Universidade Federal de Pelotas
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Epidemiologia da proteína C reativa em adultos jovens pertencentes a uma coorte de nascimentos no sul do Brasil

Tese de doutorado

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À minha querida esposa

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Dubito ergo cogito

-René Descartes

Índice

Apresentação

Conforme o regimento do Programa de Pós-graduação em Epidemiologia da Universidade Federal de Pelotas, esta tese é composta por cinco partes: projeto de pesquisa, relatório do trabalho de campo, artigos, reportagem para ser divulgada na imprensa e anexos.

O projeto de pesquisa foi defendido no dia 31 de maio de 2006, sendo a banca composta pelos professores Bernardo Horta e Paulo Orlando Monteiro. A versão apresentada nesta tese inclui as modificações sugeridas pela banca examinadora, além de outras conforme a evolução dos objetivos do projeto. As três modificações principais foram: 1- um quarto artigo para apresentar dados gerais sobre a distribuição de proteína C reativa na coorte (Artigo 4); 2- o objetivo do artigo de revisão que, a princípio, era revisar os determinantes dos níveis de proteína C reativa, foi refinado para incluir somente variáveis socioeconômicas e de raça/etnia (Artigo 1); e 3- os períodos de crescimento (ganho de peso) a serem examinados foram ampliados, para incluir também os seguimentos da coorte nos anos de 1997, 2000 e 2001 (Artigo 3).

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Projeto de Pesquisa

Doutorando: Aydin Nazmi
Orientador: Cesar G Victora

31.05.2006

RESUMO

A carga global das doenças cardiovasculares (DCVs) é enorme em termos de morbi-mortalidade e custos econômicos. Teorias atuais sugerem que a inflamação tenha um papel fundamental na etiologia das doenças cardiovasculares. A proteína C reativa (PCR) é um marcador bioquímico da inflamação geral não-específica e tem sido associada positivamente com a incidência e a progressão das DCVs. Evidências epidemiológicas implicam a PCR como um possível mediador nos processos patológicos associados com as DCVs. O fato de que níveis elevados podem ser detectados em adultos jovens, muitos anos antes da incidência das DCVs, abre uma perspectiva extremamente importante para atividades de prevenção. A hipótese de que exposições no início da vida, incluindo peso ao nascer, crescimento e posição socioeconômica, possam afetar o desenvolvimento futuro de doenças crônicas requer estudos de coorte, preferencialmente acompanhadas prospectivamente desde a gestação ou nascimento. O estudo dos nascidos em Pelotas em 1982, incluindo informações desde a gestação até a vida adulta, fornece uma fonte rica de dados para investigar os fatores precoces associados com níveis de PCR em adultos jovens. O projeto atual pretende investigar níveis da PCR em relação ao crescimento precoce e trajetória socioeconômica. Dada a importante associação entre níveis de PCR e a ocorrência subseqüente de DCVs, o estudo permitirá identificar estratégias para sua prevenção.

ARTIGOS PLANEJADOS

1. Tamanho ao nascer, crescimento pós-natal e proteína C reativa: estudo prospectivo baseado em uma coorte de nascimentos

2. Trajetórias socioeconômicas e proteína C reativa: estudo prospectivo baseado em uma coorte de nascimentos no Sul do Brasil

3. Determinantes dos níveis de proteína C reativa: uma revisão sistemática

1. INTRODUÇÃO

1.1. Doenças cardiovasculares

O presente projeto enfoca a questão das doenças cardiovasculares em uma coorte de nascimentos.

1.1.1. A carga global das doenças cardiovasculares

Sabe-se que 30% dos óbitos mundiais, mais que 16 milhões a cada ano, são devidos às doenças cardiovasculares (DCV). Dessas, 80% - mais que 12 milhões - ocorrem em países de renda média e baixa, embora a mortalidade proporcional por DCVs em relação ao total de óbitos seja maior nos países ricos (1, 2). Não existem grandes diferenças entre os sexos, embora as mulheres apresentam uma taxa de mortalidade por DCVs um pouco mais alta. Em termos da saúde pública global, as DCVs consistem na maior causa da mortalidade e em uma das maiores causas de morbidade em ambos os sexos em todas as regiões do mundo (1). Além dos custos humanos, os impactos econômicos são enormes. As DCVs custam à União Européia e aos Estados Unidos em torno de 500 bilhões de Euros anuais, quando se consideram custos médicos, redução na produtividade por causa de morbi-mortalidade e custos indiretos associados à essas doenças (3, 4).

1.1.2. Características das doenças cardiovasculares

A etiologia da DCV é multi-fatorial, com componentes genéticos, ambientais e sociais. Classicamente, a categorização dos níveis de risco das DCVs tem sido definida através de estudos epidemiológicos, de acordo

com várias manifestações físicas e fisiológicas, como medidas sanguíneas e antropométricas (glicemia, pressão arterial e peso corporal, por exemplo), que têm sido usadas como marcadores de risco. Os fatores de risco tradicionais não-modificáveis para DCV são idade, sexo e raça; os fatores modificáveis incluem alta gordura corporal (especialmente gordura central), sedentarismo, tabagismo e altos níveis de pressão arterial, glicemia e colesterol (5). Nos últimos anos, a combinação de alta-tecnologia e estudos epidemiológicos têm apresentado a oportunidade de investigar novos possíveis fatores de risco para DCV.

1.2. Inflamação

Teorias atuais sugerem que a inflamação tenha um papel fundamental na etiologia das doenças cardiovasculares.

1.2.1. Conceitos gerais

Inflamação é a resposta imune não-específica que ocorre em reação a um estímulo danoso. Este é um processo altamente orquestrado envolvendo uma rede complexa de interações celulares e moleculares, direcionada a retornar o organismo à homeostase fisiológica. A resposta inflamatória está composta de eventos locais e de uma ativação sistêmica mediada por citocinas pró-inflamatórias, como a interleucina-6 (IL-6), a interleucina-1 (IL-1) e o fator de necrose tumoral (TNF-α), que influenciam e regulam respostas fisiológicas (6-8).

1.2.2. Resposta da fase aguda

Toda vez que o organismo se depara com uma alta concentração de citocinas na circulação por causas inflamatórias, os hepatócitos são estimulados a produzir e excretar proteínas que participam coletivamente em funções protetoras (9-11). As proteínas cuja concentração varia em pelo menos 25% durante um processo inflamatório, como por exemplo a proteína C reativa (PCR), são consideradas da fase aguda, sendo que sua concentração pode variar de acordo com o estímulo recebido (Figura 1) (6). A PCR está implicada na ativação ou regulação da "cascata" de complemento clássico - um dos processos fundamentais da sistema imune - e no processo para facilitação da fagocitose - conhecido como "opsonização" - ainda que seu papel fisiológico não seja totalmente conhecido (10, 12, 13).

1.2.3. O tecido adiposo: ativo no processo pró-inflamatório

Ao contrário da noção tradicional de que o tecido adiposo seria apenas um local de armazenamento de energia, estudos recentes têm mostrado que o mesmo é um órgão endócrino, capaz de secretar sinais hormonais e citocinas pró-inflamatórias como a IL-6, uma das mais importantes estimuladoras de PCR (14-16). A IL-6 tem sido correlacionada com a gordura corporal e a PCR, com coeficientes de correlação de 0,55 ($p<0,01$) e 0,37 ($p<0,0005$), respectivamente (17, 18). Um estudo em mulheres "sadias" obesas mostrou que o nível de PCR estava positivamente associado com o IMC ($r=0,281$, $p=0,01$) e a circunferência abdominal (0,278, $p=0,01$) e que a perda de peso corporal resultou em uma

diminuição do nível de PCR de 26% (p<0,001), sendo a correlação entre peso perdido e mudança do nível de PCR de 0,309 (p=0,005) (19). O tecido adiposo, fonte de 30% da produção de IL-6, é possivelmente um dos fatores mais importantes nos estados inflamatórios crônicos associadas com a DCV (16).

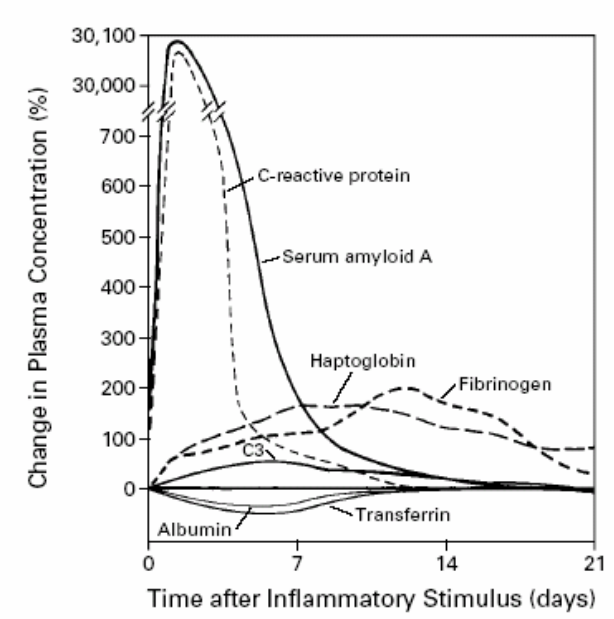


Figura 1: As respostas características nas concentrações plasmáticas de algumas proteínas da fase aguda seguindo um estímulo inflamatório moderado (6).

1.3. Proteína C reativa

Dentro do processo inflamatório, a proteína C reativa tem recebido especial atenção. Esta proteína, chamada assim por sua capacidade de reagir com o polissacarídeo C na parede celular do *Pneumococcus*, faz parte da família das proteínas pentraxinas (20, 21). Filogeneticamente antiga, a PCR tem sido altamente conservada em termos da evolução, existindo proteínas homólogas em

todos os vertebrados. Em humanos, a PCR está composta de cinco sub-unidades de polipeptídeos não-glicosilados idênticos, cada um com 206 aminoácidos com ligações não-covalentes, sendo uma estrutura muito estável (21).

1.3.1. Utilidade clínica

A PCR é um marcador bioquímico da inflamação geral não-específica. Depois de um insulto fisiológico, como um infarto, os níveis de PCR aumentam do valor basal, normalmente inferior a 1 mg/L, até mais de 5 mg/L num período de seis horas, chegando ao seu pico, até milhares de vezes acima do nível normal, em 48 horas (21) (Figura 1). Com uma meia-vida de 19 horas, os níveis de PCR voltam a diminuir logo após a fase aguda. Assim, a PCR tem sido usada clinicamente no monitoramento e rastreamento das doenças agudas e no período pós-cirúrgico.

1.3.2. Utilidade epidemiológica

Recentemente, testes de proteína C reativa de alta sensibilidade (PCR-as) têm sido desenvolvidos para detectar níveis muito inferiores aos presentes na fase aguda (22, 23). Estes testes refletem a inflamação crônica de baixo nível. Os resultados apresentados a seguir se referem a este teste de alta sensibilidade.

<u>Estudos populacionais: sexo, idade e fatores socioeconômicos</u>

O nível basal de PCR em humanos parece ter um componente genético importante (24). A variabilidade entre os sexos é controversa, sendo que alguns estudos relatam que existe uma diferença significante entre adultos

(25-28), e outros não (29-36). Por exemplo, em 2003, um estudo em 22.403 norte-americanos de 40-84 anos mostrou que os níveis medianos para homens e mulheres eram respectivamente 1,50 e 1,52 mg/L, sem uma diferença significante (34). Por outro lado, um estudo brasileiro em indivíduos de 14-74 anos concluiu que estratificação por sexo é necessária, pois houve diferenças significativas entre homens e mulheres quanto aos níveis de PCR (25). As diferenças, se existem, dos níveis de PCR entre os sexos segue sendo investigado, sendo que a plausibilidade biológica ainda não está claramente explicada. Notou-se ainda que mulheres fazendo terapia de reposição hormonal apresentam um aumento dos níveis de PCR (29, 32, 34).

Alguns estudos mostram uma associação significativa entre PCR e idade (28, 29, 37-41), mas outros não encontraram tal correlação (32, 34, 42). Os estudos que mostram essa associação indicam que o nível aumenta com a idade, sendo possivelmente influenciada pela gordura corporal ou tabagismo (38). No estudo de Bermudez et al entre mulheres de meia idade, a idade somente esteve significantemente associada com o nível de PCR após ajuste para fatores tradicionais de risco para DCVs (39).

Fatores socioeconômicos estão inversamente associados com as DCVs, mostrando um gradiente biológico entre os extremos (43, 44). Alem disso, fatores socioeconômicos parecem estar independentemente e inversamente associados com níveis de PCR (31, 45-47). No estudo de coorte de Framingham (EUA), a escolaridade esteve negativamente associada com a

PCR após ajuste para fatores de risco clínicos (incluindo o IMC) entre homens e mulheres de meia-idade. Por cada ano adicional de escolaridade, o PCR baixou 0,034 ln mg/L (0,051-0,016), p=0,0002, (31). Em outro estudo na Finlândia entre homens de 45-74 anos, a PCR mostrou uma tendência linear negativa (p=0,022) entre tercis socioeconômicos após ajuste para idade, tabagismo, razão cintura-quadril e outras doenças crônicas; a média geométrica de PCR (mg/L) era 2,11 no nível mais baixo; 1,91 no nível médio e 1,63 no nível mais alto (45). Um estudo inglês mostrou que os efeitos cumulativos de condições adversas durante o ciclo vital eram diretamente associados com níveis de PCR (46). O mesmo estudo mostrou que após ajuste para vários fatores socioeconômicos na vida precoce e adulta, a relação entre a PCR e a DCV perdeu a significância estatística. Os autores do tal estudo sugerem que estudos prospectivos devem considerar cuidadosamente os efeitos socioeconômicos durante o ciclo vital, incorporando-os nas análises de fatores precoces e contemporâneos.

Outro estudo finlandês mostrou que a posição socioeconômica durante o ciclo vital esteve inversamente associada com a PCR na vida adulta em homens e mulheres de 24-39 anos. No entanto, após ajuste para o IMC e a razão cintura-quadril, a associação perdeu significância, sugerindo que a relação entre nível socioeconômico e a PCR estava mediada por adiposidade na vida adulta (48).

É possível que fatores ambientais desfavoráveis propiciem um aumento de condições inflamatórias crônicas durante a vida, levando a um aumento do risco de fatores associados com o desenvolvimento das DCVs. Outros estudos investigando nível socioeconômico e fatores precoces são necessários para desenvolver uma perspectiva mais ampla dos determinantes e do papel de PCR em relação aos DCVs.

Estudos populacionais: tabagismo, composição corporal e atividade física

A literatura confirma que indivíduos mais gordos e tabagistas atuais ou passados apresentam níveis aumentados de PCR (19, 33, 39, 41, 42, 49-55). O estudo de Tracy et al entre indivíduos com mais de 65 anos mostrou que o tabagismo atual não estava significantemente associado com o nível de PCR, mas a exposição cumulativa ao fumo ao longo da vida mostrou-se significante, mesmo entre ex-fumantes que haviam parado de fumar por 30 anos (42). Visser et al mostraram que um IMC superior a 30 kg/m^2 em adultos de 17-39 anos esteve significantemente associado com a PCR, com razões de odds ($IC_{95\%}$) de 2,85 (1,30-6,10) para homens e 12,90 (5,61-29,65) para mulheres a apresentar níveis de PCR acima de 0,22 mg/L (51). Hak et al mostraram que a circunferência da cintura em mulheres esteve significativamente associada à PCR, mesmo após ajuste para o IMC, indicando que o tecido adiposo central é um determinante importante (50).

Estudos que testaram associações entre PCR e nível de capacidade ou atividade física, com poucas exceções (33, 56), relataram associações inversas com concentrações de PCR (26, 27, 30, 57-59). De fato, uma revisão

sistemática da literatura até 2004 mostrou que a atividade física tem efeitos anti-inflamatórios a longo-prazo (60), embora Bermudez et al tenham mostrado que a relação entre atividade física e a PCR em mulheres perdeu significância após ajuste para fatores de risco tradicionais para DCVs, incluindo o IMC (39).

Recentemente, a perda de peso, induzida por atividade física ou dieta, tem sido relacionada com a diminuição dos níveis de PCR (61-65). Um ensaio clínico randomizado de mulheres obesas de 20-46 anos mostrou que aquelas no grupo de intervenção (aconselhamento nutricional e promoção da atividade física) diminuíram seus índices de massa corporal e níveis de PCR mais que no grupo controle (-4,2 kg/m^2; $p<0,001$ e -1,6 mg/L; $p=0,008$, respectivamente) (65). Outro estudo similar mostrou que as diminuições dos níveis de PCR após a perda de peso corporal eram relacionadas às mudanças da razão cintura-quadril e metabolismo dos lipídios, e não associadas com níveis de IL-6 (66).

Variabilidade sazonal e circadiana

Estudos populacionais têm mostrado que não há variabilidade significativa nos níveis de PCR ao longo do dia (67). Com uma exceção que indicou que níveis de PCR são levemente elevados no inverno e na primavera em comparação ao verão (35), os demais estudos concordam que também não há variabilidade significante entre as estações (21, 68).

1.4. Evidências epidemiológicas

Diversos estudos têm mostrado associações entre níveis de PCR e desfechos relacionados a doenças crônicas.

1.4.1. Inflamação crônica de baixo nível e eventos cardiovasculares

A aterosclerose, processo fundamental no desenvolvimento das DCVs, tem sido descrita como uma doença inflamatória (69). De fato, muitos estudos observacionais têm mostrado que níveis elevados de inflamação crônica de baixo nível, medido por PCR-as, predizem a incidência de DCVs entre ambos sexos em vários países (40, 41, 70-81). O artigo clássico do Ridker et al em 1997, usando dados de *Physician´s Health Study*, mostrou que durante um período de seguimento de oito anos, homens de meia-idade com níveis de PCR no quartil mais alto (PCR>2,11 mg/L) tiveram um risco relativo (RR) de 2,9 ($IC_{95\%}$ 1,8-4,6) de ter um infarto em comparação aos que estavam no quartil mais baixo (PCR<0,55 mg/L). Em um estudo de casos e controles aninhado dentro de um estudo de coorte entre mulheres de meia-idade, os mesmos pesquisadores mostraram que o RR para eventos cardiovasculares foi de 4,1 ($IC_{95\%}$ 1,7-9,9) para aquelas no quartil mais alto de PCR (PCR>7,3 mg/L) em comparação ao mais baixo (PCR<1,5 mg/L) (76).

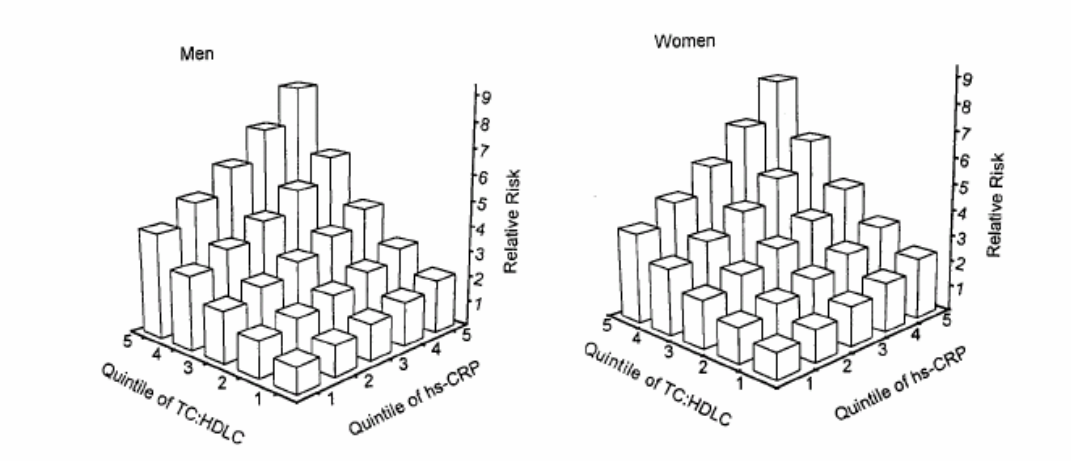


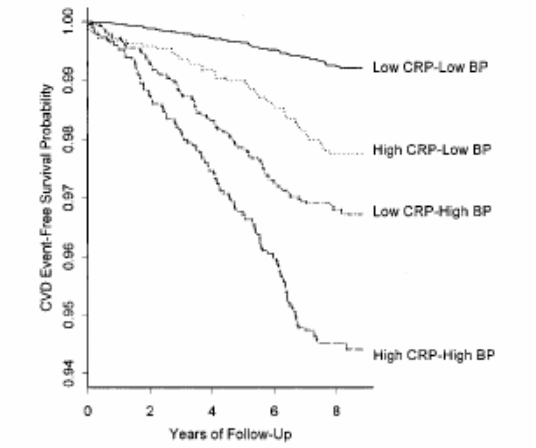
Figura 2: Riscos relativos do primeiro evento cardiovascular entre adultos aparentemente sadios associados com concentrações de PCR-as e a razão de colesterol total:HDLC em quintis (22).

1.4.2. Valor preditivo

Além de ser um fator de risco importante para DCV, tem sido provado que a PCR melhora o valor preditivo para fatores de risco mais tradicionais como colesterol e pressão arterial (73, 74, 76, 80, 82). A Figura 2 mostra os RRs entre quintis da PCR, da razão colesterol total:HDLC, e das duas variáveis, para a incidência do primeiro evento cardiovascular. Observa-se que o valor preditivo da razão colesterol total:HDL - descrito como o melhor preditor de risco lipídico para DCV - aumenta seu poder de discriminação quando associado à PCR, que foi o melhor preditor não-lipídico de risco (83).

A Figura 3 mostra a sobrevivência livre de eventos cardiovasculares entre mais de 15.000 mulheres em um modelo incluindo pressão arterial (PA elevada ≥ 130/85) e PCR (elevada ≥ 3,0 mg/L), no qual o uso de ambas as variáveis melhora a predição de DCVs. Após ajuste para idade, IMC,

tabagismo, colesterol (HDL e LDL) e diabetes, as razões de densidade de incidência ("hazard ratios") ($IC_{95\%}$) foram de 1,0 (referência); 1,87 (1,25-2,80); 2,54 (1,79-3,58) e 3,27 (2,28-4,71) para os grupos de baixo PCR/baixa PA, alto PCR/baixa PA, baixo PCR/alta PA e alta PCR/alta PA, respectivamente (p<0,0001) (74).

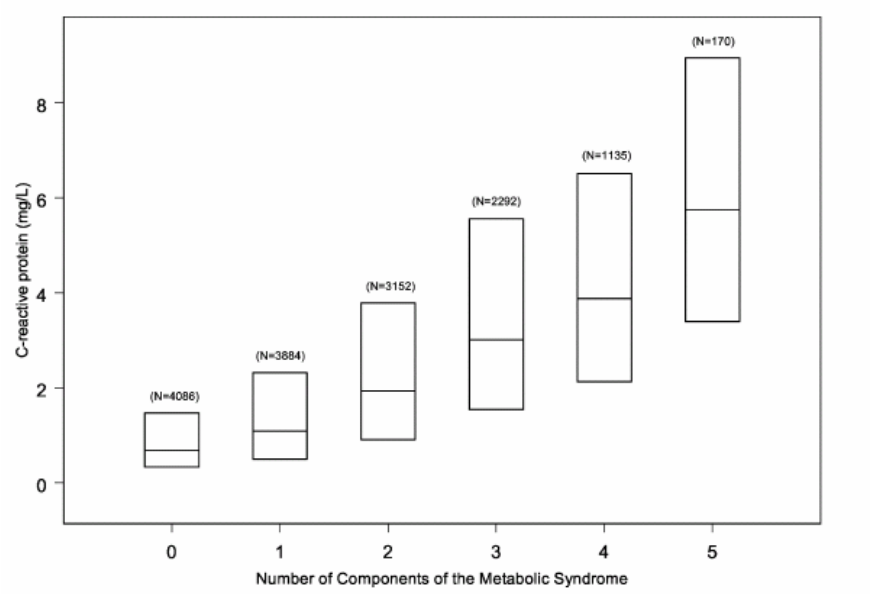


<u>Figura 3</u>: Sobrevivência sem-eventos entre mulheres com PCR (elevada ≥ 3 mg/L) e a pressão arterial (elevada ≥ 130/85 mmHg) (74).

1.4.3. PCR e síndrome metabólica: forte fator de risco para DCV

A síndrome metabólica (SM) – que inclui obesidade central, níveis elevados de triglicerídeos, glicemia, ou pressão arterial, e níveis baixos de HDL - constitui um importante fator de risco para morbi-mortalidade associada à DCV (84, 85). A presença de SM tem sido relacionada positivamente com a PCR em estudos abordando jovens e adultos de ambos os sexos, em diversos países (39, 42, 53, 77, 79, 86-93). Mais ainda, vários estudos mostraram que a coexistência de diversos componentes da SM esteve fortemente associada com a PCR. Ridker et al

mostraram que mulheres com 0, 1, 2, 3, 4 ou 5 características da SM apresentaram níveis de PCR de 0,68; 1,09; 1,93; 3,01; 3,88 e 5,75 mg/L, respectivamente ($p_{tendência}$ <0,0001) (Figura 4). Um estudo alemão, em homens e mulheres de 18-89 anos, mostrou que em indivíduos com seis ou sete componentes da SM o nível da PCR era três vezes maior (3,28 mg/L; $IC_{95\%}$ 1,82-5,91) do que em indivíduos sem a SM (94).



<u>Figura 4</u>: A distribuição dos níveis de PCR entre 14.719 mulheres norte-americanas segundo a presença de 0, 1, 2, 3, 4 ou 5 componentes da síndrome metabólica. Os diagramas de caixa demonstram níveis medianos e os percentis 25 e 75 para a PCR (77).

A Federação Internacional de Diabetes lista o estado crônico pró-inflamatório (para o qual a PCR é um dos marcadores) como um fator metabólico adicional aos critérios clássicos de SM (95). Alguns autores estão propondo que a PCR passe a ser considerada como um fator principal, e não mais adicional, na definição da SM (96).

1.4.4. Níveis de risco da proteína C reativa

Baseado em estudos epidemiológicos, os *Centers for Disease Control and Prevention* (CDC) juntamente com o *American Heart Association* (AHA) concluíram que a PCR, enquanto marcador sensível da inflamação sistêmica e importante fator de risco metabólico, pode ser utilizada adicionalmente aos fatores tradicionais de risco para DCV. Para este fim, foram sugeridas as seguintes categorias de risco: baixo (PCR<1,0 mg/L), médio (1,0-3,0 mg/L) e alto (>3,0 mg/L) (97).

1.5. O papel fisiológico da PCR: marcador, mediador ou determinante?

Há consenso de que níveis de PCR refletem com alta precisão a presença de inflamação, tendo portanto um papel importante na avaliação de risco para prevenção das DCVs (22, 98-102). Não há consenso, no entanto, sobre o papel causal da PCR em relação às DCV. A PCR poderia ser um determinante das DCVs se indivíduos geneticamente programados para apresentar maiores níveis de PCR apresentassem maior incidência de DCV. Ainda assim, poderia ser um mediador entre outros fatores de risco – como tabagismo ou obesidade – e as DCVs. Finalmente, poderia ser apenas um marcador, um fator que estaria associado a outros fatores de risco e portanto refletiria o risco de DCV, sem fazer parte da cadeia causal.

Dois estudos recentes usando randomização mendeliana avaliaram o possível papel da PCR como determinante. Os resultados mostraram que a presença de haplótipos da PCR, por si só, não aumenta o risco de DCVs, ou seja, que a PCR

não parece ser um determinante independente (103, 104). Por outro lado, a PCR tem sido implicada como um mediador nos processos de desenvolvimento das DCVs (13, 14, 99, 105-109), ou seja, que níveis elevados de PCR fazem parte de uma cadeia causal que liga diversos determinantes – como tabagismo ou obesidade – aos desfechos cardiovasculares. Finalmente, outros autores afirmam que a PCR não teria tal efeito de mediação, sendo apenas um marcador de risco por estar associada aos verdadeiros determinantes, sem fazer parte da cadeia causal (40, 46, 99). As controvérsias seguem e, além de estudos longitudinais, investigações da bio-patofisiologia da PCR ainda são necessárias para confirmar seus papéis potenciais na patogênese da DCV.

1.6. As origens desenvolvimentistas das doenças cardiovasculares

Fatores da vida intrauterina e da infância – como, por exemplo, nutrição materna durante a gravidez, o peso ao nascer e a taxa de crescimento nos primeiros meses/anos da vida - têm sido associados a um aumento no risco de doenças crônicas e seus fatores associados- incluindo doenças cardiovasculares, diabetes, obesidade e hipertensão arterial- em jovens e adultos, em muitos países (110-120).

A hipótese de que exposições no inicio da vida podem afetar o desenvolvimento futuro de doenças crônicas tem sido descrita com diversas denominações: “hipótese de Barker”, “fenótipo econômico”, “hipótese de crescimento acelerado” e “origens desenvolvimentistas”. Todas estas propõem que fatores precoces- maternos, perinatais e relativos ao crescimento na infância- através de mecanismos de plasticidade fisiológica e os efeitos de

programação, influenciam o risco para desenvolver doenças associadas com a SM e as DCVs. Os mecanismos celulares e moleculares que governam os processos metabólicos mediadores nesta cadeia causal não são claramente entendidos e ainda estão sendo investigados (121, 122).

Dois mecanismos básicos são propostos para explicar a associação entre fatores precoces e doenças na vida adulta, sendo que os dois não são necessariamente mutuamente exclusivos. O primeiro está associado com os efeitos de desnutrição precoce sobre números de células em órgãos específicos; ou seja, alterações na estrutura somática (110). A quantidade ou proporção das células são permanentemente afetados, alterando ou diminuindo a capacidade funcional de sistemas e órgãos. O segundo mecanismo que pode levar fatores precoces a doenças na vida adulta está relacionado com a determinação dos parâmetros hormonais e metabólicos (123). Programação fisiológica originando com um insulto num período crítico no desenvolvimento pode levar os tecidos e órgãos a apresentar respostas anormais nos receptores (124). Essas mudanças permanentes na estrutura somática e nos parâmetros hormonais se associam com estados metabólicos deficientes no período pós-natal e fazem parte da cadeia das síndromes associadas com as doenças crônicas.

Apenas três estudos foram localizados sobre os determinantes precoces dos níveis de PCR. O primeiro foi um estudo escocês avaliando níveis de PCR entre homens e mulheres de 30-59 anos (125). Houve uma redução de 10,7% ($IC_{95\%}$ 17,8-3,0) na média de PCR por cada aumento de 1 kg no peso ao nascer, mas apenas após o ajuste para o IMC atual do indivíduo. Este achado sugere que o

ganho de peso, e não o peso ao nascer *per se*, influencia o nível de PCR (126). O segundo artigo investigou o efeito da duração do aleitamento materno sobre os níveis de PCR em adultos (127). Em mulheres, mas não em homens, as que não foram amamentadas e as que foram amamentadas por seis meses ou mais apresentaram médias geométricas (amplitude intra-quartis) de PCR de 3,95 mg/L (2-8) e 2,22 mg/L (1-4), respectivamente ($p<0,001$), sugerindo que a nutrição precoce ou pós-natal pode influenciar estes níveis em adultos. Um terceiro estudo (48), já discutido na seção 1.3 (Estudos populacionais), avaliou o efeito da pobreza na infância, assim como na vida adulta, sobre níveis de PCR em adultos.

A análise dos efeitos a longo prazo de exposições precoces requer estudos de coorte, preferencialmente acompanhadas prospectivamente desde a gestação ou nascimento.

1.7. A coorte de nascimentos em Pelotas de 1982

A existência de uma coorte de nascimentos na cidade de Pelotas (Brasil) permite testar uma série de hipóteses relacionadas à determinação dos níveis de PCR. Em resumo, os 5914 nascidos vivos nos hospitais na zona urbana da cidade foram incluídos em uma coorte de nascimentos, representando mais de 99% dos nascimentos na cidade em 1982. Uma série de variáveis maternas e perinatais foi coletada ao nascer. Até 2006, mais de 10 visitas de acompanhamento foram realizadas em várias sub-amostras da coorte, resultando em mais de 4000 variáveis coletadas para os indivíduos que participaram em todas as fases do estudo. Os detalhes, métodos e fases de acompanhamento da

coorte estão descritos em outras publicações (128, 129). Nas análises propostas no presente projeto, serão utilizados dados das seguintes visitas:

1982: Os 5914 recém nascidos vivos nos hospitais da zona urbana da cidade no período de janeiro até dezembro, foram incluídos. As crianças foram pesadas e um questionário padronizado, incluindo informações demográficas, socioeconômicas e relacionadas à saúde, foi aplicado às mães. Idade gestacional foi avaliada pela data da última menstruação (20% das mães não souberam informar).

1983: Esta sub-amostra incluiu os nascidos de janeiro até abril de 1982 (n=1916). Foram pesadas e medidas 1457 crianças (79,3%) com idade em média de 11,3 meses (amplitude 8,0-16,0). As suas mães foram entrevistadas com um questionário padronizado com perguntas sobre fatores socioeconômicos, amamentação e nutrição, e a saúde da criança.

1984: Foram visitados todos os 70.000 domicílios de Pelotas buscando indivíduos da coorte. Após este censo, indivíduos que ainda não haviam sido localizados foram buscados no último endereço disponível. Foram medidas e pesadas 87,2% das crianças da coorte (n=4934), com idade média de 19,4 meses (amplitude 12,0-29,0). Um questionário padronizado sobre fatores socioeconômicos, amamentação, nutrição e saúde da criança foi respondido pelas mães.

1986: Utilizou-se a mesma metodologia de 1984. Foram medidas e pesadas 84,1% das crianças na coorte (n= 4742), com idade média de 43,1 meses (amplitude 35,4-53,0), sendo também aplicado um questionário às mães.

1997: Neste ano, 27% dos setores censitários da cidade foram visitados afim de buscar participantes da coorte para fazer parte de um sub-estudo. Desta maneira, 71.8% (n= 1076) dos indivíduos da sub-amostra foram entrevistados e medidos com média idade de 14.7 anos (amplitude: 14.0-15.6).

2000 e 2001: Em 2000, homens que faziam parte da coorte foram identificados durante o recrutamento militar. Dos 3037 homens da coorte, 2250 (78.9%) foram entrevistados e medidos com idade média de 18.2 anos. Em 2001, a mesma sub-amostra do 1997 foi visitada, sendo que 1031 (69.0%) participantes dela foram examinados e entrevistados. As sub-amostras dos dois seguimentos foram combinadas no presente estudo para poder examinar ambos os sexos. A idade média combinada foi de 18.4 anos (amplitude: 17.6-19.8). Para refletir os dois seguimentos da coorte, este período está descrito como a visita de 18/19 anos.

2004: Em 2004-05, foram visitados todos os domicílios de Pelotas buscando membros da coorte; após este censo, indivíduos que ainda não haviam sido localizados foram buscados no último endereço disponível. Foi aplicado um questionário e realizado exame antropométrico em 4295 indivíduos com idade média de 22,8 anos (amplitude 21,9-23,7). A entrevista incluiu informações sobre hábitos de saúde e fatores sociodemográficos. Quase 90% destes

indivíduos (n=3832) concordaram em doar uma amostra de sangue, aproximadamente 15 ml, coletada por técnicos de enfermagem e congelada a -70º C. O estudo atual utilizará estas amostras de soro congeladas.

2. JUSTIFICATIVA

A alta morbi-mortalidade associada às DCVs e sua tendência crescente em muitos países têm provocado grande interesse nas investigações sobre a epidemiologia e os mecanismos associados com a PCR. Apesar da controvérsia sobre o papel exato da PCR no desenvolvimento das DCVs, sabe-se que seu nível é um marcador altamente sensível para risco das DCVs. O fato de que níveis elevados podem ser detectados em adultos jovens, muitos anos antes da incidência das DCVs, abre uma perspectiva extremamente importante para atividades de prevenção.

Estudos longitudinais têm mostrado que fatores precoces, incluindo o crescimento, têm papéis importantes no desenvolvimento das DCVs (110, 115). Sabe-se ainda que fatores socioeconômicos ao longo do ciclo vital têm forte influência sobre as mesmas doenças (130). Apenas três estudos foram localizados sobre determinantes precoces de níveis de PCR. O estudo dos nascidos em Pelotas em 1982, incluindo informações desde a gestação até a vida adulta, fornece uma fonte rica de dados para investigar os fatores precoces associados com níveis de PCR em adultos jovens.

Pretende-se investigar as associações entre níveis de PCR e variáveis referentes ao crescimento (intra e extrauterino) e ao nível socioeconômico (medida por renda

familiar e escolaridade) ao longo da vida. A grande maioria dos estudos na literatura usam níveis de PCR como exposição enquanto o estudo atual investigará os determinantes dos níveis de PCR, ou seja, esta variável será o desfecho. Dada a importante associação entre níveis de PCR e a ocorrência subseqüente de DCVs, o estudo permitirá identificar estratégias para sua prevenção.

3. MARCO TEÓRICO

Para planejar a análise dos dados coletados nas diferentes visitas, é essencial dispor de um marco teórico mostrando a hierarquia entre as variáveis a serem estudadas. As seções 1.1-1.6 na Introdução discutem os estudos e conceitos utilizados na elaboração teórica do projeto na perspectiva do modelo teórico proposto.

3.1. Modelo hierárquico

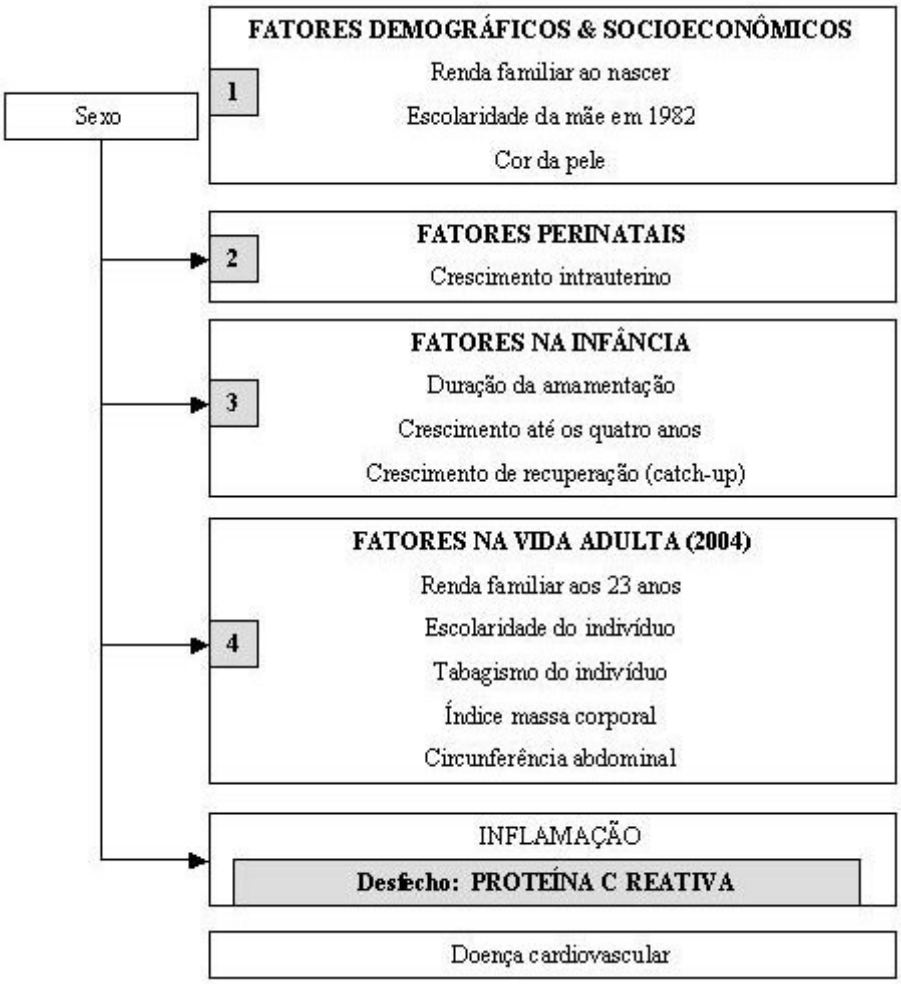


Figura 5: Modelo hierárquico com quatro níveis categorizados e fatores associados

3.2. O modelo apresenta fatores demográficos e socioeconômicos no nível mais distal da causalidade. Cada nível exerce influência sobre os níveis seguintes (mais próximos ao desfecho), em ordem de seqüência temporal dos acontecimentos e de hierarquia de determinação.

4. OBJETIVOS

4.1. Geral

4.1.1. Descrever as associações entre níveis de PCR em adultos jovens com o crescimento intra e extrauterino, assim como com fatores socioeconômicos avaliados na infância e na idade adulta, entre os nascidos em Pelotas em 1982

4.2. Específicos

4.2.1. Investigar as associações entre padrões de crescimento intrauterino e em diversos períodos da vida com níveis de PCR aos 23 anos.

4.2.2. Descrever as associações entre posição e mudança de nível socioeconômico durante a vida com níveis de PCR aos 23 anos.

4.2.3. Avaliar outros possíveis fatores de risco associados com a PCR como cor da pele, sexo, tabagismo, circunferência abdominal e índice de massa corporal.

4.2.4. Realizar revisão sistemática da literatura sobre os determinantes da PCR na população geral.

5. HIPÓTESES

5.1. As seguintes variáveis estão positivamente associadas aos níveis de PCR aos 23 anos:

5.1.1. Restrição de crescimento intrauterino

5.1.2. Crescimento rápido nos primeiros anos da vida, em especial crescimento de recuperação (*catch-up*)

5.1.3. Pobreza em qualquer fase do ciclo vital

5.1.4. Tabagismo, atual ou passado

5.1.5. Obesidade, obesidade central ou sobrepeso aos 23 anos

5.1.6. Cor da pele não-branca

5.1.7. Sexo feminino

6. METODOLOGIA

As principais características da metodologia do estudo estão listadas a seguir:

6.1. Delineamento: Estudo prospectivo tipo coorte de nascimentos

6.2. População alvo: Todos os nascidos vivos, em hospitais, de mães residentes na zona urbana de Pelotas, RS, em 1982

6.3. Critérios de inclusão na análise: Participantes da coorte de Pelotas de 1982 que disponham de informações completas para as variáveis relevantes à análise proposta

6.4. Critérios de exclusão na análise: Participantes sem informações completas

6.5. Cálculo do tamanho da amostra (Tabelas 1a, 1b e 1c)

A revisão da literatura mostrou desvios-padrão para PCR (mg/L) variando entre 0,6 e 8,2. Apenas dois dos 12 estudos com amostras da população geral mostraram desvios padrão superiores a 4,0 (estes estudos não utilizaram médias geométricas e seus DPs foram altamente influenciados pela assimetria da distribuição de PCR). Foram feitos cálculos de tamanho de amostra assumindo desvios-padrão iguais a 1,0 e 3,0, os quais estão descritos na Tabela 1 (a, b, c).

Dados os números fixos de observações disponíveis nas diversas visitas da coorte, foram estimadas as diferenças mínimas detectáveis em níveis de PCR, com α= 5% e β= 20%. De acordo com a Tabela 1, o estudo será capaz de detectar diferenças relativamente pequenas entre níveis médios de PCR,

particularmente se o desvio padrão for ao redor de 1,0. As diferenças mínimas que este estudo poderá detectar para várias exposições será de 0,09 até 0,89 mg/L. A literatura mostra diferenças muito variáveis entre grupos de expostos e não expostos a determinados fatores de risco; estas diferenças variam entre aproximadamente 0,5 e 10,0, conforme o fator estudado.

Vale notar que os poucos estudos existentes usando PCR como desfecho (não como exposição) usualmente apresentam amostras de 1 a 2 mil indivíduos. As análises principais incluirão cerca de 4000 indivíduos, sendo que aquelas em que será utilizado o peso com um ano de vida será limitada a 927 indivíduos, devido ao fato de que a visita de 1983 incluiu apenas uma sub-amostra.

6.6. Estratégia de busca para a revisão sistemática

A revisão sistemática será realizada utilizando quatro métodos de busca:

a) Uma pesquisa sistemática no PUBMED usando com palavras chaves e termos relacionados à revisão atual;

b) Revisão das referências dos artigos e publicações identificados;

c) Revisão dos artigos e publicações do próprio autor; e

d) Contato com pesquisadores renomados na área de pesquisa sobre PCR.

Tabela 1a: Cálculos para tamanho da amostra incluindo dados de 1982 e 2004 (N=3913)

Variável	N da coorte	Diferença mínima detectável com α=5% e β=20%, com desvios-padrão iguais a:	
		1,0	3,0
Cor da pele			
Não branca	989	0,11	0,32
Branca	2924		
Peso ao nascer (g)*			
<2500	282	0,17	0,52
≥ 2500	3630		
Pequeno para idade gestacional†			
Sim	270	0,18	0,55
Não	2859		
Amamentação (meses), de 1982-1986#			
<3	1803	0,09	0,27
≥ 3	1984		
Escolaridade da mãe em 1982 (anos completos)‡			
≤ 4	1304	0,10	0,28
>4	2604		
Renda familiar ao nascer (tercis)			
1°	1274	0,10	0,29
2° ou 3°	2639		
Renda familiar aos 23 anos (tercis)			
1°	1325	0,10	0,28
2° ou 3°	2588		
Escolaridade do indivíduo aos 23 anos (anos completos)			
≤ 4	312	0,16	0,49
>4	3601		
IMC aos 23 anos (kg/m^2), n=3710*§			
≥ 25	1055	0,10	0,31
<25	2655		

Tabela 1a (cont.): Cálculos para tamanho da amostra incluindo dados de 1982 e 2004 (N=3913)

Variável	N da coorte	Diferença mínima detectável com α=5% e β=20%, com desvios-padrão iguais a:	
		1,0	3,0
Circunferência abdominal (cm)			
Homens, n=1971			
≥ 94	207	0,20	0,60
<94	1764		
Mulheres, n=1744[§]			
≥ 80	410	0,16	0,47
<80	1334		
Tabagismo em 2004			
Sim	1011	0,10	0,31
Não	2902		
Mudança de renda 1982-2004			
Sempre pobre	654	0,12	0,36
Outros	3259		

* ≤ 5 valores missing
† 784 valores missing (20% da coorte total sem informações de idade gestacional)
# 126 valores missing
§ Excluindo as 198 mulheres grávidas e com ≤ 6 meses pós-parto

Tabela 1b: Cálculos de tamanho da amostra incluindo variáveis de crescimento de 1983 (N=927)

Variável	N da coorte	Diferença mínima detectável com α=5% e β=20%, com desvios-padrão iguais a:	
		1,0	3,0
Ganho de peso de 0-1 ano*			
≥ 0,67 escore-Z	262	0,21	0,64
<0,67 escore-Z	507		
Ganho de peso de 1-2 anos†			
≥ 0,67 escore-Z	102	0,30	0,89
<0,67 escore-Z	825		

* 158 valores missing (20% da coorte total sem informações de idade gestacional)
† 2 valores missing

Tabela 1c: Cálculos de tamanho da amostra incluindo variáveis de crescimento de 1982, 1984 e 1986 (N=3370)

Variável	N da coorte	Diferença mínima detectável com α=5% e β=20%, com desvios-padrão iguais a:	
		1,0	3,0
Ganho de peso de 0-2 ano*			
≥ 0,67 escore-Z	766	0,12	0,36
<0,67 escore-Z	1936		
Ganho de peso de 2-4 anos			
≥ 0,67 escore-Z	650	0,12	0,37
<0,67 escore-Z	2720		

* 635 valores missing (20% da coorte total sem informações de idade gestacional)

6.7. Principais variáveis (Tabela 3)

6.7.1. Variável dependente

- Nível de PCR-as, em mg/L, dicotômico PCR elevado ou não (ponto de corte a ser determinado) e mg/L log-transformado contínuo. Fonte de dados: 2004-05.

6.7.2. Variáveis independentes

- Cor da pele, branca ou não branca, auto-referida. Fontes de dados: 2004-05.
- Peso ao nascer, em gramas, contínuo e dicotômico (BPN <2500 g). Fonte de dados: 1982.
- Crescimento intrauterino, peso ao nascer conforme a idade gestacional, baseado nas curvas de Williams (113, 131). Crianças pequenas para a idade gestacional (PIG) foram identificadas como aquelas abaixo do percentil 10 da referência. Fonte de dados: 1982
- Amamentação, em meses, agrupado: ≤ 1; 1-2,9; 3-5,9; 6-8,9; 9-11,9; ≥12. Dados juntados das visitas: 1982, 1983, 1984 e 1986.
- Escolaridade da mãe (em 1982) e escolaridade do indivíduo (em 2004-05), anos completos e dicotômico (baixa escolaridade definida como ≤ 4 anos). Fontes de dados: 1982, 2004-05.
- Renda familiar, em salários mínimos. Classificada em categorias e tercis. Fontes de dados: 1982 e 2004-05.

- Crescimento extrauterino, em mudança de escores-z, contínuo, mudança em escores-z de peso por idade em quatro períodos: 0-1 ano, 1-2 anos, 0-2 anos, 2-4, 4-15, 15-18/19 e 18/19-23 anos. Variáveis dicotomizadas: crescimento rápido ou de recuperação definido como ganho de $\geq$ 0,67 escore-z dentro do período de tempo, conforme proposto por Ong (132). Os novos padrões de crescimento da Organização Mundial da Saúde serão utilizados para recalcular os escores-z (www.who.int/childgrowth), atualmente baseados nas curvas NCHS (133). Escores-z internos para peso nos seguimentos também serão calculados. Fontes de dados: 1982, 1983, 1984, 1986, 1997, 2000/2001, 2004-05.
- IMC, em kg/m^2, contínuo e agrupado, conforme critérios da OMS (134): <18,5, baixo peso; 18,5-24,9, adequado; 25,0-29,9, sobrepeso; $\geq$ 30, obesidade. Fonte de dados: 2004-05.
- Circunferência abdominal, em cm, contínua e dicotômica (obesidade central $\geq$ 94 cm homens e $\geq$ 80 cm mulheres (95), excluindo grávidas e as com $\leq$ 6 meses pós-parto). Fonte de dados: 2004-05.
- Tabagismo do indivíduo, atual (fuma todos os dias), passado (alguma vez na vida fumou todos os dias), ou nunca fumou. Fonte de dados: 2004-05.

- Mudança da renda familiar, criado dos tercis em 1982 e 2004. Os indivíduos no primeiro tercil (os mais pobres) serão considerados "pobres" e os demais como "não pobres", sendo assim criadas quatro categorias (Tabela 2). Fontes de dados: 1982 e 2004-05.

Tabela 2: Classificação da mudança da renda familiar de 1982 a 2004-05

Classificação	Tercil da renda familiar em 1982	Tercil da renda familiar em 2004-05
Sempre pobre	1°	1°
Pobre - não pobre	1°	2° ou 3°
Não pobre - pobre	2° ou 3°	1°
Nunca pobre	2° ou 3°	2° ou 3°

A tabela 3 resume as variáveis a serem estudadas.

Tabela 3: Descrição e tipo das variáveis estudadas

Variável	Descrição (categorias)	Tipo
Variáveis precoces		
Cor da pele	Branca ou não branca	Dicotômica
Renda familiar ao nascer	Agrupado e em tercis	Categórica ordinal
Escolaridade da mãe e baixa escolaridade	Anos completos	Numérica discreta e Dicotômica
Peso ao nascer e BPN	Gramas	Numérica contínua e Dicotômica
Crescimento intrauterino e PIG	Peso ao nascer/idade gestacional	Numérica contínua e Dicotômica
Crescimento e crescimento rápido/de recuperação	Mudança de escore-z	Numérica contínua e Dicotômica
Amamentação	Meses agrupados	Categórica ordinal
Variáveis contemporâneas		
Renda familiar aos 23 anos	Agrupado e em tercis	Categórica ordinal
Escolaridade do indivíduo e baixa escolaridade	Anos completos	Numérica discreta e Dicotômica
Tabagismo	Atual, passado ou nunca	Categórica nominal
Índice massa corporal e sobrepeso/obesidade	Peso corporal/altura (kg/m^2)	Numérica contínua e Dicotômica
Circunferência abdominal e obesidade central	Centímetros	Numérica contínua e Dicotômica
Mudança da renda familiar	Sempre pobre Pobre - não pobre Não pobre - pobre Nunca pobre	Categórica nominal
Desfecho		
Nível de proteína C reativa e PCR elevado	mg/L	Numérica contínua e Dicotômica

6.8. Instrumentos e materiais

6.8.1. Questionários padronizados para todas as fases do estudo: 1982, 83, 84, 86 e 2004-05. O questionário de 2004-05 pode ser consultado em www.epidemio-ufpel.org.br.

6.8.2. O exame físico dos membros da coorte usou os seguintes equipamentos:

Balanças

- Ao nascer (1982): Filizolla (Brasil), calibrada regularmente, precisão 10 g.
- 1983-1986: CMS Weighing Equipment (Reino Unido), precisão 10 g.
- 1997 e 2001: Uniscale UNICEF (Copenhagen), precisão 100 g.
- 2000: Tanita TBF-305 (Tóquio), precisão 200 g.
- 2004-05: Seca UNICEF (Reino Unido), precisão 110 g, até 150 kg.

Antropômetros

- 1983-1986: Modelo AHRTAG (hoje Healthlink Worldwide) padronizado, produzido localmente, sensibilidade 1 mm.
- 2004-05: Antropômetro de alumínio, produzido localmente, sensibilidade 1 mm.
- 2004-05: Fita métrica para circunferências: Cardiomed, inextensível em fibra de vidro, com 150 cm, sensibilidade 1 mm.

Dosagem de PCR

- Máquina IMMULITE para testes de PCR-as (Diagnostic Products Corporations, Los Angeles, EUA), ensaio imunométrico por quimiluminescência em fase sólida (135). Sensibilidade até 0,01 mg/L.
- As análises de PCR serão feitas em amostras de sangue coletadas em 2004-05.

7. COLETA DOS DADOS

Detalhes da coleta de dados estão descritos em diversas publicações (128, 129, 136). A seção 1.7 (A coorte de nascimentos em Pelotas de 1982) descreve os detalhes e os procedimentos na coleta dos dados nas visitas pertinentes ao estudo atual. As principais características das visitas da coorte foram a coleta dos dados com questionários padronizados aplicados por entrevistadores treinados e padronizados. As medidas antropométricas nas visitas foram feitas por antropometristas treinados por expertos nas respectivas áreas e regularmente padronizadas.

Na visita de 2004-05, a coleta do sangue foi feita por um técnico de enfermagem e o preparo para armazenamento do sangue feito por uma fisiologista experta na área de análises laboratoriais. Seção 1.3.2. (Utilidade epidemiológico) do texto atual já explicou que a hora e a época do ano da coleta do sangue não afeta os níveis da PCR. As amostras do soro que foram congeladas em -70° C serão degeladas e diluídas (1:99) anteriormente ao teste automatizado na máquina IMMULITE. Os processos relacionados aos testes de PCR-as serão feitos pelo investigador no Departamento de Fisiologia na UFPel, a partir de junho de 2006.

8. CONTROLE DE QUALIDADE

Controle de qualidade nas visitas da coorte (todas as fases) incluiu uma segunda visita ou contato telefônico, envolvendo aplicação de um questionário reduzido em 5-10% dos participantes feito por um supervisor do trabalho de campo. Os entrevistadores e antropometristas foram extensivamente treinados por expertos e

padronizados regularmente. Os dados coletados foram duplamente digitados por digitadores distintos.

Para os testes de PCR-as, três níveis de controles internos para a máquina IMMULITE serão testados todos os dias, juntos com uma lavagem diária, conforme o manual de instruções. Lavagem e calibragem da máquina serão feitos mensalmente, conforme as recomendações. Alem disso, 10% das amostras do soro serão duplamente testados e serão calculados os coeficientes de variação (CV, intra e inter). Posteriormente, um estudo avaliando vários métodos de análises para a PCR-as mostrou que a máquina IMMULITE produziu CVs de menos que 10% (137). Os resultados das análises serão confidenciais e serão exportados diretamente do computador da máquina IMMULITE, sem necessidade da digitação.

9. PROCESSAMENTO E ANÁLISE DOS DADOS

Os dados das visitas de todos as fases foram duplamente digitados num banco de dados em Epi-Info versão 6 (CDC, EUA, www.cdc.gov/epiinfo) por digitadores distintos. Os valores de PCR serão acrescentados aos bancos de dados pré-existentes.

As análises das variáveis perinatais, assim como aquelas incluindo apenas fatores de riscos contemporâneos (renda, tabagismo, IMC etc) serão realizadas em 3913 indivíduos (Tabela 1a). Análises do crescimento que incluam o peso com um ano de idade serão feitas em 927 indivíduos (Tabela 1b) e análises de crescimento aos dois até quatro anos com 3370 indivíduos (Tabela 1c).

Espera-se ser necessário realizar uma transformação logarítmica do desfecho porque a distribuição será não-normal com assimetria positiva, o que irá requerer o uso de médias geométricas. Os resultados serão exponenciados após a análise ("back-transformed") para serem expressos em escala aritmética (mg/L).

Em análises descritivas, o desfecho será agrupado em níveis de risco, conforme a referência de CDC/AHA (97) usando o nível de PCR antes da transformação logarítmica. Níveis >10 mg/L indicam inflamação aguda com significância clínica e as análises serão feitas de duas maneiras: com e sem esses indivíduos. Nas análises bi- e multi-variadas, o desfecho contínuo (nível da PCR, em log mg/L) será analisado com regressão linear e o desfecho categórico (PCR elevado ou não) através de regressão logística, ambos seguindo o modelo conceitual de análise conforme a Figura 5 (138). Os dados serão analisados com Stata versão 8 (College Station, EUA, www.stata.com).

10. ASPECTOS ÉTICOS

Todas as fases, os estudos perinatal, 1983, 1984, 1986, 1997, 2000, 2001 e 2004-05, foram aprovados pelo Comitê de Ética da Universidade Federal de Pelotas. Consentimento informado verbal foi coletado até 1986 e consentimento informado escrito nos estudos seguintes e para a coleta do sangue em 2004-05.

11. CRONOGRAMA

	2006											2007									
Atividades	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**
Controle de qualidade da visita 1982/2004-05 (03-07/2005)																					
Supervisão do trabalho do campo da subamostra 1982/2006																					
Revisão da literatura																					
Limpeza preliminar dos dados (82-86)																					
Análises das amostras de sangue																					
Digitação e limpeza dos dados																					
Análise dos dados																					
Redação da tese e artigos																					
Defesa da tese																					

12. FINANCIAMENTO

A investigação atual e o estudo de 2004-05 foram financiados pelo Wellcome Trust, Reino Unido. As fases anteriores foram financiadas pelos seguintes corpos: International Development Research Center (Canadá), WHO, Overseas Development Administration (Reino Unido), United Nations Development Fund for Women, Programa de Apoio a Núcleos de Excelência (PRONEX, Brasil), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brasil e o Ministério da Saúde (Brasil).

13. DIVULGAÇÃO DOS RESULTADOS

As formas de divulgação dos resultados do estudo serão: a) artigos para publicação em periódicos científicos (seção ii); b) tese de conclusão de curso de doutorado em Epidemiologia; c) um resumo dos principais resultados do estudo, a ser divulgado na imprensa local.

14. PARTICIPAÇÃO DO DOUTORANDO

O autor desse projeto teve (ou terá) participação nas seguintes fases do projeto:

- Controle de qualidade na visita de 2004-05 de março a julho de 2005;
- Supervisão geral da visita a uma subamostra de 27% da coorte, realizada em fevereiro a abril de 2006;
- Realização das análises laboratoriais de proteína C reativa sob supervisão de bioquímica (Isabel Oliveira);
- Realização das análises estatísticas.

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Relatório do trabalho de campo

Em agosto de 2004 começou o trabalho de localização de todos os participantes da coorte de 1982. Através de vários métodos incluindo um censo da cidade, utilização dos bancos de dados antigos, um censo escolar, cadastros do Sistema Único de Saúde, e uso de listas telefônicas, a equipe de pesquisa tentou localizar todos que fazem parte da coorte de 1982. Em quatro períodos de treinamento e padronização, foram recrutados 24 entrevistadores para realizar as visitas domiciliares e entrevistas associadas com o seguimento. O questionário em completo está disponível no site do Programa de Pós-Graduação em Epidemiologia (em anexo).

O trabalho de campo compreendeu o período de 25/10/2004 a 31/08/2005. Durante todo o período foram realizadas entrevistas domiciliares e no escritório central. Além disso, no Presídio Regional de Pelotas foram entrevistados participantes da coorte que no momento estavam cumprindo pena. Todos os entrevistados eram convidados ao final da entrevista a participar da coleta de sangue venoso periférico, com o objetivo de se obter um banco de soro e um banco de DNA. Como forma de ressarcimento pelo tempo e deslocamento para participar da coleta de sangue, cada indivíduo recebia dez reais (R$10,00) mais dois vales-transporte, além de um cupom para concorrer ao sorteio de um microcomputador.

Foi construído um banco de dados no programa Epi-Info 6.0. O banco foi validado e nos casos de inconsistências entre as duas digitações, os questionários originais foram conferidos para as respostas corretas. O controle de qualidade do

trabalho de campo é fundamental para assegurar a qualidade do estudo. Três aspectos qualitativos foram considerados nesta etapa: (a) a satisfação dos entrevistados com o trabalho realizado pelo entrevistador, buscando uma relação amistosa para futuros acompanhamentos; (b) identificação de possíveis fraudes no trabalho dos entrevistadores; (c) a repetibilidade de algumas perguntas do questionário. Aproximadamente 10% dos participantes visitados receberam uma segunda visita ou contato telefônico, envolvendo aplicação de um questionário reduzido para verificação dos aspectos qualitativos anteriormente citados.

Alguns participantes da coorte ou familiares, durante a realização da entrevista, solicitavam atendimento médico com especialista por algum problema de saúde. Sempre que possível, os casos foram encaminhados para atendimento gratuito e de qualidade.

A coordenação geral do Estudo de Coorte de Nascimentos de 1982 em Pelotas, RS é dos professores Cesar Victora e Fernando Barros. A equipe do acompanhamento realizado em 2004-05 foi composta por Bernardo Horta, Denise Gigante, Helen Gonçalves, Isabel Oliveira e Rosângela Lima. Para a supervisão e coordenação do trabalho de campo a equipe foi constituída por Gicele Minten, Mario Azevedo Júnior e os doutorandos Aydin Nazmi, Celene Longo, Vera Silveira e Vera Vieira.

O relatório completo do trabalho de campo do seguimento de 2004-05, que foi elaborado pela equipe do estudo, está disponível em versão completa, 101 páginas, através de Programa de Pós-Graduação em Epidemiologia (www.epidemio-ufpel.org.br).

Artigo 1

Socioeconomic and racial/ethnic differentials of C-reactive protein levels:
a systematic review of population-based studies

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Abstract

Background

Socioeconomic and racial/ethnic factors strongly influence cardiovascular disease outcomes and risk factors. C-reactive protein (CRP), a non-specific marker of inflammation, is associated with cardiovascular risk, and knowledge about its distribution in the population may help direct preventive efforts. A systematic review was undertaken to critically assess CRP levels according to socioeconomic and racial/ethnic factors.

Methods

Medline was searched through December 2006 for population-based studies examining CRP levels among adults with respect to indicators of socioeconomic position (SEP) and/or race/ethnicity. Bibliographies from located studies were scanned and 26 experts in the field were contacted for unpublished work.

Results

Thirty-two relevant articles were located. Cross-sectional (n=20) and cohort studies (n=11) were included, as was the control group of one trial. Only one low/middle-income country was represented. CRP levels were examined with respect to SEP and race/ethnicity in 25 and 15 analyses, respectively. Of 20 studies that were unadjusted or adjusted for demographic variables, 19 found inverse associations between CRP levels and SEP. Of 15 similar studies, 14 found differences between racial/ethnic groups such that whites had the lowest while blacks, Hispanics and South Asians had higher CRP levels. Most studies also included adjustment for potential mediating variables in the

causal chain between SEP or race/ethnicity and CRP. Most of these studies showed attenuated but still significant associations.

Conclusions

Increasing poverty and non-white race was associated with elevated CRP levels among adults. Most analyses in the literature are underestimating the true effects of racial/ethnic and socioeconomic factors due to adjustment for mediating factors.

Background

The global burden of cardiovascular disease (CVD) represents the highest cause of mortality and one of the highest causes of morbidity both in high-income and low/middle-income countries [1, 2]. It is well known that socioeconomic factors and race/ethnicity influence CVD outcomes and risk factors. Studies have consistently found inverse and independent associations between socioeconomic position (SEP) and the prevalence and incidence of CVD [3-8]. Multi-ethnic studies have pointed to significant differences between racial/ethnic groups [3, 4, 7, 9, 10]. In a Canadian study, for example, South Asians were shown to have 6 and 9% higher prevalence of CVD when compared to Europeans and Chinese [9], whereas in the US, heart disease mortality accounted for up to three times more deaths in blacks as compared to Asians [4]. The mechanisms that drive these socio-demographic risk factors to influence CVD are not fully understood, as differences in body mass index, smoking and other traditional risk factors fail to totally account for these associations. Therefore other mediating factors likely play significant roles in the relationship between sociodemographic characteristics and CVD.

Atherosclerosis, the process leading to coronary heart disease (CHD), has been described as an inflammatory disease [11]. Over the past decade, low-grade inflammation has widely been investigated as a candidate linking the association between traditional risk factors and CHD. An acute-phase protein produced by hepatocytes, C-reactive protein (CRP) has historically been used as a non-specific marker for infection, inflammation or tissue damage [12]. More recently, highly

sensitive assays have permitted evaluation of elevated, but not acute, CRP levels in the assessment of risk for several chronic diseases.

Observational studies show that CRP levels are associated with future risk of chronic diseases including CHD [13-17] and diabetes [18-20] in apparently healthy people. Furthermore, CRP has been shown to add to the predictive value of conventional markers such as cholesterol [21] and blood pressure [22] in defining risk for coronary events. These associations, though consistent, have been described to exist to varying degrees.

Some authors have implicated CRP as an independent determinant of the disease process by actively promoting the proinflammatory phenotype [23, 24]. Others are skeptical of this causal association, while not discounting that CRP may be proinflammatory under certain circumstances [25]. Researchers utilizing Mendelian Randomization techniques have found that certain genotypes are associated with higher CRP levels but that individuals with these genotypes are not necessarily at increased risk for cardiovascular events [26-29]. This calls into question the assumption that CRP levels are, per se, causally associated with risk for CHD. Nevertheless, the role of CRP as a risk marker is clear.

In order to adequately investigate the role of inflammation with respect to the processes that lead to CVD and ultimately to design effective interventions in the prevention of CVD based on these principles, the determinants of elevated CRP levels should be identified. A systematic review of the literature was undertaken to critically assess the

evidence between socioeconomic and racial/ethnic factors and CRP levels among adults.

Methods

Search strategy

Three strategies to locate suitable articles were employed. First, the Medline (PubMed) database was searched. The main keyword search employed was "(C-reactive protein OR CRP OR high-sensitivity C-reactive protein OR hs-CRP) AND (socioeconomic OR race OR ethnic* OR education OR income OR determinants)". Articles published through December 2006 were considered. No language restrictions were used. Second, reference lists in the studies identified were scanned and if relevant were sought and reviewed. Finally, 26 experts in the field were contacted for unpublished or in-progress work, in addition to being contacted for clarification of findings from published studies.

Dependent and independent variables

The independent variables of interest were socioeconomic position (SEP) and race/ethnicity. The term socioeconomic position covers a wide range of measures including, but not limited to, education, income, possession of assets, and index-based measures that inventory a number of socioeconomic factors and create a relative score. Studies that incorporated any socioeconomic variables were considered, given that they met the other inclusion criteria. For simplicity, SEP shall be used throughout this

review when making general references. Studies that analyzed any racial or ethnic variables such as skin color or ethnic background were considered.

Inclusion criteria

The review was restricted to population-based studies, including those employing methods such as random or probability-based sampling based on a given geographical area. Studies based on selected sample populations, including occupational cohorts, clinic-based or "convenience samples", were not considered. Studies that sampled either the entire population or specific age groups were included, provided that individuals were aged at least 17 years. Authors were contacted if sufficient methodological or analytical information was not provided in the article text or for possible overlapping information from the same samples in different articles.

Conceptual model

In epidemiological models, the causal, mediating and confounding factors related to risk for disease and disease status can be complex to interpret. Conceptual frameworks aid in the organization of associated proximal and distal factors, helping to define which variables may constitute confounders and which ones are likely mediators [30]. Most studies are unclear about conceptual models used in statistical analyses and interpretations of findings [30, 31].

We proposed a hierarchical model for the factors associated with CRP levels (Figure 1). In this model, variables on higher levels were considered as possible confounders for

those on lower levels. The arrows represent possible pathways. For example, the association between SEP and CRP level may be confounded by the variables on level 1, since these are independently associated with both the dependent (SEP) and independent (CRP level) variables. On the other hand, level 3 variables may be on the causal pathway from SEP to CRP level and as such are possible mediators. In analyzing the association between SEP and CRP level, for instance, adjusting for smoking or obesity (treating them as confounders) would underestimate the true effect of SEP on CRP level by removing the effects mediated through smoking and obesity, which are on the causal pathway.

Results

Figure 2 shows a flowchart according to QUOROM statement guidelines outlining the number of articles identified at each step of the literature search [32]. Initial searching identified 1146 articles and 460 were retrieved for more detail from which 154 potentially appropriate articles were reviewed. Eighty-seven studies were excluded, primarily because CRP was analyzed as an independent variable in prognostic analyses, rather than as an outcome. Finally, 35 articles were withdrawn because they were not population-based, leaving 32 articles to be included in the review.

These studies were published between 1996 and 2006 and were conducted in the USA (14 studies; n= 96746), the UK (eight studies; n= 11049), Finland (two studies; n= 3793), Greece (two studies; n= 5313), Germany (two studies; n= 2891), Canada (n=

1250), Italy (n= 1650), Turkey (n= 1046) and New Zealand (n= 822). Of these, 25 analyses included SEP as an independent variable and 15 included ethnicity/race. Given that eight studies analyzed both independent variables, Additional file 1 includes 40 analyses from the 32 included studies. There were 20 cross-sectional and 11 cohort studies, all of which were analyzed as cross-sectional; two of the latter also included retrospective analyses of SEP in early life. One article reported on the control group of a larger trial study.

Different types of adjustment for covariates were used. In light of the conceptual model, analyses that were either unadjusted or adjusted for demographic confounding factors (including age, sex and race/ethnicity) are referred to as "minimally adjusted" models. Analyses that also included adjustment for potential mediating factors in addition to demographic confounders are referred to as "fully adjusted" models. In the results section of Additional file 1, the findings from the fully adjusted models appear on the bottom row, while those from minimally adjusted models appear on the top row. Some studies in which CRP level was not the main outcome showed only unadjusted distributions of CRP levels without statistical analysis. A formal quantitative analyses of this association (a meta-analysis) was not performed because given variability in exposure and outcome definitions such analyses were not possible. Additional file 2 presents effect sizes from the studies, providing numerical description of the data when available.

In the next sections we describe the main results of the studies reviewed. We comment on the statistical significance of the findings and provide the effect sizes and confidence intervals for the main analysis in each paper, when available in the publication.

Socioeconomic status

A wide range of socioeconomic factors were tested, the most common being level of formal education and social class, based on composite scores or proxy measures. A total of 77467 analyses were represented. The Greek and Scottish studies examined the same individuals more than once; the former used different indicators of SEP in each assessment. Some studies using representative national samples (National Health and Nutrition Examination Survey, NHANES) from the USA also examined data from the same group of individuals more than once.

Of the 25 studies reporting on any SEP measure, nine presented only minimally adjusted results [20, 26, 33-39]; 12 also presented fully adjusted models [40-51]; and four only presented the latter [52-55]. Of the 21 studies presenting minimally adjusted results – 14 unadjusted and seven adjusted for demographic confounders - all but one showed inverse associations between SEP and CRP [20, 26, 33-37, 39-51]. All 12 studies presenting both minimally and fully adjusted analyses found inverse associations in the former; in five of these the magnitude of the association decreased and was no longer statistically significant in the fully adjusted model [41, 42, 45, 47, 50]. The issue of whether the fully adjusted models may have included mediating factors is addressed in the Discussion.

Of the 16 [40-55] studies presenting multivariable analyses, nine found significant associations after adjusting for demographic, anthropometric and other postulated confounding variables [40, 43, 44, 46, 48, 49, 51, 52, 54].

One study using an unadjusted model [38] and seven using fully adjusted models [41, 42, 45, 47, 50, 53, 55] failed to find associations between any socioeconomic indicator and CRP. Direct associations were not found in any of the studies.

Education and/or index measures were examined in nearly all studies. We present these findings below as sub-groups of SEP analyses.

Education

Fourteen studies examined the effect of educational indicators [20, 33, 35-37, 40, 42, 43, 45-47, 49, 52, 53]. Of the 11 presenting minimally adjusted results [20, 33, 35-37, 42, 43, 45-47, 49] – six unadjusted and five adjusted for demographic variables- 10 found inverse associations, higher education being associated with lower CRP levels [20, 33, 35, 37, 42, 43, 45-47, 49]. Three studies presenting only minimally adjusted results using NHANES data from 1988-1994 included potentially overlapping samples [33, 36, 37], but are discussed below as separate studies.

Among the nine studies that investigated this association in multivariable analysis [40, 42, 43, 45-47, 49, 52, 53], four found significant inverse associations with CRP levels after adjustment for postulated confounders such as age, smoking and body mass index (BMI= kg/m^2) [40, 46, 49, 52]. Three studies presenting fully adjusted results using NHANES data from 1999-2002 included potentially overlapping samples [40, 52, 53], but are discussed below as separate studies.

Of the four studies showing significant inverse associations in the fully adjusted analyses, three presented detailed information on effect sizes. Panagiotakos et al. (2004) observed - in a model adjusted for demographic factors as well as BMI, smoking and other behavioral factors - a 45% lower mean CRP level among those who had studied at the university level as compared to those who had not. Ford et al. (2004) found a borderline association (p=0.054) among women with less than a high school education, who presented with 0.17 mg/L (SE 0.09) higher *ln*CRP than those with more education. Loucks et al. (2005) observed a similar inverse trend in a multiple linear regression analysis; those with masters or doctoral degrees had a mean CRP (mg/L) level of 3.2 (95% CI 3.0-3.3) whereas those who had not completed high school presented a mean of 4.7 (95% CI 4.5-4.9).

Of the five studies reporting fully adjusted analyses that showed non-significant results, four showed a trend towards an inverse association. Ford et al. (2003) found that men with less than a high school education had double the regression coefficient for *ln*CRP than men with a high school diploma, although this association was not significant (β=0.132, SE 0.096 and β=0.065, SE 0.093) when smoking, BMI, alcohol intake and race/ethnicity were included in the model. Bo et al. (2005) found that those with secondary and university educations were protected against elevated CRP levels, but that these associations did not reach significance after adjustment for BMI, physical activity and smoking. Another study showed that those with post-secondary education had mean CRP levels of 1.52 mg/L (SE 0.19) whereas those with less education had 1.97 mg/L (SE 0.10) before body mass index (BMI) and waist-hip ratio (WHR) were included in statistical models, attenuating these associations to the null [45]. Similarly, McDade et al. (2006) found that the 0.06 mg/L reduction in *ln*CRP among those with

higher education was made non-significant when variables such as waist circumference and smoking were included in the model.

Index measures

Eleven studies used index measures, including the British social class system based on occupational status, to create socioeconomic scores or categories [26, 38-40, 44, 45, 48, 50, 51, 54, 55]. Of the nine studies presenting minimally adjusted results [26, 38-40, 44, 45, 48, 50, 51] – five unadjusted and four adjusted for demographic variables - eight found inverse associations, increasing SEP being associated with lower CRP levels [26, 39, 40, 44, 45, 48, 50, 51].

Among the eight studies that investigated this association in multivariable analysis [40, 44, 45, 48, 50, 51, 54, 55], five found significantly increasing CRP levels with decreasing SEP [40, 44, 48, 51, 54]. These are discussed below.

Mendall et al. (2000) found a significant inverse trend such that father's social class (as a proxy of childhood SEP) of IV (vs. I/II) was associated with a 33% (95% CI 4-69) relative increase in CRP levels among middle-aged men after adjusting for factors including age, BMI, smoking, own social class and alcohol intake. A Finnish study showed that those with low and high SEP had geometric means of CRP of 2.11 and 1.63 mg/L in models adjusted for age, smoking, WHR and prevalent longstanding disease [44]. In a representative sample from the USA, Alley et al. (2005) showed that almost 16% of individuals from families living in poverty had elevated levels of CRP (>10 mg/L), compared to 9% of the remaining subjects. Panagiotakos et al. (2005) reported

similar results, with low and high SEP groups being associated with mean CRP levels of 0.21 (SD 0.10) and 0.16 (SD 0.17) mg/L, respectively. This finding remained significant after adjustment for age, sex, smoking, BMI, diet score and physical activity level. St. James O'Reilly (2006) found a significant increase in CRP levels such that in a model adjusted for age, smoking, BMI and use of medications, women, but not men, with a one unit increase in deprivation category had 4.8% (95% CI 0.4-9.5) higher levels of CRP.

Of the three studies using multivariable analyses that showed non-significant results [45, 50, 55], two observed a trend towards an inverse association [45, 50], while a third did not provide details [55], Kivimaki et al. (2005) found that parental and own SEP indicators showed inverse non-significant trends with CRP after including BMI and WHR in statistical models. Rathmann et al. (2006) showed that CRP levels were inversely associated with SEP such that women with low and high SEP had geometric means of 2.17 (SD 2.7) and 1.32 (SD 2.6) mg/L, respectively, which were significant in analyses adjusted for age, smoking, physical activity level and alcohol consumption, but decreased in significance to the borderline level when BMI and WHR were added to the model.

Income and employment status

Onat et al. (2001) reported that income was inversely associated with CRP levels in minimally adjusted models, among women significantly, but that this association lost significance in fully adjusted models [41], Alley et al. (2005) found that higher income was protective against moderately elevated CRP levels (1.1-3.0 mg/L) when adjusted for variables including age, sex, race/ethnicity, obesity and smoking; effect sizes were not provided.

Four studies reported on variables related to employment status [34, 36, 43, 45]. In minimally adjusted analyses, Mendall et al. (1996) found that father's, but not own occupation was inversely associated with CRP levels in men (effect sizes in next section). Using data from one city in the UK, Danesh et al. (1999) reported a trend in CRP tertiles according to employment status such that 56% of those in the highest CRP tertile were employed compared to 65% employed in the second and 74% in the lowest tertile. In the same study, however, type of job (manual or not) and four other socioeconomic indicators were not associated with CRP in minimally adjusted or fully adjusted models. In minimally adjusted analyses, Ford (2002) found that 57% (SE 1.5) of individuals in the elevated CRP group (>= 85^{th} percentile) had worked during the past two weeks whereas 68% (SE 0.7) in the non-elevated (< 85^{th} percentile) group had worked in the same period. Kivimaki et al. (2005) found that parental, but not own occupation showed inverse trends with CRP but that these associations were not significant in fully adjusted models including anthropometric variables (effect sizes above).

Early life SEP

Four studies examined early life socioeconomic factors with respect to CRP in adulthood [26, 34, 45, 54]. In minimally adjusted analyses, two British studies found inverse associations between CRP in adulthood and early life SEP. Mendall et al. (1996) found that father's occupation of 75% (SE 5.6) of men in the highest quintile of median CRP was manual, compared to 61% (SE 6.3) in the lowest quintile. Lawlor et al. (2005) found an age-adjusted direct association between CRP and the number of adverse life-course socioeconomic indicators: subjects with two adverse indicators presented a geometric mean CRP level of 1.4 mg/L (SEs not given) compared to 2.2 for those with eight indicators [26]. In fully adjusted models including age, sex, BMI and smoking, two European studies yielded conflicting results. A British study found an inverse association between father's social class and CRP levels in adulthood (effect sizes presented above, Mendall et al., 2000) while a Finnish study found a non-significant inverse trend (effect sizes previous section, Kivimaki et al., 2005)[45, 54].

Race and ethnicity

The second part of this review addressed associations with variables related to race, ethnicity or skin color. Fifteen studies- twelve from the USA, two from the UK and one from Canada- examined CRP levels with respect to such variables [33, 35, 36, 38, 40, 47, 52, 53, 56-62]. A total of 87285 analyses were represented and some studies used the same sample more than once, as discussed above.

Six presented minimally adjusted results only [33, 35, 36, 38, 56, 60] and nine [40, 47, 52, 53, 57-59, 61, 62] presented both minimally adjusted (seven unadjusted and two adjusted for demographic variables) and fully adjusted results. Thus, all 15 included studies presented minimally adjusted results, of which only one study failed to report significant associations [53]. Of the nine studies presenting fully adjusted results [40, 47, 52, 53, 57-59, 61, 62], only one failed to show associations [53] and two found that these associations were no longer significant after full adjustment, but that the direction of the effect was maintained [47, 61]. The remaining six studies found that the associations remained significant in fully adjusted models.

NHANES data

Eight of the US studies used data from NHANES data sets [33, 35, 36, 40, 52, 53, 56, 60], some with overlapping samples [33, 36, 56, 60], [52, 53], [40]. Seven reports presented minimally adjusted results and all but one [53] showed some significant associations between race/ethnicity and CRP level. Three of these studies [40, 52, 53] included fully adjusted models, of which two found significant associations [40, 52]. All studies presenting significant findings reported higher CRP levels for blacks and Hispanics (or Mexican-Americans) as compared to whites.

In all five studies that reported only minimally adjusted results [33, 35, 36, 56, 60], non-whites had significantly higher CRP levels than other groups. In comparing 95th percentiles among elderly white, black and Mexican-Americans, Wener et al. (2000) showed that among men, Mexicans had the highest 95th percentiles (2.59 mg/dL, as

presented in Wener et al., 2000; 95% CI not available due to missing information), followed by blacks (2.40 mg/dL) and then whites (1.24 mg/dL, 95% CI 0.84-1.64), with women following the same pattern. Wong et al. (2001) presented similar results, showing that the mean (SD) CRP levels among white, black and Mexican men were 0.37 (0.52), 0.47 (0.75) and 0.39 (0.65) mg/dL; and 0.46 (0.62), 0.61 (0.86) and 0.64 (1.32) mg/dL among women. Ford (2002) showed that whites composed 69% (SE 1.9) and 78% (SE 1.3) of the >= 85^{th} and <85^{th} percentile of CRP levels, respectively. Abramson et al. (2002) found that African-Americans had 1.75 higher odds (calculated from given distributions; no 95% CI available) of being in the elevated CRP group (>= 0.66 mg/dL) as compared to whites.

Danner et al. (2003) found African- and Mexican-Americans at higher risk for elevated CRP (>= 0.22 mg/dL) as compared to whites. The highest prevalence ratio (PR) compared to whites of the same sex was among African-American men (PR=1.57), followed by African- and Mexican-American women (PR=1.44) and Mexican-American men (prevalence ratio=1.24, compared to white individuals of same sex, calculated from given distributions; no 95% CI available).

Conflicting results were found in the three studies that utilized fully adjusted models including age, sex, smoking and BMI among individuals aged at least 20 years. Ford et al. (2003) observed no associations between race/ethnicity and CRP levels among men. In a 2004 study, the same author reported that Mexican-American women had on average 0.29 mg/L (SE 0.07) higher lnCRP levels than their white counterparts [52]. Alley et al. (2005) found that blacks had significantly higher odds of being in either the high (OR=1.45 95% CI: 1.16-1.80) or very high (OR=2.32 95% CI: 1.76-3.08) CRP

groups as compared to other groups in fully adjusted models including demographic and lifestyle variables and BMI [40].

Other studies from North America and the UK

Four studies from the USA, which did not use NHANES data, were included. One found median CRP levels of 3.0 mg/L in blacks and 2.3 in whites of both sexes, which remained significant after adjusting for traditional cardiovascular risk factors [62]. In the same study, black men and women made up a significantly larger proportion of the high risk CRP group (>3 mg/L) than white men. Similarly, Matthews et al. (2005) used a multi-community sample and found that after adjusting for variables such as education, physical activity and % calories from fat, African-American, Hispanic and white women presented median (IQR) CRP levels of 3.0 (1.0-7.2), 2.3 (1.0-5.1) and 1.4 (0.6-3.9), respectively [58]. A small study among older individuals found no associations between blacks and whites, nor between Latinos and whites [47]. Another study using samples from multiple communities across the USA found that Hispanic men and women had the highest levels of CRP (2.51, 3.39, respectively), followed by African-Americans (2.12, 3.19), Caucasians (3.20, 2.75) and Chinese (0.95, 1.20), after adjusting for covariates including age, BMI, smoking, physical activity and estrogen medications [57]. Significance testing was not done between ethnic groups.

Both studies from the UK found higher CRP levels among South Asians compared to European whites in minimally adjusted analyses [38, 61]. Forouhi et al. (2001) observed that the median CRP level among South Asian women was 1.35 (95% CI 0.72-3.04) compared to half that level, 0.70 mg/L (95% CI 0.41-1.7), among European

women. This unadjusted association was significant; fully adjusted models were not used. In another UK study Chambers et al. (2001) showed that the age-adjusted association among the same ethnic groups lost significance after adjustment for age, BMI and smoking, but the direction of effect was maintained. The Canadian study found significant differences between ethnic groups [59]. In fully adjusted models including BMI as a covariate, Chinese, European, South Asian and Aboriginals had mean CRP levels of 1.72 (SE 0.13), 2.13 (SE 0.12), 2.72 (SE 0.12) and 2.85 (SE 0.15) mg/L, respectively, with non-significant differences between European and Chinese, and between South Asians and Aboriginals.

Discussion

The overwhelming majority of the 32 studies reported inverse associations between CRP levels and SEP and significant differences among racial/ethnic groups, even after controlling for possible confounding and mediating variables. Individuals with African, Latin American or South Asian ancestry had higher levels than those with European background. Both sets of findings are consistent with previous studies showing similar associations between other CVD risk factors and SEP and race/ethnicity [3, 4, 8-10, 63]. Although the notion that CRP levels are causally associated with CVD has been challenged by Mendelian Randomization studies, there is little question that CRP constitutes a reliable marker for low-grade inflammation that identifies high-risk individuals [26, 29].

Some strengths and limitations of this review warrant mention. It included studies using population-based studies, which minimizes selection bias. On the other hand, studies were largely from in high-income countries, notably from the USA and several European countries. The only low/middle-income country represented was Turkey; Onat et al. (2001) found inconsistent results. Further studies from low and middle-income countries are required to investigate whether the results from this review are also applicable to these regions. It is worth noting that some studies excluded individuals with CRP levels >10 mg/L (the cut-off for acute inflammation), which would make their results applicable only to low-level inflammation.

When interpreting adjusted results, we gave special emphasis to differentiating possible confounders from mediating variables, based on a conceptual model (Figure 1). In examining the association between SEP and CRP levels, adjustment for variables in level 1 of the model (age, sex and race/ethnicity, in addition to genetic factors) should account for confounding. None of the present studies adjusted for genetic markers, and these would only confound the association if they were unequally distributed among SEP groups. Also, several samples were ethnically homogeneous, rendering adjustment for this variable unnecessary. Therefore, for these studies adjustment for age and sex should take care of the issue of known and measurable confounders.

Of the 20 studies presenting minimally adjusted results, 13 presented unadjusted analyses and seven presented results adjusted for demographic factors. All of the latter showed significant inverse associations between SEP and CRP.

The fully adjusted models included age and sex in all studies, BMI in all but one (Matthews et al. 2005 used %kcal from fat) and smoking in all but one study [59]. Nine of 21 studies did not adjust for hormone replacement therapy (HRT) use [40, 41, 46-51, 59]. Thus, five common variables were adjusted for in most studies (age, sex, BMI, smoking and HRT). Therefore, the fully adjusted model in nearly every study included both confounding (age, sex) and potentially mediating (BMI, smoking, HRT) variables. These analyses answer the question "what is the effect of SEP on CRP levels that does not pass through the mediating factors that are in the model?", not the question of the overall effect of SEP.

The persistence of significant associations in most fully adjusted analyses suggest that low SEP is a risk factor for elevated CRP levels (although not necessarily cardiovascular risk), even when some of the potential mediators of this association are controlled for. It also suggests that there are other pathways by which SEP may affect CRP levels [30]. For example, it has been postulated that high levels of stress accumulated throughout the life-course, which is often the case among the poor and disadvantaged, may adversely impact health outcomes [64, 65].

Socioeconomic status in childhood, independently of adult socioeconomic conditions, has been shown to be associated with mortality among adults, indicating specific effects of early deprivation [66]. Four studies included in this review suggest a similar association between early SEP and CRP levels. The only exception was a high-quality Finnish study which reported a significant association in age and sex-adjusted analyses that lost significance after adjustment for BMI and WHR, that according to our framework represent possible mediating factors [45]. It is likely that adverse features

are programmed in intrauterine and early life under conditions of poor SEP during physiologically plastic periods and track into adulthood, manifesting as increased risk for disease, regardless of later improvement of socioeconomic conditions [64, 67, 68].

The findings on racial/ethnic groups are now addressed. The range of ethnicities represented in the studies was relatively limited. In studies from the UK, only European whites and South Asians comprised the study samples, whereas in studies from the USA, four general categories were presented (white, black/African-American, Hispanic/Mexican-American and other). Canadian studies were more diverse, including Aboriginals, Europeans and at least two Asian groups (eg: Chinese, Japanese, South Asian).

In terms of the conceptual model (Figure 1), the effects of race/ethnicity on CRP levels may be confounded by other level 1 variables (age, sex and genetic factors) [69]. Because non-whites tend to have poorer education and income than whites in North America and Europe, SEP can legitimately be considered a potential mediating factor in the association between ethnicity and health-related outcomes [70-72]. Models that adjust for SEP, therefore, are answering the question on what the effect of race/ethnicity is on CRP that is not mediated by SEP. Models that further adjust for level 3 variables (such as BMI, smoking, etc) are answering the question of what effect of race/ethnicity remains outside these pathways.

Both in the minimally and fully adjusted models, findings on the association between race/ethnicity and CRP were highly consistent. In studies from North America, blacks and Hispanics tended to have higher CRP than whites, and individuals of East Asian

descent (Chinese, Japanese) tended to have the lowest levels. In UK studies, South Asians were shown to have higher levels of CRP than European whites. The high CVD rates among black Americans and South Asians in Europe are consistent with these findings on CRP [9].

Conclusions

Socioeconomic status was independently and inversely associated with CRP levels among adults in several high-income countries. Studies regarding the effects of early life and adult SEP on risk factors such as CRP are still needed, especially from low and middle-income countries.

Race/ethnicity was independently associated with CRP levels such that those of African, Latin or South Asian descent were at higher risk for elevated CRP than subjects of European descent. Given the complex inter-relationships between exposures, confounding and mediating variables, racial/ethnic determinants of disease can be difficult to study and interpret [73]. Nevertheless, collaborative studies from multiple countries may lead to increased insight regarding the effects of these variables on risk factors and disease outcomes.

A full understanding of the associations between SEP and race/ethnicity on the one hand, and CRP on the other, was precluded by the fact that nearly all studies included statistical adjustment for variables that are likely mediating factors in this causal pathway. The fact that most studies show significant results despite such over

adjustment is reassuring, but the true magnitude of these associations is being underestimated. Epidemiological studies addressing what has been described as the "causes of causes", that is, the distal determinants of health and disease, would greatly profit from the use of conceptual models spelling out causal pathways that allow to differentiate confounding from mediating factors [74, 75].

These findings indicate that poorer, non-white individuals are the highest risk for elevated CRP levels. This is consistent with previous data showing that these groups have elevated incidence and prevalence of almost all disease states. Scientists and policy makers should capitalize upon results from the host of studies that have already confirmed such associations in attempts to curb the growing incidence of chronic disease caused by low SEP and ever-increasing socioeconomic gaps [76].

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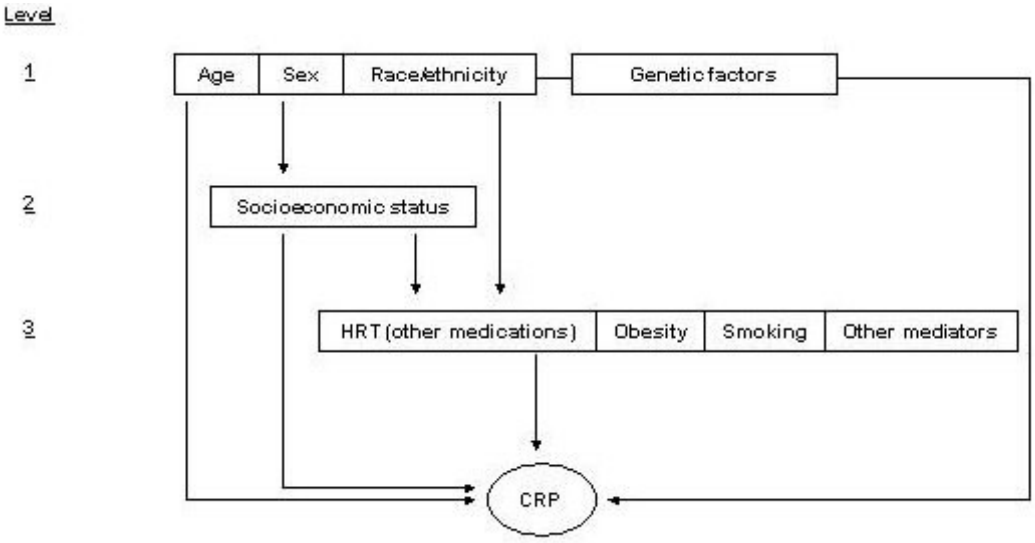

Figure 1: Conceptual model for the associations between race/ethnicity, socioeconomic position and C-reactive protein level.

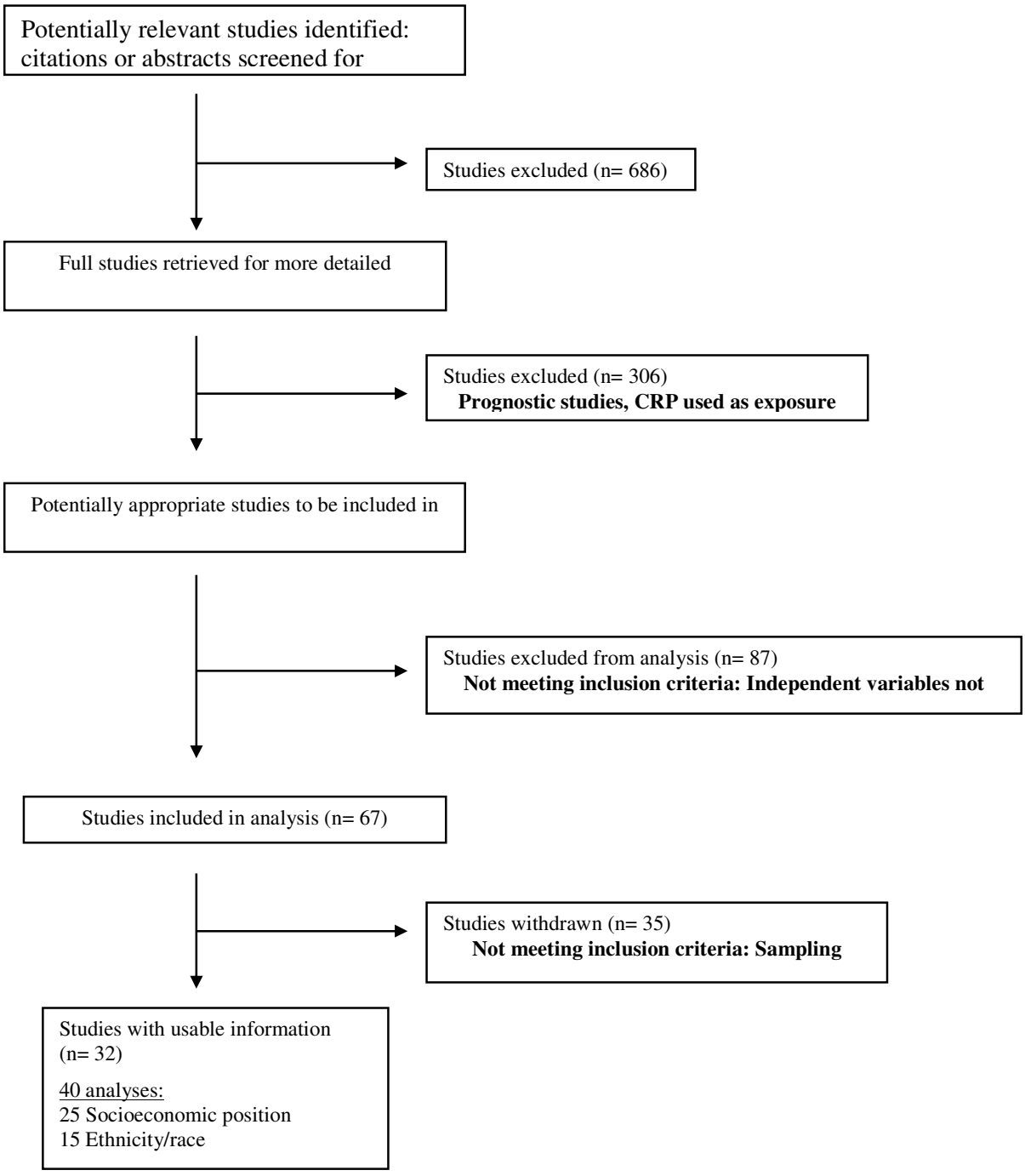

Figure 2: Number of studies associated with process of study selection (according to QUOROM guidelines).

Table 1: Population-based studies examining socioeconomic factors or race/ethnicity as independent and C-reactive protein (CRP) level as dependent variables.

[Author, year] Sample population, study type, sampling method	N	Age, mean or range (y)	Minimally-adjusted and fully adjusted association with independent variables[**] Socioeconomic factors	Race/ethnicity[#]	Treatment of dependent variable[##] and observations
[Abramson, 2002][*] US national sample[a], cross-sectional, stratified multi-stage probability sample	9867	>= 17	(-) Education	(+) African-American vs. White and "Other" categories	Dichotomous (< or >= 0.66 mg/dL)
[Alley, 2005] US national sample[a], cross-sectional, stratified multi-stage probability sample	6830	>= 20	(-) Above poverty line	(+) Black (+) Hispanic (n/s) Other White reference category At CRP 3.1-10.0 mg/L	Categorical (<=1.0, 1.1-3.0, 3.1-10, >10.0 mg/L CRP), Significant associations at age <=80 y
			(-) Above poverty line (-) Education (-) Household income At CRP>10 mg/L	(+) Black, at CRP>3 mg/L (n/s) Hispanic (n/s) Other White reference category	
[Anand, 2004] Four communities in Canada[b], cross-sectional, random sample of age-eligible	1250	35-75	--	(+) Lowest to highest: Chinese, European, South Asian, Aboriginal	Continuous
				(+) Lowest to highest: Chinese, European, South Asian, Aboriginal (n/s) European vs. Chinese (n/s) South Asian vs. Aboriginal	
[Bo, 2005] Asti province, Italy, cross-sectional, all age-eligible population from 6 GPs representative of districts in province	1650	45-64	(-) Education	--	Dichotomous (< or >= 3.0 mg/L)
			(n/s) Education		

[Chambers, 2001] London, UK, cross-sectional, random sample of Indian Asians and European Whites from 56 GPs	1025	35-60, men	--	(+) Indian Asian European White reference category Age adjusted (n/s) Indian Asian European White reference category	Continuous
[Danesh, 1999] Bedfordshire, UK, cross-sectional, randomly selected control group for trial study from five GPs	704	35-64	(-) Employment (n/s) Completed education by age 16 y (n/s) In rented housing (n/s) Car ownership (n/s) Manual worker (n/s) Marital status (-) Employment (n/s) Completed education by age 16 y (n/s) In rented housing (n/s) Car ownership (n/s) Manual worker (n/s) Marital status	--	Categorical (thirds of CRP)
[Danner, 2003][*] US national sample[a], cross-sectional, stratified multi-stage probability sample	6149	17-39	(-) Education (women)	(+) Lowest to highest (men): Mexican-American, "Other", African-American (+) Lowest to highest (women): "Other", Mexican-American / African-American White reference categories	Dichotomous (< or >= 0.22 mg/dL)
[Ford, 2000][*] US national sample[a], cross-sectional, stratified multi-stage probability sample	8850	>= 40	(-) Education	--	Categorical (<= 0.21, > 0.21-< 0.55, >= 0.55 mg/dL)

[Ford, 2002][*] US national sample[a], cross-sectional, stratified multi-stage probability sample	13748	>= 20	(-) Recently employed (n/s) Education Age adjusted	(+) Non-white Age adjusted	Dichotomous (< or >= 85th percentile)
[Ford, 2003] US national sample[a], cross-sectional, stratified multi-stage probability sample	1940	>= 20, men	Not presented	(n/s) Mexican-American (n/s) African-American (n/s) "Other" White reference category	Continuous
			(n/s) Education	(n/s) Mexican-American (n/s) African-American (n/s) "Other" White reference category	
[Ford, 2004] US national sample[a], cross-sectional, stratified multi-stage probability sample	1912	>= 20, women	Not presented	(+) Lowest to highest: White, African-American, Mexican-American	Continuous
			(-) Education (<high-school group)	(+) Mexican-American (n/s) African-American (n/s) "Other" White reference category	
[Forouhi, 2001][*] London, UK, cross-sectional, random sample of South Asians and Europeans from four GPs	113	40-55	(n/s) Social class	(+) South Asian Among women European White reference category	Continuous
[Jousilahti, 2003] Eastern and southern Finland[c], cross-sectional, stratified random sample of men	1503	45-74, men	(-) SES determined by education and total family income	--	Continuous, Association significant in <60 y groups
			(-) SES determined by education and total family income		

[Khera, 2005] Dallas County, Texas, USA, cross-sectional, probability-based random sample	2749	30-65	--	(+) Black women White reference category	Continuous and categorical
				(+) Black women (n/s) Black men White men reference category	
[Kivimaki, 2005] Finnish national sample, cross-sectional and prospective analysis within prospective cohort[d], random sample of national register	2290	24-39	(-) Parental occupation (n/s) Parental education (n/s) Own occupation (-) Own education Age and sex adjusted	--	Continuous
			(n/s) Parental occupation (n/s) Parental education (n/s) Own occupation (n/s) Own education		
[Lakoski, 2006] Six communities in the USA[e], cross-sectional analysis within prospective cohort, stratified random, geographic or random digit dialing of age and race-eligible	6814	45-84	--	(+) Lowest to highest (men): Chinese, Caucasian, African-American, Hispanic (+) Lowest to highest (women): Chinese, Caucasian, Hispanic, African-American	Continuous Racially stratified analysis of gender; no significance tests between ethnic groups
				(+) Lowest to highest: Chinese, Caucasian, African-American, Hispanic	
[Lawlor, 2005][*] UK, cross-sectional analysis within prospective cohort[f], random sample	3745	60-79, women	(-) Life-course SES, determined by index Age adjusted	--	Categorical (quartiles of CRP)

[Loucks, 2006] Framingham, Massachusetts, USA, cross-sectional analysis within prospective cohort, offspring or spouse of offspring of Framingham Heart Study (random sample of two-thirds of adult population of Framingham)	2729	62.1, mean	(-) Education Age and sex adjusted (-) Education	-- --	Continuous
[Matthews, 2005] Seven sites in the USA[g], cross-sectional analysis within prospective cohort, random digit-dialing	2834	42-52	 --	(+) Lowest to highest: Japanese, Chinese, White, Hispanic, African-American (+) Lowest to highest: Japanese, Chinese, White, Hispanic, African-American (n/s) African-American vs. Hispanic (n/s) Hispanic vs. White	Continuous
[McDade, 2006] Cook County, Illinois, USA, cross-sectional analysis within sub-sample of prospective cohort[h], multi-stage probability sample of age-eligible	173	50-67	(-) Education Age, gender and ethnicity adjusted (n/s) Education	(+) Lowest to highest: European-American, Latino-American, African-American (n/s) African-American (n/s) Latino-American European-American reference category (n=153)	Continuous
[Mendall, 1996][*] London, UK, cross-sectional, random sample of Whites from GPs in Merton, Sutton, and Wandsworth District Health Authorities	303	50-69, men	(-) Father's occupation not manual (n/s) Own occupation not manual	--	Categorical (fifths of CRP)

[Mendall, 2000] Caerphilly and 5 villages in South Wales, cross-sectional and prospective analysis within prospective cohort[i], 100% of age-eligible men	1395	45-59, men	Not presented		Continuous
			(-) Childhood SES, determined by father's social class (n/s) Current social class	--	
[Onat, 2001] Three regions of Western Turkey, cross-sectional analysis within sub-sample of prospective cohort[j], stratified random sample	1046	>= 30	(-) Family income Among women	--	Continuous
			(n/s) Family income (n=690)		
[Panagiotakos, 2004] Attica province, Greece, cross-sectional, multi-stage random sample[k]	2271	> 18	(-) SES, determined by formal education level	--	Continuous
			(-) SES, determined by formal education level		
[Panagiotakos, 2005] Attica province, Greece, cross-sectional, multi-stage random sample[k]	3042	> 18	(-) Lowest to highest, by SES tertile: 2nd, 3rd, 1st	--	Continuous
			(-) SES, determined by family income and education		
[Rathmann, 2006] Augsburg region, Germany, cross-sectional, cluster sample of region[l]	1653	55-74	(-) SES, determined by occupation; education; vocational training and income (women) Age adjusted	--	Continuous
			(n/s) SES, determined by occupation, education, vocational training and income		

[Sattar, 2004]* Two Scottish towns[m], cross-sectional analysis within prospective cohort, offspring of original cohort (all aged 45-64 y population)	1663	30-59	(-)	SES, deprivation index, determined by postcode of residence	--		Continuous
[St J O'Reilly, 2006] Two Scottish towns[m], cross-sectional analysis within prospective cohort, offspring of original cohort (all aged 45-64 y population)	2101	30-59	(-) Age adjusted	SES, deprivation index, determined by postcode of residence	--		Continuous
			(-)	SES, deprivation index, determined by postcode of residence (women)			
[Thorand, 2003]* Augsburg region, Germany, cross-sectional, cluster sample of region[l]	1238	45-74, men	(-)	Education	--		Continuous
[Wener, 2000]* US national sample[a], cross-sectional, stratified multi-stage probability sample	22467	>4	--		(+)	Lowest to highest: White, Hispanic, Black	Continuous
[Williams, 2004] Dunedin, New Zealand, cross-sectional analysis within prospective birth cohort[n], births over 1 y period	822	26	Not presented		--		Continuous
			(n/s)	SES, determined by occupation and income			
[Wong, 2001]* US national sample[a], cross-sectional, stratified multi-stage probability sample	9684	30-74	--		(+) (+)	Lowest to highest (men): White, Mexican-American, Black Lowest to highest (women): White, Black, Mexican-American	Continuous and categorical (<0.5, >=0.5-<1.0, >=1.0 mg/dL)

(+) and (-) indicate statistically significant positive and negative associations, respectively, (n/s) indicates statistically non-significant associations

* Study reported on findings from unadjusted or minimally adjusted (for demographic variables) models only (n=11). [Wener, 2000] reported on individuals aged >4 and we report on participants aged >=20 y and without inflammatory conditions (N unknown).

** Results of unadjusted or minimally adjusted analyses appear on one row while those from studies including multivariable (fully adjusted) models appear on two rows (unadjusted or minimally adjusted analyses top, fully adjusted model bottom). Details for minimally adjusted models noted. Effect sizes discussed in Results section of text and in Table 2.

Classification of race/ethnicity given as presented in original study
Continuous variables analyzed as *ln*CRP due to skewed distribution
[a] National Health and Nutrition Examination Survey (NHANES). Studies including the same years and age groups include partially overlapping samples. Studies used data from varying periods, as follows: NHANES 1988-1994: Abramson (2002), Danner (2003), Ford (2000 and 2002), Wener (2000), Wong (2001); NHANES 1999-2000: Ford (2003 and 2004); NHANES 1999-2002: Alley (2005).
[b] Hamilton, Toronto, Edmonton, the Six Nations Reservation (Oshweken, Ontario)
[c] Finnish Platelet Aggregation and Inflammation Study (PAIS)
[d] The Cardiovascular Risk in Young Finns Study
[e] Multi-Ethnic Study of Atherosclerosis (MESA): Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN.
[f] British Women's Heart and Health Study: participants from 23 British towns
[g] Study of Women's Health Across the Nation (SWAN): Boston, MA; Chicago, IL; the Detroit area, MI; Newark, NJ; Pittsburgh, PA; Los Angeles and Oakland, CA
[h] The Chicago Health, Aging, and Social Relations Study
[i] The Caerphilly Prospective Heart Disease Study
[j] Turkish Adult Risk Factor Study. Study includes participants from three of seven regions included in cohort: Marmara, Aegean, and Mediterranean.
[k] The ATTICA Study. Overlapping sample populations (same individuals examined more than once).
[l] The KORA (Cooperative Health Research in the Region of Augsburg) Survey 2000, [Rathmann, 2006]; The MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg Project, [Thorand, 2003]
[m] Midspan family study in Renfrew and Paisley, Scotland. [St J O'Reilly, 2006] also included data from West of Scotland coronary prevention study (WOSCOPS), which did not meet inclusion criteria and was excluded. Overlapping sample populations (same individuals examined more than once).
[n] Dunedin Multidisciplinary Health and Development Study

Table 2: Summary of results and effect sizes for the associations between socioeconomic factors and race/ethnicity with C-reactive protein (CRP) levels.

Author, year	Effect sizes for association with C-reactive protein	
	Socioeconomic factors	Race/ethnicity
Abramson, 2002	Odds ratio* of CRP> 0.66 mg/L: <12 y of education= 1.66 12 y of education= 1.99 (>12 y education ref)	Odds ratio* of CRP> 0.66 mg/L: African-American= 1.75 "Other"= 0.58 (White ref)
Alley, 2005	50^{th} / 75^{th} / 90^{th} percentiles of CRP (mg/L): In poverty= 2.3 / 5.6 / 13.4 Above poverty= 2.0 / 4.5 / 9.1	Adjusted odds ratio[a] (95% CI) for high CRP (3.1-10.0 mg/L): Black= 1.33 (1.09, 1.62) Mexican-American= 1.26 (1.01, 1.58) Other= 1.10 (0.91, 1.32) (White ref)
	Fully adjusted odds ratio[a] (95% CI) for CRP levels, those in poverty: 1.1-3.0 mg/L= 0.95 (0.80, 1.13) 3.1-10.0 mg/L = 0.88 (0.73, 1.06) > 10 mg/L = 1.27 (1.01, 1.62) (CRP ≤ 1.0 mg/L ref)	Fully adjusted odds ratio[a] (95% CI) for high CRP (3.1-10.0 mg/L): Black= 1.45 (1.16, 1.80) Mexican-American= 1.19 (0.94, 1.53) Other= 1.13 (0.93, 1.38) (White ref)
Anand, 2004	--	Sex/age adjusted mean (SE) CRP levels (>10 excluded), mg/L: Chinese= 1.18 (0.13) European= 2.06 (0.12) South Asian= 2.59 (0.12) Aboriginal= 3.74 (0.14)
		Fully adjusted[b] mean (SE) CRP levels, mg/L: Chinese= 1.72 (0.13) European= 2.13 (0.12) South Asian= 2.72 (0.12) Aboriginal= 2.85 (0.15)

Bo, 2005	Unadjusted effect size data not available	
	Adjusted odds ratio[c] (95% CI) for CRP≥ 3 mg/L according to years of education: Secondary school= 0.85 (0.61, 1.19) University= 0.99 (0.60, 1.64) (Primary school ref)	--
Chambers, 2001	--	Age adjusted geometric mean (SD) CRP levels, mg/L: European= 1.47 (1.62) Indian Asian= 1.71 (1.81)
		Adjusted estimated percentage difference[d] (95% CI) in CRP, Indian Asian-European= 4 (-10, 24)
Danner, 2003	Prevalence ratio[*] of CRP≥ 0.22 mg/dL among men / women: < High school= 1.46 / 1.18 High school= 1.25 / 1.35 (At least some college ref)	Prevalence ratio[*] of CRP≥ 0.22 mg/dL among men / women: African-American= 1.57 / 1.44 Mexican-American= 1.24 / 1.44 "Other"= 1.34 / 1.12 (Non-Hispanic white ref)
Ford, 2000	Mean years (SE) of education according to level of CRP: ≤ 0.21 mg/L= 12.4 (0.1) > 0.21< 0.55 mg/dL= 12.0 (0.2) ≥ 0.55 mg/dL= 11.3 (0.1)	--
Ford, 2003	Unadjusted effect size data not available	Age adjusted beta coefficient[e] (SE) for *ln*CRP: African-American= 0.03 (0.09) Mexican-American= 0.09 (0.10) "Other"= 0.20 (0.25) (White ref)
	Fully adjusted beta coefficient[e] (SE) for *ln*CRP: < High school= 0.13 (0.10) High school/equivalent= 0.07 (0.09) (> High school ref)	Fully adjusted beta coefficient[e] (SE) for *ln*CRP: African-American= -0.02 (0.09) Mexican-American= 0.02 (0.11) "Other"= 0.16 (0.21) (White ref)

Ford, 2004	Unadjusted effect size data not available	Median (IQR) of CRP levels: White= 2.5 (0.9, 5.8) African-American= 3.5 (1.1, 7.5) Mexican-American= 3.6 (1.4, 7.7)
	Adjusted beta coefficient[f] (SE) for *ln*CRP: < High school= 0.17 (0.09) High school/equivalent= -0.04 (0.08) (> High school ref)	Adjusted beta coefficient[f] (SE) for *ln*CRP: African-American= -0.01 (0.09) Mexican-American= 0.29 (0.07) "Other"= 0.00 (0.13) (White ref)
Forouhi, 2001	Effect size data not available	Median (IQR) CRP (mg/L) of men / women: European= 0.92 (0.34, 1.61) / 0.70 (0.41, 1.70) South Asian= 1.07 (0.76, 1.50) / 1.35 (0.72, 3.04)
Jousilahti, 2003	Age adjusted geometric mean of CRP according to socioeconomic status: Low= 2.32 Middle= 1.90 High= 1.52	--
	Fully adjusted[g] geometric mean of CRP according to socioeconomic status: Low= 2.11 Middle= 1.91 High= 1.63	
Kivimaki, 2005	Age/sex adjusted mean (SE) CRP level (mg/L) according to socioeconomic indicators (lowest to highest level): Parental occupation= 2.10 (0.13) / 1.91 (0.13) / 1.40 (0.20) Own education= 1.97 (0.28) / 1.97 (0.10) / 1.52 (0.19)	--
	Fully adjusted beta coefficient[h] with *ln*CRP for: Parental occupation= -0.03 (0.03) Own education= -0.04 (0.05)	

Lakoski, 2006	--	Median (IQR) of CRP (mg/L) according to ethnicity in men / women: Chinese= 0.80 (1.10) / 0.99 (1.50) Caucasian= 1.30 (2.20) / 2.47 (4.10) African-American= 1.80 (2.80) / 3.40 (6.10) Hispanic= 1.93 (2.90) / 3.00 (5.00) Adjusted geometric mean[i] of CRP (mg/L) according to ethnicity in men / women: Chinese= 0.95 / 1.20 Caucasian= 2.03 / 2.75 African-American= 2.12 / 3.19 Hispanic= 2.51 / 3.39
Loucks, 2006	Age/sex adjusted mean (95% CI) CRP (mg/L) according to education: ≤ High school= 4.7 (4.5, 4.9) Associate's degree= 4.7 (4.5, 4.9) Bachelor's degree= 3.6 (3.4, 3.7) >Bachelor's degree= 3.2 (3.0, 3.3) Fully adjusted beta coefficient[j] (95% CI) between years of education and *ln*CRP= -0.03 (-0.05, -0.02)	--
Matthews, 2005	--	Median (IQR) CRP (mg/L) according to ethnicity: Japanese= 0.5 (0.2, 1.2) Chinese= 0.7 (0.3, 1.4) White= 1.4 (0.6, 3.9) Hispanic= 2.3 (1.0, 5.1) African-American= 3.0 (1.0, 7.2) Adjusted[k] effect size data not available

McDade, 2006	Age/sex/ethnicity adjusted beta coefficient (SE) between education and *ln*CRP= -0.06 (0.03)	Median (IQR) CRP (mg/L) in men / women: European-American= 0.59 (0.44, 1.50) / 1.05 (0.44, 1.88) Latino-American= 1.00 (0.55, 1.65) / 1.49 (0.78, 3.10) African-American= 1.07 (0.37, 1.70) / 3.30 (1.39, 4.47)
	Fully adjusted[l] beta coefficient (SE) between education and *ln*CRP= -0.05 (0.03)	Fully adjusted beta coefficient[l] (SE) with *ln*CRP: African-American= 0.12 (0.09) Latino-American= 0.08 (0.09) (European-American ref)
Onat, 2001	Partial coefficient correlation between *ln*CRP and family income: Men= -0.06 Women= -0.10	--
	Adjusted effect size data not available	
Panagiotakos, 2004	Mean (SD) CRP (mg/dL) according to education: Low= 2.04 (1.04) Medium= 1.42 (1.01) High= 1.12 (1.71)	--
	Beta coefficient[m] (SE) of education with *ln*CRP= -0.012 (0.001)	
Panagiotakos, 2005	Mean (SD) CRP (mg/dL) according to tertile of socioeconomic index: Low= 2.1 (1.0) Medium= 1.5 (1.2) High= 1.6 (1.7)	--
	Adjusted beta coefficient[m] (SE) of socioeconomic index score with *ln*CRP= -0.10	

Rathmann, 2006	Age-adjusted geometric mean (SD) CRP (mg/L) according to socioeconomic index in men / women: Low= 1.66 (3.10) / 2.17 (2.70) Intermediate= 1.75 (3.20) / 1.68 (2.60) High= 1.49 (3.30) / 1.32 (2.60) Fully adjusted effect size data not available	--
Sattar, 2004	Geometric mean CRP (mg/L) in men / women according to socioeconomic index: Affluent= 0.70 / 0.70 Intermediate= 0.87 / 0.91 Deprived= 0.94 / 1.15	--
St J O'Reilly, 2006	Age adjusted estimated percentage increase (95% CI) in CRP (mg/L) with one unit difference in deprivation category in two studies: WOSCOPS= 8.3 (6.5, 10.2) MIDSPAN men / women= 6.4 (1.4, 11.5) / 11.3 (6.2, 16.7) Fully adjusted[o] estimated percentage increase (95% CI) in CRP (mg/L) with one unit difference in deprivation category in two studies: WOSCOPS= 5.4 (3.6, 7.1) MIDSPAN men / women= 2.3 (-2.2, 7.0) / 4.8 (0.4, 9.5)	--
Thorand, 2003	Antilog mean (SE) CRP (mg/L) according to education: <12 years= 1.53 (1.03) ≥ 12 years= 1.26 (1.04)	--
Wener, 2000	--	95th percentile (95% CI) of CRP levels among men / women aged 20-39: White= 0.65 (0.55, 0.75) / 1.16 (0.96, 1.36) Hispanic= 0.69 (0.53,0.85) / 1.67 (1.23, 2.11) Black= 0.94 (0.78, 1.10) / 1.65 (1.45, 1.85)

Williams, 2004	Unadjusted effect size data not available	
	Adjusted[p] ratio change (95% CI) in CRP related to low socioeconomic status in men / women= 1.03 (0.90, 1.18) / 0.85 (0.70, 1.04)	--
Wong, 2001	--	Percent of men / women with CRP> 10 mg/L: White= 5.5 / 10.3 Mexican-American= 5.1 / 14.2 Black= 9.1 / 16.3

Results of unadjusted or minimally adjusted analyses appear on one row while those from studies including multivariable (fully adjusted) models appear on two rows (unadjusted or minimally adjusted analyses top, fully adjusted model bottom). Results shown as given in original article unless otherwise noted.
Inadequate numerical data on effect size was not available from the following articles: Danesh (1999), Ford (2002), Khera (2005), Lawlor (2005)
[*] Calculated from prevalence data appearing in article
[a] Top row adjusted for age and poverty; full model (bottom row) adjusted for age, sex, poverty or race, recent illness, leukocyte count, asthma, chronic bronchitis, rheumatoid arthritis, obesity, smoking, heavy drinking, exercise (data from personal communication with the author)
[b] Adjusted for age, sex, BMI, waist circumference, triglycerides, HDL, systolic BP, and HbA1c.
[c] Adjusted for age, sex, BMI, smoking, alcohol intake, physical activity, living in rural area
[d] Adjusted for age, smoking, diabetes, hypertension, hypercholesterolemia, social classs, waist to hip ratio, insulin resistance score
[e] Adjusted for age, education, smoking status, body mass index, and alcohol intake
[f] Adjusted for age, race, education, smoking status, total cholesterol concentration, systolic blood pressure, waist circumference, alcohol use, hormone replacement therapy
[g] Adjusted for age, smoking, waist to hip ratio, prevalent longstanding diseases
[h] Adjusted for age, sex, smoking, physical activity, BMI, waist to hip ratio, systolic and diastolic blood pressure, insulin, glucose, HOMA, HDL and LDL cholesterol, triglycerides
[i] Adjusted for age, BMI, diabetes, hypertension, smoking, alcohol use, HMG-CoA reductase inhibitors, aspirin use, estrogen medications, physical activity, LDL and HDL cholesterol
[j] Adjusted for age, sex, smoking, systolic and diastolic blood pressure, total cholesterol:high density lipoprotein cholesterol ratio, BMI, lipid-lowering medication, antihypertensive medication, prevalent cardiovascular disease, depression
[k] Adjusted for study site, education, leisure physical activities, total calories, percent calories from fat
[l] Adjusted for age, sex, ethnicity or education, waist circumference, time to fall asleep
[m] Adjusted for age, sex, smoking, compliance to medication, BMI, diet score, physical activity
[n] Adjusted for age, smoking, BMI, waist circumference, alcohol intake, physical activity
[o] Adjusted for age, smoking, BMI, medication
[p] Adjusting for systolic blood pressure, apolipoproteins A1 and B, health problems and oral contraceptive use

Artigo 2

Epidemiology of C-reactive protein in young adults belonging to a Brazilian birth cohort: a tale of rich men and poor women

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Abstract

Objective

To evaluate the impact of lifecourse socioeconomic indicators on C-reactive protein levels in young adults in a middle-income setting

Design

Population-based prospective birth cohort study

Setting

Pelotas, Southern Brazilian city

Participants

3827 young adults aged 23 y belonging to the 1982 Pelotas birth cohort study

Main outcome measure

Serum C-reactive protein (mg/L)

Results

Geometric mean (95% CI) C-reactive protein levels were 0.89 mg/L (0.84 to 0.94) and 1.66 mg/L (1.54 to 1.78) in men and women, respectively. In women, maternal education was inversely associated with CRP levels even when adjusted for current education and income (53% higher among women whose mothers had ≤ 4 vs. ≥ 12 years of schooling; p=0.01). This association was attenuated and no longer significant when adjusted for adult BMI. Neither early income nor current education or income had

an association with CRP after adjustment for confounding. In men, family income at birth was directly associated with levels of CRP; effect sizes were attenuated when mediators (ie adiposity) were adjusted for, but remained significant (39% higher among men in the top vs. bottom income group; p=0.02). Maternal education showed no association in men in the crude analyses, but after adjustment for income and current variables, a protective association became apparent (25% higher among men whose mothers had ≤ 4 vs. ≥ 12 years of schooling; p=0.04). Wealthier men with low attained education had the highest CRP levels.

Conclusions

Socioeconomic conditions at birth showed lasting associations with C-reactive protein levels in both sexes, but operated in inverse directions in men and women. Adiposity mediated inflammation in both sexes. C-reactive protein levels mirrored obesity patterns from middle-income settings where rich men and poor women are most affected. Public health strategies should not overlook the importance of developmental factors and social influences, especially in regions undergoing the epidemiological transition.

Introduction

Socioeconomic factors are powerful determinants of cardiovascular disease (CVD). It has been widely demonstrated that poorer and less educated individuals suffer significantly higher levels of mortality and morbidity associated with CVD than richer and more educated ones and that these patterns follow marked dose-response patterns[1-7]. Several of these studies have addressed potential pathways through which low socioeconomic position (SEP) may lead to CVD, reporting that lifestyle factors such as diet, exercise and smoking fail to completely account for differences in outcome. Poorly understood or unknown biological pathways are therefore likely to play important roles.

Over the past decade C-reactive protein (CRP), a non-specific indicator of systemic inflammation associated with the acute phase response, has extensively been studied as a potential candidate linking traditional risk factors and the atherosclerotic process[8-12]. Used clinically for monitoring and screening of acute processes such as myocardial infarction and infection, CRP in highly-sensitive assays has been shown to predict a number of coronary events, as well as type 2 diabetes mellitus and sudden death associated with CVD in prospective observational studies[10 11 13-16]. As such, CRP has become a widely accepted marker for the incidence and prognosis of CVD. Guidelines put forth by the Centers for Disease Control and the American Heart Association suggest that chronically elevated CRP should be considered in conjunction with traditional risk indicators[17]. Although recent Mendelian Randomization studies have shown that CRP is not likely to be causally associated with coronary heart disease

(CHD)[18-21], its importance as a biomarker for a number of chronic disease processes is clear.

Socioeconomic factors are inversely associated with CRP levels in adults[22-26]. A recent systematic review of 25 population-based studies concluded that individuals with lower SEP were more likely to have elevated CRP levels than those with higher SEP even after adjustment for a number of covariates[27]. This suggests that CRP may be one of the factors that mediate the association between poverty and CHD. This review located only one study from a middle-income population (Turkey), and few authors attempted to disentangle factors that confound the SEP-CRP association from those that may act as possible mediators[20 28 29]. There were also few studies that examined lifecourse socioeconomic exposures. It is postulated that early life exposures, including socioeconomic factors, may contribute to the onset of CVD and associated risk factors in adulthood, though purported mechanisms remain largely speculatory[30 31].

The objective of this study was to examine the impact of socioeconomic indicators throughout the lifecourse on levels of CRP among young adults belonging to a Brazilian prospective birth cohort study.

Methods

The 1982 Pelotas birth cohort recruited over 99% of births occurring in the city that year. All newborns whose mothers gave birth in one of the city's hospitals and who lived in the urban area of the city were included (n= 5914). Newborns and their

mothers were weighed and a questionnaire on socioeconomic and demographic variables was applied. Cohort members have been prospectively followed up over the years in numerous visits; the main phases being at one, two, four, 15, 18 (males only), 19 (females only) and 23 years old. Information on follow up methods, sampling fractions and variables collected has been detailed elsewhere[32-34].

In 2004-05, a citywide census of all 98000 households in the urban area of Pelotas was performed in an attempt to locate members of the original cohort. Additional strategies included searching at the last known address, contacting relatives of the cohort members, performing searches at educational institutions and registration with the universal health system. Trained interviewers applied questionnaires from October 2004 to September 2005.

Several socioeconomic and demographic variables are available. Self-described skin color of participants was categorized into five groups: white, mulatto, black, indigenous and Asian, the latter two groups being excluded in the analyses due to insufficient numbers. Family income data at birth and at age 23 y was categorized into groups representing <1, 1.1-3.0, 3.1-6.0, 6.1-10.0 and ≥ 10 minimum wage units. Minimum wage was approximately 50 and 180 USD at birth and at the time of the 2004-05 cohort visit, respectively. Number of years of formal education completed by the participant was also collected. Further details on behavioral and anthropometric variables collected and methods utilized is available[35].

During the 2004-05 cohort visit, non-fasting venous blood was collected from volunteers and high sensitivity C-reactive protein was measured using the automated

DPC (Siemens) Immulite chemiluminescent immunoassay (Los Angeles, USA). The coefficients of variation within and between assays were 10 and 7%, respectively.

C-reactive protein samples with results below the assay sensitivity threshold of 0.1 mg/L were converted to 0.05 mg/L for analysis. CRP levels presented a positively skewed distribution and were natural log-transformed (*ln* mg/L) prior to undertaking statistical analyses. CRP levels are presented as geometric mean (95% CI). CRP distributions were analyzed by linear regression as a continuous (*ln* mg/L) variable and by logistic regression as a dichotomous variable (>10 mg/L), using Wald tests for trend and heterogeneity where appropriate. The beta coefficients and 95% confidence intervals that appear in the tables may therefore be interpreted as ratios.

Variables were tested in crude and adjusted analyses based on a conceptual model based on a proposed hierarchy of causal relationships. Analyses were stratified by sex. The model (Figure 1) had demographic variables (skin color and age) and socioeconomic indicators at birth (maternal education and family income) in its first hierarchical level; the second level included socioeconomic indicators at 23 y (own education and family income) that may be influenced by the variables in the first level; and the third and last level included behavioral and anthropometric variables at 23 y that may be influenced by all of the above.

To elucidate the effects on the outcome at various levels of adjustment, exposure variables were tested in crude analyses, adjusted for level 1 (sociodemographic+early SEP variables), levels 1 and 2 (+later SEP variables) and all three levels (+anthropometric and behavioral variables) of the model.

Pregnant women (n= 93) and those using oral contraceptive therapy (OCT; n=445) were excluded from these analyses and those pregnant or up to six months post-partum (n= 79) were excluded from analyses including BMI and waist circumference.

The Federal University of Pelotas Ethical Committee approved all phases and aspects of the 1982 Pelotas birth cohort study. Verbal informed consent was obtained in 1982 and written informed consent in 2004-05 for the questionnaires and blood draw.

Results

Adding together subjects known to have died before the 2004 visit (n= 282) and those successfully interviewed (n= 4297) accounted for 77.4% of the original cohort. The mean age of those interviewed was 22.8 y (21.9 to 23.7) and 75% of individuals described themselves as white. CRP levels were assessed in 89% of interviewees, 1919 men and 1908 women. Individuals who did not have CRP measured had higher current family income, but were otherwise similar to those who did. After excluding pregnant women and those using OCT during the time of the interview, geometric mean (95% CI) CRP levels were 0.89 mg/L (0.84 to 0.94) and 1.66 mg/L (1.54 to 1.78) in men and women, respectively. The difference between the sexes was significant ($p<0.0001$) but there were no differences in CRP levels according to skin color in either sex.

Distributions of socioeconomic indicators across the lifecourse for men and women are presented in Tables 1 and 2, respectively. In both sexes, there were positive shifts in

family income from 1982 to 2004 and in education level compared to maternal education. Women were better educated than men, who were generally richer.

Maternal education and family income at birth were tested for associations with CRP levels. Unadjusted associations between CRP levels and early socioeconomic indicators were inconsistent between the sexes. In men (Table 3), family income at birth was directly associated with CRP levels whereas in women (Table 4) this association was not apparent. Maternal education, on the other hand, was inversely associated with CRP levels in women and not associated in men. In crude analyses, men in the highest family income group at birth had 42% higher CRP levels than men in the lowest group, whereas women whose mothers had the least education had 43% higher CRP levels than those whose mothers had the most.

When controlled for age, skin color and for one another, maternal education and family income at birth retained associations with CRP levels in both sexes- directly in men and inversely in women. These effects remained when also adjusted for socioeconomic factors at age 23 years, which are possible mediators (levels 1+2).

Potential behavioral and anthropometric mediating variables were then included into the model (levels 1+2+3). In men (Table 3), the effect of family income at birth was slightly attenuated but still significant. The protective association with maternal education, on the other hand, increased after such adjustment and became significant. For women (Table 4) there was no association of CRP and income at birth in any of the models. The effect of maternal education was attenuated and no longer significant. For

both sexes, BMI and waist circumference were the only two variables that changed effect sizes and significance levels.

Summing up the early indicators of SEP, maternal education showed protective effects against elevated CRP levels in both sexes. Notably, adjusting for indicators of obesity attenuated the association in women whereas it amplified the association in men, indicating the mediating effects of these anthropometric indices. Family income at birth was a risk factor in men only, regardless of level of adjustment.

Own education and family income in 2004 were also tested for associations with CRP levels. In unadjusted analyses, family income showed direct and inverse associations in men and women, respectively. Men in the top family income group had 30% higher CRP levels than men in the lowest group. Education was inversely associated with CRP levels in women but not in men. Women with the least education had 34% higher levels than those who had the most.

In men (Table 3), after adjustment for confounders (age, skin color, early and current indicators of SEP) current family income maintained a direct association with CRP levels and the protective effects of own education were made more apparent. These effects disappeared when adjusted for anthropometric and behavioral variables. In women (Table 4), associations between current indicators of SEP and CRP levels were not significant when adjusted for confounders.

Figure 2 explores the interaction between own education and current income. Men and women with more than four years of education have similar CRP levels whether poor

(bottom tertile of current income) or not. There was an interaction between income and education in men such that subjects who had low education and high income had much higher CRP levels than those in the other three categories of income and education.

All analyses were repeated using logistic regression, treating CRP as a dichotomous variable using the proposed cut-off for acute inflammation (10 mg/L). Results were largely consistent with the linear regression findings reported above, but associations tended to be less significant. There was also a significant interaction between sex and current income when the outcome was acute-level CRP.

Another approach to investigating lifecourse SEP is to build a variable that shows change in income from birth to current age. This approach was also employed in our analyses, and the results did not add upon the findings described above (results available upon request).

Discussion

CRP levels in the current cohort were similar to those from population-based samples in young adults from the USA[36 37] and those reported by the Framingham study[38] in which subjects were older, but slightly lower than a New Zealand cohort of similar age[39]. Four and nine percent of men and women had CRP levels higher than 10 mg/L (acute-level inflammation), whereas 17% and 35% of men and women had levels higher than 3 mg/L (high-risk category[17]).

It has been widely observed that risk for cardiovascular disease begins early in life and our results supports that stance[40-42]. Our conceptual model included lifecourse indicators of SEP and had the advantage of prospective data, including concurrent behavioral and anthropometric variables. This is one of only five studies to investigate lifecourse SEP factors in relation to an inflammatory marker in a representative sample, and the first study from Latin America. We have previously examined the epidemiology of CRP levels in this cohort in relation to a number of distal and proximal factors, however, without investigating the effects of socioeconomic trajectories[43].

The first message from our findings is that CRP levels show similar socioeconomic patterns as obesity. In middle-income, transitional societies, overweight and obesity are directly related to social class in men, and inversely in women, as shown by previous studies and a recent systematic review by McLaren[44-47]. Adiposity in the current cohort follows these trends[48]. Moreover, observational studies have widely found that obesity is directly and strongly associated with CRP levels in both sexes[49-51]. Adipose tissue is said to act as an endocrine organ controlling the secretion of hormones such as interleukin-6 and tumor necrosis factor-alpha that are strongly and positively linked with the inflammatory process[52-54].

The present investigation contributes to the study of cardiovascular risk in a middle-income setting by showing that the direct association between SEP and adiposity in men, and the inverse association in women, are confirmed when studying an inflammatory marker strongly associated adipose tissue. These patterns have never been described with respect to an inflammatory marker, but it is plausible given the association between adipose tissue and CRP levels. Social factors involved in the

associations related to these paradoxical findings deserve further research, especially in the context of dietary patterns and perceptions of body image related to gender and socioeconomic standing in low and middle-income countries.

A second finding was that the effects of early SEP persisted in both sexes even when adjusted for later indicators of social position. In men, a direct association between CRP levels and early life family income was retained regardless of the level of adjustment. In women, maternal education had protective effects in spite of adjustment for own educational level and current family income. Early life environmental and nutritional exposures, therefore, appear to have lifelong effects independent of later life exposures. This supports the notion that physiological plasticity at critical windows of development permits early exposures to exert permanent effects on hormonal and metabolic parameters[30 55 56]. Further research is needed to elucidate the mechanisms by which social factors throughout the lifecourse may impact immune response and inflammation.

A third relevant finding was that income and education seem to have different, and in some cases even opposite effects. This pattern held true with early and concurrent indicators of SEP. High family income at birth was a risk factor for elevated CRP levels in men whereas high maternal education was protective in both sexes. Similarly, in unadjusted analyses, high family income at age 23 y was a risk factor in men but protective for women. Socioeconomic indicators are widely described as having overall inverse associations CRP levels in both sexes, as indicated by a recent systematic review of population-based studies[27]. The literature represented in this review, however, was almost exclusively from high-income countries and only one study from a

low or middle-income country was located (Turkey)[29]. Data on the specific effects of socioeconomic indicators on CRP levels in low and middle-income countries is very limited. It is likely that the influence of SEP on inflammation, and indeed on numerous pathological processes, in these settings is quite different than in rich countries. This calls for more global research on the effects of individual and population-level social conditions on disease incidence.

Because patterns of obesity vary according to the level of socioeconomic development, it is understandable that the effects of income and education on CRP may also vary from country to country. Education and income represent similar but not equal constructs- education represents level of skill or learning, whereas income reflects access to material resources, often related to occupational opportunities[57]. In the current study, the (protective) effects of education are clearer and more consistent than those of income, and as shown in Figure 2, the combination of low education and high income was particularly hazardous for men.

A final message to come from these analyses is related to mediating factors. In women, adjusting for BMI and waist circumference attenuated the higher risk in poor women, suggesting that this effect was partially mediated by adiposity. In men, on the other hand, the protective effects of maternal education only became apparent when adjusted for BMI and waist circumference. This suggests that there are pathways through which maternal education can help lower CRP levels, but these effects are offset by greater adiposity in subjects born to educated mothers, and only become evident after adjustment for fatness.

Our findings indicate that BMI and waist circumference are strong mediators of these associations in both sexes. Cigarette smoking, fat intake and minor psychiatric disorder also act as mediators in men, but to a much smaller degree[43]. By examining the effects of socioeconomic exposures at various levels of adjustment, we were able to show to what degree key factors such as obesity mediate the association between SEP and inflammation.

Potential limitations of this study should be noted. Ongoing inflammatory disease status at the time of the blood draw was not assessed. However, given the relatively young age of the cohort, it is likely that few, if any, of the participants had diseases that would significantly contribute to acute-level inflammation. Further, the recommendation for classification of clinical risk for CRP levels is two measurements at least two weeks apart, our study relied on a single measure[17]. Notwithstanding, CRP levels have been shown to remain relatively stable over time and this likely does not limit our study[58 59].

On the positive side, the fact that this sample is part of an ongoing birth cohort opens possibilities for future studies as members of the cohort age. Lifecourse socioeconomic factors will be especially interesting to examine with disease outcomes commonly associated with aging, such as hypertension, CVD and other chronic diseases.

This study found that early socioeconomic exposures exert significant and lasting effects on an inflammatory marker, but that the direction of the effect was different in men and women. This warrants further investigation, especially in the context of socio-cultural and environmental conditions specific to middle-income countries that may

impact adiposity, a key mediator in the associations between SEP and CRP levels. Public health strategies aimed at decreasing incidence of chronic disease, in addition to highlighting the risks associated with adult obesity, should not overlook the importance of key developmental factors and social determinants, especially in regions undergoing the epidemiological transition.

What is already known on this subject

Early life poverty programs the organism for susceptibility to risk factors associated with cardiovascular and other chronic diseases through a number of speculated pathways

Serum C-reactive protein levels are inversely associated with socioeconomic indicators and predict cardiovascular disease endpoints in high-income countries

There have been no population-based studies from Latin America investigating the impact of lifecourse socioeconomic indicators on an inflammatory marker

What this study adds

Early socioeconomic exposures influence C-reactive protein levels in both sexes, independent of demographic factors and later socioeconomic position

Higher income in early and later life is a risk factor for elevated C-reactive protein levels in men, whereas educational indicators are protective in both sexes

C-reactive protein levels in both sexes are heavily mediated by indicators of adiposity, and follow the same patterns as obesity in other middle-income countries where rich men and poor women are more obese

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Level	Variable
1	Age Skin color Family income at birth Maternal education
2	Family income at 23 y Own education
3	**Anthropometric and behavioral factors:**
	Parity (women) BMI and waist circumference
	Diet and alcohol intake Smoking
	Physical activity Minor psychiatric disorder
Outcome	C-reactive protein level

Figure 1: Proposed hierarchical model for the associations between socioeconomic indicators at birth and age 23 years and C-reactive protein levels in young adulthood.

Table 1: Distribution of C-reactive protein levels according to lifecourse socioeconomic factors, men.

Independent variable	*% in group*	Geometric mean (95% CI) CRP
Family income in 1982, minimum wage units*		
≤ 1	20.3	0.77 (0.67 to 0.87)
1.1-3.0	50.0	0.90 (0.82 to 0.97)
3.1-6.0	19.4	0.93 (0.81 to 1.06)
6.1-10.0	5.5	0.93 (0.74 to 1.17)
≥ 10	4.8	1.31 (1.01 to 1.70)
Maternal education, years*		
0-4	32.8	0.90 (0.81 to 0.99)
5-8	44.3	0.88 (0.80 to 0.96)
9-11	10.5	0.83 (0.70 to 0.99)
≥ 12	12.4	0.98 (0.84 to 1.16)
Family income in 2004, minimum wage units		
≤ 1	4.6	0.78 (0.59 to 1.03)
1.1-3.0	31.6	0.87 (0.78 to 0.96)
3.1-6.0	34.1	0.85 (0.77 to 0.94)
6.1-10.0	16.7	0.91 (0.79 to 1.05)
>10	12.9	1.10 (0.94 to 1.28)
Own education, years		
0-4	9.4	0.94 (0.76 to 1.15)
5-8	32.5	0.92 (0.83 to 1.02)
9-11	46.7	0.83 (0.76 to 0.90)
≥ 12	11.4	1.06 (0.90 to 1.25)
N	1919	

*Due to missing data, the numbers of observations for analyses were: family income in 1982 n= 1912; maternal education n= 1916.

Table 2: Distribution of C-reactive protein levels according to lifecourse socioeconomic factors, women.

Independent variable	*% in group*	Geometric mean (95% CI) CRP
Family income in 1982, minimum wage units*		
≤ 1	19.6	1.57 (1.32 to 1.86)
1.1-3.0	50.5	1.70 (1.53 to 1.89)
3.1-6.0	19.3	1.87 (1.60 to 2.20)
6.1-10.0	5.9	1.36 (1.03 to 1.80)
≥ 10	4.7	1.17 (0.86 to 1.60)
Maternal education, years*		
0-4	32.7	1.81 (1.59 to 2.07)
5-8	42.3	1.72 (1.53 to 1.93)
9-11	11.8	1.49 (1.24 to 1.80)
≥ 12	13.2	1.27 (1.05 to 1.54)
Family income in 2004, minimum wage units		
≤ 1	7.0	1.46 (1.06 to 2.02)
1.1-3.0	33.5	1.83 (1.60 to 2.09)
3.1-6.0	32.1	1.72 (1.52 to 1.95)
6.1-10.0	14.9	1.58 (1.31 to 1.90)
>10	12.5	1.29 (1.07 to 1.56)
Own education, years		
0-4	6.4	1.75 (1.29 to 2.36)
5-8	22.9	1.76 (1.50 to 2.06)
9-11	52.3	1.74 (1.57 to 1.93)
≥ 12	18.4	1.30 (1.11 to 1.53)
N	1370	

*Due to missing data, the numbers of observations for analyses were: family income in 1982 n= 1360; maternal education n= 1368.

Excludes pregnant women (n= 93) and those using oral contraceptive therapy (n= 445) at the time of the 2004-05 cohort visit.

Table 3: Beta coefficients (95% confidence intervals) of linear regression between log-transformed C-reactive protein and lifecourse socioeconomic indicators at various levels of adjustment according to conceptual model, men (n=1919). Coefficients are interpretable as ratios.

Level	Independent variable	Level of adjustment			
		Crude	Level 1	Levels 1+2	Levels 1+2+3
1	Family income in 1982, minimum wage units*	<0.001	0.001	0.001	0.02
	≤ 1	0.58 (0.44 to 0.79)	0.52 (0.37 to 0.73)	0.52 (0.36 to 0.74)	0.61 (0.43 to 0.86)
	1.1-3.0	0.68 (0.52 to 0.90)	0.63 (0.46 to 0.86)	0.62 (0.45 to 0.86)	0.67 (0.50 to 0.91)
	3.1-6.0	0.71 (0.53 to 0.95)	0.67 (0.49 to 0.91)	0.66 (0.48 to 0.91)	0.68 (0.50 to 0.91)
	6.1-10.0	0.71 (0.49 to 1.02)	0.69 (0.48 to 1.00)	0.69 (0.47 to 0.99)	0.72 (0.51 to 1.02)
	≥ 10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	Maternal education, years*	0.6	0.09	0.1	0.04
	0-4	0.91 (0.75 to 1.11)	1.19 (0.93 to 1.51)	1.19 (0.92 to 1.53)	1.25 (0.98 to 1.59)
	5-8	0.89 (0.74 to 1.08)	1.12 (0.89 to 1.39)	1.12 (0.89 to 1.40)	1.15 (0.93 to 1.43)
	9-11	0.85 (0.67 to 1.08)	0.99 (0.77 to 1.29)	1.00 (0.77 to 1.29)	1.05 (0.82 to 1.34)
	≥ 12	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2	Family income in 2004, minimum wage units	0.02	--	0.07	0.8
	≤ 1	0.71 (0.52 to 0.97)		0.69 (0.48 to 0.99)	0.88 (0.62 to 1.25)
	1.1-3.0	0.79 (0.65 to 0.96)		0.82 (0.65 to 1.03)	0.97 (0.78 to 1.21)
	3.1-6.0	0.78 (0.64 to 0.94)		0.80 (0.64 to 0.99)	0.85 (0.70 to 1.05)
	6.1-10.0	0.78 (0.64 to 0.94)		0.87 (0.69 to 1.09)	0.94 (0.75 to 1.16)
	>10	1 (ref)		1 (ref)	1 (ref)
2	Own education, years	1.0	--	0.06	0.5
	0-4	0.88 (0.68 to 1.14)		1.15 (0.84 to 1.57)	0.99 (0.73 to 1.34)
	5-8	0.87 (0.71 to 1.06)		1.05 (0.83 to 1.34)	0.94 (0.74 to 1.19)
	9-11	0.78 (0.64 to 0.94)		0.91 (0.73 to 1.12)	0.85 (0.69 to 1.05)
	≥ 12	1 (ref)		1 (ref)	1 (ref)

P values for trend by linear regression using *ln*CRP (mg/L) as dependent variable

(Table 3 cont.)

*Due to missing data, the numbers of observations for analyses were: family income in 1982 n= 1912; maternal education n= 1916.

Level 1 adjusted for demographic variables (skin color and age) and early socioeconomic indicators (family income in 1982 and maternal education)

Level 1+2 adjusted for demographic variables, early socioeconomic indicators, and later socioeconomic indicators (family income in 2004 and own education)

Level 1+2+3 adjusted for demographic variables, early and later socioeconomic indicators, and anthropometric and behavioral variables (BMI, waist circumference, smoking, fat and fiber intake, alcohol consumption, physical activity level and minor psychiatric disorder)

Table 4: Beta coefficients (95% confidence intervals) of linear regression between log-transformed C-reactive protein and lifecourse socioeconomic indicators at various levels of adjustment according to conceptual model, women (n=1370). Coefficients are interpretable as ratios.

Level	Independent variable	Level of adjustment			
		Crude	Level 1	Levels 1+2	Levels 1+2+3
1	Family income in 1982, minimum wage units*	0.3	0.2	0.1	0.2
	≤ 1	1.33 (0.92 to 1.94)	0.93 (0.60 to 1.44)	0.85 (0.54 to 1.33)	0.86 (0.55 to 1.34)
	1.1-3.0	1.45 (1.02 to 2.06)	1.06 (0.71 to 1.58)	0.99 (0.66 to 1.49)	1.01 (0.68 to 1.50)
	3.1-6.0	1.60 (1.10 to 2.32)	1.31 (0.88 to 1.95)	1.27 (0.85 to 1.89)	1.17 (0.80 to 1.73)
	6.1-10.0	1.16 (0.74 to 1.82)	1.03 (0.65 to 1.63)	1.01 (0.64 to 1.60)	0.96 (0.62 to 1.49)
	≥ 10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	Maternal education, years*	0.002	0.001	0.01	0.1
	0-4	1.43 (1.12 to 1.81)	1.66 (1.23 to 2.23)	1.53 (1.12 to 2.09)	1.34 (0.99 to 1.83)
	5-8	1.35 (1.08 to 1.70)	1.53 (1.17 to 2.02)	1.45 (1.10 to 1.93)	1.36 (1.03 to 1.79)
	9-11	1.18 (0.88 to 1.57)	1.27 (0.94 to 1.73)	1.24 (0.91 to 1.69)	1.23 (0.91 to 1.65)
	≥ 12	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2	Family income in 2004, minimum wage units	0.04	--	0.4	0.9
	≤ 1	1.13 (0.80 to 1.59)		1.02 (0.68 to 1.53)	0.98 (0.65 to 1.47)
	1.1-3.0	1.42 (1.11 to 1.80)		1.28 (0.96 to 1.72)	1.12 (0.83 to 1.49)
	3.1-6.0	1.33 (1.05 to 1.70)		1.25 (0.95 to 1.64)	1.19 (0.91 to 1.56)
	6.1-10.0	1.22 (0.93 to 1.62)		1.16 (0.87 to 1.56)	1.14 (0.86 to 1.52)
	>10	1 (ref)		1 (ref)	1 (ref)
2	Own education, years	0.03	--	0.3	0.6
	0-4	1.34 (0.96 to 1.87)		1.31 (0.88 to 1.96)	1.18 (0.77 to 1.79)
	5-8	1.35 (1.08 to 1.70)		1.24 (0.92 to 1.66)	1.12 (0.82 to 1.52)
	9-11	1.34 (1.10 to 1.63)		1.26 (1.00 to 1.59)	1.24 (0.98 to 1.56)
	≥ 12	1 (ref)		1 (ref)	1 (ref)

P values for trend by linear regression using *ln*CRP (mg/L) as dependent variable

(Table 4 cont.)

*Due to missing data, the numbers of observations for analyses were: family income in 1982 n= 1360; maternal education n= 1368

Excludes pregnant women (n= 93) and those using oral contraceptive therapy (n= 445) at the time of the 2004-05 cohort visit, analyses including BMI and waist circumference exclude women up to 6 months post-partum (n=82)

Level 1+2+3 adjusted for demographic variables, early and later socioeconomic indicators, and anthropometric and behavioral variables (parity, BMI, waist circumference, smoking, fat and fiber intake, alcohol consumption, physical activity level and minor psychiatric disorder), Levels 1, 1+2 as in men

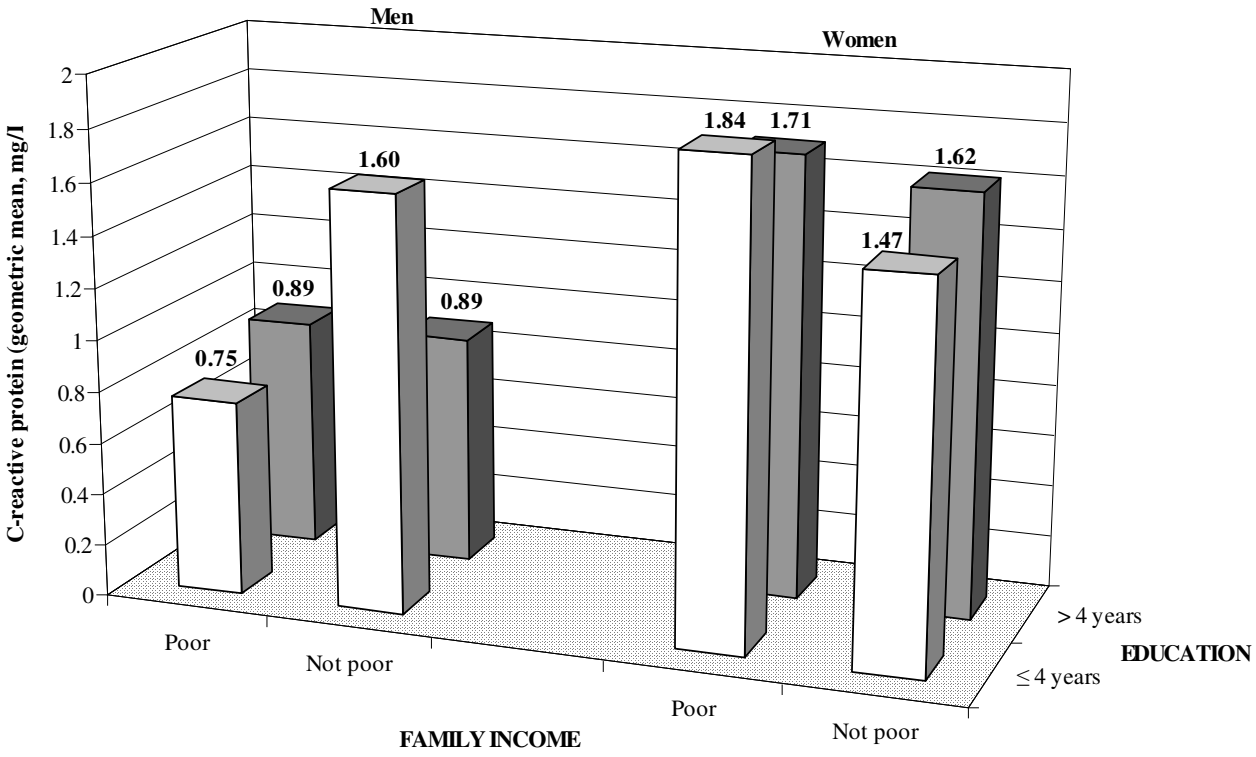

Figure 2: Levels of C-reactive protein in poor (bottom tertile of family income in 2004-05) and not poor (top two tertiles) men and women with ≤ 4 or >4 years of education.

Artigo 3

Life-course weight gain and C-reactive protein levels in young adults: findings from a Brazilian birth cohort

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Preparado para submissão

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Abstract

Rapid weight gain in childhood has been associated with increased risk of chronic diseases in adults. C-reactive protein (CRP) is a mediator of atherosclerosis and chronically elevated levels predict cardiovascular outcomes. No studies have examined the effects of lifecourse weight gain in relation to levels of CRP levels. The 1982 Pelotas (Brazil) Birth Cohort Study has prospectively collected weight and health data at various intervals since birth. The most recent follow-up was in 2004-05, when 77.4% of the cohort was traced and CRP levels were measured in 89% of those interviewed (n= 3827). Geometric mean (95% CI) C-reactive protein levels were 0.89 mg/L (0.84 to 0.94) and 1.66 mg/L (1.54 to 1.78) in men and women, respectively. In analyses adjusted for confounding variables, weight gain in infancy showed a non-significant protective effect among males; from the second year onwards, weight gain was directly associated with CRP levels. In females, weight gain in three periods was associated with higher CRP: in infancy, from 4-15 years and from 18-23 years periods. The strongest associations were observed in the 18-23 years age range; CRP ratios (95% CI) were 1.77 (0.93-1.70) and 1.90 (1.52-2.39) for men and women, respectively. Males who were stunted at 2 years and centrally obese at 23 years had the highest CRP levels. In summary, rapid weight gain throughout life directly impacted CRP levels, but the effects varied by sex. Public health efforts need to tackle undernutrition in infancy, together with rapid weight gain in later childhood and adolescence.

Introduction

Low birthweight is associated with cardiovascular risk in adult life in studies from developed countries, though mechanisms remain largely speculatory (Barker 1994). Early hypotheses centered on in-utero exposures but recently, rapid postnatal growth has been implicated in increased risk levels (Singhal and Lucas 2004). Several recent studies have shown that growth in childhood, especially rapid weight gain, is associated with increased risk for overweight (Ekelund and others 2006; Monteiro and others 2003; Victora and others 2007b), elevated blood pressure (Horta and others 2003), clustered metabolic risk (Ekelund and others 2007) and coronary events (Barker and others 2005). Data suggest that individuals who are small in the first years of life and subsequently put on weight rapidly present the greatest levels of risk (Adair and Cole 2003; Barker and others 2005; Bhargava and others 2004; Eriksson and others 2001).

C-reactive protein (CRP), an acute phase reactant used as a marker for systemic inflammation, is recognized as a mediator in the atherosclerotic process (Pepys and Hirschfield 2003; Yeh 2004). Observational studies have shown that chronically elevated CRP levels predict coronary heart disease related outcomes in adults, though most data are from high-income countries (Albert and others 2002; Cesari and others 2003; Ridker and others 1998). The associations between early life variables and CRP levels have not been examined in depth. Sattar et al (2004) showed an inverse association between birthweight and CRP levels among adult men and women from the MIDSPAN Family Study (Sattar and others 2004). No other studies have examined the effects of early life weight or growth on inflammatory markers in later life.

Lifecourse models are fundamental for the study of early risk exposures for chronic disease in later life (Ben-Shlomo and Kuh 2002; Kuh and others 2003). However, literature from countries undergoing the epidemiological transition is sparse and few cohorts have adequate longitudinal data to explore these associations (Gillman and Kleinman 2007). The 1982 Pelotas (Brazil) birth cohort study has prospectively collected data from participants at numerous follow-up visits, the most recent being in 2004-05 when the cohort was aged 23 years. We used this data to examine weight gain throughout life in relation to levels of CRP levels in young adults.

Methods

The city of Pelotas in Southern Brazil has a population of approximately 350,000 (estimated, 2007). The 1982 Pelotas birth cohort began as a perinatal survey of all hospital births taking place in the city that year (Victora and Barros 2006). Over 99% of births (n=5914) to mothers living in the urban area of the city were registered. Newborns were weighed using calibrated pediatric scales sensitive to 100 g and mothers were interviewed on a number of sociodemographic and general health variables. Gestational age was estimated by mother's recall of last menstrual period, but about 20% of the sample had missing values. Maternal smoking was defined as smoking at least one cigarette per day. Height of the mother was taken using a portable stadiometer to the nearest mm. Maternal education was categorized by years of completed formal schooling. Family income was collected as a categorical variable representing less than 1, 1.1-3.0, 3.1-6.0, 6.1-10.0, and greater than 10 minimum wage units. Minimum wage at the time was equivalent to approximately 50 USD. Birth length was not measured.

In 1983, cohort members born from January to April were sought, resulting in 79% (n=1457) of the sub-sample being examined. The 1984 and 1986 follow-ups began with a city census in attempts to locate the entire cohort; 87% (n=4934) and 84% (n=4742) of the cohort were examined, respectively. Mean ages of the children were 11.3, 19.4 and 43.1 months at the 1983, 1984 and 1986 visits, respectively. In 1997, a random selection of 27% of the city's census tracts were visited in search of members of the cohort, resulting in a 72% follow-up rate (n=1076) at a mean age of 14.7 years. Follow-up rates reported here include those known to have died.

The next examination took place in 2000, when cohort males were legally obligated to report to the army. Of the 3037 cohort males, 2250 were interviewed at a mean age of 18.2 years (78.9% follow-up rate). In 2001, the same 27% sub-sample as in 1997 was re-visited and 1031 cohort members were successfully examined and interviewed at a mean age of 18.9 years. In the current study, the 2000 and 2001 follow-ups were combined in order to include males and females, and mean age of this group is reported as 18/19 years. Extensive questionnaires were applied and members were weighed and measured at each of the above follow-ups using methods previously described (Victora and others 2003).

The most recent cohort follow-up was conducted in 2004-05. During this follow-up, 4297 members of the cohort (mean age 22.8 years) were interviewed and examined, resulting in a follow-up rate of 77.4%. Trained interviewers applied questionnaires that included sections on health, behavior, and socioeconomic factors. Skin color was self-reported. Weight to the nearest 100 g was measured using the Seca (UNICEF) scale. Waist circumference was measured at the narrowest girth of the trunk or halfway

between the costal margin and iliac crest. Central obesity was defined using cutoffs of ≥ 94 cm for men and ≥ 80 cm for women (WHO 2006).

Current smoking was defined as smoking at least one cigarette per week. Fat and fiber intake were assessed using a modified Block method (Block and others 1989). Information on consumption of wine, beer and liquors was used to calculate an overall alcohol intake score. Sedentary behavior (<150 minutes of moderate intensity per week of activity) was classified according to the long version of the International Physical Activity Questionnaire (www.ipaq.ki.se). Interviewers applied the Self-Reported Questionnaire-20, which has been validated in Brazil, to evaluate minor psychiatric disorder (Mari and Williams 1986). Age at menarche was collected by recall. Quality control procedures included standardization of interviewers prior to and during the study at regular intervals and re-evaluation of 10% of the interviewees by study supervisors.

Non-fasting blood was collected from volunteers during the 2004-05 follow-up. Serum C-reactive protein was measured using the automated Immulite (Siemens) chemiluminescent immunoassay (Los Angeles, USA). The lower detection limit (0.1 mg/L) registered as "<0.1 mg/L" and measures below that value were converted to 0.05 mg/L. Detailed methods for the 2004-05 follow-up visit and the high-sensitivity C-reactive protein assay are available (Nazmi and others 2007).

Internal weight z scores were calculated using sex-specific distributions from all follow-up visits; 1982, 1983, 1984, 1986, 1997, 2000/2001 (combined), and 2004-05 at approximate ages of 1, 2, 4, 15, 18/19, and 23 years, respectively. Pregnant women in

the last two follow-ups – who were not included in the CRP analyses - were excluded from calculations to generate z scores. Weight change in a given period was obtained by subtracting the initial from the final z score. Stunting at age 2 years was defined as equal to or less than –2 standard deviations of height-for-age z score using the 2007 WHO growth standards (www.who.int/childgrowth/en/).

All analyses were adjusted for exact age in months at each visit, and stratified by sex. Analyses of weight gain in the first year of life were adjusted for gestational age, and because results were virtually identical to the unadjusted values, and because 20% of the sample had no information on gestational age and had to be excluded from the adjusted analyses, only unadjusted values are presented.

Linear regression was used to compare log-normalized CRP levels (mg/L) with age-adjusted internal weight gain z scores. Two further models were used: the first adjusted for weight at the beginning of the period being examined and was used to account for regression to the mean (Barnett and others 2005). The final model was adjusted for age, weight at the beginning of the period, and potential confounders (skin color, maternal height, maternal smoking, family income at birth, maternal education, and parity in women). This model was also stratified by intra-uterine growth restriction (IUGR), defined as less than the 10^{th} percentile of Williams' curves (Williams and others 1982). Beta values and corresponding confidence intervals for CRP are shown in antilog form and may be interpreted as ratios.

Pregnant women and those using oral contraceptives were excluded from all analyses involving CRP. CRP was dichotomized in some analyses, using a cut-off of 3 mg/L to

indicate elevated levels (Pearson and others 2003). Logistic regression was used to compute risk for elevated CRP in relation to weight gain.

The Federal University of Pelotas Ethical Committee approved all phases of the 1982 Pelotas birth cohort study. Verbal informed consent was obtained until 1986 and written informed consent thereafter.

Results

Mean (SD) birthweight was 3.24 kg (0.57) and 3.13 kg (0.55) for cohort males (n= 3035) and females (n=2873) respectively. At the 2004-05 follow-up, when the cohort was aged 23 years, respective mean (SD) weights were 71.9 kg (14.0) and 60.9 kg (12.8). Individuals who had CRP measured were born heavier than those who did not, but weight at 23 years and family income at birth were not different between the groups (data not shown).

Using serum from the 2004-05 follow-up, 1919 men and 1908 women had CRP levels evaluated. Excluding 93 pregnant women and 445 women using oral contraceptives at the time of the blood draw, geometric mean levels of CRP (95% CI) in men and women were 0.89 mg/L (0.84-0.94) and 1.66 mg/L (1.54-1.78), respectively ($p<0.001$). Subjects with CRP levels above 3 mg/L included 16.8% of the males and 40.5% of the females.

There was no association between birthweight and CRP levels in men, but women born low birthweight (<2500 g) had lower levels of CRP than those born heavier. Table 1 describes weight gain (in kg) between follow-up periods from birth to age 23 years.

Males tended to gained more weight in every period except from 1-2 years and 2-4 years, when females gained more. Weight gain was significantly different between males and females in every period.

Table 2 shows the associations between weight gain z scores with CRP levels using three different types of adjustments. Betas greater than 1.0 suggest a direct association.

Age-adjusted weight gains (model 1) are presented first. In men, weight gain in the first year of life showed a non-significant, inverse association with CRP levels. There was a borderline direct association with weight gain from age 1-2 years, and from age 2 years upwards there were strong direct associations with CRP levels in all periods. Weight change in adolescence and early adulthood were more powerfully associated than in earlier periods, with a 29% (95% CI 3-62) and 51% (95% CI 33-71) increase in CRP levels for every z-score increment of weight gain between 15-18/19 and 18/19-23 years, respectively. Accounting for regression to the mean (model 2), all positive effects were strengthened. Further adjustment for confounders did not have a marked effect on the coefficients, and weight gain from 2 years and up maintained strong direct associations. The non-significant inverse association with weight gain in infancy observed in the crude analyses was maintained. Effects increased per period of follow-up, with the strongest associations in the latter periods.

Weight gain in women showed less consistent effects. In the fully adjusted analyses, weight gains in infancy, 4-15 years and 18/19-23 years showed significant direct associations with CRP, whereas weight gains in the other three periods (1-2, 2-4 and 15-

18/19 years) were directly but not significantly associated with CRP. The strongest associations were observed in the 18/19-23 years age range.

There was a possible interaction ($p<0.20$) between intra-uterine growth restriction (IUGR) and rapid weight gain (defined as higher than the mean for each period) in relation to CRP levels in the last period (18/19-23 years) in males and in the 4-15 years period in females. Analyses were therefore stratified by IUGR, and results were very similar to the full model shown in Table 2 in males and females who did not experience IUGR. In individuals who did experience IUGR, on the other hand, there were direct and significant associations with CRP levels only in periods in which interaction was suspected (Table 3).

Figure 1 plots the average weight trajectories of subjects according to CRP levels above or below/equal to 3 mg/L. Although those with high CRP were slightly heavier throughout their lives – except for males at 15 yr - the differences only become marked at the age of 18 years for men and 15 years for women.

To test the hypothesis that early growth restriction coupled with later life obesity is associated with excess risk, we evaluated the combined effects of stunting (length-for-age) at age 2 years and central obesity at age 23 years in relation to CRP levels (Figure 2). Males who were stunted and subsequently became centrally obese had nearly six times higher CRP levels than those who were stunted and did not become obese (ratio 5.98; 95% CI 3.23-11.06) and more than twice as high (ratio 2.48; 95% CI 1.42-4.34) as those who were not stunted and subsequently became centrally obese. The interaction between stunting and central obesity was statistically significant ($p=0.002$). A similar

but not as marked pattern was observed among women, among whom the interaction was not significant (p=0.3).

A fourth model (not shown) was fitted that also included current smoking, fat and fiber intake, alcohol consumption, sedentary lifestyle and minor psychiatric disorder measured at age 23 years. The results were very similar to those presented in model 3.

Discussion

This is the first study to examine associations between weight gain trajectories and an inflammatory marker outside high-income countries. Serum CRP levels in the current sample were similar to those from population-based studies of similar age samples in the USA but slightly lower than those from a New Zealand cohort (Ford and others 2004; Ford and others 2003; Williams and others 2004).

In our sample, those born lighter gained more weight in the first year of life, showing catch up growth (data not shown) (Tanner 1989). Earlier analyses of the 1982 and 1993 Pelotas cohorts suggest that early weight gain is associated with accumulation of a greater proportion of lean body mass (Victora and others 2007b; Wells and others 2005), while also being protective against early life morbidity and mortality . Weight gain later in childhood, however, has been associated with deposition of fat mass (Wells and others 2005).

Our finding that weight gain in the first year of life in men is not associated with higher adult CRP levels, whereas weight gain after two years leads to increased levels,

supports the hypothesis that rapid weight gain in the first year does not incur higher risk. Weight gain in men after 2 years, however, was consistently associated with higher CRP levels, indicating increased risk beginning in later childhood.

Our observations for women were not as clear-cut. Weight gain in the first year was significantly associated with increased CRP levels. Although the coefficients for all periods were positive suggesting a direct association with CRP, the gradual increase in the magnitude of the coefficients observed for men was not present in women. The reasons for sex-specific differences with respect to the mechanisms associated with weight gain patterns and consequences on later risk profiles are not known. This is an area of growing interest in the lifecourse epidemiology literature and more research is needed to examine these associations.

In line with the above findings, rapid weight gain was associated with elevated CRP levels (>3 mg/L) after the second year in males, and after the fourth year in females (Figure 1). These effects became more pronounced in the periods following adolescence. These findings highlight the risks associated with sustained rapid weight gain beginning in late childhood (Eriksson and others 2001; Victora and others 2007b), and are plausible given the mediating role of adipose tissue in inflammation (Mohamed-Ali and others 1998; Yudkin and others 1999).

Behavioral factors such as smoking, fat and fiber intake, alcohol consumption, physical activity and stress have also been shown to have independent associations with CRP levels (de Maat and Kluft 2001), but their inclusion in our analyses did not affect the conclusions.

The high risk associated with being undernourished in the first few years of life and then gaining weight rapidly later in childhood has been described with respect to diabetes-related disorders (Bhargava and others 2004; Newsome and others 2003), increased blood pressure (Adair and Cole 2003), coronary events (Barker and others 2005), and mortality (Eriksson and others 1999). This may result from metabolic programming following early exposure to undernutrition (Bogin and others 2007; Gluckman and others 2007), which becomes maladaptive in populations undergoing nutritional transition, leading to excess risk for chronic disease. Mechanisms that have been proposed to explain this increased risk include compromised pancreatic beta cell formation and altered metabolic parameters (Barker 1994). We found that being stunted at 2 years coupled with central obesity at age 23 years was associated with a marked increase in the risk for inflammation, particularly for males (Figure 2). This suggests that risk for inflammation may in part be due mechanisms resulting from mismatched conditions between early and adult life.

The immune system is sensitive to in-utero and early life exposures, that may have permanent effects on postnatal immune response (Dietert and others 2000; Holladay and Smialowicz 2000). Also, greater levels of inflammation may be associated with the endocrine role of excess fat tissue in individuals who became centrally obese after being undernourished in childhood (Mohamed-Ali and others 1998). Further research is needed to elucidate which pathways are affected and how early programming impacts the chronic inflammatory response.

In males and females who experienced IUGR, rapid weight gain before the fourth year had no impact on CRP levels (Table 3). This suggests a delayed effect of early life programming. The differences between the sexes may indicate that among males, post-adolescent weight trajectories have more impact on inflammation, whereas in IUGR females, the adolescent period itself seems to be strongly associated. We did not have information within the 4-15 years period and thus could not analyze the specific effects of the adolescent growth spurt. Also, small sample sizes in the IUGR groups may have precluded the detection of significant associations.

Other limitations of this study should be considered. CRP was evaluated on a single occasion so we cannot draw inferences as to chronic inflammatory states. Similarly, this study did not exclude individuals with clinical inflammatory conditions at the time of the blood draw, however given the young age of the participants, it is unlikely that this affected our analyses. We did not have information on weight within the first months of life, a period that has been described as having important effects on later risk (Ekelund and others 2007; Singhal and others 2004). On the other hand, we were able to examine the cohort at numerous follow-ups, allowing for a lifecourse perspective.

In summary, rapid weight gain throughout life directly impacted CRP levels in both sexes, but the effects varied by sex. In males, the risk increased markedly with the age range when rapid weight gain took place, starting around the age of 2 years. In females, rapid gain in the first year of life was already associated with higher risk, as was rapid gain at 4-15 years and 18/19-23 years. In both sexes, rapid weight gain in the most recent period (18/19-23 years) was associated with the highest risk for elevated CRP

levels. A significant additional risk was observed among individuals who were stunted at age 2 years then subsequently became obese adults, particularly for males.

Our results for males support previous research showing that rapid weight gain in infancy is not hazardous (Fisher and others 2006) and may be beneficial in terms of preventing disease as well as in promoting human capital (Victora and others 2007a). The association between rapid weight gain in infancy and latter inflammation levels in women needs to be confirmed by other studies, but even if it is confirmed, this apparent hazard has to be weighed against the benefit of rapid weight gain in a transitional society.

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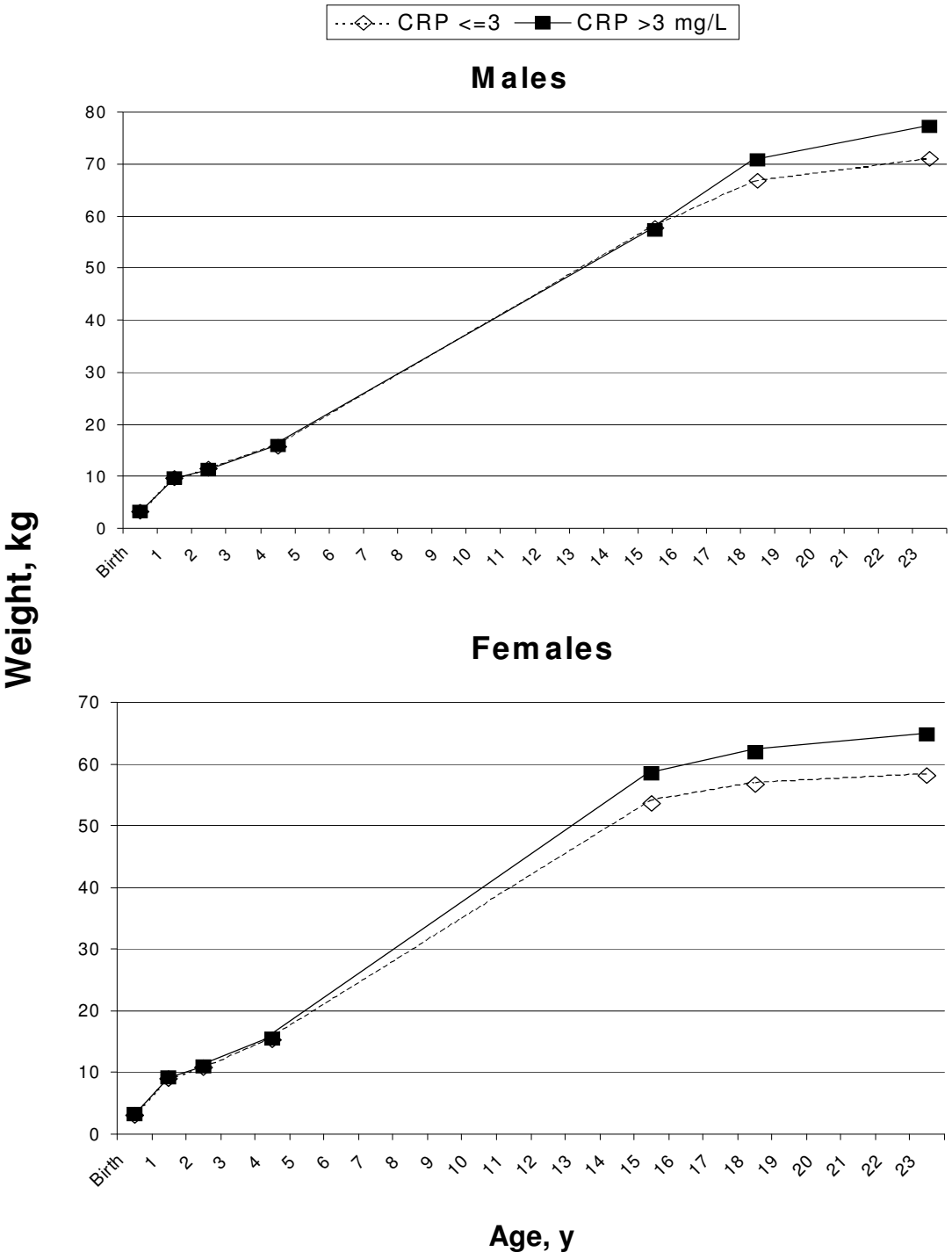

Figure 1: Lifecourse weight trajectories of cohort males and females with and without elevated C-reactive protein levels (> 3 mg/L) at age 23 years. Cohort members were weighed at birth, 1, 2, 4, 15, 18, and 23 years of age.

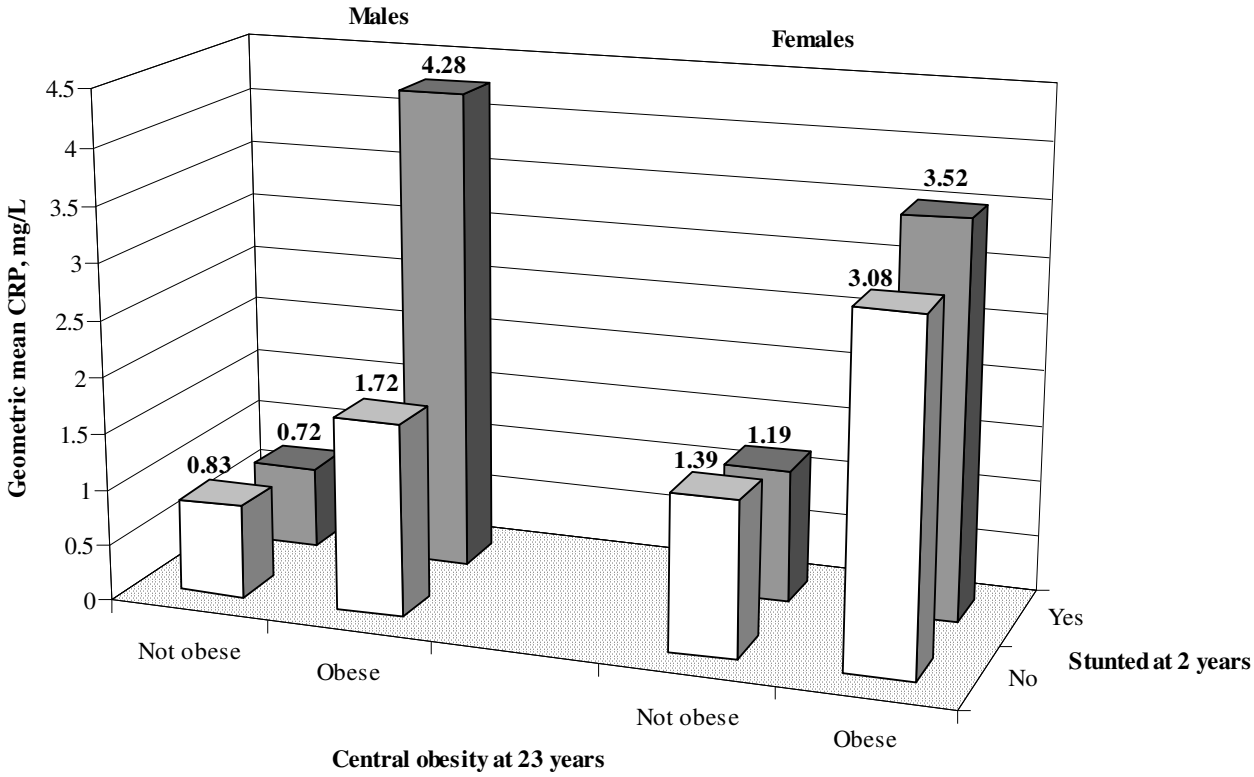

Figure 2: Combined effects of stunting at 2 years with central obesity at 23 years on C-reactive protein levels. P-values for interaction: 0.002 for males and 0.3 for females.

Table 1: Weight gain from birth to age 23 years in cohort males and females, in kg

Weight gain	Males		Females	
	Mean (SD)	N	Mean (SD)	N
Birth to 1 year	6.33 (1.12)	714	5.88 (1.11)	742
1 to 2 years	2.55 (0.88)	653	2.70 (0.87)	683
2 to 4 years	4.33 (1.39)	2291	4.46 (1.47)	2185
4 to 15 years	41.86 (11.40)	517	39.51 (9.51)	480
15 to 18/19 years	9.50 (7.06)	536	3.16 (5.95)	470
18/19 to 23 years	5.04 (6.52)	1982	3.03 (6.18)	772

Excluding pregnant women at ages 18/19 and 23 years

P< 0.001 for all differences in weight gain between males and females

Table 2: Linear regression between log-transformed C-reactive protein levels and weight change z score in 3 models. Coefficients are interpretable as ratios. Significant coefficients in bold.

Weight change z score		Beta coefficients (95% confidence intervals)		
Males	N	1: Adjusted for age at both follow-ups	2: Adjusted for age and initial weight	3: Adjusted for age, initial weight, and confounders[a]
Birth to 1 year	492	0.94 (0.83-1.06)	0.98 (0.85-1.13)	0.89 (0.77-1.04)
1 to 2 years	466	1.24 (0.99-1.55)	1.32 (1.04-1.67)	1.15 (0.90-1.48)
2 to 4 years	1653	1.22 (1.09-1.36)	1.27 (1.14-1.42)	1.22 (1.09-1.38)
4 to 15 years	393	1.20 (1.01-1.41)	1.23 (1.03-1.47)	1.20 (1.00-1.44)
15 to 18/19 years	414	1.29 (1.03-1.62)	1.39 (1.10-1.76)	1.37 (1.07-1.74)
18/19 to 23 years	1740	1.51 (1.33-1.71)	1.79 (1.58-2.03)	1.77 (1.55-2.01)
Females[b]				
Birth to 1 year	361	1.08 (0.93-1.24)	1.17 (0.99-1.37)	1.26 (1.06-1.49)
1 to 2 years	345	0.99 (0.76-1.28)	1.14 (0.87-1.51)	1.28 (0.95-1.71)
2 to 4 years	1188	1.02 (0.89-1.17)	1.04 (0.91-1.20)	1.09 (0.94-1.25)
4 to 15 years	291	1.23 (1.04-1.45)	1.37 (1.13-1.65)	1.36 (1.12-1.65)
15 to 18/19 years	294	1.10 (0.83-1.47)	1.28 (0.95-1.72)	1.25 (0.93-1.70)
18/19 to 23 years	538	1.61 (1.30-1.99)	2.01 (1.62-2.50)	1.90 (1.52-2.39)

[a] Adjusted for age, weight at beginning of period, skin color, maternal height, maternal smoking, family income at birth, years of maternal education and parity at age 23 years for women

[b] Excluding pregnant women at ages 18/19 and 23 years and those using oral contraceptives at age 23 years

Table 3: Linear regression between log-transformed C-reactive protein levels and weight change z score in fully adjusted[a] model from Table 2, stratified by intra-uterine growth restriction (IUGR). Coefficients are interpretable as ratios. Significant coefficients in bold.

Males	Did not experience IUGR		Experienced IUGR	
Weight change z score	N	Beta (95% CI)	N	Beta (95% CI)
Birth to 1 year	317	0.93 (0.77-1.12)	66	0.85 (0.53-1.34)
1 to 2 years	302	1.30 (0.95-1.79)	62	0.87 (0.43-1.78)
2 to 4 years	1067	1.23 (1.07-1.42)	192	1.23 (0.81-1.85)
4 to 15 years	255	1.22 (0.98-1.50)	40	1.56 (0.59-4.15)
15 to 18/19 years	267	1.37 (1.01-1.84)	43	1.99 (0.91-4.34)
18/19 to 23 years	1125	1.69 (1.44-1.98)	206	2.34 (1.52-3.61)
Females[b]				
Birth to 1 year	239	1.41 (1.16-1.72)	45	0.99 (0.60-1.63)
1 to 2 years	231	1.35 (0.97-1.88)	42	2.01 (0.65-6.21)
2 to 4 years	788	1.06 (0.90-1.25)	130	1.27 (0.69-2.34)
4 to 15 years	203	1.37 (1.09-1.72)	28	1.92 (1.06-3.48)
15 to 18/19 years	200	1.12 (0.77-1.63)	28	0.95 (0.30-3.07)
18/19 to 23 years	332	1.99 (1.48-2.69)	63	1.35 (0.66-2.76)

[a] Adjusted for age, weight at beginning of period, skin color, maternal height, maternal smoking, family income at birth, years of maternal education and parity at age 23 years for women

[b] Excluding pregnant women at ages 18/19 and 23 years and those using oral contraceptives at age 23 years

Intra-uterine growth restriction (IUGR) defined as below the 10th percentile of birthweight for gestational age according to Williams' curves

Artigo 4

Correlates of C-reactive protein levels in young adults:
a population-based study in Brazil

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Abstract

The socio-demographic, behavioral and anthropometric correlates of C-reactive protein levels were examined in a representative young adult Brazilian population. The 1982 Pelotas (Brazil) Birth Cohort Study recruited over 99% of births in the city that year (n= 5914) and individuals belonging to the cohort have been prospectively followed up. In 2004-05, 77.4% of the cohort was traced, members were interviewed and 3827 individuals donated blood. Analyses of the outcome were based on a conceptual model that differentiated confounders from potential mediators. The following independent variables were studied in relation to levels of C-reactive protein in sex-stratified analyses: skin color, age, family income, education, parity, body mass index, waist circumference, smoking, fat/fiber/alcohol intake, physical activity and minor psychiatric disorder. Geometric mean (95% confidence interval) C-reactive protein levels for the 1919 males and 1908 females were 0.89 (0.84-0.94) and 1.96 mg/L (1.85-2.09), respectively. Pregnant women and those using oral contraceptive therapies presented the highest C-reactive protein levels and all sub-groups of women had higher levels than men ($p<0.001$). Significant associations between C-reactive protein levels were observed with age, socioeconomic indicators, obesity status, smoking, fat intake and minor psychiatric disorder. Associations were stronger at higher levels of C-reactive protein and some associations were sex-specific. We conclude that both distal (sociodemographic) and proximal (anthropometric and behavioral) factors exert strong effects on C-reactive protein levels and that the former are mediated to some degree by the latter.

Keywords

C-reactive protein, inflammation, cohort studies, prospective studies, Brazil

Introduction

There has recently been increasing interest in identifying factors associated with inflammation, a fundamental process in atherogenesis. C-reactive protein (CRP) has received special attention not only due its characteristics as a highly specific marker for coronary events, but also because of its potential pathogenic role.(1) While recent Mendelian Randomization studies suggest that CRP does not have an independent role in causing coronary heart disease related outcomes, its role as an atherogenic risk marker remains unchallenged.(2)

Racial/ethnic, socioeconomic and demographic correlates have been studied as potential distal determinants of CRP levels. Proximal factors that have been examined include diet,(3) alcohol intake,(4) smoking,(5) anthropometric indicators of body fat,(6) physical activity,(7) and stress.(8) Results from these studies have not always been consistent, though age, female sex and poverty have widely been shown to be positively associated with CRP levels as have proximal factors including smoking, poor diet, higher body fat, lower levels of physical activity and high stress. These studies, however, have been limited almost exclusively to data from rich countries.

Few studies have investigated the epidemiology of CRP in low and middle-income countries, and there is little data from Latin America, where the nutrition and epidemiological transitions are already exerting a heavy toll. There is no population-based data on these associations in Brazil, where cardiovascular disease is a growing public health problem and was the leading cause of death in 2005.(9, 10)

Identifying factors associated with CRP levels could lead to strategies designed to combat the causes or long-term consequences of chronic inflammation. Identification of these factors in young adults would be particularly useful. The purpose of this study was to examine the correlates of C-reactive protein levels in a young adult Brazilian population.

Methods

The 1982 Pelotas birth cohort is one of the largest and longest-running prospective birth cohorts in the low and middle-income countries. It enrolled 5914 live births to mothers who lived in the urban area of the city that year (population in 1982: 214,000), representing over 99% of total births. A questionnaire on sociodemographic and health factors was applied to the mothers soon after delivery. The cohort has been followed up numerous times throughout the years. More detailed information on methods, variables and sampling fractions has been published.(11)

In 2004-05, members of the cohort were searched for using a variety of methods. Family income data was categorized into groups representing ≤ 1, 1.1-3.0, 3.1-6.0, 6.1-10 and >10 minimum wage units. These groupings capture the wide income gaps common in Brazil more precisely than a division into, say, quintiles. The minimum wage at the time of the cohort visit was equivalent to approximately 180 USD. Number of years of formal education completed by the participant was also collected and grouped in 0-4, 5-8, 9-11 and ≥ 12 years.

Self-described skin color of the participant was collected. In the main analyses, it was input using the white, black and mulatto groups, others being excluded due to small numbers (n= 76 Indigenous and 74 Asian). Current smoking was defined as smoking at least one cigarette per week and analyzed as a dichotomous variable.

A food frequency questionnaire was applied and relevant elements were used to calculate intake of fat and fiber as suggested by Block.(12) Fat intake was grouped as "best low fat", "lower fat", "American diet", "high fat" and "very high fat" and analyzed as an ordinal variable. Fiber intake was dichotomized into "adequate/moderate" or "low fiber intake". An overall score for alcohol intake was calculated and categorized into three groups: "non-drinker", "up to one drink per day" (one drink equivalent to 350 ml of beer, 150 ml of wine or 30 ml of liquor), or "more than one drink per day ".

Information on physical activity (leisure time, transportation, occupation, and housework) was collected using long version of the International Physical Activity Questionnaire (IPAQ; www.ipaq.ki.se). Total and leisure time physical activity variables were dichotomized, defining as "sedentary" those with less than 150 minutes of moderate-intensity physical activity per week.

Interviewers applied the Self-Reported Questionnaire-20 (SRQ), which has been validated in Brazil, to evaluate mental health.(13) SRQ score was dichotomized into sex-specific groups representing those without and those with an elevated score ($\geq$ 6 for

men and ≥ 8 for women). An elevated score was used in this study as a proxy for mental stress.

Individuals were weighed using the Seca (UNICEF) scale (100 g precision). A locally manufactured aluminum anthropometer (1 mm precision) was used to measure standing height. Body mass index (BMI) was calculated as kg/m^2 and categorized into WHO recommended groups: <18.5 (underweight), 18.5-24.9 (normal), 25.0-29.9 (overweight) and ≥ 30.0 (obese).(14)

Waist circumference was measured at the narrowest girth of the trunk or halfway between the costal margin and iliac crest using a fiberglass measuring tape (Cardiomed, Brazil, 1 mm precision). Central obesity was analyzed both as a continuous variable and dichotomous variable, using cutoffs of ≥ 94 cm for men and ≥ 80 cm for women.(15)

Quality control measures throughout the 2004-05 cohort visit included telephoning or re-visiting 10% of the interviewed participants by study supervisors to test reliability, regular training and standardizing of interviewers, and double data input.

Non-fasting venous blood was collected from volunteers being interviewed. High sensitivity C-reactive protein assays were performed using the automated DPC (Siemens) Immulite chemiluminescent immunoassay (Los Angeles, USA). The intra and inter-assay coefficients of variation were 10 and 7%, respectively. Samples with results below the assay sensitivity threshold, which registered as "<0.1 mg/L", were converted to 0.05 mg/L for statistical analysis.

Statistical analysis

Since the cohort has a fixed N, the minimum detectable differences in CRP values relative to independent variables were calculated using a two-tailed level of significance of 95% with 80% power. Sample size calculations were based on standard deviations (SD) of 1.0 and 3.0 mg/L CRP, reflecting the variations described in the literature. The minimum detectable differences between groups were thus calculated and ranged from 0.10 and 0.60 mg/L, depending on the exposure.

C-reactive protein values (mg/L) were natural log-transformed (*ln*mg/L) for greater symmetry prior to undertaking statistical analyses (Figure 1). CRP values are presented in the text as the geometric mean (95% CI), which were similar to median values. Linear and logistic regression were used, the former for continuous *ln*CRP values and the latter for CRP>10 mg/L, the suggested cut-off value for acute-level inflammation. Wald tests for trend and heterogeneity were used where appropriate. Analyses were stratified by sex. Statistical analyses were based on a conceptual framework based on a hierarchy of levels of determination (Figure 2). Sociodemographic factors were adjusted for one another, and behavioral/anthropometric factors were adjusted for each other and also for sociodemographic factors. To investigate possible mediating factors, sociodemographic factors that were still significant after adjustment for one another were further adjusted for behavioral/anthropometric factors, and these analyses are mentioned in the text when relevant. Socio-demographic variables may be confounders for anthropometric and behavior variables, whereas the latter are potential mediators of the former. Adjusted beta coefficients and their 95% confidence intervals from the

analyses of geometric means are interpretable as ratios. Analyses were performed on Stata version 8.

BMI and waist circumference- as continuous and categorical variables- were entered in the analyses individually and simultaneously in an attempt to disentangle the contributions of body mass versus fat distribution in influencing CRP levels.

Ethical approval

The Federal University of Pelotas Ethical Committee approved all aspects of the 1982 Pelotas birth cohort study. Informed written consent was collected for the questionnaire and blood draw associated with the 2004-05 cohort visit.

Results

From October 2004 to September 2005, 4297 individuals were interviewed, representing 77.4% of the original cohort (this percentage includes 282 individuals who had died prior to 2004). The mean (range) age was 22.8 y (21.9-23.7). Those who donated blood for CRP tests (89.1% of those interviewed) tended to be poorer and less educated than those who did not and those with black skin color were over-represented (data not shown).

Geometric mean (95% CI) CRP levels for the 1919 males and 1908 females were 0.89 (0.84-0.94) and 1.96 mg/L (1.85-2.09), respectively. Figure 1 shows the crude and log-transformed distributions for CRP levels in both sexes. Seventy-nine (4.1%) men and 194 (10.2%) women had CRP levels >10 mg/L.

There were 445 women using oral contraceptive therapy (OCT) at the time of the blood draw and 93 others were pregnant. Women who were neither pregnant nor using OCT had the lowest CRP levels; 1.66 mg/L (1.54-1.78), followed by women using OCT; 2.88 (2.58-3.22) and pregnant women had the highest levels; 3.90 (3.11-4.90). Differences between men and all categories of women were significant ($p<0.0001$), as were differences between each of the three groups of women ($p<0.0001$). Men (n=1919) and women who were neither pregnant nor using OCT (n=1370) formed the sample for the main analyses.

Figure 2 shows the hierarchical conceptual model for associations between sociodemographic, anthropometric and behavioral factors and CRP levels. The distribution of risk factors and their associations with characteristics for the cohort and with CRP levels appear in Tables 1 and 2 for men and women, respectively.

Skin color did not show any associations with CRP levels in either sex in unadjusted or adjusted analyses. In unadjusted analyses, age showed a strong direct association in women only, maintaining a significant association and consistent effect size, even when adjusted for all other variables in the model.

Family income distribution was similar between men and women. In unadjusted analyses and when adjusted for confounders, a significant and direct association between family income and CRP levels was observed in men, with the poorest at 65% the geometric mean CRP levels compared to the richest. When potential mediators (i.e. anthropometric and behavioral factors) were adjusted for, effect size and significance were lost (data not shown). In contrast, unadjusted analyses revealed an inverse trend

between family income and CRP levels in women. This association lost significance with adjustment for confounding variables. In crude analyses, there was a significant interaction between sex and income that lost significance when adjusted for skin color and age.

On average, women had more years of education than men. Education was inversely associated with CRP levels in women but there was no association in men. When adjusted for confounders, this association lost significance in women.

Parity showed a significant and direct association with CRP levels in women such that those with three or more children had 30% higher geometric mean CRP levels than those with no children. When adjusted for sociodemographic factors, this association was no longer significant.

Similar distributions in BMI were observed between the sexes, but more women (23%) than men (10%) were centrally obese. Unadjusted analyses in both sexes showed strong direct associations between BMI and CRP levels. Men and women in the obese category of BMI ($\geq$ 30.0 kg/m^2) had approximately five times higher geometric mean CRP levels than those in the underweight category (<18.5 kg/m^2). Similarly, the centrally obese had more than double the CRP levels of those without central obesity. When BMI and central obesity were adjusted for all other variables, including one another, the association between the latter and CRP disappeared in men, but not in women where both variables remained significant. Because there was some concern about the adequacy of the waist circumference cutoff for our young sample, analyses were repeated using the continuous variable. Even after adjustment for BMI, waist

circumference was associated with higher CRP for men and women (1.02 and 1.03 times the CRP per cm of waist circumference, p= 0.004 and <0.001, respectively).

The distribution of smoking was similar between men and women, and showed a significant positive association with CRP levels in men only. This association was maintained when adjusted for confounders.

About half of both sexes had diets very high in fat and almost 70% consumed insufficient fiber. Women in the highest category of fat consumption showed higher but non-significant levels of CRP. When adjusted for confounders, this association reached the borderline level (p for trend= 0.06). In men, there was no association between dietary indicators and CRP levels. Fiber intake showed no associations in either sex.

Men drinking more than one unit of alcohol per day were at higher risk for elevated CRP than those who did not drink but this association was no longer significant after adjusting for all other variables. No association was observed for women.

Half of men and 80% of women were sedentary during leisure time, whereas only about 8% of each were sedentary during total time that included transportation, housework and occupational activities. Leisure time physical activity was not associated with CRP levels in either sex. In men but not in women, those classified as sedentary had somewhat higher levels of CRP, although statistical significance was borderline. In adjusted analyses, this association lost significance.

SRQ scores indicated that 25% of men and 33% of women had minor psychiatric disorders. This variable was not associated with geometric mean CRP levels.

All analyses were repeated using logistic regression with CRP >10 mg/L (acute-level inflammation) as a cut-off (available upon request). Results were consistent with analyses using linear regression, with a few exceptions. Whereas obesity remained a risk factor, there was some indication that underweight (BMI <18.5) was also associated with acute levels of CRP in both sexes; 1.86 (95% CI 0.90-3.85) and 1.25 mg/L (0.43-3.61) for men and women, respectively. Also, minor psychiatric illness in men, assessed by elevated SRQ, was associated with a prevalence of acute level SRQ that was 1.79 times (95% CI 1.14-2.82, p=0.01) higher than individuals with normal SRQ.

Discussion

CRP levels in this group were similar to some representative samples among comparable age groups from the USA (16, 17), but slightly lower than a New Zealand cohort,(18) and higher than an older cohort from Japan.(19, 20) Females tended to have higher levels than males in numerous population-based studies,(21, 22) though not all authors observed a significant difference.(23) The reasons for sex-specific ranges of CRP levels is likely due to the effects of hormonal profiles, although more research is needed to examine the mechanisms associated with these pathways. Almost a third (27%) of non-pregnant women not using OCT from our sample - compared to only 13% of the men - were in the highest relative risk category (>3.0 and <10.0 mg/L CRP) for cardiovascular disease risk according to CDC/AHA guidelines, suggesting sex-independent criteria may be inadequate.(24)

Age was strongly associated with CRP levels in women, even within the cohort's narrow age range. Other studies, including samples with similarly restricted age ranges, found direct associations, although both sexes were affected in most studies.(25, 26) The mechanisms behind the direct influence of increasing age on CRP levels have not been well studied. These effects could arguably be due to proximal factors such as obesity, but in the current study, the effect of age in women persisted even when adjusted for all socioeconomic, anthropometric and behavioral variables, suggesting other pathways.

Skin color was not associated with CRP levels in either sex in this group. A recent systematic review of population-based studies, nearly all from high-income countries, showed higher risk for individuals of African, South Asian and Hispanic descent, compared to those of European descent, and lower risk for Chinese and Japanese.(27) Correct classification of race is complex in a highly miscigenated society such as Brazil but this has not precluded authors from detecting associations between African descent and higher risk of several chronic conditions. (28, 29)

In women, income and education were inversely associated with CRP levels in unadjusted analyses, indicating strong protective effects of increasing socioeconomic position. Confounding largely accounted for these associations. In men, however, CRP levels increased with income, even when adjusted for confounders including attained education. Other studies in Brazil have described that overweight and obesity are directly related to socioeconomic factors in men and inversely related in women, but this has not been shown with respect to inflammatory markers.(30, 31)

We found that body mass and distribution of body fat strongly influence CRP levels. Similar effect sizes between the sexes for BMI and waist circumference suggest that the inflammatory consequences of adipose tissue are comparable in men and women. Higher BMI tended to have stronger inflammatory effects in men whereas the effects of central obesity were more pronounced in women. Our findings on fatness and CRP levels are consistent with the notion that excess adipose tissue contributes to a chronic inflammatory state through a range of metabolic pathways.(32) In our study, only those with BMI >30 kg/m^2 (obese) were at increased risk for acute inflammation (CPR>10 mg/L), suggesting that more extreme levels of obesity may be directly associated with "chronic acute" inflammation.

Most studies that examined smoking in relation to CRP levels found strong direct associations (33) and as observed here, some authors detected an association in men only.(34, 35) It is possible that sex-specific smoking behaviors- such as inhalation patterns- may impact health outcomes.(36)

Healthier dietary profiles are associated with lower levels of CRP and other inflammatory markers. (37, 38) When adjusted for all other variables including potential mediators such as BMI, we found that women with very high fat intake showed elevated CRP levels but the overall significance for linear trend was borderline (p=0.06). These findings suggest that fat intake *per se* may be involved in pathways that impact inflammation independently of those associated with paracrine activity attributable to adipose tissue. Recent studies indicate that metabolic signals in response

to various nutrients differ, making it feasible that certain metabolites exert specific inflammatory effects.(39)

Our finding that high alcohol intake is associated with higher CRP levels has been described previously, but not among younger adults. (40, 41) The literature describes a U-shaped curve of cardiovascular disease according to alcohol intake, (42) but in our adjusted model, this pattern did not maintain significance.

It has been proposed that repeated psychological stressors chronically activate the innate immune response, driving an inflammatory stimulus and contributing to the progression of atherosclerosis.(43) This is supported by observations that stress is a powerful risk factor for the onset and outcome of cardiovascular-related outcomes. In the logistic regression analysis, elevated SRQ score was a significant risk factor for acute CRP levels in men, although this result was not apparent in the linear regression of geometric means. This finding underscores the importance of investigating psychosocial risk factors, even relatively early in life, for CVD risk.

Individuals with ongoing inflammatory conditions were not excluded, this being a potential limitation of this study. However, given the young age of the cohort, it is likely that very few individuals had chronic disorders that could have distorted the results. The methods we used to evaluate adiposity, though indirect, are adequate for large samples, widely used in the literature and easily applicable to clinical settings. The high follow-up rate of the cohort makes our results more readily applicable to populations with similar sociodemographic profiles. This study was unique because it investigated a novel inflammatory biomarker in a representative sample of young Latin

American adults and the fact that the sample is part of a prospective birth cohort opens possibilities for lifecourse analyses as the cohort ages.

In sum, we have shown that CRP levels in young adults are affected by demographic, socioeconomic, anthropometric and behavioral factors and that many effects are sex-specific. Associations were observed with age, socioeconomic indicators, obesity status, smoking, fat and alcohol intake and minor psychiatric disorder. We conclude that both distal and proximal factors exert strong effects on CRP levels and that the former are mediated to some degree by the latter. This is evidenced by the fact that many associations lost significance when mediators such as indicators of adiposity, smoking, and dietary factors were included in statistical models. The identification of factors that, among young adults, are amenable to intervention reinforces the need for population-based preventive strategies.

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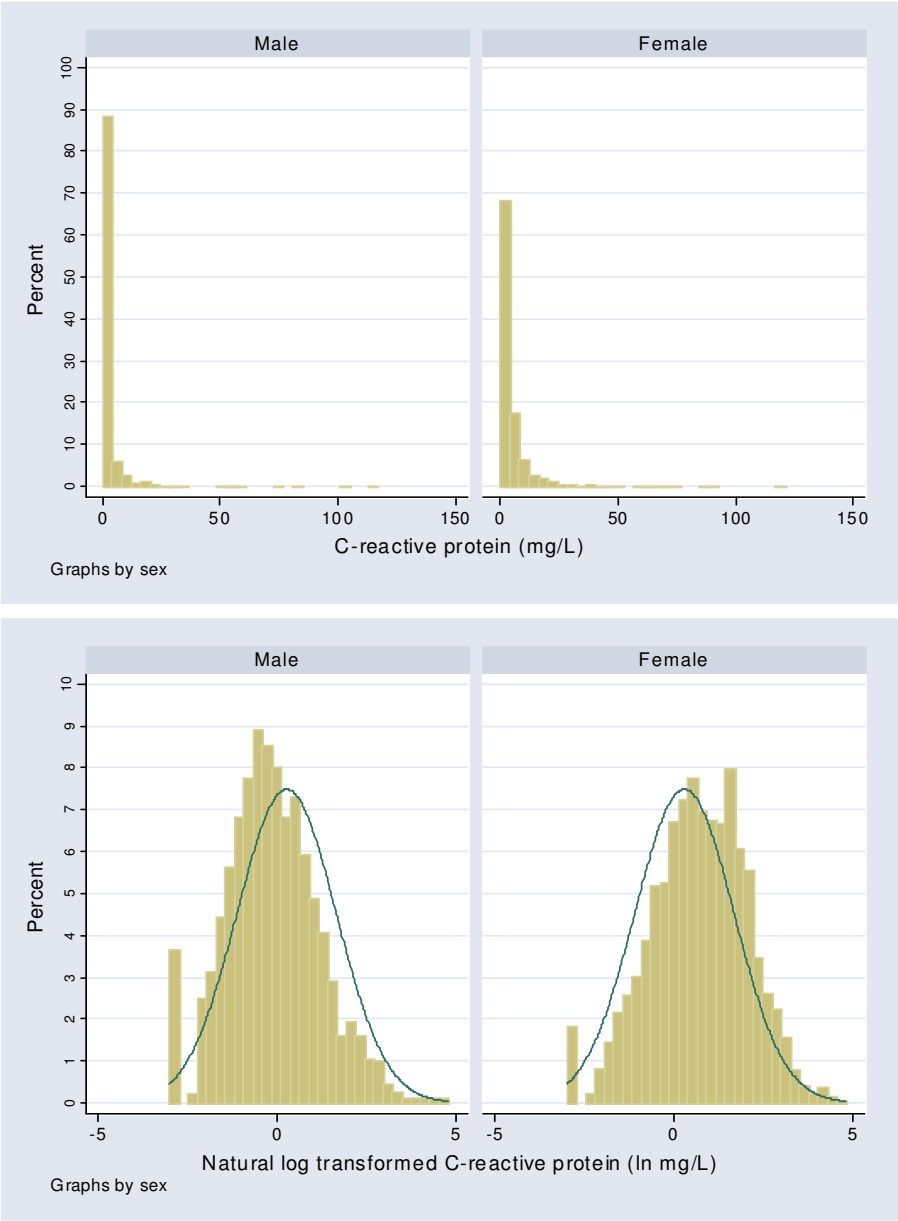

Figure 1: Raw and natural log-normalized distribution of C-reactive protein in men (n=1919) and women (n=1908) belonging to the 1982 Pelotas Birth Cohort (2004-05). Values (in mg/L) that registered as "<0.1" were transformed to 0.05 prior to analysis; the gap in the normalized distributions reflects this transformation.

Level	Variables		
	Socio-demographic characteristics:		
1	Skin color	Age	
2	Family income	Years of education	
3	Parity (women)		
4	Anthropometric and behavioral factors:		
	Body mass index	Waist circumference	Smoking
	Fat and fiber intake	Alcohol intake	Physical activity
	Minor psychiatric disorder		
Outcome	C-reactive protein level		

Figure 2: Proposed hierarchical model for the associations between sociodemographic, anthropometric and behavioral factors and C-reactive protein levels in young adulthood.

Table 1: Distribution and associations of C-reactive protein (CRP) levels with sociodemographic, anthropometric and behavioral factors, men.

				Crude analyses		Adjusted analyses	
Level	Independent variable	% in group	Geometric mean (95% CI)	**β (95% CI)**	**P**	**β (95% CI)**	**P**
1	Age, y	-	-	1.03 (0.88-1.20)	0.7	1.05 (0.90-1.24)	0.5
	Skin color[#]				0.4[*]		0.5[*]
	White	77.2	0.92 (0.86-0.98)	1 (ref)		1 (ref)	
	Mulatto	6.4	0.85 (0.67-1.07)	0.93 (0.73-1.18)		0.95 (0.74-1.21)	
	Black	16.4	0.82 (0.71-0.95)	0.90 (0.76-1.05)		0.91 (0.77-1.07)	
	Family income in 2004, minimum wage units				0.02		0.01
	≤ 1	4.6	0.78 (0.59-1.03)	0.71 (0.52-0.97)		0.65 (0.46-0.92)	
	1.1-3.0	31.6	0.87 (0.78-0.96)	0.79 (0.65-0.96)		0.77 (0.62-0.96)	
	3.1-6.0	34.1	0.85 (0.77-0.94)	0.78 (0.64-0.94)		0.75 (0.62-0.92)	
	6.1-10.0	16.7	0.91 (0.79-1.05)	0.78 (0.64-0.94)		0.83 (0.66-1.03)	
	>10	12.9	1.10 (0.94-1.28)	1 (ref)		1 (ref)	
	Education, y				1.0		0.2
	0-4	9.4	0.94 (0.76-1.15)	0.88 (0.68-1.14)		1.04 (0.78-1.39)	
	5-8	32.5	0.92 (0.83-1.02)	0.87 (0.71-1.06)		0.99 (0.79-1.23)	
	9-11	46.7	0.83 (0.76-0.90)	0.78 (0.64-0.94)		0.85 (0.70-1.04)	
	≥ 12	11.4	1.06 (0.90-1.25)	1 (ref)		1 (ref)	
2	BMI, kg/m^{2}[@]				<0.001		<0.001
	<18.5	4.6	0.43 (0.32-0.58)	0.57 (0.43-0.75)		0.60 (0.42-0.85)	
	18.5-24.9	64.7	0.76 (0.71-0.82)	1 (ref)		1 (ref)	
	25.0-29.9	23.2	1.17 (1.06-1.29)	1.54 (1.34-1.76)		1.55 (1.31-1.84)	
	≥ 30.0	7.5	2.30 (1.91-2.78)	3.03 (2.44-3.76)		2.84 (1.88-4.28)	
	Central obesity[@##]				<0.001		0.2
	No	89.8	0.81 (0.77-0.86)	1 (ref)		1 (ref)	
	Yes	10.2	1.90 (1.62-2.22)	2.33 (1.94-2.82)		1.23 (0.92-1.64)	

(Table 1 cont.)

				Crude analyses		Adjusted analyses	
Level	Independent variable	% in group	Geometric mean (95% CI)	**β (95% CI)**	**P**	**β (95% CI)**	**P**
	Current smoking				0.05		0.02
	No	72.1	0.86 (0.80-0.92)	1 (ref)		1 (ref)	
	Yes	27.9	0.98 (0.88-1.09)	1.14 (1.00-1.30)		1.21 (1.03-1.42)	
	Fat intake category				0.2		0.3
	Best low fat	11.7	1.01 (0.83-1.23)	1 (ref)		1 (ref)	
	Lower fat	10.9	1.03 (0.85-1.25)	1.02 (0.77-1.35)		0.96 (0.73-1.27)	
	American diet	12.3	0.83 (0.68-1.00)	0.81 (0.62-1.07)		0.81 (0.62-1.06)	
	High fat	14.1	0.80 (0.67-0.96)	0.79 (0.60-1.03)		0.78 (0.60-1.02)	
	Very high fat	51.0	0.90 (0.81-0.99)	0.88 (0.71-1.10)		0.88 (0.71-1.09)	
	Fiber intake[@]				0.7		1.0
	Moderate/adequate	30.5	0.92 (0.80-1.05)	1 (ref)		1 (ref)	
	Low	69.5	0.89 (0.83-0.96)	1.03 (0.89-1.19)		1.01 (0.87-1.17)	
2	Alcohol intake				0.02[*]		0.5[*]
	Non-drinker	24.7	0.85 (0.75-0.96)	1.01 (0.87-1.17)		1.00 (0.84-1.18)	
	Up to 1 drink/day	41.8	0.83 (0.77-0.91)	1 (ref)		1 (ref)	
	More than 1 drink/day	33.5	1.00 (0.91-1.11)	1.20 (1.05-1.38)		1.09 (0.90-1.30)	
	Physical activity, total				0.07		0.4
	Not sedentary	92.3	0.88 (0.83-0.93)	1 (ref)		1 (ref)	
	Sedentary	7.7	1.08 (0.85-1.36)	1.23 (0.99-1.53)		1.11 (0.87-1.431)	
	Physical activity, leisure				0.8	-	-
	Not sedentary	50.4	0.90 (0.83-0.97)	1 (ref)		-	
	Sedentary	49.6	0.88 (0.81-0.96)	0.98 (0.87-1.10)		-	
	SRQ result[@]				0.8		0.4
	Normal	75.7	0.88 (0.83-0.94)	1 (ref)		1 (ref)	
	Elevated	24.4	0.90 (0.80-1.02)	1.02 (0.89-1.17)		1.07 (0.91-1.25)	
	N total	**1919**					

P-values for trend by linear regression, *ln*CRP as dependent variable

(Table 1 cont.)

[*]Wald test for heterogeneity

[#]Other categories excluded due to small numbers (n=43 Indigenous and 27 Asian)

[@]Due to missing data, the numbers of observations for analyses were: BMI=1916; central obesity=1915; fiber intake=1917; SRQ (minor psychiatric disorder)=1914

[##]Defined as waist circumference ≥ 94 cm (WHO, 2000)

Level 1 analyses adjusted for skin color, age, family income and years of education

Level 2 analyses adjusted for all variables (except leisure time physical activity)

Table 2: Distribution and associations of C-reactive protein (CRP) levels with sociodemographic, anthropometric and behavioral factors, women.

				Crude analyses		Adjusted analyses	
Level	Independent variable	% in group	Geometric mean (95% CI)	**β (95% CI)**	**P**	**β (95% CI)**	**P**
1	Age, y	-	-	1.35 (1.11-1.65)	0.003	1.37 (1.12-1.67)	0.003
	Skin color[#]						
	White	78.6	1.67 (1.54-1.82)	1 (ref)	0.8[*]	1 (ref)	0.5[*]
	Mulatto	5.1	1.72 (1.25-2.36)	1.03 (0.73-1.44)		0.97 (0.69-1.37)	
	Black	16.3	1.56 (1.27-1.91)	0.93 (0.76-1.14)		0.88 (0.71-1.08)	
	Family income in 2004, minimum wage units				0.04		0.3
	≤ 1	7.0	1.46 (1.06-2.02)	1.13 (0.80-1.59)		1.01 (0.69-1.49)	
	1.1-3.0	33.5	1.83 (1.60-2.09)	1.42 (1.11-1.80)		1.30 (0.99-1.72)	
	3.1-6.0	32.1	1.72 (1.52-1.95)	1.33 (1.05-1.70)		1.31 (1.01-1.69)	
	6.1-10.0	14.9	1.58 (1.31-1.90)	1.22 (0.93-1.62)		1.19 (0.89-1.58)	
	>10	12.5	1.29 (1.07-1.56)	1 (ref)		1 (ref)	
	Education, y				0.03		0.4
	0-4	6.4	1.75 (1.29-2.36)	1.34 (0.96-1.87)		1.19 (0.80-1.77)	
	5-8	22.9	1.76 (1.50-2.06)	1.35 (1.08-1.70)		1.20 (0.90-1.60)	
	9-11	52.3	1.74 (1.57-1.93)	1.34 (1.10-1.63)		1.28 (1.03-1.60)	
	≥ 12	18.4	1.30 (1.11-1.53)	1 (ref)		1 (ref)	
	Parity				0.01		0.2
	0	61.8	1.55 (1.42-1.71)	1 (ref)		1 (ref)	
	1	25.0	1.77 (1.53-2.05)	1.14 (0.96-1.35)		1.06 (0.88-1.28)	
	2	9.0	1.82 (1.44-2.29)	1.17 (0.90-1.52)		1.05 (0.79-1.40)	
	3+	4.2	2.30 (1.54-3.43)	1.48 (1.03-2.13)		1.44 (0.96-2.18)	

(Table 2 cont.)

				Crude analyses		Adjusted analyses	
Level	Independent variable	% in group	Geometric mean (95% CI)	**β (95% CI)**	**P**	**β (95% CI)**	**P**
2	BMI, kg/m$^{2@}$				<0.001		0.001
	<18.5	8.1	1.03 (0.77-1.39)	0.73 (0.56-0.96)		0.75 (0.54-1.05)	
	18.5-24.9	67.2	1.41 (1.29-1.54)	1 (ref)		1 (ref)	
	25.0-29.9	16.1	2.36 (2.01-2.77)	1.68 (1.37-2.05)		1.19 (0.88-1.62)	
	≥ 30.0	8.6	4.70 (3.75-5.87)	3.34 (2.56-4.34)		2.01 (1.29-3.12)	
	Central obesity$^{@\#\#}$				<0.001		0.001
	No	77.4	1.37 (1.26-1.49)	1 (ref)		1 (ref)	
	Yes	22.6	3.15 (2.73-3.64)	2.29 (1.93-2.74)		1.63 (1.21-2.19)	
	Current smoking				0.4		0.6
	No	76.4	1.63 (1.50-1.77)	1 (ref)		1 (ref)	
	Yes	23.6	1.75 (1.51-2.03)	1.07 (0.90-1.27)		1.06 (0.84-1.33)	
	Fat intake category				0.1		0.06
	Best low fat	10.3	1.63 (1.23-2.17)	1 (ref)		1 (ref)	
	Lower fat	12.2	1.47 (1.14-1.89)	0.90 (0.63-1.29)		0.99 (0.68-1.43)	
	American diet	13.8	1.55 (1.25-1.92)	0.95 (0.66-1.35)		0.98 (0.69-1.41)	
	High fat	12.7	1.33 (1.05-1.70)	0.82 (0.57-1.17)		0.79 (0.55-1.15)	
	Very high fat	50.1	1.84 (1.63-2.07)	1.12 (0.84-1.51)		1.21 (0.90-1.64)	
	Fiber intake				0.8		0.5
	Moderate/adequate	31.0	1.63 (1.41-1.88)	1 (ref)		1 (ref)	
	Low	69.0	1.67 (1.50-1.85)	0.98 (0.81-1.18)		0.93 (0.77-1.12)	
	Alcohol intake				1.0*		0.7*
	Non-drinker	41.3	1.63 (1.46-1.83)	0.98 (0.84-1.14)		0.93 (0.77-1.13)	
	Up to 1 drink/day	46.7	1.67 (1.50-1.86)	1 (ref)		1 (ref)	
	More than 1 drink/day	12.0	1.66 (1.37-2.01)	0.99 (0.78-1.26)		1.03 (0.77-1.37)	
	Physical activity, total				0.8		0.5
	Not sedentary	91.9	1.66 (1.54-1.79)	1 (ref)		1 (ref)	
	Sedentary	8.1	1.60 (1.24-2.07)	0.96 (0.74-1.26)		1.13 (0.82-1.56)	

(Table 2 cont.)

				Crude analyses		Adjusted analyses	
Level	Independent variable	% in group	Geometric mean (95% CI)	**β (95% CI)**	**P**	**β (95% CI)**	**P**
2	Physical activity, leisure				0.6	-	-
	Not sedentary	19.8	1.59 (1.35-1.87)	1 (ref)		-	
	Sedentary	80.2	1.67 (1.54-1.81)	1.05 (0.88-1.26)		-	
	SRQ result				0.6		0.9
	Normal	66.9	1.64 (1.50-1.80)	1 (ref)		1 (ref)	
	Elevated	33.1	1.71 (1.50-1.94)	1.04 (0.89-1.21)		0.99 (0.81-1.20)	
	N total	**1370**					

P-values for trend by linear regression, *ln*CRP as dependent variable
[*]Wald test for heterogeneity
[#]Other categories excluded due to small numbers (n=30 Indigenous and 15 Asian)
[@]Due to missing data, the numbers of observations for analyses were: BMI=1369; central obesity=1368; SRQ (minor psychiatric disorder)=1366
[##]Defined as waist circumference ≥ 80 cm (WHO, 2000)
Excludes pregnant women (n=93) and those using oral contraceptive therapy (n=445) at the time of the 2004-05 cohort visit

BMI and central obesity categories exclude those up to 6 months post-partum (n=62)
Level 1 analyses adjusted for skin color, age, family income, years of education and parity
Level 2 analyses adjusted for all variables (except leisure time physical activity

Divulgação

"Risco para doença cardiovascular começa antes do que se imaginava"

Nos dias de hoje, doença cardiovascular está entre as principais causas de morbi-mortalidade em âmbito mundial. No Brasil, mais que um quarto dos óbitos são devido à estas doenças. A patologia básica responsável pelas complicações das doenças cardiovasculares é a aterosclerose, processo inflamatório que se caracteriza por lesões espessadas e endurecidas das artérias. Esta inflamação pode resultar de fatores prejudiciais crônicos e bastante comuns, como obesidade, tabagismo e estresse.

Uma pesquisa elaborada no Programa de Pós-Graduação em Epidemiologia da UFPel (RS), financiado pelo Capes (Brasil) e o Wellcome Trust (Reino Unido), teve como população alvo a Coorte dos nascidos em Pelotas em 1982. O doutorando em epidemiologia, Aydin Nazmi, com a orientação de Cesar Victora, como parte do seu projeto, avaliou níveis de proteína C reativa, um marcador sensível de inflamação, através de amostras de sangue que foram coletados em 2004-05 durante a visita aos membros da coorte.

Foi observado neste estudo que os níveis de inflamação foram maiores nas pessoas que apresentavam sobrepeso ou obesidade, que eram tabagistas e, ainda, em indivíduos expostos a um maior nível de estresse.

Além destes fatores atuais, certificou-se que exposições no inicio da vida e condições socioeconômicas também tinham um forte impacto nos níveis de inflamação, como por exemplo a relação com a educação materna: quanto menor o grau de escolaridade da mãe, maior foi o nível de inflamação encontrado no filho aos 23 anos de idade. Uma outra observação foi que o ganho de peso excessivo começando na infância pode resultar em níveis elevados de inflamação na vida adulta.

Embora seja conhecido que fatores comportamentais, sedentarismo, tabagismo e obesidade têm papel fundamental no desenvolvimento das doenças cardiovasculares, os resultados deste estudo mostraram que os riscos podem começar ainda na vida intra-uterina e durante a infância.

Portanto, medidas de saúde pública direcionadas ao combate da incidência de doença cardiovascular, além de enfocar nos fatores contemporâneos como obesidade e tabagismo, deveriam também considerar a importância das influências que atuam silenciosamente desde a vida intra-uterina. Assistência a saúde materna, amamentação e alimentação adequada na infância e ganho de peso saudável durante da vida podem resultar em benefícios para uma incidência reduzida das doenças cardiovasculares a longo prazo.

Anexo

Links do internet relevantes à projeto

1. Questionário completo de seguimento de coorte de 1982 em 2004-05: http://www.epidemio-ufpel.org.br/_projetos_de_pesquisas/coorte1982/

2. Siemens IMMULITE e as informações detalhadas sobre a sistema de ensaio imunométrico por quimiluminescência: http://diagnostics.siemens.com/webapp/wcs/stores/servlet/ProductDisplay~q_catalogId~e_-111~a_catTree~e_100001,1009257~a_langId~e_-111~a_productId~e_172961~a_storeId~e_10001.htm