, which is not the objective of the present study, but it is not required to draw valid scientific inferences for associations found in well-conducted epidemiological studies (Rothman *et al*., 2013; Richiardi *et al*., 2013).

We believe that the associations found in this study are not confounded by disease status as we have excluded individuals with previous history of stroke or who were using medication for neurologic or psychiatric conditions that are known to interfere with the performance on cognitive tests. The influence of maternal education, birth weight and trunk length on cognition found is not confounded by current markers of socioeconomics condition presented in this paper. However, it is possible that other early socioeconomic factors such as paternal schooling might also play some role in the associations found, but it is not available in ELSA-Brasil.

Some participants may have incorrectly informed their birth weight or mother education, but there is no reason to suppose that such misclassifications biased the associations found with poor cognitive performance. Because the percentage of missing was high for low birth weight, we performed multiple imputations for this variable, so that the final OR (and 95%CI) reported for low birth weight take into account the uncertainty due to the missing data values (Donders *et al.*, 2006). We also conducted complete case analysis considering only the participants who had information on all the variables considered in the analysis, and the results were similar those reported here.

Conclusion

The present study found that the exposure to unfavorable socioeconomic and nutritional conditions during early life, represented here by low maternal educational level, low birth weight and smaller trunk length, have independent negative effects on semantic memory, learning, attention, executive control and language in a cohort of Brazilian adults. Our results suggest that educational attainment in adulthood reduces, but does not remove, the associations between worse SEP during childhood and poor cognitive performance, especially in the executive function test.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors Barreto SM, Giatti L and Araújo LF conducted the literature review, designed the study's analytic strategy and prepared the first and final version of the manuscript. Passos VMA and Chor D contributed to the discussion and to the final version of the manuscript. The ELSA investigators Passos VMA, Giatti L and Barreto SM implemented and evaluated cognitive function tests in ELSA Brasil, including quality assurance and control, supervision of field activities, data processing and treatment.

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4.2 Artigo Original 2

Araújo LF, Giatti L, Passos VMA, Benseñor IM, Reis RCP, Ikram MA, Tiemeier H, Barreto SM: Adverse socioeconomic trajectories and higher cardiovascular risk predict worse performance on cognitive function tests in adults (ELSA-Brasil)

"Adverse socioeconomic trajectories and higher cardiovascular risk predict worse performance on cognitive function tests in adults: The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)"

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Abstract

Background: The onset of cognitive decline in old age is the result of a long-term pathological process that evident starts around at the age of 45 years. **Methods:** We examined the effects of early nutritional and social conditions, cardiovascular disease risk and also the cumulative disadvantage from childhood through adulthood on the cognitive performance among 10,773 civil servants, aged 35–64 years, workers of public universities and research institutes, in six Brazilian states. **Results:** After mutual adjustments for all exposures, the lower maternal educational attainment, smaller trunk lengths and higher cardiovascular disease risk assessed by the Framingham Risk Score were associated with worse performance in general cognitive factor and also with specific domains task, by the learning, recall and word recognition tests, semantic and phonemic verbal fluency tests, and the trail-making test version B. **Conclusions:** Life course disadvantages seem to operate through biological and social mechanisms representing active cognitive reserve. Prevention of dementia should start early in life and continue through life span as seen with many other chronic diseases.

Keywords: maternal education; nutritional markers of malnutrition; cardiovascular disease risk; life course; cognitive function.

Background

The vascular risk factors and cardiovascular disease (CVD) influence the cognitive impairment and dementia in elderlies (Viswanathan *et al*., 2009; Rusanen *et al.*, 2014). Also, CVD risk factors cluster and interact multiplicatively to promote vascular risk (Barnes *et al.*, 2011). Evidences suggest a negative effect of modifiable risk factors, such as obesity, smoking and hypertension, on cognitive performance in young adults (Fried *et al.*, 2006; Gunstad *et al.*, 2006; Elias *et al.*, 2004). Thus, there is some evidence that an adverse impact of cardiovascular risk factors on cognitive performance is not limited to older adults. Recently, it was found that cognitive decline in old age is the result of a long-term pathological process that starts around the age of 45 years (Singh-Manoux *et al.*, 2012, Hoogendam *et al.*, 2014).

Adult height, leg and trunk lengths are widely available biomarkers that reflect the interplay of genetic endowment and early-life experiences and exposures (such as fetal, dietary, social and psychological circumstances) (Kuh, Ben-Shlomo, 2004; Perola *et al*., 2007; Lango *et al*., 2010; Batty *et al*., 2009). Studies have reported negative associations between adverse nutritional markers and increased risk of subsequent cardiovascular disease outcomes (Waaler, 2011; Paajanen *et al*., 2010; Lee *et al.*, 2009) and also adverse effects on cognitive function in adulthood (Abbott *et al.*, 1998; Case, Paxson, 2008a; Mak *et al.*, 2006).

Strong inverse socioeconomic gradients in CVD exist in many developed countries (Kaplan *et al*., 1993; González *et al*., 1998). Evidence is fairly consistent that childhood socioeconomic position (SEP) (often measured as parents' occupation or education) is inversely associated with CVD (Galobardes *et al.*, 2008). There also tend to be socioeconomic gradients in the expected directions for CVD risk factors including smoking, diabetes, blood pressure, total cholesterol, and, for women, obesity (Kaplan *et*

al., 1993; Gilman *et al.*, 2008; Maty *et al.*, 2005; McLaren, 2007). Similarly, evidence shows that early social and economic conditions are related to adult cognitive function (Singh-Manoux *et al*., 2005; Hazzouri *et al*.,2011; Brunner, 2005). Individuals from low childhood SEP are exposed to various social and economic barriers to success and well-being, resulting in worse health, reduced emotional resilience and impaired cognitive skills (Bowles *et al*., 2005).

Previous analysis of the ELSA-Brasil cohort corroborate these findings and showed that adults (35-64 years old) with low educated mothers, low birth weight, and smaller trunk length exhibited higher chances of poor performance in cognitive function tests, especially executive function test, during adulthood (Araújo *et al*., 2014). However, the cumulative effect of socioeconomic and nutritional conditions through life, cardiovascular disease risk, and the relationship with cognition in adults without dementia to predict one possible mechanism for cognition decline with ageing needs to be further explored. In order to test this hypothesis, we first explore the association separately between maternal education, trunk length, cardiovascular disease risk in 10 years by the Framingham Risk Score (FRS), and the performance on the cognitive function tests, and then examine the extent to which this association is explained by the cumulative effect over the life.

Methods

Setting and study population

This study was embedded within ELSA-Brasil, which enrolled 15,105 workers from universities and research institutes, in six Brazilian states. The baseline

examination (2008–2010) included detailed interviews, clinical, laboratory and anthropometric examinations. More details about the study's methodology were described by Aquino *et al.* (2012) and Schmidt *et al.* (2014).

The present analysis includes adults (35-64 years old) who undertook cognitive tests in the baseline of ELSA-Brasil. Since intrinsic aspects of ageing and certain clinical conditions affect cognitive function, participants aged 65 years or more (N= 1,592) and those who reported previous diagnosis (N=2,410) of myocardial revascularization, acute myocardial infarction, angina pectoris, heart failure, stoke and/or who were using neuroleptics, anticonvulsants, anticholinesterase or antiparkinsonian drugs (n=330), were exclude of this study.

Life-course socioeconomic conditions

Maternal educational attainment was determined by the question: "Which is your mother's educational level?" For the analysis, the answers were categorized into: high school or more, elementary school, incomplete elementary school, and never went to school. The trunk length was calculated by subtracting the height of the bench (46 cm) used to obtain sitting height from the total sitting height (in centimeter). The anthropometric parameters are measured using standard equipment and techniques (CDC, 2004). In order to avoid multicolinearity with the FRS, for the regression analysis we created centered variable trunk length by means of subtracting each individual measure of trunk lengths from their gender-specific means. The centered trunk length was entered as continuous variable in the analysis.

Measurement of Framingham Risk Score

Systolic blood pressure measurement was made by the OMRON equipment on the left arm of the seated participants with an appropriately sized cuff; three measures was obtained, and for this analysis was used the average of the last two measures. Serum total and HDL cholesterol levels were determined with standardized enzymatic methods. Cigarette smoking status was ascertained by self-report and was defined as current smoker how had smoked at least 100 cigarettes (five packs of cigarettes) throughout life and still being a smoker. Diabetes was defined as fasting glucose $\geq$ 126 mg/dl, or glycated hemoglobin > 6.5%, or 2 hour after glucose overload $\geq$ 200mg/dl, or self-report diabetes status, or use of insulin or oral antidiabetics medications. Blood pressure–lowering and antidiabetic agents use were ascertained after verification of medical leaflets, prescriptions or boxes of medicines.

The cardiovascular risk was measured by Framingham Risk Score (FRS) for cardiovascular disease (D'Agostino *et al*., 2008) a composite measure designed to predict the risk of developing a cardiovascular, cerebrovascular, or peripheral vascular event within the next 10 years. Calculation of the score is based on age, gender, diabetes mellitus, current smoker, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol and HDL-cholesterol levels.

Cognitive test battery and general cognitive factor

The response variables were the final scores obtained in the following cognitive function tests: The **learning, recall and word recognition tests** of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Bertolucci *et al.*, 1998), validated for the elderly Brazilian population, were used to evaluate declarative verbal memory. The score corresponds to the sum of the scores in these three tests from total

number of correct words measured on a scale of 0–50. The **semantic (animal category) and phonemic (letter F) verbal fluency tests,** which are also part of the CERAD's (Bertolucci *et al.*, 1998) group of tests, were used to efficiency of searching in long-term memory semantic and language. The score corresponds to the total number of correct animal names and words beginning with the letter "F" given by the participant. Initially, the tests semantic verbal fluency (animals) and phonemic verbal fluency (letter F) were analyzed separately, but there were no differences in the direction and magnitude of the associations found. For this reason, they were analyzed together, just the sum of the scores in these two tests. The **trail-making test** was used to evaluate executive function, as it is related to attention, concentration and psychomotor speed (Lezak *et al.*, 2004). Trail-making test A was used to train the participants. The score corresponded to the time taken to complete the trail-making test B.

The higher scores on the learning, recall and word recognition tests and of the semantic and phonemic verbal fluency test indicate a better cognitive function, while higher duration of time to perform the trail-making test B indicate a worse performance. The reliability of these tests varied from moderate, for the learning and word recall test (Kappa= 0.56; 0.33-0.79), to very good, for the trail making test B (Kappa=0.91; 0.87-0.95) (Batista *et al.*, 2013).

To calculate a general cognitive factor (g-factor) we performed a principal component analysis with all the cognitive tests, considering the form they were analyzed separately. Principal component analysis was performed unrotated on complete case data of 10,194 persons. The g-factor was identified as the first component of the principal component analysis and explained 64% of all variance of the correlation between the cognitive tests. This is a typical amount of variance accounted for by the g-factor (Deary, 2012).

Confounders

All the confounders included in this analysis were self-reported measured by standardized questionnaire. *Age* in years (categorical in the descriptive analysis and continuous in the multivariate analysis); *gender* (male and female); c*urrent educational level* (undergraduate school or more, high school, elementary school and incomplete elementary school); *alcohol consumption* (moderate, heavy, former user and never consumption); and *physical activity* (vigorous, moderate and mild). Age was not entered as an adjusting variable in the models that included the FRS, as it is a collider of FRS and the cognitive function tests. I*ncome per capita* was not included as a control variable due to its moderate correlation with educational attainment (Rho = 0.60, $p<0.001$).

Statistical analysis

Descriptive statistics presented as means and standard error (SE) or frequencies. The associations between the variables was estimated by the T test using a significance level of $p<0.05$ in univariate analysis. Correlations between variables were analyzed by Spearman's correlation coefficient. Trial-making B was log-transformed due to the skewed distribution.

Using multiple linear regressions, in the primary analysis (Model 1) we aimed to remove the confounding effects of age, gender, current educational attainment, alcohol consumption, and physical activity to our estimate of the association between each variable of interest (maternal educational attainment, centered trunk length, and Framingham Risk Score) and the general cognitive factor (g-factor) in the adulthood. Afterwards, we added in Model 1 the mutual adjustments for maternal education attainment, centered trunk length, and Framingham Risk Score to explore the extent to

which they accounted for any remaining association (Model 2). Also, after mutual adjustments (Model 2) we explore if remaining association for each cognitive function domains by the learning, recall and word recognition tests, semantic and phonemic verbal fluency tests, and the trail-making test version B (Model 3).

In the multivariate model the least squares test was estimated to define the final models with a significance level of 5% ($p < 0.05$). The coefficient of determination, R^2, gave us the percentage of total variation in the cognitive function tests that are explained by the Model 1 and Model 2. We examined the basic assumption for linear regression (linearity, normality and collinearity). The analyses were conducted using the Stata 12.0 (Stata Corporation, College Station, USA).

Ethical aspects

All participants signed a free and informed consent form. The study was approved by the National Committee of Ethics in Research (approval n^o 976/2006).

Results

Characteristics of the study population are presented in the Table 1. From a total of 10,773 participants, 10,684 performed the learning, recall and word recognition test, 10,729 the semantic and phonemic verbal fluency tests, 10,240 the trail-making B, resulting in 10,194 the g-factor scores composing the different totals in the multivariable analysis. The majority of the participants' mothers did not complete elementary school (55.4%). The mean trunk length for men was 90.17 cm (SE=0.06) and for women was 84.06 (SE=0.04), and the mean FRS was 9.11% (SE=0.09).

Table 1. Characteristics of the study population in the ELSA-Brasil (2008-2010)

Variables	Total, n (%)
Gender	
Male	4,844 (45.0)
Female	5,929 (55.0)
Age	
35-39	933 (8.7)
40-44	1,780 (16.5)
45-49	2,556 (23.7)
50-54	2,254 (20.9)
55-59	2,009 (18.7)
60-64	1,241 (11.5)
Educational attainment	
Under Graduate school or more	5,783 (53.7)
High school	3,818 (35.4)
Elementary school	652 (6.1)
Incomplete elementary school	520 (4.8)
Maternal Educational Attainment	
High school or more	2,664 (25.2)
Elementary school	2,043 (19.4)
Incomplete Elementary school	4,494 (42.6)
Never went to school	1,359 (12.9)
Physical activity	
Vigorous	1,004 (9.4)
Moderate	1,427 (13.3)
Mild	8,284 (77.3)
Alcohol Consumption	
Moderate	6,792 (63.1)
Heavy	853 (7.9)
Former user	2,031 (18.9)
Never consumption	1,081 (10.1)
Smoking Status	
No	9,353 (86.8)
Yes	1,420 (13.2)
Diabetes Status	
No	8,969 (83.3)
Yes	1,802 (16.7)
Systolic Blood Pressure (mmHg)	
<120	5,899 (55.5)
120-129	2,258 (21.3)
130-139	1,279 (12.0)
140-149	628 (5.9)
150-159	309 (2.9)
>160	252 (2.4)
Blood-pressure lowering medication use	
No	8,226 (76.4)
Yes	2,536 (23.6)
Total Cholesterol (mg/dl)	
<160	753 (7.0)
160-199	3,188 (29.6)
200-239	4,121 (38.3)
240-279	2,019 (18.7)
>280	692 (6.4)
HDL-Cholesterol, Men (mg/dl)	
>60	935 (19.3)
50-59	1,381 (28.5)
45-49	946 (19.5)
35-44	1,421 (29.3)
<35	161 (3.3)
HDL-Cholesterol, Women (mg/dl)	
>60	3,013 (50.8)
50-59	1,719 (29.0)
45-49	698 (11.8)
35-44	461 (7.8)
<35	38 (0.6)

There was strong evidence that being a male, to have higher age, to do moderate or mild physical activity, to have lower current educational attainment and also maternal educational attainment, to have smaller centered trunk length and higher Framingham Risk Score (FRS) for CVD in 10 years were linearly associated with worse performance in the g-factor and also in all cognitive function tests ($p<0.001$). There was also strong evidence ($p<0.001$) of an association with alcohol consumption, but this did not appear to be linear, as those who never consumed alcohol had worse performances in the semantic and phonemic verbal fluency tests and the trail-making B, and former user had worse performance in the g-factor, and in the learning, recall and word recognition test (Supplementary Table 1).

The table 2 shows the associations of maternal attainment, trunk length, FRS with the g-factor and each cognitive function test. In the model 1 the maternal educational attainment showed a dose-response gradient in the association with worse score on g-factor, with individuals whose mothers never went to school showing the most stronger effect (β=-0.41, 95%CI -0.45, -0.36). The higher centered trunk length was associated with better score on g-factor (β=0.02, 95%CI 0.02, 0.03). As well, the higher FRS was associated with worse score on g-factor (β=-0.01, 95%CI -0.02, -0.01). We observed only negligible changes in the regression coefficients after mutual controlling for maternal educational attainment, centered trunk length and the FRS (Model 2), remaining all of these factors associated with same directions with the g-factor ($p<0.001$). The Model 2 explained 39% of the variance (the adjusted R^2 from the regression analyses) on the g-factor.

In analysis considering each cognitive function test (Model 3), after mutual controlling for maternal educational attainment, centered trunk length and the FRS, all of these factors also remained associated with the same directions with learning, recall and

word recognition tests, semantic and phonemic verbal fluency tests and trail-making B ($p<0.001$). The Model 3 explained 20% of the variance on the learning, recall and word recognition tests, also explained 27% of the variance on the semantic and phonemic verbal fluency test, while on the trail making test B it explained 37% (Table 2). After adjustments, physical activity did not remain statistically associated with worse performance on g factor and also in any of the cognitive tests examined.

Table 2. Multivariable linear regression (Models 1, 2 and 3) between maternal educational attainment, centered trunk length and Framingham Risk Score and the g-factor, learning recall and word recognition tests, semantic and phonemic verbal fluency tests, and trail-making test B among the participants (35 to 64 years of age) in the ELSA-Brasil (2008-2010)

Variables	Model 1		Model 2		Model 3		Model 3		Model 3	
	G-factor		G-factor (N=9,996)		Learning, recall and word recognition tests (N=10,454)		Semantic and phonemic verbal fluency tests (N=10,489)		Trail-making test B* (N=10,040)	
	Difference of the mean (95% CI)	p-value	Difference of the mean (95% CI)	p-value	Difference of the mean (95% CI)	p-value	Difference of the mean (95% CI)	p-value	Difference of the mean (95% CI)	p-value
Maternal Educational Attainment										
High school or more	Reference		Reference		Reference		Reference		Reference	
Elementary school	-0.13 (-0.16, -0.09)	<0.001	-0.12 (-0.15 -0.09)	<0.001	-0.56 (-0.87, -0.26)	<0.001	-1.35 (-1.76, -0.93)	<0.001	1.09 (1.07, 1.12)	<0.001
Incomplete Elementary school	-0.19 (-0.22, -0.16)	<0.001	-0.17 (-0.20, -0.14)	<0.001	-0.89 (-1.16, -0.63)	<0.001	-1.82 (-2.18, -1.46)	<0.001	1.13 (1.10, 1.15)	<0.001
Never went to school	-0.41 (-0.45, -0.36)	<0.001	-0.39 (-0.43, -0.34)	<0.001	-2.01 (-2.39, -1.62)	<0.001	-3.01 (-3.53, -2.49)	<0.001	1.32 (1.28, 1.36)	<0.001
Centered Trunk Length (cm)	0.02 (0.02, 0.03)	<0.001	0.02 (0.02, 0.03)	<0.001	0.08 (0.05, 0.11)	<0.001	0.21 (0.17, 0.24)	<0.001	0.98 (0.98, 0.98)	<0.001
Framingham Risk Score (%)	-0.01 (-0.02, -0.01)	<0.001	-0.01 (-0.01, -0.01)	<0.001	-0.07 (-0.08, -0.05)	<0.001	-0.10 (-0.11, -0.08)	<0.001	1.01 (1.01, 1.01)	<0.001

Model 1 for maternal educational attainment and centered trunk length were adjusted for age, gender, educational attainment and alcohol consumption. **Model 1** for FRS was adjusted for gender, educational attainment and alcohol consumption. **Models 2 and 3:** Mutual adjustment for maternal educational attainment, centered trunk length and Framingham Risk Score and cofounders that remained statistically associated with each cognitive function test in the Model 1. **Framingham Risk Score (FRS):** age, gender, diabetes mellitus, current smoker, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol and HDL-cholesterol. *Trail-making test B, the beta was exponentiated for better interpretation of the log transformation from this variable.

Discussion

Evidence from our cohort of Brazilian public servants, supported an association of cumulative effects of poor socioeconomic and nutritional conditions though life and higher cardiovascular disease risk on worse performance in the global cognition and also in different domains of cognitive function in adults. Previously reported enduring effects of childhood SEP on cognition (Fors *et al.*, 2009; Kaplan *et al.*, 2001; Osler *et al.*, 2012), with plausible pathways including maternal exposures during gestation, maternal stress, nutrition, childhood health, parenting practices, mental stimulation, and childhood poverty. Early years are crucial for brain development, and it is conceivable that neurocognitive inefficiencies resulting from early life insults become exacerbated with cognitive aging (Moceri *et al*., 2001). Our findings support previous ones, which indicate the influence of lower maternal educational attainment (a marker of SEP until the adulthood) on worse cognitive function, tend to persist during adulthood after considering the formal education of the participants. Similar association was found witch suggests that the cognitive function in mid and later life reflects the influence of SEP at different stages of the life-course (childhood, adulthood, and middle-older age) (Horvat *et al.*, 2014).

In our study the smaller trunk length (a marker of nutritional statement after early infancy and before puberty), which also reflects SEP through life, was associated with worse performance in global cognition and in different cognitive function tests. Eppig and cols. (2010) also suggest that height can act as a protective factor in cognitive aging. As a cause of observed cognitive improvements over time, it is generally accepted that nutrition plays an important role in less developed nations and in developed nations before 1950 (Flynn, 2009). For example, Case and Paxson (2008a, 2008b) document a strong association between self-reported height and cognitive functioning in later life using the

U.S. Health and Retirement Study (HRS). Their results suggest that height could be an indicator of higher cognitive potential in the sense that people who do not reach their full genetic height potential do not reach their full genetic cognitive potential either. However, we cannot discard the possibility of a common genetic pathway underlying both trunk growth and worse cognition because in our study as we have no information on parental height.

Another study using data from the Survey of Health, Ageing, and Retirement in Europe (SHARE) and about 17,000 respondents from 11 countries found that height serves as a protective factor against age related deterioration in cognitive functioning (Guven and Lee, 2014). Childhood SEP affects some neurocognitive systems more than others. Studies that assessed multiple neurocognitive systems found that the largest effects of SEP are on language processing, with more moderate effects on executive function — particularly on working memory and cognitive control (Noble *et al*., 2007, Farah *et al.*, 2006, Noble *et al*., 2005, Kishiyama *et al.*, 2009). Additionally, some studies found moderate effects of SEP on declarative memory and spatial cognition (Noble *et al*., 2007, Farah *et al.*, 2006, Levine *et al*., 2005). In this study, maternal educational attainment and trunk length were associated with global cognitive function and also with semantic and declarative memory, learning, attention and executive function.

Childhood SEP has been shown to be inversely associated with several cardiovascular disease risk factors in adulthood, including smoking, blood pressure, cholesterol, and adiposity (Blane *et al.*, 1996; Poulton *et al*., 2002; Gilman *et al*., 2003). A systematic review reported inverse associations of childhood SEP with risk of cardiovascular disease in 31 of 40 studies (Galobardes *et al*., 2006). The accumulation-of-risk SEP framework suggests that as the duration and severity of socioeconomic

disadvantage increase, resulting cumulative damage could place individuals at higher risk of cardiovascular disease (Kuh, Ben-Shlomo, 2004). Van den Berg and cols. (2010) showed that the cognitive abilities of those who suffer from strokes later in life are more heavily affected if individuals were born in adverse socioeconomic conditions.

Whitmer and cols. (2005) reported that the presence of multiple cardiovascular risk factors at midlife independent of age, race, sex, and education substantially increased risk of dementia in old age. Those having simultaneously high cholesterol, hypertension, diabetes, and being smokers had more than a two-fold greater risk of dementia than those with no such risk factors. The cross sectional associations between cardiovascular disease risk factors and cognitive function, observed in our study, are largely consistent with results obtained in this previous study. Moreover, the mutual adjustment for maternal educational attainment and trunk length did not attenuate the association, and most importantly, this association was found in young adults. Also there were a weak negative correlation between maternal educational attainment and FRS (in quintile) (Rho=-0.15, $p<0.001$); also between maternal educational attainment and centered trunk length (in quintile) (Rho-0.04, $p<0.001$); and a weak positive correlation between centered trunk length and FRS (Rho= 0.20; $p<0.001$), showing that each factor it measures different exposures on the cognitive function.

ELSA-Brasil is a longitudinal study that will evaluate cognitive function in Brazilian adults. The longitudinal design will enable the measurement of changes in cognitive function during the follow-up visits and to examine whether maternal education, trunk length and cardiovascular risk factors predict cognitive decline. One important limitation of the present analysis is that it is cross-sectional using data form the baseline, without a measure of prior cognitive ability, raising the challenge of reverse causality.

Anyway, there is no doubt that those indicators precede the measures of cognitive function, especially maternal education and trunk length. Even if we had no relevant data to investigate the issue of reverse causality, both social selection and causation mechanisms are likely to be important.

The participants of the ELSA-Brasil cohort are civil servants and not representative of the country population, as the cohort does not include the unemployed and has a much higher percentage of people with university degree. Thus, the distribution of the risk factors and the outcome analyzed here are unlikely to be generalizable. However, the social and regional diversity of the ELSA-Brasil cohort is large enough to allow the investigation of important inequities in health in Brazil (Santos *et al.*, 2014, Mueller *et al.*, 2014), such as the ones examined in this work. As extensively debated recently, sampling representativeness is necessary when we aim to estimate the prevalence of a condition in a given population, which is not the objective of the present study, but it is not required to draw valid scientific inferences for associations found in well-conducted epidemiological studies (Rothman *et al.*, 2013, Richiardi *et al.*, 2006).

Conclusion

These findings are consistent with published literature demonstrating the importance of the social circumstances early in life and cardiovascular disease risk in 10 years by the Framingham Risk Score on cognitive skills and abilities at younger adult ages. That is, a comprehensive understanding of the social and health determinants of cognitive functioning in later life require attention to exposures to disadvantageous conditions throughout the whole of the life-course, with a special focus on certain, critical, periods (during childhood and earlier adulthood), as well as on chains of associated social exposures stretched out

over the life course. Applying a life-course perspective on health and cognition in later life should have implications for social policy, public health interventions, and further research. Social and material interventions throughout the life-course, and especially during early life, could impact the health burden in later life substantially.

Competing interests

The authors declare that they have no competing interests.

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Supplementary Table

Table 1. Analysis of simple linear regression between explanatory variables of interest, control variables and the g-factor, learning, recall and word recognition tests, semantic and phonemic verbal fluency tests, and trail-making test B among the participants (35 to 64 years of age) in the ELSA-Brasil (2008-2010)

Variables	G-factor		Learning, recall and word recognition tests		Semantic and phonemic verbal fluency tests		Trail-making test B*	
	Difference of the mean (95% CI)	p-value	Difference of the mean (95% CI)	p-value	Difference of the mean (95% CI)	p-value	Difference of the mean (95% CI)	p-value
Age (years)	-0.02 (-0.02, -0.02)	<0.001	-0.14 (-0.15, -0.12)	<0.001	-0.21 (-0.23, -0.18)	<0.001	1.02 (1.01, 1.02)	<0.001
Gender								
Male	Reference		Reference		Reference		Reference	
Female	0.17 (0.14, 0.20)	<0.001	2.45 (2.23, 2.66)	<0.001	1.10 (0.79, 1.42)	<0.001	0.97 (0.95, 0.99)	0.007
Schooling Level								
Under Graduate school or more	Reference		Reference		Reference		Reference	
High school	-0.57 (-0.60, -0.55)	<0.001	-2.99 (-3.21, -2.77)	<0.001	-5.63 (-5.93, -5.34)	<0.001	1.44 (1.42, 1.47)	<0.001
Elementary school	-1.18 (-1.24, -1.13)	<0.001	-5.83 (-6.27, -5.39)	<0.001	-10.70 (-11.28, -10.11)	<0.001	2.13 (2.05, 2.21)	<0.001
Incomplete elementary school	-1.64 (-1.71, -1.57)	<0.001	-8.19 (-8.71, -7.67)	<0.001	-13.81 (-14.46, -13.15)	<0.001	2.90 (2.77, 3.03)	<0.001
Physical Activity								
Vigorous	Reference		Reference		Reference		Reference	
Moderate	-0.14 (-0.20, -0.07)	<0.001	-0.71(-1.18, -0.24)	0.003	-1.22 (-1.88, -0.55)	<0.001	1.11 (1.07, 1.16)	<0.001
Mild	-0.22 (-0.27, -0.17)	<0.001	-1.04 (-1.42, -0.66)	<0.001	-2.29 (-2.83, -1.74)	<0.001	2.18 (1.14, 1.22)	<0.001
Alcohol Consumption								
Moderate	Reference		Reference		Reference		Reference	
Heavy	-0.14 (-0.19, -0.08)	<0.001	-1.12 (-1.53, -0.71)	<0.001	-1.29 (-1.88, -0.71)	<0.001	1.08 (1.05, 1.1)	<0.001
Former user	-0.28 (-0.32, -0.24)	<0.001	-1.50 (-1.79, -1.21)	<0.001	-2.50 (-2.91, -2.10)	<0.001	1.22 (1.19, 1.25)	<0.001
Never consumption	-0.29 (-0.34, -0.24)	<0.001	-1.25 (-1.63, -0.88)	<0.001	-2.98 (-3.51, -2.46)	<0.001	1.26 (1.22, 1.30)	<0.001
Maternal Educational Attainment	Reference		Reference		Reference		Reference	
High school or more	-0.27 (-0.31, -0.23)	<0.001	-1.26 (-1.59, 0.94)	<0.001	-2.89 (-3.34, -2.44)	<0.001	1.21 (1.18, 1.25)	<0.001
Elementary school	-0.43 (-0.46, -0.40)	<0.001	-2.14 (-2.41, -1.87)	<0.001	-4.45 (-4.82, -4.08)	<0.001	1.34 (1.31, 1.37)	<0.001
Incomplete Elementary school	-0.97 (-1.01, -0.92)	<0.001	-5.00 (-5.38, -4.64)	<0.001	-8.83 (-9.34, -8.32)	<0.001	1.94 (1.88, 2.01)	<0.001
Never went to school								
Centered Trunk Length (cm)	0.05 (0.05, 0.06)	<0.001	0.27 (0.24, 0.30)	<0.001	0.55 (0.51, 0.60)	<0.001	0.96 (0.95,0.96)	<0.001
Framingham Risk Score (%)	-0.02 (-0.02, -0.02)	<0.001	-0.16 (-0.17, -0.15)	<0.001	-0.20 (-0.22, -0.19)	<0.001	1.02 (1.01, 10.2)	<0.001

Framingham Risk Score (FRS): age, gender, diabetes mellitus, current smoker, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol and HDL-cholesterol. *Trail-making test B, the beta was exponentiated for better interpretation of the log transformation from this variable.

4.3 Artigo Original 3

Araújo LF, Giatti L, Schmidt MI, Duncan BB, Goulart A, Ikram MA, Barreto SM: Coffee consumption and cognitive function in adults and elderlies (ELSA-Brasil)

“Coffee consumption predicts cognitive function in adults and elderly (ELSA-Brasil)”

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Abstract

Background: Recent epidemiological evidence suggests that coffee consumption might reduce the risk of cognitive decline, dementia, and Alzheimer's disease, but results are inconsistent and the effect of caffeine appear to be task specific. **Method:** In a population-based study of 15,105 workers of public universities and research institutes (35-74 years old), in six Brazilian States we investigated by linear regression and generalize linear regression with logarithmic link and gamma distribution the relation of coffee consumption (no consumption, >0-99 ml/day, 100-199 ml/day, 200-299 ml/day, 300-399 ml/day, and ≥ 400 ml/day) in the last 12 months and the performance on global cognition and specific domains of cognitive function. **Results:** After adjustments for age, sex, current educational attainment, alcohol consumption, total/HDL-cholesterol ratio, body mass index, smoking, depressive symptoms, diabetes, hypertension and coronary heart disease, we observed the consumption of more than 200 ml per day of coffee in the last 12 months increased the mean words remembered on learning, recall and word recognition tests. However, the consumption of more than 400 ml per day increased the mean time to complete the trial-making B test. Coffee consumption was not associated with g-factor, and semantic and phonemic verbal fluency test. **Conclusions:** Results suggest that high coffee consumption may have a protective effect on memory, but a detrimental effect on executive function.

Keywords: coffee consumption; diet bioactive compounds; global cognition; cognitive function tasks.

Background

There is a general agreement on the existence of a normal cognitive decline from early to late adulthood and that disorders, such as Alzheimer's disease (AD), are associated with an overall impairment of higher functions and cognitive faculties, one of which is a symptomatic loss of memory (Ritchie *et al*., 2010). There is a critical need to identify prophylactics that reduce risk, or delay onset of cognitive decline particularly from the standpoint of lifestyle choices (Cao *et al*., 2012).

In recent years, based on a possible link between oxidative damage and cognitive decline, there has been a growing interest in studying diet bioactive compounds that delay or prevent cell damage, provide symptomatic relief, and improve people's quality of life. Coffee, a very popular beverage consumed worldwide, especially in Brazil that is an important coffee producer (Sousa *et al*., 2015). It is a rich source of caffeine which acts as a psychoactive stimulant and has been shown to improve cognitive performance in the short term (Head, 2009; Martin and Grotewiel, 2006). By increasing the activity of the central nervous system, caffeine consumption can result in heightened alertness, vigilance, attention, and mood as well as improved complex, higher cognitive functions including memory (Battig K and Buzzi, 1986; Smith *et al*., 1993).

Caffeine is known to be an adenosine receptor antagonist in the brain. Cognitive effects of caffeine are believed to be a function of its ability to antagonize A_1 adenosine receptors in the hippocampus and cortex. As endogenous adenosine inhibits long-term synaptic plasticity phenomena A_1 adenosine receptor antagonists have been proposed as treatment for memory disorders (Cauli *et al*., 2005; Fisone *et al*., 2004; Ribeiro *et al*., 2010). Results from previous studies of the effect of caffeine on cognition have been inconsistent, indicating that caffeine may have either a facilitative or a detrimental

effect on cognition and that the effect of caffeine may be task specific, such as memory, language or executive function (Heckman *et al*., 2010, Smith, 2002; Lieberman *et al.*, 2002; Nehlig, 2010, Einother *et al*., 2010). The most convincing of the epidemiologic studies in establishing an association between caffeine and AD reported that AD patients consumed markedly less caffeine during the 20 years preceding diagnosis of AD, compared with age-matched individuals without AD (Maia and de Mendonça, 2002).

Still, how coffee consumption is related to better cognition remains unclear. The present study aims to address the following questions: Is coffee consumption in the last 12 months associated with better global and specific domains of cognitive function among Brazilian adults and elderly? Which doses of coffee consumption are associated with improved performance on global and specific domains of cognitive function tests?

Method

Setting and study population

The ELSA-Brasil study was established in 2008 as a longitudinal study to examine development and progression of clinical and subclinical chronic diseases, particularly cardiovascular diseases and diabetes among 15,105 civil servants from universities and research institutes in six Brazilian states (Aquino *et al*., 2012; Schmidt *et al.*, 2014). This study used data regarding who undertook cognitive tests in the baseline study; those that reported previous diagnosis of stroke and/or were using neuroleptics, anticonvulsants, anticholinesterase or antiparkinsonian drugs were excluded from the present analysis (n=514). From 14,591 study participants, 14,563 had information about coffee consumption composing the total in the analysis. Only 316

persons informed drink coffee without caffeine and were not excluded from the analysis since coffee has others antioxidants compounds that influences on cognition as well. All participants signed a free and informed consent form. The study was approved by the National Committee of Ethics in Research (approval n^{o} 976/2006).

Measurement of coffee consumption

Dietary data was collected during the visit in the base line of ELSA-Brasil using a validated semi quantitative food frequency questionnaire that indicated all foods and drinks in the last 12 months (Molina *et al*., 2013). Participants were further asked to specify the type of coffee normally consumed (filter, instant, espresso, moka pot), whether this coffee contained caffeine (caffeinated or decaffeinated), whether additional items were typically added to the coffee (sugar, artificial sweetener, none), and the size of the cup. Answer choices were provided as ordinal categories: "More than 3 times per day", "2-3 times per day", "once a day", "5-6 times per week", "2-4 per week", "once a week", 1-3 times a month" and "hardly never". The dietary coffee consumption was converted to milliliters intake per day and then categorized as: no consumption, >0-99 ml/day, 100-199 ml/day, 200-299 ml/day, 300-399 ml/day, and ≥ 400 ml/day.

Measurement of cognitive test battery and general cognitive factor

The response variables were the final scores obtained in the following cognitive function tests: The **learning, recall and word recognition tests** of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Bertolucci *et al.*, 1998), validated for the elderly Brazilian population, were used to evaluate verbal learning, retrieval from verbal memory, and recognition of verbal memory. The score corresponds to the sum of the correct words in all tests (range: 0-50). The **semantic**

(animal category) and phonemic (letter F) verbal fluency tests, which are also part of the CERAD's (Bertolucci *et al.*, 1998) group of tests, were used to evaluate efficiency of searching in long-term memory and language. The score corresponds to the total number of correct animal names and words beginning with the letter "F" given by the participant. The **trail-making test** was used to evaluate executive function, as it is related to attention, concentration and psychomotor speed (Lezak *et al.*, 2004). Trail-making test A was used to train the participants. The score corresponded to the time taken to complete the trail-making test B.

The higher scores on the learning, recall and word recognition tests and of the semantic and phonemic verbal fluency test indicate a better cognitive function, except for the trail-making test B in which a higher score indicates a worse performance. The score signal for the trail-making test B were thus inverted for comparison to other tests. The reliability of these tests varied from moderate, for the learning and word recall test (Kappa= 0.56; 0.33-0.79), to very good, for the trail making test B (Kappa=0.91; 0.87-0.95) (Batista *et al.*, 2013).

To calculate a general cognitive factor (g-factor) we performed a principal component analysis incorporating recall word test, phonemic verbal fluency tests, and trail-making test B. For test with multiple subtasks we chose only one subtask in order to prevent highly correlated task distorting the factor loadings. Principal component analysis was performed on complete case data of 13,673 persons that performed all the tests, comprising the total of this analysis. The g-factor was identified as the first unrotated component of the principal component analysis and explained 60% of all variance of the correlation between the cognitive tests. This is a typical amount of variance accounted for by the g-factor (21-68%) (Deary, 2012).

Measurement of cofounders

All the cofounders included in this analysis were self-reported measured by standardized questionnaire, procedures and laboratory exams measurements (Aquino *et al.*, 2012; Bensenor *et al*., 2013). To control for confounding, we selected established risk factors for cognition decline and factors known to be associated with coffee consumption based on prior studies and theoretical considerations as follows: *Age* in years; sex (male and female); c*urrent educational attainment* was assessed as the highest qualification attained (graduate school or more, high school, elementary school and incomplete elementary school); *alcohol consumption* (never or former user, moderate, heavy); cigarette *smoking status* was defined as current smoker how had smoked at least 100 cigarettes (five packs of cigarettes) throughout life and still being a smoker; *diabetes status* was defined as fasting glucose $\geq$ 126 mg/dl, or glycated hemoglobin > 6.5 ml/dl, or 2 hour after glucose overload $\geq$ 200mg/dl, or self-report, or use of insulin or oral antidiabetics medications; blood pressure was measured using an oscillametric method (Omron HEM 705CP) and *hypertension status* was defined as systolic pressure $\geq$140 mmHg and diastolic $\geq$90 mmHg, or drug treatment for hypertension al blood pressure assessment; height and weight were measured according to standardized procedures and techniques (CDC, 2004), and the *body mass index* (BMI) was calculated (Kg/m^2); *Serum total* and *HDL cholesterol levels* were determined with standardized enzymatic methods and was calculated the ration of them; *coronary heart diseases status* is defined as report of myocardial revascularization (as a proxy for significant coronary artery disease) and/ or myocardial infarction; and *depressive symptoms* was used as yes and no.

Data analysis

The characteristics of the study population are presented using unadjusted means (SD), median (1º and 4º quartile) and frequencies. Two strategies of analysis were employed to investigate the association between coffee intake and each of the outcome variables. We performed multiple linear regressions for the scores of the outcomes variables g-factor and the semantic and phonemic verbal fluency tests because they presented normal distributions and almost unlimited values. We used a generalized linear model (GLM) with logarithmic link and gamma distribution to indicate the differences between categories of explanatory variables for the outcomes learning, recall and word recognition tests and the number of seconds taken to complete the trail-making B test in order to take into account the skewed distribution of these variables. For better interpretation, we exponentiated the coefficients obtained from the GLM which represent the arithmetic mean ratios (AMR) in continuous outcome variables between the categories of the explanatory variables being compared. The results interpretation in terms of the arithmetic mean is an advantage of this GLM with logarithmic link in comparison with a linear regression with log-transformed outcome, which gives interpretation in terms of the geometric mean.

Using coffee consumption as categories of consumption (no consumption, >0-99 ml/day, 100-199 ml/day, 200-299 ml/day, 300-399 ml/day, and ≥ 400 ml/day) the analyses were adjusted for age, sex and educational attainment (model 1), and additionally for alcohol consumption, cigarette smoking, diabetes status, hypertension status, body mass index, total/HDL-cholesterol ratio, coronary heart disease status and depressive symptoms (model 2). Persons with missing values were excluded from these analyses. The analyses were conducted using the Stata 13.0 (Stata Corporation, College Station, USA).

Results

Characteristics of the study population are presented in the Table 1. The mean age of the study population was 51.96 (SD=9.04) years, and 54% were women (Table 1). The median coffee consumption was 149.35 (SD= 127.39). Table 2 shows the univariate analysis between coffee consumption and all the confounders with the g-factor and also specific cognitive function tests. The coffee consumption more than 200ml until 400ml per day increase the mean words remembered on learning, recall and word recognition tests (p-value<0.001). However, especially the consumption of more than 400ml of coffee per day was associated with worse performance on g-factor, semantic and phonemic verbal fluency tests and trail-making B (p-value<0.001) (Table 2).

Table 1. Characteristics of the study population (35-74 years old) and in the ELSA-Brasil (2008-2010)

Variables	Total Population
Sex, n (%)	
Women	7,899 (54.3)
Age(years), mean (SD)	51.96 (9.04)
Educational Attainment, n (%)	
Under graduate school or more	7,684 (52.8)
High school	5,045 (34.6)
Elementary school	988 (6.8)
Incomplete elementary school	846 (5.8)
Alcohol Consumption, n (%)	
Never or former user	4,399 (30.2)
Moderate	9,059 (62.2)
Heavy	1,102 (7.6)
Smoking Status, n (%)	
Never	8,316 (57.1)
Former	4,365 (30.0)
Current	1,881 (13.9)
Diabetes Status, n (%)	
Yes	2,830 (19.4)
Hypertension Status, n (%)	
Yes	5,563 (37.04)
Depressive Symptoms, n(%)	
Yes	1,879 (12.9)
Coronary Heart Disease Status, n (%)	
Yes	366 (2.5)
Total / HDL-Cholesterol (mg/dl), mean (SD)	3.97 (1.06)
Body Mass Index (Kg/m^2), mean (SD)	27.01 (4.74)
Coffee (cups/day), n (%)	
No consumption	1,398 (9.6)
>0-99 ml/day	3,249 (22.3)
100-199 ml/day	6,500 (44.6)
200-299 ml/day	1,341 (9.2)
300-399 ml/day	1,392 (9.6)
≥ 400 ml/day	683 (4.7)
g-factor, mean (SD)	0.00 (0.69)
Learning, recall and word recognition tests (words), median (1º and 4º quartile)	38 (34-42)
Semantic verbal fluency test (words), mean (SD)	18.47 (5.28)
Phonemic verbal fluency test (words), mean (SD)	12.49 (4.49)
Trail-making test B (seconds), median (1º and 4º quartile)	98 (73-140)

Table 2. Analysis of simple linear regression between coffee consumption, confounders and g-factor, learning, recall and word recognition tests, semantic and phonemic verbal fluency tests, and trail-making test B among the participants (35 to 74 years of age) in the ELSA-Brasil (2008-2010)

Variables	g-factor[a]	Learning, recall and word recognition tests[b]	Semantic verbal fluency test[a]	Phonemic verbal fluency test[a]	Trail-making test B[b]
	Difference of the mean (95%CI)	AMR (95%CI)	Difference of the mean (95%CI)	Difference of the mean (95%CI)	AMR (95%CI)
Sex					
Male	Ref.	Ref.	Ref.	Ref.	Ref.
Female	0.12 (0.09, 0.14)**	1.07 (1.06, 1.07)**	0.41 (0.23, 0.57)**	0.46 (0.31, 0.60)**	1.00 (1.00, 1.01)**
Age (years)	-0.02 (-0.02, -0.02) **	0.99 (0.99, 0.99)**	-0.11 (-0.12, -0.10)**	-0.08 (-0.08, -0.07)**	0.99 (0.99, 0.99)**
Educational attainment					
Under Graduate school or more	Ref.	Ref.	Ref.	Ref.	Ref.
High school	-0.52 (-0.54, -0.50)**	0.93 (0.93, 0.94)**	-3.34 (-3.51, -3.17)**	-2.23 (-2.38, -2.08)**	0.97 (0.97, 0.97)**
Elementary school	-1.06 (-1.11, -1.02)**	0.86 (0.85, 0.86)**	-5.85 (-6.17, -5.54)**	-4.51 (-4.78, -4.24)**	0.92 (0.92, 0.93)**
Incomplete elementary school	-1.43 (-1.49, -1.38)**	0.79 (0.78, 0.80)**	-7.42 (-7.76, -7.09)**	-6.24 (-6.53, -5.94)**	0.87 (0.87, 0.88)**
Alcohol Consumption					
Never or former user	Ref.	Ref.	Ref.	Ref.	Ref.
Moderate	0.29 (0.27, 0.32)**	1.04 (1.03, 1.05)**	1.62 (1.43, 1.81)**	1.24 (1.08, 1.41)**	1.02 (1.02, 1.02)**
Heavy	0.16 (0.12, 0.21)**	1.02 (1.00, 1.03) **	1.36 (1.01, 1.70)**	0.61 (0.32, 0.91)**	1.01 (1.01, 1.02)**
Smoking Status					
Never	Ref.	Ref.	Ref.	Ref.	Ref.
Former	-0.10 (-0.13, -0.08)**	0.96 (0.96, 0.97)**	-0.40 (-0.59, -0.21)**	-0.13 (-0.30, 0.03)	0.99 (0.99, 0.99)**
Yes	-0.19 (-0.23, -0.16)**	0.95 (0.94, 0.96)**	-1.04 (-1.31, -0.78)**	-0.66 (-0.88, -0.43)**	0.98 (0.98, 0.99)**
Diabetics Status					
No	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	-0.34 (-0.37,- 0.31)**	0.95 (0.94, 0.95)**	-1.61 (-1.82,-1.39)**	-1.47 (-1.66,-1.29)**	0.97 (0.97, 0.98)**
Hypertension Status					
No	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	-0.27 (-0.30, -0.25)**	0.96 (0.95, 0.96)**	-1.40 (-1.57, -1.22)**	-1.19 (-1.34, -1.04)**	0.98 (0.97, 0.98)**
Depressive Symptoms					
No	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	-0.15 (-0.19, -0.12)**	0.98 (0.97, 0.99)**	-0.73 (-0.98, -0.47)**	-0.50 (-0.72, -0.30)**	0.98 (0.98, 0.99)**
Total / HDL-Cholesterol (mg/dl), mean (SD)	-0.05 (-0.06, -0.04)**	0.98 (0.98, 0.99)**	-0.23 (-0.32, -0.15)**	-0.19 (-0.27, -0.12)**	0.99 (0.99, 0.99)**
Body Mass Index (Kg/m^2)	-0.01 (-0.02, -0.01)**	0.99 (0.99, 0.99)**	-0.05 (-0.06, -0.03)**	-0.06 (-0.08, -0.05)**	0.99 (0.99, 0.99)**
Coronary Heart Disease Status					
No	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	-0.29 (-0.36, -0.21)**	0.94 (0.92, 0.95)**	-1.26 (-1.80, -0.71)**	-0.99 (-1.46, -0.53)**	0.98 (0.97, 0.98)**
Coffee cups/day					
No consumption	Ref.	Ref.	Ref.	Ref.	Ref.
>0-99 ml/day	-0.04 (-0.08, 0.01)	0.99 (0.98, 1.00)	-0.30 (-0.63, 0.04)	-0.02 (-0.30, 0.26)	0.99 (0.99, 1.00)
100-199 ml/day	-0.01 (-0.05, 0.03)	1.00 (0.99, 1.01)	-0.12 (-0.43, 0.18)	0.11 (-0.15, 0.37)	0.99 (0.99, 1.00)
200-299 ml/day	-0.05 (-0.10, 0.01)	1.01 (1.00, 1.02)**	-0.52 (-0.92, -0.13)*	-0.18 (-0.51, 0.16)	0.99 (0.98, 1.00)
300-399 ml/day	0.04 (-0.01, 0.10)	1.02 (1.01, 1.04)**	0.21 (-0.18, 0.60)	0.22 (-0.11, 0.55)	1.00 (0.99, 1.00)
≥ 400 ml/day	-0.11 (-0.18, -0.04)**	1.01 (0.99, 1.03)	-0.83 (-1.31, -0.35)**	-0.65 (-1.07, 0.24)**	0.99 (0.98, 0.99)**

*0.01<p< 0.05 and **p<0.01. [a]Performed linear regression. [b]AMR: arithmetic mean ratios obtained by generalized linear model (GLM) with logarithmic link and gamma distribution.

Table 3 shows the multivariate associations between coffee consumption and with the global cognition and various cognitive function domains. In the Model 1 after adjustments of age, sex, and educational attainment, the consumption of more than 200ml per day of coffee in the last 12 months increase the mean words remembered on learning, recall and word recognition tests (AMR.=1.02, 95%CI: 1.01-1.03). The consumption of more than 300ml until 399ml per day of coffee was associated with better performance on semantic verbal fluency test (Coef.=0.45, 95%CI: 0.10-0.80) and phonemic verbal fluency test (Coef.=0.38, 95%CI: 0.08-0.69). Coffee consumption did not remain associated with g-factor, and trail-making B test in the Model 1.

In the model 2 (Table 3), there were only negligible changes in the regression coefficients for coffee consumption after further adjustments for hypertension status, coronary heart disease status, diabetes status, current smoker, depressive symptoms, alcohol consumption, body mass index, total/HDL-cholesterol ratio in the performance on learning, recall and word recognition tests. Interestingly, after full adjustments the consumption of more than 400 ml per day of coffee increase the mean time on trail-making B test performance (AMR=0.99, 95%CI 0.98, 0.99). In the model 2 coffee consumption was not associated with semantic and phonemic verbal fluency test.

Table 3. Analysis of multivariable linear regression between the coffee consumption and g-factor, learning, recall and word recognition tests, phonemic verbal fluency tests, and trail-making test B among the participants (35 to 74 years of age) in the ELSA-Brasil (2008-2010)

Cognitive Function tests	Coffee consumption (cups/day)			
	Model 1		Model 2	
	Coefficient (95%CI)	p-value	Coefficient (95%CI)	p-value
G-Factor[a]				
No consumption	Ref.		Ref.	
>0-99 ml/day	0.03 (-0.01, 0.06)	0.151	0.01 (-0.03, 0.04)	0.606
100-199 ml/day	0.03 (-0.00, 0.06)	0.093	0.01 (-0.03, 0.04)	0.708
200-299 ml/day	0.01 (-0.03, 0.06)	0.579	-0.01 (-0.05, 0.03)	0.617
300-399 ml/day	0.07 (0.003 0.12)	**0.001**	0.05 (0.01, 0.109	**0.020**
≥ 400 ml/day	-0.04 (-0.09, 0.01)	0.140	-0.05 (-0.10, 0.00)	0.052
Learning, recall and word recognition tests [b]				
No consumption	Ref.		Ref.	
>0-99 ml/day	1.00 (0.99, 1.01)	0.573	1.00 (0.99, 1.02)	0.772
100-199 ml/day	1.01 (1.00, 1.01)	0.170	1.01 (1.00, 1.01)	0.178
200-299 ml/day	1.02 (1.01, 1.03)	**<0.001**	1.02 (1.01, 1.03)	**0.001**
300-399 ml/day	1.03 (1.02, 1.04)	**<0.001**	1.03 (1.02, 1.04)	**<0.001**
≥ 400 ml/day	1.03 (1.02, 1.04)	**<0.001**	1.03 (1.02, 1.04)	**<0.001**
Semantic verbal fluency test[a]				
No consumption	Ref.		Ref.	
>0-99 ml/day	0.04 (-0.25, 0.33)	0.785	-0.04 (-0.33, 0.26)	0.798
100-199 ml/day	0.03 (-0.24, 0.30)	0.831	-0.08 (-0.35, 0.19)	0.559
200-299 ml/day	-0.17 (-0.52 0.18)	0.352	-0.26 (-0.61 0.09)	0.150
300-399 ml/day	0.45 (0.10, 0.80)	**0.011**	0.32 (-0.03, 0.67)	0.076
≥ 400 ml/day	-0.28 (-0.70, 0.15)	0.204	-0.34 (-0.77, 0.09)	0.124
Phonemic verbal fluency test[a]				
No consumption	Ref.		Ref.	
>0-99 ml/day	0.23 (-0.02, 0.49)	0.073	0.16 (-0.10, 0.41)	0.230
100-199 ml/day	0.21 (-0.02, 0.45)	0.078	0.10 (-0.14, 0.34)	0.401
200-299 ml/day	0.07 (-0.23, 0.38)	0.639	-0.02 (0.33, 0.28)	0.875
300-399 ml/day	0.38 (0.08, 0.69)	**0.014**	0.27 (-0.03, 0.58)	0.080
≥ 400 ml/day	-0.26 (-0.63, 0.12)	0.177	-0.33 (-0.70, 0.05)	0.087
Trail-making test B [b]				
No consumption	Ref.		Ref.	
>0-99 ml/day	1.00 (0.99 1.00)	0.169	1.00 (0.99, 1.00)	0.590
100-199 ml/day	1.00 (0.99, 1.00)	0.084	1.00 (0.99, 1.00)	0.698
200-299 ml/day	0.99 (0.99 1.00)	0.492	0.99 (0.99, 1.00)	0.118
300-399 ml/day	1.00 (1.00, 1.00)	**0.049**	1.00 (0.99, 1.00)	0.353
≥ 400 ml/day	0.99 (0.99, 1.00)	0.052	0.99 (0.99, 0.99)	**0.013**

Model 1: Adjusted for age, sex and educational attainment. **Model 2:** Model 1+ adjusted hypertension status, coronary heart disease status, diabetes status, current smoker, alcohol consumption, body mass index, total/ HDL-cholesterol ratio and depressive symptoms. [a]Performed linear regression (difference of the mean).[b]Performed generalized linear model with logarithmic link and gamma distribution (arithmetic mean ratios obtained).

Discussion

We examined the relations between coffee consumption in the last 12 months with outcomes included 6 cognitive test scores spanning the domains of global cognition, verbal memory, efficiency of searching in long-term memory, language and executive function in participants of the ELSA-Brasil. This study provides support to the association between coffee consumption and better verbal learning, retrieval from

verbal memory and recognition of verbal memory, but worse executive function in adults and older participants of a cohort free living Brazilians.

Brazil is one of the greatest coffee growers in the world. Moreover, coffee is one of the most commonly consumed beverages by Brazilians and a major source of antioxidants and stimulants in the diet. According to a recent survey the estimated average usual daily coffee intake from the total population was 163 (SE=2.8) ml, and the median was 129 ml, with the 5th and 95th percentiles 3 (SE=0.5) and 442 (SE=7.9) ml, respectively (Sousa *et al.*, 2015). The average intake in the ELSA-Brasil cohort is thus close to that of the overall population in the country (149.35ml, SE= 1.1).

In the Rancho Bernardo Study (Johnson-Kozlow *et al*., 2002), including 1,538 participants aged 52-98 years from Southern California, higher lifetime caffeine intake was associated with better performance on 6 of 12 neuropsychological tests assessing short- and long-term memory of spoken words, long-term memory for geometric forms, fluency, and orientation, registration attention, language, calculation, and recall, and borderline associated with two other cognitive tests assessing concentration and short-term memory for geometric forms only in women. In cross-sectional survey of a representative sample of 9,003 British adults (the Health and Lifestyle Survey) (Jarvis, 1993), participants completed tests of simple reaction time, choice reaction time, incidental verbal memory, visuo-spatial reasoning and also provided self-reports of habitual coffee consumption. After adjustment for potential confounders, a dose-response trend to improved performance with higher levels of coffee consumption was detected for all four tests.

Besides caffeine, coffee contains many other substances, like magnesium and many phenolic acids, and chlorogenic acid is the most abundant one (Nardini *et al.*,

2002). Consumption of coffee increases the antioxidant capacity in plasma (Natella *et al.*, 2002; Svilaas *et al.*, 2004), which may provide a protective effect against free radicals that cause oxidative damage to neurons, and appear to be very vulnerable to the effects of free radicals (Christen, 2000), and then preventing the dementia . Cao and colleagues (2012), observed in case-control study that caffeine/coffee intake is associated with a reduced risk of dementia or delayed onset, particularly for those who already have mild cognitive impairment. In another study of ELSA-Brasil was found a protective effect of coffee consumption on risk of adult-onset diabetes (Yarmolinsky et al., 2015) suggesting a possible prevention effect for vascular dementia.

In this cross sectional study with adults and elderly, we observed that the effect of coffee consumption may be related with high consumption per day and also with some specific domains. After adjustment for all confounders we found that the consumption of more than 200 ml per day of coffee in the last 12 months increase the mean words remembered on learning, recall and word recognition tests . However, the consumption of more than 400 ml per day increases the mean time on trial-making B performance. It suggests that the consumption until 400 ml per day may have a protective neurodegenerative effect on memory and prevents the detrimental effect on executive function.

Four longitudinal studies have examined the relationship of coffee consumption to cognitive decline with inconsistent results. Two of the studies showed no relationship (Ng *et al*., 2008, Laitala *et al*., 2009) while the other two showed isolated statistically significant findings but without demonstrating a dose-response relationship (Eskelinen *et al.*, 2009, van Gelder *et al*., 2007). A small case-control study found lower caffeine intake during the preceding 20 years in AD patients compared to controls (Maia and Mendonca, 2002), and a prospective study found regular consumption of coffee was

associated with a reduced risk of AD at 5 year follow-up (Lindsay *et al.*, 2002). In a meta-analysis of longitudinal studies on caffeine intake and cognitive decline by different measures conducted by Santos and colleagues (2010), the total effect of the risk relative from three publications was statistically insignificant at 0.98 (CI 0.87–1.11). In other reported an association between coffee drinking and somewhat attenuated rates of cognitive decline in women (Arab *et al*., 2011).

Nonetheless, the present study has limitations, as with all dietary exposures, measurement error is inevitable. Individuals poorly remember their usual consumption of foods and beverages. This concern is in addition to the potential effect of unmeasured confounders and residual confounding that is inevitable in studies of this nature. But, the advantage of large epidemiological data is that it may take into account multiple biological, environmental, and clinical confounding factors which may have obscured the true cause of this association. We reported that these results persisted even when all known potential confounding factors (age, education, gender, diabetes, hypertension, total and HDL-Cholesterol, cardiovascular disease, depressive symptoms, smoking, and alcohol use) were taken into account. The major strengths of this study are its sample size and the opportunity to adjust for several possible confounding factors. Also, we used the generalized linear models to estimate the relation between coffee consumption and all memory tests and trail-making B test considering the nature and distribution of these variables. The ELSA-Brasil is a longitudinal study with has a wide battery of cognitive function tests which measure different domains of cognition allowing evaluate whether coffee consumption prevent the cognitive decline during follow up waves.

Conclusion

These findings are consistent with published literature reinforcing the importance of lifestyle choices on cognitive skills and abilities at younger and older ages. Individuals, especially with more than 200 ml per day of coffee consumption in the last 12 months performed better in the verbal learning and delayed verbal memory. However the consumptions of more than 400 ml per day increase the mean time of performance on trial-making B test. It suggests that the consumption until 400 ml per day may have a protective neurodegenerative effect on memory and also prevents the detrimental effect on executive function. Before advocating the benefits of coffee on verbal memory, or admonish correlates to executive control further research is needed, especially prospective studies and also studies in brain imaging in human beings to fully understand the nature of these associations and rule out confounding by other factors.

Competing interests

The authors declare that they have no competing interests.

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CONSIDERAÇÕES FINAIS

5.0 CONSIDERAÇÕES FINAIS

Na presente tese, observamos que a baixa escolaridade materna esteve associada a uma maior chance de pior desempenho em todos os testes de função cognitiva em adultos. Já o baixo peso ao nascer esteve associado a uma maior chance de pior desempenho no teste de trilha B, e menores comprimentos de tronco aos testes de aprendizado, reconhecimento e retenção de palavras, e de trilha B. Sendo que a chance de pior desempenho cognitivo, especialmente no controle executivo, não foi atenuada quando considerou o efeito acumulado de desfavoráveis condições sociais e nutricionais no decorrer da vida.

Observamos também, que o efeito da baixa escolaridade materna e de menores comprimentos do tronco no pior desempenho cognitivo permaneceu quando consideramos o risco para doenças cardiovasculares estimado por meio do Score de Framingham na fase adulta. Além disso, verificamos que o consumo de até quatro xícares de café por dia esteve associado a um melhor desempenho cognitivo relacionado a memória verbal recente e de longo prazo e preveniria a relação encontrada com o pior controle executivo em adultos e idosos. Nossos resultados sugerem que a escolaridade atual atenua, mas não remove completamente a associação entre piores condições socioeconômicas e nutricionais durante a infância e adolescência, alto risco para doenças cardiovasculares na vida adulta, maior quantidade de consumo de café, na performance cognitiva.

Os resultados observados neste estudo reforçam a importância da aplicação de uma perspectiva de curso de vida na cognição na vida adulta. E uma compreensão extensiva dos determinantes sociais e de saúde na cognição com o envelhecimento, requer atenção as exposições desfavoráveis a saúde em todo decorrer da vida, com

especial foco em certos períodos (como na infância, adolescência e início da vida adula), e também do efeito acumulado dessas exposições. O que salienta a relevância de intervenções sociais, nutricionais e materiais em todo o ciclo de vida, e especialmente durante o início da vida, por impactar substancialmente na saúde com o envelhecimento.

ANEXOS

ANEXO 1

Aprovação da Comissão Nacional de Ética em Pesquisa (CONEP)

Fls. nº 109
Rubrica

MINISTÉRIO DA SAÚDE
Conselho Nacional de Saúde
Comissão Nacional de Ética em Pesquisa

CARTA Nº 976 CONEP/CNS/MS Brasília, 04 de agosto de 2006.

Senhora Coordenadora,

Tendo a CONEP recebido desse CEP o projeto de pesquisa ***"Estudo Longitudinal de Saúde do Adulto – ELSA"*** Registro CEP-HU/USP 659/06 - CAAE 0016.1.198.000-06, Registro Sipar MS: nº 25000.083729/2006-38, Registro CONEP nº 13065, verifica-se que:

Trata-se de protocolo a ser desenvolvido por consórcio vencedor da Chamada Pública DECIT/MS/FINEP/CNPq que foi constituído por sete instituições de ensino superior e pesquisa de seis estados, das regiões Nordeste (Universidade Federal da Bahia), Sudeste (FIOCRUZ/RJ, USP, UERJ, UFMG e UFES) e Sul (UFRS). Será um estudo de coorte de 15 mil funcionários de instituições públicas com idade igual ou superior a 35 anos. A coorte será acompanhada anualmente para verificação do estado geral e, a cada três anos, será chamada para avaliações mais detalhadas que incluem exames clínicos. Os sujeitos de pesquisa serão entrevistados por pessoas treinadas e certificadas e os exames serão realizados por profissionais de saúde. O estudo tem como objetivos principais: estimar a incidência do diabetes e das doenças cardiovasculares e estudar sua história natural; investigar associações entre fatores biológicos, comportamentais, ambientais, ocupacionais, psicológicos e sociais relacionados a essas doenças e complicações decorrentes, buscando compor modelo causal que contemple suas inter-relações; descrever a evolução temporal desses fatores e os determinantes dessa evolução; identificar modificadores de efeito das associações observadas; identificar diferenciais nos padrões de risco entre os centros participantes que possam expressar variações regionais relacionadas a essas doenças no país. Dentre os objetivos secundários *consta "estocar material biológico, para estudos futuros com diversos tipos de marcadores relacionados à inflamação, coagulação, disfunção endotelial, resistência à insulina, obesidade central, estresse e fatores de risco tradicionais, bem como prover a extração de DNA para exames genéticos futuros"*. De acordo com informação da pág. 11 do protocolo, item "coleta de sangue", as amostras de sangue serão estocadas para

Esplanada dos Ministérios, Bloco "G ", Ministério da Saúde -Edifício Anexo, Ala "B"- 1º andar – Sala 145 – CEP 70058-900- Brasília / DF
Telefones : (61) 3315.2951/ 3226.6453 Fax : (61) 3226.6453 - *E-mail*: conep@saude.gov.br - *homepage* : http://conselho.saude.gov.br

exames adicionais e formação de banco de DNA. Haverá um laboratório central que fará as "determinações básicas do estudo em amostras encaminhadas pelos centros de investigação", as "determinações simples" serão feitas nos próprios laboratórios. O banco de material biológico está em fase de planejamento com local e coordenador a serem definidos.

Diante do exposto, embora nos objetivos do estudo verifica-se que haverá também pesquisa genética, pelas informações do protocolo tal pesquisa não será realizada no momento, não estando descrito ainda (nem no protocolo, nem no Termo de Consentimento Livre e Esclarecido-TCLE) os procedimentos para tal. Portanto, nesse primeiro momento do estudo não se trata de projeto da área temática especial "genética humana" (Grupo I), conforme registrado na folha de rosto, mas sim, do grupo III. Nesse caso, a aprovação ética é delegada ao Comitê de Ética em Pesquisa da instituição, devendo ser seguido o procedimento para projetos do grupo III, conforme o fluxograma disponível no site : http://conselho.saude.gov.br e no Manual Operacional para CEP. Não cabe, portanto, a referência a CONEP no 3º parágrafo da pág. 1 e no 6º parágrafo da pág.2 do TCLE. Evidenciamos, entretanto, que o armazenamento e utilização de materiais biológicos humanos no âmbito de projetos de pesquisa está regulamentado pela Resolução CNS 347/2005 e que o projeto em questão deve incluir as determinações dessa resolução. Quando for elaborado o protocolo para os estudos genéticos, deverá também ser cumprida a Resolução CNS 340/04 incluindo obtenção de TCLE específico. Em se tratando de pesquisa com funcionários de instituições públicas, cabe ressaltar o disposto no item IV.3 "b" da Res. 196/96.

Atenciosamente ,

CORINA BONTEMPO DUCA DE FREITAS
Secretária Executiva da
COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

Á Sua Senhoria
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C/ cópia para os CEPs: UFBA, FIOCRUZ/RJ,UERJ, UFMG, UFES e UFRS