Universidade de São Paulo
Faculdade de Saúde Pública

Determinantes do crescimento linear e ganho de peso de crianças em Acrelândia, Estado do Acre, Amazônia Ocidental Brasileira

Bárbara Hatzlhoffer Lourenço

Tese apresentada ao Programa de Pós-Graduação em Nutrição em Saúde Pública para obtenção do título de Doutora em Ciências

Área de concentração: Nutrição em Saúde Pública

Orientadora: Profa. Dra. Marly Augusto Cardoso

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Para cada uma das minhas crianças,
que me fizeram observadora, perguntadora, pesquisadora.
Para todas as crianças de Acrelândia.

"When it all goes quiet behind my eyes, I see everything that made me flying around in invisible pieces. When I look too hard, it goes away. But when it all goes quiet, I see they are right here. I see that I am a little piece of a big, big universe. And that makes things right. When I die, the scientists of the future, they are gonna find it all. They gonna know, once there was a Hushpuppy, and she lived with her daddy in the Bathtub."

– Hushpuppy. Beasts of the Southern Wild, 2012.

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RESUMO

Lourenço BH. Determinantes do crescimento linear e ganho de peso de crianças em Acrelândia, Estado do Acre, Amazônia Ocidental Brasileira [tese de doutorado]. São Paulo: Faculdade de Saúde Pública da Universidade de São Paulo; 2014.

Introdução: Investigações sobre o crescimento linear e o ganho de peso durante a infância em regiões de baixa e média renda são relevantes ao avanço do conhecimento científico e ao planejamento de ações para promoção da saúde no contexto de transição nutricional que afeta tais áreas. **Objetivo:** Investigar determinantes do crescimento linear e ganho de peso de crianças residentes no município de Acrelândia, Estado do Acre, Amazônia Ocidental Brasileira. **Métodos:** O presente estudo longitudinal de base populacional foi constituído a partir de dois inquéritos transversais de base populacional conduzidos em 2003 e 2007, com dois inquéritos de seguimento realizados em 2009 e 2012. Foram realizadas entrevistas domiciliares para levantamento de informações sociodemográficas, características maternas e morbidade recente da criança, além de coleta de amostra de sangue e exame antropométrico. Os desfechos de interesse foram a variação em escores Z de altura e índice de massa corporal (IMC) para idade. Utilizaram-se modelos de regressão linear mistos para a análise dos dados longitudinais. **Resultados:** Os principais determinantes do crescimento linear mensurado em escores Z de altura para idade durante a infância foram o índice de riqueza domiciliar e a posse de terra, além da altura materna e de peso e comprimento da criança ao nascer. O ganho de peso verificado por escores Z de IMC para idade foi positivamente associado ao índice de riqueza domiciliar e ao IMC materno até os 10 anos de idade. Houve associação positiva entre estado inflamatório de baixo grau na linha de base do estudo (definido por maiores concentrações de proteína C-reativa até 1 mg/L) e incremento em escores Z de IMC para idade durante o seguimento entre crianças a partir de 5 anos de idade. O alelo de risco do gene associado à massa gorda e obesidade (*FTO* rs9939609) relacionou-se a maior ganho em escores Z de IMC para idade durante a infância, com modificação de efeito pelo estado inicial de vitamina D, com papel genético mais pronunciado entre crianças com concentrações

insuficientes de vitamina D. O aumento em escores Z de IMC durante a idade escolar foi também associado à resistência à insulina nas crianças estudadas. **Conclusão:** Em uma área de baixa renda, confirmou-se a influência do contexto socioeconômico e de fatores intergeracionais representados por características maternas sobre o crescimento linear e o ganho de peso na infância. O incremento de peso foi influenciado também por um cenário em que deficiências de micronutrientes, elevada morbidade e interação entre fatores genéticos e nutricionais coexistem com panorama crescente de sobrepeso e obesidade.

Descritores: Crianças, crescimento linear, ganho de peso, estado nutricional, determinantes, Amazônia Ocidental Brasileira.

ABSTRACT

Lourenço BH. Determinants of linear growth and weight gain among children in Acrelândia, Acre State, Western Brazilian Amazon [doctoral dissertation]. São Paulo (BR): School of Public Health of the University of São Paulo; 2014.

Background: Investigations on linear growth and weight gain during childhood in low- to middle-income regions are relevant to scientific knowledge and for the planning of actions focused on health promotion in the context of nutrition transition that affects such areas. **Objective:** To investigate determinants of linear growth and weight gain among children residing in the town of Acrelândia, Acre State, Western Brazilian Amazon. **Methods:** This population-based longitudinal study comprised two population-based cross-sectional surveys conducted in 2003 and 2007, and two follow-up assessments conducted in 2009 and 2012. Household interviews collected data on sociodemographic information, maternal characteristics, and child's recent morbidity. Children were also invited for blood sample collection and anthropometric evaluation. Outcomes of interest were change in height for age and body mass index (BMI) for age Z scores. Mixed-effect linear regression models were used in longitudinal data analysis. **Results:** Main determinants of linear growth in height for age Z scores during childhood were household wealth index and land ownership, as well as maternal height and child's birth weight and length. Weight gain ascertained with BMI for age Z scores was positively associated with household wealth and maternal BMI up to age 10 years. Baseline low-grade inflammatory status (defined as C-reactive protein concentrations up to 1 mg/L) was related to a higher gain in BMI for age Z scores during follow-up among children aged >5 years. Each risk allele of the fat mass and obesity associated gene (*FTO* rs9939609) was related to a higher increase in BMI for age Z score during childhood, with a significant interaction with baseline vitamin D status, with more pronounced genetic effects among children with vitamin D insufficiency. The increase in BMI for age Z scores during school-aged years was also associated with insulin resistance in children. **Conclusion:** In a low-income area, we confirmed the influence of the socioeconomic context and intergenerational factors represented by maternal

characteristics on linear growth and weight gain during childhood. Increases in weight were also influenced by a scenario where micronutrient deficiencies, high morbidity, and interaction between genetic and nutritional factors are coupled with a rising panorama of overweight and obesity.

Descriptors: Children, linear growth, weight gain, nutritional status, determinants, Western Brazilian Amazon.

ÍNDICE

APRESENTAÇÃO

A presente tese de doutorado foi organizada segundo diretrizes da Comissão de Pós-Graduação da Faculdade de Saúde Pública da Universidade de São Paulo, deliberadas na sessão 9ª/2008 de 05/06/2008, sendo apresentada sob a forma de artigos. O presente documento compreende uma introdução ao tema, a exposição dos objetivos propostos e a descrição de aspectos gerais do delineamento do estudo e dos métodos empregados, a serem abordados mais especificamente em cada um dos artigos. A seguir, a seção de resultados e discussão é composta por seis manuscritos resultantes deste estudo, os quais foram formatados segundo as normas dos periódicos a que foram ou serão submetidos e publicados. Finalmente, considerações finais são elencadas para complementar as conclusões presentes nos artigos e contextualizar os principais achados da tese em conjunto.

A execução do projeto de pesquisa contou com auxílio financeiro em diferentes fases do inquérito populacional longitudinal (Conselho Nacional de Desenvolvimento Tecnológico e Científico – CNPq, processos nº 551359/2001-3, 502937/2003-3, 307728/2006-4 e 470573/2007-4; Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP nº 2007/53042-1). Para a presente tese, uma bolsa de doutorado direto foi concedida pela FAPESP, entre março de 2009 e fevereiro de 2014 (processo FAPESP nº 2008/57796-3; ANEXO 1). Durante esse período, o treinamento em análise de dados incluiu estágios de pesquisa realizados no *Center for Social Epidemiology and Population Health, University of Michigan School of Public Health,* Ann Arbor, MI, EUA, sob a supervisão do Prof. Dr. Eduardo Villamor, entre 2010 e 2011 (com apoio complementar de bolsa acadêmica da Organização dos Estados Americanos, BR *Self Grad* 2010/11 ID 20100656, *United States Department of State's Exchange Visitor Program* nº P-3-03822; ANEXO 2), e no *Department of Nutrition, Harvard School of Public Health*, Boston, MA, EUA, sob a supervisão do Prof. Dr. Lu Qi e em colaboração com o Prof. Dr. Walter Willett, em 2013 (ANEXO 3).

1 INTRODUÇÃO

1.1 ESTADO NUTRICIONAL DURANTE A INFÂNCIA: AVALIAÇÃO ANTROPOMÉTRICA E APLICAÇÕES EM INQUÉRITOS EPIDEMIOLÓGICOS

O estado nutricional exibido durante a infância pode influenciar até a idade adulta o desenvolvimento físico e metabólico, a capacidade cognitiva e indicadores de morbidade e mortalidade, além de ter impacto sobre a produtividade econômica e o desempenho reprodutivo futuros, com consequências individuais e sociais perceptíveis de curto a longo prazo (BLACK et al., 2008; VICTORA et al., 2008). Regiões de baixa e média renda comumente enfrentam problemas de saúde pública relacionados à má nutrição entre crianças, a qual pode apresentar-se sob a forma de desnutrição, incluindo deficiências de micronutrientes e déficits de crescimento, bem como pode ser resultado do panorama emergente de sobrepeso e obesidade (BLACK et al., 2013).

Entre fatores relacionados a condições de saúde e nutrição desde os primeiros anos de vida, um levantamento recente conduzido por BLACK et al. (2013) apontou que restrição do crescimento fetal durante a gestação, aleitamento materno inadequado, deficiências de vitamina A e zinco, déficits no crescimento linear e no ganho de peso são responsáveis conjuntamente por 3,1 milhões de mortes por ano entre crianças menores de 5 anos de idade ao redor do mundo. No ano de 2011, esse total foi equivalente a 45% das mortes nesse grupo etário globalmente. Os danos ocasionados pela má nutrição na infância podem, ainda, perdurar durante a vida adulta, com impactos ao capital humano e à saúde. MARTORELL et al. (2010), por exemplo, fizeram uso de dados de coortes conduzidas na África do Sul, Brasil, Filipinas, Guatemala e Índia e constataram que a baixa estatura estava associada de forma significante com a ocorrência de repetência escolar e com a redução de 0,9 ano da escolaridade atingida na idade adulta, sendo a relação mais expressiva quando considerado o crescimento linear averiguado até os dois primeiros anos de idade. Em análises com essas mesmas cinco coortes de nascimentos, ADAIR et al. (2013)

verificaram que ganho de peso mais acelerado durante a infância, entre 2 e 8 anos de idade, foi positivamente associado a um risco 51-76% maior para sobrepeso e 7-22% maior para pressão arterial elevada na idade adulta.

A avaliação do crescimento e do desenvolvimento infantil por meio de medidas antropométricas consiste em metodologia simples e de baixo custo, utilizada amplamente para a detecção e o manejo de problemas nutricionais (WHO, 1995). Considerando a disposição organizacional de diferentes níveis da composição corporal humana, a interpretação de medidas antropométricas básicas como peso e comprimento ou altura depende da combinação de tais aferições em índices antropométricos que considerem variáveis como idade e sexo do indivíduo em comparação a padrões de referência. Assim, em nível populacional, os índices antropométricos podem ter aplicação como indicadores para identificação de riscos nutricionais e planejamento de intervenções, além da investigação de determinantes e consequências da má nutrição (WHO, 1995).

No tocante a padrões de referência, a Organização Mundial da Saúde (OMS) iniciou esforços na década de 1990 para estruturar um estudo multicêntrico internacional para o desenvolvimento de curvas de crescimento infantil a partir de rigorosa coleta de dados nos Estados Unidos, Omã, Noruega, Brasil, África do Sul e Índia. Publicadas em 2006, as curvas de crescimento da OMS para meninos e meninas até 5 anos de idade compõem um padrão de referência normativo que retrata o crescimento normal esperado sob exposições ambientais ótimas, o qual pode ser empregado independentemente de raça/etnia, nível socioeconômico e práticas alimentares (WHO, 2006). Em paralelo, a OMS reformulou as referências recomendadas para crianças em idade escolar e adolescentes e, em 2007, publicou curvas de crescimento para indivíduos de 5 a 19 anos de ambos os sexos. Com a adaptação, as curvas se adequaram, aos 5 anos, ao padrão de crescimento saudável preconizado para pré-escolares nas curvas de 2006 e, aos 19 anos, aos pontos de corte utilizados entre adultos para definição de sobrepeso e obesidade (DE ONIS et al., 2007). Nas curvas de crescimento da OMS, os índices antropométricos de comprimento ou altura para idade e de índice de massa corporal (IMC) para idade estão disponíveis dos 0 aos 19 anos de idade, cobrindo continuamente as fases pré-escolar, escolar e adolescente. Os índices em questão podem ser expressos em

escores Z (desvio do valor individual em relação ao valor mediano de referência, dividido pelo desvio-padrão para a população de referência) ou em percentis (posição relativa do valor individual em relação à referência) (WHO, 1995; 2006; DE ONIS et al., 2007).

A relação de comprimento ou altura para idade representa o crescimento linear atingido e é sensível a influências cumulativas das condições de saúde e alimentação pregressas. O déficit de altura para idade, definido quando escore Z é inferior a -2, reflete, portanto, o comprometimento do crescimento linear esperado em um processo de longa duração (WHO, 1995). Entre crianças até 5 anos de idade, estima-se que 164,8 milhões de meninos e meninas ao redor do mundo apresentaram déficit de altura para idade em relação às curvas de crescimento da OMS, um total equivalente a 25,7% deste estrato populacional em perspectiva global no ano de 2011. Dessas crianças, 159,7 milhões estavam concentradas em países de baixa e média renda, representando 28,0% do grupo etário nessas áreas. Na região da América Latina e do Caribe, 7,1 milhões ou 13,4% das crianças até 5 anos apresentaram déficit de altura para idade em 2011 (BLACK et al., 2013).

Apesar da tendência mundial de redução observada nas últimas décadas para os números absolutos e para a prevalência de crianças com crescimento linear comprometido, este continua a ser um problema de saúde pública e diferenças regionais importantes persistem. Especificamente, no caso do Brasil, a Pesquisa Nacional de Demografia e Saúde da Criança e da Mulher – PNDS 2006 evidenciou que 7,0% das crianças do país com menos de 5 anos apresentaram déficit de altura para idade. Na região Norte, tal prevalência foi mais de duas vezes maior que a média nacional, equivalendo a 14,8% (BRASIL, 2008). De forma similar, os resultados da Pesquisa de Orçamentos Familiares – POF 2008-2009 apontaram que 6,8% das crianças entre 5 e 9 anos de idade apresentaram déficit de altura; segundo sexo e situação domiciliar, a região Norte do Brasil novamente exibiu as maiores prevalências deste distúrbio nutricional, variando entre 8,8% e 16,0% (IBGE, 2010).

Concomitantemente à ocorrência de déficits do estado nutricional, nota-se que a população infantil é afetada de forma crescente pelo ganho de peso excessivo. A prevalência de sobrepeso se mostra superior em países de alta renda quando comparada à prevalência observada em países de baixa e média renda. Nos Estados

Unidos, por exemplo, estudo com os dados da *National Health and Nutrition Examination Survey* referentes ao período 2009-2010 empregou como padrão de referência as curvas de crescimento do *Centers for Disease Control and Prevention* de 2000. Crianças e adolescentes com sobrepeso ou obesidade (IMC igual ou acima do percentil 85 para idade) e obesidade (IMC igual ou acima do percentil 95 para idade), respectivamente, corresponderam a 26,7% e 12,1% dos indivíduos entre 2 e 5 anos, 32,6% e 18,0% daqueles entre 6 e 11 anos, e 33,6% e 18,4% daqueles entre 12 e 19 anos (OGDEN et al., 2012).

Deve-se notar, contudo, que a maior parte da população mundial de crianças com excesso de peso, em números absolutos, vive atualmente em países de baixa e média renda. Duas séries sobre nutrição materno-infantil em países de baixa e média renda foram publicadas no periódico *Lancet* em 2008 e 2013, e a compilação mais recente incluiu tópico sobre perspectivas e implicações de condições de sobrepeso e obesidade desde os primeiros anos de vida (BLACK et al., 2008; 2013), evidenciando a importância da discussão fora do âmbito de regiões mais desenvolvidas. Entre 1990 e 2010, houve incremento de 54% no número de crianças menores de 5 anos de idade com sobrepeso ao redor do mundo. No ano de 2011, 7,0% ou 43 milhões de crianças menores de 5 anos apresentaram índice de peso para altura 2 escores Z acima da mediana das curvas de crescimento da OMS, sendo classificadas com sobrepeso –destas, 32 milhões residiam em países de baixa e média renda (BLACK et al., 2013).

No Brasil, dados da PNDS apontam que 6,6% das crianças menores de 5 anos apresentaram índice de peso para altura superior a 2 escores Z no ano de 2006 (BRASIL, 2008). Segundo levantamento da última POF, que empregou o índice de IMC para idade em relação às curvas da OMS, crianças e adolescentes com risco para sobrepeso e obesidade (definido como escore Z de IMC para idade superior a 1) e com obesidade (escore Z de IMC para idade superior a 2), respectivamente, corresponderam a 33,5% e 14,3% daqueles entre 5 a 9 anos, e a 20,5% e 4,9% daqueles entre 10 a 19 anos no período 2008-2009 (IBGE, 2010). Alguns padrões regionais puderam ser observados em ambas as pesquisas e as menores prevalências de excesso de peso foram detectadas entre as regiões Norte e Nordeste do país para todos os grupos etários.

O avanço das condições de sobrepeso e obesidade na população infantil, em antagonismo às tendências temporais de desnutrição, pode ser interpretado como uma das características mais marcantes do processo de transição nutricional. Este processo engloba mudanças cíclicas no perfil nutricional de populações, produzidas por transformações no padrão alimentar e no padrão de gasto energético em decorrência da interação entre alterações culturais, ambientais, demográficas e econômicas ocorridas na sociedade (POPKIN, 2001).

Há um extenso debate em relação a como o estágio atual de transição nutricional afeta as mudanças no IMC de populações em países de baixa e média renda. Entre adultos, enquanto alguns estudos apontaram a manutenção do ganho de peso excessivo em tais áreas entre estratos mais ricos (NEUMAN et al., 2011), outras análises já indicaram que um incremento mais rápido nas taxas de sobrepeso pode ocorrer nas camadas socioeconômicas mais baixas, sugerindo uma transferência da carga de doença relacionada ao excesso de peso para os mais pobres (JONES-SMITH et al., 2012). No Brasil, comparações temporais entre o Estudo Nacional de Despesa Familiar no período 1974-1975, a Pesquisa Nacional sobre Saúde e Nutrição de 1989, a POF 2002-2003 e a POF 2008-2009 evidenciam que excesso de peso e obesidade foram observados consistentemente em proporções mais elevadas nos estratos mais ricos, porém o aumento das prevalências destes distúrbios nutricionais ocorreu nas últimas décadas em todos os quintos de rendimento total e variação patrimonial mensal familiar per capita, em ambos os sexos e em todas as faixas etárias da infância até a idade adulta (IBGE, 2010).

A coexistência de problemas em ambos os extremos do espectro da má nutrição desde a infância em países de baixa e média renda precisa considerar, ainda, que, nessas regiões, desigualdades sociais e em saúde são comuns e impactam o desenvolvimento durante a infância (BARROS et al., 2010). Nesse sentido, nota-se a existência de um gradiente em que, quanto maior a desvantagem social, em geral maiores são a exposição a condições ambientais adversas e a prevalência de doenças, e menor é o acesso a serviços de saúde de qualidade e a programas de prevenção e tratamento (VICTORA et al., 2006; WOOLFENDEN et al., 2013). Visando à promoção de condições adequadas de saúde e nutrição ao longo do ciclo vital, a investigação de determinantes do crescimento linear e do ganho de peso desde os

primeiros anos de vida e potenciais fatores modificáveis envolvidos deve atentar, por conseguinte, a diferentes esferas que envolvem o contexto da carga dupla de doença em países de baixa e média renda.

1.2 DETERMINANTES DO CRESCIMENTO LINEAR E GANHO DE PESO NA INFÂNCIA

Devido a uma dinâmica comum de recursos sociais e materiais insuficientes que podem impactar o potencial ótimo de desenvolvimento, a investigação de determinantes e seus efeitos sobre desfechos como o crescimento linear e o ganho de peso entre crianças em regiões de baixa e média renda pode beneficiar-se pela formulação de modelos conceituais de causalidade (VICTORA et al., 1997). A aplicação de modelos hierárquicos de determinação possibilita a interpretação e a organização de exposições ou fatores de risco (variáveis independentes) em diversos níveis de determinação em relação ao evento de interesse (variável dependente).

Níveis de determinação superiores abarcam determinantes considerados distais, a exemplo de condições socioeconômicas, ao passo que níveis mais inferiores reúnem determinantes intermediários e proximais, como variáveis ambientais, de morbidade e dieta. Reconhece-se que determinantes distais podem influenciar ou atuar por meio dos determinantes intermediários e proximais, viabilizando a observação de efeitos diretos ou de efeitos mediados sobre o desfecho. Assim, os modelos hierárquicos são úteis à investigação de mecanismos resultantes de inter-relações entre os níveis de determinação, ao controle de potenciais variáveis de confusão, e à identificação de causas suficientes, componentes e necessárias. No estudo de determinantes, os modelos hierárquicos são importantes para orientar o uso de técnicas de análises múltiplas e para a discussão adequada dos resultados obtidos, ponderando desde aspectos sociais a fatores biológicos envolvidos (VICTORA et al., 1997; OLINTO, 1998; SCHISTERMAN et al., 2009). No esquema adaptado apresentado na FIGURA 1, estão presentes fatores associados ao desenvolvimento infantil em diferentes níveis de determinação.

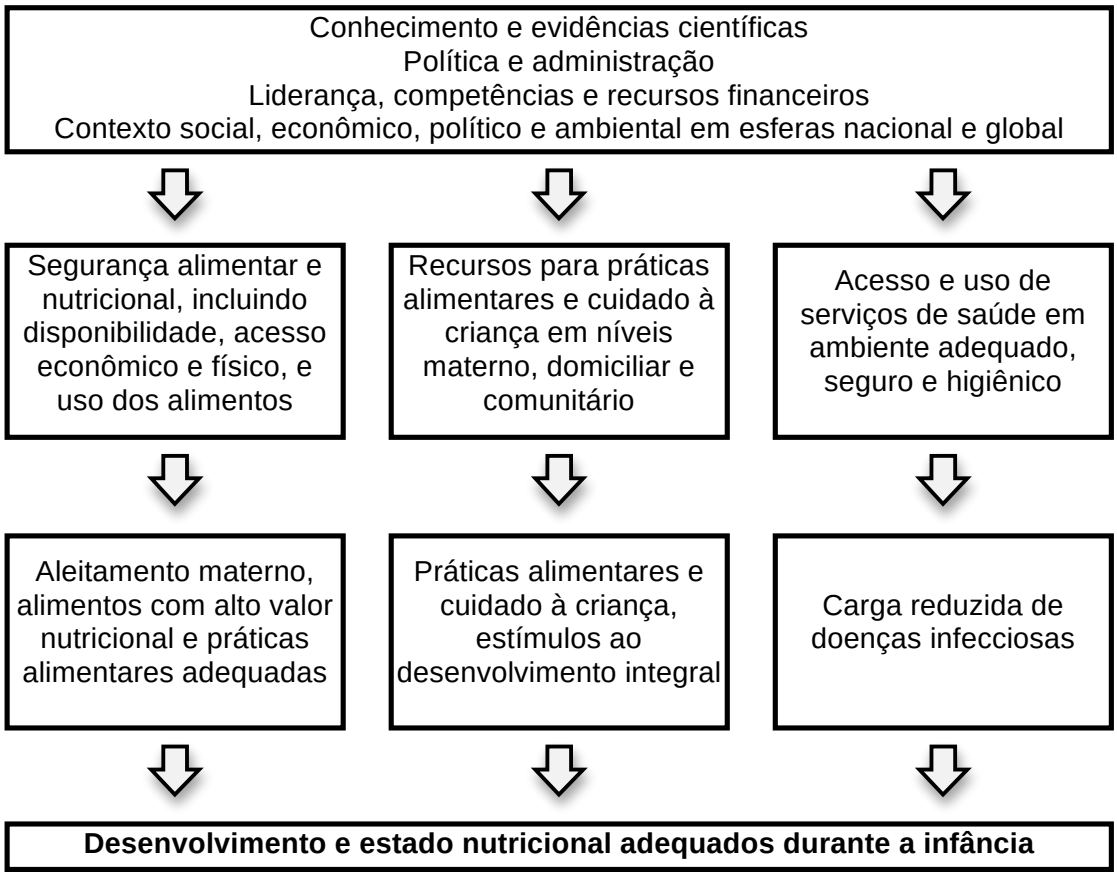

Figura 1 – Fatores envolvidos no desenvolvimento e estado nutricional adequados durante a infância. Adaptada de: BLACK et al. (2013).

A importância do contexto socioeconômico e ambiental e do acesso a serviços públicos para o estado nutricional infantil pode ser verificada na investigação de tendências temporais da desnutrição no Brasil ao longo de um intervalo de 33 anos. Por meio da comparação de inquéritos transversais probabilísticos de abrangência nacional realizados entre 1974 e 2007, MONTEIRO et al. (2010) observaram redução de 37,1% para 7,1% no déficit de altura para idade entre crianças menores de 5 anos, com diminuição importante na diferença das prevalências do distúrbio entre os estratos mais ricos e mais pobres do país. Em sub-análise referente ao período compreendido entre 1996 e 2007, foi possível atribuir tal

evolução à melhoria do poder de compra nos domicílios e ao aumento da escolaridade materna, à maior cobertura dos serviços de saneamento básico e ao acesso mais abrangente à assistência pré-natal e a métodos contraceptivos, com diminuição da paridade (MONTEIRO et al., 2010). Nesse período, a estruturação de programas sociais em âmbito nacional culminou no lançamento do Programa Bolsa Família em 2003, um programa de transferência de renda voltado a famílias extremamente pobres e pobres com crianças e adolescentes até 17 anos de idade ou mulheres gestantes e lactantes, e cujo repasse de recursos financeiros é condicionado ao atendimento de condições específicas relacionadas à saúde e à educação. Em análise referente ao período 2004-2009 com 2.853 municípios brasileiros, verificou-se efeito significante do Programa Bolsa Família na redução de 58,2% na mortalidade de crianças até 5 anos de idade por 1.000 nascidos vivos por causas associadas à desnutrição (RASELLA et al., 2013). No México, similarmente ao observado no cenário brasileiro, o programa nacional de transferência condicional de renda teve implicações positivas comprovadas prospectivamente no crescimento linear infantil, especialmente entre indivíduos até 2 anos de idade e nos estratos populacionais mais pobres (LEROY et al., 2008).

Para o ganho de peso, enquanto em regiões de alta renda se observa consistentemente uma relação inversa do nível socioeconômico com trajetórias de adiposidade durante a infância (HOWE et al., 2011), países em desenvolvimento como o Brasil apresentam em geral evidências provenientes de inquéritos nacionais com desenho transversal, como a POF 2008-2009, que reportam proporções mais elevadas de sobrepeso e obesidade nos estratos mais ricos da população durante a infância (IBGE, 2010). Um padrão bastante semelhante foi encontrado entre crianças e adolescentes de países em desenvolvimento como África do Sul, Colômbia, Guatemala, Índia, Irã, Sri Lanka, Ucrânia e Vietnã, incluídos em revisão sistemática que constatou associação positiva entre nível socioeconômico e excesso de peso em análises também majoritariamente transversais (DINSA et al., 2012). Na África do Sul, especificamente, uma análise longitudinal com 281 meninos e meninas até 10 anos de idade encontrou associação positiva entre nível socioeconômico e ganho de peso durante a infância com impactos distintos interessantes na composição corporal –o nível socioeconômico registrado ao nascer associou-se com a quantidade de

massa magra aos 10 anos, ao passo que o nível socioeconômico registrado da idade escolar associou-se significantemente com indicadores da quantidade de massa gorda aos 10 anos (GRIFFITHS et al., 2008).

Características maternas também exercem influências importantes sobre o crescimento linear e o ganho de peso de crianças. Em análises de Pesquisas de Demografia e Saúde representativas em 54 países em desenvolvimento conduzidas entre 1991 e 2008, ÖZALTIN et al. (2010) constataram a associação positiva da altura materna com a diminuição da probabilidade de déficit de altura para idade entre crianças até 5 anos de idade. Corroboram com esses achados análises longitudinais de coortes de nascimentos no Reino Unido, com indivíduos de ambos os sexos acompanhados até os 33 anos (LI et al., 2004), e em Pelotas, na região Sul do Brasil, com meninas acompanhadas até os 19 anos (GIGANTE et al., 2006). De forma análoga, evidências de associação entre o excesso de peso dos progenitores e seus filhos em regiões de baixa e média renda são principalmente de desenho transversal, a exemplo de investigação em âmbito nacional conduzida na China em que a razão de prevalência ajustada para sobrepeso em 6.826 crianças e adolescentes de 7 a 17 anos variou de 1,9 (intervalo de confiança de 95% [IC 95%]: 1,4-2,7) quando apenas um dos pais apresentava sobrepeso a 9,5 (IC 95%: 5,5-16,3) quando pai e mãe eram ambos obesos (LI et al., 2007). Considerando estudos longitudinais, o IMC materno mostrou-se preditor tanto do peso ao nascer de crianças acompanhadas em coorte com mais de 152 mil pares de mães e filhos primogênitos na Suécia (CNATTINGIUS et al., 2012), como da ocorrência de sobrepeso entre os filhos acompanhados até os 7 anos em coorte no Chile (n = 652) (RIOS-CASTILLO et al., 2012) e até os 16 anos de idade em coorte na Finlândia (n = 4.788) (JÄÄSKELÄINEN et al., 2011).

Com relação a exposições perinatais relacionadas ao crescimento linear e ao ganho de peso, variáveis antropométricas ao nascer foram preditoras da altura e do peso corporal na adolescência e vida adulta em países desenvolvidos como Dinamarca (SORENSEN et al., 1997), Finlândia (PIETLÄINEN et al., 2001) e Noruega (EIDE et al., 2005), sugerindo papel do desenvolvimento intrauterino sobre o estado nutricional em anos posteriores. Dados de três coortes nas Filipinas, Guatemala e Índia apontaram que cada unidade de escore Z do comprimento ao

nascer em relação às curvas de crescimento da OMS foi associada com um acréscimo significante de 0,25 (IC 95%: 0,24-0,27) escore Z na altura atingida aos 19 anos (STEIN et al., 2010). Quanto à composição corporal, KUZAWA et al. (2012) reuniram informações sobre os participantes dessas mesmas três coortes em conjunto com duas outras coortes de nascimentos da África do Sul e do Brasil (*n* = 3.432) e constataram que, apesar de diferenças entre as regiões estudadas e entre indivíduos do sexo feminino e masculino, o peso ao nascer esteve associado mais fortemente à massa magra na idade adulta, com impacto modesto sobre a variação na quantidade de massa gorda.

Práticas alimentares adequadas podem influir positivamente sobre o crescimento linear sobretudo nos 24 primeiros meses de vida, conforme reportado em pesquisas recentemente conduzidas na Índia (MENON et al., 2013) e no Senegal (BORK et al., 2012). Nos últimos anos, interesse especial tem sido destinado à relação com ganho de peso na investigação das práticas alimentares na primeira infância, sendo o aleitamento materno um dos aspectos mais explorados. Em estudo multicêntrico na Europa, envolvendo crianças de Itália, Estônia, Chipre, Bélgica, Suécia, Hungria, Alemanha e Espanha, o aleitamento materno exclusivo por 6 meses, conforme reportado pelos pais, foi associado à redução de 29% (IC 95%: 0,58-0,85) no risco para sobrepeso exibido entre 2 e 9 anos de idade e esteve negativamente associado a outros indicadores de adiposidade, como a razão cintura-altura e a porcentagem de massa gorda (HUNSBERGER et al., 2013). Entre crianças finlandesas, houve associação negativa entre a duração do aleitamento e o IMC no primeiro ano de vida (*P* tendência linear <0,05), mas tal relação desapareceu aos 7 anos (O'TIERNEY et al., 2009). Indicadores de práticas alimentares incluindo duração do aleitamento materno exclusivo e idade de introdução de alimentos complementares não explicaram de forma significante a variação em peso ou comprimento ao final do primeiro ano de vida em estudo longitudinal que incluiu crianças em áreas urbanas na China, no México e nos EUA (WOO et al., 2013). Na coorte de nascimentos de Pelotas, não foi observada redução significante na ocorrência de obesidade aos 4 e aos 11 anos de idade em crianças que haviam sido amamentadas (ARAÚJO et al., 2006; NEUTZLING et al., 2009). Em análises restritas apenas a indivíduos do sexo masculino, acompanhados no momento do

alistamento militar, o aleitamento materno exclusivo ou predominante também não demonstrou efeito protetor consistente sobre IMC ou quantidades de massa magra e massa gorda após 18 anos nessa mesma região brasileira (VICTORA et al., 2003).

Além dos fatores em níveis distais e intermediários de determinação para desfechos do crescimento durante a infância, faz-se necessário contextualizar condições de vida com impacto potencialmente mais proximal ao estado nutricional de crianças em países de baixa e média renda. Como apontado anteriormente, apesar dos avanços econômicos observados, o cenário de desigualdades sociais e em saúde pode ser expressivo nessas regiões. Em áreas em desenvolvimento, condições estruturais ainda inadequadas em níveis comunitário, domiciliar e familiar podem propiciar a exposição continuada a fatores ambientais adversos, tais como agentes patogênicos, estresse psicossocial, deficiências de micronutrientes e padrões alimentares inadequados. Em 2011, a prevalência mundial de deficiência de vitamina A e de anemia por deficiência de ferro entre crianças menores de 5 anos de idade equivaleu, respectivamente, a 33,3% e 18,7% (BLACK et al., 2013). Ademais, de acordo com Pesquisas de Demografia e Saúde conduzidas em 55 países de baixa e média renda, a ocorrência de diarreia (mensurada de acordo com relato materno, referente às duas semanas anteriores à entrevista) atingiu 32,6% das crianças até 5 anos (FINLAY et al., 2011). Mais especificamente, nas Filipinas, por exemplo, pesquisa com 1.784 crianças de 6 a 23 meses residentes em áreas urbanas averiguou que as prevalências de anemia e de deficiências de ferro e vitamina A foram independentemente associadas a fatores socioeconômicos e condições sanitárias piores e a indicadores de inflamação da criança, como proteína C-reativa e alfa 1-glicoproteína ácida (ROHNER et al., 2013).

Assim, a avaliação dos padrões de crescimento infantil deve considerar de forma mais ampla as possíveis influências de altas taxas de morbidade, mesmo na ausência de sintomas clínicos, as quais podem ter efeito cumulativo sobre o desenvolvimento e a função metabólica ao longo do tempo (MARGOLIS, 2010). Observadas desde os primeiros anos de vida, tais exposições adversas à saúde alinham-se à noção de carga dupla de doença observada nos estágios de transição nutricional (POPKIN, 2001) e foram propostas como um “fenótipo de morbidade de coorte”, que poderia influir sobre processos inflamatórios e sobre a regulação

hormonal no organismo humano durante anos posteriores (FINCH & CRIMMINS, 2004). Em estudo na Guatemala, apesar de não haver marcadores inflamatórios disponíveis para análises, verificou-se que a maior ocorrência de infecções durante a infância entre participantes do estudo longitudinal INCAP foi associada tanto a maior IMC, circunferência de cintura e concentrações sanguíneas de glicose e triacilgliceróis, como também a menores concentrações sanguíneas da fração HDL-colesterol na idade adulta (MARGOLIS, 2010). EGGER & DIXON (2009; 2011) propuseram, inclusive, o ganho de peso excessivo como um possível marcador resultante da exposição a fatores ambientais e de estilo de vida que induziriam a ativação de vias inflamatórias no organismo humano com potencial impacto sobre o desenvolvimento de doenças crônicas ao longo do tempo.

Reconhece-se, por fim, que parte das associações observadas em relação aos determinantes dos padrões de crescimento observados durante a infância seja devida a fatores genéticos. Crianças do *Avon Longitudinal Study of Parents and Children* no Reino Unido e do *Raine Study* na Austrália (n = 9.328) foram incluídas em análise que avaliou as trajetórias de IMC ao longo da infância em relação ao efeito de um escore de risco genético que reuniu 32 polimorfismos associados ao IMC entre adultos, entre os quais os polimorfismos próximos aos genes *FTO, MC4R, RBJ, CADM2* e *MTCH2*, entre outros. O escore explicou 0,58% e 0,44% da variância total do IMC em meninas e meninos, respectivamente, sendo que interações significantes com sexo não foram identificadas (WARRINGTON et al., 2013). Dentre as influências genéticas descritas até o presente momento, o *FTO* (gene associado à massa gorda e obesidade) (FRAYLING et al., 2007) parece exercer os efeitos mais contundentes sobre o IMC desde os primeiros anos de vida, os quais, em perspectiva longitudinal, resultam em maior peso corporal ao final da infância (SOVIO et al., 2011). Entre adultos, há evidências de que os efeitos da variação no gene *FTO* possam ser modificados por fatores relacionados à dieta e à atividade física (ZHANG et al., 2012; KILPELÄINEN et al., 2011). Neste caso, no âmbito das transições epidemiológica e nutricional, em que a substituição de hábitos e itens alimentares tradicionais é progressivamente observada em populações de baixa e média renda (MONTEIRO et al., 2011), a exploração de mecanismos envolvidos no ganho de

peso desde os primeiros anos de vida, incluindo a interação de fatores genéticos com determinantes de saúde mais proximais, merece particular atenção.

1.3 JUSTIFICATIVA

Estudos transversais de base populacional são úteis ao diagnóstico de saúde infantil, porém não permitem avaliar a sequência temporal entre exposições e desfechos de interesse. Estudos prospectivos, por sua vez, são essenciais para investigação dos determinantes do estado nutricional nesse segmento populacional. No entanto, há poucos estudos longitudinais em países de média e baixa renda, e alguns dos determinantes do perfil de saúde infantil podem ser distintos daqueles observados em países mais desenvolvidos ou mesmo em diferentes regiões do país.

Apesar de se reconhecer que o crescimento pré e pós-natal associa-se ao estado nutricional que será exibido pelo indivíduo futuramente, a importância do crescimento em outros períodos da infância recebeu menor atenção até o momento, notadamente em relação a determinantes observados após os 5 anos de idade. Além disso, aponta-se que comumente o delineamento e as características de área e população de estudo priorizam a avaliação de categorias específicas do estado nutricional, impossibilitando a observação ampla da progressão dos padrões de crescimento infantil e fatores de risco e/ou proteção envolvidos.

Considerando a magnitude dos problemas nutricionais descritos entre crianças e adolescentes e sua influência nas condições de vida em anos posteriores, a identificação de potenciais fatores modificáveis até o fim da idade escolar para a promoção do estado nutricional adequado permanece uma prioridade em saúde pública. Fazendo uso da abordagem com modelos conceituais de determinação que respeitem relações de hierarquia e temporalidade entre as variáveis analisadas, a identificação de tais fatores modificáveis mostra-se especialmente útil para a interpretação da influência da exposição a uma carga dupla de doença desde os primeiros anos de vida, em uma dinâmica de transição epidemiológica e nutricional na qual a ocorrência de sobrepeso e obesidade é ainda inferior àquela observada em áreas mais desenvolvidas. A presente investigação acompanhou crianças residentes

na Amazônia Ocidental Brasileira e justifica-se, portanto, pela necessidade de fornecer subsídios para uma abordagem mais completa em relação a determinantes do crescimento linear e do ganho de peso de crianças em regiões de baixa e média renda desde fases iniciais de desenvolvimento.

1.4 HIPÓSTESE CENTRAL DE INVESTIGAÇÃO

Há associação entre exposição contínua a condições socioeconômicas e ambientais adversas, morbidade e deficiência de micronutrientes na infância com indicadores do crescimento linear e ganho de peso excessivo na idade escolar?

2 OBJETIVOS

2.1 OBJETIVO GERAL

Investigar prospectivamente determinantes do perfil de crescimento linear e ganho de peso entre crianças residentes no município de Acrelândia, Estado do Acre, Amazônia Ocidental Brasileira.

2.2 OBJETIVOS ESPECÍFICOS

- Identificar evidências disponíveis a partir de estudos longitudinais sobre a relação entre práticas alimentares na primeira infância, padrão de crescimento infantil e estado nutricional exibido na vida adulta (Artigo 1);

- Investigar a influência de fatores socioeconômicos, ambientais, maternos e de primeira infância (exposições distais e intermediárias), aferidos no início da vida, sobre as trajetórias de crescimento linear até a idade escolar (Artigo 2);

- Investigar a influência de fatores socioeconômicos, ambientais, maternos e de primeira infância (exposições distais e intermediárias), aferidos no início da vida, sobre as trajetórias de ganho de peso até a idade escolar (Artigo 3);

- Investigar a influência de indicadores de estado inflamatório, morbidade recente e deficiências nutricionais (exposições proximais) sobre o incremento de peso em crianças (Artigo 4);

- Investigar a influência da interação gene-nutriente, sob a perspectiva de deficiências nutricionais (exposições proximais), sobre o incremento de peso em crianças (Artigo 5);

- Investigar o potencial impacto do ganho de peso na infância sobre a resistência à insulina averiguada na idade escolar (Artigo 6).

3 MÉTODOS

3.1 ÁREA DE ESTUDO

Este estudo integra um conjunto de pesquisas epidemiológicas sobre condições de saúde e nutrição realizadas no município de Acrelândia, Estado do Acre, Amazônia Ocidental Brasileira, em uma parceria estabelecida entre a Universidade Federal do Acre, a Faculdade de Saúde Pública e o Instituto de Ciências Biomédicas da Universidade de São Paulo.

Acrelândia foi criada em 1993 a partir do desmembramento de partes dos municípios de Plácido de Castro e Senador Guiomard, ocupando área de 1.607,5 km^2 na mesorregião do Vale do Acre, entre os rios Abunã e Iquiri (latitude 09º43’ sul, longitude 66º53’ oeste). A cidade está localizada a 112 km da capital Rio Branco e faz fronteiras estaduais ao norte com Amazonas e Rondônia e fronteira internacional ao leste com a Bolívia (FIGURA 2). Suas principais atividades econômicas relacionam-se a agricultura familiar e lavouras permanentes (a exemplo de café e banana), à extração de madeira e castanha-do-Brasil, e à pecuária extensiva.

De acordo com o Índice de Desenvolvimento Humano Municipal (IDH-M)[*], estimativa sintética das dimensões de saúde, educação e renda populacionais, Acrelândia exibia desenvolvimento humano muito baixo no ano 2000 (IDH-M: 0,451), tendo alcançado a classificação de desenvolvimento humano médio em 2010 (IDH-M: 0,604). Durante a referida década, entretanto, a posição relativa ocupada pela cidade segundo o IDH-M caiu da 3.904ª para a 4.055ª colocação, em um total de 5.565 municípios brasileiros. Em todo o período, o IDH-M de Acrelândia manteve-se abaixo da média do IDH para o Estado do Acre e para o Brasil (em 2010: 0,663 e 0,727, respectivamente) (PNUD, 2013).

[*] Para o cálculo do IDH-M, o Programa das Nações Unidas para o Desenvolvimento utilizava, até o relatório referente aos dados coletados no Censo Demográfico de 2000, a média aritmética de três subíndices para expectativa de vida, acesso à educação e padrão de vida (renda). Segundo a metodologia antiga, o IDH-M 2000 de Acrelândia equivaleu a 0,680 –conforme citado em manuscritos que compõem a seção de Resultados e Discussão desta tese. No relatório com dados do Censo Demográfico de 2010, o índice passou por ajustes e foi reformulado como a média geométrica dos referidos subíndices, tendo sua série histórica recalculada. Os valores apresentados na presente seção de métodos consideram a nova metodologia para o IDH-M para fins de comparação.

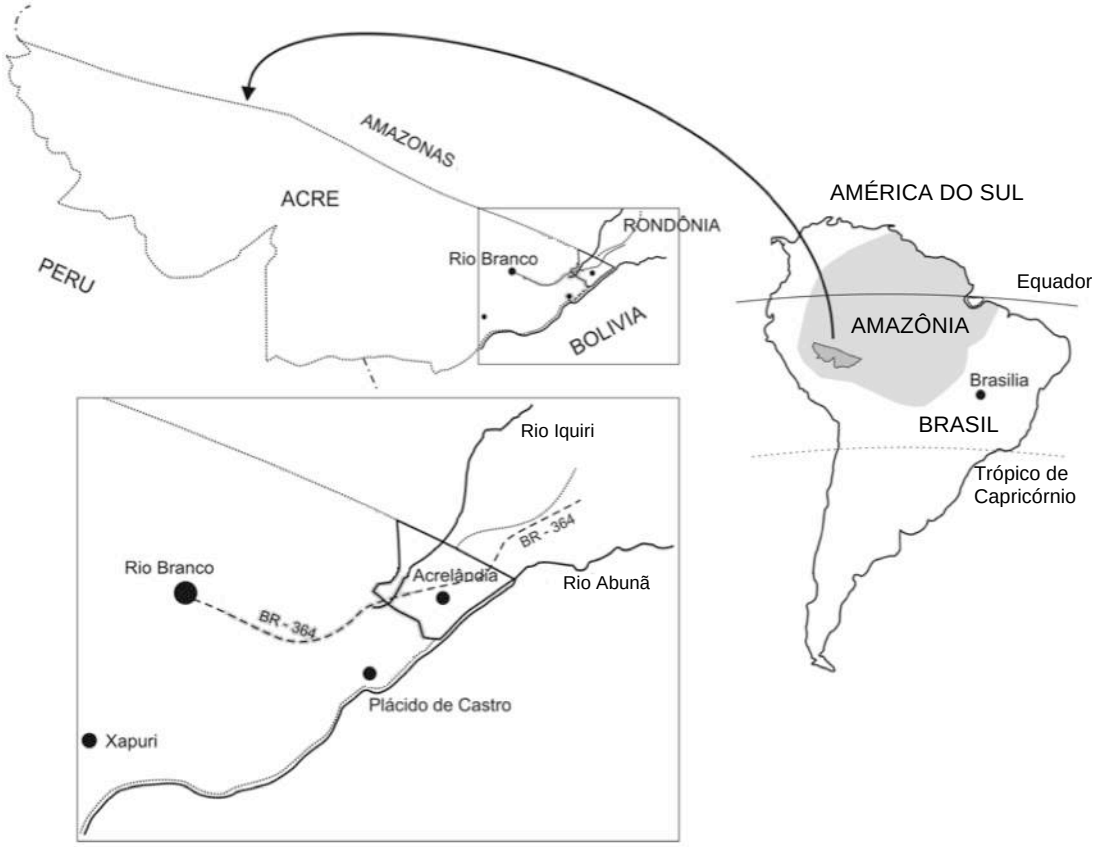

Figura 2 – Localização geográfica do município de Acrelândia, Acre, Brasil. Adaptada de: SOUZA et al. (2007).

3.2 DELINEAMENTO

O presente estudo observacional tem delineamento longitudinal prospectivo, constituído a partir de dois inquéritos transversais de base populacional conduzidos independentemente na área urbana de Acrelândia em janeiro de 2003 e dezembro de 2007, com dois inquéritos de seguimento realizados em dezembro de 2009 e julho de 2012 (FIGURA 3). Para explorar os determinantes do crescimento linear e do ganho de peso durante a infância, os dados coletados foram combinados considerando seguimentos distintos, sendo o primeiro com linha de base em 2003 e acompanhamento em 2007 e 2009 (seguimento 2003–2009), e o segundo com linha de base em 2007 e acompanhamento em 2009 e 2012 (seguimento 2007–2012).

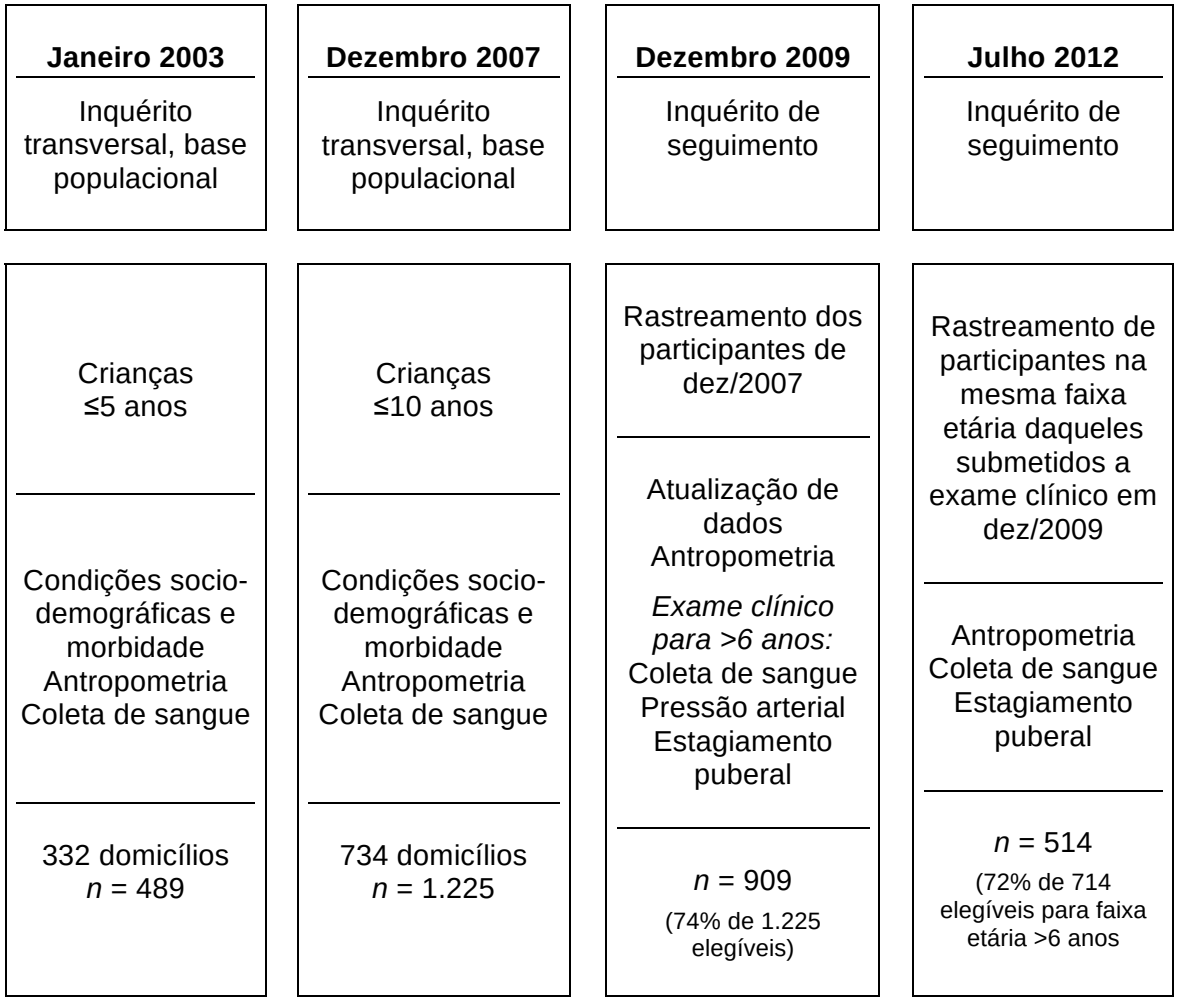

Figura 3 – Delineamento do estudo entre crianças residentes na área urbana de Acrelândia, 2003–2012.

3.3 ASPECTOS ÉTICOS

Em todas as fases do trabalho de campo em Acrelândia, a equipe de pesquisa identificou-se devidamente durante visitas domiciliares e expôs objetivos, metodologia, riscos e benefícios do estudo. Um termo de consentimento livre e esclarecido para participação voluntária foi coletado dos pais e/ou responsáveis pelas crianças antes do recrutamento, com a garantia de sigilo das informações prestadas, acesso aos resultados do estudo e possibilidade de recusar participação a qualquer momento sem nenhum prejuízo. Todos os resultados foram entregues às famílias dos participantes e ofereceu-se tratamento completo conforme orientação médica da equipe de pesquisadores quando necessário.

Os inquéritos que compõem o presente estudo têm a aprovação dos Comitês de Ética em Pesquisa da Universidade Federal do Acre e da Faculdade de Saúde Pública da Universidade de São Paulo. O protocolo de pesquisa para a análise dos dados longitudinais foi submetido ao Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo e aprovado sob o nº. 2083 (ANEXO 4).

3.4 POPULAÇÃO DE ESTUDO E PROCEDIMENTOS DE CAMPO

Em 2003, a população estimada de Acrelândia era de 8.697 habitantes, dos quais 43% residiam na área urbana (IBGE, 2003). Para o primeiro inquérito transversal de base populacional no município, todos os 334 domicílios da área urbana com crianças até 5 anos de idade foram identificados por meio de um levantamento realizado com auxílio dos registros das equipes locais do Programa Saúde da Família (MUNIZ et al., 2007). Destes, houve apenas duas recusas para participação no estudo. A coleta de dados foi realizada, portanto, em 332 domicílios, envolvendo 489 crianças ≤5 anos.

Um segundo inquérito transversal de base populacional foi conduzido em Acrelândia no ano de 2007 (CARDOSO et al., 2012). À época, a população estimada era de 11.520 habitantes, sendo que aproximadamente 44% residiam na área urbana do município (IBGE, 2007). Fazendo uso da mesma estratégia junto ao Programa

Saúde da Família, 749 domicílios com crianças até 10 anos de idade foram identificados, dos quais 13 recusaram participação e outros dois estavam fechados, sem possibilidade de contato. Dessa forma, 1.225 crianças ≤10 anos residindo em 734 domicílios na área urbana foram inicialmente recrutadas.

A coleta de dados dos inquéritos transversais de base populacional realizados em Acrelândia em janeiro de 2003 e dezembro de 2007 foi baseada na aplicação de um questionário estruturado durante entrevistas domiciliares para identificação de: (a) sexo e data de nascimento da criança, registrados diretamente de certidões de nascimento ou cartões de saúde da criança; (b) condições socioeconômicas (presença de bens para cálculo de índice de riqueza, posse de terra, escolaridade dos pais, presença do pai no domicílio, trabalho materno e número de residentes) e ambientais do domicílio (condições de moradia, tipo de esgoto e de abastecimento de água, coleta de lixo); (c) características reprodutivas maternas, incluindo idade materna e intercorrências durante a gestação; (d) história nutricional da criança, incluindo práticas alimentares relacionadas à duração de aleitamento materno total e exclusivo, época de desmame e introdução de alimentos complementares, e consumo de alguns grupos de alimentos; e (e) morbidade recente (ocorrência de diarreia, febre, vômitos, tosse e chiado no peito nos 15 dias que antecederam a visita domiciliar, malária, pneumonia e hospitalizações nos últimos 12 meses). O peso e o comprimento ao nascer da criança foram registrados pela equipe de pesquisa segundo informações presentes no cartão de saúde da criança.

Após a entrevista domiciliar, as crianças e seus responsáveis foram convidados para uma visita a uma unidade do Programa de Saúde da Família local para realização de um exame clínico em horários previamente agendados. Em ambas as fases do trabalho de campo, a equipe de pesquisadores conduziu uma avaliação antropométrica para verificação de peso e comprimento ou altura corporal de todas as crianças recrutadas, fazendo uso de procedimentos padronizados e equipamentos calibrados para tomar todas as medidas em duplicata. Seguindo os mesmos procedimentos, o peso e a altura das mães foram medidos diretamente pela equipe. Finalmente, amostras de fezes e amostras de sangue venoso em jejum foram obtidas das crianças participantes. No inquérito de 2003, os exames laboratoriais de sangue quantificaram as concentrações de hemoglobina, ferritina e receptor solúvel de

transferrina, visando à identificação de casos de anemia, deficiência de ferro e anemia por deficiência de ferro. Em 2007, além do diagnóstico de anemia e estado de ferro, as amostras sanguíneas foram utilizadas para quantificação de proteína C-reativa, vitaminas A, D, E, B12, folato, beta-caroteno, licopeno, perfil lipídico e genotipagem de polimorfismos de interesse.

Dois inquéritos de seguimento foram planejados a partir do estudo de 2007. Para tanto, após a realização de um estudo piloto em julho de 2009 para averiguar as condições de seguimento, programou-se um novo levantamento de todos os domicílios de Acrelândia por meio da equipe de agentes comunitários de saúde. Visando facilitar o rastreamento da maior parcela possível de crianças avaliadas anteriormente, os registros de informações de endereço e contato obtidas por meio do levantamento foram comparados ao banco de dados do inquérito transversal de 2007, de forma a atualizar o cadastro dos domicílios participantes no estudo, sempre que possível.

Em dezembro de 2009, o inquérito de seguimento atualizou as informações referentes à saúde da criança, às condições socioeconômicas e ambientais do domicílio e à frequência de consumo de alguns grupos de alimentos por meio de questionário estruturado semelhante ao aplicado na linha de base, durantes visitas domiciliares a todas as crianças recrutadas no inquérito de 2007. Na ocasião das visitas, a equipe de pesquisa também conduziu exame antropométrico para verificação de peso e altura das crianças e de suas mães. Adicionalmente, realizou-se um exame clínico em uma unidade do Programa de Saúde da Família para estagiamento puberal, rastreamento de sintomas de asma, avaliação de pressão arterial e coleta de sangue, entre aquelas acima de 6 anos de idade. As amostras sanguíneas foram utilizadas para quantificação das concentrações de hemoglobina, ferritina, receptor solúvel de transferrina, proteína C-reativa, vitaminas A, D, E, beta-caroteno, licopeno, glicose e insulina.

Por fim, em julho de 2012 conduziu-se a última fase de trabalho de campo entre crianças que iniciaram participação no estudo em 2007. O inquérito de seguimento foi focado no rastreamento de participantes a partir de 6 anos de idade, em faixa etária equivalente a das crianças que realizaram o exame clínico em 2009. A estratégia de rastreamento das crianças elegíveis para participação utilizou os

registros presentes no banco de dados do inquérito de 2009 para otimizar as chances de localização e contou com o auxílio da equipe de agentes comunitários de saúde de Acrelândia para atualização cadastral dos indivíduos que atendiam ao critério de idade previamente estabelecido. A equipe de pesquisa realizou exame clínico uma unidade do Programa de Saúde da Família do município, incluindo avaliação antropométrica, estagiamento puberal, teste de espirometria e coleta de sangue.

3.5 CASUÍSTICA PARA ANÁLISE

No seguimento 2003–2009, de um total de 489 crianças inicialmente incluídas na linha de base, 250 participantes foram também examinados no inquérito de 2007, após processo de cruzamento das informações presentes nos bancos de dados dos inquéritos transversais de 2003 e 2007. No inquérito realizado em 2009, 205 crianças foram novamente localizadas, sendo 193 crianças avaliadas em 2003 e 2007 e outras seis crianças que foram recrutadas em 2003 mas não haviam participado no inquérito de 2007. Assim, o período mediano de acompanhamento de crianças avaliadas em 2003 e em pelo menos mais um momento no seguimento 2003–2009 equivaleu a 6,9 anos, com variação entre 4,9 a 7,5 anos.

No seguimento 2007–2012, por sua vez, das 1.225 crianças avaliadas na linha de base, 909 foram identificadas em 2009. Na última fase de trabalho de campo, conduzida em 2012, foram localizadas 514 crianças (de um total de 714 participantes elegíveis segundo a faixa etária almejada para o exame clínico), as quais haviam sido anteriormente avaliadas em 2007 e 2009. O período mediano de acompanhamento de crianças avaliadas inicialmente em 2007 e em pelo menos mais um momento no seguimento 2007–2012 foi de 4,6 anos, variando entre 1,7 e 4,7 anos.

3.6 DEFINIÇÃO DE DESFECHOS E VARIÁVEIS DE EXPOSIÇÃO DE INTERESSE PARA ANÁLISE DE DADOS

3.6.1 Análise de Crescimento Linear e Ganho de Peso: Artigos 2–5

Os determinantes do crescimento linear e do ganho de peso durante a infância foram avaliados nos Artigos 2 a 5 da presente tese, conforme exposto na seção de Resultados e Discussão a seguir. Para tanto, os desfechos de interesse no presente estudo longitudinal foram, respectivamente, as mudanças observadas ao longo do seguimento nos escores Z de comprimento ou altura e de IMC para idade e sexo de acordo com as curvas de crescimento da Organização Mundial da Saúde.

A definição das variáveis de exposição de interesse, bem como das covariáveis de ajuste, foi baseada em um modelo conceitual geral para análise conforme FIGURA 4 a seguir. Tendo em vista as medidas disponíveis nas linhas de base de 2003 e 2007, o modelo apresenta diferentes níveis possíveis de determinação dispostos de forma hierárquica em relação aos desfechos estudados. Progressivamente, dos determinantes mais distais aos determinantes mais proximais, cada nível exerce potencial influência sobre os níveis inferiores, obedecendo uma sequência temporal de acontecimentos (VICTORA et al., 1997).

Figura 4 – Modelo conceitual de análise de determinantes do crescimento linear e ganho de peso até a idade escolar.

Assume-se o controle por características biológicas da criança desde o início do modelo conceitual, incluindo idade e sexo. No nível mais distal de determinação (nível 1), foram incluídas as variáveis socioeconômicas, além de cor da pele e genótipo, quando aplicável, seguidas de variáveis ambientais do domicílio e reprodutivas maternas como possíveis determinantes intermediários no nível 2. Os blocos de características da criança ao nascimento (nível 3), práticas alimentares na primeira infância (nível 4), indicadores de morbidade recente (nível 5), estado nutricional na linha de base (índices antropométricos, deficiências de vitaminas e minerais, e frequência do consumo de alguns grupos alimentares; nível 5), e estágio de maturação sexual (nível 6) foram alocados como possíveis determinantes mais proximais das mudanças observadas nos escores Z de altura e de IMC para idade e sexo.

Considerando a disponibilidade de informações na linha de base, os determinantes relativos aos níveis 1 a 4 da Figura 2 foram estudados especificamente nos Artigos 2 e 3 desta tese. Os referidos artigos empregaram os dados do seguimento 2003–2009 para investigar, respectivamente, o padrão de crescimento linear e a trajetória do IMC da primeira infância até a idade escolar.

Fatores associados ao déficit de altura e ao sobrepeso entre as crianças de Acrelândia foram explorados no corte transversal de 2007 (ANEXO 5). A partir desses achados, os Artigos 4 e 5 desta tese foram planejados com dados do seguimento 2007–2012, de forma a enfocar determinantes mais proximais, relativos ao nível 5 do modelo conceitual exposto, com influência sobre o ganho de peso durante a infância.

Instrumentos e técnicas de mensuração, critérios de classificação inerentes às variáveis utilizadas e métodos estatísticos empregados encontram-se detalhados e devidamente referenciados na descrição de métodos em cada um dos artigos originais que compõem esta tese, na seção de Resultados e Discussão a seguir.

3.6.2 Análise de Desfechos Metabólicos: Artigo 6

Para complementar a discussão dos determinantes do ganho de peso até a idade escolar no seguimento com linha de base em dezembro de 2007, foram

investigados fatores associados em um período de dois anos a desfechos metabólicos medidos na subamostra de participantes que realizou o exame clínico no inquérito de dezembro de 2009. No Artigo 6 da presente tese, consideraram-se como desfechos concentrações sanguíneas de glicose e insulina, resistência à insulina e pressão arterial sistólica e diastólica, mensurados na idade escolar. As exposições de interesse obedeceram à disposição geral de níveis exposta no modelo conceitual da Figura 4, com acréscimo da variação de IMC entre os inquéritos de 2007 e 2009 como principal determinante investigado, no nível mais proximal aos desfechos estudados –equivalente a um sexto nível no modelo.

Instrumentos e técnicas de mensuração, critérios de classificação inerentes às variáveis utilizadas e métodos estatísticos empregados também encontram-se detalhados na descrição de métodos do Artigo 6, na seção de Resultados e Discussão a seguir.

4 RESULTADOS E DISCUSSÃO

Esta tese de doutorado é composta ao todo por seis artigos, sendo um artigo de revisão em tópico pertinente à temática abordada e cinco artigos originais que combinam dados dos seguimentos 2003–2009 e 2007–2012 em Acrelândia, a saber:

- Lourenço BH, Cardoso MA. Infant feeding practices, childhood growth and obesity in adult life. *Arquivos Brasileiros de Endocrinologia e Metabologia*. 2009;53:528-539. DOI: 10.1590/S0004-27302009000500006.

- Lourenço BH, Villamor E, Augusto RA, Cardoso MA. Determinants of linear growth from infancy to school-aged years: a population-based follow-up study in urban Amazonian children. *BMC Public Health*. 2012;12:265. DOI: 10.1186/1471-2458-12-265.

- Lourenço BH, Villamor E, Augusto RA, Cardoso MA. Influence of early life factors on body mass index trajectory during childhood: a population-based longitudinal analysis in the Western Brazilian Amazon. *Maternal & Child Nutrition*. 2012. DOI: 10.1111/mcn.12005.

- Lourenço BH, Cardoso MA, for the ACTION Study Team. C-reactive protein concentration predicts change in body mass index during childhood. *Plos One*. 2014;9:e90357. DOI: 10.1371/journal.pone.0090357.

- Lourenço BH, Qi L, Willett WC, Cardoso MA, for the ACTION Study Team. *FTO* genotype, vitamin D status and weight gain during childhood. *Diabetes*. 2014;63:808-814. DOI: 10.2337/db13-1290.

- Lourenço BH, Gimeno SGA, Cardoso MA, for the ACTION Study Team. Prospective weight gain and metabolic outcomes in school-aged children living in the Brazilian Amazon. 2014.

4.1 ARTIGO 1

Infant feeding practices, childhood growth and obesity in adult life

Bárbara Hatzlhoffer Lourenço, Marly Augusto Cardoso

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DOI: 10.1590/S0004-27302009000500006.

Infant feeding practices, childhood growth and obesity in adult life

Práticas alimentares na infância, crescimento infantil e obesidade na vida adulta

Bárbara Hatzlhoffer Lourenço[1], Marly Augusto Cardoso[1]

ABSTRACT

Child health is widely affected by nutritional status, and there is growing interest surrounding the possibility that child nutritional status and infant feeding practices may be linked to obesity in adulthood, increasing risks of metabolic complications. Prospective studies enable appropriate investigation and evaluation of the determinants of childhood development. The present paper therefore aimed to provide a review of the main evidence to date from longitudinal studies concerning the associations of infant feeding practices, patterns of childhood growth and nutritional status exhibited in adult life. Arq Bras Endocrinol Metab. 2009;53(5):528-39.

Keywords

Infant feeding practices; diet; growth; overweight; obesity

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RESUMO

A saúde infantil é amplamente afetada pelo estado nutricional. Há um interesse crescente acerca da possibilidade do estado nutricional apresentado pela criança e das práticas alimentares na primeira infância estarem relacionados à obesidade em indivíduos adultos, aumentando os riscos para complicações metabólicas. Sabe-se que estudos prospectivos possibilitam a investigação e a avaliação apropriadas de determinantes do desenvolvimento infantil. Consequentemente, o presente artigo objetivou revisar as principais evidências disponíveis a partir de estudos longitudinais sobre associações entre práticas alimentares na primeira infância, padrões de crescimento infantil e estado nutricional verificados durante a vida adulta. Arq Bras Endocrinol Metab. 2009;53(5):528-39.

Descritores

Práticas alimentares na infância; dieta; crescimento; sobrepeso; obesidade

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INTRODUCTION

Child health is widely affected by nutritional status. Malnutrition encompasses different forms of undernutrition as well as obesity, and, when detected in early life, commonly leads to permanent damage which, in turn, can also affect future generations (1). There is growing interest surrounding the possibility that child nutritional status and infant feeding practices may be linked to abdominal obesity in adult life, increasing risks of metabolic complications.

Along these lines, a number of cross-sectional investigations have been conducted among developing countries. In Brazil, Hoffman and cols. (2,3) performed a resident study to examine metabolic and dietetic variables in a group of shantytown stunted and normal height children. They concluded that the condition of childhood stunting was associated with impaired fat oxidation and with opportunistic overeating, revealing that stunted children may be at increased risk of excess weight gain over time under favorable environmental conditions. In another study among a rural low-income Mexican population, a community-based survey indicated that stunting coexisted with overweight and obesity in pre-school children aged 24 to 72 months, especially in conjunction with lower socioeconomic status (4).

Likewise, investigating the relationship between infant feeding practices and overweight, Jingxiong and cols. (5) evaluated children aged 12 to 35 months in a sub-sample from randomly selected communities drawn from an urban area of Beijing. Even in this young age

group, they were able to demonstrate that, compared to their normal weight peers, a lower percentage of overweight children were breastfed for, at least, four months, while these children also received significantly more infant formulas or semi-solid food during their first four months of life.

Bearing in mind that prospective studies enable appropriate investigation and evaluation of the determinants of childhood development, the present paper aimed to provide a review of the main evidence to date from longitudinal studies concerning the associations of infant feeding practices, patterns of childhood growth and nutritional status exhibited in adult life.

METHODS

Relevant articles published between 1980 and 2009 were identified by searching the MedLine database (National Library of Medicine, Bethesda, MD, USA). Search terms included birth cohort or longitudinal studies, infant feeding practices, childhood growth, adolescence, adulthood, obesity and weight gain. Studies were examined through their abstracts and included in the review if they prospectively examined the association of feeding practices assessed in early life (e.g. breastfeeding, use of milk thickeners, complementary diet, from birth to three years) or dietary factors throughout childhood (e.g. energy and/or nutrient intake, dietary patterns, household food insecurity status) with parameters of childhood growth and/or obesity in adult life. Articles were classified according to sample size, length of follow-up, exposure variables analyzed, main outcomes and key findings.

OVERVIEW OF STUDIES AND MAIN FINDINGS

Applying the inclusion criteria, 22 relevant original articles were included in this review following the literature search. The main findings of each of these articles are depicted in tables 1 and 2, which also include exposures and outcomes evaluated. In table 1, studies that assessed specific infant feeding parameters as exposures of interest – such as breastfeeding duration, bottle-feeding, introduction of complementary or solid food and use of formulas and milk thickeners – are listed. Additionally, table 2 summarizes studies that appraised other dietary factors as exposures of interest, mainly related to food, nutrient and energy intake.

Studies defined different aspects of infant feeding practices. Duration of total breastfeeding was established in weeks or months before full weaning, and the dichotomous variable "ever breastfed" was also commonly applied. Exclusive breastfeeding, defined as no supplementing with formula, evaporated milk or other solid or fluid foods beyond breast milk, was extremely short. Furthermore, some investigations were unable to determine the exact beginning of supplemental feeding among their subjects. As a result, predominant breastfeeding (breast milk in addition to water and/or teas, only) and partial breastfeeding (breast milk used in combination with other milk supplements and foods) were most frequently assessed. Age at formula and complementary food or solid food introduction in weeks or months was also estimated in several studies. Food, energy and nutrient intakes had been analyzed using different dietary assessment methods, such as multiple-pass 24-hour recalls, and weighted or unweighted dietary records, ranging from one to four-day records. More specific features and designations of each study will be described when discussing their results.

Overweight and obesity status during childhood were evaluated in some studies – included in this review. Nevertheless, classification criteria varied among authors. The assessments of childhood overweight and obesity were based on:

- the National Center for Health Statistics (NCHS) and World Health Organization (WHO) 1977 growth charts;
- the NCHS and Center for Disease Control and Prevention (CDC) 2000 growth charts;
- the International Obesity Task Force (IOTF) body mass index (BMI) cut-off points based on age-specific values (from 2 to 18 years) that project to the adult cut-offs of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity, using data from six different reference populations (6).
- A brief description of the criteria adopted in each study will be provided.

Overall, the analyses of these articles included 105 to 177,304 subjects, and the period of follow-up varied from 1 to 62 years. These 22 publications draw conclusions from 19 separate longitudinal investigations conducted in different countries, namely, Australia, Brazil, Denmark, Finland, Sweden, the United Kingdom and the United States, as shown in tables 1 and 2. According to the distribution found in the tables of this review, studies are discussed under the following sections.

Table 1. Longitudinal studies on the associations of infant feeding practices, childhood growth and nutritional status in adult life

Study	City, country	Sample's characteristics	Period of follow-up	Main dietary exposures	Outcomes	Findings
Wilson and cols. (14)	Dundee, United Kingdom	n = 545 45.9% male Dundee Infant Feeding Study	7 years	Duration of breast and formula feeding, age of introduction of formula and solid foods	Growth and BC (skinfold thickness and electrical impedance) in childhood	Inverse association between age of introduction of solid foods and weight ($p < 0.025$) and percentage of body fat ($p < 0.01$) at 7 years. Adjusted for sex, birth weight, weight at first solid feed
Tulldahl and cols. (17)	Sweden	n = 781 50.7% male 194 individuals with dual energy X-ray data	2 years	BF duration (data assessed at 15 to 16 years, retrospectively)	High BMI and BC (dual energy X-ray) at 17 to 18 years	Inverse association between exclusive BF < 2 months and BMI (χ^2 test; $p = 0.038$). No significant association between BF duration and BC. No adjustment for confounders
Ong and cols. (13)	Avon, United Kingdom	n = 1,335 ALSPAC Children in Focus Cohort	5 years	Breast or bottle feeding	Childhood growth (weight and length or height) from birth to 5 years	Breastfed children showed a slower weight and length gain when compared to bottle-fed children, despite having similar birth weight. Weight was significantly different at 31 months ($p = 0.02$), excluding maternal smokers.
Victora and cols. (18)	Pelotas, Brazil	n = 2,250 Only male Pelotas Birth Cohort Population based	18 years	Total and predominant BF duration	Adiposity at 18 years (BMI, OW and OB, lean and fat mass by electrical impedance)	No association between total and predominant BF and overweight status, mean BMI, lean and fat mass Protective relationship between total BF duration and obesity (for total BF ≥ 12 months, OR = 0.41; $p = 0.006$), and between predominant BF duration and obesity ($p = 0.03$ for linear trend). Adjusted for family income, maternal education, maternal BMI, skin color, maternal smoking during pregnancy, gestational age, birth weight, current behavioral variables – smoking, alcohol drinking, type of diet and physical activity
Bogen and cols. (11)	Ohio, USA	n = 73,458 72.0% white Low-income children Retrospective cohort study	4 years	BF duration with and without concurrent formula usage	Prevalence of obesity at 4 years	For white children whose mothers did not smoke during pregnancy, BF showed a protective effect against obesity at 4 years: OR = 0.55 (95%CI = 0.42-0.71) for BF > 26 weeks without early formula introduction. Adjusted for maternal age, education, parity, marital status, pregnancy conditions, delivery method, child sex, birth weight, birth year, birth order
Grummer-Strawn and cols. (12)	USA	n = 17,7304 52.1% white non-Hispanic Low-income children enrolled in public health programs 12,587 children with mothers' data available	4 years	BF duration	OW at 4 years	Dose-response, protective relationship of BF duration with the risk of OW among non-Hispanic whites: BF for 6 to 12 months, OR = 0.70 (95%CI = 0.50-0.99); BF > 12 months, OR = 0.49 (95%CI = 0.25-0.95). Adjusted for child's gender, birth weight, race/ethnicity, and mother's age, education, pre-pregnancy BMI, weight gain during pregnancy, postpartum smoking
Baker and cols. (7)	Denmark	n = 3,768 50.5% male Denmark National Birth Cohort	1 year	Duration of any BF and CF introduction	Infant weight gain from birth to 1 year	Positive association between weight gain from birth to 1 year and decreasing duration of any BF and earlier introduction of CF, especially at the lowest quartile of any BF ($p < 0.0001$). At longer durations of any BF, timing of CF introduction was not associated with weight gain. Adjusted for primiparity, gestational weight gain, duration of gestation, smoking during pregnancy, infant sex, infant birth weight, infant length at 1 year, infant age at time of the 1-year anthropometric measurements

Table 1. Longitudinal studies on the associations of infant feeding practices, childhood growth and nutritional status in adult life (cont.)

Study	City, country	Sample's characteristics	Period of follow-up	Main dietary exposures	Outcomes	Findings
Agras and cols. (16)	San Francisco, USA	n = 150 49.3% male	9.5 years	Infant feeding practices and behaviors, childhood eating behaviors, 24 hours child caloric intake	Development of childhood OW	Positive association between OW at 9.5 years and tantrums over food during childhood (R = 0.26), which in turn correlate significantly with anger/frustration (R = 0.25) and soothability (R = -0.24)
Stettler and cols. (15)	USA	n = 5,479 (individuals with information on initial infant feeding method) National Collaborative Perinatal Project (CPP)	7 years	BF initiation*	OW at 7 years	No significant association between BF initiation and overweight at 7 years (OR = 1.28; 95%CI = 087-1.88). No interaction detected for BF initiation in association of early rate of weight gain and overweight at 7 years
Nelson and cols. (20)	USA	n = 11,998 850 sibling pairs were assessed to account for unmeasured genetic and environmental factors National Longitudinal Study of Adolescent Health	2 years	Duration of any BF	Adolescent OW	Inverse association between duration of any BF and OW among girls in the full cohort: BF ≥ 9 months, OR = 0.78 (95%CI = 0.64-0.96). No significant associations found in sibling pairs analyses. Adjustment for confounders in full cohort (ethnicity, family income) and in sibling pairs (age, sex, birth order, low birth weight status)
Santos and cols. (9)	Pelotas, Brazil	n = 596 Pelotas Birth Cohort	1 to 4 years	Use of milk thickeners between 3 and 6 months	Weight, length/height, and anthropometric indices (WA, L/HA, WL/H) at 1 and 4 years	Positive association between use of milk thickeners and weight (β = 0.160; 95%CI = 0.009-0.312), length (β = 0.540; 95%CI = 0.141-0.939), WA (β = 0.155; 95%CI = 0.013-0.296) and LA (β = 0.188; 95%CI = 0.051-0.325) at 1 year. No significant associations between use of milk thickeners and anthropometric indices at 4 years. Adjusted for maternal skin color, age, education, marital status, parity, multiple birth, birth weight, gestational age, sex, cough, hospitalization, anthropometric parameters at 3 months
Araújo and cols. (10)	Pelotas, Brazil	n = 1,273 49.2% male 76.9% white Pelotas Birth Cohort Population based	4 years	BF duration (total and predominant) and ever breastfed	Prevalence of OW and WH at 4 years	No linear trends and no significant associations between duration of total and predominant BF and outcomes (p > 0.05). OR = 1.83 (95%CI = 0.53-6.28) for OW if ever breastfed. Coefficient = 0.24 (95%CI = -0.09-0.57) for mean WH if ever breastfed. Adjusted for infant sex, skin color and birth weight, assets index, maternal schooling, smoking during pregnancy, pregestional BMI and weight gain during pregnancy
Michels and cols. (19)	USA	n = 35,526 Only female 96% Caucasian white Nurses' Health Study II (1989-2001) Nurses' Mothers' Cohort Study (maternal report of infant feeding practices, familial, maternal and birth variables)	12 years	BF initiation and duration	OW and OB at 18 years and in adulthood (mean age of breastfed nurses = 40.5 years; not breastfed nurses = 39.3 years)	No significant association between BF initiation or duration and OW and OB at 18 years and in adulthood. Adjusted for age of nurse, year of birth of the nurse, maternal pre-pregnancy weight and weight gain during pregnancy, birth weight and gestational age of the nurse, mother's and father's education and occupation, home ownership of parents at time of nurse daughter's birth, age of nurse at menarche, parity of nurse, nurse's age at first birth, nurse's physical activity, daily energy intake

Table 1. Longitudinal studies on the associations of infant feeding practices, childhood growth and nutritional status in adult life (cont.)

Study	City, country	Sample's characteristics	Period of follow-up	Main dietary exposures	Outcomes	Findings
Griffiths and cols. (8)	England, Wales, Scotland and Northern Ireland, United Kingdom	n = 10,533 49.9% male UK Millennium Cohort Study – MCS Nationally representative	3 years	BF initiation and duration, age of introduction of solid foods	Conditional weight gain z-score from birth to 3 years (adjusted for birth weight)	Conditional weight gain was significantly higher among infants given no breast milk (R = 0.06; 95%CI = 0.02-0.09). Negative association between conditional weight gain and BF duration (R = 0.05; 95%CI = 0.01-0.09; adjusted for age of introduction of solid food). Overall adjustment (3-year height z-score, maternal social class, pre-pregnancy BMI, parity, smoking during pregnancy)
O'Tierney and cols. (21)	Helsinki, Finland	n = 1,823 Breastfed individuals belonging to sibships Helsinki Birth Cohort	62 years	BF duration	Later BMI and adiposity (percentage of body fat measured by electrical impedance)	Negative association between BF duration and BMI at 1 year ($p < 0.05$ for linear trend), which disappeared at 7 years. U-shaped association between BF duration and BMI ($p = 0.08$ for quadratic trend) and percentage of body fat ($p = 0.03$ for quadratic trend) in later life. Adjusted for sex, year of birth, size of sibship

* Assumed in Stettler and cols. (2002) study as a potential confounder in the relationship between early rate of weight gain and overweight at 7 years.

BF: breastfeeding; BMI: body mass index; BC: body composition; OW: overweight; OB: obesity status; OR: odds ratio; 95%CI: 95% confidence interval; R: regression coefficient; CF: complementary food; weight for age, length/ height for age, weight for length/height z scores: WA, L/HA, WL/H, respectively.

Table 2. Longitudinal studies on the associations of dietary factors and body composition throughout childhood and adult life

Study	City, country	Sample's characteristics	Period of follow-up	Main dietary exposures	Outcomes	Findings
Magarey and cols. (27)	Adelaide, Australia	n = 143-243 between ages 2 and 15 years* 51.1-57.9% male between ages 2 and 15 years Adelaide Nutrition Study	13 years	Energy-adjusted macronutrient intake at 2, 4, 6, 8, 11, 13 and 15 years (assessed through 3 to 4 days weighted dietary records)	Body fatness at 2, 4, 6, 8, 11, 13 and 15 years (BMI, TC and SS)	Positive association between fat intake and SS ($\beta = 0.008$; $p = 0.003$) and negative association ($\beta = -0.003$; $p = 0.006$) between carbohydrate intake and SS across 2 to 15 years according to generalized estimating equations. In multiple regression analyses, macronutrient intake was not a good predictor for adiposity in successive ages. Adjusted for gender parental adiposity, total energy intake, level of fatness at the begging of age interval)
Hoppe and cols. (26)	Copenhagen, Denmark	n = 105 48.6% male Copenhagen Cohort Study on Infant Nutrition and Growth	10 years	Protein intake in infancy (9 months)	Body size and composition in late childhood (10 years)	No significant association between fatness in late childhood and protein intake at 9 months. Adjusted for sex, energy from protein was a predictor of weight ($\beta = 0.44$; 95%CI = 0.12-0.76) and height ($\beta = 0.51$; 95%CI = 0.13-0.90) at 10 years. Associations were attenuated and/or disappeared following inclusion of parental size and body size at 9 months in regression models
Laitinen and cols. (28)	Lapland and Oulu, Finland	n = 5,771 49.2% male Northern Finland 1966 Birth Cohort Study	31 years	AC at 14 and 31 years, healthy or unhealthy diet (depend on frequency of intake of foods rich in fiber and consumption of sausages) at 31 years	AO at 31 years	Positive association between AO in men and high AC at 31 years (OR = 1.82; 95%CI = 1.17-2.85) and unhealthy diet (OR = 1.53; 95%CI = 1.03-2.27), considering BMI at 31 years in regression model. Positive association between AO in women and regular AC at 14 years (OR = 2.63; 95%CI = 1.44-4.80), but it disappeared when BMI at 31 years was included in model. Among women, AC at 31 years showed a dose-response, protective relationship with AO (for highest AC at 31 years, OR = 0.54; 95%CI = 0.34-0.85), considering BMI at 31 years in regression model. Adjusted for maternal age and BMI before pregnancy, and parity and use of hormonal contraception at 31 years among women

Table 2. Longitudinal studies on the associations of dietary factors and body composition throughout childhood and adult life (cont.)

Study	City, country	Sample's characteristics	Period of follow-up	Main dietary exposures	Outcomes	Findings
Garnett and cols. (25)	Sydney, Australia	n = 342 280 individuals completed dietary assessment Longitudinal Nepean Study	5.4 years	Nutrient intake at 7 to 8 years (assessed through 3-day food record)	Total adiposity (BMI) and central adiposity (waist circumference) at 12 to 13 years	No significant association between OW and OB at 12 to 13 years (according to BMI or waist circumference) and macronutrient intake at 7 to 8 years. No adjustment for confounders
Rose and Bodor (23)	USA	n = 16,889 51.4% male 58.8% white 12,890 individuals with data about weight gain ECLS-K – Early Childhood Longitudinal Study-Kindergarten Cohort Nationally representative	2 years	Household food insecurity at 6 years	Child OW at 6 years and 2 years later	Protective relationship between food insecurity and OW at 6 years (OR = 0.80; 95%CI = 0.66-0.98). Considering child OW 2 years later, food insecurity was also inversely associated with OW (OR = 0.73; 95%CI = 0.57-0.93). Adjusted for gender, age, race/ethnicity, birth weight, maternal schooling, poverty index ratio, country region, urbanization, physical activity, family meal patterns
Ong and cols. (24)	Avon, United Kingdom	n = 881 ALSPAC Children in Focus Cohort	5 years	Total dietary energy intake from a 1-day unweighted dietary record at 4 months in breastfed and formula- or mixed-fed children	Weight gain from birth to 5 years	Positive association between energy intake at 4 months and rates of rapid weight gain from 0 to 2 years ($p < 0.0001$ for trend). Higher energy intake at 4 months predicted larger weight and BMI at 1, 2, 3 (OR = 1.46; 95%CI = 1.20-1.78) and 5 years (OR = 1.25; 95%CI = 1.00-1.55) only among formula- or mixed-fed children. Adjusted for gender, body weight at 4 months
Butte and cols. (22)	Houston, USA	n = 879 Hispanic 4 to 19 years children Viva La Familia Study	1 year	Food intake (assessed through two multiple-pass dietary 24-hours recalls)	1-year weight gains	Positive correlation between weight gain and energy intake normalized for fat-free mass and fat mass and energy from fats ($p < 0.05$). Negative correlation between weight gain and energy from carbohydrates ($p = 0.007$). Adjusted for age, age squared, sex, and Tanner stage, the final model to predict weight gain did not retain these dietary variables as independent predictors

TC: triceps skinfolds; SS: subscapular skinfolds; 95%CI: 95% confidence interval; AC: abdominal circumference; AO: abdominal obesity; OW: overweight; OB: obesity.
* Magarey and cols. (27): at 2 years: n = 153 (57.5% male); at 4 years: n = 155 (56.8% male); at 6 years: n = 152 (57.9% male); at 8 years: n = 143 (54.5% male); at 11 years: n = 243 (53.5% male); at 13 years: n = 237 (51.1% male); at 15 years: n = 218 (52.3% male).

Infant feeding practices

During one year after birth, Baker and cols. (7) followed 3,768 boys and girls belonging to the Denmark National Birth Cohort. They observed infant weight gain over this period according to duration of any kind of breastfeeding and to introduction of complementary food (mush or porridge). Analyses were controlled for some confounding variables, including primiparity, gestational weight gain, duration of gestation, smoking during pregnancy, infant sex, infant birth weight, infant length at one year, and infant age at time of one-year anthropometric measurements. Weight gain from birth to one year was positively associated with decreasing duration of any breastfeeding and earlier introduction of complementary food, especially within the lowest quartile of any breastfeeding ($p < 0.0001$). Nonetheless, in longer duration of any breastfeeding, timing of complementary food introduction was not associated with weight gain.

Conditional weight gain from birth to three years (defined as the standardized residuals from the linear regression of three-year weight Z-score on birth weight Z-score, with age and sex as covariates) was calculated according to the British 1990 growth references for 10,533 subjects in a study performed in the United Kingdom (8). After adjustment for confounders, among

infants given no breast milk, conditional weight gain was significantly higher (regression coefficient = 0.06; 95% confidence interval, 95%CI = 0.02-0.09), and a negative association was detected between conditional weight gain and breastfeeding duration (regression coefficient = 0.05; 95%CI = 0.01-0.09).

Using data from a smaller study sample (n = 596), but over a slightly longer period of follow-up, Santos and cols. (9) tracked weight and length or height, as well as related anthropometric indices (weight for age, length/height for age, weight for length/height z scores) at one and four years in the Pelotas Birth Cohort children. The exposure of interest was the addition of corn or rice flour to cow's milk, i.e. the use of a milk thickener, between three and six months of life. Adjustment for confounders was performed. The use of milk thickener was identified in 44.6% of children during the third and sixth months of life. Positive association between use of milk thickener and weight (β = 0.160; 95%CI = 0.009-0.312), length (β = 0.540; 95%CI = 0.141-0.939), weight for age Z-score (β = 0.155; 95%CI = 0.013-0.296) and length for age Z-score (β = 0.188; 95%CI = 0.051-0.325) was found in the adjusted analysis at one year, but no significant associations were present between the exposure variable and anthropometric indices at four years.

The prevalence of overweight and weight for height Z-score of 1,273 boys and girls from this same Brazilian birth cohort study were measured four years after birth, aiming to investigate possible relationships with total and predominant breastfeeding duration (10). Overweight was defined as weight for height Z-score > 2 using the NCHS/WHO reference curve. Authors conducted analysis adjusting for potential confounders (infant sex, skin color and birth weight, assets index, maternal schooling, smoking during pregnancy, prepregnancy BMI and weight gain during pregnancy) and found no linear trends and no significant associations between duration of total and predominant breastfeeding and outcomes (p > 0.05). Among subjects who had been "ever breastfed", the odds ratio (OR) for overweight at four years was 1.83 (95%CI = 0.53-6.28), and the coefficient for mean weight for height Z-score was 0.24 (95%CI = -0.09-0.57).

Some protective effect of breastfeeding has been indicated in study subjects with more specific characteristics, as shown in two studies conducted in American settings. Bogen, Hanusa and Whitaker analyzed 73,458 white and black low-income children for 4 years in a retrospective cohort, considering breastfeeding duration with and without concurrent use of formula (11). The outcome of interest was prevalence of obesity at four years, defined as BMI at or above the 95th percentile for age, based on the NCHS/CDC 2000 growth charts. Adjusting for various potential confounders – maternal age, education, parity, marital status, pregnancy conditions, delivery method, child gender, birth weight, birth year, and birth order –, breastfeeding showed a protective effect against obesity at four years for white children whose mothers had not smoked during pregnancy: OR = 0.71 (95%CI = 0.56-0.92) for breastfeeding for 16 to 26 weeks without formula; OR = 0.70 (95%CI = 0.61-0.81) for breastfeeding for more than 26 weeks with formula; and OR = 0.55 (95%CI = 0.42-0.71) for breastfeeding for more than 26 weeks without early formula introduction. Moreover, based on 177,304 low-income children evaluated in the Grummer-Strawn and Mei's study, a dose-response, protective relationship of breastfeeding duration with the risk of overweight at four years was established among non-Hispanic whites, considering the same anthropometric references and adjusting analysis for confounders (child gender, birth weight, race/ethnicity, and mother's age, education, pre-pregnancy BMI, weight gain during pregnancy, postpartum smoking). The OR (95%CI) for obesity when breastfeeding for 6 to 12 months was 0.70 (0.50-0.99), and 0.49 (0.25-0.95) when breastfeeding duration was greater than 12 months (12).

Along the same lines, the ALSPAC Children in Focus Cohort also studied 1,335 non-smoking mothers' children from birth to five years to observe growth patterns in both breast- and bottle-fed individuals. Despite similar birth weight, breastfed children showed slower weight and length gain *versus* bottle-fed children, and weight differed significantly up to 31 months of age (p = 0.02) (13).

The earliest published study selected for this review followed 545 children for seven years in the Dundee Infant Feeding Study. The study analyzed the influence of breastfeeding and formula feeding, as well as the age at the introduction of formula and solid foods, on growth and body composition during childhood. Body composition was defined through skinfold thickness and electrical impedance and, again, analysis were conducted while adjusting for sex, birth weight, and child weight at first solid feed. An inverse association between age at introduction of solid foods and both weight (p < 0.025) and percentage of body fat (p < 0.01) at seven years was found (14).

Overweight status at seven years, defined as BMI at/or above the 95th percentile for age, according to the NCHS/CDC 2000 growth charts, was also the variable of interest in the study by Stettler and cols. (15), with regard to breastfeeding initiation, which was assumed to be a potential confounder in the relationship with early rate of weight gain. Information on initial infant feeding method was available for 5,479 subjects, and no significant association between breastfeeding initiation and overweight at seven years was noted (OR = 1.28; 95%CI = 0.87-1.88), while no interaction was detected for breastfeeding initiation, in the association of early rate of weight gain and overweight at seven years.

Another prospective study from birth to 9.5 years investigated childhood eating behaviors (such as picky or rapid eating, tantrums over food and nonnutritive food uses) and infant feeding behaviors (such as sucking behavior and number of feeds per day) in a group of 150 American children, as possible risk factors of childhood overweight development (BMI at/or above the 85th percentile for age), within certain time frames (birth, infancy and childhood). Agras and cols. concluded that from among these behavioral factors, as well as an assessment of 24 hours child caloric intake, the development of childhood overweight was primarily linked to tantrums over food observed between two and five years which, in turn, correlated significantly with anger/frustration and soothability (16).

In 1999, exclusive breastfeeding duration was retrospectively investigated among 781 Swedish subjects followed between 15-16 and 17-18 years, in order to determine possible association with high BMI in adolescence (≥ 85th percentile for age and sex). In addition, 194 individuals had data regarding body composition measured by dual energy X-ray. After 18 years, exclusive breastfeeding for less than two months was correlated to high BMI values (χ^2 test; p = 0.038), whereas no significant associations were observed in relation to body composition. It should be outlined, nonetheless, that no adjustment for potential confounders was made (17). In a more recent study using a period of 18 years of follow-up, however, Victora and cols. (18) observed no protective effect of total or predominant breastfeeding on mean BMI, overweight status and lean or fat mass, measured by electrical impedance, in 2,250 Brazilian male adolescents from a population based sample. In this study, using the NCHS/WHO reference curve, overweight was defined as BMI ≥ 85th percentile for age and sex, and obesity as BMI ≥ 85th percentile for age and sex plus subscapular and triceps skinfolds ≥ 90th percentile. They found only an inverse association between obesity status and total breastfeeding of over 12 months (OR = 0.41; p = 0.006, likelihood ratio test) and predominant breastfeeding (p = 0.03 for linear trend). Adjustment for confounders (family income, maternal education, maternal BMI, skin color, maternal smoking during pregnancy, gestational age, birth weight and current behavioral variables – smoking, alcohol drinking, type of diet and physical activity) was performed, and the authors concluded that no strong result regarding the protective role of breastfeeding against adolescence obesity could be drawn, in view of the fact that associations with other adiposity variables studied were not confirmed.

A study comprising 35,526 women from the Nurses' Mothers' Cohort Study explored maternal reports of infant feeding practices, familial, maternal and birth variables of subjects allied to the Nurses' Health Study II (1989-2001). Authors evaluated the impact of breastfeeding initiation and duration on overweight and obesity at 18 years and also in late adulthood (mean age of breastfed nurses = 40.5 years; non breastfed nurses = 39.3 years). No significant association between exposure variables and overweight (BMI between 25 and 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) at 18 years or in late adulthood was found, even after adjustment for many confounding variables (age of nurse, year of birth of the nurse, maternal pre-pregnancy weight and weight gain during pregnancy, birth weight and gestational age of the nurse, mother's and father's education and occupation, home ownership of parents at time of nurse child's birth, age of nurse at menarche, parity of nurse, nurse's age at first birth, nurse's physical activity, daily energy intake) (19).

Nelson and cols. (20) evaluated 11,998 American adolescents in the nationally representative National Longitudinal Study of Adolescent Health. Data on infant feeding practices were retrospectively assessed while 850 full-sibling, non twin pairs were also assessed to account for unmeasured genetic and environmental factors. Adjusting for ethnicity and family income, an inverse association was established between the duration of any breastfeeding and overweight (BMI ≥ 95th percentile for age, according to the NCHS/CDC 2000 growth charts) among girls in the full cohort (for breastfeeding duration over nine months: OR = 0.78; 95%CI = 0.64-0.96). Nevertheless, no significant associations were found in sibling pairs' analyses, after

adjustment for the suitable confounders (age, sex, birth order, and low birth weight status), suggesting that the effect of breastfeeding on overweight may be weak or even absent.

Complementarily, the study with the longest follow-up period observed in this review, spanning 62 years, found a negative association between breastfeeding duration and BMI at one year ($p < 0.05$ for linear trend), which disappeared at seven years. Besides, in 1,823 breastfed individuals belonging to sibling pairs of the Helsinki Birth Cohort, results with adjustment for confounders (sex, year of birth, size of sibship) showed a possible U-shaped association between breastfeeding duration and BMI ($p = 0.08$ for quadratic trend) and percentage of body fat measured by electrical impedance ($p = 0.03$ for quadratic trend) in later life (21).

Food, energy and nutrient intake

Regarding a potential relationship between metabolic and behavioral predictors of one-year weight gain, the Viva La Familia Study investigated 879 Hispanic 4-19-year-old children. Two multiple-pass dietary 24-hour recalls were applied to measure food intake. Authors observed positive correlation between weight gain and energy intake normalized for fat-free mass and fat mass and energy from fats ($p < 0.05$). Energy from carbohydrates was negatively correlated to weight gain ($p = 0.007$). After adjusting for age, age squared, sex, and Tanner stage, however, the final model to predict weight gain did not retain these dietary variables as independent predictors (22).

Also in the United States, the nationally representative Early Childhood Longitudinal Study-Kindergarten Cohort aimed to verify child overweight status at six years and, again, two years later in regard to household food insecurity at six years (23). Overweight was defined as BMI $\geq 95^{th}$ percentile for age and sex, according to the NCHS/CDC 2000 growth charts, and households were classified as food secure or food insecure (with or without hunger) on the basis of answers to the US Department of Agriculture Household Food Security Scale, according to scarcity of food, for example. Out of 16,889 subjects participating in the cohort, 12,890 boys and girls had weight gain data available. Gender, age, race/ethnicity, birth weight, maternal schooling, poverty index ratio, country region, urbanization, physical activity, and family meal patterns were treated as potential confounders in the analysis. Food insecurity had a protective relationship with overweight at six years (OR = 0.80; 0.66-0.98), and, considering child overweight status two years later, food insecurity was also inversely associated with overweight (OR = 0.73; 95%CI = 0.57-0.93).

Ong and cols. (24) investigated the weight gain of 881 British children for five years, since their birth. These children were breastfed and formula- or mixed-fed and completed a one-day unweighted dietary record at four months, through which total dietary energy intake was calculated. Gender and body weight at four months constituted confounding variables, and there was a positive association between energy intake at four months and rates of rapid weight gain from zero to two years ($p < 0.0001$ for trend). Higher energy intake at four months predicted higher weight and BMI at one, two, three (OR = 1.46; 95%CI = 1.20-1.78) and five years (OR = 1.25; 95%CI = 1.00-1.55) only among children who had been formula- or mixed-fed.

In a similar period of follow-up, the Longitudinal Nepean Study assessed nutrient intake at seven to eight years using a three-day food record. The outcome of interest was total adiposity (BMI) and central adiposity (waist circumference) at 12 to 13 years. Given that no adjustment for potential confounders was performed, authors were not able to confirm significant associations between overweight and obesity at 12 to 13 years (according to the IOTF BMI criteria or waist circumference) and macronutrient intake at seven to eight years (25).

A total of 105 children were accompanied for ten years, at Denmark, under the Copenhagen Cohort Study on Infant Nutrition and Growth. When subjects attained nine months of age, their parents completed a five-day weighted food record, which included three weekdays and a weekend, in order to assess protein intake during infancy. In terms of body size and composition (dual-energy X-ray absorptiometry scanning) at ten years, no significant association between fatness in late childhood and protein intake at nine months was found. However, data suggested that a high protein intake may stimulate growth, considering that energy from protein was a predictor of weight ($\beta = 0.44$; 95%CI = 0.12-0.76) and height ($\beta = 0.51$; 95%CI = 0.13-0.90) at ten years, after adjustment for gender (26).

Magarey and cols. (27) investigated the energy and the energy-adjusted macronutrient intake of a minimum of 143 and a maximum of 243 Australian individuals aged between 2 and 15 years. Dietary exposure was measured by 3-4 day weighted dietary records, which

were analyzed in order to observe alterations in body fatness at 2, 4, 6, 8, 11, 13 and 15 years (BMI, triceps and subscapular skinfolds). Adjustment for confounders (gender parental adiposity, total energy intake, level of fatness at the beginning of age interval) was carried out, and authors found a positive association between fat intake and subscapular skinfolds ($\beta = 0.008$; $p = 0.003$) and a negative association ($\beta = -0.003$; $p = 0.006$) between carbohydrate intake and subscapular skinfolds across 2 to 15 years, according to generalized estimating equations. However, on multiple regression analyses, macronutrient intake was again shown to be a poor predictor of adiposity at successive ages.

Finally, the study of Laitinen and cols. (28) sought some association between abdominal obesity and dietary parameters at 14 and 31 years, among 5,771 men and women, attending the Northern Finland 1966 Birth Cohort Study. Dietary variables analyzed included alcohol consumption at 14 and 31 years, and a healthy or unhealthy diet pattern (based on frequency of intake of foods rich in fiber and consumption of sausages) at 31 years. Several confounding variables were considered, such as maternal age and BMI before pregnancy, and parity and use of hormonal contraception at 31 years among women. Considering BMI at 31 years in a regression model, a positive association between abdominal obesity in men and high alcohol consumption at 31 years (comparing the highest with the lowest quartile of alcohol intake, OR = 1.82; 95%CI = 1.17-2.85) and unhealthy diet (OR = 1.53; 95%CI = 1.03-2.27, compared to healthy diet) was detected. Among women, alcohol consumption at 31 years also showed a dose-response, protective relationship with abdominal obesity (when comparing the highest with the lowest quartile of alcohol intake, OR = 0.54; 95%CI = 0.34-0.85). Female abdominal obesity was positively associated with regular alcohol consumption at 14 years (OR = 2.63; 95%CI = 1.44-4.80, compared to no alcohol intake at 14 years), but disappeared when BMI at 31 years was included in the model.

STRENGTHS AND LIMITATIONS OF REVIEWED STUDIES

Associations between infancy feeding practices and the development of overweight and obesity are thought to explain some features of the association of infancy weight gain with later nutritional status. In this sense, one of the most studied aspects is breastfeeding, which promotes slow weight gain in children, protecting against overweight development. Conversely, individuals who are formula-fed or have an earlier introduction of complementary food are set to experience more rapid weight gain in early infancy and an increased risk of obesity in childhood and adolescence, given the possibility of overfeeding – which would be unlikely to happen with breastfed children, who have to stimulate breast milk production by suckling.

Our review of these 22 longitudinal investigations has revealed some inconsistency across results regarding associations among infant feeding practices, patterns of childhood growth and the nutritional status exhibited in later life. Studies with shorter periods of follow-up, generally between birth and one to three years of life, seemed to indicate some protective effect of breastfeeding in the prevention of overweight and obesity, observing decreasing weight gain with longer durations of breastfeeding. In longer follow-up periods, however, the majority of associations between nutritional status in childhood, adolescence or adulthood and breastfeeding initiation and duration, as well as the use of milk thickeners and introduction of complementary food, were actually weakened or completely disappeared. In the study with the longest period of follow-up examined in this review, an interesting U-shaped association between breastfeeding duration and BMI and fat mass at 60 years of life was established, suggesting that breastfeeding for periods which are either too short or too long could be detrimental to growth and development. Food insecurity was negatively associated with overweight in childhood, and some articles provided evidence linking higher energy intake in infancy to higher weight and BMI during childhood, especially among non-breastfed children, as well as higher energy from protein in infancy to higher weight and height at ten years. In several other studies, however, energy and macronutrient intake were not prospectively linked to body composition, overweight or obesity. Other dietary variables measured in infancy and childhood were also not included in regression models to predict weight gain and adiposity in later life.

Possible reasons for these inconsistencies may include variations in study setting and design, number of subjects, statistical power, use of different dietary assessment methods, definitions of infant feeding practices, dietary variables and overweight or obesity status, age at outcome assessment, and extent of adjustment for potentially confounding factors.

In this review, the main controlled confounding variables were sex, skin color, family income, birth weight and several maternal characteristics (age, BMI, education level, smoking during pregnancy etc). Evidently, more recent studies were able to overcome confounding variables in a more effectively by using refined statistical techniques. In spite of this, it should be emphasized that the measurement of confounding factors may often be poor and underestimated, because of the difficulties in selecting and analyzing proper proxy variables. Some studies therefore advise new design approaches, such as comparisons with sibling pairs, which can manage unmeasured environmental and genetic characteristics (20,21), and conceptual frameworks that allow the organization of risk factors into a model with diverse hierarchical levels of determination (distal and proximal determinants) related to the outcome of interest, to properly identify causal mechanisms (29,30).

In addition, it is noteworthy that out of the longitudinal study results illustrated in the articles included in this review, only the Pelotas Birth Cohort presented evidence from a developing country. There are certainly distinct behaviors influencing dietary practices together with contrasting socioeconomic status, between developing and developed countries, and even among different regions within the same country (31). Consequently, different variables exert influence and can act as confounding factors in the relationship between infant feeding practices, patterns of childhood growth and the nutritional status exhibited in adult life. In Brazil's case, the city of Pelotas, located in the Southern region, represents a wealthier area inhabited by a majority of white subjects, and thus is not representative of other regions of the country.

Along with these limitations, some studies evaluated in this review were not population-based or involved a small representative sample as depicted in tables 1 and 2. Other investigations were characterized by brief periods of follow-up, thereby preventing further conclusions on the nutritional status in later phases of life. Moreover, it is noteworthy that accurate dietary assessment often represents a challenge for researchers. There is, indeed, a higher frequency of longitudinal studies detailing growth and development parameters spanning longer periods from birth to late adulthood which employ anthropometric variables only, than there are longitudinal studies using dietary variables to evaluate this relationship. In some studies presented, infant feeding practices had to be assessed retrospectively through health records or mothers' reports, where this is considered a reliable approach for this purpose (32). When delving into food, energy and nutrient intake, assessment methods were satisfactorily exploited, but undoubtedly relied on self-report and always have inherent advantages and shortcomings that ultimately dictate their adoption under the situation at hand (33).

Therefore, in a bid to contribute further consistent evidence to the current literature, future studies are clearly needed in the field of infant feeding practices and dietary variables associated to childhood growth and nutritional status in adulthood. Such studies should have adequate designs to determine causal relationships, made feasible by means of longitudinal investigations that preferentially appraise population-based samples for periods of follow-up that cover the key phases of human growth. Lastly, given the current lack of studies in developing countries, future studies should focus on developing countries, and provide adequate measurement and treatment of potential confounding factors.

CONCLUSIONS

In conclusion, this non-systematic review showed that longitudinal studies yield some inconsistent associations among infant feeding practices, childhood growth and obesity in adult life. Over short follow-up periods, breastfeeding may play a role in preventing overweight development, while energy and protein intake during infancy might be associated with weight and height attained in later years. Nevertheless, these associations seem to be weakened or even eliminated when longer periods of monitoring are considered. Further research particularly in developing countries, would be valuable to contribute more solid findings to the current literature.

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4.2 ARTIGO 2

Determinants of linear growth from infancy to school-aged years: a population-based follow-up study in urban Amazonian children

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RESEARCH ARTICLE Open Access

Determinants of linear growth from infancy to school-aged years: a population-based follow-up study in urban Amazonian children

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Abstract

Background: Although linear growth during childhood may be affected by early-life exposures, few studies have examined whether the effects of these exposures linger on during school age, particularly in low- and middle-income countries.

Methods: We conducted a population-based longitudinal study of 256 children living in the Brazilian Amazon, aged 0.1 y to 5.5 y in 2003. Data regarding socioeconomic and maternal characteristics, infant feeding practices, morbidities, and birth weight and length were collected at baseline of the study (2003). Child body length/height was measured at baseline and at follow-up visits (in 2007 and 2009). Restricted cubic splines were used to construct average height-for-age Z score (HAZ) growth curves, yielding estimated HAZ differences among exposure categories at ages 0.5 y, 1 y, 2 y, 5 y, 7 y, and 10 y.

Results: At baseline, median age was 2.6 y (interquartile range, 1.4 y–3.8 y), and mean HAZ was −0.53 (standard deviation, 1.15); 10.2% of children were stunted. In multivariable analysis, children in households above the household wealth index median were 0.30 Z taller at age 5 y ($P = 0.017$), and children whose families owned land were 0.34 Z taller by age 10 y ($P = 0.023$), when compared with poorer children. Mothers in the highest tertile for height had children whose HAZ were significantly higher compared with those of children from mothers in the lowest height tertile at all ages. Birth weight and length were positively related to linear growth throughout childhood; by age 10 y, children weighing >3500 g at birth were 0.31 Z taller than those weighing 2501 g to 3500 g ($P = 0.022$) at birth, and children measuring ≥51 cm at birth were 0.51 Z taller than those measuring ≤48 cm ($P = 0.005$).

Conclusions: Results suggest socioeconomic background is a potentially modifiable predictor of linear growth during the school-aged years. Maternal height and child's anthropometric characteristics at birth are positively associated with HAZ up until child age 10 y.

Keywords: Children, Linear growth, Height-for-age Z score, School-aged years, Determinants

Background

Linear growth during childhood may be influenced by the cumulative effects of many environmental exposures, including nutritional, psychosocial, and infectious factors [1]. It is estimated that 167 million children aged <5 y in developing countries (29.2%) were growth-stunted in 2010 [2]. The individual and societal consequences of restricted linear growth are substantial and include increased risks of mortality, infection, neurocognitive delays, and other disabilities [3,4]. In addition, stunted children may become shorter adults with decreased economic productivity and reproductive performance [4,5]. Identifying potentially modifiable causes of linear growth retardation thus remains an important public health priority.

Studies of the determinants of linear growth have focused largely on the period before the age of 5 y [6-8]. However, little is known about the influences of early-life exposures on linear growth during school age, especially in low- and middle-income countries. Understanding these influences would provide critical information as to

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whether the adverse impact of early exposures on growth lingers on throughout childhood or may be reversed. The aim of this study was to investigate socioeconomic, maternal, and child determinants of linear growth up to age 10 y in a population-based cohort study of children living in the Brazilian Amazon.

Methods

Study area and population

This longitudinal study was conducted in Acrelândia, a town located 100 km from Rio Branco, the capital of the state of Acre, in northwest Brazil. Acrelândia is a frontier town inhabited by migrants from southeast and south Brazil who are engaged in commercial agriculture and cattle raising. In 2003, the city had 8697 inhabitants (43% residing in the urban area), covering a territory of 1607.5 km^2. Child health indicators in Acrelândia are significantly lower than the country average: infant mortality rate was 71/1000 live births, and the Human Development Index was 0.680 according to data from 2000 [9].

In January 2003, we performed a population-based cross-sectional study in the urban area of Acrelândia [10]. All households with children aged <5 y (n = 334) were identified through a census performed by local teams of the Family Health Program of the Brazilian Ministry of Health. All children in these 334 households were invited to participate, and only two households declined participation. Thus, data were collected from 332 households (99.4%) involving a total of 489 children. Structured household interviews and anthropometric evaluations were completed for 468 children (95.7% of those eligible).

As previously reported [11], in December 2007 we conducted a second population-based cross-sectional survey in the same town with all children aged <10 y. The assessment included 250 of the children who had previously been examined in 2003. In December 2009, our group performed another follow-up assessment, which included 193 children evaluated in both 2003 and 2007, plus six other children who participated in 2003 but were not located in 2007. We included in these analyses 256 children who had been evaluated in 2003 and at least once more. These children contributed a total of 705 measurements. The distribution of the number of measurements was as follows: 0 to <6 mo: 21; 6 mo to <12 mo: 27; 12 mo to <2 y: 47; 2 y to <5 y: 162; 5 y to <7 y: 100; 7 y to <10 y: 274; and ≥10 y: 74.

Children included in the analyses were not different from those who were not included in terms of sex, age, length/height, and the socioeconomic, maternal, and child characteristics investigated. Written informed consent for participation was obtained from parents or guardians before enrollment. This study was approved by the ethical review board of the School of Public Health, University of São Paulo, Brazil.

Field procedures

At baseline of the study (2003), trained fieldworkers performed structured face-to-face interviews with each child's mother or guardian during household visits. The following data were collected: demographic characteristics (child's sex and age, race/ethnicity), socioeconomic status (household assets, land ownership, parental educational level) and access to public services (treated water, garbage collection), maternal characteristics (maternal age, smoking during pregnancy), child characteristics at birth (birth weight and length retrieved from child's health card), infant feeding practices (child's age at introduction of weaning foods), and morbidity (diarrhea, vomiting, or cough with fever in the 15 days before the home visit).

Trained research assistants obtained anthropometric measurements from the children at a local Family Health Clinic (in 2003 and 2007 surveys) or at the households (in 2009), using standardized procedures and calibrated equipment [12]. The date of birth was recorded directly from birth certificates or child health cards. In 2003, among children aged <24 mo, recumbent length was measured to the nearest millimeter with a locally made infant measuring board. Children aged ≥2 y were measured to the nearest 0.1 cm with a stadiometer (Seca, Hamburg, Germany, in 2003 and 2007; WCS, Curitiba, Brazil, in 2009) affixed to a flat surface on a wall, without a baseboard and perpendicular to the floor. Children were positioned barefoot in the vertical standing position in the middle of the stadiometer, with their head, shoulders, buttocks, and heels against the wall. Mother's height was measured following similar procedures. Each measurement was repeated, and the mean value was calculated.

Data analyses

The main outcome of interest was length/height-for-age and sex Z score (HAZ). HAZ was calculated according to the World Health Organization (WHO) Child Growth Standards [13] for children aged 0 to 5 y and the WHO Growth Reference Data [14] for children >5 y. Stunting was defined as HAZ < −2 [15].

Predictors of interest included maternal and household sociodemographic characteristics, child anthropometry at birth, infant feeding practices, and morbidities at baseline. A wealth index based on the presence of 14 home appliances was used to assess socioeconomic status [16]. Principal component analysis was used to define the weight of household assets with the XLSTAT software, version 7.5.2 (Addinsoft, New York, NY). As previously reported [10], after standardizing the weights assigned to each item, scores were added to produce an estimated index of household wealth. In order to account for potential non-linearity of associations, predictors were

categorized according to previously used cut-off points in this population. The wealth index was examined in quartiles, tertiles, and as less than or as greater than or equal to the median. As similar results were observed, we opted to present the associations for this variable according to the latter classification. Maternal height and child's birth length were divided into tertiles, and child's birth weight was categorized as ≤2500 g, 2501 g to 3500 g, or >3500 g. Age at introduction of cow's milk, an indicator of infant feeding practices, was classified as <3 mo vs. ≥3 mo.

We first compared the distribution of HAZ by categories of socioeconomic, maternal, and child characteristics at baseline, using tests of trend for ordinal predictors and the mean-comparison t-test for dichotomous predictors. We also examined the prevalence of stunting in relation to baseline characteristics using the Cochrane-Armitage and chi-square tests for ordinal and dichotomous variables, respectively.

Subsequently, the associations of socioeconomic, maternal, and child characteristics with linear growth were assessed by estimating average HAZ-for-age growth curves for each category of the predictors of interest, using mixed-effect models for repeated measurements with restricted cubic splines. Cubic splines represent non-linear terms for age at each assessment that allow the smoothing of the relation between HAZ and age. Piecewise cubic polynomials are smoothly joined at joint points or "knots" [17]. In this case, knots were placed at ages 0.18 y, 0.50 y, 1.50 y, 3 y, and 10 y, as these ages seem important reference points in the curvilinear segments of the WHO Child Growth Standard and Reference Data [13,14]. In the models, the outcome was HAZ, and covariates included the categories of the predictor of interest, linear and spline terms for child age in decimal years, and predictor category*age interaction terms. Random effects for the intercept and the linear term for age (slope) were included to account for the within-person correlation of measurements in the estimation of the variance [18]. Since these methods do not require an equal number of measurements in all children or that measurements be obtained at exactly the same time points on every participant, all available measurements were included in the models. Because the age distribution of children at baseline ranged from 0 to 5 y, we tested for possible birth cohort effects on the construction of the curves by including additional terms for year of birth. These terms were not statistically significant and did not change the magnitude of the associations.

We obtained adjusted mean HAZ-for-age curves using multivariable mixed-effect models based on a hierarchical conceptual framework as proposed by Victora et al [19]. The following levels of determination were considered: (1) socioeconomic characteristics, (2) access to public services, (3) maternal characteristics before pregnancy, (4) maternal characteristics during pregnancy, (5) child characteristics at birth, (6) infant feeding practices, and (7) morbidity indicators. For each level, variables were retained in the model if they were considered conceptually relevant or if there was a clear association with the outcome in the unadjusted analysis, including dose–response patterns for ordinal variables. Statistical significance ($P < 0.100$) was an additional criterion for retaining a variable in the model at each level of determination.

For both unadjusted and adjusted analyses, we estimated HAZ from the growth curves at ages 6 mo, 12 mo, 2 y, 5 y, 7 y, and 10 y, as the predicted values of the spline function, with values of predictor covariates at the reference category. Differences in the estimated values of HAZ and their 95% confidence intervals (CI) were calculated among the categories of each predictor at these ages. All reported P values are two-tailed. We used SAS 9.2 (SAS Institute Inc., Cary, NC) for all analyses.

Results

Median age at recruitment was 2.6 y (interquartile range [IQR], 1.4 y–3.8 y; range, 0.1 y–5.5 y), 52.7% of the children were female, and 88.1% were mulatto. At baseline, mean HAZ was −0.53 (standard deviation [SD], 1.15), and 10.2% of the children were stunted. In 2003, HAZ was positively associated with wealth index, maternal education and height, non-smoking during pregnancy, and child's birth weight and length. No association with child's sex was observed (Table 1).

Median follow-up time was 6.9 y (IQR, 6.8 y–6.9 y), during which time a median of three height measurements was collected for each child (IQR, 3–3; 63 children had two and 193 children had three measurements). We estimated an average HAZ-for-age curve for the study population (Figure 1) from age 0 to 10 years using restricted cubic splines. The curve's shape was comparable with curves for Brazil and for the Latin America and the Caribbean region (PAHO/AMRO) estimated from the WHO Database on Child Growth and Malnutrition, which is available for children aged <5 y [20]. Brazilian and PAHO/AMRO estimates are derived from nationally representative demographic and health cross-sectional surveys conducted from 1999 to 2006. For all ages, HAZ values of Acrelândia children were slightly lower than those from the Brazilian national average, but above the PAHO/AMRO regional mean.

In unadjusted analyses (Table 2), socioeconomic status, land ownership, and maternal education were positively associated with mean HAZ values at ages 2 y, 5 y, 7 y, and 10 y. Monotonically increasing children's mean HAZ were observed across categories of mother's height, child's birth weight, and child's birth length. Linear growth patterns did not differ by sex.

Table 1 Mean height-for-age Z score and prevalence of stunting according to baseline characteristics, Acrelândia, Brazil

	n[1]	Mean HAZ (SD)[2]	P[3]	% stunted[4]	P[5]
Overall	**256**	**−0.53 (1.15)**		**10.2**	
Child's sex			0.376		0.866
Female	132	−0.59 (1.10)		9.8	
Male	124	−0.47 (1.21)		10.5	
Child's age			<0.001		0.875
0-5 months	21	−0.24 (1.33)		19.0	
6-11 months	27	0.30 (1.04)		0.0	
12-23 months	47	−0.41 (1.17)		8.5	
24-35 months	56	−0.83 (1.04)		12.5	
≥36 months	105	−0.70 (1.09)		10.5	
Socioeconomic characteristics					
Wealth index			0.008		0.035
Below median	136	−0.70 (1.16)		14.0	
Above median	118	−0.32 (1.12)		5.9	
Land ownership			0.035		0.136
No	208	−0.60 (1.16)		11.5	
Yes	47	−0.21 (1.09)		4.3	
Mother's educational level			0.003		0.074
0-4 years	102	−0.68 (1.12)		11.8	
≥5 years	88	−0.19 (1.12)		4.5	
Access to treated water			0.866		0.242
No	82	−0.54 (1.34)		13.4	
Yes	173	−0.52 (1.06)		8.7	
Access to public garbage collection			0.206		0.005
No	53	−0.70 (1.40)		20.8	
Yes	199	−0.47 (1.08)		7.5	
Maternal characteristics					
Mother's age			0.915		0.468
≤20 years	27	−0.45 (1.28)		18.5	
21-30 years	143	−0.51 (1.14)		9.1	
>30 years	55	−0.50 (1.28)		10.9	
Mother's height			<0.001		0.008
1st tertile: ≤154.0 cm	77	−0.95 (1.16)		18.2	
2nd tertile: 154.1-159.4 cm	77	−0.55 (1.02)		7.8	
3rd tertile: ≥159.5 cm	78	−0.22 (1.10)		5.1	
Smoking during pregnancy			0.016		0.193
No	176	−0.43 (1.18)		8.5	
Yes	55	−0.85 (1.00)		14.5	
Child characteristics					
Child's birth weight			<0.001		0.013
≤2500 g	18	−1.45 (0.73)		16.7	
2501-3500 g	156	−0.66 (1.11)		12.2	
>3500 g	76	−0.01 (1.08)		2.6	
Child's birth length			<0.001		0.003
1st tertile: ≤48 cm	77	−0.96 (1.06)		14.3	
2nd tertile: 49–50 cm	73	−0.17 (1.00)		4.1	

Table 1 Mean height-for-age Z score and prevalence of stunting according to baseline characteristics, Acrelândia, Brazil *(Continued)*

3rd tertile: ≥51 cm	39	0.15 (1.25)	0.0	
Age at cow's milk introduction			0.689	0.867
<3 months	77	−0.60 (1.15)	10.4	
≥3 months	165	−0.53 (1.14)	9.7	
Morbidities 15 days before baseline visit:				
Diarrhea			0.892	0.985
No	195	−0.53 (1.19)	10.3	
Yes	59	−0.56 (1.04)	10.2	
Vomiting			0.291	0.910
No	233	−0.51 (1.16)	10.3	
Yes	21	−0.79 (0.99)	9.5	
Cough with fever			0.206	0.951
No	222	−0.50 (1.17)	10.4	
Yes	30	−0.79 (1.03)	10.0	

1. Totals may differ from 256 due to missing values.
2. HAZ: height-for-age Z score, calculated according to the WHO growth references [13,14].
3. Test for linear trend for ordinal predictors; mean-comparison t-test for dichotomous predictors.
4. Stunting: HAZ < −2, classified according to the WHO reference [15].
5. Cochrane-Armitage test for trend for ordinal predictors; chi-square test for dichotomous predictors.

After multivariable adjustment, wealth and land ownership remained significantly related to HAZ (Table 3). At ages 5 y and 7 y, children from households above the wealth index median had a 0.30 and 0.25 higher HAZ ($P = 0.017$ and $P = 0.034$, respectively) compared with children from households below the median. Land ownership was positively related to HAZ during the school-aged years; by age 10 y, children whose families owned

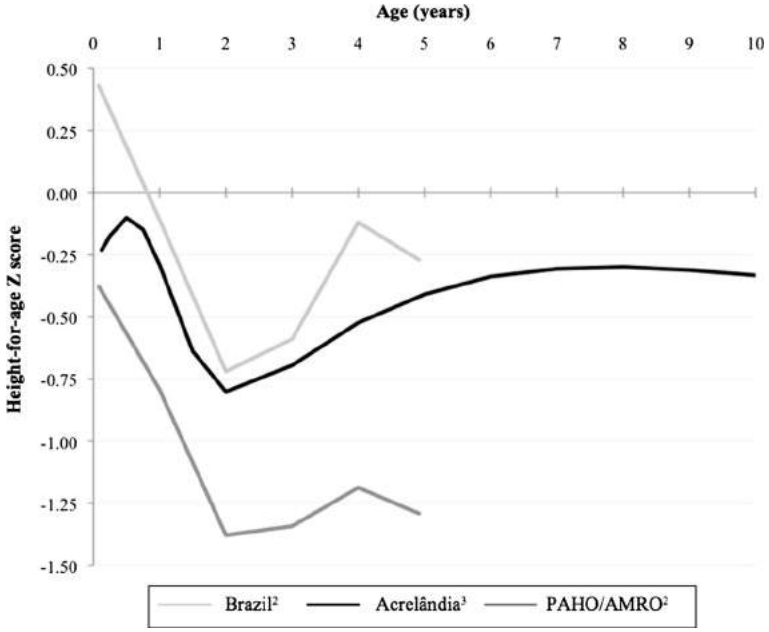

Figure 1 Mean height-for-age by age for Acrelândia in comparison to mean height-for-age by age for Brazil and Latin America and the Caribbean (PAHO/AMRO) region[1]. 1. Height-for-age Z scores in all curves were calculated according to the WHO growth references [13,14]. Height-for-age Z score curves are compared to the WHO growth references, whose median height-for-age values by age form the reference horizontal line at 0.00. 2. Curves estimated based on information from the WHO Global Database on Child Growth and Malnutrition [20]. 3. Curve estimated based on restricted cubic spline regression models.

Table 2 Height-for-age Z scores by socioeconomic, maternal and child characteristics, Acrelândia, Brazil, unadjusted analysis

		Mean HAZ (SE) according to age[2,3]					
	n[1]	6 mo	12 mo	2 y	5 y	7 y	10 y
Child's sex	256						
Female		−0.25 (0.18)	−0.31 (0.19)	−0.90 (0.13)	−0.41 (0.08)	−0.32 (0.07)	−0.42 (0.08)
Male		0.09 (0.27)	−0.25 (0.17)	−0.74 (0.13)	−0.40 (0.09)	−0.29 (0.09)	−0.26 (0.09)
Difference [95% CI]		0.34 [−0.29, 0.97]	−0.06 [−0.44, 0.56]	0.16 [−0.20, 0.52]	−0.01 [−0.23, 0.25]	0.03 [−0.20, 0.26]	0.16 [−0.08, 0.40]
Socioeconomic characteristics							
Wealth index	254						
Below median		−0.33 (0.20)	−0.40 (0.17)	−0.99 (0.12)	−0.57 (0.08)	−0.44 (0.08)	−0.43 (0.08)
Above median		0.20 (0.24)	−0.16 (0.19)	−0.61 (0.14)	−0.21 (0.09)	−0.13 (0.08)	−0.20 (0.09)
Difference		0.53 [−0.08, 1.15]	0.24 [−0.26, 0.74]	0.38 [0.02, 0.74]	0.36 [0.12, 0.60]	0.31 [0.09, 0.54]	0.23 [−0.01, 0.47]
Land ownership	255						
No		−0.19 (0.16)	−0.38 (0.14)	−0.88 (0.10)	−0.48 (0.07)	−0.38 (0.06)	−0.41 (0.07)
Yes		0.47 (1.10)	0.08 (0.38)	−0.52 (0.20)	−0.08 (0.13)	0.04 (0.12)	0.00 (0.13)
Difference		0.66 [−1.52, 2.85]	0.46 [−0.32, 1.25]	0.36 [−0.09, 0.81]	0.40 [0.11, 0.69]	0.42 [0.14, 0.69]	0.41 [0.12, 0.70]
Mother's educational level	190						
0-4 years		−0.01 (0.18)	−0.23 (0.16)	−1.02 (0.14)	−0.56 (0.09)	−0.42 (0.09)	−0.41 (0.10)
≥5 years		0.08 (0.19)	−0.14 (0.21)	−0.41 (0.17)	−0.12 (0.10)	−0.08 (0.10)	−0.17 (0.10)
Difference		0.09 [−0.43, 0.61]	0.09 [−0.42, 0.61]	0.61 [0.19, 1.03]	0.44 [0.18, 0.70]	0.33 [0.08, 0.59]	0.24 [−0.04, 0.51]
Access to treated water	255						
No		0.25 (0.24)	−0.30 (0.21)	−0.85 (0.19)	−0.58 (0.11)	−0.48 (0.10)	−0.43 (0.11)
Yes		−0.25 (0.18)	−0.35 (0.16)	−0.80 (0.10)	−0.32 (0.07)	−0.22 (0.07)	−0.28 (0.07)
Difference		−0.50 [−1.09, 0.09]	−0.05 [−0.57, 0.46]	0.05 [−0.37, 0.46]	0.26 [−0.01, 0.52]	0.26 [0.01, 0.50]	0.14 [−0.12, 0.40]
Access public garbage collection	252						
No		−0.52 (0.39)	−0.45 (0.27)	−0.78 (0.27)	−0.70 (0.16)	−0.60 (0.15)	−0.44 (0.14)
Yes		−0.02 (0.17)	−0.28 (0.15)	−0.80 (0.09)	−0.33 (0.07)	−0.23 (0.06)	−0.31 (0.07)
Difference		0.50 [−0.32, 1.33]	0.17 [−0.44, 0.77]	−0.02 [−0.58, 0.54]	0.37 [0.04, 0.70]	0.37 [0.05, 0.68]	0.12 [−0.18, 0.43]
Maternal characteristics							
Mother's height	232						
a. 1st tertile: ≤154.0 cm		−0.67 (0.26)	−0.59 (0.23)	−1.17 (0.15)	−0.78 (0.12)	−0.64 (0.11)	−0.61 (0.11)
b. 2nd tertile: 154.1-159.4 cm		−0.20 (0.35)	−0.38 (0.23)	−0.81 (0.17)	−0.36 (0.09)	−0.29 (0.09)	−0.42 (0.11)
c. 3rd tertile: ≥159.5 cm		0.33 (0.25)	0.06 (0.24)	−0.58 (0.16)	−0.19 (0.11)	−0.06 (0.10)	−0.05 (0.09)
Difference (b-a)		0.47 [−0.37, 1.32]	0.21 [−0.41, 0.84]	0.35 [−0.10, 0.80]	0.41 [0.12, 0.71]	0.35 [0.07, 0.63]	0.18 [−0.13, 0.49]
Difference (c-a)		1.00 [0.30, 1.70]	0.65 [0.01, 1.29]	0.58 [0.15, 1.01]	0.59 [0.28, 0.90]	0.58 [0.28, 0.88]	0.56 [0.27, 0.84]
P for trend		0.458	0.412	0.323	0.314	0.313	0.299
Smoking during pregnancy	231						
No		0.06 (0.19)	−0.17 (0.15)	−0.70 (0.11)	−0.35 (0.08)	−0.26 (0.07)	−0.32 (0.07)
Yes		−0.52 (0.26)	−0.65 (0.23)	−1.23 (0.16)	−0.64 (0.12)	−0.49 (0.12)	−0.51 (0.13)
Difference		−0.58 [−1.21, 0.05]	−0.48 [−1.03, 0.05]	−0.53 [−0.91, −0.15]	−0.29 [−0.57, −0.02]	−0.22 [−0.49, 0.05]	−0.19 [−0.49, 0.10]
Child characteristics							
Child's birth weight	250						
a. ≤2500 g		−1.23 (0.34)	−1.14 (0.35)	−1.89 (0.25)	−0.97 (0.12)	−0.74 (0.13)	−0.81 (0.16)
b. 2501-3500 g		−0.27 (0.19)	−0.47 (0.16)	−0.94 (0.12)	−0.53 (0.08)	−0.42 (0.08)	−0.43 (0.08)
c. >3500 g		0.77 (0.17)	0.25 (0.19)	−0.30 (0.14)	0.02 (0.10)	0.08 (0.10)	−0.01 (0.11)

Table 2 Height-for-age Z scores by socioeconomic, maternal and child characteristics, Acrelândia, Brazil, unadjusted analysis *(Continued)*

Difference (a-b)		−0.96 [−1.72, −0.21]	−0.67 [−1.42, 0.08]	−0.95 [−1.50, −0.40]	−0.44 [−0.72, −0.16]	−0.32 [−0.62, −0.03]	−0.39 [−0.74, −0.03]
Difference (c-b)		1.04 [0.54, 1.54]	0.72 [0.23, 1.21]	0.64 [0.27, 1.01]	0.55 [0.30, 0.80]	0.50 [0.26, 0.73]	0.42 [0.16, 0.67]
P for trend		0.163	0.146	0.108	0.061	0.050	0.043
Child's birth length	189						
a. 1st tertile: ≤48 cm		−0.60 (0.27)	−0.69 (0.23)	−1.46 (0.15)	−0.63 (0.11)	−0.48 (0.10)	−0.67 (0.10)
b. 2nd tertile: 49–50 cm		0.44 (0.21)	−0.12 (0.19)	−0.52 (0.13)	−0.23 (0.09)	−0.15 (0.09)	−0.16 (0.10)
c. 3rd tertile: ≥51 cm		1.20 (0.28)	0.36 (0.29)	−0.15 (0.24)	0.12 (0.18)	0.18 (0.16)	0.11 (0.16)
Difference (a-b)		−1.04 [−1.71, 0.37]	−0.57 [−1.15, 0.00]	−0.94 [−1.33, −0.54]	−0.40 [−0.68, −0.13]	−0.33 [−0.60, −0.07]	−0.51 [−0.80, −0.22]
Difference (c-b)		0.76 [0.06, 1.45]	0.47 [−0.21, 1.15]	0.37 [−0.17, 0.91]	0.35 [−0.05, 0.75]	0.32 [−0.04, 0.69]	0.26 [−0.11, 0.64]
P for trend		0.051	0.053	0.053	0.019	0.016	0.020
Age at cow's milk introduction	242						
<3 months		−0.05 (0.27)	−0.44 (0.24)	−1.00 (0.15)	−0.48 (0.09)	−0.36 (0.09)	−0.44 (0.10)
≥3 months		−0.12 (0.21)	−0.22 (0.16)	−0.79 (0.11)	−0.42 (0.08)	−0.31 (0.08)	−0.32 (0.08)
Difference		0.07 [−0.60, 0.74]	−0.22 [−0.79, 0.34]	−0.21 [−0.58, 0.15]	−0.06 [−0.30, 0.18]	−0.05 [−0.28, 0.18]	−0.12 [−0.36, 0.13]
Morbidities 15 days before baseline visit:							
Diarrhea	254						
No		−0.01 (0.19)	−0.21 (0.16)	−0.83 (0.11)	−0.41 (0.07)	−0.29 (0.07)	−0.30 (0.07)
Yes		−0.26 (0.29)	−0.42 (0.22)	−0.78 (0.16)	−0.41 (0.10)	−0.37 (0.09)	−0.52 (0.11)
Difference		−0.24 [−0.92, 0.43]	−0.21 [−0.74, 0.32]	0.05 [−0.33, 0.43]	0.00 [−0.23, 0.24]	−0.08 [−0.30, 0.15]	−0.22 [−0.48, 0.04]
Vomiting	254						
No		−0.03 (0.17)	−0.21 (0.13)	−0.79 (0.10)	−0.43 (0.07)	−0.32 (0.06)	−0.33 (0.06)
Yes		−0.58 (0.30)	−0.81 (0.33)	−1.31 (0.29)	−0.32 (0.15)	−0.19 (0.14)	−0.48 (0.16)
Difference		−0.55 [−1.23, 0.13]	−0.61 [−1.30, 0.09]	−0.52 [−1.13, 0.08]	0.10 [−0.22, 0.43]	0.13 [−0.17, 0.44]	−0.15 [−0.48, 0.19]
Cough with fever	252						
No		−0.07 (0.17)	−0.24 (0.14)	−0.76 (0.10)	−0.40 (0.07)	−0.29 (0.06)	−0.30 (0.07)
Yes		−0.21 (0.38)	−0.53 (0.31)	−1.35 (0.21)	−0.57 (0.12)	−0.44 (0.13)	−0.65 (0.14)
Difference		−0.14 [−0.97, 0.68]	−0.28 [−0.96, 0.39]	−0.59 [−1.04, −0.13]	−0.17 [−0.45, 0.11]	−0.15 [−0.43, 0.14]	−0.35 [−0.65, −0.05]

1. Totals may differ from 256 due to missing values.
2. HAZ: height-for-age Z score, calculated according to the WHO growth references [13,14].
3. Unadjusted mean HAZ values and standard errors were estimated from restricted cubic spline regression models. The age distribution of available measurements used in these models was: 0 to <6 mo: 21; 6 mo to <12 mo: 27; 12 mo to <2 y: 47; 2 y to <5 y: 162; 5 y to <7 y: 100; 7 y to <10 y: 274; and ≥10 y: 74.

land were 0.34 Z taller ($P = 0.023$) than children from landless families. Inclusion of mother's educational level did not appreciably change the estimates, and, after adjusting for socioeconomic variables, access to public services was not found to be related to HAZ.

Maternal height was related to HAZ at all ages. Mothers in the highest tertile of height had children whose HAZ was significantly higher compared with those of children whose mothers were in the lowest height tertile after adjusting for socioeconomic status. Smoking during pregnancy was not related to growth in height after adjusting for other covariates.

Birth weight and birth length were positively and significantly related to linear growth throughout childhood. By age 10 y, children weighing >3500 g at birth were 0.31 Z taller ($P = 0.022$) than those who weighed 2501 g to 3500 g. However, low-birth-weight babies were not significantly shorter than normal-weight babies after age 2 y. Shorter babies remained short during the school-aged years; the HAZ difference between extreme tertiles of birth length was 0.51 by age 10 y ($P = 0.005$). In a subsample comprising of 168 children with both birth weight and birth length information, the association between birth weight and linear growth was attenuated after further adjustment for birth length. By age 10 y, the HAZ difference between children weighing >3500 g and children weighing 2501 g to 3500 g at birth decreased to 0.19 ($P = 0.315$).

Early introduction of cow's milk and the occurrence of diarrhea were related to HAZ at 12 mo and 10 y, respectively, but these associations were not statistically significant ($P = 0.078$ and $P = 0.069$, respectively).

Table 3 Multivariable models for height-for-age Z scores by socioeconomic, maternal and child characteristics, Acrelândia, Brazil

	Adjusted mean HAZ (SE) according to age[1,2]					
	6 mo	**12 mo**	**2 y**	**5 y**	**7 y**	**10 y**
MODEL 1 (n = 231)[3]						
Wealth index						
Below median	−0.37 (0.20)	−0.43 (0.17)	−1.01 (0.12)	−0.60 (0.09)	−0.47 (0.08)	−0.47 (0.08)
Above median	0.07 (0.25)	−0.29 (0.21)	−0.68 (0.16)	−0.30 (0.10)	−0.23 (0.09)	−0.30 (0.10)
Difference [95% CI]	0.44 [−0.18, 1.06]	0.14 [−0.39, 0.67]	0.33 [−0.06, 0.72]	0.30 [0.06, 0.54]	0.25 [0.02, 0.48]	0.17 [−0.07, 0.40]
Land ownership						
No	−0.37 (0.20)	−0.43 (0.17)	−1.01 (0.12)	−0.60 (0.09)	−0.47 (0.08)	−0.47 (0.08)
Yes	0.16 (1.12)	0.00 (0.46)	−0.77 (0.27)	−0.29 (0.16)	−0.14 (0.15)	−0.13 (0.15)
Difference	0.53 [−1.68, 2.73]	0.43 [−0.41, 1.28]	0.24 [−0.24, 0.73]	0.31 [0.01, 0.61]	0.33 [0.06, 0.61]	0.34 [0.05, 0.63]
MODEL 2 (n = 231)[4]						
Mother's height						
a. 1st tertile: ≤154.0 cm	−1.12 (0.33)	−0.73 (0.26)	−1.33 (0.17)	−0.95 (0.13)	−0.80 (0.13)	−0.72 (0.12)
b. 2nd tertile: 154.1-159.4 cm	−0.48 (0.33)	−0.45 (0.24)	−0.95 (0.17)	−0.52 (0.11)	−0.43 (0.10)	−0.52 (0.12)
c. 3rd tertile: ≥159.5 cm	−0.02 (0.30)	−0.12 (0.30)	−0.73 (0.19)	−0.38 (0.12)	−0.25 (0.12)	−0.18 (0.11)
Difference (b-a)	0.64 [−0.16, 1.43]	0.28 [−0.35, 0.91]	0.37 [−0.07, 0.82]	0.43 [0.14, 0.72]	0.37 [0.09, 0.64]	0.20 [−0.10, 0.51]
Difference (c-a)	1.10 [0.35, 1.84]	0.61 [−0.06, 1.28]	0.60 [0.17, 1.03]	0.57 [0.27, 0.87]	0.55 [0.27, 0.84]	0.54 [0.26, 0.81]
P for trend	0.252	0.222	0.172	0.157	0.153	0.147
MODEL 3 (n = 226)[5]						
Child's birth weight						
a. ≤2500 g	−1.78 (0.50)	−1.43 (0.47)	−2.13 (0.30)	−1.22 (0.13)	−0.96 (0.14)	−0.94 (0.16)
b. 2501-3500 g	−1.23 (0.31)	−0.76 (0.26)	−1.35 (0.18)	−1.03 (0.13)	−0.88 (0.13)	−0.78 (0.14)
c. >3500 g	−0.03 (0.33)	−0.25 (0.31)	−0.84 (0.22)	−0.50 (0.17)	−0.42 (0.16)	−0.47 (0.16)
Difference (a-b)	−0.55 [−1.53, 0.43]	−0.67 [−1.64, 0.30]	−0.78 [−1.39, −0.16]	−0.19 [−0.49, 0.10]	−0.08 [−0.39, 0.22]	−0.16 [−0.51, 0.19]
Difference (c-b)	1.20 [0.62, 1.78]	0.51 [−0.03, 1.05]	0.51 [0.14, 0.88]	0.53 [0.26, 0.78]	0.46 [0.21, 0.70]	0.31 [0.05, 0.57]
P for trend	0.279	0.262	0.221	0.180	0.162	0.141
MODEL 4 (n = 168)[6]						
Child's birth length						
a. 1st tertile: ≤48 cm	−1.10 (0.47)	−0.98 (0.33)	−1.76 (0.20)	−0.97 (0.16)	−0.79 (0.16)	−0.88 (0.15)
b. 2nd tertile: 49–50 cm	0.18 (0.48)	−0.93 (0.30)	−1.00 (0.22)	−0.76 (0.17)	−0.66 (0.15)	−0.56 (0.17)
c. 3rd tertile: ≥51 cm	1.07 (0.65)	−0.42 (0.36)	−0.72 (0.28)	−0.42 (0.21)	−0.35 (0.19)	−0.37 (0.18)
Difference (a-b)	−1.28 [−1.91, −0.64]	−0.05 [−0.59, 0.50]	−0.76 [−1.18, -0.34]	−0.21 [−0.52, 0.09]	−0.13 [−0.41, 0.16]	−0.32 [−0.63, −0.01]
Difference (c-b)	0.89 [−0.03, 1.80]	0.51 [−0.24, 1.26]	0.28 [−0.22, 0.79]	0.34 [−0.03, 0.70]	0.31 [−0.03, 0.64]	0.19 [−0.16, 0.54]
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
MODEL 5 (n = 213)[7]						
Age at cow's milk introduction						
<3 months	−1.62 (0.37)	−1.20 (0.35)	−1.52 (0.19)	−1.11 (0.15)	−0.98 (0.14)	−0.93 (0.16)
≥3 months	−1.75 (0.30)	−0.62 (0.29)	−1.35 (0.21)	−1.08 (0.15)	−0.94 (0.14)	−0.84 (0.15)
Difference	0.13 [−0.51, 0.79]	−0.58 [−1.22, 0.06]	−0.17 [−0.53, 0.20]	−0.03 [−0.26, 0.20]	−0.04 [−0.26, 0.18]	−0.09 [−0.34, 0.15]
MODEL 6 (n = 210)[8]						
Diarrhea 15 days before baseline visit						

Table 3 Multivariable models for height-for-age Z scores by socioeconomic, maternal and child characteristics, Acrelândia, Brazil *(Continued)*

No	−1.80 (0.36)	−0.46 (0.28)	−1.32 (0.22)	−1.12 (0.16)	−0.96 (0.15)	−0.80 (0.16)
Yes	−2.26 (0.49)	−0.47 (0.37)	−1.18 (0.27)	−1.13 (0.17)	−1.07 (0.16)	−1.04 (0.17)
Difference	−0.46 [−1.27, 0.34]	−0.01 [−0.63, 0.61]	0.14 [−0.28, 0.56]	−0.01 [−0.25, 0.23]	−0.11 [−0.35, 0.13]	−0.24 [−0.50, 0.02]

1. HAZ: height-for-age Z score, calculated according to the WHO growth references [13,14].
2. Adjusted mean HAZ values and standard errors were estimated from restricted cubic spline regression models. The age distribution of available measurements used in these models was: 0 to <6 mo: 21; 6 mo to <12 mo: 27; 12 mo to <2 y: 47; 2 y to <5 y: 162; 5 y to <7 y: 100; 7 y to <10 y: 274; and ≥10 y: 74.
3. Co-variates in the model: wealth index and land ownership.
4. Co-variates in the model: model 1 plus mother's height.
5. Co-variates in the model: model 2 plus child's birth weight.
6. Co-variates in the model: model 2 plus child's birth length.
7. Co-variates in the model: model 3 plus age at cow's milk introduction.
8. Co-variates in the model: model 5 plus morbidities in the past 15 days.

Discussion

In this population-based cohort study of children from the Brazilian Amazon, socioeconomic background was positively related to linear growth during the school-aged years, whereas maternal height and child birth weight and length were associated with height up until age 10 y.

Previous prospective studies in developed and developing countries have shown associations between socioeconomic variables and attained height. The 1958 British birth cohort found that manual social class, family size, and household crowding were inversely related to considerable differences in height at ages 7 y, 11 y, 16 y, and 33 y [21]. Although in past decades these characteristics affected linear growth throughout childhood, results from a more recent generation of British children have shown that socioeconomic disparities now have a major impact on birth length – an indication that, in a high-income setting, socioeconomic position expresses its effects on height mostly through mechanisms before birth rather than during childhood [22].

Among low- to middle-income settings, nationally representative studies performed in India and Thailand have concluded that linear growth retardation is disproportionately concentrated among children from poor households [23,24], but few studies have been conducted in cohorts followed for several years. Our findings indicate that the socioeconomic background is an important predictor of linear growth in this population of pre-school and school-aged children from the Brazilian Amazon. Interventions to ameliorate poverty could have positive effects on linear growth. A conditional cash transfer program in Mexico was found to enhance linear growth among infants by approximately 0.40 Z after 2 year's implementation [25]. It is unknown whether this effect can be sustained through school age. Four Brazilian cross-sectional national household surveys performed over a 33-year period showed a steep decline in the overall prevalence of stunting among children aged <5 y due to economic growth coupled with equity-oriented public policies and improvements in the population's purchasing power, maternal education, sanitation, and access to health care [26]. These surveys, however, did not include older children, nor were they representative of Amazonian populations.

Our results are consistent with the literature regarding the constant and positive association of maternal height with child's linear growth. An analysis of 109 cross-sectional demographic and health surveys in 54 low- to middle-income countries confirmed that maternal stature is inversely associated with the likelihood of stunting of offspring up until age 5 y [27]. Among these Brazilian Amazon children, and as reported from Great Britain [21] and Pelotas [8] birth cohorts, maternal nutrition may represent the combined effects of genetics and early-life environmental factors, reflecting the intergenerational transfer of both socioeconomic conditions and biologic mechanisms that have consequences for child health. For example, shorter mothers might provide an inadequate supply of nutrients to their fetuses and have narrower pelvises, thereby increasing risk for deliveries with complications [28].

Concerning perinatal exposures, child's birth weight and length were strong and positive determinants of HAZ throughout school age, in agreement with previous studies [6,8,29]. Although birth weight is in some ways conditioned to maternal height [21], it is noteworthy that the association of birth weight with HAZ was virtually unchanged after controlling for socioeconomic and maternal characteristics, suggesting that the influence of birth weight is independent of maternal stature. Consistent with this notion, a cohort of Belgian monozygotic twin girls (allowing control for genetic and maternal factors) found that the twin who was at least 5% heavier at birth was also taller as an adult [30].

In our study, early introduction of cow's milk was not significantly associated with HAZ. Only a few previous longitudinal investigations have reported long-term associations between infant feeding practices and anthropometric outcomes [8,21,31]. Evidence linking untimely introduction of cow's milk with diseases such as type 1 diabetes [32] suggests that complementary feeding should provide appropriate foods in addition to breast

milk at around age 6 mo [33,34] to ensure satisfactory nutritional status during infancy.

The present findings should be considered in light of the limitations and strengths of our study. Although this was a population-based study, sample size was relatively small. Because of the high mobility of Acrelândia's residents, mostly driven by job offers, the follow-up rate was 55% (256 of 468 children who participated at baseline). However, children included in the analyses were not statistically different from those who were not included with respect to sex, age, length/height, and the socioeconomic, maternal, and child characteristics at baseline. Another limitation is that we lacked information on child's father. Birth weight and length were obtained from child health cards rather than through direct measurement by the research team. Nonetheless, there is evidence that these birth weight records have high validity in Brazil [35]. There are several strengths to the study, including its longitudinal design, the extended follow-up period, the large number of determinants examined, and the fact that a dropout analysis involving baseline determinants showed no significant differences between children lost to follow-up and those who stayed in the cohort. Furthermore, our results were based on direct and standardized length/height measurements for both children and their mothers.

Conclusions

In conclusion, we found that socioeconomic background, a potentially modifiable factor, is a predictor of linear growth during the school-aged years, and maternal height and infant characteristics at birth influence growth throughout childhood. Because height measured during late childhood is highly correlated with adult height, interventions to enhance population health should begin by focusing on distal determinants of linear growth and consider social inequalities in early life.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BHL contributed to the study design and data collection; BHL, EV, and RAA participated in statistical data analyses; BHL conducted data analyses, interpreted results, and wrote the initial draft of the manuscript; MAC implemented and supervised all study protocols and was responsible for project management; BHL, EV and MAC participated in data interpretation and were involved in the review of the manuscript. All authors read and approved the final manuscript.

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4.3 ARTIGO 3

Influence of early life factors on body mass index trajectory during childhood: a population-based longitudinal analysis in the Western Brazilian Amazon

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Original Article

Influence of early life factors on body mass index trajectory during childhood: a population-based longitudinal analysis in the Western Brazilian Amazon

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Abstract

Low- to middle-income countries may experience the occurrence of a dual burden of under and overnutrition. To better understand the overall progression of body mass index (BMI) during childhood, we estimated average BMI-for-age *z*-score (BAZ) growth curves in a population-based longitudinal study of 255 children living in the Brazilian Amazon. Children were aged 0.1–5.5 years at recruitment (2003). We collected data on socio-economic and maternal characteristics, children's birthweight and infant feeding practices. Child anthropometric measurements were taken in 2003, 2007 and 2009. BAZ differences among categories of exposure variables were calculated at 6 and 12 months, and 2, 7 and 10 years. At baseline, the mean (standard deviation) age was 2.6 (1.4) years; 12.9% were overweight and 3.9% thin. After adjustment, mean BAZ estimates were mostly negative. Boys were close to the median value for BAZ until 12 months, whereas girls were below the median ($P = 0.05$). Children from households above the wealth median were 0.36 *z*- and 0.49 *z*-less underweight than poorer children at 7 and 10 years, respectively ($P < 0.01$). Maternal BMI was positively associated with children's BAZ since 12 months old; BAZ in children from overweight mothers was higher by 0.69 compared with their counterparts at 10 years ($P < 0.01$). Birthweight was positively related to BAZ up until 2 years ($P = 0.01$). Socio-economic background and maternal nutritional status are important predictors of BAZ throughout childhood. Although excessive weight gain is a public health concern, it is critical to restrict inequities, while promoting healthier growth in developing countries.

Keywords: child growth, BMI-for-age *z*-score, trajectory, school-age years, developing countries.

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Introduction

Low- to middle-income countries have been experiencing modifications in the nutritional profile of their populations because of alterations in environmental, socio-economic and demographic factors during the last decades (Popkin 2001). Consequently, excessive weight gain has affected adults (Finucane *et al*. 2011), as well as children and adolescents (Wang & Lobstein 2006), in both developed and developing settings worldwide. It is debatable regarding how the current stage of nutrition transition affects changes in body mass index (BMI) in low- to middle-income countries. Some studies concluded that excessive weight gain is still concentrated among the wealthier groups of these countries (Neuman *et al*. 2011). In contrast, other investigations have suggested that a faster increase in overweight rates occurs in the lower socio-

economic strata, which could be an indication of a shift in the overnutrition burden to the poor (Jones-Smith *et al.* 2012).

Studies on BMI determinants from birth to school-age years have prioritised the investigation of factors associated with overweight and obesity (Li *et al.* 2007; Kleiser *et al.* 2009; Manios *et al.* 2010). However, there is consistent evidence that developing countries commonly face critical social and health inequities (Barros *et al.* 2010). This can result in the occurrence of a dual burden of concomitant under and overnutrition from early childhood, increasing short- to long-term morbidity and mortality risks because of higher susceptibility to infectious diseases (Black *et al.* 2008) or to the development of chronic metabolic disorders (Han *et al.* 2010). As a result, it is important to better understand the mechanisms determining the overall progression of body weight during childhood in low- to middle-income countries, rather than to solely assess specific categories of child nutritional status. Furthermore, it would be informative to make use of a normative measure for growth and development when examining BMI values among children, because this might assist the efforts for adequate implementation of public health policies.

This study aimed to investigate socio-economic, maternal and child early life determinants of BMI up to the age of 10 years in a population-based cohort study of children living in the Brazilian Amazon. For this purpose, we examined growth trajectories of BMI-for-age and sex *z*-scores (BAZ) throughout childhood according to the World Health Organization (WHO) international references. We particularly focused on BAZ estimates during infancy (up until 2 years old), the period associated with adiposity rebound (occurs up to 7 years old) and late childhood (10 years old).

Materials and methods

Study design and population

This longitudinal study was conducted in the urban area of Acrelândia, a town located 100 km from Rio Branco, the capital of the state of Acre, in the Western Brazilian Amazon region. Covering a territory of 1607.5 km^2, the main economic activities in this town are commercial agriculture and raising cattle. By 2003, Acrelândia had 8697 inhabitants, of whom 43% resided in the urban area.

In January 2003, we conducted a population-based cross-sectional study in Acrelândia with the assistance of local teams of the Family Health Program of the Brazilian Ministry of Health (Muniz *et al.* 2007). All households from this urban area with children aged <5 years were identified and invited to participate ($n = 334$), and only two declined participation. Data were collected from 332 households (99.4%) involving a total of 489 children. Complete anthropometric information was available for 467 children (95.5% of those eligible).

As reported elsewhere (Garcia *et al.* 2011), in December 2007, a second population-based cross-sectional survey was carried out in the same area among all children aged <10 years, and included 250 of the children who had previously been examined in 2003. In December 2009, another follow-up assessment included 205 of the children who had been evaluated in 2003 and/or 2007. The current longitudinal analyses comprised 255 children with valid weight

Key messages

- Socio-economic background and maternal nutritional status are the most important predictors of BMI throughout childhood in a population-based cohort study in the Brazilian Amazon.
- Because BMI-for-age estimates were mostly negative, the positive associations with socio-economic and maternal characteristics found in our study indicate that children in the upper categories of wealth and maternal nutritional status were not more overweight, but less underweight than their counterparts.
- Although being overweight and obese have become a major public health concern worldwide, public health policies should consider the reduction of inequities to promote healthier child growth in low- to middle-income settings.

and length/height measurements in 2003 and at least at one other time point. These children contributed a total of 703 anthropometric measurements. The age distribution of the number of measurements in children was as follows: 0 to <6 months: 20; 6 to <12 months: 27; 12 months to <2 years: 47; 2 to <7 years: 261; 7 to <10 years: 274; and ≥10 years: 74.

Written informed consent for participation was obtained from parents or guardians before enrolment. This study was approved by the ethical review board of the School of Public Health, University of São Paulo, Brazil.

Data collection and anthropometry

At baseline (2003), trained fieldworkers performed structured face-to-face interviews with each child's mother or guardian during household visits. Information was collected on child's sex, age and race, presence of household assets, maternal age, education level and occurrence of hypertension during pregnancy, and child's age at introduction of weaning foods. Birthweight was retrieved from child health cards (Muniz *et al*. 2007).

Trained research assistants obtained anthropometric measurements from the children at a local family health clinic (in the 2003 and 2007 surveys) or at the households (in 2009), using standardised procedures and calibrated equipment (Lohman *et al*. 1988). The date of birth was recorded directly from birth certificates or child health cards. In 2003, among children aged <24 months, weight was measured in light clothing and without shoes to the nearest 10 g on an electronic paediatric scale (Tanita model 1583, Tanita Corporation, Tokyo, Japan), and recumbent length was measured to the nearest millimetre with a locally made infant measuring board. For children aged ≥2 years, weight was measured in light clothing and without shoes to the nearest 100 g on an electronic scale (Tanita model HS-302), and height was measured to the nearest millimetre with a stadiometre (Seca, Hamburg, Germany in 2003 and 2007; WCS, Curitiba, Brazil in 2009) affixed to a flat surface on a wall, without a baseboard and perpendicular to the floor. Children were positioned barefoot in the vertical standing position in the middle of the stadiometre, with their head, shoulders, buttocks and heels against the wall. Mother's weight and height were subsequently measured by the research assistants, following the same standardised procedures (Lohman *et al*. 1988). Each measurement was repeated, and the mean value was calculated.

Data management

BMI was computed as weight in kg divided by length/height in m^2. We then calculated BAZ, our main outcome of interest, according to the WHO Child Growth Standards (WHO 2006) for children aged 0–5 years and the WHO Growth Reference Data (de Onis *et al*. 2007) for children >5 years. The measured exposures comprised baseline household socio-economic status, maternal characteristics and child's birthweight. We also examined associations with infant feeding practices and height at baseline.

To assess the household socio-economic status, we performed a principal component analysis to generate a wealth index based on the presence of 14 home appliances (Muniz *et al*. 2007). After standardising the weight of household assets, scores were added to produce an estimated index of household wealth (Filmer & Pritchett 2001). Predictors were categorised according to previously used cut-off points in this population. The wealth index was examined in quartiles, tertiles, and as less than or as greater than or equal to the median. Because similar results were observed, we opted to present the associations for this variable according to the latter classification. Maternal nutritional status was classified according to BMI categories as non-overweight (<25 kg m^{-2}) and overweight (≥25 kg m^{-2}), because only 16 mothers had BMI values ≥30 kg m^{-2}. Child's birthweight was categorised as ≤2500, 2501–3500 or >3500 g. The age at introduction of cow's milk, an indicator of infant feeding practices, was classified as <3 vs. ≥ 3 months. According to the WHO growth curves, stunting at baseline was defined as a height-for-age *z*-score <–2, thinness as BAZ <–2 and risk of overweight or obesity as BAZ >1.

From a total of 467 children included at baseline (2003), the distribution of sex, age, weight, length/height, and socio-economic, maternal, and child char-

acteristics of children who were followed-up in the 2007 and/or 2009 assessments, and therefore were included in the longitudinal analyses ($n = 255$), was similar to the distribution of those who were not followed ($n = 212$).

Statistical analysis

First, we compared the distribution of BAZ by categories of socio-economic, maternal and child characteristics at baseline, using tests of trend for ordinal predictors and the Wilcoxon rank–sum test for dichotomous predictors.

We then examined the associations between the exposures of interest and BAZ by estimating average BAZ-for-age growth curves for each category of the predictors with the use of mixed-effect models for repeated measurements with restricted cubic splines (see Appendix 1). Cubic splines represent non-linear terms for age at each assessment that allow smoothing of the relation between BAZ and age. Piecewise cubic polynomials are smoothly joined at joint points or 'knots' (Durrleman & Simon 1989; Lourenço *et al.* 2012). Knots were placed at the ages 0.25, 0.75, 1.50, 3.50 and 9 years, because these ages appear to be important reference points in the curvilinear segments of the WHO growth curves (de Onis *et al.* 2007, WHO 2006). In each model, the outcome was BAZ, and covariates comprised the predictor of interest, linear and spline terms for child age in decimal years, and predictor category × age interaction terms. Random effects for the intercept and the linear term for age (slope) were included to account for the within-person correlation of measurements in the estimation of the variance (Diggle *et al.* 2002). These methods do not require an equal number of measurements in all children, nor that measurements must be obtained at exactly the same time points on every participant; therefore, all available measurements were included in the models. Because the age distribution of children at baseline ranged from 0 to 5 years, we tested for possible birth cohort effects on the construction of the curves by including terms for year of birth. These terms were not statistically significant and their introduction did not change the magnitude of the associations. Estimates also remained similar when we considered additional adjustment for potential correlations among siblings within the same household.

Adjusted mean BAZ-for-age curves were obtained using multivariable mixed-effect models. Variables were included in the model if they were considered conceptually relevant or if there was a clear association with the outcome in the unadjusted analyses. Statistical significance was an additional criterion for retaining a variable in the model. Missing observations were included in the multivariable model by creating missing-value categories. We compared results from the model with missing-value categories with those from a complete case analysis. Because magnitude and direction of all associations were similar, we decided on the first approach to preserve all 255 children in the multivariable model.

We estimated BAZ from the growth curves at the ages of 6 months, 12 months, 2 years, 7 years and 10 years, as the predicted values of the spline function, with values of predictor covariates at the reference category. Differences in the values of BAZ and their 95% confidence intervals (CIs) were calculated among the categories of each predictor at these ages. All reported *P*-values are two-tailed. We used SAS 9.2 (SAS Institute Inc., Cary, NC, USA) for all analyses.

Results

At baseline, among 467 children with complete anthropometric information, the mean (standard deviation) age of children was 2.6 (1.4) years (range: 0.1–5.5 years), 50.8% were male, and 88.1% were mulatto. BAZ was positively associated with male sex and maternal BMI (Table 1). In 2003, the prevalence of thinness was 3.9% (4.4% among girls and 3.4% among boys), and 12.9% of the children were considered at risk of being overweight or obese (9.6% among girls and 16.0% among boys).

The median follow-up time for the 255 children who were evaluated in 2007 and/or 2009 was 6.9 years (range: 4.9–7.5 years), during which time a median of three anthropometric measurements was collected for each child (range: 2–3, 62 children had two and 193 children had three measurements). In 2007 and 2009,

Table 1. Mean body mass index-for-age *z*-score according to baseline characteristics of children with complete anthropometric information [Acrelândia, Brazil (2003)]

	n (%)*	Mean BAZ (SD)†	*P*‡	Missing (%)
Child's sex			<0.001	0.0
Female	230 (49.2)	–0.33 (1.08)		
Male	237 (50.8)	–0.06 (1.12)		
Child's age (months)			<0.001	0.0
0–5	32 (6.9)	–0.17 (1.05)		
6–11	53 (11.3)	0.29 (1.03)		
12–23	80 (17.1)	0.44 (1.19)		
24–35	100 (21.4)	–0.32 (1.00)		
≥36	202 (43.3)	–0.51 (1.01)		
Wealth index			0.32	1.5
Below median	245 (53.3)	–0.23 (1.15)		
Above median	215 (46.7)	–0.13 (1.07)		
Mother's educational level (years)			0.88	39.6
0–4	148 (52.5)	–0.23 (1.07)		
≥5	134 (47.5)	–0.19 (0.99)		
Mother's age (years)			0.07	31.5
≤20	44 (13.8)	0.09 (0.99)		
21–30	194 (60.6)	–0.20 (1.03)		
>30	82 (25.6)	–0.30 (1.17)		
Mother's BMI (kg m^{-2})			0.05	10.3
Non-overweight (<25)	278 (66.4)	–0.26 (1.08)		
Overweight (≥25)	141 (33.6)	–0.04 (1.15)		
Hypertension during pregnancy			0.04	6.2
No	392 (89.5)	–0.21 (1.07)		
Yes	46 (10.5)	0.19 (1.35)		
Child's birthweight (g)			0.09	3.0
≤2500	44 (9.7)	–0.07 (1.45)		
2501–3500	277 (61.2)	–0.34 (0.98)		
>3500	132 (29.1)	0.11 (1.15)		
Age at cow's milk introduction (months)			0.54	9.0
<3	136 (32.0)	–0.11 (1.21)		
≥3	289 (68.0)	–0.21 (1.06)		
Stunting at baseline			0.75	0.0
No	420 (89.9)	–0.20 (1.12)		
Yes	47 (10.1)	–0.12 (0.99)		

BMI, body mass index; SD, standard deviation. *Totals may be less than 467 because of missing values. †BAZ: BMI-for-age *z*-scores, calculated according to the World Health Organization (WHO) growth curves (de Onis *et al*. 2007, WHO 2006). ‡Test for linear trend for ordinal predictors; for dichotomous predictors, Wilcoxon rank–sum test.

9.6 and 17.6% of the children were at risk of being overweight or obese, respectively.

In unadjusted analyses, male sex was positively associated with mean BAZ from 6 months to 7 years. Household wealth and maternal BMI were also positively related to children's mean BAZ at ages 7 and 10 years. Children weighing >3500 g at birth had significantly higher BAZ values compared with children who weighed 2501–3500 g up until 2 years of age (Table 2).

In the multivariable model (Table 3), boys had a significantly higher BAZ than girls until 12 months and at 7 years. Socio-economic status remained significantly associated with BAZ during school-age years. Children from households above the wealth median had BAZ values higher by 0.36 (95% CI: 0.10, 0.61) at 7 years and by 0.49 (95% CI: 0.19, 0.81) at 10 years compared with children from households below the wealth index median. Maternal BMI was associated with children's BAZ since 12 months of age. By

Table 2. Body mass index-for-age *z*-scores according to age and baseline characteristics. Acrelândia, Brazil, unadjusted analysis (2003–2009)

	*n**	Mean BAZ (SE) according to age†‡				
		6 months	12 months	2 years	7 years	10 years
Child's sex	255					
Female		–0.27 (0.24)	0.09 (0.21)	–0.28 (0.11)	–0.57 (0.09)	–0.14 (0.10)
Male		0.44 (0.22)	0.93 (0.20)	0.04 (0.13)	–0.09 (0.10)	0.06 (0.13)
Difference (95% CI)		0.71 (0.07, 1.35)	0.84 (0.27, 1.41)	0.32 (–0.01, 0.64)	0.48 (0.22, 0.74)	0.20 (–0.12, 0.52)
Wealth index	253					
Below median		0.03 (0.14)	0.42 (0.17)	–0.20 (0.12)	–0.47 (0.09)	–0.25 (0.11)
Above median		0.08 (0.34)	0.58 (0.24)	–0.05 (0.12)	–0.17 (–0.10)	0.18 (0.12)
Difference		0.05 (–0.68, 0.78)	0.16 (–0.43, 0.74)	0.15 (–0.18, 0.48)	0.30 (0.03, 0.56)	0.43 (0.11, 0.75)
Mother's BMI (kg m^{-2})	229					
Non-overweight (<25)		–0.04 (0.19)	0.28 (0.17)	–0.22 (0.10)	–0.50 (0.08)	–0.27 (0.10)
Overweight (≥25)		0.32 (0.43)	1.20 (0.27)	0.13 (0.16)	0.05 (0.15)	0.41 (0.15)
Difference		0.36 (–0.56, 1.29)	0.92 (0.28, 1.56)	0.35 (–0.02, 0.72)	0.55 (0.22, 0.88)	0.68 (0.33, 1.04)
Hypertension during pregnancy	228					
No		0.10 (0.17)	0.35 (0.16)	–0.16 (0.09)	–0.36 (0.07)	–0.08 (0.09)
Yes		0.13 (0.49)	1.21 (0.35)	0.18 (0.22)	0.06 (0.24)	0.37 (0.25)
Difference		0.03 (–0.99, 1.05)	0.86 (0.10, 1.61)	0.34 (–0.14, 0.81)	0.42 (–0.06, 0.91)	0.45 (–0.06, 0.97)
Child's birthweight (g)	249					
a. ≤2500		0.96 (0.47)	1.00 (0.43)	–0.05 (0.35)	–0.30 (0.37)	0.14 (0.39)
b. 2501–3500		–0.31 (0.19)	0.15 (0.19)	–0.27 (0.10)	–0.39 (0.08)	–0.09 (0.09)
c. >3500		0.67 (0.23)	1.02 (0.22)	0.18 (0.15)	–0.18 (0.11)	0.05 (0.17)
Difference (a – b)		1.27 (0.27, 2.27)	0.85 (–0.06, 1.77)	0.22 (–0.50, 0.94)	0.09 (–0.65, 0.83)	0.23 (–0.55, 1.02)
Difference (c – b)		0.98 (0.40, 1.57)	0.87 (0.31, 1.43)	0.45 (0.09, 0.81)	0.21 (–0.07, 0.49)	0.14 (–0.24, 0.52)
Age at cow's milk introduction (months)	241					
<3		0.34 (0.22)	0.89 (0.27)	0.03 (0.16)	–0.18 (0.13)	0.01 (0.15)
≥3		–0.03 (0.33)	0.32 (0.18)	–0.17 (0.10)	–0.40 (0.08)	–0.10 (0.10)
Difference		0.37 (–0.40, 1.15)	0.57 (–0.07, 1.21)	0.20 (–0.17, 0.58)	0.22 (–0.08, 0.52)	0.11 (–0.24, 0.47)
Stunting at baseline	255					
No		0.00 (0.18)	0.49 (0.15)	–0.14 (0.09)	–0.36 (0.07)	–0.06 (0.08)
Yes		0.77 (0.78)	1.25 (1.09)	–0.29 (0.23)	0.56 (0.50)	0.21 (0.21)
Difference		0.77 (–0.79, 2.34)	0.76 (–1.39, 2.91)	–0.15 (–0.61, 0.31)	0.92 (–0.07, 1.90)	0.27 (–0.14, 0.68)

BMI, body mass index; CI, confidence interval; SE, standard error. *Totals may be less than 255 due to missing values. †BAZ: BMI-for-age *z*-scores,calculated according to the World Health Organization (WHO) growth references (de Onis *et al*. 2007,WHO 2006). ‡Unadjusted mean values and standard errors were estimated from restricted cubic spline regression models.

the age of 10 years, children whose mothers were overweight had a mean BAZ value higher by 0.69 (95% CI: 0.35, 1.04) in relation to children from non-overweight mothers. Birthweight also remained positively related to BAZ during the first 2 years of life after multivariable adjustment. From 6 months to 2 years, the difference in BAZ between children weighing >3500 g and those weighing 2501–3500 g at birth ranged from 0.92 (95% CI: 0.26, 1.59) to 0.44 (95% CI: 0.10, 0.80). This difference considerably decreased to 0.20 *z* at 7 years old and 10 years old, and was not significant at this time. Low-birthweight babies had a higher mean BAZ value at 6 months compared with that in babies in the reference category (difference: 1.40; 95% CI: 0.21, 2.58).

Early introduction of cow's milk was not associated with BAZ after adjustment for sex, socio-economic status, maternal nutritional status and birthweight. A positive association between stunting at baseline and BAZ was significant only at 7 years (difference: 0.98; 95% CI: 0.04, 1.90).

To assess the influence of the most important early life predictors on the overall progression of children's body weight, we present adjusted mean BAZ-for-age

Table 3. Multivariable model for body mass index-for-age *z*-scores by socio-economic, maternal and child characteristics [Acrelândia, Brazil (2003–2009)]

	Adjusted mean (SE) BAZ according to age*† ($n = 255$)				
	6 months	12 months	2 years	7 years	10 years
Child's sex					
Female	–0.92 (0.35)	–0.42 (0.26)	–0.59 (0.15)	–0.94 (0.11)	–0.66 (0.14)
Male	–0.10 (0.27)	0.23 (0.30)	–0.35 (0.17)	–0.47 (0.13)	–0.45 (0.16)
Difference (95% CI)	0.82 (0.10, 1.54)	0.65 (0.08, 1.23)	0.24 (–0.10, 0.59)	0.47 (0.21, 0.72)	0.21 (–0.09, 0.52)
Wealth index					
Below median	–0.92 (0.35)	–0.42 (0.26)	–0.59 (0.15)	–0.94 (0.11)	–0.66 (0.14)
Above median	–0.62 (0.35)	–0.22 (0.28)	–0.39 (0.15)	–0.58 (0.12)	–0.17 (0.14)
Difference	0.30 (–0.38, 0.98)	0.20 (–0.33, 0.75)	0.20 (–0.14, 0.54)	0.36 (0.10, 0.61)	0.49 (0.19, 0.81)
Mother's BMI (kg m^{-2})					
Non-overweight (<25)	–0.92 (0.35)	–0.42 (0.26)	–0.59 (0.15)	–0.94 (0.11)	–0.66 (0.14)
Overweight (≥25)	–0.80 (0.43)	0.31 (0.36)	–0.23 (0.21)	–0.40 (0.17)	0.03 (0.19)
Difference	0.12 (–0.57, 0.79)	0.73 (0.11, 1.35)	0.36 (0.01, 0.73)	0.54 (0.22, 0.85)	0.69 (0.35, 1.04)
Child's birthweight (g)					
a. ≤2500	0.48 (0.51)	0.09 (0.47)	–0.39 (0.36)	–0.70 (0.35)	–0.28 (0.38)
b. 2501–3500	–0.92 (0.35)	–0.42 (0.26)	–0.59 (0.15)	–0.94 (0.11)	–0.66 (0.14)
c. >3500	0.00 (0.26)	0.35 (0.31)	–0.15 (0.20)	–0.74 (0.14)	–0.46 (0.20)
Difference (a – b)	1.40 (0.21, 2.58)	0.51 (–0.46, 1.48)	0.20 (–0.53, 0.94)	0.24 (–0.47, 0.94)	0.38 (–0.39, 1.15)
Difference (c – b)	0.92 (0.26, 1.59)	0.77 (0.24, 1.30)	0.44 (0.10, 0.80)	0.20 (–0.06, 0.45)	0.20 (–0.16, 0.56)

BMI, body mass index; CI, confidence interval; SE, standard error. *BAZ: BMI-for-age *z*-scores, calculated according to the WHO growth references (de Onis *et al*. 2007, WHO 2006). †Adjusted mean values and standard errors were estimated from restricted cubic spline regression models.

curves up to the age of 10 years using restricted cubic splines (Fig. 1). Mean BAZ estimates for all categories of exposure variables were mostly negative. While the influence of being born weighing >3500 g appeared to be more substantial during infancy, children from households above the wealth index median and from overweight mothers presented higher BAZ values, especially during school-age years compared with the growth trajectory for the reference category.

Discussion

Using data from a population-based prospective study of children residing in the Brazilian Amazon, we found that the BAZ during childhood was positively associated with the male sex, household wealth, maternal BMI and a child's birthweight. At baseline, the prevalence of being overweight in Acrelândia was lower than that observed in more affluent countries (Kipping *et al*. 2008; Kleiser *et al*. 2009) and wealthier regions of Brazil (Wang *et al*. 2002), and it increased by approximately 5% until the last follow-up assessment performed in 2009.

In our study, boys were close to the WHO median value for BAZ at 6 and 12 months of age, whereas girls were below this value. Previous evidence suggests that boys may be heavier than girls during childhood in some developed (Eriksson *et al*. 2001) and developing countries (Li *et al*. 2007; Mushtaq *et al*. 2011), but this is not a consensus (Kleiser *et al*. 2009; Maddah & Nikooyeh 2009). Social and cultural factors could affect childbearing practices and favour a specific sex group, especially at earlier ages. However, trend analyses comparing national cross-sectional surveys in the last decades have shown consistently higher increases in BMI for boys during childhood and adolescence in Brazil (Veiga *et al*. 2004) and in the United States (Ogden *et al*. 2012).

We found that higher household wealth was related to a greater BAZ at and after the age of 7 years. The association of socio-economic indicators with BMI may substantially differ according to the study's setting. While in high-income countries, there is a well-established inverse relationship (Howe *et al*. 2011), in low- to middle-income countries, greater BMI is usually related to higher socio-economic

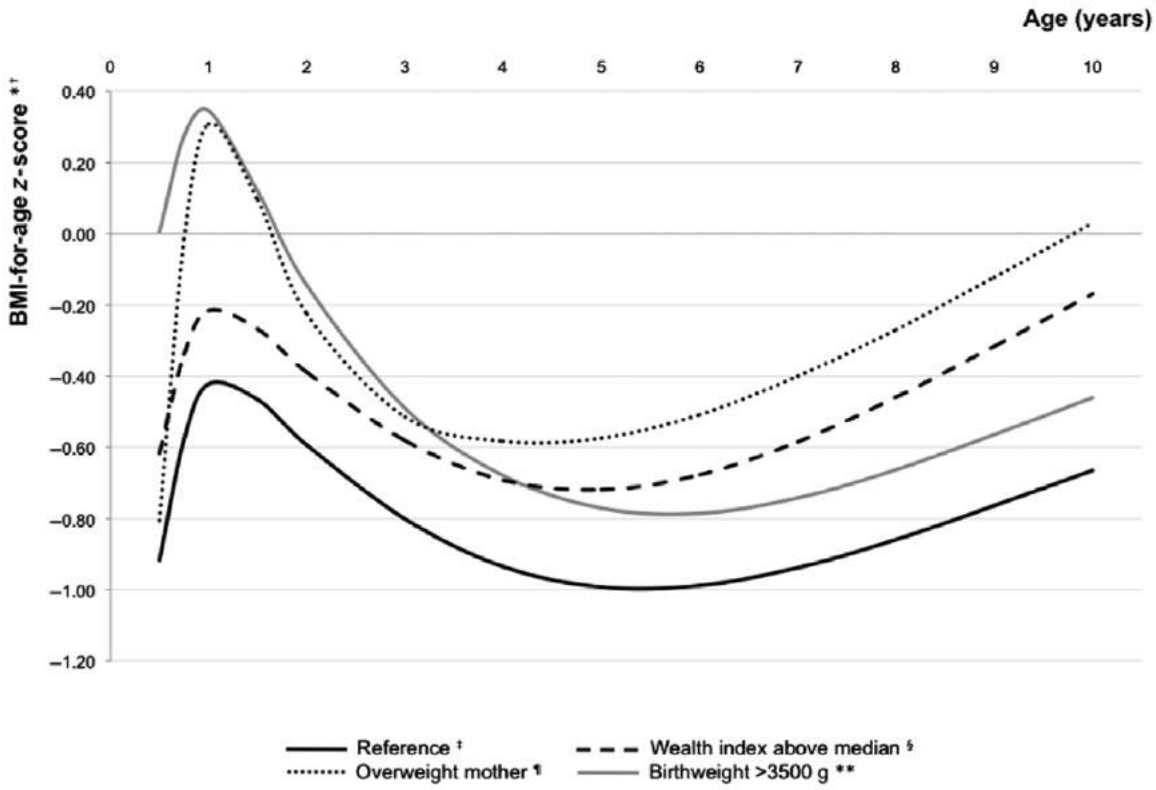

Fig. 1. Mean adjusted body mass index (BMI)-for-age *z*-score (BAZ) growth trajectories according to early life predictors, Acrelândia, Brazil. *Curves estimated from a restricted cubic splines multivariable model (Table 3). Covariates in the model: sex, wealth index, mother's BMI and child's birthweight.†BMI-for-age *z*-scores calculated according to the World Health Organization (WHO) growth references (de Onis *et al*. 2007, WHO 2006). ‡Reference category: wealth index below median, mother's BMI < 25 kg m^{-2} and child's birthweight 2501–3500 g. §Wealth index above the median predicts higher BAZ at 7–10 years. ¶Mother's BMI ≥ 25 kg m^{-2} predicts higher BAZ at 12 months to 10 years. **Child's birthweight > 3500 g predicts higher BAZ at 6 months to 2 years.

status (Griffiths *et al*. 2008; Maddah & Nikooyeh 2009). Notably, despite the positive association with household wealth, we observed in the present analysis, the mean BAZ value in the better-off group was still below the WHO reference median at any age. At the time of our study, Acrelândia had an estimated human development index of 0.68, which was considered intermediate and below the Brazilian national mean estimate of 0.75 (UNDP, Brazil 2000). Therefore, it is expected that affording proper and continuous access to food may be challenging in this region. In 2006, the prevalence of household food insecurity in the Brazilian macroregion that comprises the town of Acrelândia was 53.0% (Brazilian Ministry of Health 2009). By 2009, 53.9% of the children in this cohort were in households with food insecurity (M. Cardoso, unpublished observations). Because mean BAZ values were mostly negative, our results indicate that children from households above the wealth index median are not more overweight, but are less underweight than their counterparts, particularly during school-age years. Therefore, although the 'obesity epidemic' has become a major public health problem worldwide, it seems important to acknowledge within-country inequities affecting child populations from low- to middle-income countries (Barros *et al*. 2010), in spite of their overall emergent economic development.

In our study, maternal nutritional status was positively associated with children's BAZ since at a young age. This is an indication that shared genetic and environmental factors, as well as behavioural influences,

may act concomitantly in determining BMI in the offspring (Bouchard 2009; Fontaine *et al*. 2011). Moreover, in light of the socio-economic context of our study's population, it is noteworthy that children from overweight mothers had a BAZ that was nearly 0.70 higher than that of children from non-overweight mothers, yet it was not significantly above zero. These findings are consistent with other longitudinal studies showing that maternal BMI is a strong predictor of child's BMI and a major factor in the intergenerational transfer of body weight status (Cnattingius *et al*. 2011; Jääskeläinen *et al*. 2011).

In the current study, birthweight was positively related to a child's BAZ up until 2 years old, and this association was no longer statistically significant at 7 years or 10 years of age. While high birthweight has been positively associated with BMI during childhood in cross-sectional studies (Kleiser *et al*. 2009), our results are similar to a follow-up study in a Finnish rural community, where birthweight was not a good predictor of BMI at 7 years and 15 years of age, even though it was associated with BMI during infancy (Fuentes *et al*. 2003). Another population-based longitudinal investigation showed that birthweight could not satisfactorily explain the BMI distribution during school-age years (Rughlom *et al*. 2005).

In agreement with other reports (Lourenço & Cardoso 2009), early introduction of cow's milk was not related to BAZ during childhood in our study. Some surveys have shown that babies who have been breastfed for longer periods may exhibit slower weight gain (Karaolis-Danckert *et al*. 2007), but a long-term effect of infant feeding practices on the mean BMI from childhood to early adulthood is not supported by evidence from prospective studies (Victora *et al*. 2003; Bonuck *et al*. 2010). We also did not find consistent associations between stunting at baseline and BAZ. A cross-sectional metabolic study that provided a self-selection menu to shantytown pre-pubertal children suggested that growth-stunted individuals might eat opportunistically and display signs of impaired regulation of energy intake (Hoffman *et al*. 2000). Conversely, a longitudinal study in South Africa showed that urban children who were stunted at 2 years of age had no differences in BMI and body composition 7 years later compared with non-stunted children (Cameron *et al*. 2005).

Our study has some limitations. First, this was a population-based study at baseline, but our follow-up rate was mainly affected by the high mobility of Acrelândia's residents in search for job offers in the region. The inability to contact participants because of migration out of the study's area was probably related to the sociodemographic context of their families. Therefore, caution should be taken when extrapolating our findings to the general population. Nevertheless, children included in the analyses (255 of 467 children who participated at baseline) were not different from those who were not included with respect to all the exposure variables observed at baseline, including socio-economic, maternal and child characteristics. Although it is not possible to ascertain that dropout was not related to unobserved covariates, losses to follow-up were also not differential with regard to child's sex, age and observed BAZ, our main outcome of interest. Second, lack of information on some exposure variables could potentially lead to the occurrence of missing data bias; however, we believe our results might not be influenced on average because the proportion of missing information for these variables in our longitudinal analysis was low (<10%). Third, even though information on children's fathers was not available, a recent large study with objectively measured data from both parents concluded that the maternal influence is stronger than the paternal effect on the intergenerational transmission of weight status (Whitaker *et al*. 2010). Fourth, birthweight was not directly measured by the research team, but there is evidence that child health records are valid in Brazil (Mascarenhas & Gomes 2011). Lastly, while the use of cubic splines provides flexibility to data, there is some indication that overfitting may be possible (especially with a large number of knots or a very small number of observations). In our analysis, the cubic spline function was constrained to be linear at the tails (i.e. before the first knot and after the last knot) and we considered the fewest possible number of knots, which were placed at essential age points considering the WHO growth curves. Our study also has several strengths, including its longitudinal design, a long follow-up period and the use of

direct and standardised weight and length/height measurements in both children and their mothers.

In conclusion, the present findings suggest that the socio-economic background and the maternal nutritional status are important predictors of a child's BAZ throughout childhood. In view of the magnitude of estimates in our study's population, it is possible that the nutritional status of children from the poorest families still suffer the consequences of a lack of resources from a young age, and public health policies should consider the reduction of economic and health inequities to promote healthier child growth. Given the increase in the percentage of children classified at risk of overweight from baseline to the last follow-up assessment, additional follow-up will be required to ascertain whether these exposures may actually lead to excessive weight gain in later years and adulthood.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

BHL contributed to the study design and data collection; BHL, EV and RAA participated in statistical data analyses; BHL conducted data analyses, interpreted results and wrote the initial draft of the paper; MAC implemented and supervised all study protocols and was responsible for project management; BHL, EV and MAC participated in data interpretation and were involved in the review of the paper. All authors read and approved the final paper.

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Appendix 1

Use of restricted cubic splines to estimate growth curves

The use of smoothing splines is a relatively simple method to avoid problems that arise from inadequate linearity assumptions for regression models. The cubic spline function is a piecewise polynomial of degree $n = 3$, constrained in its two first derivatives to be continuous at the joint points, or knots. The number (K) and position ($t_1 < t_2 < \ldots < t_K$) of the knots are fixed according to how the phenomenon under study varies over its covariate space. 'Restricted' cubic splines are cubic splines constrained to be linear at the tails (i.e. before the first knot t_1 and after the last knot t_K). The use of restricted cubic splines in a multivariable model implies the introduction of $K - 2$ new variables, and results in the estimation of $K - 1$ regression coefficients. Using the '+' notation to indicate that $a_+ = a$ if $a > 0$, or $a_+ = 0$ if $a \leq 0$, the restricted cubic spline for a variable x is represented by:

$$S(x) = \beta_{00} + \beta_{01}x + \sum_{i=1}^{K-2} \beta_{i3}[(x - t_i)^3_+ - (x - t_{K-1})^3_+ (t_K - t_i)/(t_K - t_{K-1}) + (x - t_K)^3_+ (t_{K-1} - t_i)/(t_K - t_{k-1})]$$

When estimating growth curves, the piecewise cubic polynomials represent non-linear terms connected across different intervals of the linear term for age, and the placement of knots should consider how growth rates are expected to vary along the years. This can be of special interest because growth trajectories are usually complex and may not be accurately represented by a linear function.

In our study, knots were placed at five age points (0.25, 0.75, 1.50, 3.50 and 9 years); therefore, three new spline variables were generated (namely, age1, age2 and age3). The spline variables were included in the mixed-effect models along with each predictor of interest, the linear term for child age, and the interaction terms between predictor categories and linear and spline variables for age. An example of the SAS code is provided below, with child's sex as the predictor of interest and the estimation of BAZ values for girls (reference category, coded as '0'), boys (coded as '1'), and the difference among these categories, at age 7 years.

It is possible to use cubic splines with multiple covariates in the model (as shown in Table 3) and to determine the significance of non-linearity by comparing the log-likelihood for a model with spline variables to the log-likelihood of a model with the linear variable only.

```
PROC MIXED data = cohort EMPIRICAL NOCLPRINT;
 CLASS id;
 MODEL BAZ = age age1 age2 age3 sex age*sex age1*sex age2*sex age3*sex /S;
 RANDOM intercept age/TYPE = UN SUBJECT = id G;
estimate 'girls_7y' intercept 1
                    age     7.00  age1     3.12603†  age2     2.34878  age3     1.40942;
estimate 'boys_7y'  intercept 1
                    sex 1
                    age     7.00  age1     3.12603  age2     2.34878  age3     1.40942
                    age*sex 7.00  age1*sex 3.12603  age2*sex 2.34878  age3*sex 1.40942;
estimate 'diff_7y'  sex 1
                    age*sex 7.00  age1*sex 3.12603  age2*sex 2.34878  age3*sex 1.40942;
run;
```

†The constants after spline terms for age represent the values of the spline variables at the estimated ages

4.4 ARTIGO 4

C-reactive protein concentration predicts change in body mass index during childhood

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for the ACTION Study Team

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PLOS ONE

C-Reactive Protein Concentration Predicts Change in Body Mass Index during Childhood

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Abstract

Objective: Inflammation may constitute an underlying mechanism for increased risk of developing chronic diseases in later years, but few prospective studies have assessed the influence of low-grade inflammation on body weight gain, particularly among children in low- to middle-income settings with lower prevalence of overweight and obesity. We aimed to investigate whether C-reactive protein (CRP), as a biomarker of low-grade inflammation, predicts changes in body mass index-for-age *z* scores (BAZ) during childhood.

Methods: A population-based longitudinal study was conducted in the Brazilian Amazon among children aged ≤10 years in 2007, with follow-up visits in 2009 and 2012. Outcome was annual change in BAZ. As the main exposure of interest, CRP concentrations were divided into four categories, with values <1 mg/L divided in tertiles plus a fourth category with values ranging from 1 to 10 mg/L. Children were simultaneously screened for iron and vitamin A deficiencies, diarrhea, and wheezing. We used mixed-effect linear regression models to measure the effect of CRP concentrations on annual BAZ change and linear regression models to explore CRP predictors at baseline.

Results: At baseline, 1007 children had CRP and anthropometric data [mean (SD) age: 5.3 (2.9) years; 50.9% male, 84.5% mulatto/mixed-race, 14.0% at risk for overweight or obesity, 4.8% stunted]; 737 were successfully followed up. Morbidities and nutritional deficiencies were widespread. Among participants aged >5 years, children in the highest tertile of CRP <1 mg/L at baseline, regarded as an indicator of low-grade inflammation, had a 0.04 *z*/y higher gain in BAZ (95% CI: 0.01, 0.09 *z*/y) during follow-up. CRP was positively associated with household poverty and worse nutritional indicators.

Conclusions: We found evidence of a role for low-grade inflammation in predicting annual BAZ gain among children aged >5 years.

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Introduction

A state of low-grade inflammation, as measured by biomarkers as C-reactive protein (CRP), can be promoted by exposure to adverse events such as pathogenic agents, psychosocial stress, inadequate sleep, and poor diet [1–4], and has also been associated with increased adiposity and cardiometabolic risk [4,5]. The persistent activation of inflammatory pathways has been proposed as a possible underlying mechanism for increased risk of developing chronic diseases, for which weight gain could be a marker of cumulative environmental derangements, such as cycles of infection and malnutrition, poor living conditions, social disparities, among others [6,7].

Few longitudinal studies to date, however, have assessed inflammatory status as a possible predictor of future changes in body weight. The ARIC Cohort Study in the United States in men and women aged 45–64 years and the Malmö Preventive Study Cohort in Sweden in men aged 38–50 years observed larger weight gains over three- and six-year periods, respectively, among individuals with higher concentrations of inflammatory markers at baseline [8,9]. A population-based study conducted in Germany in adults aged 25–74 years found the adjusted odds ratio for a mean annual weight gain of approximately 1 kg/year over a 10-year period was 1.45 for those in the highest quartile of CRP concentrations at baseline, with similar findings for fibrinogen and white blood cell counts [10]. In children, a nationally representative cross-sectional analysis in the United States demonstrated that, although more than 75% of those aged 1–17 years had CRP values below 1 mg/L, there were significant linear trends for the prevalence of higher CRP concentrations with increasing age and body mass, from age 3 years [11]. Prospective

analyses using birth cohorts in Finland, Brazil, and India lacked data on markers of inflammation at young ages but identified associations between weight gain over the life course and CRP concentrations in adulthood [12–14].

Low- to middle-income regions worldwide experience wide social and health inequities, with high rates of childhood morbidities and deficiencies for nutrients such as iron and vitamin A from early life [15–17], resulting in potential consequences for physical development, immunity, and inflammatory status. Concomitantly, these regions are undergoing significant economic and dietary changes, leading to the emergence of excessive weight gain as a public health concern, particularly among the young [18–19]. Thus, the identification of early determinants of weight gain is an important step towards understanding the role of low-grade inflammation on body weight. Our objective was to prospectively investigate the association between CRP concentrations at recruitment and change in body mass index (BMI) during childhood in a population-based cohort study in the Brazilian Amazon. We hypothesized that a low-grade inflammation status beginning in childhood could impact increasing weight within a transitional scenario where the lack of resources is coupled with rising overnutrition.

Methods

Study population and field procedures

In December 2007, a baseline population-based cross-sectional study on child health and nutrition was conducted in the urban area of Acrelândia (11520 inhabitants, 44% in the urban area), in the Brazilian Amazon region, as previously described [17,18]. Briefly, alongside local teams from the Family Health Program of the Brazilian Ministry of Health, all 749 households with children aged ≤10 years were identified and invited to participate in the study, of which 13 declined participation and two could not be reached. We initially enrolled 1225 children living in 734 households (98.0% of those identified). Follow-up assessments were carried out in December 2009 for all participants included at baseline, and in July 2012 for children aged >6 years at the time of this last visit. We identified 909 children (74.2%) in 2009 and 514 children out of 714 eligible participants (72.0%) in 2012.

At baseline [17], household interviews with each participant's mother or guardian collected information on child's sex, age and race/ethnicity, birth weight, and occurrence of diarrhea or wheezing in the previous 15 days. The presence of 12 household assets was assessed to generate a wealth index through principal component analysis, and maternal characteristics (educational level and age) were also recorded. For children aged >4 years, data from a validated food frequency questionnaire were used to produce a food frequency index for fruit and vegetable consumption ranging from 0 (lowest category, including children who did not consume vegetables, but consumed fruit ≤3 times/week) to 4 (highest category, including children who consumed vegetables and fruits ≥1 time/day) [20,21]. A sample (5 mL) of fasting venous blood was collected from children; serum and plasma samples were shipped to São Paulo on dry ice and frozen at −70°C until further analysis.

At all study assessments, children's anthropometric measurements were obtained by trained research assistants using standardized procedures and calibrated equipment [22]. BMI was computed as weight (kg)/length or height (m^2). BMI-for-age (BAZ) and height-for-age (HAZ) z scores were calculated using the World Health Organization (WHO) Child Growth Standards [23] for children ≤5 years and the WHO Growth Reference Data [24] for children >5 years. According to the WHO growth curves, risk of overweight or obesity was defined as BAZ>1 and stunting as HAZ<-2 [23,24]. Pubertal development according to Tanner stages was ascertained during follow-up examinations conducted in 2009 and 2012 [25].

Written informed consent for participation was obtained before enrollment from parents or guardians of all participating children. The study was approved by the ethical review board of the School of Public Health, University of São Paulo, Brazil.

Laboratory methods

At baseline, whole blood aliquots in EDTA-containing vacuum tubes were used to perform full blood cell counts and measure hemoglobin on an automated cell counter (Horiba ABX Micro 60, Montpellier, France). Plasma CRP was measured using a high-sensitivity chemiluminescent assay (DPC Immulite, Los Angeles, CA, USA). Plasma ferritin and soluble transferrin receptor were measured with enzyme immunoassays (Ramco, Houston, TX, USA) to determine iron deficiency (soluble transferrin receptor >8.3 mg/L, or ferritin <12 μg/L for children aged up to 5 years or <15 μg/L for those above 5 years) [26]. Serum vitamin A (retinol) was measured using standard HPLC methods [27], to determine vitamin A deficiency (<0.70 μmol/L) [28].

Statistical analyses

Our primary outcome was defined as the change in BAZ during follow-up (z/y), while CRP was the main exposure of interest. Complete CRP and anthropometric data were available for 1048 children (85.6%) at baseline. We excluded 41 children with CRP concentrations >10 mg/L from all analyses because these concentrations have been usually associated with active inflammatory processes (as shown in Figure S1 in File S1). Based on the distribution and cut-off points for CRP concentrations used in a large representative survey of children in the United States [11], baseline plasma CRP concentrations below 1 mg/L were categorized as tertiles to assess the influence of low-grade inflammation on BAZ change, while a fourth category contained values ranging from 1 to 10 mg/L. Although there is insufficient evidence to date to define a cut-off related to health outcomes in children, the abovementioned study reported that more than 75% of children and adolescents aged 1–17 years had CRP values below 1 mg/L [11]. In the present study, we referred to the lowest tertile of CRP values <1 mg/L as the reference category, while the highest tertile of CRP<1 mg/L was regarded as an indicator of low-grade inflammation. Other child health indicators at baseline including vitamin A and iron deficiencies, and occurrence of diarrhea or wheezing were also considered as explanatory variables.

The distribution of BAZ was compared by categories of baseline characteristics, using tests for linear trend for ordinal predictors and the Wilcoxon's rank-sum test for dichotomous predictors. Changes in BAZ during follow-up were estimated from mixed-effect linear regression models with an unstructured covariance matrix and random effects for the intercept and slope. For each category of the exposure variables, these models provided estimates for the mean differences in BAZ at the first age of assessment and a coefficient for the interaction term with age representing the mean difference in annual BAZ change. These methods inherently adjust for baseline anthropometric status by clustering repeated outcome measurements within individuals and do not require equal numbers of measurements at exactly the same time points on every participant, allowing for the inclusion of all available measurements. In preliminary analyses, separate models for each child health indicator were adjusted for child's sex and age. Next, we fitted a multiple mixed-effect model with CRP and all other health indicators, while further adjusting for household

wealth, maternal age, birth weight, and HAZ at baseline. Other potential covariates were not significantly associated with the outcome and did not affect the estimates of association with children's BAZ. Missing observations (<8%) were included in the multiple models by creating missing-value categories. We also estimated changes in BAZ separately for girls and boys and associations with the exposures of interest remained similar in terms of direction and magnitude; besides, interaction terms with child's sex were not statistically significant. Therefore, we present results for girls and boys altogether. Finally, we explored baseline factors potentially associated with log-transformed CRP concentrations using linear regression models.

We divided children in two age groups (≤5 years and >5 years at baseline) in all analyses. For the older age group only, an additional CRP measurement was available in 2009; therefore, as detailed in File S1, supplemental analyses with a combined CRP score, accounting for the 2007 and 2009 measurements (as a proxy of chronic CRP status) were performed in this sub-sample of our study. We used STATA 11.2 (StataCorp, College Station, TX, USA) for descriptive analyses and SAS 9.3 (SAS Institute, Cary, NC, USA) for mixed-effect linear regression models.

Results

General child characteristics at each study assessment are presented in Table 1. At baseline in 2007, among 1007 participants with complete anthropometry data and CRP concentrations <10 mg/L, 50.9% were boys and 84.5% mulatto. Distribution of BAZ according to baseline characteristics and age groups are shown in Table 2. In the group of 469 children aged ≤5 years [mean age (SD): 2.7 (1.4) years], the mean BAZ was 0.24 (1.01); 15.4% of girls and 24.1% of boys were at risk for overweight and obesity. Vitamin A and iron deficiencies affected 12.5% and 65.2% of the children, respectively (16.4% anemia due to iron deficiency) while 31.8% reported episodes of diarrhea up to 15 days prior the baseline interview. BAZ was significantly higher in boys than in girls, in children with higher birth weight, and among those with iron deficiency. On the other hand, BAZ was significantly lower among children with diarrhea when compared to those without diarrhea. Among the 538 children aged >5 years at baseline [mean age: 7.6 (1.5) years], the mean BAZ was equal to −0.30 (0.99), with 8.7% of girls and 9.2% of boys at risk for overweight and obesity. Vitamin A and iron deficiencies affected 14.6% and 26.6% of the children, respectively (2.8% with iron deficiency anemia). BAZ was significantly higher in males than in females, in children with higher birth weight, higher HAZ, and higher CRP concentrations (Table 1).

A total of 737 children with baseline data were evaluated in 2009, of which 401 were assessed again in 2012. The median follow-up period was 4.6 years (range: 1.7–4.7 years), during which time each child contributed a median of three anthropometric measurements (336 children had two and 401 children had three anthropometric measurements). Children lost to follow-up were not different from those included in analyses, except for household wealth and serum vitamin A concentrations. Among those children successfully followed-up, 21.6% were in the lowest quartile of household wealth compared with 29.6% among those lost to follow-up. Children with follow-up data exhibited a mean vitamin A concentration of 1.25 (0.50) μmol/L, which was higher than the mean 1.16 (0.54) μmol/L among children lost to follow-up.

Mean BAZ at baseline was significantly higher among children aged ≤5 years with iron deficiency (adjusted difference: 0.55 *z*; 95% CI: 0.26–0.85 *z*), but significant associations between baseline health indicators and annual change in BAZ in this age group were not detected (Table 3). Among children aged >5 years, there was no significant difference in the mean BAZ at baseline according to categories of exposure variables. Nevertheless, children in this age group falling within the second and third tertiles of CRP concentrations below 1 mg/L had a larger annual gain in BAZ of 0.04 *z*/y (95% CI: 0.00–0.09 *z*/y in second tertile, and 95% CI: 0.01–0.09 *z*/y in third tertile) when compared with children in the first tertile (Table 3).

As shown in the Table S1 in File S1, the association between CRP and weight gain was further explored for participants aged >5 years with CRP measurements available in both 2007 and 2009. Children in the second and third tertiles of CRP concentrations below 1 mg/L in both assessments experienced a 0.05 *z*/y higher increase in BAZ at follow-up compared with those with the lowest CRP concentrations (95% CI: 0.01–0.09 *z*/y). Children with CRP>1 mg/L in 2007 and/or 2009 also had a 0.05 *z*/y higher increase in BAZ (95% CI: 0.01–0.10 *z*/y).

To further elucidate the associations with CRP concentrations, we investigated possible baseline predictors of log-transformed CRP (Table 4). For both age groups, models accounting for approximately 8% of the variance showed a significant association between log-CRP and worse nutritional and socioeconomic indicators. Higher CRP at baseline was associated with lower household wealth, lower serum vitamin A concentrations, and higher values of soluble transferrin receptor. Among children aged >5 years, higher CRP was also significantly associated with higher ferritin concentrations, which can be regarded as a marker of cellular responses to infection and injury.

Discussion

This longitudinal population-based study was conducted in the Brazilian Amazon region, where childhood morbidities and nutritional deficiencies were widespread. Within this context we observed a positive association between low-grade inflammation detected using CRP tertiles <1 mg/L and annual BAZ gain among older children.

It is widely recognized that children's susceptibility to disease during the first years of life can have short-term consequences for growth and nutrition [29]. We could not detect associations between baseline CRP concentrations and change in BAZ in children aged ≤5 years, but in our study the prevalence of nutritional deficiencies and diarrhea were especially elevated among younger children and were associated with CRP concentrations. Alongside the negative association observed between CRP concentrations and household wealth, these findings could be interpreted as a possible indication of the health burden associated with adverse living conditions. In a recent study, lower maternal education as a measure of socioeconomic position was associated with higher CRP concentrations during childhood, with similar results for family income, paternal education, and the head of the household's occupational class [30].

Research in high morbidity contexts conceives that the continued exposure to infectious diseases, even in the absence of clinical symptoms, may have a cumulative effect on later development and metabolic function [29,31]. Under chronic activation of the immune system, immediate responses to infections such as increases in CRP concentrations can become maladaptive in the long term. These enduring influences have been proposed as a "cohort morbidity phenotype", which supports the notion that inflammatory processes persist from early age into adult life [6]. Of note, outcomes observed for the younger group in our analysis do not necessarily mirror the older group's social and

Table 1. General characteristics of urban Amazonian children at each study assessment.

		2007 ($n=1007$)[a]	2009 ($n=737$)[a]	2012 ($n=401$)[a]
Sex, *n* (%)	Female	494 (49.1)	374 (50.7)	207 (51.6)
	Male	513 (50.9)	363 (49.3)	194 (48.4)
Age (y), *mean (SD)*		5.3 (2.9)	7.3 (2.9)	10.6 (2.3)
Race/ethnicity, *n* (%)	White	94 (10.1)	71 (10.4)	41 (10.9)
	Mulatto	790 (84.5)	582 (85.5)	315 (84.3)
	Black	51 (5.4)	28 (4.1)	18 (4.8)
BMI-for-age *z* score[b], *mean (SD)*		−0.05 (1.03)	0.08 (1.13)	0.07 (1.25)
Risk for overweight, *n* (%)	No	866 (86.0)	621 (84.3)	336 (83.8)
	Yes	141 (14.0)	116 (15.7)	65 (16.2)
Height-for-age *z* score[b], *n* (%)	<−2.0	48 (4.8)	33 (4.5)	12 (3.0)
	−2.0 to −1.1	194 (19.3)	159 (21.6)	75 (18.7)
	−1.0 to 0.9	667 (66.2)	483 (65.5)	272 (67.8)
	≥1.0	98 (9.7)	62 (8.4)	42 (10.5)
Tanner stage, *n* (%)	Pre-pubertal	-	553 (80.0)	199 (49.8)
	Pubertal	-	138 (20.0)	201 (49.2)

[a]Totals may be less than numbers indicated in brackets for each study assessment because of missing values.
[b]BMI-for-age and height-for-age *z* scores calculated according to the WHO Child Growth Standards for children ≤5 years and the WHO Growth Reference Data for children >5 years.
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health background, but previous reports on child health and nutrition in the same region do not indicate that better structural conditions had existed a decade ago [32], and the prevalence of nutritional deficiencies and morbidities among children in the older age group was also relatively high. We may speculate, therefore, that children aged >5 years residing in the Brazilian Amazon have been exposed to these adverse living conditions for a longer period, with downstream consequences for their CRP concentrations and future BAZ gain.

In a cross-sectional analysis from the United States, where the prevalence of overweight and obesity in children and adolescents is higher [33], a relationship between adiposity and increasing CRP was observed from 3 years of age [11]. In our study, there was no difference in mean adjusted BAZ at baseline according to categories of exposure variables given the lower rate of excessive weight; though this figure has risen in the past decade [34]. In children aged >5 years, we were able to identify significantly higher increases in BAZ during follow-up among those in the higher tertiles of CRP concentrations below 1 mg/L in 2007, indicating a state of low-grade inflammation. In addition, in supplemental analysis we verified larger BAZ gain among those who maintained these higher CRP concentrations between the 2007 and 2009 assessments. Analogously, morbidity data collected in the 1970s for the INCAP Longitudinal Study in Guatemala showed that the number of years that participants experienced serious illness during childhood was positively related to the risk for high waist circumference and obesity 30 years later [31], although no specific measurements of inflammatory markers were available.

Our data do not dispute previous investigations on the role of excessive adiposity in elevating concentrations of inflammatory markers such as CRP via secretion of cytokines. Instead, the present results provide further evidence of the potential factors related to weight gain during childhood. Both positive and negative associations found between low-grade inflammation and change in body weight seem to be implicated in disrupted metabolic outcomes. Further studies, however, are still needed to elucidate these pathways.

Among the possible mechanisms for increased weight gain due to low-grade inflammation, several hypotheses integrate the hypothalamic-pituitary-adrenal axis and point to a close connection between nutrition and immunity. Imbalanced energy intake and storage can be a result of the expression of anti-inflammatory mediators such as glucocorticoids in response to the low-grade inflammatory stimulus, possibly leading to weight gain through the upregulation of neuropeptide Y secretion [35]. Leptin, whose secretion is upregulated by pro-inflammatory cytokines as interleukin-6 and tumor necrosis factor-α during acute inflammation, is suggested as a key link between neuroendocrine functions, the immune system, and nutritional status. However, chronic inflammation results in lower leptin concentrations, probably affecting appetite and food intake control while increasing susceptibility to infectious diseases [36,37]. In particular, CRP is considered a major leptin-interacting protein that may impair leptin signaling and promote leptin resistance [38]. While previous studies have found an association between markers of low-grade inflammation (including CRP and leptin) and dietary intake of fats and antioxidant vitamins in children aged 6-14 years [39], our study found that CRP concentrations in children aged >5 years were negatively associated with vitamin A concentrations and frequency scores for fruit and vegetable consumption. With the progressive replacement of minimally processed and traditional food items by industrialized food products in settings undergoing a nutrition transition [40], mechanisms for weight gain can be increasingly exacerbated by a "pro-inflammatory" diet characterized by high energy density, low fiber, in addition to the consumption of more saturated fat, sodium and added sugar.

Our study has some limitations. Although the overall follow-up rate was high, children lost to follow-up were predominantly from poorer households and presented lower vitamin A concentrations. Although attrition is common in prospective studies, its implications are difficult to assess. Associations might have been

Table 2. Mean BMI-for-age *z* score in urban Amazonian children with complete C-reactive protein and anthropometric information, according to age groups and baseline characteristics (2007).

		Children ≤5 years at baseline			Children >5 years at baseline		
		n (%)[a]	Mean BAZ (SD)[b,c]	*P*[d]	*n* (%)[a]	Mean BAZ (SD)[b,c]	*P*[d]
Child's sex	Female	228 (48.6)	0.12 (0.89)	0.01	266 (49.4)	−0.40 (0.95)	<0.01
	Male	241 (51.4)	0.36 (1.09)		272 (50.6)	−0.20 (1.01)	
Child's race/ethnicity	White	47 (10.6)	0.26 (0.90)	0.74	47 (9.6)	−0.37 (1.11)	0.76
	Mulatto	374 (84.0)	0.25 (1.04)		416 (84.9)	−0.28 (0.99)	
	Black	24 (5.4)	0.15 (0.94)		27 (5.5)	−0.32 (1.02)	
Household wealth index	Below median	236 (50.3)	0.18 (0.96)	0.36	259 (48.2)	−0.37 (0.91)	0.10
	Above median	233 (49.7)	0.30 (1.05)		278 (51.8)	−0.24 (1.05)	
Maternal education	≤4 years	152 (33.7)	0.18 (0.94)	0.16	223 (42.8)	−0.36 (0.90)	0.09
	5–8 years	140 (31.0)	0.21 (1.00)		154 (29.6)	−0.30 (1.04)	
	≥9 years	159 (35.3)	0.34 (1.06)		144 (27.6)	−0.18 (1.09)	
Maternal age	≤21 years	75 (16.0)	0.24 (1.11)	0.97	16 (3.0)	0.21 (1.10)	0.56
	22–34 years	318 (67.8)	0.24 (0.92)		362 (67.3)	−0.32 (0.99)	
	≥35 years	76 (16.2)	0.24 (1.23)		160 (29.7)	−0.30 (0.96)	
Birth weight	≤2500 g	24 (5.5)	0.03 (0.81)	<0.01	31 (6.5)	−0.37 (1.31)	<0.01
	2501–3500 g	263 (60.0)	0.10 (1.01)		284 (59.0)	−0.41 (0.94)	
	>3500 g	151 (34.5)	0.52 (0.98)		166 (34.5)	−0.03 (1.01)	
Height-for-age *z* score[c]	<−2.0	30 (6.4)	0.20 (0.97)	0.06	18 (3.4)	−0.37 (0.95)	<0.01
	−2.0 to −1.1	104 (22.2)	0.06 (0.81)		90 (16.7)	−0.50 (0.91)	
	−1.0 to 0.9	287 (61.2)	0.28 (1.02)		380 (70.6)	−0.30 (0.97)	
	≥1.0	48 (10.2)	0.41 (1.25)		50 (9.3)	0.13 (1.14)	
Food frequency index for fruit and vegetable consumption[e]	Lowest consumption (score 0)	-	-	-	64 (12.3)	−0.28 (1.00)	0.66
	Intermediate consumption (score-1–2)		-		281 (53.7)	−0.27 (1.00)	
	Higher consumption (score 3–4)	-	-		178 (34.0)	−0.33 (0.97)	
C-reactive protein[f]	1st tertile	129 (27.5)	0.21 (1.03)	0.39	149 (27.7)	−0.47 (0.89)	<0.01
	2nd tertile	96 (20.5)	0.20 (1.01)		124 (23.0)	−0.34 (0.94)	
	3rd tertile	107 (22.8)	0.20 (0.97)		138 (25.7)	−0.24 (0.94)	
	>1 mg/L	137 (29.2)	0.32 (1.02)		127 (23.6)	−0.10 (1.15)	
Vitamin A deficiency	No	386 (87.5)	0.27 (1.03)	0.85	450 (85.4)	−0.32 (0.98)	0.14
	Yes	55 (12.5)	0.26 (0.86)		77 (14.6)	−0.10 (1.02)	
Iron deficiency	No	163 (34.8)	0.03 (0.88)	<0.01	395 (73.4)	−0.31 (0.98)	0.81
	Yes	306 (65.2)	0.35 (1.05)		143 (26.6)	−0.25 (1.03)	
Diarrhea, past 15 days	No	317 (68.2)	0.29 (0.99)	0.05	452 (85.0)	−0.31 (1.01)	0.65
	Yes	148 (31.8)	0.12 (1.03)		80 (15.0)	−0.26 (0.91)	
Wheezing, past 15 days	No	389 (84.4)	0.24 (1.02)	0.72	499 (94.0)	−0.31 (0.99)	0.36
	Yes	72 (15.6)	0.24 (0.97)		32 (6.0)	−0.14 (0.97)	

[a]Totals may be less than 469 for children ≤5 years and less than 538 for children >5 years at baseline because of missing values.
[b]Results are mean BMI-for age *z* score (BAZ) and standard deviation (SD).
[c]BMI-for-age and height-for-age *z* scores calculated according to the WHO Child Growth Standards for children ≤5 years and the WHO Growth Reference Data for children >5 years.
[d]Test for linear trend for ordinal predictors; for dichotomous predictors, Wilcoxon rank-sum test.
[e]Information on food frequency index for fruit and vegetable consumption was available for children >4 years only.
[f]C-reactive protein was categorized as tertiles below 1 mg/L and >1 mg/L. Categories were distributed as follows: 1st tertile: 0.01–0.15 mg/L; 2nd tertile: 0.16–0.38 mg/L; 3rd tertile: 0.39–1.00 mg/L; >1 mg/L: 1.01–9.81 mg/L. Children with C-reactive protein values >10 mg/L were excluded from the analyses (*n* = 41).
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underestimated because children with worse health and socioeconomic indicators were lost to follow-up. The statistical methodology enabled us to include all existing outcome measurements from the participants to minimize the impact of attrition, but caution should be taken when extrapolating our findings to the general population. Also, we lacked data on use of nutritional supplements and were unable to further explore their relationship with CRP or weight gain. Major strengths of our study include its

Table 3. Differences in BMI-for-age *z* score change per year over childhood among urban Amazonian children (2007–2012), according to age groups and baseline health indicators.

		Children ≤5 years at baseline			Children >5 years at baseline		
		n (%)[a]	Unadjusted difference in BAZ change per year (95% CI)[b,c]	Adjusted difference in BAZ change per year (95% CI)[b,c]	n (%)[a]	Unadjusted difference in BAZ change per year (95% CI)[b,c]	Adjusted difference in BAZ change per year (95% CI)[b,c]
C-reactive protein[d]	1st tertile	93 (26.9)	Reference	Reference	113 (28.9)	Reference	Reference
	2nd tertile	76 (22.0)	−0.03 (−0.11, 0.05)	−0.01 (−0.09, 0.07)	84 (21.5)	**0.04 (0.00, 0.09)**	**0.04 (0.00, 0.09)**
	3rd tertile	79 (22.8)	−0.04 (−0.12, 0.04)	−0.04 (−0.12, 0.04)	104 (26.6)	**0.04 (0.00, 0.09)**	**0.04 (0.01, 0.09)**
	>1 mg/L	98 (28.3)	**−0.08 (−0.15, −0.01)**	−0.07 (−0.15, 0.00)	90 (23.0)	0.02 (−0.03, 0.07)	0.02 (−0.03, 0.08)
Vitamin A deficiency	No	286 (88.3)	Reference	Reference	338 (88.7)	Reference	Reference
	Yes	38 (11.7)	0.04 (−0.05, 0.13)	0.06 (−0.03, 0.15)	43 (11.3)	−0.03 (−0.10, 0.04)	−0.02 (−0.09, 0.05)
Iron deficiency	No	123 (35.5)	Reference	Reference	279 (71.4)	Reference	Reference
	Yes	223 (64.5)	−0.05 (−0.10, 0.00)	−0.05 (−0.11, 0.00)	112 (28.6)	−0.02 (−0.06, 0.02)	−0.02 (−0.06, 0.03)
Diarrhea, past 15 days	No	242 (70.6)	Reference	Reference	318 (82.6)	Reference	Reference
	Yes	101 (29.4)	0.01 (−0.05, 0.06)	0.01 (−0.04, 0.07)	67 (17.4)	0.04 (−0.01, 0.08)	0.04 (−0.01, 0.08)
Wheezing, past 15 days	No	289 (85.0)	Reference	Reference	360 (93.8)	Reference	Reference
	Yes	51 (15.0)	0.02 (−0.06, 0.10)	0.04 (−0.04, 0.11)	24 (6.2)	0.02 (−0.09, 0.13)	0.02 (−0.09, 0.13)

[a]Totals may be less than 346 for children ≤5 years and less than 391 for children >5 years at baseline because of missing values. Missing observations among the covariates were included in the multiple models by creating missing-value categories.

[b]BMI-for-age *z* scores (BAZ) were calculated according to the WHO Child Growth Standards for children ≤5 years and the WHO Growth Reference Data for children >5 years.

[c]Mean differences in BAZ change per year and their 95% confidence intervals (CI) were from mixed-effect linear regression models. For each age group, unadjusted differences refer to preliminary models that included each child health indicator with adjustment for sex. Fully adjusted differences were estimated from models including CRP and all other health indicators with further adjustment for household wealth, maternal age, birth weight, and HAZ at baseline. $P<0.05$ for results in bold.

[d]C-reactive protein categories were distributed as follows: 1st tertile: 0.01–0.15 mg/L; 2nd tertile: 0.16–0.38 mg/L; 3rd tertile: 0.39–1.00 mg/L; >1 mg/L: 1.01–9.81 mg/L.

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Table 4. Multiple linear regression analysis of baseline predictors of log-transformed C-reactive protein (mg/L) among urban Amazonian children.

Independent variables	Children ≤5 years at baseline[a]	Children >5 years at baseline[a]
	β (95% CI)[b]	β (95% CI)[b]
Male sex	−0.35 (−0.76, 0.06)	-
Household wealth (continuous)	**−0.07 (−0.12, −0.01)**	**−0.06 (−0.11, −0.01)**
Serum vitamin A (μmol/L)	**−0.60 (−0.98, −0.22)**	**−0.70 (−1.07, −0.34)**
Log soluble transferrin receptor (mg/L)	**0.98 (0.36, 1.60)**	**1.15 (0.40, 1.90)**
Log ferritin (μg/L)	-	**0.35 (0.09, 0.60)**
Diarrhea in the past 15 days (yes)	0.42 (−0.03, 0.87)	-
Food frequency index for fruit and vegetable consumption (continuous)	-	−0.12 (−0.26, 0.02)

[a]Totals are 438 for children ≤5 years and 511 for children >5 years at baseline because of missing values.
[b]β coefficients and their 95% confidence intervals (CI) were from linear regression models. $P<0.05$ for results in bold.
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longitudinal design and use of direct anthropometric measurements. In contrast to the majority of prospective investigations in children, inflammatory status was assessed at baseline, with repeated CRP measurements in a sub-sample to account for chronic CRP status over five years. In addition, we used a broad range of covariates including nutritional deficiencies, morbidities, pubertal development, and nutritional indicators to control for possible confounding.

It is noteworthy that, although magnitude of change in BAZ per year among children in the second and third tertiles of CRP<1 mg/L was small, our outcome was measured in sex and age-specific WHO *z* scores. Therefore, these estimates of change stand for increases in relation to expected growth patterns. In our study population, we found evidence for a role of low-grade inflammation in predicting annual BAZ gain among children aged >5 years who were followed up for nearly five years, living in a resource-poor setting in which nutritional deficiencies and childhood morbidities are common. Our findings may provide a better understanding of the predictors of weight change in low- to middle-income countries, and such increase in BAZ may impose a concern particularly for eutrophic children in this age group in regions experiencing the epidemiological transition from nutritional deficiencies to excessive weight gain. Considering low-grade inflammation as a possible underlying path, there are important implications for the formulation of public health policies, which should address social and health inequities, with potential benefits at reducing both susceptibility to infection and the chronic disease burden.

Supporting Information

File S1 Information on study design and subsample analysis with a combined C-reactive protein score.
(PDF)

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Author Contributions

Conceived and designed the experiments: MAC. Performed the experiments: BHL. Analyzed the data: BHL. Contributed reagents/materials/analysis tools: BHL MAC. Wrote the paper: BHL MAC.

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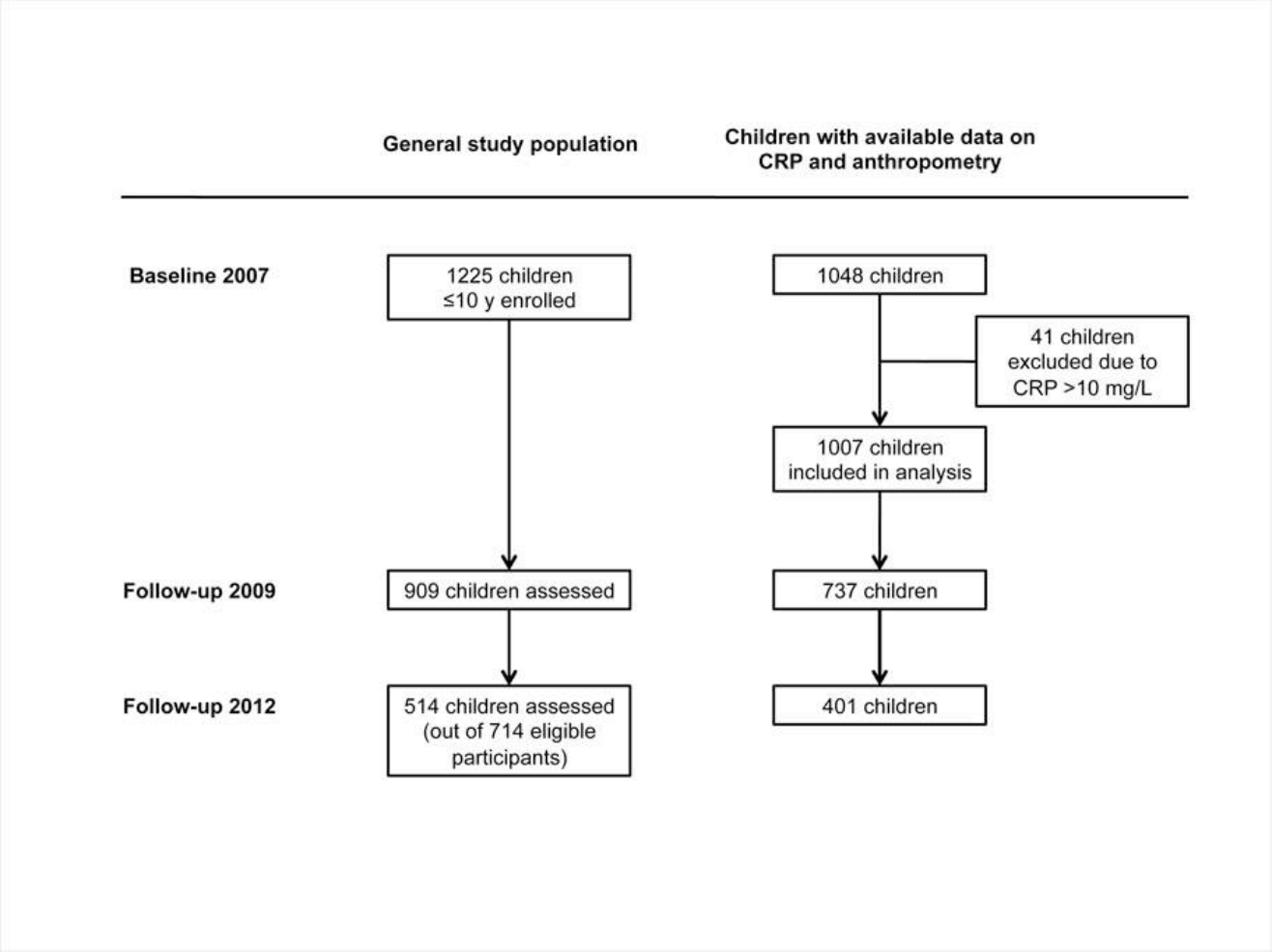
Supporting information

Figure S1. Study design and participants at each assessment.



Subsample analysis with a combined C-reactive protein score

The association between CRP and weight gain was further explored for a sub-sample of participants aged >5 years at baseline of the present study, with CRP measurements available in 2007 and 2009.

In the follow-up assessment carried out in December 2009, sociodemographic and anthropometric data were updated for all eligible children enrolled at baseline, and a clinical examination was performed among older participants. After the clinical examination, blood samples from these children were stored away from light and centrifuged within 1 h of collection at the field

laboratory in Acrelândia; serum and plasma aliquots were shipped to São Paulo on dry ice and frozen at -70°C until analysis. Plasma CRP in the 2009 assessment was measured using the same protocol as described for baseline, with a high-sensitivity chemiluminescent assay (DPC Immulite, Los Angeles, CA, USA).

Overall, CRP measurements <10 mg/L in both 2007 and 2009 assessments were available for *n*=349 children aged >5 years at baseline. For both assessments, we classified these CRP levels into tertiles below 1 mg/L plus a fourth category with values ranging from 1 to 10 mg/L. Next, we generated a combined CRP score, as a proxy of chronic CRP status, by allocating participants to three categories as follows: children who were classified in the first tertile in both assessments (reference category), children who were classified in up to the second and third tertiles of CRP levels below 1 mg/L in 2007 and/or 2009, and children who presented CRP >1 mg/L in 2007 and/or 2009.

In statistical analysis for this sub-sample, the combined CRP score was entered as the main exposure variable in mixed-effect linear regression models to estimate changes in BAZ during follow-up, with preliminary adjustment for child's sex. Subsequently, we fitted a multiple mixed-effect model by including the combined CRP score and all other health indicators explored in the present study (vitamin A and iron deficiencies, and occurrence of diarrhea and wheezing, measured at baseline), with further adjustment for household wealth, maternal age, birth weight, and HAZ at baseline. Other potential covariates were not significantly associated or did not affect the estimates of association with children's BAZ. Missing observations (<8%) were included in the multiple model by creating missing-value categories. The results are presented in the Table S1 below.

Table S1. Differences in BMI-for-age *z* score change per year over childhood among urban Amazonian children aged >5 years at baseline (2007-2012), according to combined C-reactive protein score based on measurements from 2007 and 2009.

		n (%)	Unadjusted difference in BAZ change per year (95% CI)[a,b]	Adjusted difference in BAZ change per year (95% CI)[a,b]
Combined C-reactive protein score	1st tertile in both 2007 and 2009	58 (16.6)	Reference	Reference
	2nd to 3rd tertile in 2007 and/or 2009	144 (41.3)	0.05 (0.01, 0.09)	0.05 (0.01, 0.09)
	>1 mg/L in 2007 and/or 2009	147 (42.1)	0.05 (0.01, 0.10)	0.05 (0.01, 0.10)

[a] BMI-for-age *z* scores (BAZ) were calculated according to the WHO Growth Reference Data.
[b] Mean differences in BAZ change per year and their 95% confidence intervals (CI) were from mixed-effect linear regression models. For each age group, unadjusted differences refer to a preliminary model that included the combined CRP score with adjustment for sex. Fully adjusted differences were estimated from models including the combined CRP score and all other health indicators (vitamin A and iron deficiencies, and occurrence of diarrhea and wheezing, measured at baseline), with further adjustment for household wealth, maternal age, birth weight, and HAZ at baseline.

4.5 ARTIGO 5

***FTO* genotype, vitamin D status and weight gain during childhood**

Barbara H. Lourenço, Lu Qi, Walter C. Willett, Marly A. Cardoso,
for the ACTION Study Team

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Diabetes. 2014;63:808-814.
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Comentário publicado sobre o manuscrito (ANEXO 6)

Engelman CD. Toward personalized prevention of obesity: can vitamin D negate the *FTO* effect? Diabetes. 2014;63:405-406.

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FTO Genotype, Vitamin D Status, and Weight Gain During Childhood

Previous evidence suggests that variants in the fat mass and obesity-associated gene (*FTO*) affect adiposity in an age-dependent fashion in children, and nutritional factors may modify genotype effects. We assessed the effect of *FTO* rs9939609 on BMI and BMI-for-age *Z* score changes during childhood in a population-based longitudinal study in the Brazilian Amazon and investigated whether these effects were modified by vitamin D status, an important nutritional factor related to adiposity. At baseline, 1,088 children aged <10 years had complete genotypic and anthropometric data; 796 were followed up over a median 4.6 years. Baseline vitamin D insufficiency was defined as <75 nmol/L. We observed a 0.07 kg/m^2/year increase in BMI and a 0.03 *Z*/year increase in BMI-for-age *Z* score per rs9939609 risk allele over follow-up (*P* = 0.01). Vitamin D status significantly modified *FTO* effects (*P* for interaction = 0.02). The rs9939609 risk allele was associated with a 0.05 *Z*/year increase in BMI-for-age *Z* score among vitamin D–insufficient children (*P* = 0.003), while no significant genetic effects were observed among vitamin D–sufficient children. Our data suggest that *FTO* rs9939609 affects child weight gain, and genotype effects are more pronounced among children with insufficient vitamin D levels.

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Genome-wide association studies have reliably identified variation at the fat mass and obesity-associated gene (*FTO*) locus as the strongest genetic effect for obesity risk (1). Age-dependent effects of *FTO* on BMI have been proposed in studies conducted among children mainly in developed regions worldwide. This locus was associated with lower BMI at the first years of life and earlier adiposity rebound, followed by subsequent greater BMI gain from the end of infancy through childhood (2). Few studies have assessed *FTO* genotype effects on longitudinal weight gain in children. In addition, there is evidence that physical activity and diet might modify *FTO* effects in adult populations (3,4). However, such research is still scarce for children.

Vitamin D concentrations have been inversely associated with adiposity indicators mainly in cross-sectional reports. Lower 25-hydroxyvitamin D [25(OH)D] levels are prevalent among overweight and obese children and adolescents aged 6–18 years, according to recent nationally representative analyses conducted in the U.S. (5). Among Mexican boys and girls aged 6–12 years, higher percentages of body fat, as measured by bioimpedance, BMI, triceps skinfold, and waist circumference, were associated with decreased vitamin D levels (6). Decreasing quartiles of 25(OH)D levels were associated with higher odds ratios for obesity and metabolic syndrome indicators among Korean children 9 years of age (7). In a prospective investigation with Colombian school children

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See accompanying commentary, p. 405.

aged 5–12 years, circulating 25(OH)D was inversely associated with the development of adiposity over 29 months of follow-up (8).

Excessive weight gain is an emerging public health problem in low- to middle-income countries, where rapid increases in weight during childhood, specifically after 2 years of age, have been consistently associated with unfavorable metabolic outcomes in later years (9). In the current study, we aimed to assess the effect of *FTO* variation on changes in BMI during childhood in a population-based longitudinal study in the Brazilian Amazon area and particularly investigated whether vitamin D status might modify these genetic effects.

RESEARCH DESIGN AND METHODS

A baseline population-based cross-sectional study on child health and nutrition was conducted in December 2007 in the urban area of Acrelândia (9°49'S, 66°53'W), Western Brazilian Amazon area. A total of 1,225 children aged <10 years (98.0% of those eligible) were initially enrolled for household interviews, blood sample collection, and anthropometric measurements (10). Follow-up assessments were carried out in December 2009 for all participants included at baseline and in July 2012 for children aged >6 years at the time of this last visit. We identified 909 children (74.2%) in 2009 and 514 children of 714 eligible participants (72.0%) in 2012. Written informed consent for participation was obtained before enrollment. The study was approved by the ethics review board of the School of Public Health, University of São Paulo.

Field Procedures

In December 2007, household interviews with each participant's mother or guardian collected information on child's sex, age, race/ethnicity, nutritional history, and recent morbidity; the presence of 12 household assets was determined to generate a wealth index, as previously detailed (10). A sample (5 mL) of fasting venous blood was collected from children at baseline; serum and plasma samples were shipped to São Paulo on dry ice and frozen at −70°C until further analysis. Children's anthropometric measurements were obtained directly by trained research assistants using standardized procedures and calibrated equipment at all study assessments. BMI (kg/m^2) was used to calculate BMI-for-age *Z* scores using the World Health Organization (WHO) Child Growth Standards (11) for children ≤5 years old and the WHO Growth Reference Data for children >5 years old (12). Pubertal development according to Tanner stages was ascertained during follow-up examinations conducted in 2009 and 2012 (13).

Genotyping

DNA was extracted from EDTA-containing whole blood aliquots using DNA kits (Qiagen, Hilden, Germany). The single nucleotide polymorphism rs9939609 near the *FTO* gene was genotyped by allele-specific PCR with molecular beacons (Prevention Genetics, Marshfield, WI). Quality-control samples (10%) were typed in duplicate with >99% agreement.

Vitamin D Status Assessment

Serum 25-hydroxivitamin D_3 concentrations were measured using high-performance liquid chromatography (14) in a separate aliquot stored away from light. The detection limit was 6.2 nmol/L; intra- and interassay variation was <7%. Baseline vitamin D insufficiency was defined as <75 nmol/L (15).

Statistical Analyses

Complete data on *FTO* rs9939609 genotype and anthropometric measurements were available for 1,088 children (88.8%) at baseline. Characteristics of children across each study assessment were compared using χ^2 tests for categorical variables and ANOVA for continuous variables. Cross-sectional effects of genetic variation on mean BMI and BMI-for-age *Z* scores at each assessment were estimated from linear regression models for each A allele of the rs9939609 variant, assuming an additive genetic model. Main genetic effects and potential interactions with baseline vitamin D status on mean changes in BMI and BMI-for-age *Z* scores per year were estimated from mixed-effect linear regression models. Random-effects included subject-specific intercepts for the 2007–2009 follow-up period and subject-specific intercepts and slopes for the 2007–2012 follow-up period. All models were initially adjusted for a child's age, sex, and race/ethnicity (model 1) and further adjusted for a child's pubertal stage at the last follow-up visit and baseline household wealth (model 2). Missing observations (<8%) were included in the multiple models by creating missing-value categories. We used STATA 11.2 (Stata, College Station, TX) for all analyses.

RESULTS

At baseline, the minor allele frequency of *FTO* rs9939609 (A allele) was 0.384 among all 1,088 children with complete genotypic and anthropometric data; genotype distribution fitted the Hardy-Weinberg equilibrium (P = 0.23). In 2007, there were no significant differences in genotype distribution according to sex, age, and vitamin D status, but differences were observed among ethnicity groups ($P < 0.001$) and household wealth quartiles (P = 0.01). Self-reported race/ethnicity, on the other hand, was not associated with either children's BMI or vitamin D status.

A total of 796 children with baseline data were evaluated in 2009, of whom 436 were assessed again in 2012. Children lost to follow-up were not different from those included in analyses, except for household wealth; 30.8% of children lost to follow-up were in the lowest quartile of household wealth compared with 22.4% of children successfully followed up. The median follow-up period was 4.6 years (range 1.7–4.7). Table 1 presents the main characteristics across the study assessments.

Table 1—Characteristics of urban Amazonian children at each study assessment

	2007	2009	2012	*P**
n	1,088	796	436	
Sex, *n* (%)				0.76
Female	546 (50.2)	411 (51.6)	226 (51.8)	
Male	542 (49.8)	385 (48.4)	210 (48.2)	
Age (years), mean (SD)	5.2 (2.8)	7.2 (2.8)	10.5 (2.3)	<0.001
Race/ethnicity, *n* (%)				0.84
White	95 (9.4)	69 (9.4)	38 (9.3)	
Mulatto/mixed race	864 (85.5)	638 (86.7)	351 (86.0)	
Black	52 (5.1)	29 (3.9)	19 (4.7)	
BMI (kg/m^2), mean (SD)	15.8 (1.7)	16.3 (2.2)	17.7 (3.3)	<0.001
BMI-for-age *Z* score, mean (SD)†	−0.02 (1.02)	0.12 (1.11)	0.11 (1.25)	<0.001
Risk for overweight, *n* (%)				0.24
No	926 (85.1)	659 (82.8)	358 (82.1)	
Yes	162 (14.9)	137 (17.2)	78 (17.9)	
Height (cm), mean (SD)	106.5 (20.3)	119.7 (17.6)	139.9 (14.5)	<0.001
Height-for-age *Z* score, mean (SD)†	−0.34 (1.05)	−0.40 (0.97)	−0.21 (0.97)	0.004
Stunting, *n* (%)				0.07
No	1,029 (94.6)	762 (95.7)	424 (97.2)	
Yes	59 (5.4)	34 (4.3)	12 (2.8)	
FTO rs9939609 genotype, *n* (%)				0.99
TT	422 (38.8)	315 (39.6)	172 (39.4)	
TA	496 (45.6)	357 (44.8)	197 (45.2)	
AA	170 (15.6)	124 (15.6)	67 (15.4)	
Baseline vitamin D status (nmol/L), *n* (%)				0.34
<75	297 (32.1)	224 (32.0)	138 (35.9)	
≥75	629 (67.9)	477 (68.0)	246 (64.1)	
Tanner stage, *n* (%)				<0.001
Prepubertal	—	610 (81.1)	222 (51.0)	
Pubertal	—	142 (18.9)	213 (49.0)	
Baseline household wealth, *n* (%)				0.38
1st quartile (lowest)	268 (24.7)	178 (22.4)	94 (21.6)	
2nd quartile	272 (25.0)	195 (24.5)	95 (21.8)	
3rd quartile	286 (26.3)	215 (27.0)	121 (27.7)	
4th quartile (highest)	261 (24.0)	208 (26.1)	126 (28.9)	

Totals may be different from 1,088 because of missing data. **P* values were calculated by χ^2 test for categorical variables and ANOVA for continuous variables. †BMI-for-age and height-for-age *Z* scores were calculated according to the WHO growth references (11,12).

No statistically significant increase in the proportion of children at risk for overweight was detected during follow-up from 2007 to 2012.

In cross-sectional analyses (Table 2), association of *FTO* with children's BMI was not significant in 2007 (mean [SD] age 5.2 [2.8] years) and 2009 (7.2 [2.8] years), but effect size increased over follow-up (Fig. 1). At the last assessment in 2012 (10.5 [2.3]), each A allele was significantly associated with a 0.57 kg/m^2 higher mean BMI and 0.25 *Z* higher mean BMI-for-age *Z* score ($P < 0.01$) after adjustment for age, sex, ethnicity, pubertal stage, and baseline household wealth.

We then performed mixed-effect linear regression models to evaluate the main effect of rs9939609 on the annual change in children's BMI (Table 3). In adjusted models, each A allele was positively associated with a mean larger annual gain of 0.08 kg/m^2/year in BMI ($P = 0.002$) and 0.03 *Z*/year in BMI-for-age *Z* score ($P = 0.03$) from 2007 to 2009. These associations were maintained when extending the follow-up period to 2012, with a mean 0.07 kg/m^2/year higher increase in BMI and a mean 0.03 *Z*/year higher increase in BMI-for-age *Z* score per A allele ($P = 0.01$).

In addition, we observed that baseline vitamin D status significantly modified the effects of *FTO* rs9939609 on changes in children's BMI during follow-up (Table 3). From 2007 to 2009, among those who presented with insufficient 25(OH)D levels at baseline ($n = 217$; 32.0%), the A allele in an additive model was positively associated with a mean 0.13 kg/m^2 higher gain per year in BMI ($P = 0.004$; P for interaction = 0.04) and with a mean 0.07 *Z* higher increase per year in

Table 2—Cross-sectional associations of BMI at each assessment with *FTO* rs9939609 genotype among urban Amazonian children

	2007 (n = 1,088)		2009 (n = 796)		2012 (n = 436)	
rs9939609 genotype	β (SE)*	*P*	β (SE)*	*P*	β (SE)*	*P*
BMI (kg/m^2)						
Model 1	0.04 (0.07)	0.61	0.14 (0.11)	0.21	0.55 (0.21)	0.008
Model 2	0.04 (0.07)	0.57	0.15 (0.11)	0.17	0.57 (0.22)	0.008
BMI-for-age *Z* score†						
Model 1	0.03 (0.04)	0.52	0.06 (0.06)	0.31	0.24 (0.09)	0.006
Model 2	0.03 (0.04)	0.46	0.06 (0.06)	0.30	0.25 (0.09)	0.005

Model 1 was adjusted for child's age, sex, and race/ethnicity, and model 2 was further adjusted for child's pubertal stage at the last follow-up visit and baseline household wealth. *β-Coefficients and their SE were estimated from linear regression models for each A allele of the *FTO* rs9939609 genotype. †BMI-for-age *Z* scores were calculated according to the WHO growth references (11,12).

BMI-for-age *Z* score (P = 0.01; P for interaction = 0.03). The genetic interaction with baseline vitamin D status remained significant up to the last follow-up visit in 2012 when the annual change in BMI-for-age *Z* score is considered (P for interaction = 0.02), and each A allele of rs9939609 was associated with a mean larger increase of 0.05 *Z*/year in vitamin D–insufficient children (P = 0.003). No significant genetic effects were observed among participants with sufficient 25(OH)D levels at baseline (n = 461).

DISCUSSION

In this population-based longitudinal study in the Brazilian Amazon area, the A allele of *FTO* rs9939609 was significantly associated with higher BMI gain during childhood. The genotype effects were modified by baseline vitamin D status—children with insufficient 25(OH)D levels presented larger increases in BMI for each A allele compared with those with normal 25(OH)D concentrations.

Our findings of the longitudinal effects of *FTO* genotype on child weight gain are in line with previous reports. A large meta-analysis including data from eight European cohorts with 9,143 children on average per age stratum found an additive effect of rs9939609 A allele on BMI starting at 5.5 years of age (2). *FTO* variants have also been associated with higher BMI among African American subjects as young as 10 years old (16) and Brazilian children since age 4 years (17). There is indication that variation at the *FTO* locus may impact developmental age in relation to BMI in childhood by accelerating adiposity rebound and fat mass deposits (2), which may have potential implications for later metabolic disease risk (18).

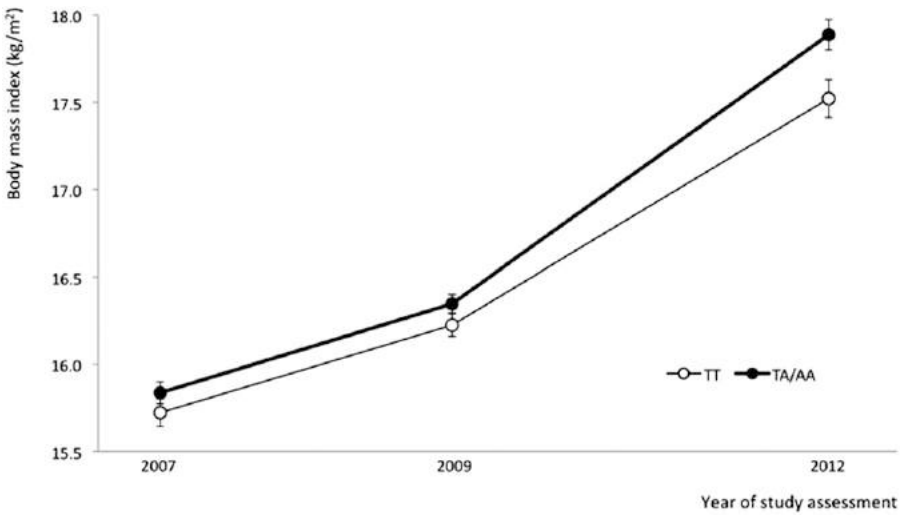

Figure 1—Mean BMI among urban Amazonian children according to *FTO* rs9939609 genotype at each study assessment (2007: n = 1,088; 2009: n = 796; 2012: n = 436). Estimates were adjusted for a child's age, sex, race/ethnicity, pubertal stage at the last follow-up visit, and baseline household wealth. TT, rs9939609 TT genotype; TA/AA, rs9939609 TA/AA genotypes.

Table 3—Annual change in BMI among urban Amazonian children according to *FTO* rs9939609 genotype and baseline vitamin D status

			Baseline vitamin D status*				
	Overall (n = 796)		Sufficient (n = 461)		Insufficient (n = 217)		P for
rs9939609 genotype	β (SE)†	P	β (SE)†	P	β (SE)†	P	interaction
2007–2009							
Change in BMI (kg/m^2/year)							
Model 1	0.07 (0.03)	0.003	0.05 (0.03)	0.15	0.13 (0.05)	0.006	0.022
Model 2	0.08 (0.02)	0.002	0.05 (0.03)	0.17	0.13 (0.05)	0.004	0.036
Change in BMI-for-age Z score (Z/year)‡							
Model 1	0.03 (0.01)	0.025	0.02 (0.02)	0.32	0.07 (0.02)	0.005	0.013
Model 2	0.03 (0.01)	0.027	0.01 (0.02)	0.42	0.07 (0.02)	0.006	0.032
2007–2012							
Change in BMI (kg/m^2/year)							
Model 1	0.07 (0.03)	0.010	0.04 (0.04)	0.32	0.10 (0.05)	0.04	0.033
Model 2	0.07 (0.03)	0.013	0.03 (0.04)	0.39	0.10 (0.05)	0.04	0.099
Change in BMI-for-age Z score (Z/year)‡							
Model 1	0.03 (0.01)	0.010	0.01 (0.01)	0.27	0.05 (0.02)	0.003	0.011
Model 2	0.03 (0.01)	0.009	0.01 (0.01)	0.31	0.05 (0.02)	0.003	0.024

Random-effects included subject-specific intercepts for follow-up from 2007 to 2009 and subject-specific intercepts and slopes for follow-up from 2007 to 2012. Model 1 was adjusted for a child's age, sex, and race/ethnicity, and model 2 was further adjusted for a child's pubertal stage at the last follow-up visit and baseline household wealth. *Vitamin D insufficiency was defined as <75 nmol/L (15). †Mean changes in BMI and BMI-for-age Z score per year and their SE were estimated from mixed-effect linear regression models for each A allele of the *FTO* rs9939609 genotype. ‡BMI-for-age Z scores were calculated according to the WHO growth references (11,12).

Lower 25(OH)D levels have been associated with higher adiposity measures in children in several cross-sectional reports (5–7), and there is also indication from a longitudinal study that insufficient levels of vitamin D could be related to increases in BMI during childhood (8). In the present analysis, prevalence of vitamin D insufficiency was lower than that observed among children in the U.S. (5), which is conceivable considering that circulating levels of vitamin D depend mainly on sunlight exposure (15) and our study setting is at a subtropical location. Correspondingly, the proportion of children at risk for overweight in our study population was smaller than the figures observed in the U.S. and other wealthier regions in Brazil (5,17).

We found a significant interaction between *FTO* and vitamin D status in relation to child weight gain. The mechanisms underlying such interactions remain unclear. The *FTO* gene is expressed in the human brain, and there is evidence of association between its risk allele and reduced cerebrocortical insulin sensitivity (19). Previous studies have suggested a functional role for insulin in the regulation of energy homeostasis and body weight in the central nervous system (20). *FTO* variation could impact weight gain through a decreased insulin effect in brain tissues, affecting appetite, food choice, and dietary intake from an early age (21). Vitamin D is also essential for proper insulin secretion and activity (22), and lower circulating 25(OH)D has been related to insulin resistance in children after adjustment for BMI and puberty (23) as well as late-onset type 2 diabetes among adults (24). Additionally, a randomized controlled trial among obese adolescents indicated that vitamin D supplementation improved markers of insulin sensitivity and resistance (25). Therefore, a possible mechanism for the interaction between *FTO* genotype and vitamin D status might involve insulin action at a central level.

The major strengths of our study include its longitudinal design and use of direct anthropometric measurements. There are also limitations to this study. Follow-up rates were generally high, but children lost to follow-up were predominantly from poorer households. Although attrition is common in prospective studies, its implications are difficult to assess and caution should be taken when extrapolating our findings to the general population. While we could not completely rule out possible confounding by genetic ancestry, we adjusted all analyses by self-reported race/ethnicity, which in turn was not significantly associated with BMI, BMI-for-age Z score, or vitamin D status at baseline. Also, we were not able to adjust the present analyses by children's physical activity, which could influence weight status as well as exposure to sunlight and, therefore, vitamin D levels. Our present findings still need to be replicated in other populations, and underlying mechanisms involved in the interaction between *FTO* genotype and vitamin D status still need to be clarified.

In conclusion, *FTO* rs9939609 is positively associated with weight gain among children residing in the Brazilian Amazon. We found evidence that vitamin D status might modify *FTO* genetic effects, which were

more pronounced among children with insufficient vitamin D levels.

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Appendix

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4.6 ARTIGO 6

Weight gain during childhood and insulin resistance in Amazonian school-aged children

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Weight gain during childhood and insulin resistance in Amazonian school-aged children

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Abstract

Background and Aims: Investigation of determinants of metabolic outcomes associated with non-communicable diseases is increasingly important in low- to middle-income countries, but such parameters have been less explored during childhood. The present study assessed the impact of weight gain, measured in body mass index (BMI)-for-age Z score, on glucose and insulin concentrations, insulin resistance (HOMA-IR), and systolic and diastolic blood pressure during school-aged years among Amazonian children.

Methods and Results: We conducted a population-based prospective study from 2007- 2009, including 696 children aged >4 years with complete anthropometric information at baseline (51% girls, 86% mulatto/mixed race); 411 children had data on metabolic parameters after clinical examination at follow-up. During the follow-up period, there was a significant increase in the proportion of children at risk for overweight, from 10.1% to 15.8% (p=0.003). In linear regression models adjusted for child's sex, age, race/ethnicity, baseline household wealth, birth weight, and pubertal development stage, for each unit of BMI-for-age Z score variation during follow-up, we observed an increase of 1.43 (95% CI: 1.28; 1.60) mU/L in insulin concentrations and 1.47 (95% CI: 1.30; 1.66) in HOMA-IR.

Conclusion: We found evidence for an impact of weight gain in a 2-year period on insulin resistance during school-aged years. Considering a significant increase in the risk for overweight in this age group, special focus should be addressed in monitoring increases in adiposity in children.

Keywords: children, weight gain, insulin, insulin resistance, glucose, blood pressure

Introduction

Estimates for mortality rates suggest an increase of 30% for non-communicable diseases worldwide from 1990 to 2010 because of a broad epidemiological transition [1]. Investigation of determinants has been increasingly important, especially in low- to middle-income, high disease burden countries [2].

There is evidence for the association of growth and weight status in early life with compromised metabolic parameters in adulthood. Data from five prospective birth cohort studies from Brazil, Guatemala, India, the Philippines, and South Africa pointed out to a higher likelihood of overweight and elevated blood pressure among young adults due to faster relative weight gain after age 2 years [3]. Using the same dataset, faster weight gain after age 4 years was positively associated with glucose intolerance. Insulin resistance, on the other hand, was associated with weight gain from birth to adulthood in India, the Philippines, and South Africa [4].

Determinants of such metabolic parameters during childhood, however, are less explored, particularly in low- to middle-income regions with lower prevalence of overweight and obesity. In view of the social and health inequities related to non-communicable diseases, which are greatest among the poor [5], such monitoring could improve the discussion of modifiable factors before adulthood and help optimizing healthier development. Our aim, therefore, was to assess the impact of weight gain on glucose and insulin concentrations, insulin resistance, and systolic and diastolic blood pressure ascertained during school-aged years in a population-based prospective study in the Brazilian Amazon area.

Methods

Study population

This longitudinal study was conducted in Acrelândia, a frontier town located 112 km from Rio Branco, the capital of the state of Acre, in the Western Brazilian Amazon region. By 2007, the town had 11520 inhabitants at baseline (of which 44% resided in the urban area) comprising mainly migrants from Southeastern and Southern regions of Brazil engaged in commercial agriculture and cattle farming. An initial population-based cross-sectional survey on child health and nutrition enrolled a total of 1225 children aged ≤10 years (98.0% of those eligible) [6]. A follow-up assessment was carried out in December 2009 and identified 909 children of those included at baseline (74.2%).

The present analyses focus on school-aged children who were >4 years old and had complete anthropometric information in 2007 (*N*=696; 96.0% of those initially enrolled in this age group). In 2009, these children were invited for a clinical examination for evaluation of pubertal development, blood pressure measurement, and blood sample collection, and had anthropometric data updated as well.

Written informed consent for participation was obtained from parents or guardians before enrollment. The study was approved by the ethical review board of the School of Public Health, University of São Paulo, Brazil.

Field procedures and laboratory methods

As previously detailed [6], baseline household interviews with each participant's mother or guardian collected information on child's sex, age, race/ethnicity, nutritional history, and recent morbidity. The presence of 12 household assets was

determined to generate a wealth index, which was divided into quartiles [7]. We recorded maternal characteristics including educational level (≤4 years, 5-8 years, and ≥9 years) and age (≤21 years, 22-34 years, and ≥35 years). Birth weights were retrieved from child health cards (≤2500 g, 2500-3500 g, or >3500 g).

Children's anthropometric measurements were obtained in duplicate by directly by trained research assistants using standardized procedures and calibrated equipment at all study assessments [8]. Weight measurements were taken to the nearest 100 g using an electronic scale (Tanita model HS-302) and height was measured to the nearest millimeter using a stadiometer (in 2007: Seca model 208, Hamburg, Germany; in 2009: WCS, Curitiba, Brazil). Body mass index (BMI) was computed as weight in kg divided by height in m^2 and was used to calculate BMI-for-age Z scores using the World Health Organization (WHO) Child Growth Standards [9] for children ≤5 years old and the WHO Growth Reference Data for children >5 years old [10].

During clinical examinations in 2009, trained research assistants ascertained pubertal development according to Tanner stages [11] and measured blood pressure after 5 min of rest using an automatic digital device with appropriate cuff sizes. The mean of three measurements of systolic and diastolic blood pressure was used. A sample (5 mL) of fasting venous blood was collected from children; serum and plasma samples were shipped to São Paulo on dry ice and frozen at -70°C until further analysis. Glucose was determined by the automatic enzymatic method. For children aged ≥10 years, increased plasma glucose was defined as glucose concentrations ≥100 mg/dL [12]. Insulin was determined by fluoroimmunoassay, and hyperinsulinemia was defined when fasting insulin was above 15 mU/L or 20 mU/L for pre-pubescent and

pubescent children, respectively [13,14]. The homeostasis model assessment index of insulin resistance (HOMA-IR) was calculated as insulin (mU/L) x glucose (mmol/L)/22.5 [15]. Based on a population-based study among U.S. adolescents, participants with HOMA-IR >4.39 were classified as insulin resistant [16].

Statistical analyses

Outcomes of interest were the metabolic parameters ascertained among school-aged children in 2009 (systolic and diastolic blood pressure, glucose, insulin, HOMA-IR). Main exposure was variation in weight gain, measured as differences in BMI-for-age Z score from 2007 to 2009 in this age group.

First, we compared general socioeconomic, maternal, and child characteristics in each study assessment using chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. Metabolic parameters were compared by sex and Tanner stages in 2009 with the Wilcoxon rank-sum test. We used linear regression models to estimate the impact of variation in weight gain during follow-up on each of the metabolic parameters. Estimates were initially adjusted for baseline BMI-for-age Z score, child's sex, age, and race/ethnicity. Final models further included baseline household wealth, child's birth weight and Tanner stage at the last assessment. Other potential covariates were not significantly associated or did not affect the estimates of association with the outcomes. Two-tailed p values are presented for all statistical tests. We used STATA 11.2 (StataCorp, College Station, TX, USA) for all analyses.

Results

Among 696 children with complete anthropometric information and age >4 years at baseline, 50.6% were girls and 86.1% were mulatto. By 2007, BMI-for-age Z score was positively associated with male sex (p=0.01), household wealth (p=0.04), and child's birth weight (p<0.001). Main characteristics across study assessments are presented in Table 1. During follow-up from 2007 to 2009 in this age group, there was a significant increase in mean (SD) BMI-for-age Z score from -0.24 (0.99) to -0.05 (1.13) (p=0.01), and in the proportion of children at risk for overweight from 10.1% to 15.8% (p=0.003).

A total of 507 children with exposure information at baseline were evaluated in 2009. Of these, 411 had data on metabolic parameters after clinical examination. The median follow-up period was 2.0 years (range: 1.7-2.6 years). Children lost to follow-up were not different from children included in the analyses, except for mean age at baseline and sex distribution. Participants not included in the analysis were slightly younger at baseline (difference: 1.01 years, 95% CI: 0.75; 1.26 years), and follow-up rate was 3.7% higher among girls (p=0.02).

Metabolic characteristics of school-aged children in 2009 were compared according to sex and Tanner stages in 2009 (Table 2). While glucose concentrations were higher among boys, girls presented higher insulin levels and higher insulin resistance according to HOMA-IR. Pubescent participants had higher glucose, insulin, and HOMA-IR values. Increased plasma glucose, as defined when age ≥10 years (*N*=164), was detected in 20.1% of children. For pre-pubescent (*N*=223) and pubescent (*N*=131) participants altogether, hyperinsulinemia was observed in 5.1%

of children. In addition, 5.9% of all children were considered insulin resistant, with HOMA-IR values >4.39.

Weight gain from 2007 to 2009 measured as the difference in BMI-for-age Z score was associated with higher insulin concentrations and HOMA-IR values among school-aged children, after adjustment for sex, age, race/ethnicity, baseline household wealth, birth weight, and Tanner stage (Table 3). For each unit of BMI-for-age Z score, insulin levels and HOMA-IR increased by 1.43 (95% CI: 1.28; 1.60) mU/L and 1.47 (95% CI: 1.30; 1.66), respectively. No association with either systolic or diastolic blood pressure values was found.

Discussion

In the present study, weight gain during follow-up was related to higher insulin concentrations and insulin resistance, as measured by HOMA-IR, among generally euthophic school-aged children living in the Brazilian Amazon area. Also, there was a significant increase in the risk for overweight in this age group from 2007 to 2009. Similarly to our findings for boys and girls in Acrelândia, higher insulin levels and HOMA-IR values have been reported for girls when compared to boys aged 12-19 years in cross-sectional analysis of the National Health and Nutrition Examination Survey (1999-2002) in the United States [16]. As expected, our results confirmed the physiological increase in insulin resistance with pubertal development [14], as insulin concentrations and values of HOMA-IR were significantly higher among pubescent participants.

Mean HOMA-IR and occurrence of hyperinsulinemia were lower during school-aged years in Acrelândia when compared to other investigations in low- to middle-income areas, such as a population-based study with 6132 healthy children and adolescents in Mexico [17], where the absolute mean HOMA-IR was equal to 2.89 (0.70). Nonetheless, we could observe a significant influence of weight gain on insulin resistance, after adjustment for child's sex, age, and Tanner stage, among other covariates. In line with these findings, weight gain during childhood, and more specifically fat mass measured with dual-energy X-ray absorptiometry, was associated to higher insulin resistance among 238 children from 7 to 13 years of age in the United Kingdom [18]. Similar associations have also been reported for low- to middle-income areas mostly when considering insulin resistance ascertained among adults as an outcome in longitudinal investigations. Higher increases in BMI between childhood or adolescence and adulthood were positively related to higher HOMA-IR values in rural communities in India [19]. Conditional weight gains as early as from birth to age 2 years were associated with insulin resistance during young adulthood in other three birth cohort studies conducted in developing countries [4].

As insulin resistance has a key role in metabolic changes and later risk for type 2 diabetes, and is closely related to BMI since youth [20], it is important to note that the longitudinal impact of weight gain in our study was accompanied in fact by a significant increase in the risk for overweight during a relatively short period of follow-up, from 10.1% to 15.8% in 2 years. While these figures may be not extremely high yet, the increasing prevalence of overweight and obesity worldwide [21] is a public health concern. In this sense, our results shed light on the dual burden of disease affecting children in rapidly changing environments, which commonly

lack material and structural resources, but progressively promote the development of chronic disease risk and therefore call for action for preventing both under- and overnutrition in a timely manner [22,23].

There are some limitations to our study. Although the overall follow-up rate was high, there were differences between children included and not included in the analyses regarding baseline age and sex, and potential implications are difficult to assess. In addition, there was only one measurement available for the metabolic outcomes studied, but assessment of such parameters was done during earlier stages of life when compared to other prospective investigations. While several cohorts found evidence for a role of growth on blood pressure in adulthood [3,24-26], we could not verify associations of weight gain with systolic and diastolic blood pressure during school-aged years in the present analyses, possibly because of a shorter period of follow-up. Our study has several strengths as well, including its longitudinal, population-based design, ability to control for pubertal development, and use of direct and standardized anthropometric measurements expressed in WHO Z scores.

In conclusion, we found evidence for an impact of weight gain in a 2-year period on insulin resistance already during school-aged years. Considering a significant increase in the risk for overweight in this age group, special focus should be addressed in monitoring increases in adiposity.

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Table 1. Characteristics of school-aged children with complete anthropometric information at each study assessment, Acrelândia, Brazil.

	2007	2009	p[a]
N[b]	696	507	
Sex, *n* (%)			0.36
Female	352 (50.6)	270 (53.2)	
Male	344 (49.4)	237 (46.8)	
Age (years), mean (SD)	7.1 (1.8)	9.1 (1.8)	<0.001
Race/ethnicity, *n* (%)			0.90
White	57 (8.9)	39 (8.4)	
Mulatto/mixed race	551 (86.1)	402 (87.0)	
Black	32 (5.0)	21 (4.6)	
Household wealth index, *n* (%)			0.81
1st quartile (lowest)	156 (22.5)	104 (20.5)	
2nd quartile	191 (27.4)	140 (27.6)	
3rd quartile	178 (25.6)	129 (25.5)	
4th quartile (highest)	170 (24.5)	134 (26.4)	
Maternal educational level, *n* (%)			0.93
≤4 years	286 (42.4)	210 (41.5)	
5-8 years	200 (29.7)	150 (29.6)	
≥9 years	188 (27.9)	146 (28.9)	
Maternal age, *n* (%)			0.88
≤21 years	25 (3.6)	16 (3.2)	
22-34 years	477 (68.5)	345 (68.0)	

≥35 years	194 (27.9)	146 (28.8)	
Birth weight, *n* (%)			0.64
≤2500 g	42 (6.7)	37 (8.0)	
2501-3500 g	372 (59.6)	266 (57.3)	
>3500 g	210 (33.7)	161 (34.7)	
Tanner stage, *n* (%)			–
Prepubertal	–	313 (67.9)	
Pubertal	–	148 (32.1)	
BMI-for-age Z score, mean (SD)[b]	-0.24 (0.99)	-0.05 (1.13)	0.01
Risk for overweight, *n* (%)[c]			0.003
No	626 (89.9)	427 (84.2)	
Yes	70 (10.1)	80 (15.8)	
Height-for-age Z score, mean (SD)[b]	-0.29 (0.95)	-0.35 (0.93)	0.23
Stunting, *n* (%)[d]			0.71
No	674 (96.8)	489 (96.4)	
Yes	22 (3.2)	18 (3.6)	

Totals may ne different from 696 because of missing data. [a] P values were calculated by chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. [b] BMI-for-age and height-for-age Z scores were calculated according to the WHO growth references. [c] Risk for overweight was defined as BMI-for-age Z score above 1. [d] Stunting was defined as height-for-age Z score below -2.

Table 2. Mean and standard deviation values of metabolic parameters of school-aged children according to sex and Tanner stage, Acrelândia, Brazil, 2009.

	Sex					Tanner stages				
	Female		Male			Pre-pubertal		Pubertal		
	N	Mean (SD)	*N*	Mean (SD)	p[a]	*N*	Mean (SD)	*N*	Mean (SD)	p[a]
Glucose (mg/dL)	217	90.4 (7.6)	185	92.8 (8.2)	**0.004**	235	90.6 (8.4)	145	92.9 (7.2)	**0.003**
Insulin (mU/L)	203	8.4 (8.3)	173	6.1 (3.9)	**0.01**	223	5.7 (4.0)	131	9.7 (6.8)	**<0.001**
HOMA-IR[b]	201	1.96 (2.13)	170	1.43 (1.00)	**0.02**	218	1.32 (1.04)	131	2.24 (1.68)	**<0.001**
Systolic blood pressure (mmHg)	223	99.1 (9.2)	188	100.3 (9.2)	0.19	242	100.1 (8.6)	148	98.8 (10.0)	0.21
Diastolic blood pressure (mmHg)	223	62.9 (6.4)	188	62.1 (6.8)	0.26	242	62.4 (6.3)	148	62.6 (7.0)	0.82

[a] P values were calculated by Wilcoxon rank-sum test. [b] HOMA-IR: homeostasis model assessment-insulin resistance.

Table 3. Linear regression coefficients (ß; 95% CI) for the association of weight gain (in units of BMI-for-age Z score) with metabolic parameters among school-aged children, Acrelândia, Brazil, 2007-2009.

		Weight gain BMI-for-age Z score difference[a]	
		Crude[b]	Adjusted[c]
	N	ß (95% CI)	ß (95% CI)
Glucose (mg/dL)	402	1.34 (-0.15; 2.82)	1.35 (-0.17; 2.87)
Insulin (mU/L)	376	**1.47 (1.31; 1.64)**	**1.43 (1.28; 1.60)**
HOMA-IR[d]	371	**1.52 (1.35; 1.71)**	**1.47 (1.30; 1.66)**
Systolic blood pressure (mmHg)	411	-0.27 (-2.01; 1.48)	-0.43 (-2.20; 1.34)
Diastolic blood pressure (mmHg)	411	0.25 (-1.00; 1.51)	0.17 (-1.11; 1.44)

[a] BMI-for-age Z scores were calculated according to the WHO growth references. [b] Linear regression models for crude estimates (beta coefficient and 95% confidence intervals) included the difference in BMI-for-age Z score for the 2007-2009 period, the baseline value for the respective anthropometric variable, child's sex, age, and race/ethnicity. [c] Adjusted estimates further considered baseline household wealth, child's birth weight and Tanner stage at the last assessment. [d] HOMA-IR: homeostasis model assessment-insulin resistance.

5 CONSIDERAÇÕES FINAIS

A presente investigação longitudinal de base populacional em Acrelândia, estruturada a partir de inquéritos de base populacional com crianças residentes no município entre 2003 e 2012, identificou um conjunto amplo de determinantes do crescimento linear e ganho de peso durante a infância.

No seguimento 2003–2009 (Artigos 2 e 3), o crescimento linear medido em escores Z de comprimento/altura para idade foi positivamente influenciado por fatores socioeconômicos. Aos 5 anos de idade, a riqueza domiciliar acima da mediana para o município impactou o ganho de altura em 0,30 escore Z (IC 95%: 0,06-0,54), ao passo que a posse de terra foi associada a altura 0,34 escore Z (IC 95%: 0,05-0,63) maior aos 10 anos. De maneira semelhante, o ganho de peso de acordo com escores Z de IMC para idade foi maior entre crianças residentes em domicílios acima da mediana do índice de riqueza, atingindo diferença significante de 0,49 escore Z (IC 95%: 0,19-0,81) aos 10 anos de idade em relação às crianças em domicílios mais pobres. Tais achados enfatizam a importância de determinantes distais sobre o desenvolvimento infantil e confirmam em perspectiva longitudinal a relação positiva de fatores socioeconômicos sobre o crescimento na infância, no atual estágio de transição epidemiológica e nutricional em uma região de baixa renda.

Considerando a influência do estado nutricional materno sobre as condições de nutrição exibidas pela criança, a altura materna foi positivamente associada ao crescimento linear da criança durante toda a infância no seguimento 2003–2009. Crianças cujas mães foram classificadas no maior tercil de altura tiveram crescimento significantemente maior em 0,55 a 1,10 escores Z de altura para idade no período compreendido entre 6 meses e 10 anos de idade. Crianças cujas mães apresentaram sobrepeso também obtiveram maiores ganhos em escores Z de IMC até os 10 anos de idade, sendo que, aos 10 anos, a diferença foi equivalente a 0,69 escore Z (IC 95%: 0,35-1,04). Confirmou-se prospectivamente a indicação de que fatores genéticos e ambientais desde o início da vida, além de influências comportamentais, são compartilhados entre gerações e exercem efeito sobre a saúde infantil durante toda a infância.

Em relação ao peso ao nascer, as presentes análises observaram influência mais expressiva sobre o crescimento linear quando comparada ao ganho de peso. Com controle para condições socioeconômicas e características maternas, crianças na categoria de peso ao nascer >3.500 g eram mais altas que aquelas na categoria de referência (entre 2.500 e 3.500 g) até os 10 anos de idade (diferença: 0,31 escore Z; IC 95%: 0,05-0,57).

Fatores em níveis de determinação mais proximais foram analisados em relação ao ganho de peso durante a infância principalmente no seguimento 2007–2012 (Artigos 4 e 5), após controle por variáveis distais e intermediárias. A exposição à falta de recursos estruturais e a condições ambientais adversas ao longo da vida, a exemplo de agentes patogênicos, estresse psicossocial e dieta inadequada, foi explorada em hipóteses biológicas sobre seu possível efeito cumulativo sobre o desenvolvimento e a função metabólica, com provável impacto no risco para doenças crônicas na adolescência e vida adulta.

Crianças participantes do presente estudo foram comumente afetadas durante o período de acompanhamento por condições de morbidade e deficiências de micronutrientes, como ferro e vitamina A. Em linha com tais observações, maiores concentrações de proteína C-reativa na infância, um biomarcador do estado inflamatório, foram associadas a baixo nível socioeconômico, segundo índice de riqueza domiciliar, e a piores indicadores nutricionais, tais como menores concentrações sanguíneas de vitamina A e ferritina e baixo índice de frequência de consumo de frutas e hortaliças. A partir da influência de concentrações de proteína C-reativa sobre o ganho de peso na infância observada em Acrelândia, foi possível corroborar a hipótese de que a exposição contínua a processos inflamatórios pode, como um mecanismo subjacente, interferir no desenvolvimento do indivíduo ao longo do tempo. Entre crianças >5 anos de idade, apesar de não haver diferença na média de escore Z de IMC para idade na linha de base segundo categorias de proteína C-reativa, aquelas com um estado inflamatório de baixo grau tiveram ganho modesto porém significante de 0,04 escore Z de IMC (IC 95%: 0,01-0.09) por ano durante o seguimento quando comparadas àquelas com concentrações mais baixas do marcador.

No presente estudo, a influência do gene *FTO* sobre o ganho de peso durante a infância foi confirmada em 0,03 escore Z de IMC por ano por alelo de risco. Houve interação genética com fatores nutricionais, com modificação do efeito do gene *FTO* pelo estado inicial de vitamina D, conforme apresentado na única publicação original a considerar e reportar tal associação até o presente momento. Na mesma perspectiva de exposição concomitante a condições ambientais desfavoráveis, crianças com concentrações insuficientes de vitamina D apresentaram incremento significantemente maior de IMC, de 0,07 escore Z por ano por alelo de risco, ao longo do seguimento (*P* de interação <0,03). Apesar do potencial efeito protetor da vitamina D sobre a influência do alelo de risco do gene *FTO* na predisposição ao ganho de peso, mais investigações sobre a interação gene-nutriente serão necessárias para confirmar e contextualizar os achados em questão. É importante considerar de forma mais abrangente outros fatores relacionados ao estilo de vida, exposição solar, atividade física e dieta, por exemplo, os quais têm sofrido constantes modificações frente ao processo de transição nutricional e epidemiológica.

Observou-se entre os seguimentos 2003–2009 e 2007–2012 uma redução na proporção de crianças afetadas pelo déficit de altura para idade e um aumento na proporção daquelas sob risco de sobrepeso e/ou obesidade. Em 2003, 10,2% das crianças incluídas nas análises (todas até 5 anos de idade) foram classificadas com escore Z de altura para idade abaixo de -2 e 12,9% apresentaram escore Z de IMC para idade acima de 1. Em 2012, entre as crianças acompanhadas no último inquérito realizado em Acrelândia (todas a partir dos 6 anos de idade), a proporção de déficit de altura para idade equivaleu a apenas 2,8%, enquanto a proporção de risco para sobrepeso foi de 17,9%. Na perspectiva de um ambiente que progressivamente favorece o desenvolvimento de doenças crônicas, averiguou-se que o ganho de peso avaliado em apenas dois anos de seguimento, entre 2007 e 2009, foi associado positivamente à maior resistência à insulina entre crianças de forma geral eutróficas em idade escolar (Artigo 6).

As presentes análises conjeturam, portanto, o panorama de carga dupla de doença que pode afetar o desenvolvimento desde estágios iniciais da vida em regiões de baixa e média renda sob processo de transição nutricional. Contextualizando os fatores associados aos desfechos estudados em diferentes níveis de determinação,

condições sub-ótimas durante a infância potencialmente influem sobre indicadores do crescimento linear esperado de forma negativa e, ao longo do tempo, podem favorecer o ganho de peso excessivo e o comprometimento de parâmetros metabólicos.

Em conclusão, confirmou-se o papel de fatores socioeconômicos e intergeracionais sobre o crescimento linear e o ganho de peso entre crianças residentes na região da Amazônia Ocidental Brasileira. O incremento de peso foi, ainda, influenciado por um cenário em que deficiências de micronutrientes, elevada morbidade e interação entre fatores genéticos e nutricionais coexistem com panorama crescente de sobrepeso e obesidade. Fatores potencialmente modificáveis podem ter impacto no planejamento de intervenções visando à prevenção de doenças infecciosas e redução da carga de morbidade em conjunto ao perfil de risco para distúrbios nutricionais e metabólicos na adolescência e vida adulta.

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ANEXOS

ANEXO 1

Apreciação geral da proposta inicial e pareceres sobre os relatórios científicos apresentados à Fundação de Amparo à Pesquisa do Estado de São Paulo e referentes à bolsa de doutorado direto processo nº 2008/57796-3

FAPESP

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO
Formulário para Parecer Inicial de Assessoria Científica
Bolsa de Doutoramento
Disponível em: http://orion.fapesp.br/formularios/arquivos/pibpddr.doc

Proc. No: 08/57796-3	Candidato(a): Bárbara Hatzlhoffer Lourenço Orientador (a): Marly Augusto Cardoso

APRECIAÇÃO GERAL DA PROPOSTA - A Fapesp denomina "Proposta" o conjunto de três partes a serem analisadas, composto por: 1. Projeto de Pesquisa; 2. Histórico Escolar e Acadêmico do Candidato; e, 3. Histórico de Pesquisa do Orientador. Por favor preencha os itens de análise desta página depois de preencher o restante do formulário.

Trata-se de estudo que faz parte de um projeto maior financiado pela FAPESP, a ser desenvolvido como projeto de doutorado direto por aluna do curso de Nutrição da FSP-USP em fase final de conclusão do curso de graduação. A candidata à bolsa tem excelente histórico escolar, foi bastante ativa durante a graduação do ponto de vista do envolvimento em atividades científicas, tendo desenvolvido projeto de Iniciação Científica que resultou em trabalho apresentado em congresso e publicado em periódico com seletiva política editorial, além de lhe render prêmio em que a qualidade do trabalho foi reconhecida. Dessa forma, entendo que a candidata está adequadamente preparada para enfrentar o desafio de um doutorado direto, visto ainda que será orientada pela responsável pelo projeto maior do qual este estudo faz parte; além disso, a orientadora tem experiência comprovada na área onde este projeto se insere. A proposta apresenta embasamento científico consistente, metodologia adequada, proposta de análise dos dados pertinente aos objetivos pretendidos e seu desenvolvimento é viável dentro do prazo previsto.

ANÁLISE FINAL DA PROPOSTA - Compreendendo: Qualidade do Projeto; Histórico Escolar e Acadêmico do Candidato; Histórico de Pesquisa do Orientador

[X] Excelente.

[ ] Muito Boa.

[ ] Muito Boa, com algumas deficiências facilmente sanáveis.

[ ] Boa.

[ ] Boa com deficiências.

[ ] Regular.

[ ] Com sérias deficiências.

1. Por favor, analise o PROJETO DE PESQUISA proposto, conforme roteiro abaixo:

1.a Definição e pertinência dos objetivos.

O projeto é integrante de um programa de pesquisas epidemiológicas sobre condições de saúde e nutrição em cidade do estado do Acre, desenvolvido em cooperação pela Universidade Federal do Acre, a Faculdade de Saúde Pública e o Instituto de Ciências Biomédicas da USP, com financiamento da FAPESP. O objetivo deste projeto específico é investigar determinantes medidos na primeira infância associadas ao perfil de ganho de peso e crescimento de crianças em idade escolar em um município do estado do Acre. Os objetivos estão claros e se inserem dentro da proposta geral do projeto maior do qual faz parte.

1.b Importância da contribuição pretendida para a área de conhecimento em que o projeto se insere.

O projeto vai permitir conhecer o perfil nutricional da população infantil estudada e alguns de seus fatores determinantes, em uma região do país que registra um dos piores indicadores socioeconômicos. A pesquisa pretende trazer subsídios para o planejamento de ações de intervenção para redução do perfil de risco para distúrbios nutricionais e metabólicos em outras fases da vida.

1.c Fundamentação científica e os métodos empregados.

O estudo será do tipo longitudinal e prospectivo, utilizando-se dados de crianças já avaliadas em dois inquéritos populacionais, que tinham menos de 5 anos na primeira avaliação em 2003, entre 0 e 10 anos na segunda avaliação em 2007 (inclui as crianças do inquérito anterior e mais novas crianças com menos de 5 anos), e que serão rastreadas para serem submetidas a uma nova avaliação no final de 2009. Em todos os inquéritos as variáveis estudadas compreendem condições sócio-demográficas e morbidade recente, avaliação antropométrica e de práticas alimentares, sendo que no último está prevista a aplicação de um questionário de freqüência alimentar para as crianças maiores de 7 anos, desenvolvido e validado em sub-amostra de escolares que participaram do segundo inquérito; também está prevista a coleta de amostras de sangue para avaliar o status de ferro e anemia dessas crianças. Para a análise dos dados propõe-se a utilização de modelos de regressão linear múltiplos para avaliar os determinantes do padrão de crescimento linear e de ganho de peso dos participantes. Pretende-se ainda um treinamento pra a análise dos dados longitudinais na Harvard School of Public Health como parte das atividades de doutorado da candidata à bolsa.

O delineamento do estudo e a análise proposta me parecem adequados para se atingir o objetivo pretendido.

1.d Adequação do projeto a um programa de doutorado direto e viabilidade de sua execução dentro do prazo previsto.

O projeto é adequado a um programa de doutorado direto, visto que trará contribuições originais para o estado da arte e poderá fornecer subsídios para intervenção, e é viável para ser executado no prazo previsto. Embora parte dos dados já tenha sido coletada em fases anteriores, a doutoranda participará da terceira fase de coleta de dados, bem como da organização e análise dos mesmos, em conjunto com os dados das outras fases, o que será importante para o seu desenvolvimento científico.

1.e Caso se trate de um candidato que já tenha iniciado o doutorado direto, avalie o andamento do projeto de pesquisa e a viabilidade de sua execução no prazo previsto.

A candidata está finalizando o curso de graduação e ainda não iniciou o doutorado direto.

Conclusão sobre a análise do Projeto de Pesquisa proposto

[X] Excelente.
[ ] Muito Boa.
[ ] Muito Boa, com algumas deficiências facilmente sanáveis.
[ ] Boa.
[ ] Boa com deficiências.
[ ] Regular.
[ ] Com sérias deficiências.

2. As bolsas de Doutorado direto se destinam a estudantes com bom desempenho acadêmico avaliado, principalmente, pelo histórico escolar de graduação e pós-graduação. A concessão a estudantes com histórico escolar irregular, exibindo um padrão de reprovações ou aprovações com nota mínima, é possível apenas em circunstâncias excepcionais à vista de outras evidências sobre o potencial acadêmico do candidato, como por exemplo, projeto bem sucedido de Iniciação Científica. Por favor, analise o HISTÓRICO ESCOLAR E ACADÊMICO DO CANDIDATO seguindo o roteiro abaixo:

2.a Histórico Escolar do candidato

O histórico escolar da candidata é excelente, sendo 8,0 a sua menor nota em disciplina do primeiro semestre do terceiro ano do curso, e a nota ponderada até o momento é de 9,5, considerando que a conclusão do curso está prevista para o final de 2008.

2.b Histórico Acadêmico do candidato (participação em projetos de pesquisa, bolsas anteriores, publicações científicas, premiações)

A candidata fez curso profissionalizante na área de Nutrição e Dietética, portanto em área afim ao curso superior que escolheu posteriormente. Durante o curso de graduação em Nutrição na FSP-USP foi monitora em quatro disciplinas e participou de um projeto de extensão universitária no ICB-USP. Desenvolveu projeto de iniciação científica com bolsa da FAPESP durante um ano. Tem dois artigos completos publicados em periódicos internacionais, sendo um deles relacionado ao seu tema de iniciação científica. Tem ainda um artigo aceito para publicação em periódico internacional e dois capítulos de livros aceitos para publicação. Recebeu dois prêmios, um em primeiro lugar por trabalho apresentado em evento científico, e outro em terceiro lugar por seu trabalho de iniciação científica, concedido pela Faculdade de Medicina da USP.

Pelo exposto verifica-se que a candidata foi muito ativa e desempenhou extensa atividade de pesquisa durante o seu curso de graduação.

2.c Outros itens que compõem a descrição das atividades acadêmicas, científicas e profissionais desenvolvidas pelo candidato.

Participou de estágios extracurriculares em áreas afins ao seu objeto de pesquisa tanto de iniciação científica quanto ao agora proposto, envolvendo atividades em ambulatórios de transtornos alimentares, de obesidade infantil e em serviço hospitalar de nutrição e dietética. Participou ainda de organização de curso relacionado à obesidade na infância e adolescência, vinculado à Liga de Obesidade Infantil da FMUSP.

Conclusão sobre a análise do Histórico Escolar e Acadêmico do candidato

[X] Excelente
[ ] Muito Bom

[ ] Bom

[ ] Regular.
[ ] Com sérias deficiências.

3. Por favor, analise o HISTÓRICO DE PESQUISA DO ORIENTADOR, seguindo o roteiro abaixo

3.a Qualidade, regularidade e importância da produção científica e/ou tecnológica, com destaque para a produção recente. Elementos importantes para essa análise são: lista de publicações em periódicos com seletiva política editorial; livros ou capítulos de livros; patentes em que figure como inventor; outros instrumentos de propriedade intelectual; resultados de pesquisa efetivamente transferidos e adotados por empresas ou pelo governo; e outras informações que possam ser relevantes.

A produção recente da orientadora mostra artigos completos divulgados em periódicos de ampla circulação internacional, portanto submetido à avaliação rigorosa de seus pares, vários deles relacionados a trabalhos que orientou no programa de pós-graduação do qual faz parte, além de livros e capítulos de livros publicados.

Pelo exposto verifica-se que a produção científica da orientadora é de excelente qualidade.

3.b Experiência e competência demonstrada na liderança de projetos de pesquisas relacionados ao tema da proposta em análise.

Pela descrição da produção científica apresentada na súmula curricular, verifica-se que a orientadora tem grande experiência na área de pesquisa que se relaciona com a presente proposta e tem competência e disponibilidade para orientar trabalhos nessa área. É coordenadora do projeto maior do qual a presente proposta faz parte, com financiamento da FAPESP (proc. 2007/53042-1).

3.c Capacidade demonstrada para formar pesquisadores, com destaque para a atividade recente de orientação de estudantes.

A orientadora demonstra capacidade comprovada de formar pesquisadores, na medida em que, nos últimos 5 anos, tem 4 teses de doutorado concluídas, sendo que 2 já resultaram em publicações e 2 têm trabalhos enviados para publicação; também relata 4 dissertações de mestrado concluídas, das quais 3 já resultaram em publicações. Refere 60 publicações em periódicos com seletiva política editorial, 5 livros organizados e 16 capítulos de livros produzidos.

3.d Resultados obtidos pelo orientador com financiamentos anteriores da FAPESP.

Embora não descreva os resultados obtidos com financiamentos anteriores da FAPESP, vários dos trabalhos publicados foram produzidos por alunos de pós-graduação bolsistas da FAPESP ou que seus projetos tiveram auxílio financeiro dessa financiadora.

3.e Disponibilidade para orientação considerando o regime de trabalho e o número total de estudantes sob a sua orientação.
Número atual de orientandos....IC:_____;MS:_____; DR: 2
Regime de trabalho: dedicação exclusiva

Comentários: A orientadora relata duas orientações de doutorado, uma delas com bolsa da FAPESP e outra com bolsa do CNPq. Não relata orientação de mestrado e de IC em andamento no momento.

3.f Outras considerações sobre a produção científica, tecnológica e acadêmica do orientador, relevantes para a Análise da viabilidade da proposta.

É pesquisadora nível 2 do CNPq, assessora *ad hoc* de vários periódicos nacionais e internacionais e de órgãos nacionais de fomento à pesquisa (CNPq e FAPESP). Pertence a entidade de classe na sua área de atuação e é coordenadora do Programa de Pós-Graduação em Nutrição em Saúde Pública da Faculdade de Saúde Pública da USP. Realizou dois estágios de pós-doutoramento no exterior, na área de Epidemiologia Nutricional, em 1995-97 e 2005-06.

Conclusão sobre Histórico de Pesquisa do Orientador

[X] Excelente
[ ] Muito Bom

[ ] Bom

[ ] Regular.
[ ] Com sérias deficiências

São Paulo, 13 de Abril de 2010.

Ilmo(a). Sr(a).
MARLY AUGUSTO CARDOSO

Referente Transcrição de Parecer do Relatório Científico
Processo **08/57796-3** BOLSA NO PAIS
Beneficiário **BARBARA HATZLHOFFER LOURENCO**

Prezado(a) Sr(a),

Recebemos o Relatório Científico em 10/02/10, o qual foi examinado pelos Assessores, tendo recebido o parecer anexo.

Atenciosamente,

Setor de Controle de Processos
Diretoria Científica

Obs: A transcrição do parecer está sendo enviada exclusivamente ao Orientador(a), sendo de sua responsabilidade compartilhar as partes que considerar relevantes com o estudante candidato, o qual receberá uma cópia desta carta (sem a transcrição do parecer).

Cópia Orientador

RUA PIO XI, 1500 - CEP 05468-901 - SÃO PAULO - SP - TEL: 11 3838.4000 - FAX: 11 3645.2383
e-mail: expedientedc@fapesp.br

FAPESP

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

Formulário para parecer de Acompanhamento de Assessoria Científica

Bolsas de [ ] IC [ ] MS [ ] DR [X] DD [ ] PD/PAÍS [ ] BP/EXTERIOR

(Este formulário está disponível em formato eletrônico no endereço http://**www.fapesp.br**)

Processo **08/57796-3**

Bolsista: Bárbara Haltzlhoffer Lourenço

Por favor, emita o parecer, comentários, críticas e sugestões.

Durante o período que o relatório cobre foram realizados o planejamento e a execução de um estudo piloto na cidade de Acrelância, que forneceu subsídios para a estruturação da fase posterior de coleta de dados. Nesse estudo foram feitas visitas domiciliares com realização de medidas antropométricas das crianças, diagnóstico nutricional, pré-teste dos questionários que serão utilizados no estudo, identificação de crianças com anemia e realização de diversas atividades com a população e com os agentes comunitários de saúde sobre temas relacionados à saúde e nutrição. Com base na experiência adquirida no projeto piloto e na revisão da literatura atual foi decidida a inclusão da aferição da pressão arterial e avaliação do estadiamento puberal das crianças acima de sete anos que participarão da fase seguinte do estudo, e também da avaliação da situação de insegurança alimentar em todos os domicílios

O projeto também foi revisado e atualizado em relação à literatura científica pertinente, visando à realização do exame de qualificação pela aluna bolsista, no programa de pós-graduação em que está inserida, no próximo período.

Além das atividades relacionadas diretamente à sua pesquisa, a aluna cursou disciplinas do programa de pós-graduação, publicou artigo de revisão vinculado ao seu tema de pesquisa, participou de seminários e foi selecionada para participar de curso de treinamento em epidemiologia do diabetes no Canadá (outubro de 2009), publicou dois artigos originais em periódicos indexados, publicou um capítulo de livro internacional sobre tema vinculado ao projeto de IC que desenvolveu durante a graduação com bolsa da FAPESP, e tem dois capítulos em livros nacionais no prelo. Elaborou ainda texto para revista, apresentou trabalho em congresso nacional, organizou um evento científico e participou de disciplina de graduação.

Foi ainda contemplada para realização de estágio acadêmico no exterior– Universidade de Michigan, EUA - com auxílio da Organização dos Estados Americanos, para treinamento estatístico em análise de dados longitudinais, que será muito importante na análise dos dados do seu projeto de doutorado. O cronograma de atividades proposto para o próximo período inclui esse estágio de 3 meses, após a coleta de dados complementar em Acrelândia.

Pelo exposto, observa-se que o desempenho da bolsista foi excelente em todas as fases do trabalho desenvolvidas até o momento.

RELATÓRIO APROVADO

RESERVA TÉCNICA [exceto para as bolsas de IC, PD-PAÍS e BP/EXTERIOR]

As normas da FAPESP permitem a utilização dos recursos da Reserva Técnica (RT) sem prévia avaliação pela assessoria, com utilização avaliada a posteriori. Avalie a adequada aplicação desses recursos: Os recursos da reserva técnica foram utilizados para serviços de gráfica e cópias de artigos científicos utilizados na elaboração do projeto de pesquisa e reprodução de material didático das disciplinas cursadas no período (serviços de terceiros); passagens aéreas e diárias para ida e permanência em Acrelândia para desenvolvimento de projeto piloto e de atividades de extensão junto à população do local do estudo; manutenção no exterior para participação em um simpósio internacional e um curso de treinamento em área do conhecimento relacionada ao tema da pesquisa. Considero que esses dispêndios foram importantes para o bom andamento do projeto.
Opine sobre a adequação dos novos itens solicitados, face às reais necessidades do projeto.

São Paulo, 23 de Marco de 2011.

Ilmo(a). Sr(a).
MARLY AUGUSTO CARDOSO

Referente Transcrição de Parecer do Relatório Científico
Processo **08/57796-3** BOLSA NO PAIS
Beneficiário **BARBARA HATZLHOFFER LOURENCO**

Prezado(a) Sr(a),

Recebemos o Relatório Científico em 09/02/11, o qual foi examinado pelos Assessores, tendo recebido o parecer anexo.

Atenciosamente,

RELATÓRIO APROVADO
Reserva Técnica : Adequada

Setor de Controle de Processos
Diretoria Científica

Obs: A transcrição do parecer está sendo enviada exclusivamente ao Orientador(a), sendo de sua responsabilidade compartilhar as partes que considerar relevantes com o estudante candidato, o qual receberá uma cópia desta carta (sem a transcrição do parecer).

Cópia Orientador

RUA PIO XI, 1500 - CEP 05468-901 - SÃO PAULO - SP - TEL: 11 3838.4000 - FAX: 11 3645.2383
e-mail: expedientedc@fapesp.br

FAPESP

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

Formulário para parecer de Acompanhamento de Assessoria Científica de Bolsas

[ ] IC [ ] MS [ ] DR [X] DD [ ] PD/PAÍS [ ] BP/EXTERIOR [ ] NOVAS FRONTEIRAS

(Este formulário está disponível em formato eletrônico no endereço http://**www.fapesp.br**)

Processo **0857796-3**

Bolsista: Bárbara Hatzlhoffer Lourenço

Por favor, emita o parecer, comentários, críticas e sugestões.

No período que o presente relatório cobre (março de 2010 a fevereiro de 2011) a aluna organizou os dados que foram coletados em campo entre novembro e dezembro de 2009 de forma a permitir a codificação padronizada e em seguida a digitação dos mesmos no programa Epi Info, com entrada dupla dos dados e comparação entre as duas digitações para validação do banco e correção dos possíveis erros encontrados. Após a tabulação desses dados verificou-se a necessidade de nova visita ao campo para completar a coleta de informações de tal forma a contemplar as exigências do desenho longitudinal do estudo. Essa nova visita realizou-se em duas semanas de julho de 2010.

Esses dados foram uniformizados, combinados em um único banco traduzido para o inglês, e levados para serem trabalhados durante o estágio iniciado em setembro de 2010 na *University of Michigan School of Public Health*.

Nesse estágio a aluna tem realizado estudos de métodos estatísticos que serão utilizados na análise de seus dados, participado de disciplinas sobre temas relacionados a seu projeto de pesquisa, realizado revisão periódica da literatura sobre o objeto de estudo, participado de seminários quinzenais na área de epidemiologia e saúde populacional. O desempenho da aluna no estágio tem sido considerado excepcional pelo seu supervisor e por outros membros do staff da instituição onde está trabalhando.

Outras atividades desenvolvidas no período foram a realização do exame de qualificação (04/03/2011), acumulou 10 créditos em disciplinas cursadas na FSP-USP, realizou estágio do Programa de Aperfeiçoamento de Ensino no primeiro semestre de 2010 e participou como ouvinte em dois cursos em agosto de 2010.

Tem ainda nesse período 1 artigo publicado em periódico nacional, 2 capítulos de livros nacionais publicados, ministrou palestras e aulas em cursos de pós-graduação e graduação.

Por tudo isso, entendo que o desempenho da aluna na realização do doutorado tem sido excelente, o estudo está se desenvolvendo adequadamente, dentro do cronograma previsto e o estágio no exterior está sendo muito útil para o bom andamento do projeto.

São Paulo, 11 de Abril de 2012.

Ilmo(a). Sr(a).
MARLY AUGUSTO CARDOSO

Referente Transcrição de Parecer do Relatório Científico
Processo **08/57796-3** BOLSA NO PAIS
Beneficiário **BARBARA HATZLHOFFER LOURENCO**

Prezado(a) Sr(a),

Recebemos o Relatório Científico em 10/02/12, o qual foi examinado pelos Assessores, tendo recebido o parecer anexo.

Atenciosamente, RELATÓRIO APROVADO

Setor de Controle de Processos
Diretoria Científica

Obs: A transcrição do parecer está sendo enviada exclusivamente ao Orientador(a), sendo de sua responsabilidade compartilhar as partes que considerar relevantes com o estudante candidato, o qual receberá uma cópia desta carta (sem a transcrição do parecer).

Cópia Orientador

RUA PIO XI, 1500 - CEP 05468-901 - SÃO PAULO - SP - TEL: 11 3838.4000 - FAX: 11 3645.2383
e-mail: expedientedc@fapesp.br

FAPESP

FUNDAÇAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

Formulário para parecer de Acompanhamento de Assessoria Científica de Bolsas

[ ] IC [ ] MS [ ] DR [X] DD [ ] PD/PAÍS [ ] BP/EXTERIOR [ ] NOVAS FRONTEIRAS

Disponível em: http://www.fapesp.br/docs/formularios/arquivos/Form_acomp_bolsas.doc

Processo **08/57796-3**

Bolsista: Bárbara Hatzlhoffer Lourenço

Por favor, emita o parecer, comentários, críticas e sugestões.

No período coberto pelo presente relatório (março de 2011 a fevereiro de 2012) a aluna concluiu estágio iniciado em setembro de 2010 na *University of Michigan School of Public Health*, e está aplicando os conhecimentos lá adquiridos na análise dos dados longitudinais do seu estudo. Nesse estágio, além do treinamento estatístico, participou de seminários acadêmicos e teve seu desempenho considerado excepcional por seu orientador acadêmico, que a definiu como "a melhor aluna de todos os cursos".

No seu retorno ao Brasil realizou nova visita de estudos em Acrelândia para acompanhamento dos participantes do estudo, completou os créditos em disciplinas exigidos para o doutorado, participou do Estágio no Programa de Aperfeiçoamento de Ensino (PAE) nos dois semestres de 2011, participou de oficina ministrada por membro da FAO, e ministrou duas aulas em curso de especialização do Instituto de Psiquiatria do HCFMUSP.

Teve trabalho resultante de sua tese apresentado como pôster no VIII Congresso Brasileiro de Epidemiologia, realizado em São Paulo em novembro de 2001, que recebeu menção honrosa. Encaminhou o artigo "*Determinants of linear growth from infancy to school-aged year: a population-based follow-up study in urban Amazonian children*" para publicação no periódico *BMC Public Health* em fevereiro de 2012, o qual se encontra em fase final de avaliação, tendo já recebido o parecer inicial dos revisores e enviado as respostas às criticas e sugestões apresentadas.

Apresenta neste relatório as análises preliminares dos determinantes do ganho de peso das crianças participantes de seu trabalho de tese, sendo que o aprofundamento das análises e da discussão dos achados está em andamento e farão parte de um manuscrito que está sendo preparado para ser submetido a periódico de circulação internacional.

Para o próximo período a aluna pretende ampliar a coleta de dados das crianças avaliadas em 2007 e que tiveram coleta de amostras de sangue, aferição da pressão arterial, avaliação do estadiamento puberal e do consumo alimentar em 2009, realizando nova avaliação em julho de 2012 que inclui teste de espirometria. Para tal tem financiamento do CNPq em Edital Universal para o trabalho de campo. Para a análise dos dados adicionais, cogita em solicitar prorrogação da bolsa de Doutorado Direto. Dará ainda continuidade na participação no estágio no PAE no primeiro semestre de 2012, participará do evento científico *World Nutrition Rio 2012*, em abril, onde apresentará trabalho na forma oral derivado de sua tese de doutorado; pretende ainda se inscrever no *Research Symposia for Spanish and Latin-American Students 2012*, para participar do curso *Metodology for Clinical Research* de 30 de julho a 3 de agosto de 2012 nos EUA.

Pelo exposto, considero que o desempenho da aluna tem se mantido em nível excelente.

FAPESP

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

São Paulo, 04 FEV. 2013

Ilmo(a). Sr(a). Prof(a). Dr(a).
MARLY AUGUSTO CARDOSO

Ref. Proc. 08/57796-3
Beneficiário **BARBARA HATZLHOFFER LOURENCO**

Prezado(a) Sr(a),

Comunicamos que esta Fundação concedeu a V.Sa. a prorrogação da bolsa pleiteada, de conformidade com as cláusulas e condições constantes do Termo de Prorrogação.

Observações constantes do despacho:

1) "Relatório aprovado"
2) "Concessão Improrrogável"
3) "Cópias da ata de defesa e da página da tese citando o apoio da FAPESP devem ser enviadas à Fundação para encerramento do processo."

Atenciosamente,

Carlos Henrique de Brito Cruz
Diretor Científico

Obs: A transcrição do parecer está sendo enviada exclusivamente ao Orientador(a)/Supervisor(a), sendo de sua responsabilidade compartilhar as partes que considerar relevantes com o estudante candidato, o qual receberá uma cópia desta carta (sem transcrição do parecer).

Cópia Orientador

Despacho original assinado pelo Diretor Científico

RUA PIO XI, 1500 - CEP 05468-901 - SÃO PAULO - SP - TEL. : (011) 3838.4000 - FAX: 3645.2383 e-mail: contdc@fapesp.br

FAPESP

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

Formulário para parecer de Acompanhamento de Assessoria Científica de Bolsas

[ ] IC [ ] MS [ ] DR [X] DD [ ] PD/PAÍS [ ] BP/EXTERIOR [ ] NOVAS FRONTEIRAS

Disponível em: http://www.fapesp.br/docs/formularios/arquivos/Form_acomp_bolsas.doc

Processo **08/57796-3**

Bolsista: Barbara Hatzlhoffer Lourenço

Por favor, emita o parecer, comentários, críticas e sugestões.

A aluna encaminha o relatório final da bolsa de doutorado direto com dois meses de antecedência do prazo final para solicitar prorrogação da bolsa. No período que o relatório cobre – março a dezembro de 2012 – a aluna finalizou a análise de dados e publicou dois artigos referentes à coorte de crianças de Acrelândia de 2003-2009 em periódicos de circulação internacional (BMC Public Health e Maternal and Child Nutrition) e apresentou esses resultados em evento científico de caráter internacional realizado no Rio de Janeiro. Também coletou e processou dados adicionais em nova etapa do estudo em Acrelândia. Fez ainda o planejamento da análise dos dados longitudinais das crianças acompanhadas a partir do estudo transversal de 2007 que foram reavaliadas em 2009 e/ou 2012. Essa avaliação consistiu de exame antropométrico, estadiamento puberal, teste de espirometria para função pulmonar, coleta de sangue e aplicação de questionário sobre morbidade recente, uso de broncodilatadores, questionário ISAAC para rastreamento de asma e levantamento sobre frequência de consumo alimentar. Participou do processo de separação e processamento das amostras de sangue para dosagem de vitaminas e coordenou a digitação dupla dos dados no banco de dados. Está em andamento o plano de análises longitudinais que incluem determinantes nutricionais, bioquímicos e de morbidade da variação de IMC das crianças dessa coorte, sendo apresentados no relatório alguns resultados parciais.

Cursou disciplinas no curso de pós-graduação para completar os créditos exigidos; participou de cursos sobre modelos de análise estatística na FSP-USP e no Instituto de Matemática e Estatística da USP; realizou estágio no Programa de Aperfeiçoamento de Ensino no primeiro semestre de 2012 em disciplina de graduação do curso de Nutrição da FSP-USP; participou de ciclo de reuniões científicas com supervisor do estágio sanduíche do doutorado entre 23 e 27/07/2012 em Ann Arbor, MI, EUA, para discussão sobre o artigo submetido e posteriormente publicado no periódico Maternal and Child Nutrition; participou de curso sobre metodologia em pesquisa clínica na Universidade de Harvard de 30/7 a 03/08/2012, em Cambridge, MA, EUA.

Participou ainda de análises de dados relacionados ao seu projeto, para dois manuscritos em colaboração com outros integrantes do grupo de pesquisa. Teve dois resumos publicados em anais de congressos, dois artigos não relacionados ao seu projeto de doutorado submetidos para publicação, um capítulo de livro no prelo, uma apresentação em palestra e participação em uma disciplina de graduação do curso de Nutrição da FSP-USP.

Assim, verifica-se novamente excelente desempenho acadêmico da aluna no período analisado. Sua solicitação de prolongamento da duração da bolsa de doutorado direto por mais 12 meses se justifica pela necessidade de completar as análises adicionais que já estão em andamento. O cronograma de trabalho apresentado e o desempenho da aluna até o momento permitem concluir que o projeto e, consequentemente, a tese de doutorado, serão completadas dentro do prazo previsto e com resultados que poderão gerar novos conhecimentos sobre o estado da arte da associação entre nutrição, condições socioeconômicas e desfechos metabólicos em crianças em idade pré-escolar e escolar. Existe ainda a perspectiva de investigação de potenciais fatores genéticos envolvidos nessa associação, em colaboração com pesquisador da Universidade de Harvard, e divulgação dos resultados em evento científico internacional.

As normas da FAPESP permitem a utilização dos recursos da Reserva Técnica (RT) sem prévia avaliação pela assessoria, com utilização avaliada a posteriori. Avalie a adequada aplicação desses recursos: Os recursos foram utilizados para três diárias de viagem para participação em evento científico no Rio de Janeiro; compra de passagens aéreas para os Estados Unidos para participação em ciclo de reuniões científicas e em curso de metodologia científica de curta duração; pagamento de taxa de publicação em periódico de acesso aberto; complementação de diárias para participação nas reuniões científicas e curso de curta duração nos Estados Unidos, o que resultou em saldo negativo a ser abatido da próxima parcela da reserva técnica por ocasião da renovação da bolsa. Considero que esses recursos foram utilizados estritamente, e de modo adequado, para atividades relacionadas ao projeto.
Opine sobre a adequação dos novos itens solicitados, face às reais necessidades do projeto.

ANEXO 2

Declarações referentes ao cumprimento do estágio de pesquisa realizado no *Center for Social Epidemiology and Population Health, University of Michigan School of Public Health,* Ann Arbor, MI, EUA –apoio complementar de bolsa acadêmica da Organização dos Estados Americanos, BR *Self Grad* 2010/11 ID 20100656*, United States Department of State's Exchange Visitor Program* nº P-3-03822

17th St. & Constitution Avenue N.W.
Washington, D.C. 20006
United States of America

Organization of American States

P. 202.458.3000
www.oas.org

November 30th, 2011

TO WHOM IT MAY CONCERN

This is to certify that Ms. Barbara Harzlhoffer Lourenço, a national of Brazil, received an OAS Academic Scholarship to pursue a portion of her Doctoral research at University of Michigan in the United States of America. The scholarship was effective for six months, from September 6th, 2010 to February 28th, 2011.

Ms. Harzlhoffer Lourenço successfully completed her studies in longitudinal data analysis at University of Michigan. Such knowledge was intended to be used with the data she had collected for her dissertation at University of São Paulo, Brazil, institution where she was pursuing a Doctoral degree in Nutrition in Public Health.

The scholarship benefits included funds for mandatory fees, research materials, medical insurance, and an international roundtrip ticket to and from the place of study. Additionally, the OAS scholarship provided a fixed monthly stipend of US $700.00 for subsistence expenses, and a fixed allowance of US $150.00 to help the student defray the cost for books.

This certificate is issued in Washington, D.C. on the 30th day of November 2011, at the request of the student. Should you have further inquiries, do not hesitate to contact me at (202)458-6166 or by e-mail at scholarships@oas.org.

Lesley Zark

Lesley Zark
Director
Office of Scholarships, Training and Capacity Strengthening
Department of Human Development, Education and Culture
Organization of American States

November 30, 2011

To Whom It May Concern:

This is to certify that Barbara Hatzlhoffer Lourenço completed the Organization of American States (OAS) scholarship program in good standing as a Graduate Researcher (PhD) in Infant Nutrition at the University of Michigan School of Public Health. Ms. Lourenço was the recipient of a scholarship from the Organization of American States, and was sponsored by LASPAU from September 2010 to February 2011 under the United States Department of State's Exchange Visitor Program, Program number P-3-03822. Ms. Lourenço's research internship took place during the period September 2010 to March 2011, the valid period for Ms. Lourenço's J-1 Visa, after which she returned to her home country of Brazil. LASPAU is an organization that designs, develops, and implements academic exchange programs on behalf of individuals and institutions in the United States, Canada, Latin America, and the Caribbean.

This is also to cite the grantee's strong work in the OAS Scholarship program.

During her program, Ms. Lourenço had been cited consistently and positively for her research, academic and professional abilities and achievements.

With regards to Ms. Lourenço's progress in the program, Dr. Eduardo Villamor, Associate Professor of Environmental Health Sciences and Epidemiology at the University of Michigan School of Public Health, characterized Ms. Lourenço's performance as "*outstanding*" and confirmed she was "*the best student of all the courses*." Dr. Villamor also noted the following accomplishments:

- Wrote and prepared original research paper for submission to peer-reviewed medical journal for publication
- Learned and applied new metholodologies on epidemiological analyses of growth data (statistical analysis of longitudinal data
- Earned GPA of 4.0 (A) in all courses, which included Applied Epidemiological Data Analysis, Controversial Topics in Nutrition, Methods in Nutritional Epidemiology

If any further information is needed regarding Ms. Lourenço's performance as an OAS grantee, please feel free to contact me at +1 617-495-0387 or andrew_miller@harvard.edu.

Sincerely,

Andrew Miller
Program Advisor
LASPAU
Tel: +1 617 495 0387
E-mail : andrew_miller@harvard.edu

ANEXO 3

Declarações referentes ao cumprimento do estágio de pesquisa realizado no *Department of Nutrition, Harvard School of Public Health*, Boston, MA, EUA

Harvard School of Public Health

Harvard Medical School

Brigham & Women's Hospital

July 6, 2013

To Whom It May Concern

This is to certify that Barbara Hatzlhoffer Lourenço completed her visit at the Department of Nutrition, Harvard School of Public Health, from May 1 to July 6, 2013, as part of the activities of her ongoing doctoral research project in Public Health Nutrition at the University of São Paulo, Brazil, supported by the São Paulo Research Foundation (FAPESP grant number 2008/57796-6).

Under my supervision, her program of studies focused on the longitudinal analysis of genetic and nutritional factors associated with weight gain during childhood, using data collected in the Brazilian Amazon area for her dissertation. Along her stay, Barbara has participated in academic seminars at our Department, carried out bibliographic searches and literature review relevant to her data analysis plan, and learned new methodologies on genetic and nutritional epidemiology research. Major findings resulting from this period were summarized in an original manuscript for submission to a peer-reviewed journal for publication. With regards to her progress as a visiting PhD student, she is outstanding. I was impressed by her solid background knowledge, strong statistical skills, as well as insightful thoughts.

Please let me know if any further information is needed/if you have any questions. I can be reached at 1-617-432-4116, or by email at luqi@hsph.harvard.edu

Sincerely,

Lu Qi, MD, PhD

HARVARD SCHOOL OF PUBLIC HEALTH

Department of Nutrition
Walter C. Willett, M.D., Dr. P.H., Chair
Fredrick John Stare Professor of
Epidemiology and Nutrition

July 8, 2013

TO WHOM IT MAY CONCERN:

This is to certify that Barbara Hatzlhoffer Lourenço completed her visit at the Department of Nutrition, Harvard School of Public Health, from May 1 to July 6, 2013. This was part of the activities of her ongoing doctoral research project in Public Health Nutrition at the University of São Paulo, Brazil and was supported by the São Paulo Research Foundation (FAPESP grant number 2008/57796-6).

We very much enjoyed having Ms. Hatzlhoffer with us.

Sincerely,

Walter C. Willett, M.D., Dr. P.H.

665 Huntington Avenue Boston, Massachusetts 02115 Tel: (617) 432-4680 Fax: (617) 432-0464

ANEXO 4

Aprovação do protocolo de pesquisa nº 2083 pelo Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo

COMITÊ DE ÉTICA EM PESQUISA – COEP/FSP
Universidade de São Paulo
Faculdade de Saúde Pública

OF.COEP/131/10

28 de junho de 2010.

Prezado(a) Pesquisador(a) e Orientador(a),

O Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo – COEP/FSP, ***analisou****, em sua* ***5ª/10 Sessão Ordinária****, realizada em* ***25/06/2010****, de acordo com a Resolução n.º 196/96 do Conselho Nacional de Saúde – CNS e suas complementares, o* ***ADENDO*** *ao protocolo de pesquisa n.º* ***2083****, intitulado "****CRESCIMENTO INFANTIL E COMPOSIÇÃO CORPORAL NA IDADE ESCOLAR: ESTUDO PROSPECTIVO DE BASE POPULACIONAL EM ACRELÂNDIA, ESTADO DO ACRE, AMAZÔNIA OCIDENTAL BRASILEIRA****", área temática* ***GRUPO III****, sob responsabilidade do(a) pesquisador(a)* ***Bárbara Hatzlhofer Lourenço****, sob orientação do(a) Professor(a)* ***Marly Augusto Cardoso****, considerando-o* ***APROVADO****.*

Cabe lembrar que conforme Resolução CN /196/96, são deveres do (a) pesquisador (a): ***1.*** *Comunicar, de imediato, qualquer alteração no projeto e aguardar manifestação deste CEP (Comitê de Ética em Pesquisa), para dar continuidade à pesquisa;* ***2.*** *Manter sob sua guarda e em local seguro, pelo prazo de 5 (cinco) anos, os dados da pesquisa, contendo fichas individuais e todos os demais documentos recomendados pelo CEP, no caso eventual auditoria;* ***3.*** *Comunicar, formalmente a este Comitê, quando do encerramento deste projeto;* ***4.*** *Elaborar e apresentar relatórios parciais e final;* ***5.*** *Justificar, perante o CEP, interrupção do projeto ou a não publicação dos resultados.*

Atenciosamente,

Claudio Leone
Professor Titular
Coordenador do Comitê de Ética em Pesquisa da FSP-USP

Ilm.ª Sr.ª
Prof.ª Assoc. Marly Augusto Cardoso
Departamento de Nutrição
Faculdade de Saúde Pública da USP

Av. Dr. Arnaldo, 715 – Cerqueira César – CEP 01246-904 – São Paulo – SP
Contato: (55 11) 3061 7779 | CPQ@FSP.USP.BR | WWW.FSP.USP.BR

ANEXO 5

Factors associated with stunting and overweight in Amazonian children: a population-based, cross-sectional study

Fernanda Cobayashi, Rosângela Aparecida Augusto, Bárbara Hatzlhoffer Lourenço, Pascoal Torres Muniz, Marly Augusto Cardoso

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Public Health Nutrition: 17(3), 551–560 doi:10.1017/S1368980013000190

Factors associated with stunting and overweight in Amazonian children: a population-based, cross-sectional study

Fernanda Cobayashi[1], Rosângela Aparecida Augusto[1], Bárbara Hatzlhoffer Lourenço[1], Pascoal Torres Muniz[2] and Marly Augusto Cardoso[1,3,*]

[1]Public Health Nutrition Program, Department of Nutrition, School of Public Health, University of São Paulo, São Paulo, Brazil: [2]Department of Health Sciences, Federal University of Acre, Rio Branco, Brazil: [3]Department of Nutrition, School of Public Health, University of São Paulo, Av. Dr Arnaldo 715, 01246-904 São Paulo, Brazil

Submitted 11 June 2012: Final revision received 1 November 2012: Accepted 20 December 2012: First published online 4 March 2013

Abstract

Objective: To examine the prevalence of stunting and overweight in children and identify demographic, socio-economic and maternal characteristics, as well as biochemical indicators, associated with these outcomes.

Design: A population-based, cross-sectional study was performed. Data from structured questionnaires, anthropometric measurements, and blood and stool samples were used in Poisson regression models to estimate prevalence ratios (PR) according to a hierarchical conceptual framework.

Setting: Acrelândia, western Brazilian Amazon.

Subjects: Children (*n* 1139) aged <10 years.

Results: Prevalence of stunting was 7·1% (95% CI 5·1, 9·6%) and 3·7% (95% CI 2·4, 5·7%) among children aged <5 years and ≥5 years, respectively; overweight was detected in 20·6% (95% CI 17·4, 24·2%) and 9·4% (95% CI 7·2, 12·1%) of children aged <5 years and ≥5 years, respectively. Among children <5 years of age, stunting was positively associated with the lowest maternal height tertile (PR = 3·09, 95% CI 1·26, 7·63), low birth weight (PR = 2·70, 95% CI 1·41, 5·19), diarrhoea for ≥3 d (PR = 2·21, 95% CI 1·03, 4·77) and geohelminth infections (PR = 2·53, 95% CI 1·02, 6·13). Overweight in children <5 years of age was positively associated with caesarean delivery (PR = 1·45, 95% CI 1·02, 2·06), birth weight ≥3500 g (PR = 1·82, 95% CI 1·30, 2·55) and Fe deficiency (PR = 1·64, 95% CI 1·07, 2·53). Among children aged ≥5 years, land or livestock ownership (PR = 1·85, 95% CI 1·07, 3·22), maternal overweight (PR = 2·06, 95% CI 1·23, 3·47), high C-reactive protein concentration (PR = 2·43, 95% CI 1·26, 4·70), vitamin A deficiency (PR = 1·97, 95% CI 1·13, 3·41) and high serum TAG concentration (PR = 2·16, 95% CI 1·27, 3·68) were associated with overweight.

Conclusions: Overweight was more prevalent than stunting, being associated with higher household wealth, maternal overweight, caesarean delivery, high birth weight, micronutrient deficiencies and high TAG concentration. Improvements in maternal and child health care with sustainable access to healthy food are necessary to reduce short- and long-term health complications related to overweight in this population.

Keywords
Stunting
Overweight
Stature by age
BMI
Children

The prevalence of stunting (i.e. low length- or height-for-age) from birth to 5 years has been decreasing worldwide, from 40% in 1990 to 27% in 2010[1], and this rate is expected to fall further to 22% by 2020. In Latin American countries, for instance, the prevalence of stunting in 2010 was 13·5% while a prevalence of 11·6% is predicted by the year 2015[1].

In Brazil, there has been a 50% decline in stunting among children aged <5 years, from 13·4% in 1996 to 6·7% in 2006, according to the most recent National Demographic and Health Survey[2]. Several contributory factors may explain this decline in the stunting prevalence, such as improvements in maternal schooling, increased purchasing power of low-income families, broader access to health services and the expansion of basic sanitation and water treatment[3]. However, owing to social inequalities among Brazilian regions, the north of the country, which encompasses the Amazon area, has notable financial difficulties and administrative, educational and nutritional deficiencies presenting important social and health inequities, explaining why the prevalence of stunting remains higher, affecting around 15% of children in this age group[2]. Concurrently, the incidence of overweight and obesity in children and adolescents is rising rapidly, becoming a major public health problem. Secular trend data on overweight status

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for Brazilian children aged 5–9 years, conducted by the Brazilian Institute of Geography and Statistics using BMI and the WHO classification as the diagnostic criteria, have shown that the prevalence of overweight in boys during the 1970s was 10·9 %, increasing to 15·0 % in the late 1980s and attaining 34·8 % in 2008–2009. The prevalence of overweight among girls was 8·6 %, 11·9 % and 32·0 % for the same time periods, respectively. It is noteworthy that this trend of increasing overweight occurred across all income groups in both sexes[4].

The pattern of shifts in nutritional status, characterized by persistence of stunting and increasing rates of overweight, typify the nutritional transition scenario found in many developing countries[5,6]. This transition process may be considered a particular public health concern when affecting children, since poor child growth can have important economic implications. Stunting in childhood is associated with fewer years of schooling and consequently low productivity at work[7]. Overweight and obesity in childhood and adolescence have also been associated with increased risk of both premature mortality and adult morbidity[8]. Therefore, assessing nutritional status in childhood is essential for planning preventive actions, as evidenced by several studies showing that early exposure of children to malnutrition could be associated with changes in body composition during adolescence[9,10] and adulthood[8].

Studies investigating the determinants of stunting and overweight have been conducted in developed and developing countries[11,12], highlighting the importance of socio-economic status and maternal health factors. However, little is known about the influence of micronutrient deficiencies, inflammation indicators and dyslipidaemias on stunting or overweight among children[13,14].

Therefore, in the present study, socio-economic and maternal characteristics as well as biochemical indicators were assessed in relation to both outcomes – stunting and overweight – in childhood. To our knowledge, it is the first population-based, cross-sectional study that describes the prevalence and factors associated with stunting and overweight in children <10 years of age living in an urban area of a town in the western Brazilian Amazon.

Methods

Study design and population

The present population-based, cross-sectional study on child nutrition and health was performed in December 2007 in Acrelândia, a frontier town located 112 km from Rio Branco, the capital of the state of Acre, in the western Brazilian Amazon region. At the time of the study, Acrelândia had 11 520 inhabitants (44 % residing in the urban area), predominantly migrants from south-eastern and southern regions of Brazil, engaged in commercial agriculture and raising cattle. Infant mortality was estimated as 71/1000 live births in 2000, substantially higher than the national average (28/1000 live births). The human development index (for ranking municipalities in terms of health, education and income levels, reported by the United Nations Program for Development) in Acrelândia was estimated at 0·680 according to data from 2000 (ranged from 0·359 to 0·919 for Brazilian cities)[15].

Sampling strategies and field procedures were reported previously[16]. Briefly, all households from the urban area with children up to 10 years of age (n 749) were identified with the assistance of local health workers of the Family Health Program of the Brazilian Ministry of Health. Thus, 1225 eligible children living in 734 households were enrolled (98·0 % of households identified). A structured questionnaire was administered through face-to-face interview to the mothers or guardians of 1151 children (94·0 % of those eligible). The questionnaire was pilot-tested previously and covered the following topics: demographic and socio-economic status; environmental conditions; reproductive health variables; history of infant feeding practices (duration of total and exclusive breast-feeding, child's age at introduction of weaning foods); and the occurrence of morbidities, i.e. diarrhoea (three or more liquid stools within 24 h), cough or fever up to 15 d prior to the interview, episodes of malaria and wheezing in the past 12 months and past hospitalization. After the interview, mothers and children were invited to visit the local family health clinic, where research assistants carried out a physical examination and trained phlebotomists obtained a venous blood sample from all children.

All parents or guardians of participating children provided written informed consent prior to enrolment. The study protocol was approved by the institutional review board of the School of Public Health, University of São Paulo, Brazil (no. 1681/07).

Anthropometric assessment

Length/height and weight were measured by trained research assistants following standardized procedures using calibrated equipment[17]. Among children aged <2 years, recumbent length was measured to the nearest millimetre with a locally made 1·3 m-long infant measuring board with increments of 1 mm; weight was measured to the nearest 10 g on an electronic paediatric scale (model 1583; Tanita, Tokyo, Japan). Children aged ≥2 years were measured to the nearest millimetre with a stadiometer (model 208; SECA, Hamburg, Germany) affixed to the flat surface of a wall without a baseboard, perpendicular to the floor. For readings, children were positioned barefoot in a standing position in the middle of the stadiometer, with their head, shoulders, buttocks and heels against the wall. Weight was measured on an electronic scale (model HS-302; Tanita) and recorded to the nearest 100 g. Maternal weight and height were subsequently measured by the research assistants by following the same standardized procedures[17]. Each measurement was repeated and the mean value of the two measurements calculated. Birth date

was recorded directly from birth certificates or child health cards. BMI was computed as weight in kilograms divided by the square of length/height in metres.

Z-scores for length/height-for-age (HAZ) and BMI-for-age (BAZ) were calculated according to WHO Child Growth Standards[18] for children aged 0–5 years and WHO Growth Reference Data[19] for children aged >5 years. The cut-off for stunting was defined as HAZ < -2. For the present analysis, overweight was defined as BAZ > 1 including 'at risk of overweight', overweight and obesity for children <5 years old. Among children ≥5 years old, overweight was defined as BAZ > 1[19,20].

Maternal nutritional status was classified according to BMI categories[21] as non-overweight (BMI $< 25\,kg/m^2$) and overweight (BMI $\geq 25\,kg/m^2$), since only twenty-two mothers were underweight (BMI $< 18{\cdot}5\,kg/m^2$). Of the 1151 participants, one child had HAZ > 6 and eleven children had missing data on weight or height. These children were excluded from the present analyses giving a final sample of 1139 children.

Laboratory procedures

A sample (approximately 5 ml) of fasting venous blood was collected from 1131 children (98·3 % of those eligible). At the field laboratory in Acrelândia, whole blood aliquots collected in EDTA-containing vacuum tubes were used to perform full blood cell counts and measure Hb concentrations on an ABX Micro60 automated cell counter (Horiba, Montpellier, France). A separate blood sample was protected from light and centrifuged within 1 h of collection. Plasma C-reactive protein (CRP) concentration was measured using the Immulite high-sensitivity chemiluminescent assay (Diagnostic Products Corporation, Los Angeles, CA, USA). The cut-off for high CRP was ≥5 mg/l as an indicator of inflammation[22]. Serum lipid fractions were measured enzymatically using an automatic device (ADVIA 1650; Bayer, East Walpole, MA, USA). TAG concentrations ≥100 mg/dl were considered high according to age[23]. Anaemia, iron deficiency (ID) and iron-deficiency anaemia (IDA) were defined according to Hb, serum ferritin (SF), serum transferrin receptor (sTfR) and CRP concentration, respectively[24]. The normal range of sTfR concentration, as determined by the immunoassay manufacturer, was 2·9–8·3 mg/l. ID was defined when SF concentrations were low (<12 μg/l for children aged <5 years or <15 μg/l for those aged ≥5 years) or when sTfR concentrations were high (>8·3 mg/l). IDA was defined when ID occurred in anaemic children; the cut-off for Hb concentration considered was 110·0 g/l for children aged 6 months to 5 years, and 115·0 g/l for children aged ≥5 years. Plasma concentrations of vitamin A (retinol) were measured by the standard HPLC method[25]; concentrations <0·70 μmol/l defined vitamin A deficiency[26]. Children with anaemia or nutrient deficiencies detected during the survey received adequate treatment prescribed by the medical team involved in the project.

Stool samples were collected from 1016 children (97·0 % of those eligible) at the time of the interview, for subsequent analysis. Coprotest® cups containing a preservative solution (10 % w/v formalin) were provided for this purpose. All stool examinations were analysed to search for eggs, cysts and larvae of parasites, according to the qualitative technique of sedimentation[27], as described elsewhere[16]. Geohelminths found in this population included *Ascaris lumbricoides, Trichuris trichiura* and *Strongyloides stercoralis*. Children with intestinal parasitic infections received free treatment prescribed by the research clinicians.

Statistical analysis

The main dichotomous dependent variables of interest were stunting and overweight. Explanatory variables comprised socio-economic, maternal and child characteristics as well as micronutrient deficiencies, inflammation and dyslipidaemia indicators.

Principal component analysis was used to derive a wealth index representing a proxy of household income[28], based on the presence of twelve household assets, as described elsewhere[16]. To define socio-economic status, information on the wealth index and number of residents in each household was combined to generate variables of wealth concentration. Households were classified as 'low wealth concentration' when the wealth index was below the median and the number of residents was above the median for this population. On the other hand, for the overweight outcome, households were classified as 'high wealth concentration' when the wealth index was above the median and the number of residents was below the median. This combined variable was used when analysing associations for the stunting and overweight outcomes. Other socio-economic variables investigated were land or livestock ownership and maternal schooling, categorized as <5 years *v.* ≥5 years. Maternal characteristics before pregnancy were maternal age at child's birth (<20 years, 20–30 years, ≥30 years) and maternal height in tertiles (<1·55 m, 1·55–1·59 m, ≥1·59 m). Maternal characteristics during pregnancy included the number of prenatal visits (<6 *v.* ≥6), smoking habits and caesarean delivery. Child's birth weight was categorized as ≤2500 g, 2501–3500 g or ≥3500 g. Age at introduction of cow's milk was used as an indicator of infant feeding practices and was classified as <3 months or ≥3 months based on the median age for weaning observed in our study population. Current care to child was assessed through the number of siblings (<1 *v.* ≥2). Several morbidities were taken into account: duration of diarrhoea <3 d or ≥3 d, geohelminth infection and high CRP concentration. Finally, biochemical indicators of nutritional status included ID, IDA, vitamin A deficiency and high serum TAG concentration.

Children were stratified into two age categories (<5 years and ≥5 years of age) based on sample size and distribution.

First, we compared the distribution of baseline characteristics between the two age groups, using the Pearson χ^2 test. Then for each age group, crude analyses were first conducted using Poisson regression models between the dependent variables of interest (stunting and overweight) and the explanatory variables, adjusting for sex and age. Adjusted prevalence ratios (PR) and 95% confidence intervals were obtained for the factors associated with stunting and overweight using multiple Poisson regression models with robust variance according to a hierarchical conceptual framework[29]. At each level of determination, covariates were retained in the model if they were associated with the outcome at $P < 0{\cdot}10$ and for ordinal variables when they followed a dose–response pattern or if their inclusion in the model changed the PR by 10% or more. Missing observations were included in the multiple models by creating missing-value categories. All analyses were performed using the Stata statistical software package version 11·0.

Results

Among 1139 children studied, the mean age was 5·13 (SD 2·87) years (range: 3·02 months to 9·98 years). The distribution of the children between the age groups is shown in Table 1. The prevalence of stunting among children aged <5 years and ≥5 years was 7·1% (95% CI 5·1, 9·6%) and 3·7% (95% CI 2·4, 5·7%), respectively. The prevalence of overweight was 20·6% (95% CI 17·4, 24·2%) in children <5 years of age and 9·4% (95% CI 7·2, 12·1%) in the older ones. Children aged <5 years were more likely to have mothers who had more years of schooling, achieved more prenatal visits and realized more caesarean delivery. Children <5 years old also had a higher proportion of IDA, ID and high TAG concentrations when compared with children ≥5 years of age (Table 1).

The investigation of the factors associated with stunting was performed only for children <5 years of age because of the low prevalence of stunting among older children (3·7%). In the adjusted analysis, the lowest tertile of maternal height and low birth weight were positively associated with stunting, as were diarrhoea ≥3 d and geohelminth infection (Table 2).

Among children <5 years of age, high wealth concentration and caesarean delivery were positively associated with overweight in multiple models (Table 3). The prevalence of overweight among children with birth weight ≥3500 g was 85% higher compared with children whose weight was <2500 g at birth ($P < 0{\cdot}001$). ID also remained positively associated with overweight after multiple adjustment.

Among children ≥5 years of age, high wealth concentration and maternal schooling were no longer significantly associated with overweight in multiple models. However, prevalence of overweight was 85% higher among children whose families owned land or livestock compared with children from families not possessing these assets ($P = 0{\cdot}02$). After adjusting for this socio-economic variable, overweight among older children remained positively associated with maternal overweight ($P < 0{\cdot}001$). Vitamin A deficiency, as well as high CRP and TAG concentrations, was positively associated with the prevalence of overweight in the adjusted analysis (Table 3).

Discussion

Over past years, Acrelândia has shown a decreasing prevalence of stunting (7·1%) among pre-school children, since Souza *et al.*[30], studying the same area in 2003, found a prevalence of 10%. Similar national trends have been observed by the latest Brazilian National Demographic and Health Survey[2]. Among children aged 5–10 years, the stunting prevalence of 3·7% in our study is approximately 50% lower than the national average found in the latest Brazilian Household Budget Survey (6·8%)[4].

Brazil has shown declining trends of stunting based on national surveys since the 1970s. According to Monteiro *et al.*[31], the factors that contributed most to the decline of stunting (between 1996 and 2007) in Brazil were improvements in maternal schooling, increased purchasing power of low-income families and broader access to health services. It is noteworthy that from 2003 Brazil has reactivated the economic growth with improved income distribution, the expanding coverage of cash transfer programmes and also the Family Heath Program. The latter programme is targeted to poor households and covers health prevention and education[31].

In the present study, maternal schooling was not associated with stunting related probably to the overall low literacy of the mothers (~40% with less than 5 years of schooling). We found that low maternal height, low birth weight, diarrhoea ≥3 d and geohelminth infection remained positively associated with stunting in the multiple models.

As previously reported, maternal height is an important determinant of intra-uterine growth restriction[32] and low birth weight[33]. Analysing data from fifty-four developing countries, Ozaltin *et al.*[34] found an inverse association between maternal height and infant mortality, low birth weight and stunting, suggesting that the effects of poor environmental conditions (inadequate nutrition, diseases) to which the mother was exposed can be transmitted to future generations.

Despite the routine distribution of anti-helminthic medication under the Family Health Program of the municipality[35], cases of children with episodes of diarrhoea and geohelminth infection were noted, and these variables were found to be associated with stunting. It has been suggested that this situation could be due to the lack of sanitation and water treatment in the area[35]. Moreover, it is known that infections worsen nutritional status especially among undernourished children[36].

Table 1 Characteristics of the study sample: urban children (*n* 1139) aged <10 years living in Acrelândia, western Brazilian Amazon, December 2007

	Total sample		Children aged <5 years (*n* 557)		Children aged ≥5 years (*n* 582)		
Variable	*n*	%	*n*	%	*n*	%	*P*
Gender							
Male	563	49·4	273	49·0	290	49·8	0·783
Nutritional status							
Stunting	62	5·4	40	7·1	22	3·7	0·011
Overweight	170	14·9	115	20·6	55	9·4	0·000
Socio-economic characteristics							
High wealth concentration*	290	25·6	159	28·5	131	22·5	0·019
Low wealth concentration†	341	29·9	167	29·9	174	29·9	0·975
Owner of land or livestock	203	17·9	95	17·1	108	18·6	0·518
Maternal schooling ≥5 years	674	61·3	353	66·1	321	56·8	0·002
Maternal characteristics							
Maternal age at child's birth (years)							
<20	301	29·0	121	23·8	180	34·1	0·001
20–30	569	54·9	297	58·4	272	51·6	
≥30	165	15·9	90	17·7	75	14·2	
Maternal height tertile (m)							
<1·55	319	32·5	157	31·7	162	33·4	0·691
1·55–1·59	326	33·3	171	34·5	155	32·0	
≥1·59	334	34·1	167	33·7	167	34·5	
Maternal characteristics during pregnancy							
Number of prenatal visits ≥6	698	77·3	382	82·5	316	71·9	0·000
Habitual smoker	175	17·5	74	14·8	101	20·1	0·030
Caesarean delivery	262	26·0	154	30·9	108	21·1	0·000
Child's characteristics at birth							
Birth weight (g)							
<2500	56	5·5	26	5·0	30	6·1	0·454
2501–3500	543	53·8	288	55·6	255	51·9	
≥3500	410	40·6	204	39·3	206	41·9	
Infant feeding practices							
Age at cow's milk introduction ≤3 months	311	31·8	155	31·4	156	32·2	0·791
Current attention to child care							
Number of siblings							
1 child	176	17·2	127	25·3	49	9·4	0·000
≥2 children	846	82·7	375	74·7	471	90·5	
Current maternal nutritional status							
Maternal overweight	446	45·8	229	46·4	217	45·2	0·697
Morbidities							
Duration of diarrhoea (d)‡							
<1	924	82·6	409	75·4	515	89·4	0·000
1–3	118	10·5	73	13·4	45	7·8	
≥3	76	6·8	60	11·0	16	2·7	
Geohelminth infection	38	3·7	11	2·2	27	5·2	0·014
High CRP concentration (≥5 mg/l)	100	9.5	56	11·3	44	7·9	0·063
Biochemical nutritional indicators§							
ID	502	45·2	347	65·1	155	26·8	0·000
IDA	112	10·3	96	18·8	16	2·7	0·000
Vitamin A deficiency (<0·70 μmol/l)	147	14·1	65	13·4	82	14·7	0·559
High TAG concentration (≥100 mg/dl)	268	29·7	156	38·9	112	22·4	0·000

ID, iron deficiency; IDA, iron-deficiency anaemia.
Totals may be less than 1139 due to missing values. *P* values from χ^2 tests for comparisons between age groups.
*Combination of wealth index above the median plus number of residents below the median.
†Combination of wealth index below the median plus number of residents above the median.
‡Defined by three or more liquid stools within 24 h.
§ID was defined when serum ferritin concentration was <12 μg/l for children aged <5 years or <15 μg/l for those aged ≥5 years or when serum transferrin receptor concentration was high (>8·3 mg/l). IDA was defined when ID occurred in anaemic children; the cut-off for Hb concentration was 110·0 g/l for children aged 6 months to 5 years, and 115·0 g/l for children ≥5 years.

In our study, we did not find an association between stunting and risk for overweight in the children. Meanwhile, prospective studies from developing countries have shown that adolescents who were stunted in childhood tended to gain less lean body mass and more fat mass than their non-stunted counterparts[37]. However, the body fat distribution is more likely to be central, a significant important risk factor for chronic diseases[38]. One of the potential underlying mechanisms involved in the maintenance of energy balance is the low rate of fat oxidation, which means in turn that the oxidized fat must be stored, thus favouring fat accumulation in the body[38].

Table 2 Factors associated with stunting in urban children (*n* 557) aged <5 years living in Acrelândia, western Brazilian Amazon, December 2007

	Crude			Adjusted*		
Variable	PR	95 % CI	*P*	PR	95 % CI	*P*
Wealth concentration						
High wealth concentration†	1·00	Ref.	–	1·00	Ref.	–
Low wealth concentration‡	1·60	0·87, 2·87	0·13	1·49	0·80, 2·84	0·22
Maternal schooling (years)						
≥5	1·00	Ref.	–	1·00	Ref.	–
>5	0·64	0·34, 1·21	0·18	0·70	0·40, 1·32	0·30
Maternal age at child's birth (years)						
<30	1·00	Ref.	–	1·00	Ref.	–
≥30	1·98	0·93, 3·89	0·07	1·65	0·86, 3·20	0·13
Maternal height (m)						
≥1·59	1·00	Ref.	–	1·00	Ref.	–
1·55–1·59	1·76	0·66, 4·73	0·33	1·70	0·61, 4·71	0·30
<1·55	3·50	1·44, 8·44	0·00	3·09	1·26, 7·63	0·01
P for trend		0·02			0·01	
Birth weight (g)						
2500–3500	1·00	Ref.	–	1·00	Ref.	–
≥3500	0·17	0·05, 0·55	0·00	0·18	0·05, 0·58	0·00
<2500	3·63	2·01, 6·57	0·00	2·70	1·41, 5·19	0·00
P for trend		0·44			0·40	
Age at cow's milk introduction (months)						
≥3	1·00	Ref.	–	1·00	Ref.	–
<3	2·03	1·08, 3·80	0·02	1·44	0·80, 2·60	0·18
Number of siblings						
1 child	1·00	Ref.	–	1·00	Ref.	–
≥2 children	1·94	0·81, 4·63	0·13	1·77	0·73, 4·30	0·13
Diarrhoea in past 15 d§						
No	1·00	Ref.	–	1·00	Ref.	–
Yes, during 1–2 d	1·63	0·74, 3·63	0·22	1·16	0·45, 3·02	0·75
Yes, during ≥3 d	2·51	1·20, 5·26	0·01	2·21	1·03, 4·77	0·01
P for trend		0·11			0·10	
Geohelminth infection						
No	1·00	Ref.	–	1·00	Ref.	–
Yes	4·61	1·98, 10·75	0·00	2·53	1·02, 6·31	0·02
IDA						
No	1·00	Ref.	–	1·00	Ref.	–
Yes	1·83	0·91, 3·70	0·08	1·70	0·82, 3·73	0·14

PR, prevalence ratio; IDA, iron-deficiency anaemia; Ref. reference category.
*Variables were adjusted for others in the same or higher levels following the hierarchical conceptual framework.
†Combination of wealth index above the median plus number of residents below the median.
‡Combination of wealth index below the median plus number of residents above the median.
§Diarrhoea was defined by three or more liquid stools within 24 h.

This is of great concern, especially in countries undergoing nutrition transition.

In the present study, the socio-economic indicators of high wealth concentration and land or livestock ownership were positively associated with overweight among children aged <5 years and ≥5 years, respectively. In their study of Colombian children from low- and middle-income families, McDonald *et al.*[39] found that overweight was strongly associated with socio-economic status indicated by the possession of household assets. Similarly, in other developing countries, the best indicators of income were positively associated with overweight[40]. However, the opposite occurs in developed countries where socio-economic status is inversely associated with overweight[41].

Other factors significantly associated with overweight in younger children in our study included caesarean delivery, high birth weight and ID. Children with caesarean delivery had greater risk of developing obesity in adulthood, as recently discussed in a study conducted by Goldani *et al.*[42]. The factors underlying this relationship remain unknown, but it has been suggested that the absence of breast-feeding in the first hours of life as a consequence of surgical delivery may be a risk factor for early weaning[43] and consequently for the introduction of inadequate foods during the first years of life.

A significantly higher adjusted prevalence ratio for overweight was found among children weighing ≥3500 g at birth. High weight at birth has been associated with obesity in childhood[44] and also with metabolic syndrome in older children[45]. Obesity may be transmitted across generations as recently demonstrated by Cnattingius *et al.* in Swedish women[46]. Those authors found that the combination of an obese woman born large for gestational age increased the risk of her having a large-for-gestational-age infant compared with a non-obese woman whose birth weight was appropriate for gestational age[46].

The association between ID and overweight in children <5 years of age found in the present study has been

Table 3 Factors associated with overweight according to age group in urban children (*n* 1139) aged <10 years living in Acrelândia, western Brazilian Amazon, December 2007

	Children aged <5 years (*n* 557)						Children aged ≥5 years (*n* 582)					
	Crude			Adjusted*			Crude			Adjusted*		
Variable	PR	95 % CI	*P*	PR	95 % CI	*P*	PR	95 % CI	*P*	PR	95 % CI	*P*
Wealth concentration												
High wealth concentration†	1·00	Ref.	–	1·00	Ref.	–	1·00	Ref.	–	1·00	Ref.	–
Low wealth concentration‡	1·41	1·01, 1·96	0·04	1·41	1·01, 1·96	0·04	1·81	1·08, 3·05	0·02	1·40	0·82, 2·40	0·22
Land or livestock ownership												
No	–	–	–	–	–	–	1·00	Ref.	–	1·00	Ref.	–
Yes	–	–	–	–	–	–	2·06	1·20, 3·56	0·00	1·85	1·07, 3·22	0·02
Maternal schooling (years)												
<5	–	–	–	–	–	–	1·00	Ref.	–	1·00	Ref.	–
≥5	–	–	–	–	–	–	1·85	1·06, 3·23	0·03	1·63	0·93, 2·85	0·08
Maternal age at child's birth (years)												
≥30	1·00	Ref.	–	1·00	Ref.	–	–	–	–	–	–	–
<30	1·77	1·01, 3·09	0·04	1·70	0·97, 2·96	0·06	–	–	–	–	–	–
Number of prenatal visits												
<6	1·00	Ref.	–	1·00	Ref.	–	–	–	–	–	–	–
≥6	1·77	0·96, 3·25	0·06	1·60	0·86, 2·94	0·14	–	–	–	–	–	–
Caesarean delivery												
No	1·00	Ref.	–	1·00	Ref.	–	–	–	–	–	–	–
Yes	1·52	1·07, 2·17	0·01	1·45	1·02, 2·06	0·02	–	–	–	–	–	–
Birth weight (g)‡												
2500–3500	1·00	Ref.	–	1·00	Ref.	–	–	–	–	–	–	–
≥3500	1·74	1·24, 2·45	0·00	1·82	1·30, 2·55	0·00	–	–	–	–	–	–
<2500	0·95	0·37, 2·40	0·91	1·02	0·40, 2·60	0·95	–	–	–	–	–	–
P for trend		0·30			0·27							
Number of siblings												
≥2 children	1·00	Ref.	–	1·00	Ref.	–	–	–	–	–	–	–
1 child	1·59	1·11, 2·24	0·01	1·41	0·99, 2·03	0·05	–	–	–	–	–	–
Maternal BMI (kg/m^2)												
<25	–	–	–	–	–	–	1·00	Ref.	–	1·00	Ref.	–
≥25	–	–	–	–	–	–	2·16	1·30, 3·70	0·00	2·06	1·23, 3·47	0·00
CRP concentration (mg/l)												
<5	–	–	–	–	–	–	1·00	Ref.	–	1·00	Ref.	–
≥5	–	–	–	–	–	–	2·06	1·03, 4·10	0·03	2·43	1·26, 4·70	0·00
ID												
No	1·00	Ref.	–	1·00	Ref.	–	–	–	–	–	–	–
Yes	1·70	1·11, 2·60	0·01	1·64	1·07, 2·53	0·02	–	–	–	–	–	–
Vitamin A (μmol/l)												
≥0·70	–	–	–	–	–	–	1·00	Ref.	–	1·00	Ref.	–
<0·70	–	–	–	–	–	–	1·90	1·05, 3·40	0·03	1·97	1·13, 3·41	0·01
TAG concentration (mg/l)												
<100	–	–	–	–	–	–	1·00	Ref.	–	1·00	Ref.	–
≥100	–	–	–	–	–	–	2·03	1·15, 3·60	0·01	2·16	1·27, 3·68	0·00

PR, prevalence ratio; CRP, C-reactive protein; ID, iron deficiency; Ref. reference category.
*Variables were adjusted for others in the same or higher levels following the hierarchical conceptual framework.
†Combination of wealth index above the median plus number of residents below the median.
‡Combination of wealth index below the median plus number of residents above the median.

previously documented[47]. Several hypotheses have been proposed to explain this association, such as the increased plasma volume in obese individuals and inadequate intake of nutrients[48]. Another study however suggested that higher levels of hepcidin might be involved, since obesity is considered a low-grade inflammatory disease[49]. It is noteworthy that in the present study, sTfR concentration (in addition to SF) was used as a differential diagnosis of ID because this parameter is not affected by infectious processes[50]. The poor quality of diet among the young Amazonian children studied is proposed as a likely hypothesis explaining this association. A previous study assessing the characteristics of diet among children <2 years of age in the same region indicated low consumption of fruit and vegetables, low consumption of Fe-rich foods and excessive consumption of cow's milk and porridge[51].

For children aged ≥5 years, having an overweight mother was strongly associated with overweight. This result is in line with the findings of other studies[39,52]. The association may be due to the intergenerational transmission of obesity[53], as well as environmental and/or behavioural factors, since parents play an important role in the development of their children's food preferences and energy intake[54].

Our results also indicated that higher CRP concentrations were positively associated with overweight. Besides the hypothesis of low-grade inflammatory disease caused by excess weight[55], this association may be explained by the presence of recurrent infections to which these Amazonian children are exposed.

In the present study, overweight children ≥5 years of age were also more likely to have higher TAG concentration than their counterparts. This may be an indication of inadequacies in diet from an early age[51]. Abnormal levels of TAG have been well documented in the literature among children and adolescents with overweight status as an independent risk factor for CVD[8].

Finally, in the present study vitamin A deficiency was positively associated with overweight in children aged ≥5 years, after adjusting for high CRP and TAG concentrations. It is well known that vitamin A deficiency compromises growth and is associated with low resistance to infections[26]. This may be a relevant concern among children residing in the Brazilian Amazon region, where there is high exposure to numerous aetiological agents along with insufficient services of basic sanitation and water treatment. In addition, akin to the explanation for the association of ID and high TAG levels with overweight, the association of vitamin A deficiency and overweight could also be attributed to the poor quality diet of the study population. From an early age, this group has a low intake of fruit and vegetables and substantial consumption of unhealthy foods such as processed foods high in sodium, preservatives, sugars and fats, according to previous partial analysis from our data[51]. Changes in diet quality are characteristic of the nutritional transition faced by countries undergoing rapid economic development and improvement in living standards[6,56]. Overall, Brazilians have decreased their consumption of staple foods such as rice (decline of 40·5 %) and beans (decline of 26·4 %) from 2002 to 2008. The current consumption of fruits and vegetables reaches only one-quarter of WHO recommended levels. On the other hand, the consumption of soft drinks has risen by 39·3 %[57]. Dietary patterns are established in childhood, persist into adulthood and are significantly associated with chronic disease risk factors[58]. Interestingly, a Chinese study suggested that mothers' nutritional knowledge, health consciousness and exposure to the media may influence their children's diet beyond the determining role of family resources and access to foods available to the community in developing countries undergoing rapid social and economic transition[59].

Our study has several limitations that should be considered. Because of its cross-sectional design, caution should be taken in interpreting the present findings, since no causal assumptions can be made. Furthermore, the current analysis included no evaluation of indicators of dietary consumption and physical activity in the population studied due to related logistic and methodological issues. In Acrelândia, seasonality of dietary habits has been reported, requiring more recall days, spread across seasons and a period of months to lead a more accurate dietary estimates among school-aged children[60]; however, unfortunately, this was not feasible in the present study due to the field conditions and cross-sectional design. Despite these limitations, the present population-based study used direct and standardized anthropometric measurements in both children and their mothers and employed a comprehensive set of biochemical indicators, thus contributing to the understanding of several socio-economic, maternal and individual factors associated with stunting and overweight in children.

Concerted efforts have been made to increase access to food and to improve the health of Brazilian children through conditional cash transfer programmes and expansion of basic health care. While national programmes are in place to help prevent micronutrient deficiencies and promote healthy eating habits, there remains much work to be done – from infrastructure improvements to the integration of governmental organizations, non-governmental organizations and civil society – in promoting and implementing healthy child growth initiatives.

Conclusion

The prevalence of overweight was higher than that of stunting among pre-school children in our study. Factors positively associated with stunting in children aged <5 years were low maternal height, low birth weight, diarrhoea episodes and geohelminth infection. For overweight, higher wealth concentration, caesarean delivery, high birth weight

and ID proved important factors among children <5 years of age, whereas land or livestock ownership, maternal overweight, high CRP and TAG concentrations and vitamin A deficiency were associated factors among older children. These results point to the importance of intensifying the promotion of maternal and child health practices, as well as sustainable access to healthy food, in a bid to reduce short- and long-term complications in this population against a scenario of nutritional transition.

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ANEXO 6

Toward personalized prevention of obesity: can vitamin D negate the *FTO* effect?

Corinne D. Engleman

Comentário publicado sobre o manuscrito
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Corinne D. Engelman

Toward Personalized Prevention of Obesity: Can Vitamin D Negate the *FTO* Effect?

Diabetes 2014;63:405–406 | DOI: 10.2337/db13-1714

According to the World Health Organization, the worldwide prevalence of childhood overweight and obesity increased from 4.2% in 1990 to 6.7% in 2010 and it is expected to reach 9.1% in 2020 (1). This is alarming because BMI in childhood is associated with type 2 diabetes, hypertension, coronary heart disease, and mortality in adulthood (2). The obesity epidemic is no longer merely a problem in developed countries, but is now affecting developing countries as well. In fact, more than 30 million overweight children are living in developing countries compared with 10 million in developed countries (3). In the U.S., the Surgeon General issued the *Call to Action to Prevent and Decrease Overweight and Obesity* (4) in 2001 and the reduction of overweight and obesity was an objective of *Healthy People 2010* (5). However, the ensuing public health efforts to address the obesity epidemic by promoting healthy eating and physical activity have had limited success thus far, with overweight and obesity rates continuing to increase. At the population level, the rise in overweight and obesity rates over the past few decades has been driven by shifts in the environment, such as the abundance of food (especially fast food and junk food), increasing portion sizes, city planning that promotes transportation by automobile versus walking or biking, and growth in technology that has led to increases in screen time. On an individual level, genetic factors contribute to obesity susceptibility. The strongest genetic risk factor identified thus far is the fat mass and obesity-associated gene (*FTO*). Interactions between behavioral and genetic factors may play an important role in obesity risk. These interactions can be capitalized to personalize medical practice.

In the current issue, Lourenço et al. (6) assessed the effect of *FTO* single nucleotide polymorphism (SNP) rs9939609 on changes in BMI during childhood in a population-based longitudinal study in the Brazilian Amazon and investigated whether these effects were modified by vitamin D status, a well-established correlate of BMI. They found that the A allele of *FTO* SNP rs9939609 was associated with significantly higher BMI gain during childhood. Moreover, the effect of the A allele was significantly stronger in individuals with insufficient concentrations of vitamin D in their blood (<75 nmol/L) and nearly absent in those with sufficient vitamin D. In other words, having adequate vitamin D negated the effect of the *FTO* risk allele. This relationship is conceptually similar to that seen in a meta-analysis of 218,166 adults where the effect of the rs9939609 A allele was stronger in individuals with another risk factor for obesity, physical inactivity, but weaker in those who were physically active (7).

Lourenço et al. (6) has several strengths. Most important are the longitudinal study design, with up to three study visits 2–3 years apart, and the direct measurement of BMI and serum vitamin D. Additionally, conducting the study in children with a mean age of 5 years at the baseline visit is important because this is the period when individuals start to become overweight (versus adolescence or adulthood). This would also be an opportune age to intervene with behavioral modifications, such as increasing vitamin D intake and/or physical activity, *before* an individual becomes overweight. One weakness of the study is that information on physical activity was not collected. As physical activity is associated with both BMI and vitamin D (through sun exposure), the interaction seen with vitamin D status

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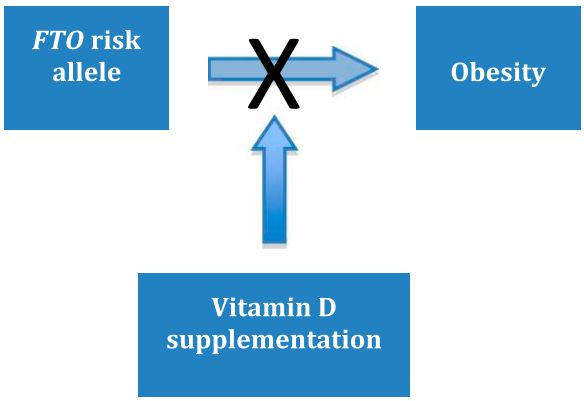

Figure 1—Vitamin D supplementation to remove obesity risk due to the *FTO* gene.

could actually reflect an interaction with physical activity instead of vitamin D. This issue should be addressed by future studies.

If the results of this study were replicated, they would have important clinical practice and public health implications because raising children's vitamin D concentrations to at least 75 nmol/L would remove the risk due to the *FTO* gene (Fig. 1). Vitamin D supplementation is inexpensive ($5–10 per month in the U.S.) and easy (most kids love the chewable fruit-flavored supplements) compared with most behavioral interventions for reducing obesity.

The role that gene-environment interactions play in health and disease has been largely overlooked. However, great promise for personalized medicine lies in uncovering these interactions because while one's genetic risk is not modifiable, behavioral factors are. Health care providers could use genetic information to personalize behavioral interventions. Pharmacogenomic panels are being developed and used in clinical laboratories and genomic information is increasingly included in electronic medical records to aid in clinical decision-making (8). To date, the decisions have involved pharmacologic treatment, particularly for cancer, but behavioral recommendations could also be tailored to individual patients. This holds promise for the prevention of obesity, type 2 diabetes, hypertension, and coronary heart disease in the future.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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