Lidyane do Valle Camelo

POSIÇÃO SOCIOECONÔMICA NO CURSO DE VIDA, INFLAMAÇÃO CRÔNICA E ATEROSCLEROSE SUBCLÍNICA NO ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL)

Universidade Federal de Minas Gerais
Programas de Pós-Graduação em Saúde Pública
Belo Horizonte - MG
2014

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Tese apresentada ao Programa de Pós-Graduação em Saúde Pública da Universidade Federal de Minas Gerais, como requisito parcial para obtenção do título de Doutor em Saúde Pública.

Orientadora: Prof.ª Dr.ª Sandhi Maria Barreto
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POSIÇÃO SOCIOECONÔMIA NO CURSO DE VIDA, INFLAMAÇÃO CRÔNICA E ATEROSCLEROSE SUBCLÍNICA NO ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL)

LIDYANE DO VALLE CAMELO

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em SAÚDE PÚBLICA, como requisito para obtenção do grau de Doutor em SAÚDE PÚBLICA, área de concentração SAÚDE PÚBLICA.

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Belo Horizonte, 21 de novembro de 2014.

ATA DA DEFESA DE TESE

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE PÚBLICA

ATA DA DEFESA DE TESE DA ALUNA
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A Comissão considerou a tese:

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( ) Reprovada

Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.
Belo Horizonte, 21 de novembro de 2014.

Prof(a). Sandhi Maria Barreto (Doutora)

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AGRADECIMENTOS

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"The first wealth is health"

Ralph Waldo Emerson

RESUMO DA TESE

RESUMO

A exposição à adversidade social no curso de vida está associada a uma maior carga de morbidade e mortalidade por doenças cardiovasculares. Entretanto, pouco se sabe sobre os mecanismos biológicos, comportamentais e os relacionados ao estresse que poderiam mediar essa associação. O objetivo desta tese foi investigar a posição socioeconômica no curso de vida e sua associação com a inflamação crônica e a aterosclerose subclínica no contexto brasileiro. Adicionalmente, foram explorados fatores que poderiam mediar essa associação como os comportamentos de risco à saúde, alterações metabólicas e o estresse no trabalho.

Como fonte de informações, utilizamos os dados da linha de base (2008-2010) do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil). A inflamação crônica foi mensurada por meio da proteína C-reativa (PCR). Utilizando modelos de regressão linear múltipla, encontramos que baixa posição socioeconômica na infância (mensurada pela escolaridade materna) foi associada a um aumento dos níveis séricos de PCR, entretanto essa associação não foi independente da posição social na juventude (aferida pela escolaridade do participante) e da posição social na vida adulta (avaliada por meio da classe social da ocupação e da renda familiar *per capita*). Apesar disso, encontramos que a PCR aumentou de forma linear à medida que o número de exposições às circunstâncias sociais desfavoráveis aumentou ao longo da vida. Utilizando modelos de equações estruturais, encontramos que a aglomeração de alterações metabólicas (obesidade, hipertensão arterial, baixo HDL, hipertrigliceridemia e diabetes) foi responsável por 49,5% do efeito total da posição socioeconômica cumulativa (variável latente composta pelos indicadores de posição social na infância, juventude e vida adulta) na PCR entre as mulheres, mas essa proporção foi inferior entre os homens (20,2%). A aglomeração de comportamentos de risco à saúde (tabagismo, inatividade física e consumo excessivo de álcool) foi responsável por 13,4% do efeito total da posição socioeconômica cumulativa na PCR entre os homens, mas esse mesmo percentual foi de apenas 4,4% entre as mulheres. Consequentemente, o efeito direto da posição socioeconômica cumulativa na PCR (não mediado pela aglomeração de alterações metabólicas e de comportamentos de risco à saúde) foi alto (63,2% e 44,6% entre homens e mulheres, respectivamente).

A aterosclerose subclínica foi aferida por meio da espessura médio-intimal carotídea (IMT – do inglês: *intima-media thickness*). Utilizando modelos de regressão linear múltipla, encontramos que apresentar baixa posição social na infância (mensurada pela escolaridade materna) foi associado a maiores níveis de IMT apenas entre as mulheres. Já a baixa posição social na juventude (mensurada pela escolaridade do participante) e na vida adulta (aferida pela classe social da ocupação) foi associada a um aumento no IMT em ambos os gêneros. O IMT também aumentou à medida que número de exposições a condições sociais adversas aumentou ao longo da vida, especialmente entre as mulheres. Foi construído um grafo acíclico dirigido para expressar as relações causais entre a posição socioeconômica ao longo da vida e o IMT com intuito de auxiliar na investigação do papel mediador do estresse no trabalho, avaliado por meio da versão brasileira do *Swedish Demand-Control-Support Questionnaire* (DCSQ). Encontramos que o estresse no trabalho, segundo o modelo teórico proposto por

Karasek, e o baixo controle no trabalho falharam em explicar substancialmente a associação entre a baixa posição socioeconômica ao longo da vida e maiores níveis de IMT em ambos os gêneros.

A baixa posição socioeconômica ao longo da vida foi associada à inflamação crônica e a aterosclerose subclínica no contexto brasileiro. Esses achados sugerem que intervenções sociais realizadas em uma única etapa da vida podem ser insuficientes para lidar com as desigualdades em saúde. Expressiva parcela da associação entre a posição social ao longo da vida e a PCR não foi mediada pelos comportamentos de risco à saúde e por alterações metabólicas, o que sugere que outros mecanismos podem estar envolvidos na mediação dessa associação, como o estresse psicossocial. Entretanto, encontramos que o estresse no trabalho não mediou à associação entre posição social ao longo da vida e o IMT. O estresse no trabalho é apenas um aspecto do estresse psicossocial e outras fontes de estresse, não avaliadas nesta tese, podem ser aspectos importantes para explicar as desigualdades sociais em saúde no contexto brasileiro, o que poderá ser explorado no futuro com dados da coorte do ELSA-Brasil.

Palavras-chave: desigualdades em saúde, posição social, curso de vida, inflamação crônica, proteína C-reativa, aterosclerose, espessura médio-intimal carotídea, mediação, estresse no trabalho, ELSA-Brasil.

ABSTRACT

ABSTRACT

The exposure to social adversity across the life course is associated with a higher burden of cardiovascular disease morbidity and mortality. However, little is known about the mechanisms that could mediate this association such as biological and behavioral mechanisms, as well as the mechanisms related to stress. The aim of this dissertation was to investigate the socioeconomic position (SEP) across the life course and its association with chronic inflammation and subclinical atherosclerosis in Brazilian context. In addition, we explored factors that could mediate this association as health-risk behaviors, metabolic alterations and job stress.

As a source of information, we use data from the baseline (2008-2010) of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Chronic inflammation was measured by C-reactive protein (CRP). Using multiple linear regression models, we found that low childhood SEP (measured by maternal education) was associated with increased CRP. However, this association was not independent of young SEP (evaluated by participants' own education) and adulthood SEP (assessed by occupational social class and by *per capita* household income). Nevertheless, we found that CRP increased linearly with increasing numbers of exposure to unfavorable social circumstances over the life course. Using structural equation modeling, we found that the clustering of metabolic alterations (obesity, hypertension, low HDL, hypertriglyceridemia and diabetes) accounted for 49.5% of the total effect of cumulative SEP (latent variable composed by indicators of SEP in childhood, young and adulthood) in CRP among women, but this proportion was lower among men (20.2%). The clustering of health-risk behaviors (smoking, physical inactivity and excessive alcohol consumption) accounted for 13.4% of the total effect of cumulative SEP in CRP in men, but this percentage was only 4.4% among women. Consequently, the direct effect of cumulative SEP in CRP (which was not mediated by the clustering of metabolic alterations and health-risk behaviors) was high (63.2% and 44.6% among men and women, respectively).

Subclinical atherosclerosis was assessed by carotid intima-media thickness (IMT). Using multiple linear regression models, we found that low childhood SEP (measured by maternal education) was associated with higher levels of IMT only among women. Low young SEP (evaluated by participants' own education) and adulthood SEP (measured by occupational social class) were associated with an increase in IMT in both genders. IMT also increased with increasing numbers of exposure to adverse social conditions throughout the life course, especially among women. We performed a directed acyclic graph (DAG) to express the causal relationships between life course SEP and IMT in order to investigate the mediating role of job stress, assessed by the Brazilian version of the Swedish Demand-Control-Support Questionnaire (DCSQ). Neither job strain, evaluated by Karasek'model, nor low job control substantially explained the association between low life course SEP and increased IMT, since job strain and low job control were not associated with IMT independently of SEP in men, and in women the passive work and low control only slightly attenuated the association between IMT and all SEP indicators.

Low life course SEP was associated with chronic inflammation and subclinical atherosclerosis in Brazilian context. These findings suggest that social interventions in a single life stage may be insufficient to deal with the health inequalities. Significant portion of the association between life course SEP and CRP was not mediated by health-risk behaviors and metabolic alterations, which suggests that other mechanisms may be involved in mediating this association, such as psychosocial stress. However, we found that job stress did not mediate the association between life course SEP and IMT. Job stress is only one aspect of psychosocial stress and other sources of stress, which were not evaluated in this dissertation, may be important in explaining the health inequalities in Brazilian context, which can be explored in the future using data of the ELSA-Brasil cohort.

Keywords: health inequalities, socioeconomic position, life course, chronic inflammation, C-reactive protein, atherosclerosis, intima-media thickness, mediation, job stress, ELSA-Brasil.

SUMÁRIO

APRESENTAÇÃO

1 APRESENTAÇÃO

Esta tese insere-se na linha de pesquisa *Epidemiologia das Doenças e Agravos Não Transmissíveis e Ocupacionais* do Programa de Pós-Graduação em Saúde Pública da Universidade Federal de Minas Gerais e integra um estudo maior intitulado "Estudo Longitudinal de Saúde do Adulto (ELSA- Brasil)". O ELSA-Brasil é um estudo prospectivo multicêntrico, desenvolvido em 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 deste estudo 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 a suas complicações, buscando compor um modelo causal que contemple suas inter-relações[1].

Este volume de tese preenche um requisito parcial para a obtenção do título de doutor em Saúde Pública e está apresentado no formato de coletânea de artigos científicos originais como previsto pela regulamentação do Programa de Pós-Graduação em Saúde Pública da Universidade Federal de Minas Gerais[2]. Esta tese teve por objetivo investigar a posição socioeconômica no curso de vida e sua associação com a inflamação crônica e a aterosclerose subclínica utilizando dados do ELSA-Brasil.

Este volume de tese contém:

1. *Considerações iniciais*: apresentação da fundamentação teórica e justificativa para a realização da tese;
2. *Objetivos da tese*: apresentação do objetivo geral e dos objetivos específicos;
3. *Artigos originais*: apresentação de dois artigos originais que respondem aos objetivos propostos;
4. *Considerações finais*: discussão de aspectos relevantes do estudo, contribuição da tese para a saúde pública e perspectivas futuras;
5. *Apêndice:* apresentação o primeiro artigo desta tese no formato publicado no periódico *Plos One;*

[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.
[2] Programa de Pós-graduação em Saúde Pública Universidade Federal de Minas Gerais. Regulamento do Programa de Pós-Graduação em Saúde Pública - 2010. Belo Horizonte, 2010.

6. *Anexos:* ata do exame de qualificação e aprovação do projeto ELSA-Brasil pelos comitês de ética das instituições envolvidas no estudo.

CONSIDERAÇÕES INICIAIS

2 CONSIDERAÇÕES INICIAIS

As doenças cardiovasculares (DCV), principalmente a doença isquêmica do coração e a doença cerebrovascular, contribuem com a maior parcela da carga global de doenças, constituindo-se na principal causa de mortes prematuras e incapacidades no Brasil [3] e em todo o mundo [4].

As DCV não são distribuídas aleatoriamente entre e intra-populações, e indivíduos em desvantagens socioeconômicas carregam uma maior carga dessas doenças[5]. A associação entre piores condições socioeconômicas e DCV vem sendo estudada há algumas décadas. A partir da década de 1950 diversos estudos começam a reportar que a morbimortalidade por DCV é desproporcionalmente maior em populações com baixas condições socioeconômicas [6]. Além disso, com frequência a associação entre a posição socioeconômica e DCV apresenta um gradiente tipo dose-resposta: quanto melhor a posição socioeconômica, mais os indivíduos vivem e menor é a morbimortalidade associada a essas doenças[7].

Desde a década de 1980, numerosos estudos tem demonstrado que a ocorrência de DCV está associada à exposição a circunstâncias sociais desfavoráveis, não somente na vida adulta, mas também na infância e juventude[8,9,10]. Galobardes et al. (2006)[8] reuniram 40 estudos, por meio de uma revisão sistemática, que avaliavam a associação entre condições socioeconômicas na infância e DCV na vida adulta. Do total de 40 publicações, 31 apontaram evidências robustas de associação inversa entre posição socioeconômica na infância e DCV. Todos esses resultados foram independentes da posição socioeconômica na vida adulta.

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[3] Schmidt MI, Duncan BB, Azevedo e Silva G, Menezes AM, Monteiro CA, Barreto SM, Chor D, Menezes PR.Chronic non-communicable diseases in Brazil: burden and current challenges. Lancet. 2011;377(9781):1949-61.

[4] Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369(5):448-57.

[5] Harper S, Lynch J, Smith GD.Social determinants and the decline of cardiovascular diseases: understanding the links. Annu Rev Public Health. 2011;32:39-69.

[6] Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation. 1993;88(4 Pt 1):1973-98.

[7] Krieger N. Historical roots of social epidemiology: socioeconomic gradients in health and contextual analysis. *Int J Epidemiol*. 2001; 30(4):899-900.

[8] Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol. 2006a;16(2):91-104.

[9] Galobardes, B, Lynch J, Smith GD. Is the association between childhood cause-specific mortality and childhood socioeconomic circumstances established? Update of a systematic review. J. Epidemiol. Community Health. 2008; 62: 387–390.

[10] Pollitt RA, Rose KM, Kaufman JS.. Evaluating evidence for models of life course socioeconomic factors and cardiovascular outcomes: a systematic review. BMC Public Health. 2005;5:7.

Apesar de essas evidências serem numerosas, pouco se sabe sobre os mecanismos pelos quais a exposição a piores condições socioeconômicas na infância pode estar relacionada com a saúde na vida adulta. Não se sabe se existe um período na infância no qual essas exposições afetam mais a saúde, quanto tempo elas precisam durar e os caminhos biológicos, psicológicos, comportamentais que podem mediar essa associação[11]. Na tentativa de compreender melhor esse fenômeno, a epidemiologia do curso de vida tornou-se uma ferramenta importante para guiar pesquisadores na realização de estudos que investigam tal hipótese [12].

2.1 EPIDEMIOLOGIA DO CURSO DE VIDA

A epidemiologia do curso de vida pode ser definida como o estudo de como exposições nas diversas fases da vida, desde a concepção, influem no processo saúde-doença dos indivíduos ao longo da vida. Objetiva compreender melhor os mecanismos biológicos, comportamentais e psicossociais que atuam no curso de vida dos indivíduos, e até mesmo entre gerações, que permeiam a relação entre exposições ocorridas em diferentes etapas e o adoecimento[13]. Essa abordagem possui uma especial relevância para o estudo das doenças crônicas, tendo em vista que elas se manifestam após longos períodos de latência e que modelos etiológicos convencionais, baseados em fatores comportamentais e clínicos são limitados e explicam apenas parcialmente as desigualdades nas distribuições dessas doenças [14].

Estudos ecológicos foram importantes para suscitar a ideia de que exposições à privação, ainda no início da vida, poderiam estar associadas ao risco de adoecer na vida adulta. Estudo realizado com dados da Inglaterra e país de Gales demostrou uma associação positiva ente as taxas de mortalidade por doença coronariana entre 1968 a 1978 e as taxas de mortalidade infantil nessas mesmas regiões cerca de 50 anos antes[15]. Posteriormente, estudos em nível

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[11] Cohen S, Janicki-Deverts D, Chen E, Matthews KA. Childhood socioeconomic status and adult health. Ann N Y Acad Sci. 2010;1186:37-55.

[12] Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. J Epidemiol Community Health. 2003;57(10):778-83.

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[15] Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986;1(8489):1077-81.

individual confirmaram esses achados[16]. O estudo clássico realizado em *Hertfordshire* na Inglaterra com 10.636 indivíduos do sexo masculino nascidos entre 1911 e 1930 é um exemplo desse grupo de estudos[16]. Nesse trabalho, foi demonstrado que a mortalidade por doença coronariana na vida adulta aumentava à medida que o peso ao nascer e o peso ao 1 ano de vida diminuía[16]. Estudos como esses embasaram a teoria de Barker, ou origem fetal das doenças, que postula que a desnutrição durante períodos críticos como a gestação e início da infância acarretaria em um crescimento intraútero prejudicado, que "programaria" o indivíduo para o desenvolvimento de doença coronariana por adaptação metabólica e estrutural permanente[17]. Mais recentemente, vários outros estudos e teorias têm sido propostas para explicar como o ambiente ao longo do desenvolvimento humano influencia o adoecimento do adulto[18].

A abordagem do curso de vida postula que os fatores biológicos e sociais ao longo da vida influenciam a saúde e a doença na vida adulta de três formas: independente, cumulativa e interativa. Vários modelos teóricos foram desenvolvidos para melhor compreender os diferentes processos em que as experiências socioeconômicas em todo o curso da vida podem influenciar o risco de adoecer. Os principais deles são: os modelos de períodos críticos, períodos sensíveis, acumulação de riscos e mobilidade social [19].

Períodos críticos são janelas de tempo limitadas, nas quais a exposição pode causar efeitos irreversíveis no organismo e que futuramente podem desencadear o processo de adoecimento. Foras dessas janelas, se a exposição ocorre, ela não tem efeito sob uma dada doença, ou seja, não há excesso de risco associado à exposição[19,20]. O modelo de períodos críticos remete a teoria de Barker e por isso também é conhecido como "modelo de programação biológica" e "modelo de latência". Este modelo pressupõe que a exposições desfavoráveis em períodos críticos, como a gestação, afetariam de forma permanente e irreversível a estrutura e funções

[16] Barker DJP, Osmond C, Winter PD, Margetts BM, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989; 2: 577–80.
[17] Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311(6998):171-174.
[18] Gluckman PD, Hanson MA, Spencer HG, Bateson P. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. Proc Biol Sci. 2005 April 7; 272(1564): 671–677.
[19] Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. J Epidemiol Community Health. 2003;57(10):778-83.
[20] Ben-Shlomo, Y, Kuh, D. A life-course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285-93.

de órgãos e tecidos. Essas alterações acarretariam em uma maior probabilidade adoecer no futuro[21].

Uma segunda versão do modelo de períodos críticos assume que o efeito de exposições em períodos críticos poderia ser modulado por exposições em outros períodos da vida. Para investigar essa versão "expandida" do modelo de períodos críticos, as investigações necessitam testar efeitos de interação entre exposições em períodos críticos e exposições em outras janelas de tempo. Por exemplo, a associação entre baixo peso ao nascer e doença coronariana existe, principalmente, em indivíduos obesos na vida adulta. Isso sugere que uma exposição na vida adulta poderia modificar o efeito de exposições que acontecem em períodos críticos [21,22].

Já períodos sensíveis são janelas de tempo em que a exposição tem um efeito mais acentuado no risco de adoecer, como a infância e adolescência. Postula-se que exposições fora dessa janela também seriam associadas ao risco de adoecer, porém com menor magnitude. Assim, a principal diferença entre o modelo de períodos críticos e o modelo de períodos sensíveis é que o último postula que exposições fora dos períodos sensíveis têm efeito, mas mais fraco, sob o risco de adoecer, enquanto exposições fora dos períodos críticos não têm efeito nenhum. O modelo de períodos sensíveis assume que existe a possibilidade do efeito de exposições em períodos sensíveis serem modificadas e mesmo revertidas em outras janelas de tempo [21,22].

Já o modelo de acumulação de risco pressupõe que a acumulação de várias exposições e experiências adversas ao longo da vida pode influenciar o risco de adoecer na vida adulta. Assim, existiria um efeito dose-resposta, já que o impacto sobre a saúde aumentaria à medida que o número, a duração e a severidade dessas exposições adversas aumentassem. Esse modelo também admite a existência de períodos onde a suscetibilidade à exposição pode ser maior, entretanto ele postula que a sequência e/ou a trajetória das exposições ao longo do tempo também seriam importantes [21,23]. O modelo de acumulação de risco está relacionado com uma "cadeia de riscos", ou seja, a existência de uma exposição adversa aumentaria a probabilidade de outra exposição negativa acontecer, que, por sua vez, aumentariam o risco

[21] Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. J Epidemiol Community Health. 2003;57(10):778-83.

[22] Ben-Shlomo, Y, Kuh, D. A life-course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285-93.

[23] Lynch J, Smith GD. A life course approach to chronic disease epidemiology. Annu Rev Public Health. 2005;26:1-35.

de adoecimento futuro. Por exemplo, crianças que nasceram em circunstâncias sociais desfavoráveis teriam um maior risco de ter tido baixo peso ao nascer, ter dietas não saudáveis, não praticar atividade física, serem tabagistas etc. Assim, a acumulação de exposições pode causar danos à saúde por meio de aglomeração de exposições (efeito *cluster*) [24,25].

O modelo de mobilidade social postula que as trajetórias sociais e econômicas ao longo da vida (ex.: ascendente ou descente) poderiam impactar o risco de doença na vida adulta. Esse conceito de mobilidade social considera e integra tanto trajetórias intrageracionais como intergeracionais. Independente das causas das mudanças na hierarquia social ou mecanismo de ação sobre a saúde, a mobilidade social é considerada um fenômeno em si, com potencial de impactar a saúde e o adoecimento[26].

Todos esses modelos de curso de vida são abordagens conceituais que tentam representar como o processo complexo de exposições ao longo da vida pode afetar a saúde do adulto. Apesar dos modelos serem apresentados separadamente, empiricamente é bastante difícil distingui-los[26]. Alguns autores defendem que não podemos separar os resultados de diferentes modelos, uma vez que existe grande interdependência entre período críticos/sensível, a acumulação de risco e os modelos de mobilidade social[26].

2.2 DESIGUALDADES EM SAÚDE: MECANISMOS EXPLICATIVOS

Os mecanismos que conectam as exposições às condições sociais adversas a uma maior ocorrência de DCV ainda não estão bem esclarecidos. Alguns pesquisadores acreditam que as condições sociais são *proxies* das verdadeiras causas das doenças, já que uma pior posição socioeconômica está relacionada a um maior engajamento em comportamentos de risco (ex. tabagismo), menor acesso a serviços de saúde e a alimentos saudáveis, etc.[27]. Entretanto, a visão mais aceita é que o contexto social atue como ponto de partida, direcionando os indivíduos para fatores de risco mais proximais[28]. Nessa perspectiva, a condição

[24] Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. J Epidemiol Community Health. 2003;57(10):778-83.
[25] Lynch J, Smith GD. A life course approach to chronic disease epidemiology. Annu Rev Public Health. 2005;26:1-35.
[26] Hallqvist J, Lynch J, Bartley M, Lang T, Blane D. Can we disentangle life course processes of accumulation, critical period and social mobility? An analysis of disadvantaged socio-economic positions and myocardial infarction in the Stockholm Heart Epidemiology Program. Soc Sci Med. 2004;58(8):1555-62.
[27] Angell M.Privilege and health--what is the connection? N Engl J Med. 1993;329(2):126-7
[28] Link BG, Phelan J. Social conditions as fundamental causes of disease. J Health Soc Behav. 1995;Spec No:80-94.

socioeconômica seria a causa fundamental das desigualdades em saúde, por ser um ponto de partida de uma trajetória que pode resultar em diferenciais de exposição e vulnerabilidade a fatores de risco e, consequentemente, ao estabelecimento de doenças de forma desigual[29].

Duas perspectivas não mutualmente excludentes também têm sido apontadas para explicar a existência de desigualdades em saúde: a *abordagem da privação material* e a *abordagem psicossocial*. A interpretação da *privação material* enfatiza a posição socioeconômica como um ponto de partida para o acesso a condições materiais diferenciadas como alimentação, moradia, serviços e bens materiais. Já a intepretação *psicossocial* atribui a existência das desigualdades em saúde aos efeitos diretos ou indiretos do estresse resultante da exposição às circunstâncias sociais desfavoráveis ou à experiência de viver em condições de desvantagem socioeconômica relativa[30]. Nessa perspectiva, os efeitos da exposição crônica ao estresse elevariam as atividades dos sistemas fisiológicos causando um desgaste denominado carga alostática. Essa carga alostática juntamente com os hormônios associados ao estresse protege o corpo no curto prazo promovendo uma adaptação, mas ao longo prazo essa carga alostática provocaria mudanças corporais que levam à doença. Além disso, a exposição ao estresse também poderia afetar a saúde indiretamente, induzindo um perfil de comportamentos adversos, como o tabagismo, dieta não saudável e consumo abusivo de álcool[31].

Vários mecanismos biológicos entre a posição socioeconômica no curso de vida e DCV podem ser conjecturados, já que as DCV tem sua gênese principal na aterosclerose, uma doença inflamatória que envolve várias alterações hormonais, imunológicas e metabólicas que ocorrem em longos períodos de evolução. Assim, o conhecimento sobre a história natural da aterosclerose é essencial para compreender em que etapa do processo de adoecimento a posição socioeconômica pode promover, prevenir ou retardar seu estabelecimento.

2.2.1 O processo inflamatório e o início da aterosclerose

A aterosclerose é uma doença progressiva caracterizada por acumulação, principalmente, de lípides e elementos fibrosos em grandes artérias[32]. O conceito inicial de que aterosclerose era

[29] Link BG, Phelan J. Social conditions as fundamental causes of disease. J Health Soc Behav. 1995;Spec No:80-94.
[30] Kawachi I, Subramanian SV, Almeida-Filho N. A glossary for health inequalities. J Epidemiol Community Health. 2002;56(9):647-52.
[31] McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. Ann N Y Acad Sci. 1999;896:30-47.
[32] Libby P. Inflammation in atherosclerosis. Nature. 2002 Dec 19-26;420(6917):868-74.

resultante apenas de uma desregulação do metabolismo de deposição lipídica foi bastante aceito no passado. Entretanto, estudos demostraram que apenas os níveis de colesterol discriminam pouco o risco para doença coronariana na população e 35% da ocorrência dessa doença acontece em indivíduos com valores de colesterol total inferior a 200mg/dl (Figura 1) [33]. Atualmente, sabe-se que a aterosclerose vai muito além da dislipidemia e que a inflamação participa de forma importante na gênese, progressão e complicações associadas à mesma[34,35,36,37,38].

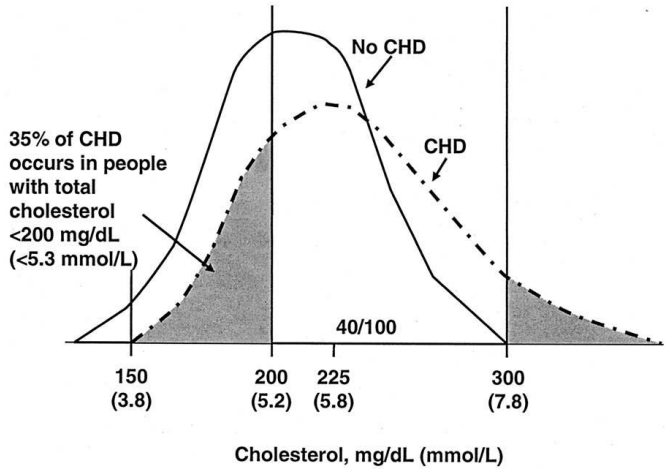

Figura 1: Distribuição dos níveis plasmáticos de colesterol total em indivíduos com e sem doença coronariana (DAC), em 26 anos de acompanhamento do Framingham Heart Study. FONTE: Castelli WP. Lipids, risk factors and ischaemic heart disease. Atherosclerosis. 1996;124(suppl):S1–S9.

Em situações normais o endotélio vascular resiste à adesão firme de leucócitos (Figura 2A), mas fatores de risco como dislipidemia (levando a presença de lipoproteínas oxidadas), hipertensão, diabetes mellitus e obesidade podem iniciar o processo inflamatório no interior das artérias e provocar alterações no modo como o endotélio interage com os componentes celulares da corrente sanguínea e da parede vascular[39]. Essas alterações irão estabelecer a disfunção endotelial, caracterizada, principalmente, pela deficiência de óxido nítrico e

[33] Castelli WP. Lipids, risk factors and ischaemic heart disease. Atherosclerosis. 1996;124(suppl):S1–S9.

[34] Libby P. Inflammation in atherosclerosis. Nature. 2002 Dec 19-26;420(6917):868-74.

[35] Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol. 2006;6(7):508-19.

[36] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.

[37] Packard RR, Libby P.Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem. 2008;54(1):24-38.

[38] Kelishadi R. Inflammation-induced atherosclerosis as a target for prevention of cardiovascular diseases from early life. Open Cardiovasc Med J. 2010;4:24-9.

[39] Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. Am J Med. 2004;116 Suppl 6A:9S-16S.

prostaciclina e um aumento da endotelina-1 e angiotensina II, resultando em uma maior tendência à vasoconstrição, vasoespasmo, trombogenicidade e proliferação celular anormal[40]. Com a disfunção endotelial estabelecida, aumenta-se a expressão de várias moléculas de adesão de leucócitos, como as moléculas de adesão celular vascular (VCAM-1), moléculas de adesão intercelular (ICAM-1), E-selectina, P-selectin e fatores quimiotáticos. Esses agentes são responsáveis pelo aumento da ligação de linfócitos T e monócitos a células endoteliais e pela promoção de sua diapedese a partir de células endoteliais para dentro da camada íntima[41,42,43], como pode ser visualizado na Figura 2B. Já dentro da camada íntima, há a diferenciação de monócitos em macrófagos, que fagocitam as lipoproteínas oxidadas e tornam-se células espumosas (Figura 2B)[41,42,43]. Estes fagócitos lípides irão aumentar a produção de moléculas de adesão, proteases e citocinas inflamatórias, que também irão estimular o fígado a produzir proteínas de fase aguda, tais como a proteína C-reativa (PCR) e fibrinogênio[43,44,45]. Descobertas recentes sugerem que as plaquetas ativadas, além de serem um dos mediadores mais importantes da formação de trombo, também induzem respostas inflamatórias em células adjacentes, como as células endoteliais e leucócitos[46]. A formação da placa de ateroma também envolve o recrutamento adicional de células do músculo liso (da camada média para a camada íntima) que proliferam em resposta a mediadores, tais como o fator de crescimento derivado das plaquetas (Figura 2C). Na camada íntima, as células no músculo liso produzem células da matriz extracelular e formam a capa fibrosa que cobre a superfície da placa (Figura 2C). Dentro da placa, devido a um *clearance* ineficaz das células mortas ocorre ainda a acumulação de detritos celulares, que junto aos lipídios extracelulares formam o núcleo necrótico da placa (Figura 2D)[44].

Todo esse conjunto de alterações causa uma remodelação importante da anatomia das artérias que irá gerar, inicialmente, a aterosclerose subclínica. Futuramente, a aterosclerose pode

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[40] Jialal I, Devaraj S, Venugopal SK. C-Reactive Protein: Risk Marker or Mediator in Atherothrombosis? *Hypertension* 2004;44(1):6-11.
[41] Libby P. Inflammation in atherosclerosis. Nature. 2002 Dec 19-26;420(6917):868-74.
[42] Packard RR, Libby P.Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem. 2008;54(1):24-38.
[43] Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. Am J Med. 2004;116 Suppl 6A:9S-16S.
[44] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.
[45] Kelishadi R. Inflammation-induced atherosclerosis as a target for prevention of cardiovascular diseases from early life. Open Cardiovasc Med J. 2010;4:24-9.
[46] O'Brien M.The reciprocal relationship between inflammation and coagulation. Top Companion Anim Med. 2012;27(2):46-52.

resultar na ocorrência de doenças clínicas ao estabelecer estenoses, isquemia tecidual, ou trombos, formados após rompimento da placa, que levam a interrupção do fluxo sanguíneo no local onde ele se estabeleceu ou por meio de embolização ao se alojar em artérias distais (Figura 2D)[47].

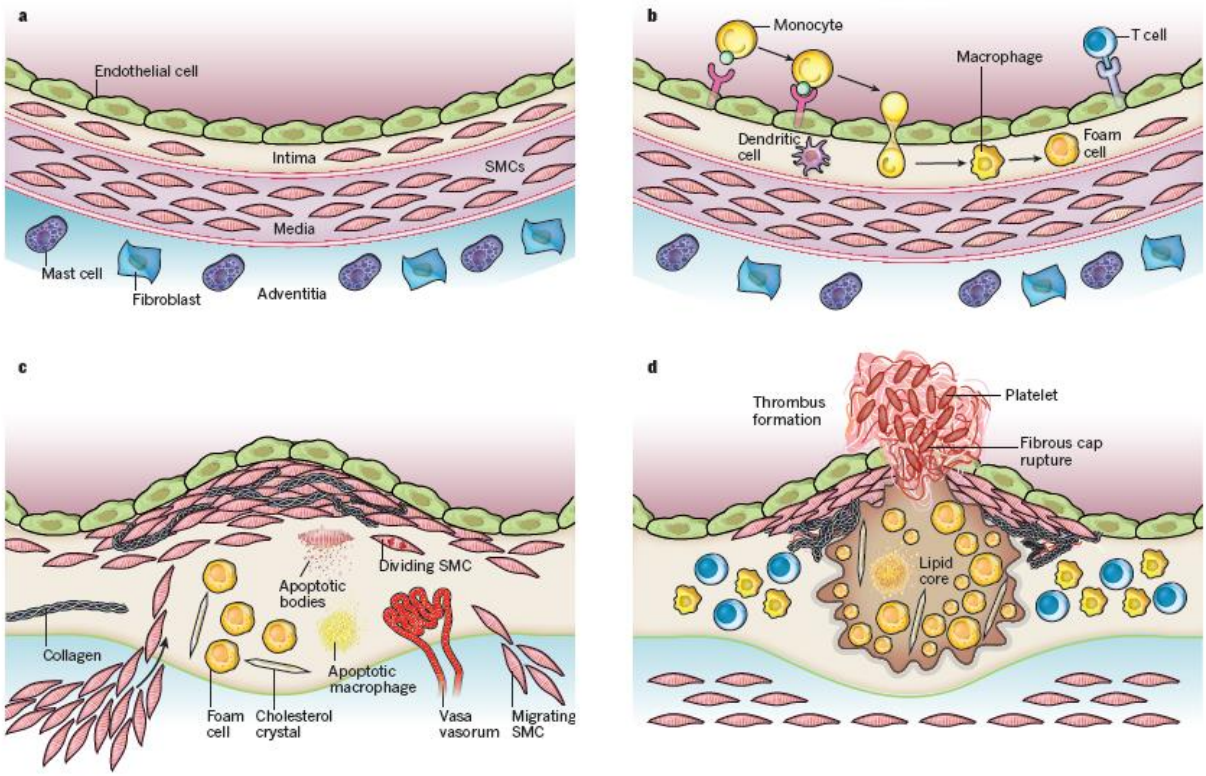

Figura 2: Estágios das lesões ateroscleróticas. FONTE: Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011 May 19;473(7347):317-25

[47] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25

2.2.2 Exposição à adversidade social, estresse psicossocial e inflamação crônica

Os indivíduos em desvantagens sociais vivenciam um maior estresse psicossocial produzido pela própria exposição à privação em si e por outras fontes de estresse que são produtos dessa privação, como viver em vizinhanças com alto índice de criminalidade, ter a percepção de privação social relativa ao se comparar com indivíduos de melhor posição social, experiências de discriminação e de traumas/abuso, viver em ambientes superlotados e exposição a trabalhos desgastantes com alta demanda e baixo controle das atividades exercidas[48]. Adicionalmente, as respostas fisiológicas a esse estresse pode desencadear a adoção de comportamentos de risco. Por exemplo, indivíduos ansiosos são mais propensos a fumar cigarros e ingerirem dietas não saudáveis[48].

Estudos recentes indicam que exposições ao estresse psicossocial podem influenciar os níveis séricos de marcadores biológicos da inflamação, coagulação e moléculas de adesão e que esse poderia ser um dos mecanismos pelos quais as desigualdades sociais "entrariam" no corpo humano e causariam diferencias no processo de saúde e doença[49]. Alterações nesses biomarcadores inflamatórios podem resultar de desregulações hormonais e metabólicas (como tais como obesidade, hipertensão e diabetes) relacionadas aos efeitos deletérios do engajamento a comportamentos de risco para a saúde (como tabagismo e consumo abusivo de álcool), ou ainda por um efeito direto do estresse psicossocial sobre o sistema nervoso central que age no eixo hipotálamo-pituitária-adrenal e no sistema nervoso simpático[49,50] como evidenciado pelo modelo explicativo proposto por Aiello & Kaplan (2009)[49] (Figura 3).

[48] Kubzansky LD, Seeman TE, Glymour MM. Biological Pathways Linking Social Conditions and Health:Plausible Mechanisms and Emerging Puzzles. In: Berkman LF, Kawachi, I, Glymour MM. Social Epidemiology. Oxford University Press, 2014.

[49] Aiello AE, Kaplan GA. Socioeconomic position and inflammatory and immune biomarkers of cardiovascular disease: applications to the Panel Study of Income Dynamics. Biodemography Soc Biol. 2009;55(2):178-205

[50] Hänsel A, Hong S, Cámara RJ, von Känel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci Biobehav Rev. 2010;35(1):115-21

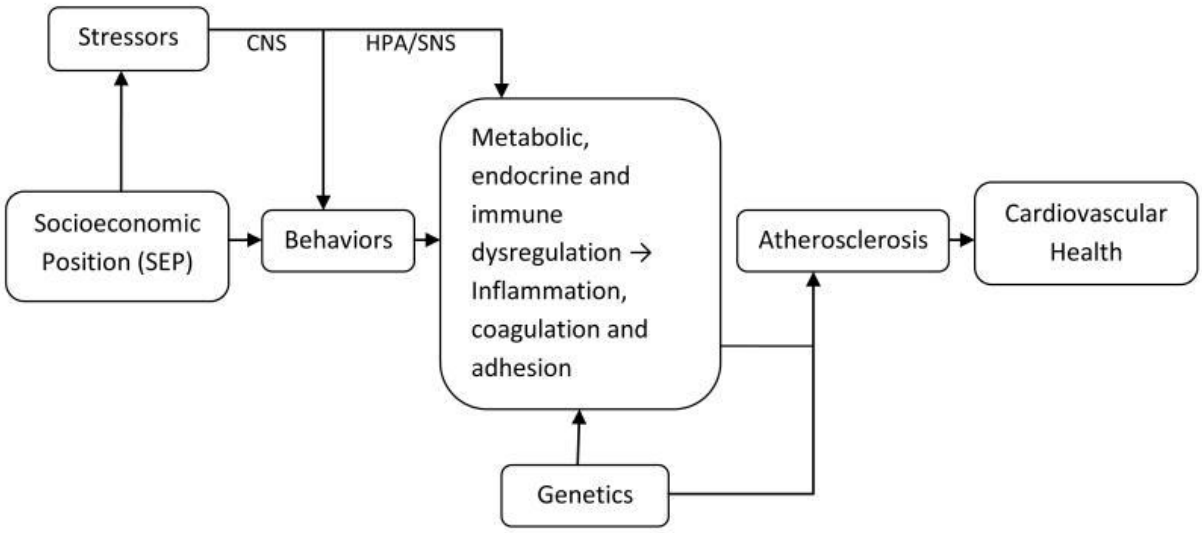

Figura 3. Caminhos entre a posição socioeconômica, biomarcadores, aterosclerose e saúde cardiovascular. CNS = Sistema nervoso central, HPA = eixo hipotálamo-pituitária-adrenal, SNS = Sistema Nervoso Simpático. FONTE: Aiello AE, Kaplan GA. Socioeconomic position and inflammatory and immune biomarkers of cardiovascular disease: applications to the Panel Study of Income Dynamics. Biodemography Soc Biol. 2009;55(2):178-205.

O sistema nervoso central, em resposta ao estresse, ativa o eixo hipotálamo-pituitária-adrenal e o sistema nervoso simpático, que resulta em uma maior concentração sérica de biomarcadores hormonais, tais como cortisol e catecolaminas, que são mediadores importantes da resposta imune[51]. A elevação nos níveis de cortisol pode influenciar diretamente a função imune levando a alterações nos processos celulares e regulação da produção de citocinas, como a interleucina-6 e o fator de necrose tumoral α (TNF- α) [52]. Além disso, a resposta do organismo a um nível elevado de cortisol pode levar ao aumento da resistência à insulina, obesidade e hipertensão que, por sua vez, elevam o risco de DCV [53]. Segundo Aiello & Kaplan (2009)[52], apesar da elevação crônica do cortisol ser um mecanismo comumente sugerido de mediação entre a posição socioeconômica e a saúde cardiovascular, os resultados empíricos que avaliaram essa relação são inconsistentes. Uma das hipóteses para essa inconsistência é o erro de mensuração do cortisol inerente à variação circadiana intraindividual do mesmo.

Além da avaliação do cortisol, vários estudos têm indicado que a exposição às circunstâncias sociais desfavoráveis está independentemente associada a maiores níveis de marcadores

[51] Herbert TB, Cohen S. Stress and immunity in humans: a meta-analytic review. Psychosom Med. 1993; 55(4):364–79.
[52] Aiello AE, Kaplan GA. Socioeconomic position and inflammatory and immune biomarkers of cardiovascular disease: applications to the Panel Study of Income Dynamics. Biodemography Soc Biol. 2009;55(2):178-205
[53] Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol. 2007;157(5):545-59.

inflamatórios como a PCR[54,55], fibrinogênio[55], receptor 2 do fator de necrose tumoral (TNFR2)[56], contagem total de leucócitos[57], interleucina-6[58] e marcadores de adesão celular ao endotélio como a molécula de adesão intercelular-1 (ICAM-1) e da endotelina-1[59]. Além disso, a exposição às circunstâncias sociais desfavoráveis na infância e juventude também parece estar independentemente relacionada a maior o nível plasmático de marcadores inflamatórios na vida adulta [56,58,60,61]. Por exemplo, maiores níveis de PCR [62,58,60] receptor 2 o fator de necrose tumoral (TNFR2)[56], leucócitos[57] e interleucina-6[58] foram encontrados em adultos expostos a ambientes sociais desfavoráveis na infância, independentemente da situação socioeconômica na vida adulta.

Adicionalmente, resultados de estudos recentes sugerem a existência de um efeito cumulativo de exposições, ou seja, quanto mais tempo os indivíduos são expostos a piores condições socioeconômicas ao longo da vida, maiores são os níveis plasmáticos dos marcadores inflamatórios [56,58,60]. Corroborando esse efeito cumulativo, alguns estudos encontraram que trajetórias sociais descendentes também estão relacionadas ao aumento dos níveis plasmáticos de marcadores inflamatórios [56,58].

Apesar de todos esses estudos citados terem reportado associações entre marcadores inflamatórios e indicadores de posição socioeconômica ao longo da vida independentemente dos comportamentos relacionados à saúde e de alterações metabólicas (como hipertensão, dislipidemia, diabetes, obesidade), esses resultados não são consistentes entre diferentes

[54] Nazmi A, Victora CG. Socioeconomic and racial/ethnic differentials of C reactive protein levels: a systematic review of population-based studies. BMC Public Health. 2007;7:212.

[55] Jousilahti P, Salomaa V, Rasi V, Vahtera E, Palosuo T. Association of markers of systemic inflammation, C reactive protein, serum amyloid A, and fibrinogen, with socioeconomic status. J Epidemiol Community Health. 2003;57(9):730-3.

[56] Loucks EB, Pilote L, Lynch JW, et al.. Life course socioeconomic position is associated with inflammatory markers: the Framingham Offspring Study. Soc Sci Med. 2010;71(1): 187–195.

[57] West DA, Leung GM, Jiang CQ, Elwell-Sutton TM, Zhang WS, Lam TH, Cheng KK, Schooling CM.Life-course origins of social inequalities in adult immune cell markers of inflammation in a developing southern Chinese population: the Guangzhou Biobank Cohort Study. BMC Public Health. 2012;12:269.

[58] Stringhini S, Batty GD, Bovet P, Shipley MJ, Marmot MG, Kumari M, Tabak AG, Kivimäki M. Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study. PLoS Med. 2013 Jul;10(7):e1001479.

[59] Hong S, Nelesen RA, Krohn PL, Mills PJ, Dimsdale JE.The association of social status and blood pressure with markers of vascular inflammation. Psychosom Med. 2006;68(4):517-23.

[60] Tabassum F, Kumari M, Rumley A, Lowe G, Power C, Strachan DP. Effects of socioeconomic position on inflammatory and hemostatic markers: a life-course analysis in the 1958 British birth cohort. Am J Epidemiol. 2008 Jun 1;167(11):1332-41.

[61] Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G.Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur J Epidemiol. 2007;22(1):55-66

[62] Nazmi A, Oliveira IO, Horta BL, Gigante DP, Victora CG. Lifecourse socioeconomic trajectories and C-reactive protein levels in young adults: findings from a Brazilian birth cohort. Soc Sci Med. 2010;70(8):1229-36.

populações, já que vários estudos encontraram associações nulas após ajustes[63,64.] Em geral as magnitudes das associações diminuem muito após ajuste por comportamentos relacionados à saúde e alterações metabólicas, principalmente a obesidade. Isso sugere que comportamentos relacionados à saúde e alterações metabólicas podem ser mediadores da associação entre posição socioeconômica no curso de vida e inflamação, como evidenciado em alguns estudos[65,66] e pelo modelo teórico proposto por Aiello & Kaplan (2009)[67] (Figura 1).

Uma hipótese alternativa é que ativação do eixo hipotálamo-pituitária-adrenal é um fenômeno "programado" por privação durante a embriogênese/gestação que retardaria o crescimento fetal[68]. Isso se justifica, pois atualmente sabe-se que o papel dos genes não é apenas determinado pela sequência do DNA, mas também pela maneira em que o gene é marcado e programado por modificação da cromatina e metilação do DNA, por exemplo. Essas alterações, denominada programação epigenética, poderiam ter o mesmo impacto que um polimorfismo genético, podendo silenciar ou enfatizar a expressão de um gene resultando em diferentes fenótipos[69]. A exposição à privação durante a embriogênese/gestação e consequente ativação do eixo hipotálamo-pituitária-adrenal seria um exemplo de programação epigenética. Essa hipótese é suportada por estudos que encontraram associações entre o baixo peso ao nascer e elevado cortisol plasmático na idade adulta, tanto no estado basal como em resposta ao estresse[68]. Além disso, estudos recentes estão sugerindo que a exposição a condições sociais desfavoráveis na infância está envolvida na programação epigenética levando a alterações que afetam a transcrição do receptor de glicocorticoide causando resistência a

[63] Gimeno D, Ferrie JE, Elovainio M, Pulkki-Raback L, Keltikangas-Jarvinen L, Eklund C, Hurme M, Lehtimäki T, Marniemi J, Viikari JS, Raitakari OT, Kivimäki M. When do social inequalities in C-reactive protein start? A life course perspective from conception to adulthood in the Cardiovascular Risk in Young Finns Study. Int J Epidemiol. 2008;37(2):290-8.

[64] Kivimäki M, Lawlor DA, Juonala M, Smith GD, Elovainio M, Keltikangas-Järvinen L, Vahtera J, Viikari JS, Raitakari OT.Lifecourse socioeconomic position, C-reactive protein, and carotid intima-media thickness in young adults: the cardiovascular risk in Young Finns Study. Arterioscler Thromb Vasc Biol. 2005;25(10):2197-202.

[65] Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G.Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur J Epidemiol. 2007;22(1):55-66.

[66] Kershaw KN, Mezuk B, Abdou CM, Rafferty JA, Jackson JS. Socioeconomic position, health behaviors, and C-reactive protein: a moderated-mediation analysis. Health Psychol. 2010;29(3):307-16.

[67] Aiello AE, Kaplan GA. Socioeconomic position and inflammatory and immune biomarkers of cardiovascular disease: applications to the Panel Study of Income Dynamics. Biodemography Soc Biol. 2009;55(2):178-205

[68] Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol. 2007;157(5):545-59.

[69] Szyf M, McGowan P, Meaney MJ. The social environment and the epigenome. Environ Mol Mutagen. 2008 Jan;49(1):46-60.

glicocorticoides e levando a um fenótipo pró-inflamatório[70,71]. Considerando essas evidências e retomando o modelo teórico de Aiello & Kaplan (2009)[72] (Figura 3) seria plausível uma seta adicional conectando a posição social diretamente aos aspectos genéticos, já que o ambiente está envolvido na expressão fenotípica, que pode promover alguma desregulação no processo inflamatório.

O modelo epigenético clássico postula que uma vez que os padrões epigenéticos tenham se formado durante o desenvolvimento (embriogênese/gestação) eles se mantem estáveis ao longo da vida[73]. Essa visão vai ao encontro da primeira versão do modelo de períodos críticos proposto pela abordagem do curso de vida[74]. Entretanto, recentemente uma hipótese alternativa vem ganhando destaque ao defender que alterações epigenéticas podem ocorrer em outras fases da vida e serem reversíveis[75,76]. Dessa forma, estaria evidente que o meio onde os indivíduos estariam inseridos ao longo da vida seria capaz de esculpir o genoma e afetar os seus fenótipos no curso de vida. Essa nova hipótese seria compatível com os modelos de acumulação de riscos e de mobilidade social da abordagem do curso de vida[74]. Entretanto, não existem evidências empíricas suficientes para sustentar essa hipótese e mais estudos são necessários para esclarecer essa questão.

2.2.3 Desfechos cardiovasculares subclínicos e investigação de mecanismos entre a posição socioeconômica e a saúde cardiovascular

Uma grande variedade de métodos está disponível para mensurar de forma não invasiva doenças cardiovasculares subclínicas (como a aterosclerose subclínica), mesmo na ausência de sintomas ou diagnósticos clinicamente relevantes. O emprego dessas medidas como

[70] Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, Cole S, Kobor MS. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009 25;106(34):14716-21.

[71] Zhang TY, Bagot R, Parent C, Nesbitt C, Bredy TW, Caldji C, Fish E, Anisman H, Szyf M, Meaney MJ. Maternal programming of defensive responses through sustained effects on gene expression. Biol Psychol. 2006 Jul;73(1):72-89.

[72] Aiello AE, Kaplan GA. Socioeconomic position and inflammatory and immune biomarkers of cardiovascular disease: applications to the Panel Study of Income Dynamics. Biodemography Soc Biol. 2009;55(2):178-205

[73] Szyf M, McGowan P, Meaney MJ. The social environment and the epigenome. Environ Mol Mutagen. 2008 Jan;49(1):46-60.

[74] Ben-Shlomo, Y, Kuh, D. A life-course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285-93.

[75] Miller CA, Sweatt JD. Covalent modification of DNA regulates memory formation. Neuron. 2007;53(6):857-69.

[76] Weaver IC, Champagne FA, Brown SE, Dymov S, Sharma S, Meaney MJ, Szyf M. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. J Neurosci. 2005;25(47):11045-54.

desfecho é útil para avaliar a relação entre a doença cardiovascular e a posição socioeconômica ao longo da vida ao minimizar alguns tipos de vieses. Por exemplo, ao utilizar a aterosclerose subclínica como desfecho pode-se minimizar a possibilidade dos resultados das pesquisas serem reflexo da causalidade reversa, ou seja, a ideia de que a saúde debilitada influenciaria a posição socioeconômica em um sentido descendente. Adicionalmente, ao utilizar desfechos clínicos, como mortalidade por infarto agudo do miocárdio, as associações encontradas com desvantagens sociais podem, muitas vezes, ser contaminadas pelo acesso diferencial aos serviços de saúde entre os indivíduos de diferentes posições socioeconômicas. Essa possibilidade de confusão é minimizada pelo uso de desfechos subclínicos como a aterosclerose. Utilizar desfechos cardiovasculares subclínicos, principalmente em estudos longitudinais, que mensuram a presença de doença subclínica e posição social em vários pontos no tempo, pode ser útil para entender os mecanismos pelos quais a posição social age no organismo ao longo da vida[77].

Estudos norte-americanos, britânicos e suecos encontraram que maior espessura médio-intimal carotídea em mulheres, mas não em homens, foi associada a piores condições socioeconômicas na infância, após o ajuste para a situação socioeconômica atual, comportamentos relacionados à saúde e alterações metabólicas[78,79,80.] No *Atherosclerosis Risk in Communities Study* foi encontrado que os indivíduos de ambos os sexos com acúmulo de exposições às circunstâncias sociais desaforáveis ao longo da vida tinham mais chance de terem aterosclerose subclínica, mensurada tanto pela espessura médio-intimal carotídea como pelo índice tornozelo-braquial [81]. Por outro lado, no *Framingham Offspring Cohort* a associação entre o índice tornozelo-braquial e a acumulação de exposições sociais desfavoráveis ao longo da vida foi encontrada somente entre os homens[82]. Em geral, as magnitudes dessas associações tendem a diminuir fortemente após ajustes por

[77] Matthews KA, Gallo LC. Psychological perspectives on pathways linking socioeconomic status and physical health. Annu Rev Psychol. 2011;62:501-30.
[78] Lemelin ET, Diez Roux AV, Franklin TG, Carnethon M, Lutsey PL, Ni H, O'Meara E, Shrager S. Life-course socioeconomic positions and subclinical atherosclerosis in the multi-ethnic study of atherosclerosis. Soc Sci Med. 2009;68(3):444-51.
[79] Lamont D, Parker L, White M, Unwin N, Bennett SM, Cohen M, et al.. Risk of cardiovascular disease measured by carotid intima-media thickness at age 49-51: Lifecourse study. BMJ. 2000;320:273–278.
[80] Rosvall M, Ostergren PO, Hedblad B, Isacsson SO, Janzon L, Berglund G. Life-course perspective on socioeconomic differences in carotid atherosclerosis. Arterioscler Thromb Vasc Biol. 2002;22:1704–1711.
[81] Carson AP, Rose KM, Catellier DJ, Kaufman JS, Wyatt SB, Diez-Roux AV, Heiss G. Cumulative socioeconomic status across the life course and subclinical atherosclerosis. Ann Epidemiol. 2007;17(4):296-303.
[82] Agha G, Murabito JM, Lynch JW, Abrahamowicz M, Harper SB, Loucks EB. Relation of socioeconomic position with ankle-brachial index. Am J Cardiol. 2011;108(11):1651-7.

comportamentos relacionados à saúde e alterações metabólicas, sugerindo que esses fatores possam mediar à associação entre posição socioeconômica na infância (ou acumulação de exposições sociais desfavoráveis ao longo da vida) e a aterosclerose subclínica.

2.3 O ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL).

O ELSA-Brasil é um estudo prospectivo multicêntrico, desenvolvido com 15.105 funcionários públicos de 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 deste estudo são: investigar a incidência e a progressão do diabetes e das DCV; e examinar os fatores biológicos, comportamentais, ambientais, ocupacionais, psicológicos e sociais relacionados a essas doenças e a suas complicações, buscando compor um modelo causal que contemple suas inter-relações[83].

A linha de base do ELSA-Brasil foi realizada entre 2008 e 2010 e incluiu entrevistas, exames clínicos, laboratoriais e medidas antropométricas.

2.3.1 Mensuração de circunstâncias socioeconômicas no curso de vida no ELSA-Brasil

Tendo em vista o contexto social brasileiro, o ELSA-Brasil priorizou a coleta de dados sobre determinantes sociais em saúde. Além de indicadores convencionais como renda familiar e escolaridade, o questionário da linha de base contemplou exposições do contexto social na infância por meio da escolaridade materna[84]. Esses indicadores serão descritos com mais detalhes nos itens a seguir.

2.3.1.1 Escolaridade materna obtida retrospectivamente

Nos estudos epidemiológicos realizados com adultos, a posição socioeconômica na infância é frequentemente mensurada por meio da escolaridade de pais, já que este indicador é considerado um *proxy* da situação socioeconômica da família e do contexto no qual a criança

[83] Aquino, EM, Barreto, SM, Bensenor, IM, Carvalho, MS, Chor D, Duncan BB, Lotufo PA, Mill JG, Molina Mdel C, Mota EL, Passos VM, Schmidt MI, Szklo M (2012) ELSA-Brazil (Brazilian Longitudinal Study of Adult Health): objectives and design. Am J Epidemiol. 2012;175(4):315-24.

[84] Chor D, Alves MGM, Giatti, L, Cade NV, Nunes, MA, Molina MCB, et al. (2013). Questionnaire development in ELSA-Brasil: challenges of a multidimensional instrument. *Revista de Saúde Pública, 47*(Supl. 2), 27-36.

nasceu e foi criada[85]. A escolaridade dos pais está relacionada às chances de escolarização das crianças, a ambiência cultural da família e reflete todo processo de formação intelectual dos indivíduos[86]. A mensuração da escolaridade dos pais retrospectivamente possui algumas limitações, entretanto existem evidencias que os adultos lembram com precisão a escolaridade dos pais e de sua classe social na infância[87].

A escolaridade materna em especial tem sido fortemente relacionada à saúde das crianças pela disponibilização de um melhor cuidado parental e um melhor uso dos serviços de saúde tanto no que diz respeito ao tratamento de doenças, como no envolvimento em atividades preventivas. Estudos empíricos tem demostrando que quanto maior escolaridade materna maior a expectativa de vida, menor as taxas de mortalidade e melhor a saúde e nutrição infantil[88].

2.3.1.2 Escolaridade

Diversos estudos que utilizam a abordagem do curso de vida utilizam a escolaridade como um indicador das circunstâncias sociais na juventude[89,90]. Isso se justifica porque a escolaridade é muito influenciada pelas características dos pais e, geralmente, é fixada cedo na vida adulta e se mantém estável ao longo da vida[91]. A escolaridade é o indicador socioeconômico mais utilizado em epidemiologia devido à facilidade de sua mensuração e obtenção, além de sua alta taxa de resposta. É altamente correlacionada à renda, principalmente, ao permitir ascensão social e inserção ocupacional [91]. Os conhecimentos e habilidades atingidas por meio da escolaridade pode influenciar também a saúde dos indivíduos ao torna-los mais receptivos

[85] Mckenzie SK, Carter KN. Are retrospective measures of childhood socioeconomic position in prospective adult health surveys useful? Australasian Epidemiologist. 2009;16.3:22-24.
[86] Kappel, DB. Índice de desenvolvimento infantil no Brasil: Uma análise regional. Revista Brasileira de Educação. 2007; 12(35), 232-240.
[87] Krieger N, Okamoto A, Selby JV. Adult female twins' recall of childhood social class and father's education: a validation study for public health research. Am J Epidemiol. 1998;147(7):704-8.
[88] Boyle MH, Racine Y, Georgiades K, Snelling D, Hong S, Omariba W, Hurley P, Rao-Melacini P. The influence of economic development level, household wealth and maternal education on child health in the developing world. Soc Sci Med. 2006;63(8):2242-54.
[89] Loucks EB, Pilote L, Lynch JW, et al.. Life course socioeconomic position is associated with inflammatory markers: the Framingham Offspring Study. Soc Sci Med. 2010;71(1): 187–195.
[90] Smith BT, Lynch JW, Fox CS, Harper S, Abrahamowicz M, Almeida ND, Loucks EB. Life-course socioeconomic position and type 2 diabetes mellitus: The Framingham Offspring Study. Am J Epidemiol. 2011;173(4):438-47.
[91] Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull.* 2007; 81-82 (1): 21-37.

a atividades de promoção de saúde, mais propensos a adotar comportamentos de vida saudáveis e mais capazes de acessar serviços de saúde [92].

2.3.1.3 Renda

A renda é o indicador que consegue captar de forma mais direta as circunstâncias materiais de vida. Esse indicador tem sido muito utilizado por ser fortemente associado à saúde ao promover recursos materiais que estão intrinsicamente relacionados a fatores proximais na causalidade das doenças, como os comportamentos, acesso à alimentação de qualidade e aos serviços de saúde. Além disso, pode exercer influência sobre outros indicadores socioeconômicos, como a escolaridade. Também é um marcador de consequências sociais, por proporcionar acesso diferenciado a bens e serviços e por correlacionar-se ao poder, influência social e autoestima. Adicionalmente, o efeito da renda na saúde pode acumular ao longo da vida[93,94].

A renda é um indicador multifacetado e dinâmico e, por isso, sua mensuração em estudos epidemiológicos é complexa e vários fatores precisam ser considerados na interpretação dos resultados. As associações entre renda e saúde pode ser resultado da causalidade reversa, já que pessoas com saúde prejudicada pode sofrer uma redução e seus rendimentos. A renda é também uma medida instável e pode flutuar consideravelmente de um período de tempo para o outro. Além disso, a renda é considerada uma questão delicada que muitas pessoas não se sentem confortáveis a fornecer informações e, por isso, é o indicador socioeconômico mais sensível a não resposta[93,94].

2.3.1.4 Ocupação

A ocupação reflete a posição social dos indivíduos e pode ser relacionada à saúde por vários mecanismos. Por exemplo, a ocupação pode expressar a escolaridade, renda, redes sociais e prestígio social. Além disso, está relacionada à exposição às circunstâncias importantes para a saúde, como os ambientes físico e psicológico do trabalho. O primeiro pode ter um impacto

[92] Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu Rev Public Health.* 1997;18:341-378.
[93] Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull.* 2007; 81-82 (1): 21-37.
[94] Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). J Epidemiol Community Health. 2006;60(2):95-101.

direto na saúde devido às condições de trabalho desfavoráveis (ambiente tóxico, a falta de segurança no trabalho, alta demanda física). Já o segundo pode afetar a saúde por meio do estresse psicossocial[95,96.]

A mensuração da ocupação é repleta de complexidades. Existem vários tipos de classificações ocupacionais utilizadas em diferentes estudos o que dificulta comparações entre populações. Desempregados e aposentados, frequentemente, são excluídos das classificações ocupacionais resultando em subestimação das desigualdades em saúde. Adicionalmente, a classificação ocupacional é problemática entre trabalhadores autônomos, em pessoas que trabalham em casa, estudantes, em pessoas envolvidas em trabalhos não remunerados ou em trabalhos ilegais [95,96].

A classificação das ocupações que será utilizada nesta tese utilizando dados do ELSA-Brasil é a classe social da ocupação, também denominada status socioeconômico da ocupação. Essa classificação consiste em uma medida sumária, que varia de 1 a 100, construída por meio da derivação de escores para um conjunto de ocupações, levando em consideração também a escolaridade, como status social, e a renda, como status econômico. A escala de status socioeconômico foi construída para os títulos ocupacionais de acordo com as seguintes etapas: (1) Mensuração do status educacional através da função escolaridade-rendimentos. Esta função estima o rendimento médio esperado (valor médio de mercado) de pessoas com determinado nível de escolaridade; (2) Mensurado o status educacional, a próxima etapa é a construção do status socioeconômico. Este consiste no cálculo da média entre os rendimentos observados (componente econômico) e os rendimentos esperados (componente educacional); (3) Calcula-se, para cada título ocupacional, o score médio do status socioeconômico dos indivíduos. Tal score médio é aplicado para as ocupações; (4) A partir dos scores de status socioeconômico das ocupações, definem-se os estratos sócio ocupacionais agrupando os escores de maneira que se obtenha uma mínima variância intra-estrato dos valores dos escores, e o máximo de variação entre os estratos. Assim, sete estratos foram construídos na

[95] Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull.* 2007; 81-82 (1): 21-37.
[96] Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). J Epidemiol Community Health. 2006;60(2):95-101.

seguinte ordem hierárquica: alto-superior, alto-inferior, médio-superior, médio-médio, médio-inferior, baixo-superior e baixo-inferior[97].

2.3.2 Medidas de Estresse no ELSA-Brasil

2.3.2.1 Estresse no trabalho

Na década de 1970, Robert Karasek de forma pioneira introduziu o Modelo Demanda-Controle (*Job Strain Model)* para descrever interações entre características do ambiente ocupacional como fontes geradoras de estresse, que resultariam em repercussões na saúde das populações[98]. Desde então diversos estudos começaram a investigar o papel da exposição a esse estresse psicossocial na ocorrência de DCV. Segundo esse modelo, o estresse no trabalho seria resultado da interação entre as demandas psicológicas e do grau de controle nas atividades execidas no ambiente ocupacional. As demandas psicológicas referem-se a sobrecarga de trabalho, tempo disponível para realizar as atividades, ritmo necessário para exercer as tarefas e quantidade de conflitos existentes nas relações de trabalho. Já o controle diz respeito ao grau de autonomia para tomar decisões sobre as atividades efetuadas, incluindo o ritmo necessário para a execução das tarefas, grau de repetitividade, possibilidade de utilizar a criatividade, aquisição de novas competências e liberdade para utilização de habilidades individuais. Dessa forma, a interação entre a demanda e o controle produziria quatro tipos diferentes de experiências no ambiente de trabalho: 1) trabalho de alto desgaste (alta tensão- *high strain*) – caracterizado por alta demanda e baixo controle; 2) trabalho passivo – caracterizado por baixa demanda e baixo controle; 3) trabalho ativo – caracterizado por alta demanda e alto controle; 4) trabalho de baixo desgaste (baixa tensão - *low strain*) – caracterizado por baixa demanda e alto controle[99,100,101].

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[97] Hermeto A (2014) Apresentação e discussão de alternativas para categorizações ocupacionais no Brasil. CEDEPLAR/UFMG – Texto para Discussão (no prelo).

[98] Karasek RA. Job demands, job decision latitude, and mental strain: implications for job redesign. Adm Sci Q. 1979;24:285-307.

[99] Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): An Instrument for Internationally Comparative Assessments of Psychosocial Job Characteristics. J Occup Health Psychol 1998; 3(4): 322-55.

[100] Karasek RA, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands and cardiovascular disease: a prospective study of Swedish men. American Journal of Public Health 1981; 71(7): 694-705.

[101] Karasek RA, Russel RS, Theorell T .Physiology of Stress and Regeneration in Job Related Cardiovascular Illness. J Human Stress. 1982 8(1):29-42.

A exposição do trabalhador à alta demanda e ao baixo controle de forma simultânea (trabalho com alto desgaste) geraria um grande desgaste psicológico que resultaria em danos à saúde. Já o trabalhador exposto à alta demanda, mas com alto controle sobre as atividades exercidas (trabalho ativo) poderia vislumbrar a demanda como motivação e oportunidade de aprendizagem e apresentar um padrão de enfrentamento positivo (efeito positivo do estresse).

De forma inversa, a exposição a trabalhos com baixa demanda e controle (trabalho passivo) poderia resultar em desmotivação, diminuição de aprendizagem e perda de habilidades e competências adquiridas. De acordo com esse modelo a situação considerada "ideal" seria os trabalhos de "baixo desgaste" que combina baixas demandas e alto controle do processo de trabalho[102,103,104].

Uma extensão do Modelo Demanda-Controle foi realizada por Johnson & Hall, com vistas a adicionar o apoio social no ambiente de trabalho como um componente relevante de interação, já que a escassez de interação social existentes no trabalho, tanto entre os colegas como entre os chefes poderia gerar consequências nocivas à saúde[105].

O instrumento originalmente desenvolvido para captar as dimensões do Modelo Demanda-Controle é o "Job Content Questionnaire", que contém 49 questões. Devido a sua grande extensão, outras escalas foram desenvolvidas utilizando menor número de itens para facilitar a coleta dessas informações em estudos populacionais. Entre elas destaca-se a escala elaborada por Töres Theorell na Suécia em 1988 (*Swedish Demand-Control-Support Questionnaire*-DCSQ), contendo 17 questões: cinco para avaliar demanda, seis para avaliar controle e seis para apoio social. Essa escala foi adaptada para o português por Alves e colaboradores em 2004[106] e foi utilizada no ELSA-Brasil. Na tabela 1 é possível visualizar todos os itens dessa escala. Nesse instrumento, todas as perguntas relativas às dimensões demanda e controle são respondidas utilizando uma escala de Likert de quatro pontos, variando de 1 (frequentemente)

[102] Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): An Instrument for Internationally Comparative Assessments of Psychosocial Job Characteristics. J Occup Health Psychol 1998; 3(4): 322-55.
[103] Karasek RA, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands and cardiovascular disease: a prospective study of Swedish men. American Journal of Public Health 1981; 71(7): 694-705.
[104] Karasek RA. Job demand, job decision latitude, and mental strain: implications for job redesign. Adm Sci Quart 1979; 24: 285-308.
[105] Berkman LF, Kawachi I, Theorell. Working Condiditions, and Health. In: Berkman LF, Kawachi, I, Glymour MM. Social Epidemiology. Oxford University Press, 2014.
[106] Alves, M.G.M., Chor, D., Faerstein, E., Lopes, C.S., Werneck, G.L. Short version of the 'job stress scale': A Portuguese-language adaptation. Rev Saude Publica 38, 1–7, 2004.

a 4 (nunca ou quase nunca). Com exceção dos itens relativos ao tempo suficiente para cumprir tarefas e ao trabalho repetitivo, todos os itens precisam ser invertidos antes da computação dos escores específicos de cada domínio. Seguindo esses procedimentos, altos escores nas dimensões demanda, que varia de 5 a 20 pontos, e controle, que varia de 6 a 24 pontos, indicarão altos níveis de controle e demanda. A mediana da distribuição de cada um desses dois domínios da escala é utilizada para dicotomizar essas dimensões em baixa *versus* alta de forma a possibilitar a construção dos quatro tipos de interações entre demanda e controle proposto por Karasek.

Tabela 1 – Versão brasileira da *Swedish Demand-Control-Support Questionnaire-DCSQ* que foi utilizada no ELSA-Brasil.

Demanda
D1. Com que frequência você tem que fazer suas tarefas de trabalho com muita rapidez?
D2. Com que frequência você tem que trabalhar intensamente (isto é, produzir muito em pouco tempo)?
D3. Seu trabalho exige demais de você?
D4. Você tem tempo suficiente para cumprir todas as tarefas de seu trabalho?
D5. O seu trabalho costuma apresentar exigências contraditórias ou discordantes?
Opções de respostas: Frequentemente; Às vezes; Raramente; Nunca ou quase nunca.
Controle
C1. Você tem possibilidade de aprender coisas novas em seu trabalho?
C2. Seu trabalho exige muita habilidade ou conhecimento especializados?
C3. Seu trabalho exige que você tome iniciativas?
C4. No seu trabalho, você tem que repetir muitas vezes as mesmas tarefas?
C5. Você pode escolher COMO fazer seu trabalho?
C6. Você pode escolher O QUE fazer no seu trabalho?
Opções de respostas: Frequentemente; Às vezes; Raramente; Nunca ou quase nunca.
Apoio Social
A1. Existe um ambiente calmo e agradável onde trabalho.
A2. No trabalho, nos relacionamos bem uns com os outros.
A3. Eu posso contar com o apoio dos meus colegas de trabalho.
A4. Se eu não estiver num bom dia, meus colegas compreendem.
A5. No trabalho, eu me relaciono bem com os meus chefes.
A6. Eu gosto de trabalhar com meus colegas
Opções de resposta: Concordo totalmente; Concordo mais que discordo; Discordo mais que concordo; Discordo totalmente.

FONTE: Alves, M.G.M., Chor, D., Faerstein, E., Lopes, C.S., Werneck, G.L. Short version of the 'job stress scale': A Portuguese-language adaptation. Rev Saude Publica 38, 1–7, 2004.

Ao longo de mais de três décadas utilizando o Modelo Demanda-Controle para investigar a associação entre estresse no trabalho e as DCV várias controversas foram levantadas. Em primeiro lugar, um debate surgiu sobre qual dimensão do modelo seria mais importante como fator de risco para DCV. Em uma revisão de literatura realizada por Everson-Rose & Lewis

em 2005[107] foi encontrado que o controle no trabalho seria o componente mais relevante. Em 2009, outra revisão sistemática [108] concluiu que a demanda seria a dimensão mais importante. Existem também dúvidas quando aos diferenciais da associação por gênero. Alguns autores sugerem que a associação entre estresse no trabalho e DCV é mais acentuada nos homens[109], enquanto que os outros veem as mulheres como mais vulneráveis[110]. As estimativas de magnitude da associação entre os estudos também são muito heterogênea, variando desde não associação[111] até um risco relativo na ordem de 9[112]. Adicionalmente, enquanto alguns estudos encontram que o efeito do estresse no trabalho para promover DCV seria maior em indivíduos de baixa posição socioeconômica, outros trabalhos não encontraram tal interação[113]. Alguns autores defendem ainda que a associação entre o estresse no trabalho e a DCV é espúria e que poderia ser atribuída a outros fatores como posição socioeconômica[114].

Na tentativa de responder essas questões em 2012 uma metanálise foi conduzida por Kivimaki e colaboradores com 13 estudos de coorte europeus (1985-2006) para compreender melhor a relação entre o estresse no trabalho e o risco de doença coronariana. O estudo concluiu que o *hazard ratio* global para doença coronariana entre participantes envolvidos em trabalhos de alto desgaste (*high strain)* foi 1,23 (IC95%: 1,10-1,37) comparando com os de baixo desgaste (*low strain*), sugerindo uma associação robusta após todos os ajustes, mas de pequena magnitude. Foi encontrado ainda que a combinação de alta demanda e baixo controle foi mais consistentemente relacionado à doença coronariana do que cada dimensão isoladamente e nenhuma interação com gênero ou com o nível socioeconômico foi encontrada[115].

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[107] Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. Annu Rev Public Health. 2005;26(1):469–500

[108] Eller NH, Netterstrom B, Gyntelberg F, et al. Work-related psychosocial factors and the development of ischemic heart disease: a systematic review. Cardiol Rev. 2009;17(2):83–97.

[109] Bosma H, Peter R, Siegrist J, et al. Two alternative job stress models and the risk of coronary heart disease. Am J Public Health. 1998;88(1):68–74.

[110] Uchiyama S, Kurasawa T, Sekizawa T, et al. Job strain and risk of cardiovascular events in treated hypertensive Japanese workers: hypertension follow-up group study. J Occup Health.2005;47(2):102–111.

[111] Lee S, Colditz G, Berkman L, et al. A prospective study of job strain and coronary heart disease in US women. Int J Epidemiol. 2002;31(6):1147–1153.

[112] Uchiyama S, Kurasawa T, Sekizawa T, et al. Job strain and risk of cardiovascular events in treated hypertensive Japanese workers: hypertension follow-up group study. J Occup Health.2005;47(2):102–111.

[113] Hoven H, Siegrist J. Work characteristics, socioeconomic position and health: a systematic review of mediation and moderation effect in prospective studies. Occup Environ Med. 2013 Sep;70(9):663-9.

[114] Macleod J, Davey Smith G. Psychosocial factors and public health: a suitable case for treatment? J Epidemiol Community Health. 2003;57(8):565–570.

[115] Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. Lancet. 2012 Oct 27;380(9852):1491-7.

Outra questão controversa na literatura é se o estresse no trabalho atuaria como mediador da associação entre posição socioeconômica e DCV. Em 1997 no *Whitehall II study* foi encontrado que o controle no trabalho explicou 64%, entre os homens, e 51%, entre as mulheres, da associação entre ocupação e doença coronariana[116]. Entretanto, outros estudos que investigaram essa mesma hipótese ou falharam em encontrar algum efeito mediador[117,118,119] ou encontraram uma mediação em magnitude muito menor variando de 9-21%[120,121,122]. Assim, mais estudos, inclusive envolvendo coortes ocupacionais como no *Whitehall II study*, são necessários para esclarecer melhor essas divergências.

2.3.3 Marcadores inflamatórios no ELSA-Brasil

2.3.3.1 Proteína C-reativa

A Proteína C-reativa (PCR) foi a primeira proteína reagente de fase aguda a ser descrita. Foi identificada em 1930 por sua capacidade de precipitar o polissacárido C de *Streptococcus pneumoniae*. A produção da PCR resulta de uma resposta fisiológica e bioquímica inespecífica diante da maioria dos danos teciduais como infecção, inflamação e neoplasias Sua síntese e secreção ocorrem principalmente no fígado e no tecido adiposo, em resposta principalmente a interleucina-6 (predominantemente produzida por macrófagos e adipócitos) [123], mas a interleucina-1 e o fator de necrose tumoral parecem também auxiliarem esse processo[124] (Figura 4). Além de promover a síntese da PCR, a interleucina-6 age

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[116] Marmot, M., Bosma, H., Hemingway, H., Brunner, E., & Stansfield, S. (1997). Contribution of job control and other risk factors to social variations in coronary heart disease incidence. Lancet, 350, 235e239.

[117] Wamala SP, Mittleman MA, Horsten M, Schenck-Gustafsson K, Orth-Gomér K. Job stress and the occupational gradient in coronary heart disease risk in women. The StockholmFemale Coronary Risk Study. SocSci Med. 2000 Aug;51(4):481-9.

[118] Kuper H, Adami HO, Theorell T, Weiderpass E. Psychosocial determinants of coronary heart disease in middle-aged women: a prospective study in Sweden. Am J Epidemiol. 2006 Aug 15;164(4):349-57.

[119] Huisman M, van Lenthe F, Avendano M, et al. The contribution of job characteristics to socioeconomic inequalities in incidence of myocardial infarction. SocSci Med 2008;66:2240–52.

[120] Virtanen, S. V., &Notkola, V. (2002). Socioeconomic inequalities in cardiovascular mortality and the role of work: A register study of Finnish men. International Journal of Epidemiology, 31, 614–621.

[121]Ferrario MM1, Veronesi G, Chambless LE, Sega R, Fornari C, Bonzini M, Cesana G.The contribution of major risk factors and job strain to occupational class differences in coronary heartdisease incidence: the MONICA Brianza and PAMELA population based cohorts. Occup Environ Med. 2011 Oct;68(10):717-22.

[122]Toivanen S, Hemström O. Income differences in cardiovascular disease: is the contribution from work similar in prevalence versus mortality outcomes? Int J Behav Med 2006;13:89–100.

[123] Genest J. C-reactive protein: risk factor, biomarker and/or therapeutic target? Can J Cardiol. 2010;26 Suppl A:41A-44A.

[124]Jialal I, Devaraj S, Venugopal SK. C-Reactive Protein: Risk Marker or Mediator in Atherothrombosis? *Hypertension* 2004;44(1):6-11.

sinergicamente com a interleucina-1, com os glicocorticoides e com produtos da ativação do complemento para melhorar a eficácia da PCR[125].

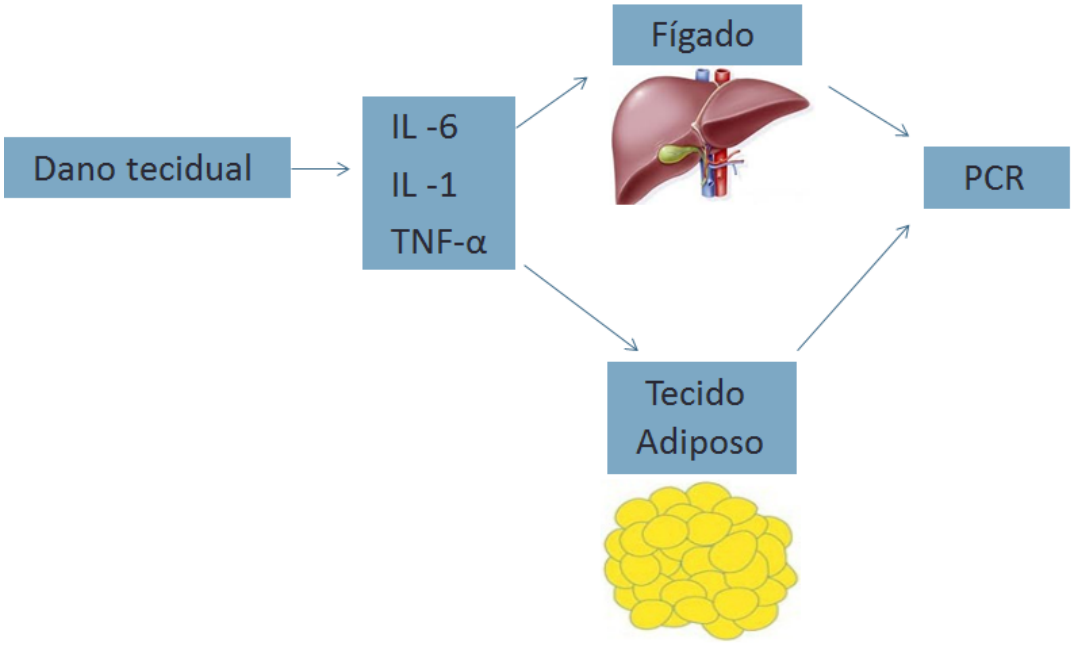

Figura 4 – Fatores envolvidos na produção da PCR e principais locais de síntese.

A PCR é responsável pelo reconhecimento de patógenos e por mediar a sua eliminação por meio de recrutamento do sistema complemento, de células fagocitárias e no auxilio do processo de fagocitose (opsonização), constituindo-se um componente importante da imunidade inata[126]. Após estímulos nocivos, a produção da PCR se inicia muito rapidamente e parte de valores inferiores a 1mg/L e atinge níveis acima de 5 mg/L em cerca de 6 horas. Alcança seu pico em aproximadamente 48 horas após o estímulo inicial e apresenta uma meia-vida plasmática de aproximadamente de 19 horas. Essa meia vida é constante, de modo que sua taxa de síntese é o único determinante de sua concentração sérica. Quando o estímulo nocivo cessa, a concentração da PCR na circulação cai rapidamente[127]. A proteína amilóide

[125] Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol. 2001;38(2-3):189-97.

[126] Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol. 2001;38(2-3):189-97.

[127] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111(12):1805-12.

sérica A é o único reagente de fase aguda que reage tão rapidamente ao estimulo nocivo quanto a PCR[128].

Numerosos estudos observacionais prospectivos têm demostrando que elevados níveis de PCR predizem, em pessoas aparentemente saudáveis, doença coronariana[129], acidente vascular cerebral[130], doença arterial periférica[131] e morte súbita[132] independentemente de outros fatores de risco cardiovasculares já estabelecidos. Entretanto, estudo recente, utilizando randomização mendeliana e informações de 194.418 participantes provenientes de 47 estudos epidemiológicos de 15 países, encontrou que a presença de polimorfismo genético relacionado a concentrações elevadas de PCR não está associado à ocorrência de doença coronariana e aos fatores de risco convencionais para DCV. Devido ao grande poder estatístico desse estudo, os autores concluíram que é improvável que a PCR seja um fator causal da doença coronariana[133].

Apesar de existir evidências de que a PCR não participa da cadeia causal das DCV, existe um consenso que a PCR é marcador de inflamação. É possível também que a PCR esteja refletindo outros verdadeiros determinantes das DCV[134,135], o que tornaria esse indicador importante para a predição de eventos cardiovasculares como demonstrado por estudos que encontraram que o uso da PCR adiciona valor de predição ao escore de risco de *Framingham*[136], principalmente nos indivíduos de risco intermediário (entre 10 e <20%).

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[128] Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. Am J Med. 2004;116 Suppl 6A:9S-16S.

[129] Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350(14):1387-97.

[130] Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, D'Agostino RB, Franzblau C, Wilson PW. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke. 200;32(11):2575-9.

[131] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation. 1998;97(5):425-8.

[132] Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. Circulation. 2002;105(22):2595-9.

[133] C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC), et al.. Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. BMJ. 2011; 342:d548.

[134] Jialal I, Devaraj S, Venugopal SK. C-Reactive Protein: Risk Marker or Mediator in Atherothrombosis? *Hypertension* 2004;44(1):6-11.

[135] Anand SS, Yusuf S. C-reactive protein is a bystander of cardiovascular disease. Eur Heart J. 2010;31(17):2092-6.

[136] Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012 Aug 22;308(8):788-95.

Níveis de PCR abaixo de 1mg/L devem ser interpretados como baixos, entre 1 e 3 mg/L moderados e acima de 3 mg/L alto risco cardiovascular [137].

2.3.4 Aterosclerose subclínica no ELSA-Brasil

2.3.4.1 Espessura médio-intimal carotídea (IMT)

A espessura médio-intimal carotídea (IMT – do inglês: *intima-media thickness*) tem sido considerada um dos melhores métodos para detecção precoce do processo aterosclerótico[138,139], tendo em vista sua natureza simples, ampla disponibilidade e capacidade de descrever a estrutura da parede arterial com melhor resolução do que qualquer outra técnica semelhante (por exemplo, a ressonância magnética ou técnicas radiográficas)[139].

A espessura médio-intimal carotídea é definida como a distância entre o a superfície do lúmen da camada íntima até a interface médio-adventícia da artéria carótida e reflete o espessamento difuso da camada íntima devido ao acúmulo aterosclerótico e avalia a extensão e da severidade da aterosclerose. É uma medida padronizada, validada e confiável mensurada por ultrassom de alta resolução [138,140].

Diferentes segmentos das artérias carótidas são estudados incluindo a carótida comum, a bifurcação carotídea, o bulbo e a carótida interna. O *Mannheim Carotid IMT Consensus* [139], com objetivo de propor uma padronização da medida, sugeriu que a mensuração do IMT na parede posterior da porção distal da carótida comum é a mais fácil e mais reprodutível entre todas as opções e, portanto, a medida mais adequada.

A mensuração do IMT pode ser dividida em duas metodologias distintas. A primeira delas consiste na quantificação do IMT médio e a segunda consiste na determinação do IMT máximo. O IMT médio é estimado como a média de todas as medições de IMT feitas ao longo de segmentos únicos ou múltiplos das carótidas direita e esquerda e dos pontos

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[137] Emerging Risk Factors Collaboration, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med. 2012;367(14):1310-20

[138] Nair SB, Malik R, Khattar RS. Carotid intima-media thickness: ultrasound measurement, prognostic value and role in clinical practice. Postgrad Med J. 2012 Dec;88(1046):694-9.

[139] Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N,et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.

[140] Feinstein SB, Voci P, Pizzuto F. Noninvasive surrogate markers of atherosclerosis. Am J Cardiol. 2002 Mar 7;89(5A):31C-43C; discussion 43C-44C.

proximais e distais das paredes das artérias. O IMT também pode ser expresso como a média das médias do IMT da artéria carótida direta e esquerda. Já o IMT máximo consiste no valor mais alto de IMT mensurado nos seguimentos da artéria carótida[138]. Os valores de IMT máximo refletem estágios mais avançados da aterosclerose, com espessamento focal e formação de placas.[141] Entretanto, o a Sociedade Americana de Ecocardiografia [142], recomenda o uso do valor médio das medidas médias das artérias carótidas comuns esquerda e direita na parede distal (média das médias), por ser a medida mais reprodutível.

Uma revisão de literatura recente sugere que os valores normais e IMT na artéria carótida comum em adultos saudáveis de meia idade variam entre 0,6 e 0,7 mm[143]. Entretanto, vários são os valores de referência que foram propostos para o IMT e, por esse indicador ser uma medida contínua, o ponto de corte pode ser arbitrário. Em geral, a definição do limite superior normal do IMT da carótida é definida utilizando-se o percentil 75 da distribuição do IMT em uma dada população[144].

O IMT aumenta com a idade e é tipicamente maior entre os homens do que entre as mulheres. Um maior IMT também é associado a diversos fatores de riscos proximais para doença cardiovascular como hipertensão, tolerância à glicose diminuída, tabagismo, dislipidemia e obesidade [142,145]. Além dessa associação com fatores de risco cardiovascular estabelecidos, o IMT prediz a ocorrência de desfechos cardiovasculares clínicos. Uma revisão sistemática e metanálise, envolvendo 8 estudos longitudinais, concluiu que para cada aumento de 1 desvio padrão do IMT, o risco global para infarto agudo do miocárdio aumentou em 1,26 vezes (IC

[141] Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N,et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.

[142] Stein JH, Korcarz CE, Hust RT, et al. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Ecocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008; 21:93-111.

[143] O'Leary D, Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J 2010;31:1682e9

[144] Nair SB, Malik R, Khattar RS. Carotid intima-media thickness: ultrasound measurement, prognostic value and role in clinical practice. Postgrad Med J. 2012 Dec;88(1046):694-9

[145] Bauer M, Delaney JA, Möhlenkamp S, Jöckel KH, Kronmal RA, Lehmann N, Mukamal KJ, Moebus S, Polak JF, Dragano N, Budoff MJ, Erbel R, McClelland RL. Comparison of factors associated with carotid intima-media thickness in the Multi-ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall Study (HNR). J Am Soc Echocardiogr. 2013; 26 (6): 667-673.

95%, 1,21-1,30) e, para acidente vascular cerebral em 1,32 vezes (IC 95%: 1,27-1,38)[146]. Apesar da evidente associação entre o IMT e as DCV [146,147], estudos recentes incluindo uma metanálise de 15 estudos longitudinais[147] demostraram que o acréscimo dessa medida em algoritmos de estratificação de risco cardiovascular, como o Escore de *Graminham,* não adiciona valor de predição para DCV.

2.4 JUSTIFICATIVA

O Brasil tem enfrentado grandes mudanças econômicas nas últimas décadas. Rapidamente passou de um país predominante rural para urbano e vem apresentado um envelhecimento populacional igualmente rápido. Os níveis de desigualdade e pobreza têm diminuído ao longo dos últimos anos devido às políticas de proteção social, incluindo o aumento real do salário mínimo, programas de transferência de renda[148,149]. No entanto, a desigualdade permanece entre as mais altas do mundo, com um índice nacional de Gini de 0,51 em 2012[150]. Assim, uma grande parcela da população brasileira ascendeu socialmente, mas carregam as marcas da exposição às circunstâncias sociais desfavoráveis no passado recente.

O Estudo Longitudinal de Saúde do Adulto (ELSA- Brasil) está inserido nesse contexto social. O ELSA-Brasil destaca-se pela variedade de informações coletadas para investigar determinantes biológicos e sociais das DCV no país e constitui-se em uma oportunidade ímpar para testar hipóteses relacionadas à posição socioeconômica ao longo da vida e marcadores biológicos bem como de estágios subclínicos de doenças.

Seguindo o referencial teórico apresentado anteriormente, pode-se dizer que a posição socioeconômica ao logo da vida pode ser associada à DCV por pelo menos três mecanismos envolvendo a inflamação crônica:

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[146] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007 Jan 30;115(4):459-67.
[147] Van den Oord SC, Sijbrands EJ, ten Kate GL, van Klaveren D, van Domburg RT, van der Steen AF, Schinkel AF. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. Atherosclerosis. 2013; 228(1):1-11.
[148] Kiggundu MN. Anti-poverty and progressive social change in Brazil: lessons for other emerging economies. International Review of Administrative Sciences.2012;78(4): 733–756.
[149] Rasella D, Aquino R, Santos CA, Paes-Sousa R, Barreto ML. Effect of a conditional cash transfer programme on childhood mortality: a nationwide analysis of Brazilian municipalities. Lancet. 2013;382(9886):57-64.
[150] Instituto Brasileiro de Geografia e Estatística (2012) *Pesquisa Nacional por Amostra de Domicílios 2012*. Rio de Janeiro, MG: Instituto Brasileiro de Geografia e Estatística.

1) Exposições às circunstâncias sociais desfavoráveis ao longo da vida proporcionam aos indivíduos maiores chances de adotar comportamentos de risco para saúde como a inatividade física e o tabagismo. Esses comportamentos levam, por sua vez, a alterações metabólicas como a obesidade e a hipercolesterolemia que promovem um estado pró-inflamatório no organismo e aumentam o risco de DCV.
2) As percepções e as experiências dos indivíduos expostos a circunstâncias sociais desfavoráveis ao longo da vida levam a uma situação de estresse psicossocial, como o representado pelo estresse no trabalho, que pode afetar diretamente o *feedback* do eixo hipotálamo-pituitária-adrenal e o sistema nervoso autônomo aumentando o processo inflamatório levando a DCV.
3) A exposição a piores condições socioeconômicas no curso de vida pode estar envolvida na programação epigenética de alterações que promovem o estabelecimento de fenótipos pró-inflamatórios levando a DCV.

Apesar de vários estudos terem investigado a associação entre a posição socioeconômica no curso de vida e marcadores inflamatórios, várias lacunas ainda persistem. Em primeiro lugar, a maioria absoluta desses estudos foi realizada em países desenvolvidos. Em segundo lugar, os resultados parecem inconsistentes após ajustes por comportamentos relacionados à saúde e alterações metabólicas que são fatores de riscos proximais para DCV (ex.: obesidade, diabetes e hipertensão). Assim, existem ainda dúvidas se essa associação é completamente mediada por comportamentos relacionados à saúde e alterações metabólicas ou se existe um caminho independente como sugerido pela perspectiva psicossocial e epigenética. Adicionalmente, essa associação parece ser fortemente mediada pela obesidade em países desenvolvidos, mas, em geral, os estudos não avaliaram essa mediação com técnicas estatísticas que permitam distinguir efeitos diretos de efeitos indiretos. Além disso, no Brasil a transição nutricional é mais recente do que nos países desenvolvidos e a associação entre a obesidade e a posição socioeconômica difere entre os gêneros[151,152]. Assim, torna-se relevante a investigação da associação entre posição social ao longo da vida e a inflamação crônica e a verificação do papel mediador dos comportamentos de risco para saúde e das alterações metabólicas nessa associação no contexto brasileiro.

[151] Monteiro CA, Moura EC, Conde WL, Popkin BM. Socioeconomic status and obesity in adult populations of developing countries: a review. Bull World Health Organ. 2004;82(12):940-6.
[152] Monteiro CA, Conde WL, Popkin BM. Income-specific trends in obesity in Brazil: 1975–2003. Am J Public Health. 2007;97(10):1808-12.

Várias lacunas existem também sobre o papel mediador do estresse no trabalho na associação entre posição social e DCV. Nenhum estudo investigou tal hipótese em países de média renda como no Brasil e todos utilizaram apenas indicadores de posição social na vida adulta. Além disso, os achados do *Whitehall II study*[153], onde foi encontrado que uma parcela substancial da associação entre posição social e DCV era mediada pelo estresse no trabalho, não são compatíveis com os outros estudos que investigaram essa mesma hipótese. Entretanto, o *Whitehall II* study é uma coorte ocupacional e, por isso, os participantes podem ter características diferentes que possam ser responsáveis por essa diferença. Adicionalmente, nesse estudo o desfecho utilizado foi doença cardiovascular autorreferida o que pode trazer certo grau de imprecisão. Dessa forma, a investigação dessa hipótese no ELSA-Brasil que, assim como o *Whitehall II study*, é uma coorte ocupacional, utilizando indicadores de posição social em diferentes fases da vida e desfechos cardiovasculares mais precisos e menos susceptíveis a vieses, como a aterosclerose subclínica, pode trazer elementos importantes para compreender melhor essa questão.

[153] Marmot, M., Bosma, H., Hemingway, H., Brunner, E., & Stansfield, S. (1997). Contribution of job control and other risk factors to social variations in coronary heart disease incidence. Lancet, 350, 235e239.

OBJETIVOS

3 OBJETIVOS

3.1 OBJETIVO GERAL

Investigar a posição socioeconômica no curso de vida e sua associação com a inflamação crônica e a aterosclerose subclínica entre os participantes do Estudo Longitudinal da Saúde do Adulto (ELSA-Brasil).

3.2 OBJETIVOS ESPECÍFICOS

- Avaliar a associação entre a posição socioeconômica ao longo da vida e níveis séricos de PCR na vida adulta (Artigo 1);

- Investigar se existe um período crítico, no qual a exposição à baixa posição socioeconômica poderia estar associada a uma maior concentração sérica de PCR na vida adulta ou se existe evidências de acumulação de riscos ao longo da vida (Artigo 1);

- Investigar se a associação entre a posição socioeconômica ao longo da vida e a PCR é mediada por comportamentos de risco à saúde e alterações metabólicas (Artigo 1);

- Examinar a associação entre posição socioeconômica ao longo da vida e o IMT utilizando três modelos da abordagem do curso de vida: períodos sensíveis/críticos, acumulação de riscos e mobilidade social (Artigo 2);

- Avaliar se a associação entre a posição socioeconômica ao longo da vida e o IMT é mediada pelo estresse no trabalho (Artigo 2);

- Explorar o possível efeito de modificação de gênero na associação entre posição socioeconômica em diferentes fases da vida e a PCR e o IMT (Artigo 1 e 2).

ARTIGO ORIGINAL 1

4 ARTIGO ORIGINAL 1

Title: Life course socioeconomic position and C-reactive protein: mediating role of health-risk behaviors and metabolic alterations. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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ABSTRACT

BACKGROUND: Chronic inflammation has been postulated to be one mediating mechanism explaining the association between low socioeconomic position (SEP) and cardiovascular disease (CVD). We sought to examine the association between life course SEP and C-reactive protein (CRP) levels in adulthood, and to evaluate the extent to which health-risk behaviors and metabolic alterations mediate this association. Additionally, we explored the possible modifying influence of gender. **METHODS AND FINDINGS:** Our analytical sample comprised 13,371 participants from ELSA-Brasil baseline, a multicenter prospective cohort study of civil servants. SEP during childhood, young adulthood, and adulthood were considered. The potential mediators between life course SEP and CRP included clusters of health-risk behaviors (smoking, low leisure time physical activity, excessive alcohol consumption), and metabolic alterations (obesity, hypertension, low HDL, hypertriglyceridemia, and diabetes). Linear regression models were performed and structural equation modeling was used to evaluate mediation. Although lower childhood SEP was associated with higher levels of CRP in adult life, this association was not independent of adulthood SEP. However, CRP increased linearly with increasing number of unfavorable social circumstances during the life course (p trend < 0.001). The metabolic alterations were the most important mediator between cumulative SEP and CRP. This mediation path accounted for 49.5% of the total effect of cumulative SEP on CRP among women, but only 20.2% among men. In consequence, the portion of the total effect of cumulative SEP on CRP that was mediated by risk behaviors and metabolic alterations was higher among women (55.4%) than among men (36.8%). **CONCLUSIONS:** Cumulative SEP across life span was associated with elevated systemic inflammation in adulthood. Although health-risk behaviors and metabolic alterations were important mediators of this association, a sizable fraction of this association was not mediated by these factors, suggesting that other pathways might play a role, especially among men.

Keywords: Life course, health inequality, socioeconomic position, inflammation, C-reactive protein, cardiovascular disease, ELSA-Brasil, structural equation modeling.

INTRODUCTION

The association between lower adulthood socioeconomic position (SEP) and increased risk of cardiovascular disease (CVD) is well-established [1]. Exposure to disadvantaged

socioeconomic circumstances during childhood and youth have also been shown to be powerful predictors of CVD [2], indicating that SEP acts across the life course, rather than just in adulthood.

A number of mechanisms have been put forward to account for the association between low life course SEP and cardiovascular risk, including higher prevalence of risk behaviors among disadvantaged individuals, such as smoking, excessive alcohol consumption, and sedentarism [3]. These behaviors may in turn lead to metabolic, endocrine and immune dysregulation, which could promote a pro-inflammatory and pro-thrombotic state [3,4]. Some evidence also suggests that chronic stress associated with socioeconomic adversity leads to epigenetic modifications affecting the transcription of the glucocorticoid receptor leading to glucocorticoid resistance. This phenotype may deregulate the neuroendocrine feedback governed by the hypothalamic-pituitary-adrenal axis resulting in elevated secretion of cortisol as well as pro-inflammatory cytokines such as interleukin-6 [5-9].

Interleukin-6 is one of the most important factor involved in the induction of synthesis of the C-reactive protein (CRP), an acute-phase reactant protein produced mainly by the liver [10]. Although the possible role of CRP as a causal factor for CVD remains debated [11,12], extensive evidence suggests that CRP serves as a marker of inflammation and their levels predict the incidence of CVD [13,14]. In high-income countries, the association between low life course SEP and elevated levels of CRP has been extensively investigated [15-20]. However, there is a lack of consistency among these studies with regard to the persistence of this association after controlling for the effect of health-related behaviors and metabolic alterations (such as obesity, hypertension, diabetes and dyslipidemia). Most studies found no remaining association between SEP and CVD after considering the effect of these variables, especially of obesity [15,16,19]. These findings suggest that health-related behaviors and metabolic alterations fully mediate the relation between life course SEP and chronic inflammation.

There is also uncertainty as to the existence of critical periods, during which SEP would exert an irreversible and independent influence on the development of chronic inflammation, or of sensitive periods, during which SEP would exert a stronger influence on chronic inflammation [21,22]. Some studies found that exposure to unfavorable social circumstances in childhood was associated with higher CRP levels independently of adulthood SEP

[17,23,24] and that current SEP was not associated with CRP levels after considering the influence of childhood SEP [17 23,24]. Yet other studies found that only adulthood SEP has an influence on CRP levels [16]. Other studies have also suggested a cumulative influence of socioeconomic disadvantage on CRP levels, i.e. the greater the exposure of disadvantage across the life course, the higher the CRP level [16-18, 25].

Brazil, like other upper-middle income countries, has faced great economic and demographic changes in recent decades. It has shifted from a predominantly rural to an urban country with a rapidly aging population. Inequality and poverty levels have decreased sharply in recent years due to anti-poverty policies including increases in the minimum wage, cash transfer programmers, and improvements in the public health system [26,27]. Thus, an important fraction of the population has experienced recent upward socioeconomic mobility. However, the country remains among the highest in the world in terms of income inequality, with a national Gini index of 0.51 in 2012 [28].

The association between SEP and obesity in Brazil differ by gender, and whereas among women there is a clear inverse relation between SEP and obesity, among men SEP is directly or not associated at all with obesity [29,30]. In addition, the association between CRP and obesity is higher in women in many North American and European studies [31], and the obesity has been shown to be the most important predictor of CRP [32-34]. Thus, the association between SEP and CRP might differ among men and women. This gender difference was supported by results from the 1982 Pelotas (Brazil) Birth Cohort Study (mean age =22.7 years). In this study childhood SEP and CRP were not associated in women, whereas among men there was an association, but in the opposite direction of what has been observed in developed countries: i.e. men reporting higher family income at birth presented higher levels of CRP in adult life independently of current SEP and metabolic alterations [23]. The explanation for this unexpected result remains unclear and further investigation is needed especially in middle aged adults, when SEP is more stable.

Thus, our aim was to evaluate the association of socioeconomic position across the life course with CRP levels in adulthood among middle aged civil servants living in a higher middle income country undergoing rapid transformation. Specifically, our objective was to investigate whether there is a critical period when exposure to lower SEP more strongly influences CRP levels, and/or if there is evidence of a cumulative SEP effect. Additionally,

we investigated whether health-risk behaviors and metabolic alterations potentially mediate the association between life course SEP and chronic inflammation, and whether gender modifies this relationship.

METHODS

Data source and study population

This study used the baseline data from ELSA-Brasil. The design and selection criteria of ELSA-Brasil were described elsewhere [35,36]. Briefly, 15,105 civil servants, aged between 35 and 74, active or retired, were enrolled from universities and research institutes in six Brazilian states (São Paulo, Minas Gerais, Bahia, Rio Grande do Sul, Rio de Janeiro and Espírito Santo). The baseline examination (2008–2010) included detailed interviews, as well as clinical, laboratory and anthropometric examinations.

Exclusion Criteria

From the 15,105 participants at baseline, we excluded from this analysis 1263 women who were using hormonal contraceptive therapy or hormonal replacement therapy at the time of the blood draw, as this group has been shown to have elevated CRP levels [37,38]. In addition, we excluded 108 participants for having missing values for CRP, and 363 for having CRP values below the detection limit (0.175 mg/L). Thus, 1,734 participants were excluded (233 men and 1501 women) and the analysis sample comprised 13,371 (88.5%) participants.

The excluded men were similar to those included with regard maternal education, occupational social class in the first job, current occupational social class, and own education attainment. However, excluded men were more likely to have higher *per capita* household income ($p=0.035$). In comparison with the women participants, those excluded presented higher maternal education ($p<0.001$), higher occupational social class in the first job ($p<0.001$), higher own education attainment ($p<0.001$), higher current social class ($p<0.001$), and higher *per capita* household income ($p<0.001$).

Study Variables

CRP levels

Serum CRP was obtained from overnight fasting blood and was measured using high-sensitivity assay by immunochemistry - nephelometry - (BN II; Siemens).

Life course SEP indicators

Childhood SEP: Maternal education was used as an indicator of childhood SEP, and it was assessed retrospectively by self-report, using years of schooling, based on the question "*What is the educational level of your mother?."*

Young adulthood SEP: Participants' own education and occupational social class of the first job were used to measure young adulthood SEP. Participants' own education was obtained by self-report, in years of schooling, using the question "*What is your education level?".* Occupational social class of the first job is a summary measure based on the first job held by the participant, obtained using the open question: *"What was your occupation or activity on your first job?.* It considers the relationship schooling-income by comparing the expected income based on the educational level required by the job and the observed income prevailing in the labor market. These scores were categorized into 7 levels (high-upper, high-low, middle-upper, middle-middle, middle-low, low-high and low-low) [39].

Adulthood SEP: Current occupational social class and *per capita* household income were used to evaluate adulthood SEP. The current occupational social class was obtained using the same approach that was used to obtain the social class of the first job, but using the current occupation, obtained by the open question: "*Please describe the main activities that you develop in your day-to-day work at this institution".* The net household income was evaluated by self-report using the question: *"During the last month, what was, approximately, your net household income, that is, the sum of incomes, already considering tax discounts, of all the people who regularly contribute with house expenses?"* and the *per capita* household income was obtained dividing this amount by the total number of people living in the household.

Cumulative SEP score: To indicate the accumulation of risk during the life course, a cumulative SEP score was generated and ranged between zero to nine (higher values reflecting worse life course SEP and higher risk), and including maternal education (≥ 11

years of study =0; 8-10 years of study=1; 1-7 years of study=2; 0 years of study=3), participant's own education (≥ 15 years of study =0; 11-14 years of study=1; 8-10 years of study=2; 0-7 years of study=3), and per capita household income (4th quartile =0; 3rd quartile =1; 2nd quartile=2; 1st quartile=3).

Potential mediators

Health-risk behaviors: current cigarette smoking was determined by self-report if the participants declared having smoked at least 100 cigarettes in their lifetime and still smoked at the time of the research. Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) – Short Form, and low leisure time of physical activity was defined according to the IPAC Guidelines for Data Processing and Analysis [40], as participants who did not meet any of the following three criteria: 3 or more days of vigorous activity during the last week, consisting of at least 20 minutes per day; or 5 or more days of moderate-intensity activity and/or walking during the last week, consisting of at least 30 minutes per day; or 5 or more days of any combination of walking, moderate or vigorous-intensity activities during the last week, achieving a minimum of at least 600 Metabolic Equivalent of Task (MET)-minutes per week [40]. The alcohol consumption was evaluated by self-report of usual type, frequency of intake, and drinking patterns. All the information obtained was summarized in quantity of grams of alcohol drank per week. Excessive alcohol consumption was defined as consuming ≥ 210g of alcohol per week among men, and ≥140g per week among women. To indicate the cluster of these health-risk behaviors, we created a score that ranged from 0 (absence of health-risk behavior) to 3 (presence of all three health-risk behaviors).

Metabolic alterations: anthropometric measurements of weight, height and waist circumference were used to define "obesity/abdominal obesity" as participants who presented body mass index ≥ 30 kg/m^2 and/or waist circumference ≥ 88 cm for women and ≥ 102 for men. Hypertension was defined as systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90 mmHg or verified treatment with anti-hypertensive medication. Low HDL cholesterol was defined as HDL < 40 mg/dL for men and <50 mg/dL for women. Hypertriglyceridemia was defined as ≥ 150 mg/dL. Diabetes was defined as a self-report of a previous diagnosis of diabetes or the use of medication for diabetes or fasting glucose ≥ 126 mg/dL or glucose tolerance test ≥ 200mg/dL or glycated hemoglobin ≥6.5%. To indicate the

cluster of these metabolic alterations, we generated a score that ranged from 0 (absence of metabolic alterations) to 5 (presence of all five metabolic alterations).

Data Analyses

We generated descriptive characteristics of the analytic sample. Categorical variables were summarized as frequencies and continuous variables were summarized as means and standard deviation (SD) or median and interquartile range (IQR). All analyses were conducted separately for men and women to explore the possible modifying influence of gender.

The prevalence of each health-risk behavior and metabolic alteration was described according to the cumulative SEP score. We compared the median CRP levels according to the presence or absence of each of the health-risk behaviors and metabolic abnormality. The statistical significance of the differences between the median values in those groups was evaluated using the Wilcoxon rank-sum test, since the levels of CRP were left-skewed.

CRP was natural log-transformed due to non-normality. We estimated the age-adjusted geometric means of CRP for each SEP indicator by exponentiating the parameter estimates from linear regression models on natural log-transformed CRP (back- transformed). We also examined geometric means of CRP adjusted for age and all SEP indicators simultaneously. The adjustment for age was necessary, since CRP increases with age [10], and socioeconomic position also differed according to age. For example, educational attainment varies by births cohort, and older people tend to have lower education than the young people in the ELSA-Brasil cohort.

To estimate the age-adjusted geometric means of CRP, the maternal education was grouped in four categories (≥ 11, 8-10, 1-7, 0 years of study), as well as the participants' own education attainment (≥ 15, 11-14, 8-10, 0-7 years of study). The occupational social class of the first job and the current occupational social class were summarized in three categories (high, middle, low), and the *per capita* household income was categorized into quartiles. However, to test the linear trends of these CRP means by SEP we entered the SEP indicators as continuous variable in these models. The normality of residuals and homoscedasticity were tested graphically and violation was not found. The multicollinearity between the explanatory variables was assessed by the variance inflation factor (VIF) and all VIF values were far below 10, the critical value for a serious problem of multicollinearity [41].

Mediation Analyses

We used structural equation modeling to test the hypothesis that the association between cumulative SEP and CRP is partly mediated by health-risk behaviors and metabolic alterations.

A latent variable was created in the measurement model to represent the cumulative SEP and included maternal education, participant's own education, occupational social class of the first job, current occupational social class and per capita household income. All SEP indicators were included in the measurement model as continuous variables, and the *per capita* household income was natural log-transformed due to non-normality. The scores created to access the clustering of health-risk behaviors and metabolic alterations were used in the structural equation models. Figure 1 shows details of the model that was tested. Figure 1A shows the total effect of cumulative SEP on CRP. Figure 1B shows that the estimate of the total effect was disaggregated into three indirect effects, which represent the effects mediated by health-risk behaviors and metabolic alterations (Cumulative SEP => Risk Behavior => ln(CRP); Cumulative SEP=> Metabolic alterations=> ln(CRP); Cumulative SEP=> Risk Behavior=> Metabolic alterations=> ln(CRP)), and the remaining direct effect of cumulative SEP on CRP that is independent of these mediators. Despite the a priori importance of age as pointed out above, the age standardized coefficient was not statistically significant in the mediation models. For this reason, we did not include age in the mediation analysis, because this inclusion did not materially alter the other estimates, but affected the model adjustment because of the existence of a non-significant variable in the model.

The maximum likelihood procedure was used to estimate the structural equation model parameters. Standardized coefficients with 95%CI, and tests of significance for standardized coefficients were reported. The absence of overlap in the 95%CI for each standardized coefficient was interpreted as evidence of a significant gender difference in a given path. Overall model fit was assessed using the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA), and the standardized root mean squared residual (SRMR). For goodness of fit, we followed the recommendation of a CFI ≥ 0.95, RMSEA ≤ 0.05, and the SRMR ≤ 0.08 [42].

All analyses were conducted using the software Stata 12.0 (Stata Corporation, College Station, United States).

Sensitivity Analyses

In epidemiologic research of chronic inflammation, CRP above 10 mg/L has been considered as acute inflammation and excluded from studies. Nevertheless, recent studies suggest that, especially in obese women, CRP above 10 mg/L can occur due to chronic inflammation [38]. Thus, we showed the results including participants with CRP above 10, but all the analyses were repeated excluding these individuals to verify for possible changes in the results.

Ethics

ELSA-Brasil research protocol was approved by the Research Ethics Committee of Universidade de São Paulo (USP), Research Ethics Committee of Universidade Federal de Minas Gerais (UFMG), Research Ethics Committee of Fundação Oswaldo Cruz (FIOCRUZ), Research Ethics Committee of Universidade Federal do Espírito Santo (UFES), Research Ethics Committee of Universidade Federal da Bahia (UFBA), Research Ethics Committee of Universidade Federal do Rio Grande do Sul (UFRGS) and also by the National Research Ethics Committee (CONEP). Informed consent was signed by all participants.

RESULTS

The baseline characteristics of the 13,371 participants (6,654 men and 6,717 women) from the ELSA-Brasil, stratified by sex, are presented in Table 1. The mean age was 52 years (range 35 – 74 years) and 39.9%of the participants were between 45 and 54 years old. Overall, more than 50% of the participants' mothers had less than eight years of schooling, but their own education attainment was high and over 50% of them had $\geq$ 15 years of schooling. On average, the participants had 17 years when they started working. The majority had low social class in their first job, more so among men. On the other hand, about one third of male and one quarter of female social class of current occupational were classified as high. Men reported higher prevalence of smoking and excessive alcohol consumption; while women reported higher prevalence of low leisure time physical activity. The clustering of two or three risk behaviors was substantially more frequent among men than women. The prevalence of obesity/abdominal obesity and low HDL were higher in women than in men. Nevertheless, hypertension and diabetes were more common among men and the prevalence of hypertriglyceridemia was twice that of women.

The prevalence of health-risk behaviors and metabolic alterations rose with increasing exposure to social adversities across the life course. The only exceptions were obesity in men, which was not associated with cumulative SEP score, and excessive alcohol consumption in women, which was directly associated with life course SEP (Table 2).

The distribution of CRP levels was skewed to lower levels, in men and women. The median (IQR) of CRP levels were 1.35 mg/L (0.71-2.81) and 1.68 (0.82-3.80) mg/L among men and women, respectively. With the exception of excessive alcohol consumption in women, all health-risk behaviors and metabolic alterations were associated with higher levels of CRP (Table 3). It was also notable that CRP levels were more strongly associated with metabolic alterations in women (Table 3).

Age-adjusted geometric means of CRP in adulthood increases with increasing socioeconomic disadvantages in all the life course periods analyzed (Table 4). However, after simultaneous adjustment for all SEP indicators, childhood SEP did not remain statistically associated to CRP in any gender. However, participants' own education, among men, and social class of current occupational and *per capita* household income, among women, remained statistically significantly associated with CRP levels in adulthood (Table 4). In men and women there were cumulative effects of exposure to adverse socioeconomic position across the life span and CRP levels increased linearly with increasing numbers of exposure to unfavorable social contexts over the life course (p for linear trend < 0.001) (Figure 2).

Table 5 shows the results of the structural equation models. The factor loadings from the measurement model suggest that each of the individual SEP indicators load highly on the cumulative SEP factor measure. There was a significant total effect between cumulative SEP and ln(CRP), showing that each SD increase in cumulative SEP was associated with a 0.134 SD decrease in ln(CRP), among men, and 0.155 SD, among women. The three indirect paths linking cumulative SEP and ln(CRP) were also statistically significant, and the most important indirect path for both men and women was "Cumulative SEP=> Metabolic alterations=> ln(CRP)". This indirect path was stronger among women than among men, since it accounted for 49.5% of the total effect of cumulative SEP on ln(CRP), among women, and only 20.2% among men. In consequence, the fraction of the total effect of cumulative SEP on ln(CRP), mediated by health-risk behaviors and metabolic alterations was statistically higher in women (55.4%) than in men (36.8%). The direct effect of cumulative

SEP on ln(CRP) was high, especially among men, since it accounted for 63.2% and 44.6% of the total effect of SEP on ln(CRP) among men and women, respectively.

Sensitivity Analyses

Of the total participants considered in this analysis, 2.96% of men and 4.56% of women presented CRP above 10mg/L. Exclusion of these participants from the analysis did not alter significantly any of the results reported above.

DISCUSSION

Although lower childhood SEP was associated with higher levels of CRP in adult life, this association was not independent of adulthood SEP. However, childhood SEP seems to play a role in chronic inflammatory states when it was considered together with young adulthood SEP and adulthood SEP, providing support to a model of cumulative effects of exposures to SEP across the life span. The cluster of metabolic alterations was the most important mediator between cumulative SEP and CRP in men and women, but for women this mediation path was stronger than for men. Together, metabolic alterations and health-risk behaviors were important mediators between cumulative SEP and CRP. However, the direct effect of cumulative SEP on CRP was substantial, suggesting that other pathways could play a role, especially among men.

According to the life course approach, a critical period is a time window during which exposures can lead to lasting physiological changes in the organism. In its most stringent form, no excess risk would be observed if exposure occurred in periods outside the window [21,22]. Our results did not support the notion that childhood is a critical period of exposure to low SEP for three reasons. Firstly, CRP was associated with SEP in all three stages of the life course, not just with childhood SEP. Secondly, after simultaneously controlling for adulthood SEP, no association was found between childhood SEP and CRP, suggesting that the exposure to low SEP in early life could matter because it leads to lower adulthood SEP (the pathways or "chain of risk" hypothesis). Thirdly, we found strong evidence of cumulative risk, indicating that exposure to low SEP at different stages of life accumulate to promote chronic inflammation. All these three aspects of our results are incompatibles with the critical period model, at least in the case of chronic inflammation. However, the results showed an important role of the exposure to low SEP in childhood, since it leads to lasting effect through

accumulation of risk. Many previous studies also reported increased of CRP levels with increasing number of adverse SEP conditions throughout life [16-19, 25].

Clustering of metabolic alterations and health-risk behaviors were important mediators of the association between cumulative SEP and CRP levels in men and women. Using regression models to measure mediation, it was also found in the *Atherosclerosis Risk in Communities* study (ARIC) that diabetes status, low HDL cholesterol, high BMI, smoking and physical inactivity were important mediators between life course SEP and a score of inflammation which included CRP, von Willebrand fator, fibrinogen, and white blood cell count [20].

In our study, metabolic alterations were the most import mediators of the association between cumulative SEP and CRP. However, while this indirect path accounted for 49.5% of the total effect of cumulative SEP on CRP among women, it accounted for only 20.2% among men. This gender difference may be explained by at least two reasons. Firstly, the association between all metabolic alterations and CRP was stronger in women than in men in the ELSA Brasil, which is consistent with other studies [31, 43, 44]. For example, in the British 1958 Birth Cohort the associations between obesity (body mass index, waist circumference), blood pressure, blood lipids, metabolic syndrome and CRP were twice as strong among women as among men [43]. In addition, recent meta-analysis also showed that in adults the Pearson correlation coefficients between body mass index and ln(CRP) was greater in women than men by 0.24 (CI, 0.09-0.37) on average [31]. Secondly, it is well known that adiposity is a major predictor of CRP [32-34], and we found that the prevalence of obesity was higher among women than among men (47.56% *versus* 29.53%). Moreover, obesity was not associated with the accumulation of exposures to low SEP during the life course in men, replicating what is currently found in the Brazilian population as a whole [29]. All these findings may explain the much greater contribution of metabolic disorders as mediating path between Cumulative SEP and CRP in women as compared to men.

The cluster of health-risk behaviors accounted for 13.4% of the total effect of Cumulative SEP on CRP among men and only 4.4% among women. Consistently with other studies [45,46], we found that excessive alcohol consumption was associated with higher CRP levels and with low life course SEP among men. However, among women, the excessive alcohol consumption was not associated with CRP levels. In addition, excessive alcohol consumption was related with higher life course SEP among women, as it was also reported in the general

population of Scotland [45]. Moreover, the prevalence of smoking, as well as the clustering of two or more health-risk behaviors, was higher among men. In sum, these facts could account for the greater role of health-risk behaviors as mediators in the association between cumulative SEP and CRP in men than in women. Different findings were reported by the *National Health and Nutrition Examination Surveys* (NHANES IV) using only measures of adulthood SEP. They found that 55.8% of the association between poverty in adulthood and CRP was mediated by 4 health-related behaviors (smoking, heavy alcohol consumption, poor diet and physical activity) and this indirect effect was higher (87.9%) when education level was used to measure adulthood SEP instead of poverty [47]. In contrast to the NHANES IV analyzes, we have not considered poor diet, and the prevalence of smoking and heavy alcohol consumption among US participants was much higher than that found in ELSA-Brasil. For instance, the prevalence of current smoking ranged from 17.7% to 32.8% among non poor and poor NHANES IV participants while heavy alcohol consumption ranged from 16.8% to 20.4%, respectively [47]. Moreover, they only used measures of adulthood SEP, and although the health-related behaviors are often acquired in adolescence [48], it is known that they are more strongly associated with adulthood SEP than with childhood SEP [49].

An important portion of the association between cumulative SEP and CRP was not mediated by metabolic alterations and health-risk behaviors, suggesting that others pathways could play an important role. Stress was not included in the present analysis and may be a relevant path between SEP and CRP levels. Life course SEP could lead to chronic inflammation by increasing exposure to psychosocial stress factors, such as crowding, growing up in poor neighborhoods, experiences of childhood trauma and abuse, discrimination, job strain, and perceptions of relative deprivation [50-52]. Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous systems, resulting in higher secretion of cortisol and catecholamines, setting off a chain of physiological consequences including inflammation, coagulation, and adhesion – the so-called model of allostatic load [53]. For instance, in the Whitehall study, job control explained about 64%, among men, and 51%, among women, of the excess risk for coronary heart disease associated with low versus high occupational group [54]. However, most studies found only a small contribution of stress measures to socioeconomic gradient in health [52].

The epigenetic modification induced by the experience of social adversity is another path that could explain some portion of the direct effect that we found between cumulative SEP and

CRP. In general, exposures to environmental stressors tend to lead the epigenomic instability (i.e.: DNA demethylation, histone modification and micro-RNA expression). The organism uses this mechanism to respond to threats and, consequently, to increase the diversity. Nevertheless, this process also has the potential to causes diseases [7]. There is growing evidence that socioeconomic adversity can influence DNA methylation and gene expression, especially in genomic regions regulating the immune function [6,7]. These studies also indicate that exposures to social adversities across the life course may cause glucocorticoid receptor resistance leading to exaggerated glucocorticoid levels in the organism. Thus, uncontrolled inflammatory responses would be typical characteristic of this phenotype created by epigenetic modification [5-9]. Originally it was believed that only exposures to SEP in early life could promote this kind of epigenetic modification; however recent evidence suggests that exposure to SEP in adulthood can also promote epigenomic instability [8, 55]. Nevertheless, the association between epigenetics modifications and SEP tend to be higher when measures of SEP in early life were used [6-8].

Some potential limitations of our analysis merit consideration. Firstly, to analyze the role of metabolic alterations and health-risk behaviors as mediators between cumulative SEP and CRP we used clusters of risk factors. In doing so, it became feasible to study the mediation process using conventional structural equation modeling. Our approach has two limitations: 1) the specific effect of each behavior or metabolic alteration could be not accessed; 2) working with clusters we considered that all variables have the same weight, but it is possible that different behaviors or metabolic alterations can have more or less influence on CRP levels. For example, among all metabolic alterations considered, it is known that obesity is a major predictor of CRP [32-34]. Thus, it was not possible to detect in this analyses which component is more important to mediate the association between cumulative SEP and CRP. Secondly, we do not have the timing of the onset of health behaviors & metabolic alterations – for example, it's possible that most behaviors began in adolescence, which would point to the need for early intervention. Thirdly, we used only maternal education to measure childhood SEP. Others studies that have used other indicators of SEP in childhood, such as parental occupational status and *in utero* SEP, could provide a better evaluation of the influence of exposure to low childhood SEP in chronic inflammation in adulthood. Fourthly, we used the participant's own education to measure young adulthood SEP, since education is generally complete in late adolescence or in the beginning of adult life [56]. However, the participants from ELSA-Brasil are civil servants from universities and research centers and

some positions require post-graduate level education. For this reason, we also used the occupational social class of the first job to capture better the SEP in young adulthood, since the mean age that the participants started to work was 16 years among men and 18 among women. Fifthly, we used only the *per capita* household income to evaluate the participants' financial situation, which did not capture other dimensions such as wealth and assets. Sixthly, the ELSA-Brasil participants are active and retired workers, have retirement plans and average education and income levels higher than that of the general population of Brazil. Thus, people who experienced extreme social difficulties in childhood as well as in adulthood could not be represented in this study. The truncated variability in SEP may have led us to underestimate the magnitude of the associations between life course SEP and CRP levels.

The linear association between number of exposures to low SEP and CRP suggests a cumulative impact of SEP in promoting chronic inflammation. These findings provide one potential biological mechanism to explain the well-established social gradient for CVD. Moreover, it suggests that social interventions in a single time point across the life course may not suffice to deal with the social inequalities in CVD. Our findings extend previous studies by using statistical techniques that allowed us to disentangle the portion of the total effect of cumulative SEP on CRP levels that is mediated by metabolic alterations and health-risk behaviors.

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DATA AVAILABILITY STATEMENT

The data used in this study is available for research proposal on request to the ELSA's Datacenter and to the ELSA's Publications Committee (publiELSA). Additional information can be obtained from the ELSA's Datacenter (estatisticaelsa@ufrgs.br) and from the ELSA Coordinator from the Research Center of Minas Gerais (sbarreto@medicina.ufmg.br).

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FIGURES AND TABLES

Figure 1 – Illustration of proposed multiple mediation of the association between life course SEP and CRP. (A) Total effect of life course SEP on CRP. (B) Hypothesized indirect effect of SEP on CRP through mediators and direct effect. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

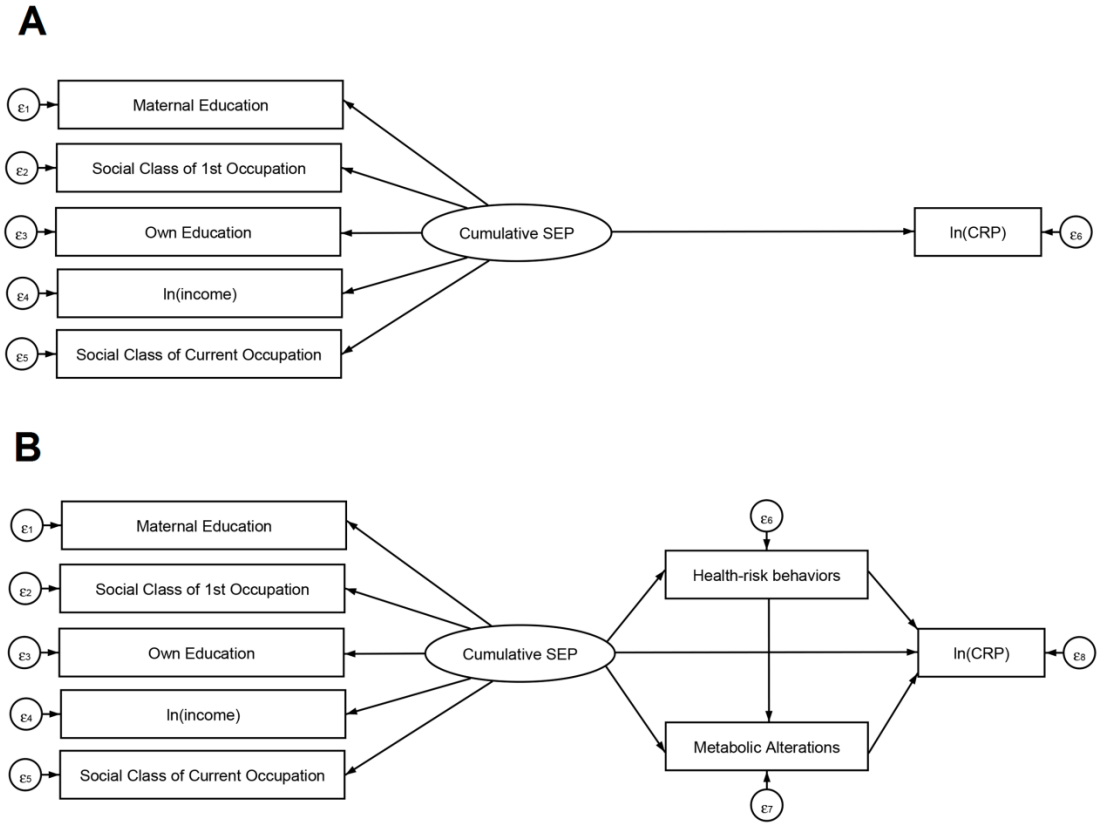

Figure 2 - Age adjusted geometric means (95% confidence interval) of C-reactive protein among men and women by the cumulative SEP score that ranged between zero to nine, with higher values reflecting worse life course SEP. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

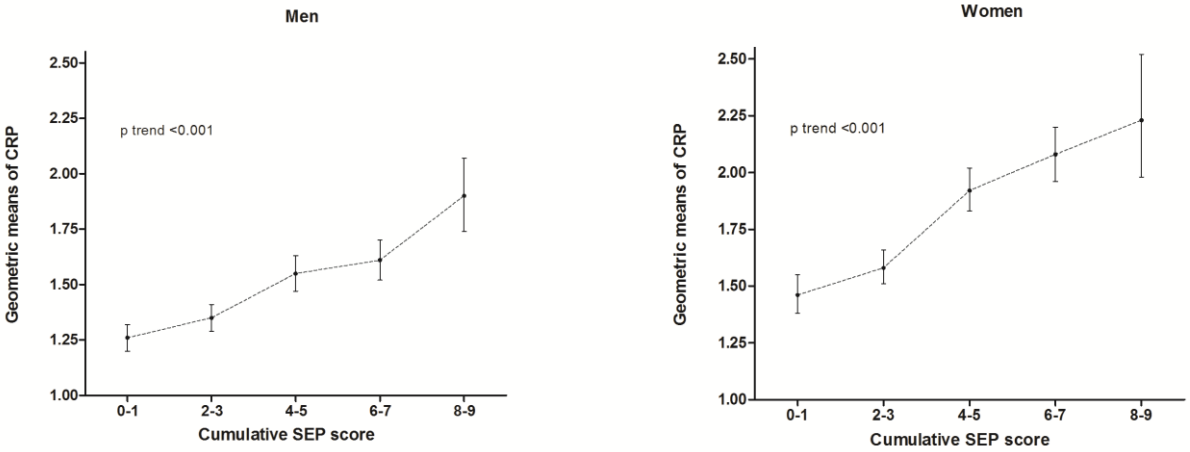

Table 1– Descriptive characteristics of the analytical sample from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), N (%) or mean (SD), 2008-2010 (N=13,371)[1].

Characteristics	Overall N=13,371	Men N=6,654	Women N=6,717
Age (years), (N=13,371), %			
35-44	2,829 (21.16)	1,490 (22.39)	1,339 (19.93)
45-54	5,338 (39.92)	2,606 (39.16)	2,732 (40.67)
55-64	3,753 (28.07)	1,806 (27.14)	1,947 (28.99)
65-74	1,451 (10.85)	752 (11.30)	699 (10.41)
Maternal education(years of study),(N=13,029), %			
≥11	3,027 (23.23)	1,624 (25.16)	1,403 (21.34)
8-10	2,531 (19.43)	1,248 (19.33)	1,283 (19.52)
1-7	5,567 (42.73)	2,637 (40.85)	2,930 (44.57)
0	1,904 (14.61)	946 (14.66)	958 (14.57)
Participants' own education (years of study), (N=13,371), %			
≥15	6,850 (51.23)	3,359 (50.48)	3,491 (51.97)
11-14	4,695 (35.11)	2,193 (32.96)	2,502 (37.25)
8-10	967 (7.23)	554 (8.33)	413 (6.15)
0-7	859 (6.42)	548 (8.24)	311 (4.63)
Age at first job, (years), (N=13,343), mean (SD)	17.15 (4.87)	16.16 (4.65)	18.13 (4.88)
Social class of first occupation, (N=10,710), %			
High	627 (5.85)	343 (6.09)	284 (5.59)
Middle	3,471 (32.41)	1,474 (26.19)	1,997 (39.30)
Low	6,612 (61.74)	3,812 (67.72)	2,800 (55.11)
Social class of current occupation, (N=12,605), %			
High	3,909 (31.01)	2,291 (35.85)	1,618 (26.04)
Middle	5,397 (42.82)	2,235 (34.97)	3,162 (50.89)
Low	3,299 (26.17)	1,865 (29.18)	1,434 (23.08)
Per capita household income in U.S. dollars, (N=13,307), mean (SD)	896.69 (747.54)	869.51 (708.65)	923.61 (783.31)
Cumulative SEP score[2] (N=12,971), %			
0-1 (lowest risk)	2,755 (21.24)	1,473 (22.92)	1,282 (19.59)
2-3	3,739 (28.83)	1,811 (28.18)	1,928 (29.46)
4-5	3,238 (24.96)	1,440 (22.41)	1,798 (27.47)
6-7	2,467 (19.02)	1,223 (19.03)	1,244 (19.01)
8-9 (highest risk)	772 (5.95)	479 (7.45)	293 (4.48)
Smoking (N=13,370), %	1,810 (13.54)	957 (14.38)	853 (12.70)
Low leisure time physical activity (N=13,169), %	10,196 (77.42)	4,835 (73.74)	5,361 (81.08)
Excessive Alcohol Consumption(N=13,346), %	1,051 (7,88)	815 (12.26)	236 (3.52)
Clustering of unhealthy behaviours[3] (N=13,148), %			
0	2,520 (19.17)	1,416 (21.62)	1,104 (16.73)
1	8,526 (64.85)	3,892 (59.41)	4,634 (70.24)
2	1,835 (13.96)	1,045 (15.95)	790 (11.98)
3	267 (2.03)	198 (3.02)	69 (1.05)
Obesity/Abdominal Obesity (N=13,367), %	5,158 (38,59)	1,964 (29.53)	3,194 (47.56)
Hypertension (N=13,358), %	4,959 (37,12)	2,697 (40.57)	2,262 (33.71)
Low HDL (N=13,367), %	2,390 (17.88)	992 (14.92)	1,398 (20.82)
Hypertriglyceridemia (N=13,366), %	4,372 (32.71)	2,764 (41.56)	1,608 (23.94)
Diabetes (N=13,370),%	2,758 (20.63)	1,567 (23.55)	1,191 (17.73)
Clustering of metabolic alterations[4] (N=13,347), %			
0	3,760 (28.17)	1,733 (26.11)	2,027 (30.21)
1	3,739 (28.01)	1,922 (28.95)	1,817 (27.08)
2	2,964 (22.21)	1,508 (22.72)	1,456 (21.70)
3	1,808 (13.55)	951 (14.33)	857 (12.77)
4	867 (6.50)	448 (6.75)	419 (6.25)
5	209 (1.57)	76 (1.14)	133 (1.98)

[1] Differences in total N for each variable are due to missing values.
[2] The cumulative SEP score ranged between zero to nine, with higher values reflecting worse life course SEP.
[3] It includes current cigarette smoking, low leisure time physical activity, excessive alcohol consumption.
[4] It includes obesity/abdominal obesity, hypertension, low hdl, hypertriglyceridemia, diabetes.

Table 2- Prevalence of health-risk behavior and metabolic alteration according to cumulative socioeconomic position (SEP) score (higher values reflecting worse life course SEP) among men and women. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

Characteristic	0-1	2-3	4-5	6-7	8-9	p for trend
Men						
Cigarette smoking	10.52	11.76	15.76	16.68	23.01	<0.001
Low leisure time physical activity	65.53	68.29	76.05	82.11	85.53	<0.001
Excessive alcohol consumption	11.41	11.49	12.72	14.06	13.15	0.026
Obesity/abdominal obesity	31.39	29.93	27.71	28.64	29.65	0.109
Hypertension	37.14	37.56	38.71	43.99	54.70	<0.001
Low HDL cholesterol	12.22	14.41	15.71	17.01	16.98	<0.001
Hypertriglyceridemia	35.78	41.96	43.71	44.56	42.26	<0.001
Diabetes	18.40	19.93	23.28	27.56	38.62	<0.001
Women						
Cigarette smoking	11.00	10.27	12.96	15.51	18.77	<0.001
Low leisure time physical activity	72.81	76.78	83.86	89.81	90.94	<0.001
Excessive alcohol consumption	5.15	3.79	3.06	2.25	2.06	<0.001
Obesity/abdominal obesity	40.80	41.65	50.36	55.14	64.51	<0.001
Hypertension	25.25	29.51	34.20	41.00	57.34	<0.001
Low HDL cholesterol	14.66	17.96	24.03	25.16	27.30	<0.001
Hypertriglyceridemia	19.97	22.21	24.92	26.77	34.81	<0.001
Diabetes	11.86	15.35	17.35	23.23	35.49	<0.001

Table 3 - Median CRP Levels (interquartile range) according to the presence or absence of health-risk behavior and metabolic alterations among men and women. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

Characteristic	Absent	Present	P-value
Men			
Cigarette smoking	1.28 (0.69-2.65)	1.95 (0.99-3.72)	<0.0001
Low leisure time physical activity	1.14 (0.62-2.39)	1.43 (0.75-3.04)	<0.0001
Excessive alcohol consumption	1.31 (0.70-2.71)	1.62 (0.81-3.68)	<0.0001
Obesity/abdominal obesity	1.14 (0.62- 2.36)	1.96 (1.06-3.96)	<0.0001
Hypertension	1.16 (0.64-2.42)	1.63 (0.87-3.48)	<0.0001
Low HDL cholesterol	1.31 (0.69-2.68)	1.61 (0.82-3.63)	<0.0001
Hypertriglyceridemia	1.17 (0.63-2.53)	1.60 (0.85-3.21)	<0.0001
Diabetes	1.22 (0.67-2.50)	1.88 (1.00-3.93)	<0.0001
Women			
Cigarette smoking	1.65 (0.80-3.76)	1.91 (0.91-4.08)	<0.0040
Low leisure time physical activity	1.29 (0.66-3.03)	1.79 (0.87-4.00)	<0.0001
Excessive alcohol consumption	1.67 (0.82-3.79)	1.90 (0.80-4.30)	0.4331
Obesity/abdominal obesity	1.07 (0.59-2.14)	2.90 (1.41-5.54)	<0.0001
Hypertension	1.39 (0.70-3.16)	2.45 (1.14-4.90)	<0.0001
Low HDL cholesterol	1.51 (0.75-3.45)	2.43 (1.15-5.23)	<0.0001
Hypertriglyceridemia	1.45 (0.73-3.37)	2.59 (1.23-4.91)	<0.0001
Diabetes	1.48 (0.75-3.37)	2.85 (1.31-5.82)	<0.0001

Table 4- Adjusted geometric means (95% confidence interval) for levels of CRP by SEP indicators throughout the life course. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

Indicators	Model adjustment			
	Age		Age and all SEP indicators simultaneously adjusted	
	Men	Women	Men	Women
	Geometric mean (95% CI)	Geometric mean(95% CI)	Geometric mean (95% CI)	Geometric Mean (95% CI)
Childhood SEP				
Maternal education(years of				
≥11	1.31 (1.25-1.37)	1.51 (1.43-1.60)	1.48 (1.39-1.57)	1.72 (1.60-1.86)
8-10	1.49 (1.41-1.57)	1.81 (1.71-1.92)	1.58 (1.48-1.68)	1.84 (1.72-1.97)
1-7	1.47 (1.41-1.53)	1.80 (1.73-1.87)	1.45 (1.39-1.51)	1.77 (1.69-1.85)
0	1.63 (1.53-1.73)	1.95 (1.82-2.09)	1.43 (1.33-1.54)	1.75 (1.61-1.90)
p value for trend	<0.001	<0.001	p=0.279	p=0.731
Young adult SEP				
Own education (years of study)				
≥15	1.29 (1.25-1.34)	1.56 (1.51-1.61)	1.33 (1.25-1.40)	1.71 (1.62-1.80)
11-14	1.59 (1.53-1.66)	1.95 (1.87-2.03)	1.55 (1.47-1.63)	1.79 (1.69-1.89)
8-10	1.68 (1.54-1.82)	2.31 (2.09-2.56)	1.68 (1.52-1.86)	2.13 (1.86-2.44)
0-7	1.87 (1.72-2.03)	2.26 (2.01-2.54)	1.92 (1.72-2.14)	1.92 (1.63-2.27)
p value for trend	<0.001	<0.001	<0.001	p=0.069
Social class of first occupation				
High	1.37 (1.23-1.52)	1.35 (1.19-1.52)	1.60 (1.43-1.79)	1.67 (1.47-1.91)
Middle	1.36 (1.29-1.43)	1.68 (1.60-1.76)	1.44 (1.36-1.52)	1.77 (1.68-1.86)
Low	1.55 (1.50-1.59)	1.90 (1.83-1.98)	1.48 (1.43-1.53)	1.78 (1.71-1.86)
p value for trend	<0.001	<0.001	p=0.850	p=0.325
Adulthood SEP				
Social class of current occupation				
High	1.24 (1.19-1.56)	1.39 (1.32-1.46)	1.37 (1.29-1.47)	1.55 (1.44-1.67)
Middle	1.56 (1.50-1.63)	1.87 (1.81-1.94)	1.58 (1.50-1.65)	1.86 (1.78-1.94)
Low	1.63 (1.56-1.71)	2.05 (1.94-2.17)	1.48 (1.38-1.58)	1.83 (1.70-1.97)
p value for trend	<0.001	<0.001	p=0.146	p=0.005
Per capita household income				
4th quartile (highest)	1.28 (1.22-1.35)	1.49 (1.42-1.58)	1.43 (1.34-1.53)	1.63 (1.52-1.75)
3rd quartile	1.39 (1.33-1.46)	1.61 (1.53-1.69)	1.52 (1.44-1.61)	1.65 (1.55-1.76)
2nd quartile	1.51 (1.44-1.59)	1.90 (1.80-2.00)	1.45 (1.37-1.53)	1.86 (1.75-1.99)
1stquartile (lowest)	1.66 (1.59-1.74)	2.10 (2.00-2.21)	1.50 (1.41-1.59)	1.93 (1.81-2.06)
p value for trend	<0.001	<0.001	p=0.270	<0.001

Table 5 – Parameters estimates from the structural equation model of cumulative SEP on CRP levels in adulthood, according to gender. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

	Parameter estimates	
	Men	**Women**
	N= 5,128[1]	**N=4,534[2]**
Measurementmodel, standardized coefficients(95%CI)[3]		
Cumulative SEP -> Maternal education	0.525 (0.504; 0.547)***	0.509 (0.484; 0.534)***
Cumulative SEP -> Social class of first occupation	0.553 (0.532; 0.574)***	0.575 (0.552; 0.598)***
Cumulative SEP -> Own education	0.858 (0.847; 0.869)***	0.844 (0.831; 0.858)***
Cumulative SEP -> ln (income)	0.715 (0.699; 0.730)***	0.634 (0.613; 0.654)***
Cumulative SEP -> Social class of current occupation	0.866 (0.855; 0.876)***	0.838 (0.824; 0.851)***
Strutural Model, standardized coefficients (95%CI)[3]		
Total Effect		
Cumulative SEP-> ln(CRP)	-0.134 (-0.163; -0.106)***	-0.155 (-0.186; -0.125)***
Direct Effects		
Cumulative SEP -> ln(CRP)	-0.085 (-0.113; -0.056)***	-0.069 (-0.099; -0.039)***
Risk Behavior -> ln(CRP)	0.088 (0.060; 0.115)***	0.043 (0.016; 0.070)***
Metabolic Alterations -> ln(CRP)	**0.256 (0.230; 0.282)*** **	**0.378 (0.353; 0.404)*** **
Indirect Effects		
Cumulative SEP-> Risk Behavior -> ln(CRP)	-0.018 (-0.024;- 0.012)***	-0.007 (-0.011; -0.002)**
Cumulative SEP -> Metabolic Alterations -> ln(CRP)	**-0.027 (-0.035; -0.019)*** **	**-0.077 (-0.090; -0.064)*** **
Cumulative SEP-> Risk Behavior-> Metabolic Alterations-> ln(CRP)	-0.004 (-0.006; -0.003)***	-0.002 (-0.004; -0.001)*
Total indirect effects: Cumulative SEP -> ln(CRP)	**-0.049 (-0.059; -0.040)*** **	**-0.086 (-0.099; -0.073)*** **
Log CRP R^2	0.095	0.164
Proportion of the effect of Cumulative SEP on ln(CRP) that was:		
Mediated by Risk Behavior	13.43%	4.44%
Mediated by Metabolic Alterations	20.16%	49.51%
Mediated by Risk Behavior and Metabolic Alteration simultaneously	3.22%	1.47%
Total indirect effect	36.81%	55.43%
Direct effect	63.19%	44.57%
Model fit[4]		
CFI	0.981	0.989
RMSEA	0.049	0.035
SRMR	0.020	0.015

[1]Of the 6,654 men participants, 5128 (77.1%) had complete data available on all covariates used in the structural equation model.

[2]Of the 6,717 women participants, 4534 (67.5%) had complete data available on all covariates used in the structural equation model

[3]The significance levels shown here are for the standardized solution (*p < 0.05, **p < 0.01, ***p < 0.001). The absence of overlap in the 95%CI was interpreted as evidence of a significant gender difference in a given path ("bolded" in the table).

[4]CFI: comparative fit index. RMSEA: root mean square error of approximation. SRMR: standardized root mean squared residual.

ARTIGO ORIGINAL 2

5 ARTIGO ORIGINAL 2

Title: Associations of Life Course Socioeconomic Position and Job Stress with Subclinical Atherosclerosis. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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ABSTRACT

Using baseline data of 8,830 current workers from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), we examined whether life course socioeconomic position (SEP) is associated with carotid intima-media thickness (IMT), and we investigated whether this association is partially mediated by job stress. Directed acyclic graph, and linear regression models were used. Maternal education was not associated with IMT in men, but low *versus* high maternal education was associated with an increase in IMT in the order of 0.022mm ($p<0.01$) in women. Compared with participants with high education attainment, men and women with low education presented 0.058mm ($p<0.001$) and 0.034mm ($p<0.01$) of increase in IMT, respectively. Low *versus* high current social class was associated with greater IMT in the order of 0.035mm ($p<0.001$) in men and 0.038mm ($p<0.001$) in women. IMT was also associated with accumulation of exposures to social adversities across the life course in both genders. Job stress did not substantially explained the association between low life course SEP and increasing IMT, since job strain and low job control were not associated with IMT independently of SEP in men, and in women the passive work and low control only slightly attenuated the association between IMT and all SEP indicators.

Keywords: Life course, health inequities, socioeconomic position, atherosclerosis, IMT, job stress, job strain, cardiovascular disease, mediation, ELSA-Brasil.

INTRODUCTION

Socioeconomic position (SEP) is robustly inversely associated with cardiovascular disease (CVD)[1]. Evidence is also accumulating for an important role of SEP in promoting early manifestations of subclinical atherosclerosis[2-7], suggesting a possible mechanism connecting SEP and CVD. For the most part, previous studies have used only current measures of SEP, which may not provide a complete picture of the social patterning of subclinical atherosclerosis, since it is known that the atherosclerosis begins even in childhood[8,9].

The few studies that investigated the association between exposures to social adversities in childhood and subclinical atherosclerosis have been inconsistent. Lower parental SEP was associated with subclinical atherosclerosis in some studies[10], but not in others[11,12]. In addition, some researchers found an association only among women[13,14]. There is also evidence that cumulative socioeconomic disadvantage across the life course can promote subclinical atherosclerosis[15], but in some studies this association was found only among men[12] or only among women[13].

Potential mechanisms for the life course SEP gradient in subclinical atherosclerosis have not been extensively explored. Health-related behaviors and proximal risk factors for cardiovascular disease, such as diabetes, hypertension and obesity, potentially mediate the association between life course SEP and subclinical atherosclerosis[10,14,15]. However, in some studies the gradient remained after the adjustment for those variables[10,12-15], suggesting that additional pathways(e.g. stress) might play a role.

In 1997, using data from the Whitehall II study, Marmot and colleagues reported that job control explained about 64%, among men, and 51%, among women, of the excess risk for coronary heart disease across occupational grades in the British civil service cohort[16]. However, other studies in developed countries that sought to replicate the Whitehall findings found only a small contribution of job stress to the socioeconomic gradient in cardiovascular disease[17-23]. To our knowledge, there has not been a previous study which attempted to replicate the Whitehall findings using subclinical CVD as the outcome (which is less susceptible to reverse causality). In addition, few studies used data from an occupation cohort as in Whitehall[16]. Moreover, little is known about the potential role of job stress in explaining the social gradient in cardiovascular risk in middle income countries. Finally, while previous studies have evaluated the contribution of job stress in explaining socioeconomic inequalities

in CVD based on current SEP[16-23], so far research has not addressed whether life-course SEP gradients in CVD could be explained by job stress.

Accordingly, using data from the baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), a multicenter prospective cohort study of civil servants, we examined whether life course SEP was related to subclinical atherosclerosis, assessed by carotid intima-media thickness (IMT). In addition, we tested the hypothesis that job stress can partially account for the life course socioeconomic gradient on IMT, as well as explored the possible modifying influence of gender.

METHODS

Data source and study population

This study used data of current workers who undertook Carotid IMT and the job stress scale in the baseline of ELSA-Brasil, which design was previously described [24,25]. Briefly, 15,105 civil servants (comprising 12,096 current workers and 3009 retired workers), aged between 35 and 74, were enrolled from universities and research institutes in six Brazilian states. The baseline examination (2008–2010) included face-to-face interview, clinical, laboratory and anthropometric examinations[26-28].

Study Variables

Carotid IMT

The ultrasound protocol to measure carotid IMT in the ELSA-Brasil study was described previously[28] and it follows the Mannheim carotid intima-media thickness and plaque consensus procedures[29]. Images of the common carotid artery were acquired within a region free of plaque in the outer wall of a pre-defined carotid segment of 1 cm in length from 1 cm below the carotid bifurcation, during three cardiac cycles, using a device (Aplio XG(tm), Toshiba) with a 7.5 MHz linear transducer. The measures were summarized as: the minimum, maximum, and mean values of each common carotid artery (right and left). In this analysis, the IMT was defined as the mean of the right and left mean values (mean-mean)[30].

Job stress

Job stress was evaluated using the 17-item Brazilian version[31] of the Swedish Demand-Control-Support Questionnaire (DCSQ)[32], and it was described previously[34]. The

psychological demands (5 items) and the control (6 items) subscales were answered and scored on a 4-point Likert-scale, ranging from 1(often) to 4 (never/almost never). The responses to each item were summed, with higher scores in the psychological demands (range from 5 to 20 points) and in the control subscales (range from 6 to 24 points) indicating higher levels of demand and control. The scores of participants who had missing value in some component of the subscales were computed based on the complete answers to the other items. To define job strain following the Karasek's model, both scales were dichotomized (high vs. low) at its gender specific median. Thus, the participants were classified in four mutually exclusive groups to express the relationship between job demand and job control: low-strain work (low demand/high control), passive work (low demand/low control), active work (high demand/high control), and high-strain work (high demand/low control)[33]. Job demand and job control were also analyzed separately, categorized according to gender specific tertiles.

Life course SEP indicators

Childhood SEP was assessed by maternal education, divided into four groups: ≥ 11, 8-10, 1-7, 0 years of study. *Young adulthood SEP* was measured by participant's own educational attainment (≥ 15, 11-14, 8-10, 0-7 years of study). *Adulthood SEP* was evaluated by social class (high, middle, low), a summary measure which considers the relationship schooling-income by comparing the expected income based on the educational level required by the job and the observed income prevailing in the labor market[35].

A cumulative SEP score was calculated with values ranging between zero to eight (higher values reflecting worse life course SEP), and including maternal education (≥ 11 years of study =0; 8-10 years of study=1; 1-7 years of study=2; 0 years of study=3), participant's own education (≥ 15 years of study =0; 11-14 years of study=1; 8-10 years of study=2; 0-7 years of study=3), and social class (high =0; middle =1; low=2).

A variable to express educational trajectories from childhood to early adulthood (education social mobility) was created, based on combining maternal education and the participant's own education attainment. For the purposes of deriving this variable, maternal education was dichotomized as high (≥ 8 years of study) vs. low (<8 years of study), as the participant's own education attainment (high ≥ 15 years vs. low<15 years). Consequently, four socioeconomic trajectories were possible: "stable high" (high childhood and high early adulthood education), "increasing" (low childhood and high early adulthood education), "decreasing" (high

childhood and low early adulthood education), and "stable low" (low childhood and low early adulthood education).

Other sociodemographic variables

Three demographic characteristics were assessed as covariates: gender, age, and self-reported race (White, Brown, Black, Asian descent, and Brazilian indigenous).

Data Analyses

All analyses were conducted separately for men and women to explore the possible modifying influence of gender. We generated descriptive characteristics of the analytic sample and the prevalence of job strain, low control and high demand according to the level of life course SEP. Chi-square tests were performed on group differences.

We constructed a directed acyclic graph (DAG) of proposed associations between life course socioeconomic position and subclinical atherosclerosis (IMT) in adulthood to guide our analyses (Figure 1). Following this DAG, to investigate the mediating role of job strain on the association between life course SEP and IMT, we cannot condition on health-related behaviors or markers of metabolic, endocrine and immune dysregulation, since all of these variables are colliders (i.e. their inclusion in the regression would induce bias).

Linear regression models were performed with IMT as the outcome of interest. Firstly, we assessed the association between job strain, job demand, job control and IMT adjusted by age. Secondly, we performed regression models with IMT as the response variable and each of the SEP indicators separately as the independent variables, adjusting only for age and self-reported race. Finally, we added in these models the job characteristics that were statistically associated with IMT and were also associated with SEP (according to chi-square tests) to evaluate the mediation role of these variables.

All analyses were conducted using the software Stata 12.0 (Stata Corporation, College Station, United States).

Ethics

The study was approved by the Research and Ethics Committees of the institutions involved: Universidade de São Paulo, Universidade Federal de Minas Gerais, Fundação Oswaldo Cruz,

Universidade Federal do Espírito Santo, Universidade Federal da Bahia, Universidade Federal do Rio Grande do Sul.

RESULTS

Of the 12,096 current workers in ELSA-Brasil, 8,830 (73%) underwent IMT measurements and had adequate image quality (4,088 men and 4,742 women) and were included in this analyses. 54.6 percent of participants were White, with mean age of 49 years (range 35 – 72 years). The distributions of the life course SEP indicators in the analytical sample, stratified by gender, are presented in Table 1. Overall, more than 50% of the participants' mothers had less than eight years of schooling, but their own education attainment was high, and over 48% among men and 55% among women had $\geq$ 15 years of schooling. About one third of male and one quarter of female participants were classified as of high social class. The prevalence of low cumulative SEP was almost twice as high among men compared to women. Most participants reported trajectories of "stable low" education social mobility, followed by "stable high", then "increasing", and a minority exhibited a "decreasing" trajectory (Table 1).

The prevalence of high job strain was 21.2% in both genders. Passive work was more common among women (35.8%) than among men (30.4%). By contrast, active work was more prevalent in men (24.2%) than in women (19.3%). Low strain work was comparable in women (23.8%) and men (24.2%). Overall, lower SEP was associated with higher prevalence of passive work, high strain, and low job control. On the other hand, higher prevalence of low strain, active work and high demand was found in individuals with higher SEP (Table 1)

The mean of IMT (SD) was 0.921mm (SD: 0.204) and 0.858mm (SD: 0.167) among men and women, respectively. In both genders, IMT was strongly associated with age and increased by 0.011mm (CI 95%: 0.010-0.012) for each additional year of life.

Independently of age, workers in high strain jobs had higher IMT (β=0.032; 95%CI: 0.015; 0.049 among men, and β=0.022; 95%CI: 0.009; 0.034 among women) compared with low strain jobs. Workers engaged in passive work also had higher IMT (β=0.018; 95%CI: 0.002; 0.034, and β=0.029; 95%CI: 0.018; 0.040, for men and women, respectively) compared with low strain jobs. Low job control was associated with higher IMT in both men (β=0.021; 95%CI: 0.006; 0.036) and women (β=0.029; 95%CI: 0.019; 0.039) compared with high

control jobs. However, in both genders high job demand was not associated with an increase in IMT.

Low maternal education was not associated with higher IMT among men (Table 2), but it was among women (Table 3). Lower participants' own education and lower social class were associated with higher IMT in both genders (Table 2 and Table 3). For instance, participants with ≤ 7 years of schooling, compared with participants with ≥15 years of schooling, had an increase in IMT of 0.058mm among men (Table 2) and 0.034mm among women (Table 3).

We found evidence for increased IMT according to increasing levels of exposure to unfavorable social circumstances over the life course, especially among women. For instance, participants with cumulative SEP score between 6 and 8 (reflecting worse life course SEP) had 0.025mm and 0.044mm higher IMT in men and women, respectively, compared with participants with cumulative SEP score between 0 and 1 (reflecting higher life course SEP) (Tables 4 and 5). Among men, participants who presented "decreasing" and "stable low" education social mobility also presented higher IMT in adulthood compared to participants with the "stable high" trajectory (Table 4), but among women only the "stable low" trajectory was associated with higher IMT (Table 5).

Among men, the association between each SEP indicator and IMT practically did not change after adjustment for job strain or job control, and job characteristics did not remain significantly associated with IMT after adjustment for social class or educational social mobility (Table 2 and 4). However, among women the association between each SEP indicator and IMT were slightly attenuated and passive work and low job control remained associated with IMT after statistical adjustment for SEP (Tables 3 and 5).

DISCUSSION

Exposure to social disadvantage in young adulthood and in adulthood was consistently associated with higher IMT in both genders. However, childhood SEP was associated with increased IMT only among women. In both genders, the higher cumulative exposure to social adversities across the life course as well as being in a "stable low" educational trajectory were also associated with higher IMT, providing support for a model of cumulative effects of exposures to SEP across the life span. Although job strain and low job control were associated with higher IMT and low SEP across the life course, both measures of job stress failed to

substantially explain the increase in IMT among participants with social disadvantage over the life span.

The biggest differences in IMT were found when participants' own education and social class were used as indicators of SEP among men and women, respectively. Using these indicators, the difference between high *versus* low SEP were in the order of 0.058 mm for men and 0.038 mm for women. Although the magnitude of this difference may seem modest, it is equivalent to a change in IMT occurring in almost 6 additional years of age for men and 4 additional years for women in the same cohort. In addition, a prior meta-analysis pointed out that for each increase of 0.1mm of IMT, the risk for myocardial infarction increases by 15%, while the risk of stroke increases by 18% [36].

In both genders social disadvantage in young adulthood as well as in adulthood were consistently associated with higher IMT. However, childhood SEP was associated with IMT only among women. The analysis of educational trajectories was consistent with these results and suggests a synergistic effect between low childhood SEP and low young adulthood SEP only among women, since women who presented a "stable low" educational trajectory exhibited higher IMT scores than women with "decreasing" trajectories. However, among men the "stable low" and "decreasing" educational trajectories were associated with roughly the same decrease in IMT. Previous studies have also documented a gender difference with regard the association between childhood SEP and IMT[10,13,14]. In the general Swedish population[13] as well as in the Newcastle Thousand Families birth cohort[10], the association between childhood SEP and IMT was also found only among women. However, in contrast to our findings, Rosvall et al (2002)[13] did not find evidence of a synergic effect of exposure to low SEP in childhood and adulthood among women, and a social gradient using a cumulative SEP score was not found among men. In the Multi-Ethnic Study of Atherosclerosis (MESA), the researchers found that childhood SEP and adulthood SEP were independently associated with IMT in adulthood in both genders. However, the association between childhood SEP was stronger among women[14]. The explanation for the gender difference in the association between early life-course SEP and IMT remains unclear. It may be due to gender differences in the interaction, articulation and simultaneity of socioeconomic disadvantages and adversity experienced by men and women early in their life course[37]. Also, childhood SEP has been found to be more strongly associated with age at natural menopause than adult position[38], and early menopause appear to be associated with increased IMT and other markers of

atherosclerosis[39,40]. It may be also due to gender differences in entry into study populations (e.g. high risk men are less likely to participate in studies). Moreover, it is known that men have higher mortality than females at every age in most countries[41] and early life socioeconomic measures are associated with mortality[42]. Thus, it is possible that men exposed to low maternal education have higher risk to die before they have opportunity to enter in the study than women with the same exposure. If so, we can be underestimating the magnitude of the associations between maternal education and IMT levels in men.

Among men, adjustment for job characteristics did not materially affect the association between SEP indicators and IMT, and job characteristics were not independently associated with IMT. These results suggest that neither job strain nor job control is sufficient to explain the social gradient on IMT in men, since mediators must be independently associated with the outcome[43]. In addition, although we found that passive work and low job control were associated with an increased IMT independently of SEP in women, the adjustment for job characteristics only slightly reduced the association between IMT and all SEP indicators in women. Our results depart from those reported in the Whitehall II study, where they found that job control explained between 51% and 64% of the occupational gradient in coronary heart disease (CHD) among women and men, respectively[16]. The prevalence of low job control in low *versus* high occupational grades in Whitehall II was respectively 77.9% and 8.7%, among men, and 75.3% and 10.1%, among women. In ELSA-Brasil the corresponding prevalence ranged from 60.4% and 8.8%, among men, and 70.7% and 11.6%, among women. Thus, although men in low occupation grades in Whitehall had a higher prevalence of low job control than participants in ELSA-Brasil, probably this difference is not enough to explain the discrepant results between the two studies. However, we used subclinical atherosclerosis as the outcome, while in the Whitehall it was used self-reported coronary heart disease, and in consequence our results are less susceptible to reverse causality[44]. Studies which have used incidence and/or mortality by myocardial infarction as outcome also failed to demonstrate that job stress acts as a mediator of the association between SEP and CVD[17,18,21,23]. For cerebrovascular disease, the mediating role of job characteristics is even less clear; for example, among women in the Finnish Public Sector Study, the social gradient in the incidence of cerebrovascular events increased after considering the role of job control and job demand[45] while in the Women's Lifestyle and Health cohort job strain was unrelated to stroke risk[22]. Besides the Whitehall II study, there are also some studies which identified some mediator role of job stress, however the percent reduction in the socioeconomic gradient in

the incidence of CVD attributable to job control or job strain is small and ranged between 9-21% [18-20]. It is important to note that there are many sources of heterogeneity among all these studies that difficult the comparisons, such as differences in scales used to measure job stress, in indicators of SEP applied, in measures of CVD, and in prevalence of job stress. All these differences raise the difficulties in performing research applying individual-participant data meta-analysis approach that would be useful to clarify this kind of question, as well as other questions in social epidemiology, as suggested previously by Kivimaki & Kawachi[46].

There were some limitations to the study. We did not exclude participants with prevalent CVD from this analysis to avoid reverse causality with regard adulthood SEP and IMT, since doing that the association between childhood SEP and IMT could be underestimated. However, we repeated the same analyses after excluding participants with prevalent CVD (self-reported medical history of acute myocardial infarction, angina, myocardial revascularization, heart failure, and stroke) and this exclusion did not materially alter our conclusions. Moreover, the use of subclinical outcomes, such as IMT, minimizes the possibility of reverse causality[44]. The ELSA-Brasil participants are all employed in the civil service with higher average education and income levels compared to the rest of the population of Brazil. Thus, people who experienced extreme social difficulties in childhood as well as in adulthood could not be represented in this study. The truncated variability in SEP may have led us to underestimate the magnitude of the associations between life course SEP and IMT levels.

Our study demonstrated that the exposures to social adversities in young adulthood and in adulthood SEP were consistently associated with higher IMT in both genders, but that childhood SEP seems to play a role only among women. We did not find that job stress (defined as low job control or job strain) explained the association between low SEP and higher IMT, suggesting that strategies to address socioeconomic inequalities in CVD should target additional steps besides reducing job stress. Others sources of psychosocial stress, which were not included in the present analysis, such as crowding, growing up in poor neighborhoods, discrimination, and experiences of childhood trauma and abuse might be important to explain health inequalities in CVD in the cohort of ELSA-Brasil.

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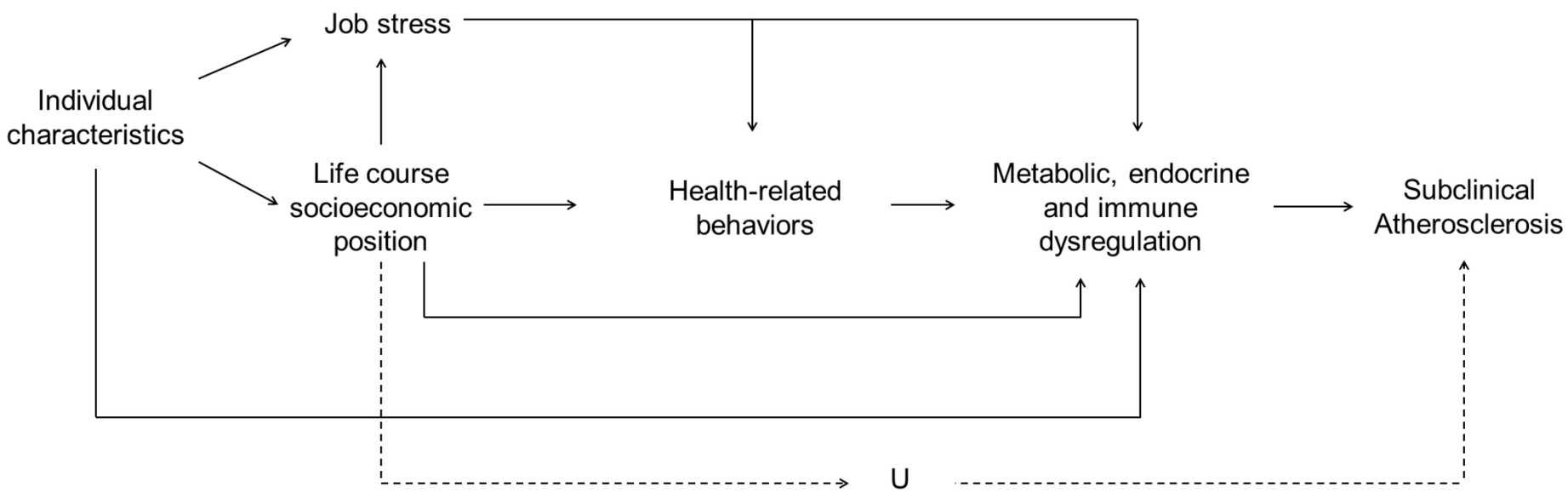
FIGURES AND TABLES

Figure 1– Directed acyclic graph (DAG) showing the association between life course socioeconomic position and subclinical atherosclerosis in adulthood.



Note: U, unknown or unmeasured variables. Individual characteristics consist of sex, age and race/color.

Table 1 – Gender specific distribution of SEP indicators and the prevalence of job strain by Karasek's model, low control and high demand in the analytical sample from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

Characteristics	Men (N=4,088)							Women (N=4,742)						
	N (%)	Job strain by Karasek's model				Low control (%)	High demand (%)	N (%)	Job strain by Karasek's model				Low control (%)	High demand (%)
		Low strain (%)	Passive (%)	Active (%)	High strain (%)				Low strain (%)	Passive (%)	Active (%)	High strain (%)		
Maternal Education (years of study), (N=8,659)														
≥11	993 (24.8)	34.4	15.4	37.1	13.1	19.7	38.0	1,057 (22.7)	34.8	21.8	29.4	14.1	25.0	29.8
8-10	775 (19.4)	24.4	26.9	28.7	20.0	33.3	35.8	923 (19.8)	25.6	32.1	20.6	21.8	39.5	28.4
1-7	1,655 (41.4)	21.0	35.3	18.7	24.9	45.9	30.1	2,085 (44.7)	20.7	39.4	16.8	23.2	49.1	26.3
0	574 (14.4)	15.7	45.7	13.1	25.5	56.2	26.5	597 (12.8)	13.5	51.6	9.8	25.0	65.1	20.8
P-value			*P* < 0.001			*P* < 0.001	*P* < 0.001			*P* < 0.001			*P* < 0.001	*P* < 0.001
Own education (years of study), (N=8,830)														
≥15	1,953 (47.8)	34.1	16.2	37.6	12.2	18.0	37.0	2,617 (55.2)	32.0	23.7	27.9	16.4	27.6	30.8
11-14	1,495 (36.6)	15.5	39.9	13.0	31.6	55.3	30.9	1,758 (37.1)	15.1	48.8	8.9	27.3	61.9	22.0
8-10	334 (8.2)	15.6	48.1	10.8	25.5	59.8	24.0	223 (4.7)	6.3	60.8	6.8	26.1	77.5	18.9
0-7	306 (7.5)	12.9	56.1	7.6	23.4	68.7	20.5	144 (3.0)	6.3	60.6	8.5	24.7	77.5	19.6
P-value			*P* < 0.001			*P* < 0.001	*P* < 0.001			*P* < 0.001			*P* < 0.001	*P* < 0.001
Social Class (N=8,475)														
High	1,303 (32.8)	38.5	9.2	44.5	7.9	8.9	40.3	1,169 (26.0)	39.8	10.1	40.0	10.0	11.6	34.7
Middle	1,437 (36.2)	19.7	36.6	16.8	26.9	47.6	30.0	2,416 (53.7)	20.6	42.0	14.3	23.1	50.6	24.2
Low	1,234 (31.1)	14.8	46.6	10.8	27.8	60.4	26.2	916 (20.4)	10.3	54.9	6.0	28.8	70.7	21.2
P-value			*P* < 0.001			*P* < 0.001	*P* < 0.001			*P* < 0.001			*P* < 0.001	*P* < 0.001
Cumulative SEP, (N=8,310)														
0-1 (highest SEP)	1,037 (26.7)	38.0	11.5	43.1	7.4	10.9	38.7	1,092 (24.7)	39.1	15.9	34.2	10.9	17.5	30.8
2-3	1,128 (29.1)	26.8	24.7	27.1	21.4	32.7	35.3	1,586 (35.8)	24.4	33.2	21.5	21.0	39.6	29.5
4-5	1,118 (28.8)	15.1	42.6	11.6	30.8	56.2	28.8	1,355 (30.6)	15.5	48.1	9.3	27.2	61.4	21.4
6-8 (lowest SEP)	600 (15.5)	13.7	51.8	10.0	24.4	63.9	22.6	394 (8.9)	6.4	61.3	6.2	26.2	77.2	19.4
P-value			*P* < 0.001			*P* < 0.001	*P* < 0.001			*P* < 0.001			*P* < 0.001	*P* < 0.001
Education Social Mobility, (N=8,659)														
High stable	1,239 (31.0)	35.4	14.3	41.0	9.3	14.4	37.9	1,462 (31.4)	35.8	19.5	30.6	14.1	22.5	30.8
Increasing	702 (17.6)	31.6	19.6	31.4	17.4	24.6	35.4	1,142 (24.5)	27.3	28.9	24.5	19.3	34.3	30.9
Decreasing	529 (13.2)	17.6	34.7	15.5	32.2	52.1	34.9	518 (11.1)	15.5	46.6	10.3	27.7	58.0	24.4
Low stable	1,527 (38.2)	14.2	46.5	10.8	28.6	59.6	26.3	1,540 (33.0)	13.1	51.9	8.3	26.8	66.3	20.8
P-value			*P* < 0.001			*P* < 0.001	*P* < 0.001			*P* < 0.001			*P* < 0.001	*P* < 0.001

Table 2 - Multivariable regression analyzes demonstrating association between SEP in different stages of life and IMT, and the mediation role of job strain and job control among men. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

	Age and color		Maternal Education				Own Education				Occupational Social Class			
			Age, color and job strain by Karasek model		Age, color and job control		Age, color and job strain by Karasek model		Age, color and job control		Age, color and job strain by Karasek model		Age, color and job control	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Maternal education (years of study)														
≥11	Ref		Ref		Ref									
8-10	-0.003	-0.021, 0.014	-0.006	-0.024, 0.012	-0.005	-0.023, 0.013								
1-7	0.003	-0.012, 0.018	-0.001	-0.017, 0.014	0.001	-0.016, 0.015								
0	-0.008	-0.028, 0.012	-0.013	-0.034, 0.008	-0.012	-0.033, 0.009								
Own education (years of study)														
≥15	Ref						Ref		Ref					
11-14	0.024	0.011, 0.038***					0.022	0.008, 0.037**	0.025	0.011, 0.039**				
8-10	0.015	-0.008, 0.037					0.013	-0.009, 0.036	0.015	-0.008, 0.038				
0-7	0.058	0.035, 0.082***					0.058	0.034, 0.082***	0.059	0.035, 0.084***				
Social Class														
High	Ref										Ref		Ref	
Middle	0.027	0.012, 0.042***									0.025	0.009, 0.041**	0.028	0.012, 0.045**
Low	0.035	0.020, 0.051***									0.033	0.016, 0.050***	0.036	0.018, 0.053***
Job strain by Karasek's model														
Low strain			Ref				Ref				Ref			
Passive			0.012	-0.004, 0.028			0.001	-0.016, 0.017			0.002	-0.015, 0.019		
Active			0.005	-0.011, 0.022			0.008	-0.009, 0.024			0.008	-0.009, 0.025		
High strain			0.027	0.009, 0.045**			0.018	0.001, 0.036*			0.018	-0.001, 0.036		
Job control														
3rd tertile (high control)					Ref				Ref				Ref	
2nd tertile					0.003	-0.012, 0.019			-0.005	-0.020, 0.011			-0.007	-0.023, 0.010
1st tertile (low control)					0.013	-0.003, 0.030			-0.004	-0.021, 0.013			-0.003	-0.021, 0.015

Notes: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Table 3 - Multivariable regression analyzes demonstrating association between SEP in different stages of life and IMT, and the mediation role of job strain and job control among women. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

	Age and color		Maternal Education				Own Education				Own Education			
			Age, color and job strain by Karasek model		Age, color and job control		Age, color and job strain by Karasek model		Age, color and job control		Age, color and job strain by Karasek model		Age, color and job control	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Maternal education (years of study)														
≥11	Ref		ref		Ref									
8-10	0.004	-0.008, 0.017	0.002	-0.011, 0.015	0.002	-0.011, 0.015								
1-7	0.003	-0.008, 0.014	-0.001	-0.012, 0.011	-0.001	-0.012, 0.010								
0	0.022	0.007, 0.037**	0.017	0.001, 0.032*	0.016	0.001, 0.032*								
Own education (years of study)														
≥15	Ref						Ref		Ref					
11-14	0.023	0.014, 0.032***					0.020	0.010, 0.030***	0.019	0.010, 0.029***				
8-10	0.047	0.026, 0.067***					0.044	0.023, 0.065***	0.043	0.022, 0.064***				
0-7	0.034	0.009, 0.059**					0.028	0.003, 0.054*	0.028	0.002, 0.053*				
Social Class														
High	Ref										Ref		Ref	
Middle	0.021	0.011, 0.031***									0.018	0.006, 0.029**	0.016	0.005, 0.028**
Low	0.038	0.025, 0.051***									0.033	0.019, 0.048***	0.031	0.017, 0.046***
Job strain by Karasek's model														
Low strain			Ref				Ref				Ref			
Passive			0.021	0.009, 0.032***			0.014	0.003, 0.026*			0.017	(0.005; 0.029)**		
Active			0.007	-0.006, 0.020			0.008	-0.004, 0.021			0.012	(-0.001; 0.025)		
High strain			0.012	-0.001, 0.024			0.007	-0.006, 0.020			0.008	(-0.005; 0.022)		
Job control														
3rd tertile (high control)					Ref				Ref				Ref	
2nd tertiles					0.007	-0.005, 0.018			0.003	-0.008, 0.015			0.006	-0.006, 0.018
1st tertile (low control)					0.018	0.007, 0.028**			0.010	-0.001, 0.021			0.013	0.001, 0.024*

Notes: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Table 4 - Multivariable regression analyzes demonstrating association between life course SEP and IMT, and the mediation role of job strain and job control among men Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

	Age and color		Cumulative SEP				Education Social Mobility			
			Age, color and job strain by Karasek model		Age, color and job control		Age, color and job strain by Karasek model		Age, color and job control	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Cumulative SEP										
0-1 (highest SEP)	Ref		Ref		Ref					
2-3	-0.002	-0.018, 0.014	-0.005	-0.021, 0.012	-0.003	-0.020, 0.013				
4-5	0.021	0.005, 0.038*	0.016	-0.002, 0.034	0.018	0.001; 0.037*				
6-8 (lowest SEP)	0.025	0.005, 0.045*	0.021	-0.001, 0.042	0.022	0.001; 0.044*				
Education Social Mobility										
Stable high	Ref						Ref		Ref	
Increasing	-0.014	-0.031, 0.004					-0.015	-0.032, 0.003	-0.014	-0.031, 0.004
Decreasing	0.024	0.005, 0.043*					0.021	0.001, 0.041*	0.024	0.004, 0.044*
Stable low	0.022	0.007, 0.037**					0.020	0.004, 0.036*	0.022	0.006, 0.039**
Job strain by Karasek's model										
Low strain			Ref				Ref			
Passive			0.006	-0.011, 0.023			0.002	-0.015, 0.019		
Active			0.006	-0.011, 0.023			0.007	-0.010, 0.023		
High strain			0.021	0.003, 0.040*			0.018	-0.001, 0.036		
Job control										
3rd tertile (high control)					Ref				Ref	
2nd tertile					-0.001	-0.017, 0.015			-0.004	-0.019, 0.012
1st tertile (low control)					0.005	-0.012, 0.023			-0.002	-0.019, 0.016

Notes: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Table 5 - Multivariable regression analyzes demonstrating association between life course SEP and IMT, and the mediation role of job strain and job control among women. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010.

			Cumulative SEP				Education Social Mobility			
	Age and color		Age, color and job strain by Karasek model		Age, color and job control		Age, color and job strain by Karasek model		Age, color and job control	
	β	95%IC	β	95%IC	β	95%IC	β	95%IC	β	95%IC
Cumulative SEP										
0-1 (highest SEP)	Ref		Ref		Ref					
2-3	0.003	-0.008, 0.015	0.001	-0.011, 0.012	-0.001	-0.012, 0.011				
4-5	0.020	0.008, 0.032**	0.015	0.003, 0.028*	0.014	0.001, 0.027*				
6-8 (lowest SEP)	0.044	0.026, 0.061***	0.037	0.019, 0.056***	0.036	0.017, 0.054**				
Education Social Mobility										
Stable high	Ref						Ref		Ref	
Increasing	-0.009	-0.021, 0.002					-0.011	-0.022, 0.001	-0.011	-0.022, 0.001
Decreasing	0.013	-0.001, 0.028					0.009	-0.006, 0.025	0.009	-0.006, 0.024
Stable low	0.023	0.013, 0.034***					0.019	0.008, 0.031**	0.019	0.007, 0.030**
Job strain by Karasek's model										
Low strain			Ref				Ref			
Passive			0.018	0.006, 0.030**			0.015	0.004, 0.027*		
Active			0.010	-0.003, 0.023			0.008	-0.005, 0.021		
High strain			0.010	-0.004, 0.023			0.008	-0.005, 0.020		
Job control										
3rd tertile (high control)					Ref				ref	
2nd tertile					0.008	-0.004, 0.020			0.004	-0.007, 0.016
1st tertile (low control)					0.015	0.003, 0.026*			0.012	0.001, 0.023*

Notes: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

CONSIDERAÇÕES FINAIS

6 CONSIDERAÇÕES FINAIS

Nesta tese encontramos que a exposição à baixa posição socioeconômica ao longo da vida foi associada a maiores níveis de um marcador biológico de inflamação crônica (PCR) e de aterosclerose subclínica (IMT) no contexto brasileiro. Além disso, demostramos que o efeito dessa exposição é acumulativo e quanto maior a exposição às adversidades sociais ao longo da vida, pior é a saúde cardiovascular. Esses achados sugerem que intervenções sociais realizadas em uma única etapa da vida podem ser insuficientes para lidar com as desigualdades em saúde. Além disso, esses resultados contribuem para o estabelecimento de causalidade e afastar a ideia de que a associação entre as adversidades sociais e a saúde cardiovascular é atribuída à causalidade reversa, já que utilizamos como desfecho cardiovascular um marcador biológico para DCV e a uma DCV subclínica. Dessa forma, seria improvável que alterações biológicas ainda sem sintomas e sinais clínicos fossem influenciar a posição socioeconômica em um sentido descendente. Esses achados são importantes porque ainda é grande a discussão sobre a causalidade reversa no campo da epidemiologia social.

Apesar da epidemiologia social se preocupar predominantemente com a identificação de fatores estruturais e macrodeterminantes da saúde das populações, a identificação de mecanismos que conectam as adversidades sociais a uma pior saúde é importante para guiar e motivar intervenções, com vistas a quebrar esse *link* de conexão. Nesta tese, também encontramos que apesar dos comportamentos de risco à saúde e as alterações metabólicas explicarem 37% do efeito da posição social cumulativa na PCR nos homens e 55% entre as mulheres, uma expressiva parcela da associação entre a posição social ao longo da vida e a PCR e não foi mediada por esses fatores. Isso sugere que outros mecanismos podem estar envolvidos na mediação dessa associação, como sugerido pela perspectiva psicossocial. Entretanto, encontramos que apesar do estresse no trabalho ser associado a piores condições sociais ao longo da vida esse fator não mediou à associação entre posição socioeconômica ao longo da vida e o IMT. Esses achados sugerem que intervenções que promovam uma diminuição no estresse no trabalho não irão impactar nas desigualdades sociais em saúde cardiovascular. Outras fontes de estresse não avaliadas nesta tese (como viver em vizinhanças em desvantagem social, percepção de privação relativa, experiências de discriminação, traumas/abuso e crescer e viver em ambientes superlotados) podem ser aspectos importantes para explicar as desigualdades sociais em saúde nas populações. Além dessas fontes de estresse, alterações epigenéticas também podem explicar uma parcela da associação entre

posição social e a saúde cardiovascular. Essas questões poderão ser avaliadas no contexto brasileiro no futuro com resultados da coorte do ELSA-Brasil.

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Life Course Socioeconomic Position and C-Reactive Protein: Mediating Role of Health-Risk Behaviors and Metabolic Alterations. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Abstract

Background: Chronic inflammation has been postulated to be one mediating mechanism explaining the association between low socioeconomic position (SEP) and cardiovascular disease (CVD). We sought to examine the association between life course SEP and C-reactive protein (CRP) levels in adulthood, and to evaluate the extent to which health-risk behaviors and metabolic alterations mediate this association. Additionally, we explored the possible modifying influence of gender.

Methods and Findings: Our analytical sample comprised 13,371 participants from ELSA-Brasil baseline, a multicenter prospective cohort study of civil servants. SEP during childhood, young adulthood, and adulthood were considered. The potential mediators between life course SEP and CRP included clusters of health-risk behaviors (smoking, low leisure time physical activity, excessive alcohol consumption), and metabolic alterations (obesity, hypertension, low HDL, hypertriglyceridemia, and diabetes). Linear regression models were performed and structural equation modeling was used to evaluate mediation. Although lower childhood SEP was associated with higher levels of CRP in adult life, this association was not independent of adulthood SEP. However, CRP increased linearly with increasing number of unfavorable social circumstances during the life course (p trend <0.001). The metabolic alterations were the most important mediator between cumulative SEP and CRP. This mediation path accounted for 49.5% of the total effect of cumulative SEP on CRP among women, but only 20.2% among men. In consequence, the portion of the total effect of cumulative SEP on CRP that was mediated by risk behaviors and metabolic alterations was higher among women (55.4%) than among men (36.8%).

Conclusions: Cumulative SEP across life span was associated with elevated systemic inflammation in adulthood. Although health-risk behaviors and metabolic alterations were important mediators of this association, a sizable fraction of this association was not mediated by these factors, suggesting that other pathways might play a role, especially among men.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. The data used in this study is available for research proposal on request to the ELSA's Datacenter and to the ELSA's Publications Committee (publiELSA). Additional information can be obtained from the ELSA's Datacenter (estatisticaelsa@ufrgs.br) and from the ELSA Coordinator from the Research Center of Minas Gerais (sbarreto@medicina.ufmg.br).

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Introduction

The association between lower adulthood socioeconomic position (SEP) and increased risk of cardiovascular disease (CVD) is well-established [1]. Exposure to disadvantaged socioeconomic circumstances during childhood and youth have also been shown to be powerful predictors of CVD [2], indicating that SEP acts across the life course, rather than just in adulthood.

A number of mechanisms have been put forward to account for the association between low life course SEP and cardiovascular risk, including higher prevalence of risk behaviors among disadvantaged individuals, such as smoking, excessive alcohol consumption, and sedentarism [3]. These behaviors may in turn lead to metabolic, endocrine and immune dysregulation, which could promote a pro-inflammatory and pro-thrombotic state [3,4]. Some evidence also suggests that chronic stress associated with socioeconomic adversity leads to epigenetic modifications affecting the transcription of the glucocorticoid receptor leading to glucocorticoid resistance. This phenotype may deregulate the neuroendocrine feedback governed by the hypothalamic-pituitary-adrenal axis resulting in elevated secretion of cortisol as well as pro-inflammatory cytokines such as interleukin-6 [5–9].

Interleukin-6 is one of the most important factor involved in the induction of synthesis of the C-reactive protein (CRP), an acute-phase reactant protein produced mainly by the liver [10]. Although the possible role of CRP as a causal factor for CVD remains debated [11,12], extensive evidence suggests that CRP serves as a marker of inflammation and their levels predict the incidence of CVD [13,14]. In high-income countries, the association between low life course SEP and elevated levels of CRP has been extensively investigated [15–20]. However, there is a lack of consistency among these studies with regard to the persistence of this association after controlling for the effect of health-related behaviors and metabolic alterations (such as obesity, hypertension, diabetes and dyslipidemia). Most studies found no remaining association between SEP and CVD after considering the effect of these variables, especially of obesity [15,16,19]. These findings suggest that health-related behaviors and metabolic alterations fully mediate the relation between life course SEP and chronic inflammation.

There is also uncertainty as to the existence of critical periods, during which SEP would exert an irreversible and independent influence on the development of chronic inflammation, or of sensitive periods, during which SEP would exert a stronger influence on chronic inflammation [21,22]. Some studies found that exposure to unfavorable social circumstances in childhood was associated with higher CRP levels independently of adulthood SEP [17,23,24] and that current SEP was not associated with CRP levels after considering the influence of childhood SEP [17,23,24]. Yet other studies found that only adulthood SEP has an influence on CRP levels [16]. Other studies have also suggested a cumulative influence of socioeconomic disadvantage on CRP levels, i.e. the greater the exposure of disadvantage across the life course, the higher the CRP level [16–18,25].

Brazil, like other upper-middle income countries, has faced great economic and demographic changes in recent decades. It has shifted from a predominantly rural to an urban country with a rapidly aging population. Inequality and poverty levels have decreased sharply in recent years due to anti-poverty policies including increases in the minimum wage, cash transfer programmers, and improvements in the public health system [26,27]. Thus, an important fraction of the population has experienced recent upward socioeconomic mobility. However, the country remains among the highest in the world in terms of income inequality, with a national Gini index of 0.51 in 2012 [28].

The association between SEP and obesity in Brazil differ by gender, and whereas among women there is a clear inverse relation between SEP and obesity, among men SEP is directly or not associated at all with obesity [29,30]. In addition, the association between CRP and obesity is higher in women in many North American and European studies [31], and the obesity has been shown to be the most important predictor of CRP [32–34]. Thus, the association between SEP and CRP might differ among men and women. This gender difference was supported by results from the 1982 Pelotas (Brazil) Birth Cohort Study (mean age = 22.7 years). In this study childhood SEP and CRP were not associated in women, whereas among men there was an association, but in the opposite direction of what has been observed in developed countries: i.e. men reporting higher family income at birth presented higher levels of CRP in adult life independently of current SEP and metabolic alterations [23]. The explanation for this unexpected result remains unclear and further investigation is needed especially in middle aged adults, when SEP is more stable.

Thus, our aim was to evaluate the association of socioeconomic position across the life course with CRP levels in adulthood among middle aged civil servants living in a higher middle income country undergoing rapid transformation. Specifically, our objective was to investigate whether there is a critical period when exposure to lower SEP more strongly influences CRP levels, and/or if there is evidence of a cumulative SEP effect. Additionally, we investigated whether health-risk behaviors and metabolic alterations potentially mediate the association between life course SEP and chronic inflammation, and whether gender modifies this relationship.

Methods

Data source and study population

This study used the baseline data from ELSA-Brasil. The design and selection criteria of ELSA-Brasil were described elsewhere [35,36]. Briefly, 15,105 civil servants, aged between 35 and 74, active or retired, were enrolled from universities and research institutes in six Brazilian states (São Paulo, Minas Gerais, Bahia, Rio Grande do Sul, Rio de Janeiro and Espírito Santo). The baseline examination (2008–2010) included detailed interviews, as well as clinical, laboratory and anthropometric examinations.

Exclusion Criteria

From the 15,105 participants at baseline, we excluded from this analysis 1263 women who were using hormonal contraceptive therapy or hormonal replacement therapy at the time of the blood draw, as this group has been shown to have elevated CRP levels [37,38]. In addition, we excluded 108 participants for having missing values for CRP, and 363 for having CRP values below the detection limit (0.175 mg/L). Thus, 1,734 participants were excluded (233 men and 1501 women) and the analysis sample comprised 13,371 (88.5%) participants.

The excluded men were similar to those included with regard maternal education, occupational social class in the first job, current occupational social class, and own education attainment. However, excluded men were more likely to have higher *per capita* household income ($p = 0.035$). In comparison with the women participants, those excluded presented higher maternal education ($p<0.001$), higher occupational social class in the first job ($p< 0.001$), higher own education attainment ($p<0.001$), higher

current social class ($p<0.001$), and higher *per capita* household income ($p<0.001$).

Study Variables

CRP levels. Serum CRP was obtained from overnight fasting blood and was measured using high-sensitivity assay by immunochemistry - nephelometry - (BN II; Siemens).

Life course SEP indicators. Childhood SEP: Maternal education was used as an indicator of childhood SEP, and it was assessed retrospectively by self-report, using years of schooling, based on the question "*What is the educational level of your mother?*."

Young adulthood SEP: Participants' own education and occupational social class of the first job were used to measure young adulthood SEP. Participants' own education was obtained by self-report, in years of schooling, using the question "*What is your education level?*". Occupational social class of the first job is a summary measure based on the first job held by the participant, obtained using the open question: "*What was your occupation or activity on your first job?*. It considers the relationship schooling-income by comparing the expected income based on the educational level required by the job and the observed income prevailing in the labor market. These scores were categorized into 7 levels (high-upper, high-low, middle-upper, middle-middle, middle-low, low-high and low-low) [39].

Adulthood SEP: Current occupational social class and *per capita* household income were used to evaluate adulthood SEP. The current occupational social class was obtained using the same approach that was used to obtain the social class of the first job, but using the current occupation, obtained by the open question: "*Please describe the main activities that you develop in your day-to-day work at this institution*". The net household income was evaluated by self-report using the question: *"During the last month, what was, approximately, your net household income, that is, the sum of incomes, already considering tax discounts, of all the people who regularly contribute with house expenses?"* and the *per capita* household income was obtained dividing this amount by the total number of people living in the household.

Cumulative SEP score: To indicate the accumulation of risk during the life course, a cumulative SEP score was generated and ranged between zero to nine (higher values reflecting worse life course SEP and higher risk), and including maternal education (≥ 11 years of study = 0; 8–10 years of study = 1; 1–7 years of study = 2; 0 years of study = 3), participant's own education (≥15 years of study = 0; 11–14 years of study = 1; 8–10 years of study = 2; 0–7 years of study = 3), and per capita household income (4th quartile = 0; 3rd quartile = 1; 2nd quartile = 2; 1st quartile = 3).

Potential mediators. Health-risk behaviors: current cigarette smoking was determined by self-report if the participants declared having smoked at least 100 cigarettes in their lifetime and still smoked at the time of the research. Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) – Short Form, and low leisure time of physical activity was defined according to the IPAC Guidelines for Data Processing and Analysis [40], as participants who did not meet any of the following three criteria: 3 or more days of vigorous activity during the last week, consisting of at least 20 minutes per day; or 5 or more days of moderate-intensity activity and/or walking during the last week, consisting of at least 30 minutes per day; or 5 or more days of any combination of walking, moderate or vigorous-intensity activities during the last week, achieving a minimum of at least 600 Metabolic Equivalent of Task (MET)-minutes per week [40]. The alcohol consumption was evaluated by self-report of usual type, frequency of intake, and drinking patterns. All the information obtained was summarized in quantity of grams of alcohol drank per week. Excessive alcohol consumption was defined as consuming ≥210 g of alcohol per week among men, and ≥140 g per week among women. To indicate the cluster of these health-risk behaviors, we created a score that ranged from 0 (absence of health-risk behavior) to 3 (presence of all three health-risk behaviors).

Metabolic alterations: anthropometric measurements of weight, height and waist circumference were used to define "obesity/abdominal obesity" as participants who presented body mass index ≥30 kg/m^2 and/or waist circumference ≥88 cm for women and ≥102 for men. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg or verified treatment with anti-hypertensive medication. Low HDL cholesterol was defined as HDL <40 mg/dL for men and <50 mg/dL for women. Hypertriglyceridemia was defined as ≥150 mg/dL. Diabetes was defined as a self-report of a previous diagnosis of diabetes or the use of medication for diabetes or fasting glucose ≥126 mg/dL or glucose tolerance test ≥ 200 mg/dL or glycated hemoglobin ≥6.5%. To indicate the cluster of these metabolic alterations, we generated a score that ranged from 0 (absence of metabolic alterations) to 5 (presence of all five metabolic alterations).

Data Analyses

We generated descriptive characteristics of the analytic sample. Categorical variables were summarized as frequencies and continuous variables were summarized as means and standard deviation (SD) or median and interquartile range (IQR). All analyses were conducted separately for men and women to explore the possible modifying influence of gender.

The prevalence of each health-risk behavior and metabolic alteration was described according to the cumulative SEP score. We compared the median CRP levels according to the presence or absence of each of the health-risk behaviors and metabolic abnormality. The statistical significance of the differences between the median values in those groups was evaluated using the Wilcoxon rank-sum test, since the levels of CRP were left-skewed.

CRP was natural log-transformed due to non-normality. We estimated the age-adjusted geometric means of CRP for each SEP indicator by exponentiating the parameter estimates from linear regression models on natural log-transformed CRP (back-transformed). We also examined geometric means of CRP adjusted for age and all SEP indicators simultaneously. The adjustment for age was necessary, since CRP increases with age [10], and socioeconomic position also differed according to age. For example, educational attainment varies by births cohort, and older people tend to have lower education than the young people in the ELSA-Brasil cohort.

To estimate the age-adjusted geometric means of CRP, the maternal education was grouped in four categories (≥11, 8–10, 1–7, 0 years of study), as well as the participants' own education attainment (≥15, 11–14, 8–10, 0–7 years of study). The occupational social class of the first job and the current occupational social class were summarized in three categories (high, middle, low), and the *per capita* household income was categorized into quartiles. However, to test the linear trends of these CRP means by SEP we entered the SEP indicators as continuous variable in these models. The normality of residuals and homoscedasticity were tested graphically and violation was not found. The multicollinearity between the explanatory variables was assessed by the variance inflation factor (VIF) and

all VIF values were far below 10, the critical value for a serious problem of multicollinearity [41].

Mediation Analyses. We used structural equation modeling to test the hypothesis that the association between cumulative SEP and CRP is partly mediated by health-risk behaviors and metabolic alterations.

A latent variable was created in the measurement model to represent the cumulative SEP and included maternal education, participant's own education, occupational social class of the first job, current occupational social class and per capita household income. All SEP indicators were included in the measurement model as continuous variables, and the *per capita* household income was natural log-transformed due to non-normality. The scores created to access the clustering of health-risk behaviors and metabolic alterations were used in the structural equation models. Figure 1 shows details of the model that was tested. Figure 1A shows the total effect of cumulative SEP on CRP. Figure 1B shows that the estimate of the total effect was disaggregated into three indirect effects, which represent the effects mediated by health-risk behaviors and metabolic alterations (Cumulative SEP = >Risk Behavior = >ln(CRP); Cumulative SEP = >Metabolic alterations = >ln(CRP); Cumulative SEP = >Risk Behavior = >Metabolic alterations = >ln(CRP)), and the remaining direct effect of cumulative SEP on CRP that is independent of these mediators. Despite the a priori importance of age as pointed out above, the age standardized coefficient was not statistically significant in the mediation models. For this reason, we did not include age in the mediation analysis, because this inclusion did not materially alter the other estimates, but affected the model adjustment because of the existence of a non-significant variable in the model.

The maximum likelihood procedure was used to estimate the structural equation model parameters. Standardized coefficients with 95%CI, and tests of significance for standardized coefficients were reported. The absence of overlap in the 95%CI for each standardized coefficient was interpreted as evidence of a significant gender difference in a given path. Overall model fit was assessed using the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA), and the standardized root mean squared residual (SRMR). For goodness of fit, we followed the recommendation of a CFI $\geq$0.95, RMSEA $\leq$0.05, and the SRMR $\leq$0.08 [42].

All analyses were conducted using the software Stata 12.0 (Stata Corporation, College Station, United States).

Sensitivity Analyses

In epidemiologic research of chronic inflammation, CRP above 10 mg/L has been considered as acute inflammation and excluded from studies. Nevertheless, recent studies suggest that, especially in obese women, CRP above 10 mg/L can occur due to chronic inflammation [38]. Thus, we showed the results including participants with CRP above 10, but all the analyses were repeated excluding these individuals to verify for possible changes in the results.

Ethics

ELSA-Brasil research protocol was approved by the Research Ethics Committee of Universidade de São Paulo (USP), Research Ethics Committee of Universidade Federal de Minas Gerais (UFMG), Research Ethics Committee of Fundação Oswaldo Cruz (FIOCRUZ), Research Ethics Committee of Universidade Federal do Espírito Santo (UFES), Research Ethics Committee of Universidade Federal da Bahia (UFBA), Research Ethics Committee of Universidade Federal do Rio Grande do Sul (UFRGS) and also by the National Research Ethics Committee (CONEP). Informed consent was signed by all participants.

Results

The baseline characteristics of the 13,371 participants (6,654 men and 6,717 women) from the ELSA-Brasil, stratified by sex, are presented in Table 1. The mean age was 52 years (range 35–74 years) and 39.9%of the participants were between 45 and 54 years old. Overall, more than 50% of the participants' mothers had less than eight years of schooling, but their own education attainment was high and over 50% of them had $\geq$15 years of schooling. On average, the participants had 17 years when they started working. The majority had low social class in their first job, more so among men. On the other hand, about one third of male and one quarter of female social class of current occupational were classified as high. Men reported higher prevalence of smoking and excessive alcohol consumption; while women reported higher prevalence of low leisure time physical activity. The clustering of two or three risk behaviors was substantially more frequent among men than women. The prevalence of obesity/abdominal obesity and low HDL were higher in women than in men. Nevertheless, hypertension and diabetes were more common among men and the prevalence of hypertriglyceridemia was twice that of women.

The prevalence of health-risk behaviors and metabolic alterations rose with increasing exposure to social adversities across the life course. The only exceptions were obesity in men, which was not associated with cumulative SEP score, and excessive alcohol consumption in women, which was directly associated with life course SEP (Table 2).

The distribution of CRP levels was skewed to lower levels, in men and women. The median (IQR) of CRP levels were 1.35 mg/L (0.71–2.81) and 1.68 (0.82–3.80) mg/L among men and women, respectively. With the exception of excessive alcohol consumption in women, all health-risk behaviors and metabolic alterations were associated with higher levels of CRP (Table 3). It was also notable that CRP levels were more strongly associated with metabolic alterations in women (Table 3).

Age-adjusted geometric means of CRP in adulthood increases with increasing socioeconomic disadvantages in all the life course periods analyzed (Table 4). However, after simultaneous adjustment for all SEP indicators, childhood SEP did not remain statistically associated to CRP in any gender. However, participants' own education, among men, and social class of current occupational and *per capita* household income, among women, remained statistically significantly associated with CRP levels in adulthood (Table 4). In men and women there were cumulative effects of exposure to adverse socioeconomic position across the life span and CRP levels increased linearly with increasing numbers of exposure to unfavorable social contexts over the life course (p for linear trend $<$0.001) (Figure 2).

Table 5 shows the results of the structural equation models. The factor loadings from the measurement model suggest that each of the individual SEP indicators load highly on the cumulative SEP factor measure. There was a significant total effect between cumulative SEP and ln(CRP), showing that each SD increase in cumulative SEP was associated with a 0.134 SD decrease in ln(CRP), among men, and 0.155 SD, among women. The three indirect paths linking cumulative SEP and ln(CRP) were also statistically significant, and the most important indirect path for both men and women was "Cumulative SEP = >Metabolic alterations = >ln(CRP)". This indirect path was stronger among women than among men, since it accounted for 49.5% of the total effect of cumulative SEP on ln(CRP), among women, and only

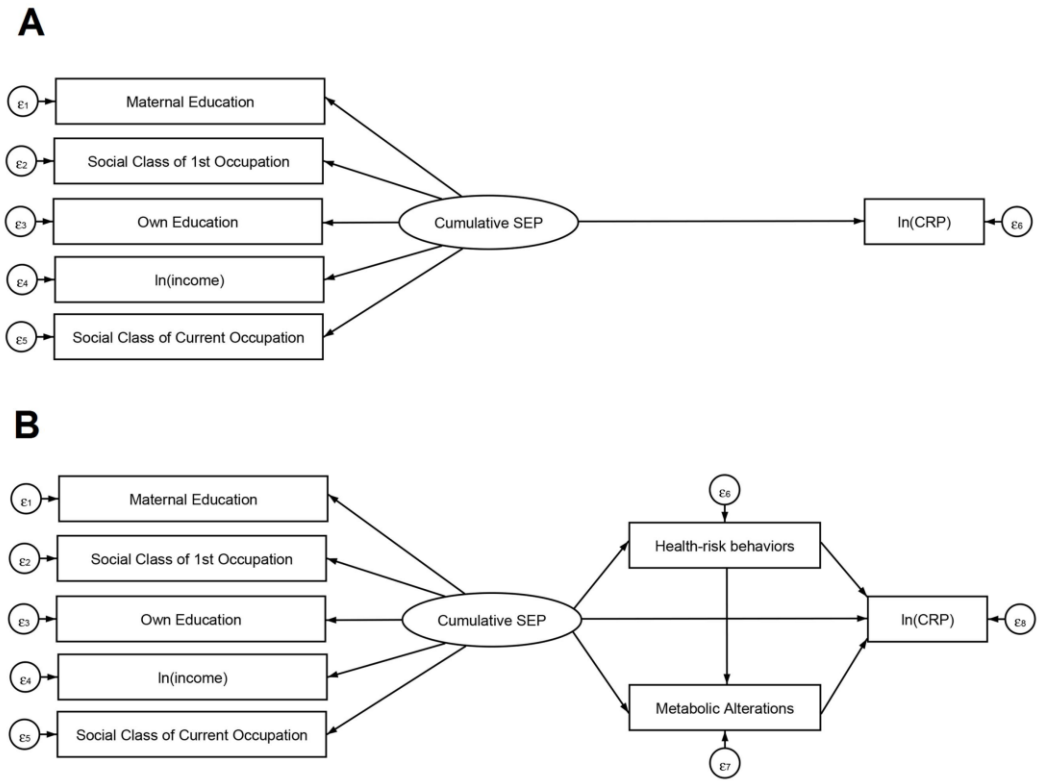

Figure 1. Illustration of proposed multiple mediation of the association between life course SEP and CRP. (A) Total effect of life course SEP on CRP. (B) Hypothesized indirect effect of SEP on CRP through mediators and direct effect. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010.
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20.2% among men. In consequence, the fraction of the total effect of cumulative SEP on ln(CRP), mediated by health-risk behaviors and metabolic alterations was statistically higher in women (55.4%) than in men (36.8%). The direct effect of cumulative SEP on ln(CRP) was high, especially among men, since it accounted for 63.2% and 44.6% of the total effect of SEP on ln(CRP) among men and women, respectively.

Sensitivity Analyses

Of the total participants considered in this analysis, 2.96% of men and 4.56% of women presented CRP above 10 mg/L. Exclusion of these participants from the analysis did not alter significantly any of the results reported above.

Discussion

Although lower childhood SEP was associated with higher levels of CRP in adult life, this association was not independent of adulthood SEP. However, childhood SEP seems to play a role in chronic inflammatory states when it was considered together with young adulthood SEP and adulthood SEP, providing support to a model of cumulative effects of exposures to SEP across the life span. The cluster of metabolic alterations was the most important mediator between cumulative SEP and CRP in men and women, but for women this mediation path was stronger than for men. Together, metabolic alterations and health-risk behaviors were important mediators between cumulative SEP and CRP. However, the direct effect of cumulative SEP on CRP was substantial, suggesting that other pathways could play a role, especially among men.

According to the life course approach, a critical period is a time window during which exposures can lead to lasting physiological changes in the organism. In its most stringent form, no excess risk would be observed if exposure occurred in periods outside the window [21,22]. Our results did not support the notion that childhood is a critical period of exposure to low SEP for three reasons. Firstly, CRP was associated with SEP in all three stages of the life course, not just with childhood SEP. Secondly, after simultaneously controlling for adulthood SEP, no association was found between childhood SEP and CRP, suggesting that the exposure to low SEP in early life could matter because it leads to lower adulthood SEP (the pathways or "chain of risk" hypothesis). Thirdly, we found strong evidence of cumulative risk, indicating that exposure to low SEP at different stages of life accumulate to promote chronic inflammation. All these three aspects of our results are incompatibles with the critical period model, at least in

Table 1. Descriptive characteristics of the analytical sample from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), N (%) or mean (SD), 2008–2010 (N = 13,371)[1].

Characteristics	Overall N = 13,371	Men N = 6,654	Women N = 6,717
Age (years), (N = 13,371), %			
35–44	2,829 (21.16)	1,490 (22.39)	1,339 (19.93)
45–54	5,338 (39.92)	2,606 (39.16)	2,732 (40.67)
55–64	3,753 (28.07)	1,806 (27.14)	1,947 (28.99)
65–74	1,451 (10.85)	752 (11.30)	699 (10.41)
Maternal education(years of study),(N = 13,029), %			
≥11	3,027 (23.23)	1,624 (25.16)	1,403 (21.34)
8–10	2,531 (19.43)	1,248 (19.33)	1,283 (19.52)
1–7	5,567 (42.73)	2,637 (40.85)	2,930 (44.57)
0	1,904 (14.61)	946 (14.66)	958 (14.57)
Participants' own education (years of study), (N = 13,371), %			
≥15	6,850 (51.23)	3,359 (50.48)	3,491 (51.97)
11–14	4,695 (35.11)	2,193 (32.96)	2,502 (37.25)
8–10	967 (7.23)	554 (8.33)	413 (6.15)
0–7	859 (6.42)	548 (8.24)	311 (4.63)
Age at first job, (years), (N = 13,343), mean (SD)	17.15 (4.87)	16.16 (4.65)	18.13 (4.88)
Social class of first occupation, (N = 10,710), %			
High	627 (5.85)	343 (6.09)	284 (5.59)
Middle	3,471 (32.41)	1,474 (26.19)	1,997 (39.30)
Low	6,612 (61.74)	3,812 (67.72)	2,800 (55.11)
Social class of current occupation, (N = 12,605), %			
High	3,909 (31.01)	2,291 (35.85)	1,618 (26.04)
Middle	5,397 (42.82)	2,235 (34.97)	3,162 (50.89)
Low	3,299 (26.17)	1,865 (29.18)	1,434 (23.08)
Per capita household income in U.S. dollars, (N = 13,307), mean (SD)	896.69 (747.54)	869.51 (708.65)	923.61 (783.31)
Cumulative SEP score[2] (N = 12,971), %			
0–1 (lowest risk)	2,755 (21.24)	1,473 (22.92)	1,282 (19.59)
2–3	3,739 (28.83)	1,811 (28.18)	1,928 (29.46)
4–5	3,238 (24.96)	1,440 (22.41)	1,798 (27.47)
6–7	2,467 (19.02)	1,223 (19.03)	1,244 (19.01)
8–9 (highest risk)	772 (5.95)	479 (7.45)	293 (4.48)
Smoking (N = 13,370), %	1,810 (13.54)	957 (14.38)	853 (12.70)
Low leisure time physical activity (N = 13,169), %	10,196 (77.42)	4,835 (73.74)	5,361 (81.08)
Excessive Alcohol Consumption(N = 13,346), %	1,051 (7,88)	815 (12.26)	236 (3.52)
Clustering of unhealthy behaviours[3] (N = 13,148), %			
0	2,520 (19.17)	1,416 (21.62)	1,104 (16.73)
1	8,526 (64.85)	3,892 (59.41)	4,634 (70.24)
2	1,835 (13.96)	1,045 (15.95)	790 (11.98)
3	267 (2.03)	198 (3.02)	69 (1.05)
Obesity/Abdominal Obesity (N = 13,367), %	5,158 (38,59)	1,964 (29.53)	3,194 (47.56)
Hypertension (N = 13,358), %	4,959 (37,12)	2,697 (40.57)	2,262 (33.71)
Low HDL (N = 13,367), %	2,390 (17.88)	992 (14.92)	1,398 (20.82)
Hypertriglyceridemia (N = 13,366), %	4,372 (32.71)	2,764 (41.56)	1,608 (23.94)
Diabetes (N = 13,370),%	2,758 (20.63)	1,567 (23.55)	1,191 (17.73)
Clustering of metabolic alterations[4] (N = 13,347), %			
0	3,760 (28.17)	1,733 (26.11)	2,027 (30.21)
1	3,739 (28.01)	1,922 (28.95)	1,817 (27.08)
2	2,964 (22.21)	1,508 (22.72)	1,456 (21.70)
3	1,808 (13.55)	951 (14.33)	857 (12.77)

Table 1. Cont.

Characteristics	Overall N = 13,371	Men N = 6,654	Women N = 6,717
4	867 (6.50)	448 (6.75)	419 (6.25)
5	209 (1.57)	76 (1.14)	133 (1.98)

[1]Differences in total N for each variable are due to missing values.
[2]The cumulative SEP score ranged between zero to nine, with higher values reflecting worse life course SEP.
[3]It includes current cigarette smoking, low leisure time physical activity, excessive alcohol consumption.
[4]It includes obesity/abdominal obesity, hypertension, low hdl, hypertriglyceridemia, diabetes.
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the case of chronic inflammation. However, the results showed an important role of the exposure to low SEP in childhood, since it leads to lasting effect through accumulation of risk. Many previous studies also reported increased of CRP levels with increasing number of adverse SEP conditions throughout life [16–19,25].

Clustering of metabolic alterations and health-risk behaviors were important mediators of the association between cumulative SEP and CRP levels in men and women. Using regression models to measure mediation, it was also found in the *Atherosclerosis Risk in Communities* study (ARIC) that diabetes status, low HDL cholesterol, high BMI, smoking and physical inactivity were important mediators between life course SEP and a score of inflammation which included CRP, von Willebrand fator, fibrinogen, and white blood cell count [20].

In our study, metabolic alterations were the most import mediators of the association between cumulative SEP and CRP. However, while this indirect path accounted for 49.5% of the total effect of cumulative SEP on CRP among women, it accounted for only 20.2% among men. This gender difference may be explained by at least two reasons. Firstly, the association between all metabolic alterations and CRP was stronger in women than in men in the ELSA Brasil, which is consistent with other studies [31,43,44]. For example, in the British 1958 Birth Cohort the associations between obesity (body mass index, waist circumference), blood pressure, blood lipids, metabolic syndrome and CRP were twice as strong among women as among men [43]. In addition, recent meta-analysis also showed that in adults the Pearson correlation coefficients between body mass index and ln(CRP) was greater in women than men by 0.24 (CI, 0.09–0.37) on average [31]. Secondly, it is well known that adiposity is a major predictor of CRP [32–34], and we found that the prevalence of obesity was higher among women than among men (47.56% *versus* 29.53%). Moreover, obesity was not associated with the accumulation of exposures to low SEP during the life course in men, replicating what is currently found in the Brazilian population as a whole [29]. All these findings may explain the much greater contribution of metabolic disorders as mediating path between Cumulative SEP and CRP in women as compared to men.

Table 2. Prevalence of health-risk behavior and metabolic alteration according to cumulative socioeconomic position (SEP) score (higher values reflecting worse life course SEP) among men and women.

Characteristic	0–1	2–3	4–5	6–7	8–9	p for trend
Men						
Cigarette smoking	10.52	11.76	15.76	16.68	23.01	<0.001
Low leisure time physical activity	65.53	68.29	76.05	82.11	85.53	<0.001
Excessive alcohol consumption	11.41	11.49	12.72	14.06	13.15	0.026
Obesity/abdominal obesity	31.39	29.93	27.71	28.64	29.65	0.109
Hypertension	37.14	37.56	38.71	43.99	54.70	<0.001
Low HDL cholesterol	12.22	14.41	15.71	17.01	16.98	<0.001
Hypertriglyceridemia	35.78	41.96	43.71	44.56	42.26	<0.001
Diabetes	18.40	19.93	23.28	27.56	38.62	<0.001
Women						
Cigarette smoking	11.00	10.27	12.96	15.51	18.77	<0.001
Low leisure time physical activity	72.81	76.78	83.86	89.81	90.94	<0.001
Excessive alcohol consumption	5.15	3.79	3.06	2.25	2.06	<0.001
Obesity/abdominal obesity	40.80	41.65	50.36	55.14	64.51	<0.001
Hypertension	25.25	29.51	34.20	41.00	57.34	<0.001
Low HDL cholesterol	14.66	17.96	24.03	25.16	27.30	<0.001
Hypertriglyceridemia	19.97	22.21	24.92	26.77	34.81	<0.001
Diabetes	11.86	15.35	17.35	23.23	35.49	<0.001

Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010.
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Table 3. Median CRP Levels (interquartile range) according to the presence or absence of health-risk behavior and metabolic alterations among men and women.

Characteristic	Absent	Present	P-value
Men			
Cigarette smoking	1.28 (0.69–2.65)	1.95 (0.99–3.72)	<0.0001
Low leisure time physical activity	1.14 (0.62–2.39)	1.43 (0.75–3.04)	<0.0001
Excessive alcohol consumption	1.31 (0.70–2.71)	1.62 (0.81–3.68)	<0.0001
Obesity/abdominal obesity	1.14 (0.62–2.36)	1.96 (1.06–3.96)	<0.0001
Hypertension	1.16 (0.64–2.42)	1.63 (0.87–3.48)	<0.0001
Low HDL cholesterol	1.31 (0.69–2.68)	1.61 (0.82–3.63)	<0.0001
Hypertriglyceridemia	1.17 (0.63–2.53)	1.60 (0.85–3.21)	<0.0001
Diabetes	1.22 (0.67–2.50)	1.88 (1.00–3.93)	<0.0001
Women			
Cigarette smoking	1.65 (0.80–3.76)	1.91 (0.91–4.08)	<0.0040
Low leisure time physical activity	1.29 (0.66–3.03)	1.79 (0.87–4.00)	<0.0001
Excessive alcohol consumption	1.67 (0.82–3.79)	1.90 (0.80–4.30)	0.4331
Obesity/abdominal obesity	1.07 (0.59–2.14)	2.90 (1.41–5.54)	<0.0001
Hypertension	1.39 (0.70–3.16)	2.45 (1.14–4.90)	<0.0001
Low HDL cholesterol	1.51 (0.75–3.45)	2.43 (1.15–5.23)	<0.0001
Hypertriglyceridemia	1.45 (0.73–3.37)	2.59 (1.23–4.91)	<0.0001
Diabetes	1.48 (0.75–3.37)	2.85 (1.31–5.82)	<0.0001

Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010.
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The cluster of health-risk behaviors accounted for 13.4% of the total effect of Cumulative SEP on CRP among men and only 4.4% among women. Consistently with other studies [45,46], we found that excessive alcohol consumption was associated with higher CRP levels and with low life course SEP among men. However, among women, the excessive alcohol consumption was not associated with CRP levels. In addition, excessive alcohol consumption was related with higher life course SEP among women, as it was also reported in the general population of Scotland [45]. Moreover, the prevalence of smoking, as well as the clustering of two or more health-risk behaviors, was higher among men. In sum, these facts could account for the greater role of health-risk behaviors as mediators in the association between cumulative SEP and CRP in men than in women. Different findings were reported by the *National Health and Nutrition Examination Surveys* (NHANES IV) using only measures of adulthood SEP. They found that 55.8% of the association between poverty in adulthood and CRP was mediated by 4 health-related behaviors (smoking, heavy alcohol consumption, poor diet and physical activity) and this indirect effect was higher (87.9%) when

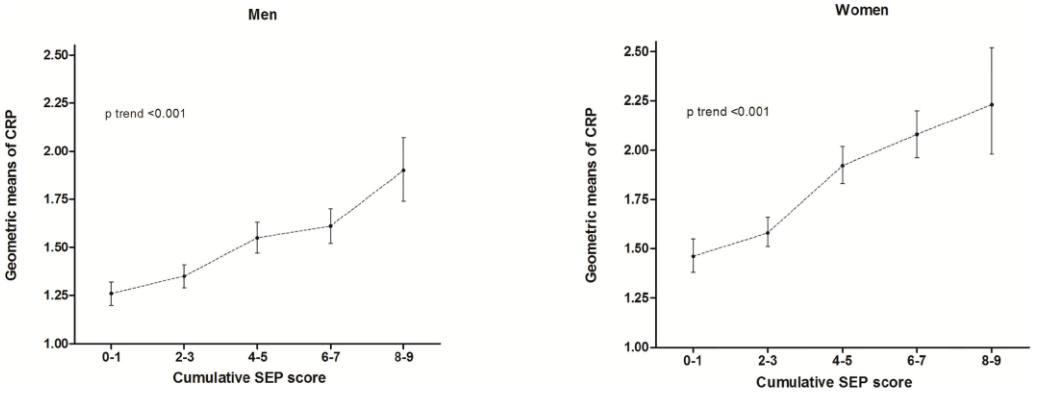

Figure 2. Age adjusted geometric means (95% confidence interval) of C-reactive protein among men and women by the cumulative SEP score that ranged between zero to nine, with higher values reflecting worse life course SEP. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010.
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Table 4. Adjusted geometric means (95% confidence interval) for levels of CRP by SEP indicators throughout the life course.

Indicators	Model adjustment			
	Age		Age and all SEP indicators simultaneously adjusted	
	Men	Women	Men	Women
	Geometric mean (95% CI)	Geometric mean(95% CI)	Geometric mean (95% CI)	Geometric Mean (95% CI)
Childhood SEP				
Maternal education(years of study)				
≥11	1.31 (1.25–1.37)	1.51 (1.43–1.60)	1.48 (1.39–1.57)	1.72 (1.60–1.86)
8–10	1.49 (1.41–1.57)	1.81 (1.71–1.92)	1.58 (1.48–1.68)	1.84 (1.72–1.97)
1–7	1.47 (1.41–1.53)	1.80 (1.73–1.87)	1.45 (1.39–1.51)	1.77 (1.69–1.85)
0	1.63 (1.53–1.73)	1.95 (1.82–2.09)	1.43 (1.33–1.54)	1.75 (1.61–1.90)
p value for trend	<0.001	<0.001	p = 0.279	p = 0.731
Young adult SEP				
Own education (years of study)				
≥15	1.29 (1.25–1.34)	1.56 (1.51–1.61)	1.33 (1.25–1.40)	1.71 (1.62–1.80)
11–14	1.59 (1.53–1.66)	1.95 (1.87–2.03)	1.55 (1.47–1.63)	1.79 (1.69–1.89)
8–10	1.68 (1.54–1.82)	2.31 (2.09–2.56)	1.68 (1.52–1.86)	2.13 (1.86–2.44)
0–7	1.87 (1.72–2.03)	2.26 (2.01–2.54)	1.92 (1.72–2.14)	1.92 (1.63–2.27)
p value for trend	<0.001	<0.001	<0.001	p = 0.069
Social class of first occupation				
High	1.37 (1.23–1.52)	1.35 (1.19–1.52)	1.60 (1.43–1.79)	1.67 (1.47–1.91)
Middle	1.36 (1.29–1.43)	1.68 (1.60–1.76)	1.44 (1.36–1.52)	1.77 (1.68–1.86)
Low	1.55 (1.50–1.59)	1.90 (1.83–1.98)	1.48 (1.43–1.53)	1.78 (1.71–1.86)
p value for trend	<0.001	<0.001	p = 0.850	p = 0.325
Adulthood SEP				
Social class of current occupation				
High	1.24 (1.19–1.56)	1.39 (1.32–1.46)	1.37 (1.29–1.47)	1.55 (1.44–1.67)
Middle	1.56 (1.50–1.63)	1.87 (1.81–1.94)	1.58 (1.50–1.65)	1.86 (1.78–1.94)
Low	1.63 (1.56–1.71)	2.05 (1.94–2.17)	1.48 (1.38–1.58)	1.83 (1.70–1.97)
p value for trend	<0.001	<0.001	p = 0.146	p = 0.005
Per capita household income				
4th quartile (highest)	1.28 (1.22–1.35)	1.49 (1.42–1.58)	1.43 (1.34–1.53)	1.63 (1.52–1.75)
3rd quartile	1.39 (1.33–1.46)	1.61 (1.53–1.69)	1.52 (1.44–1.61)	1.65 (1.55–1.76)
2nd quartile	1.51 (1.44–1.59)	1.90 (1.80–2.00)	1.45 (1.37–1.53)	1.86 (1.75–1.99)
1stquartile (lowest)	1.66 (1.59–1.74)	2.10 (2.00–2.21)	1.50 (1.41–1.59)	1.93 (1.81–2.06)
p value for trend	<0.001	<0.001	p = 0.270	<0.001

Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010.
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education level was used to measure adulthood SEP instead of poverty [47]. In contrast to the NHANES IV analyzes, we have not considered poor diet, and the prevalence of smoking and heavy alcohol consumption among US participants was much higher than that found in ELSA-Brasil. For instance, the prevalence of current smoking ranged from 17.7% to 32.8% among non poor and poor NHANES IV participants while heavy alcohol consumption ranged from 16.8% to 20.4%, respectively [47]. Moreover, they only used measures of adulthood SEP, and although the health-related behaviors are often acquired in adolescence [48], it is known that they are more strongly associated with adulthood SEP than with childhood SEP [49].

An important portion of the association between cumulative SEP and CRP was not mediated by metabolic alterations and health-risk behaviors, suggesting that others pathways could play an important role. Stress was not included in the present analysis and may be a relevant path between SEP and CRP levels. Life course SEP could lead to chronic inflammation by increasing exposure to psychosocial stress factors, such as crowding, growing up in poor neighborhoods, experiences of childhood trauma and abuse, discrimination, job strain, and perceptions of relative deprivation [50–52]. Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous systems, resulting in higher secretion of cortisol and catecholamines, setting off a chain of physiological consequences including inflammation, coagulation, and adhesion – the so-called model of allostatic load [53]. For instance, in the Whitehall study, job control explained about 64%, among men, and 51%, among women, of the excess risk for coronary heart disease associated with low versus high occupational group [54]. However, most studies found only a

Table 5. Parameters estimates from the structural equation model of cumulative SEP on CRP levels in adulthood, according to gender.

	Parameter estimates	
	Men N = 5,128[1]	**Women N = 4,534[2]**
Measurementmodel, standardized coefficients(95%CI)[3]		
Cumulative SEP→Maternal education	0.525 (0.504; 0.547)***	0.509 (0.484; 0.534)***
Cumulative SEP→Social class of first occupation	0.553 (0.532; 0.574)***	0.575 (0.552; 0.598)***
Cumulative SEP→Own education	0.858 (0.847; 0.869)***	0.844 (0.831; 0.858)***
Cumulative SEP→ln (income)	0.715 (0.699; 0.730)***	0.634 (0.613; 0.654)***
Cumulative SEP→Social class of current occupation	0.866 (0.855; 0.876)***	0.838 (0.824; 0.851)***
Strutural Model, standardized coefficients (95%CI)[3]		
Total Effect		
Cumulative SEP→ln(CRP)	−0.134 (−0.163; −0.106)***	−0.155 (−0.186; −0.125)***
Direct Effects		
Cumulative SEP→ln(CRP)	−0.085 (−0.113; −0.056)***	−0.069 (−0.099; −0.039)***
Risk Behavior→ln(CRP)	0.088 (0.060; 0.115)***	0.043 (0.016; 0.070)***
Metabolic Alterations→ln(CRP)	**0.256 (0.230; 0.282)*** **	**0.378 (0.353; 0.404)*** **
Indirect Effects		
Cumulative SEP→Risk Behavior→ln(CRP)	−0.018 (−0.024; −0.012)***	−0.007 (−0.011; −0.002)**
Cumulative SEP→Metabolic Alterations→ln(CRP)	**−0.027 (−0.035; −0.019)*** **	**−0.077 (−0.090; −0.064)*** **
Cumulative SEP→Risk Behavior→Metabolic Alterations→ln(CRP)	−0.004 (−0.006; −0.003)***	−0.002 (−0.004; −0.001)*
Total indirect effects: Cumulative SEP→ln(CRP)	**−0.049 (−0.059; −0.040)*** **	**−0.086 (−0.099; −0.073)*** **
Log CRP R^2	0.095	0.164
Proportion of the effect of Cumulative SEP on ln(CRP) that was:		
Mediated by Risk Behavior	13.43%	4.44%
Mediated by Metabolic Alterations	20.16%	49.51%
Mediated by Risk Behavior and Metabolic Alteration simultaneously	3.22%	1.47%
Total indirect effect	36.81%	55.43%
Direct effect	63.19%	44.57%
Model fit[4]		
CFI	0.981	0.989
RMSEA	0.049	0.035
SRMR	0.020	0.015

Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010.
[1]Of the 6,654 men participants, 5128 (77.1%) had complete data available on all covariates used in the structural equation model.
[2]Of the 6,717 women participants, 4534 (67.5%) had complete data available on all covariates used in the structural equation model
[3]The significance levels shown here are for the standardized solution (*p<0.05, **p<0.01, ***p<0.001). The absence of overlap in the 95%CI was interpreted as evidence of a significant gender difference in a given path ("bolded" in the table).
[4]CFI: comparative fit index. RMSEA: root mean square error of approximation. SRMR: standardized root mean squared residual.
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small contribution of stress measures to socioeconomic gradient in health [52].

The epigenetic modification induced by the experience of social adversity is another path that could explain some portion of the direct effect that we found between cumulative SEP and CRP. In general, exposures to environmental stressors tend to lead the epigenomic instability (i.e.: DNA demethylation, histone modification and micro-RNA expression). The organism uses this mechanism to respond to threats and, consequently, to increase the diversity. Nevertheless, this process also has the potential to causes diseases [7]. There is growing evidence that socioeconomic adversity can influence DNA methylation and gene expression, especially in genomic regions regulating the immune function [6,7]. These studies also indicate that exposures to social adversities across the life course may cause glucocorticoid receptor resistance leading to exaggerated glucocorticoid levels in the organism. Thus, uncontrolled inflammatory responses would be typical characteristic of this phenotype created by epigenetic modification [5–9]. Originally it was believed that only exposures to SEP in early life could promote this kind of epigenetic modification; however recent evidence suggests that exposure to SEP in adulthood can also promote epigenomic instability [8,55]. Nevertheless, the association between epigenetics modifications and SEP tend to be higher when measures of SEP in early life were used [6–8].

Some potential limitations of our analysis merit consideration. Firstly, to analyze the role of metabolic alterations and health-risk behaviors as mediators between cumulative SEP and CRP we used clusters of risk factors. In doing so, it became feasible to study the mediation process using conventional structural equation

modeling. Our approach has two limitations: 1) the specific effect of each behavior or metabolic alteration could be not accessed; 2) working with clusters we considered that all variables have the same weight, but it is possible that different behaviors or metabolic alterations can have more or less influence on CRP levels. For example, among all metabolic alterations considered, it is known that obesity is a major predictor of CRP [32–34]. Thus, it was not possible to detect in this analyses which component is more important to mediate the association between cumulative SEP and CRP. Secondly, we do not have the timing of the onset of health behaviors & metabolic alterations – for example, it's possible that most behaviors began in adolescence, which would point to the need for early intervention. Thirdly, we used only maternal education to measure childhood SEP. Others studies that have used other indicators of SEP in childhood, such as parental occupational status and *in utero* SEP, could provide a better evaluation of the influence of exposure to low childhood SEP in chronic inflammation in adulthood. Fourthly, we used the participant's own education to measure young adulthood SEP, since education is generally complete in late adolescence or in the beginning of adult life [56]. However, the participants from ELSA-Brasil are civil servants from universities and research centers and some positions require post-graduate level education. For this reason, we also used the occupational social class of the first job to capture better the SEP in young adulthood, since the mean age that the participants started to work was 16 years among men and 18 among women. Fifthly, we used only the *per capita* household income to evaluate the participants' financial situation, which did not capture other dimensions such as wealth and assets. Sixthly, the ELSA-Brasil participants are active and retired workers, have retirement plans and average education and income levels higher than that of the general population of Brazil. Thus, people who experienced extreme social difficulties in childhood as well as in adulthood could not be represented in this study. The truncated variability in SEP may have led us to underestimate the magnitude of the associations between life course SEP and CRP levels.

The linear association between number of exposures to low SEP and CRP suggests a cumulative impact of SEP in promoting chronic inflammation. These findings provide one potential biological mechanism to explain the well-established social gradient for CVD. Moreover, it suggests that social interventions in a single time point across the life course may not suffice to deal with the social inequalities in CVD. Our findings extend previous studies by using statistical techniques that allowed us to disentangle the portion of the total effect of cumulative SEP on CRP levels that is mediated by metabolic alterations and health-risk behaviors.

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We would like to thank all ELSA-Brasil participants for their valuable contribution to this study.

Author Contributions

Conceived and designed the experiments: LVC LG SMB. Performed the experiments: LVC. Analyzed the data: LVC LG JABN SMB. Wrote the paper: LVC LG JABN PAL IMB DC RHG MJMF PGV IK MIS SMB.

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ANEXO 1

Ata do exame de qualificação

UNIVERSIDADE FEDERAL DE MINAS GERAIS

UFMG

ATA DO EXAME DE QUALIFICAÇÃO DA ALUNA
LIDYANE DO VALLE CAMELO

Realizou-se, no dia 14 de fevereiro de 2014, às 09:00 horas, FACULDADE DE MEDICINA, da Universidade Federal de Minas Gerais, a apresentação do exame de qualificação da aluna **LIDYANE DO VALLE CAMELO**, número de registro 2012783257, intitulado *POSIÇÃO SOCIOECONÔMIA NO CURSO DE VIDA, INFLAMAÇÃO CRÔNICA E ATEROSCLEROSE SUBCLÍNICA NO ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL)*, perante a Comissão Examinadora composta pelos professores: Prof(a). Sandhi Maria Barreto - Orientador (UFMG), Prof(a). Luana Giatti Gonçalves (UFMG), Prof(a). Antonio Luiz Pinho Ribeiro (UFMG), Prof(a). Enrico Antonio Colosimo (UFMG), Prof(a). Bernardo Lessa Horta (UFPEL). Terminada a apresentação, foi considerada:

(X) aprovada ( ) reprovada

e, para constar, foi lavrada a presente ata que, lida e aprovada, vai assinada pelos membros da Comissão.

Belo Horizonte, 14 de fevereiro de 2014.

Prof(a). Sandhi Maria Barreto (Doutora)

Prof(a). Luana Giatti Gonçalves (Doutora)

Prof(a). Antonio Luiz Pinho Ribeiro (Doutor)

Prof(a). Enrico Antonio Colosimo (Doutor)

Prof(a). Bernardo Lessa Horta (Doutor)

ANEXO 2

Aprovação do ELSA-Brasil pelos comitês de ética das instituições participantes

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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

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Cont. Carta CONEP nº 976/2006

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
Sr(a) Maria Teresa Zulini da Costa
Cordenadora Comitê de Ética em Pesquisas
Hospital Universitário da Universidade de São Paulo - HU/USP
Av. Profº Lineu Prestes, 2565
Cidade Universitária São Paulo
Cep:05.508-900

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

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São Paulo, 19 de maio de 2006.

Il^mo(a). S^r(a).
Prof. Dr. Paulo Andrade Lotufo
Superintendência
Hospital Universitário da USP

Referente: Projeto de Pesquisa *"Estudo Longitudinal de Saúde do Adulto - ELSA"* – Cadastro CEP-HU: 669/06 - Cadastro SISNEP: FR – 93920 – CAAE – 0016.1.198.000-06 - Área temática especial: Grupo I – I.1. Genética Humana

Prezado(a) Senhor(a)

O Comitê de Ética em Pesquisa do Hospital Universitário da Universidade de São Paulo, em reunião realizada no dia 19 de maio de 2006, analisou o projeto de pesquisa acima citado, considerando-o como **APROVADO**, bem como, seu Termo de Consentimento Livre e Esclarecido. Informamos que **o projeto estará sendo encaminhado para apreciação da Comissão Nacional de Ética em Pesquisa – CONEP- Brasília, devendo ser iniciado o estudo somente após a aprovação da referida Comissão.**

Lembramos que cabe ao pesquisador elaborar e apresentar a este Comitê, relatórios semestrais (e relatório final ao término do trabalho), de acordo com a Resolução do Conselho Nacional de Saúde 251/97, item V.1.c. **O primeiro relatório** está previsto para **19 de novembro de 2006.**

Atenciosamente,

Dra. Maria Teresa Zulini da Costa
Coordenadora
Comitê de Ética em Pesquisa – CEP

Comitê de Ética em Pesquisa do Hospital Universitário da USP
Av. Prof. Lineu Prestes, 2565 – Cidade Universitário – CEP: 05508-900 - São Paulo – SP
Tels.: (011) 3039-94557 ou 9479 Fax: (11) 3039-9452 E-mail: cep@hu.usp.br

Ministério da Saúde
Fundação Oswaldo Cruz
COMITÊ DE ÉTICA EM PESQUISA-CEP/FIOCRUZ

Rio de Janeiro, 18 de setembro de 2006.

PARECER

Título do Projeto: "Estudo longitudinal de saúde do adulto - ELSA"
Protocolo CEP: 343/06
Pesquisador Responsável: Dora Chor
Instituição: ENSP
Deliberação: APROVADO

Trata-se de uma pesquisa sobre doenças cardiovasculares, diabetes e outras doenças crônicas, pioneiro no Brasil, multicêntrico e com um grande número de sujeitos envolvidos (15.000).

O estudo objetiva investigar os fatores que estejam relacionados a essas doenças em qualquer estagio de desenvolvimento, visando sugerir medidas mais eficazes de prevenção e tratamento.

O CEP da USP já aprovou o referido projeto de pesquisa no ultimo dia 19 de maio do corrente ano assim como já fez o correspondente encaminhamento ao CONEP, conforme declaração anexa assinada pela coordenação do CEP-USP.

Os pesquisadores envolvidos no Rio de Janeiro apresentam currículos experientes, os capacitando plenamente para a realização do estudo no estado do Rio de janeiro.

Após análise das respostas às pendências emitidas no parecer datado de 19/06/2006 por este colegiado, tendo por referência as normas e diretrizes da Resolução 196/96 foi decidido pela APROVAÇÃO do referido protocolo.

Informamos, outrossim, que deverão ser apresentados relatórios parciais/anuais e relatório final do projeto de pesquisa.

Além disso, qualquer modificação ou emenda ao protocolo original deverá ser submetida para apreciação do CEP/FIOCRUZ.

Marlene Braz
Coordenadora do Comitê de Ética em Pesquisa
Em Seres Humanos da Fundação Oswaldo Cruz

UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
COMITÊ DE ÉTICA EM PESQUISA DO
CENTRO DE CIÊNCIAS DA SAÚDE

Vitória-ES, 01 de junho de 2006

Do: Prof. Dr. Fausto Edmundo Lima Pereira
Coordenador
Comitê de Ética em Pesquisa do Centro de Ciências da Saúde

Para: Prof. José Geraldo Mill
Pesquisador Responsável pelo Projeto de Pesquisa intitulado: **"Estudo longitudinal de saúde do adulto - ELSA"**

Senhor Pesquisador,

Através deste informamos à V.Sa., que o Comitê de Ética em Pesquisa do Centro de Ciências da Saúde da Universidade Federal do Espírito Santo, após analisar o Projeto de Pesquisa, No. de Registro no CEP-041/06, intitulado**: "Estudo longitudinal de saúde do adulto - ELSA)",** bem como o **Termo de Consentimento Livre e Esclarecido** cumprindo os procedimentos internos desta Instituição, bem como as exigências das Resoluções 196 de 10.10.96, 251 de 07.08.97 e 292 de 08.07.99, APROVOU o referido projeto, em reunião ordinária realizada em 31 de maio de 2006,

Gostaríamos de lembrar que cabe ao pesquisador elaborar e apresentar os relatórios parciais e finais de acordo com a resolução do Conselho Nacional de Saúde nº 196 de 10/10/96, inciso IX.2. letra "c".

Atenciosamente,

Prof Dr. Fausto Edmundo Lima Pereira
Coordenador
Comitê de Ética em Pesquisa
Centro Biomédico / UFES

Universidade Federal de Minas Gerais
Comitê de Ética em Pesquisa da UFMG - COEP

Parecer nº. ETIC 186/06

Interesse: Prof. (a) Sandhi Maria Barreto
Depto. De Medicina Preventiva e Social
Faculdade de Medicina -UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP, aprovou no dia 28 de junho de 2006 o projeto de pesquisa intitulado **"ELSA - Estudo longitudinal da saúde do adulto."** bem como o Termo de Consentimento Livre e Esclarecido do referido projeto.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

Profa. Dra. Maria Elena de Lima Perez Garcia
Presidente do COEP/UFMG

Av. Presidente Antônio Carlos, 6627, Prédio da Reitoria – 7º andar sala: 7018 - 31.270-901– BH - MG
(31) 3499-4592 - FAX: (31) 3499-4027 - coep@prpq.ufmg.br

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 06-194 **Versão do Projeto:** 15/05/2006 **Versão do TCLE:** 15/05/2006

Pesquisadores:
MARIA INES SCHMIDT
ALVARO VIGO
BRUCE BARTOLOW DUNCAN
FLAVIO DANNI FUCHS
MURILO FOPPA
SANDRA CRISTINA COSTA FUCHS
SOTERO SERRATE MENGUE

Título: ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO - ELSA

Este projeto foi Aprovado em seus aspectos éticos e metodológicos, inclusive quanto ao seu Termo de Consentimento Livre e Esclarecido, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde. Os membros do CEP/HCPA não participaram do processo de avaliação dos projetos onde constam como pesquisadores. Toda e qualquer alteração do Projeto, assim como os eventos adversos graves, deverão ser comunicados imediatamente ao CEP/HCPA. Somente poderão ser utilizados os Termos de Consentimento onde conste a aprovação do GPPG/HCPA.

Porto Alegre, 18 de agosto de 2006.

Profª Nadine Clausell
Coordenadora do GPPG e CEP-HCPA

Universidade Federal da Bahia
Instituto de Saúde Coletiva
COMITÊ DE ÉTICA EM PESQUISA

Formulário de Aprovação do Comitê de Ética em Pesquisa

Registro CEP: 027-06/CEP-ISC
Projeto de Pesquisa: "Estudo Longitudinal de Saúde do Adulto - ELSA "
Pesquisador Responsável: Estela Maria Motta Lima Leão de Aquino
Área Temática: Grupo II

Os Membros do Comitê de Ética em Pesquisa, do Instituto de Saúde Coletiva/Universidade Federal da Bahia, reunidos em sessão ordinária no dia 26 de maio de 2006, e com base em Parecer Consubstanciado, resolveu pela sua aprovação.

Situação: APROVADO

Salvador, 29 de maio de 2006

VILMA SOUSA SANTANA
Presidente do Comitê de Ética em Pesquisa
Instituto de Saúde Coletiva
Universidade Federal da Bahia