OBESIDADE E FATORES DE RISCO CARDIOVASCULAR DA ADOLESCÊNCIA À VIDA ADULTA

Tese de Doutorado

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“Someday, when you get where you’re going, you will look around and you will know that it was you, and the people who love you, who put you there. And that will be the greatest feeling in the world.”

- Taylor Swift

SUMÁRIO

RESUMO

O objetivo desta tese é avaliar a associação entre obesidade e fatores de risco cardiovascular da adolescência à vida adulta. Para abordar essa temática foram realizados três estudos com delineamentos e fontes de dados distintos. O primeiro estudo que compõe esta tese investigou a prevalência de excesso de peso em adolescentes brasileiros e suas mudanças temporais por meio de uma revisão sistemática com metanálise. A busca na literatura recuperou 10.144 estudos, dos quais 151 foram incluídos na análise. Verificou-se aumento expressivo na prevalência de excesso de peso, sobrepeso e obesidade nas últimas décadas. A prevalência de excesso de peso encontrada foi de 8,2% (IC95% 7,7-8,7) até o ano 2000, 18.9% (IC95% 14,7-23,2) entre 2000 e 2010, e 25,1% (IC95% 23,4-26,8) após 2010. Também foram encontradas diferenças regionais significativas, com as regiões Sudeste e Sul apresentando as maiores prevalências gerais. O segundo estudo avaliou a associação entre o grau de obesidade e fatores de risco cardiometabólicos em adolescentes brasileiros participantes do Estudo de Riscos Cardiovasculares em Adolescentes (ERICA). De um total de 37.892 indivíduos, 8.708 apresentaram excesso de peso, sendo 17,2% com sobrepeso, 5,6% com obesidade e 1,3% com obesidade severa. Foi observada associação do aumento da gravidade da obesidade com pior perfil cardiometabólico na amostra, mesmo após ajuste para múltiplas variáveis. O terceiro estudo investigou a associação entre níveis de NT-proBNP e risco de obesidade em adultos da coorte do *Atherosclerosis Risk in Communities Study* (ARIC). Dados de 9.681 participantes foram analisados, provenientes de duas visitas com seis anos de intervalo entre elas. Comparados com indivíduos no quartil de NT-proBNP mais elevado, aqueles no quartil mais baixo tinham maior chance de apresentar obesidade na visita inicial (OR 1,25; IC95% 1,08-1,45) e de desenvolver obesidade no seguimento (OR 1,35; IC95% 1,07-1,69). Diante dessas informações, conclui-se que o excesso de peso é importante problema de saúde pública que vem aumentando nos últimos anos entre adolescentes, causando inúmeros problemas de saúde que estão intimamente relacionados com o grau de obesidade. O estudo de novos fatores de risco para a obesidade, como os níveis de peptídeos natriuréticos, é necessário para o entendimento da etiologia da obesidade e possível prevenção por meio de intervenções precoces.

Palavras-chave: Obesidade, Sobrepeso, Síndrome metabólica, Adolescentes, Peptídeos natriuréticos.

ABSTRACT

The objective of this thesis is to evaluate the association between obesity and cardiovascular risk factors from adolescence to adulthood. To address this theme, three studies were carried out with different designs and data sources. The first study that composes this thesis investigated the prevalence of excess weight in Brazilian adolescents and its temporal changes through a systematic review with meta-analysis. The literature search retrieved 10,144 studies, of which 151 were included in the analysis. A significant increase in the prevalence of overweight, overweight and obesity in recent decades was observed. The prevalence of excess weight was 8.2% (95% CI 7.7-8.7) until the year 2000, 18.9% (95% CI 14.7-23.2) between 2000 and 2010, and 25.1% (95% CI 23.4-26.8) after 2010. Significant regional differences were also found, with the Southeast and South regions showing the highest overall prevalence. The second study evaluated the association between the degree of obesity and cardiometabolic risk factors in Brazilian adolescents participating in the Study of Cardiovascular Risks in Adolescents (ERICA). Of a total of 37,892 individuals, 8,708 had excess weight, being classified with overweight (17.2%), obesity (5.6%) and severe obesity (1.3%). It was observed that increasing severity of obesity was associated with a worse cardiometabolic profile in the sample, even after adjusting for multiple variables. The third study investigated the association between NT-proBNP levels and risk of obesity in adults in the Atherosclerosis Risk in Communities Study (ARIC) cohort. Data from 9,681 participants were analyzed, from two visits with a six-year interval between them. Compared with individuals in the highest NT-proBNP quartile, those in the lowest quartile were more likely to have obesity at the baseline (OR 1.25; 95% CI 1.08-1.45) and to develop obesity at follow-up (OR 1.35; 95% CI 1.07-1.69). Considering this information, it is concluded that weight excess is an important public health problem that has been increasing in recent years among adolescents, causing numerous health problems that are closely related to the degree of obesity. The study of new risk factors for obesity, such as levels of natriuretic peptides, is necessary to understand the etiology of obesity and possible prevention through early interventions.

Keywords: Obesity, Overweight, Metabolic Syndrome, Adolescents, Natriuretic peptides.

INTRODUÇÃO

A prevalência de excesso de peso triplicou entre 1975 e 2016 e atualmente atinge 39% da população mundial[1]. Segundo dados da Organização Mundial da Saúde (OMS), em 2016 mais de 1,9 bilhão de adultos estavam com excesso de peso; dentre esses, 650 milhões eram classificados com obesidade. A mesma tendência ocorre na população brasileira[1]: entre 1975 e 2016, a prevalência de excesso de peso em adultos aumentou de 24,8% para 56,9%, semelhante em homens (22,4% para 57,6%) e mulheres (27,2% para 56,2%). No mesmo período, a prevalência de obesidade aumentou em cinco vezes: de 4,5% para 22,3%.

A população pediátrica é igualmente atingida pela epidemia da obesidade. Entre 1975 e 2016, a prevalência mundial de excesso de peso em crianças e adolescentes aumentou de 4% para 18%, enquanto a prevalência de obesidade cresceu de 0.8% para 6,8% no mesmo período[1]. Estimativas da OMS apontam que, até o ano de 2030, a prevalência de obesidade nessa população pode alcançar 30%. No Brasil, a prevalência de excesso de peso em adolescentes também vem aumentando nas últimas décadas - segundo inquéritos nacionais, entre 1974 e 2009, a prevalência aumentou em seis vezes no sexo masculino (3,7% para 21,5%) e em três vezes no sexo feminino (7,6% para 19,4%)[2].

O excesso de peso está intimamente associado a diversos problemas de saúde, dentre eles doenças cardiovasculares (aterosclerose, infarto agudo do miocárdio, acidente vascular cerebral), dislipidemia e diabetes mellitus tipo 2[3]. O risco de morte, em especial prematura, também é aumentado nesses indivíduos[4]. Além disso, o risco de desenvolvimento dessas doenças está relacionado com o grau de excesso de peso, sendo menor em pacientes com sobrepeso e ascendendo conforme o grau de obesidade[3]. Essas associações são bem definidas na população adulta; no entanto, ainda se questiona como a obesidade e seus diferentes graus de gravidade impactam na saúde dos jovens. Diversos estudos mostram que, se não houver qualquer intervenção, crianças e adolescentes com obesidade são propensos a manter o excesso de peso na vida adulta, o que pode aumentar a carga de doenças, desenvolvidas precocemente, relacionadas à obesidade[5].

A etiologia da obesidade é complexa, o que aumenta o interesse pelo estudo de possíveis determinantes e fatores de risco para essa morbidade. Estudos genéticos demonstraram que mais de 290 genes/loci são associados com o desenvolvimento da obesidade[6]. A composição da dieta, como percentual de gorduras, açúcares e grãos, também é bem estabelecida como um fator de risco para excesso de peso. Da mesma forma, nível de atividade física e sedentarismo são fatores de risco para o desenvolvimento da obesidade.

Mais recentemente, os níveis do peptídeo natriurético cerebral (BNP) e do fragmento N-terminal do pró-peptídeo natriurético tipo B (NT-proBNP) foram associados com excesso de peso, mesmo em pacientes com insuficiência cardíaca - condição que notavelmente eleva os níveis desses hormônios[7,8]. Análises posteriores fizeram com que o NT-proBNP emergisse como um possível fator de risco para síndrome metabólica e diabetes mellitus. No entanto, o risco de desenvolvimento de obesidade de acordo com o nível de NT-proBNP ainda é pouco explorado na literatura médica.

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REVISÃO DA LITERATURA

Definição e classificações de excesso de peso

A obesidade pode ser definida como acúmulo de gordura corporal excessivo que represente algum risco para saúde. A classificação de excesso de peso mais utilizada em adultos é a da Organização Mundial da Saúde (OMS), a qual é baseada no índice de massa corporal (IMC), calculado pela divisão do peso (em quilogramas - kg) pela altura (em metros - m) ao quadrado[1]. O excesso de peso é definido como IMC maior ou igual a 25 kg/m², sobrepeso como IMC maior ou igual a 25 kg/m² e menor que 30 kg/m², e obesidade como IMC maior ou igual a 30 kg/m². A obesidade é ainda dividida em graus: I ou moderada (IMC entre 30 e 34,9 kg/m²), II ou severa (IMC entre 35 e 39,9 kg/m²) e III ou muito severa (IMC maior ou igual a 40 kg/m²). O cálculo de IMC é um método válido, de baixo custo e de fácil aplicação, podendo ser utilizado em larga escala, sendo o mesmo para ambos os sexos e para todos os adultos acima de 18 anos. No entanto, sabe-se que esses valores não são fixos para predição de risco em todas as populações - a população asiática apresenta risco aumentado de diabetes mellitus e hipertensão arterial sistêmica em faixas de IMC mais baixas se comparado a não-asiáticos, portanto, foi proposta por Inoue e Zimmet uma classificação diferenciada[2], considerando sobrepeso um IMC entre 23 e 24,9 kg/m² e obesidade um IMC maior ou igual a 25 kg/m².

Em crianças e adolescentes, a classificação de excesso de peso pode ser feita por meio de percentis, baseando-se em uma curva de distribuição normal de crescimento em uma população saudável. Utiliza-se também o escore-z, que se relaciona com um valor de percentil correspondente conforme padronização. Em 1995, a OMS publicou uma diretriz baseando o diagnóstico de sobrepeso e obesidade na distribuição de escores-Z de peso para altura[3]. No entanto, essa forma de classificação tornou-se rapidamente obsoleta, e para minimizar suas falhas foi desenvolvido um índice de maior sensibilidade e especificidade para detecção de excesso de peso em jovens - o IMC por idade. Must et al propuseram em 1991 percentis de IMC para crianças a partir de 6 anos, gerados a partir de dados do *National Health and Nutrition Examination Survey I* (NHANES I)[4]. No entanto, as curvas mais difundidas com essa classificação foram as do *Centers for Disease Control and Prevention* (CDC), publicadas em 2000[5, 6], que foram formuladas a partir das curvas do *National Centre for Health Statistics* (NCHS) de 1977, que utilizou cinco estudos transversais norte-americanos (*National Health Examination Surveys* (NHES II e III) e NHANES I, II e III). Os pontos de corte definem sobrepeso quando IMC igual ou maior ao percentil 85 e menor que percentil 95, e obesidade quando IMC maior ou igual ao percentil 95.

Em 2007, visando unificar a forma de acompanhamento nutricional de crianças e adolescentes, a OMS passou a recomendar um novo índice baseado no IMC, com curvas construídas utilizando dados de um estudo que envolveu Brasil, Gana, Índia, Noruega, Omã e Estados Unidos[7]. De modo a garantir que os indivíduos fossem representativos de uma população saudável, critérios de elegibilidade como *status* socioeconômico favorável ao crescimento e aleitamento materno exclusivo até os quatro meses foram utilizados. Desde a sua publicação, as curvas foram amplamente implementadas globalmente, e são recomendadas pelo Ministério da Saúde do Brasil, sendo incluídas na Caderneta de Saúde da Criança e do Adolescente[8]. A classificação de IMC em adolescentes está descrita na **Tabela 1**.

TABELA 1. Pontos de corte de IMC-para-idade em adolescentes de 10 a 19 anos, conforme classificação da Organização Mundial da Saúde (OMS).

PERCENTIL	ESCORE-Z	DIAGNÓSTICO NUTRICIONAL
< Percentil 0,1	< Escore-z -3	Magreza acentuada
≥ Percentil 0,1 e < Percentil 3	≥ Escore-z -3 e < Escore-z -2	Magreza
≥ Percentil 3 e ≤ Percentil 85	≥ Escore-z -2 e ≤ Escore-z +1	Eutrofia
> Percentil 85 e ≤ Percentil 97	≥ Escore-z +1 e < Escore-z +2	Sobrepeso
> Percentil 97 e ≤ Percentil 99,9	≥ Escore-z +2 e ≤ Escore-z +3	Obesidade
> Percentil 99,9	> Escore-z +3	Obesidade grave/severa

Diversos outros critérios de classificação do IMC, de acordo com a idade, são utilizados em adolescentes. Cole et al estabeleceram pontos de corte de IMC baseados nas recomendações da *International Obesity Task Force* (IOTF) utilizando estudos representativos de seis locais (Brasil, Grã-Bretanha, Hong-Kong, Holanda, Singapura e Estados Unidos)[9, 10]. Esse autor propôs uma relação entre ponto de corte de IMC em adultos aos 18 anos com percentil do IMC em crianças e adolescentes. Desta forma, considera-se sobrepeso e obesidade nos indivíduos que, aos 18 anos, se encontram na curva de crescimento que passa pelo IMC maior ou igual a 25 kg/m² e maior ou igual a 30 kg/m², respectivamente. Ainda, são classificados com obesidade severa aqueles com IMC maior ou igual a 35 kg/m². Outra classificação bastante utilizada é a de Conde e Monteiro[11], cujos dados utilizados para estabelecimento da curva de IMC para idade provêm de pesquisa do Instituto Brasileiro de Geografia e Estatística realizada com

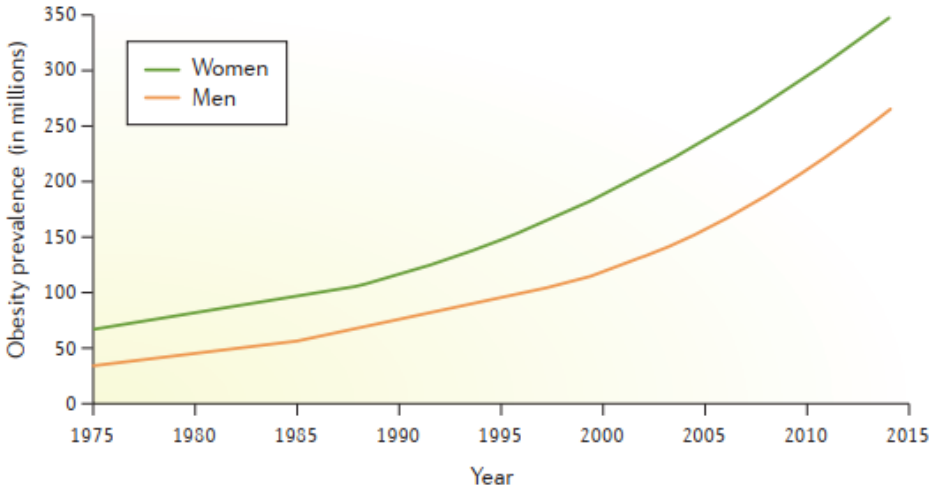
jovens brasileiros em 1989. Nesta classificação, são utilizados os mesmos pontos de corte de IMC de Cole et al para definição de sobrepeso e obesidade. A diferença entre Cole et al e Conde e Monteiro é a definição de baixo peso, considerada menor que 17 kg/m² no primeiro e menor que 18 kg/m² no segundo[10, 11].

Desde 2009, diversos estudos vêm utilizando uma classificação derivada da proposta pelo CDC, com algumas modificações de modo a estratificar a classificação de obesidade em crianças e adolescentes [12-14]. Desta forma, há a divisão nas seguintes classes: classe I (IMC ≥ percentil 95 até < 120% do percentil 95), classe II (≥ 120% até < 140% do percentil 95, ou IMC ≥ 35 kg/m², o que for mais baixo), e classe III (≥ 140% do percentil 95, ou IMC ≥ 40 kg/m², o que for mais baixo). São consideradas como obesidade severa as classes II e III.

Prevalência de excesso de peso

A prevalência do excesso de peso aumentou em todo o mundo nos últimos anos, atingindo níveis pandêmicos **(Figura 1)**[15]. Nas últimas quatro décadas, o percentual de adultos com excesso de peso aumentou de 20,2% para 39,1%. A prevalência de obesidade isoladamente em adultos subiu de 4,3% em 1975 para 13,2% em 2016, tendo quadruplicado em homens (2,7% para 11,1%) e duplicado em mulheres (5,9% para 15,3%)[16]. Neste mesmo período, a região das Américas teve um crescimento importante na prevalência de obesidade, que passou de 9% para 29%.

FIGURA 1. Prevalência mundial de obesidade, em milhões, por sexo.



Fonte: González-Muniesa, P., Mártinez-González, MA., Hu, F. et al. Obesity. Nat Rev Dis Primers **3**, 17034 (2017).

Um crescimento semelhante ao mundial nos níveis de sobrepeso e obesidade foi observado na população brasileira. Segundo dados da Pesquisa de Orçamentos Familiares[17], entre 1974 e 2009, a prevalência de excesso de peso em adultos triplicou entre os homens (18,5 para 50,1%) e duplicou entre as mulheres (28,7% para 48%). Neste mesmo período, a prevalência de obesidade quadruplicou entre os homens (2,8% para 12,4%) e duplicou entre as mulheres (8% para 16,9%).

Além da prevalência geral de obesidade estar constantemente aumentando nos últimos anos, sua distribuição de acordo com a severidade está mudando - o número de indivíduos com obesidade grau II e III vem crescendo em ritmo exponencialmente maior do que o número daqueles com obesidade grau I e sobrepeso[18]. Apesar de ser pouco prevalente hoje, estimativas mostram que, até o ano de 2030, a categoria de obesidade severa poderá se tornar a mais frequente em adultos norte-americanos, afetando 1 em cada 4 indivíduos[19]. Dados da população brasileira, segundo o VIGITEL (Vigilância de Doenças Crônicas por Inquérito Telefônico)[20], são demonstrados na **Tabela 3**. Entre o período de 2006 e 2016, a prevalência de obesidade grau II teve um aumento relativo maior do que sobrepeso e obesidade grau I em ambos os sexos. Ainda, em mulheres, o maior aumento de prevalência do período foi no grupo de obesidade grau III.

TABELA 3. Prevalência de sobrepeso e diferentes graus de obesidade na população brasileira adulta no período de 2006 à 2016, segundo pesquisa VIGITEL.

	2006	2016	Aumento relativo no período
Homens			
Sobrepeso (25 kg/m² ≤ IMC < 30 kg/m²)	36,5%	39,4%	7,9%
Obesidade grau I (30 kg/m² ≤ IMC < 35 kg/m²)	9,1%	13,8%	51,6%
Obesidade grau II (35 kg/m² ≤ IMC < 40 kg/m²)	1,7%	3,1%	82,4%
Obesidade grau III (IMC ≥ 40 kg/m²)	0,9%	1,2%	33,3%
Mulheres			
Sobrepeso (25 kg/m² ≤ IMC < 30 kg/m²)	25,7%	29,4%	14,4%
Obesidade grau I (30 kg/m² ≤ IMC < 35 kg/m²)	8,3%	12,8%	54,2%
Obesidade grau II (35 kg/m² ≤ IMC < 40 kg/m²)	2,5%	4,0%	60%
Obesidade grau III (IMC ≥ 40 kg/m²)	1,2%	2,0%	66,7%

Adaptado de: Flores-Ortiz R, Malta DC, Velasquez-Melendez G. Adult body weight trends in 27 urban populations of Brazil from 2006 to 2016: A population-based study. PLoS One. 2019;14(3):e0213254.

O excesso de peso na população pediátrica também cresceu de forma alarmante nas últimas décadas. Entre 1975 e 2016, a prevalência de excesso de peso entre adolescentes com 10 a 19 anos de idade passou de 4,3% para 17,3%; enquanto a prevalência de obesidade foi de 0,7% para 5,6% [16]. Particularmente, a categoria de excesso de peso que mais aumentou nos últimos anos nessa faixa etária foi a de obesidade severa[21]. Em adolescentes norte-americanos, as taxas de obesidade severa triplicaram nos últimos anos, alcançando 9,1% em 2013[22]. Um estudo realizado no Reino Unido que incluiu mais de um milhão de jovens de 10 e 11 anos demonstrou que 2,9% das meninas e 3,9% dos meninos apresentavam obesidade severa[23]. Em jovens israelenses, houve um aumento de 45 vezes na prevalência de obesidade grau III nos últimos 40 anos[24].

No Brasil, dados do Estudo de Riscos Cardiovasculares em Adolescentes (ERICA), que incluiu mais de 73 mil adolescentes brasileiros em 2013-2014, demonstraram que 17,1% dos participantes apresentavam sobrepeso e 8,4% obesidade[25]. Prevalências semelhantes de sobrepeso foram encontradas entre os sexos, sendo 17,6% nas meninas e 16,6% nos meninos. A prevalência de obesidade, no entanto, foi discretamente maior entre os meninos (9,2% *vs* 7,6%). Algumas diferenças regionais foram observadas, com as regiões Norte, Nordeste e Centro-Oeste apresentando as menores prevalências de excesso de peso. A região Sul apresentou as maiores taxas de excesso de peso, com 18,7% de sobrepeso e 11,1% de obesidade. Dados sobre a prevalência de obesidade por graus de severidade em adolescentes ainda são escassos na literatura. Em um estudo com 1055 adolescentes da região Sudeste[26], 1,6% dos meninos e 1,9% das meninas apresentavam IMC acima de 35 kg/m². De forma similar, outro estudo encontrou uma prevalência de 1,4% de obesidade para ambos os sexos entre estudantes de escolas públicas[27].

A obesidade é considerada de etiologia multifatorial, envolvendo elementos ambientais, comportamentais e genéticos. Fatores relacionados ao período pré-natal, como peso pré-gestacional materno e fumo durante a gravidez, estão diretamente relacionados com o peso na infância[28-30]. Os primeiros anos da criança são períodos críticos para o seu desenvolvimento e influenciam no peso em todas as etapas da vida. Indivíduos que receberam aleitamento materno, por exemplo, têm menor prevalência de sobrepeso e obesidade na infância, adolescência e vida adulta[31]. Fatores genéticos, como história familiar de obesidade e variantes em diversos genes, também estão associados com o desenvolvimento da obesidade[32, 33]. Polimorfismos no *fat mass- and obesity-associated gene* (FTO), por exemplo, elevam o risco de obesidade e diabetes mellitus[34].

Também é reconhecido como importante determinante do excesso de peso durante a juventude o comportamento sedentário[35, 36]. Em um estudo publicado em 1985, a prevalência de obesidade aumentava 2% para cada hora adicional passada na frente da televisão em jovens do estudo NHANES II e III[37]. Mais recentemente, Hancox et al demonstraram que maior tempo em frente à televisão em dias da semana durante a infância estava associado com o IMC mais alto cerca de dez anos depois[38]. Em adolescentes da coorte de nascimentos de Pelotas de 1993, a prevalência de comportamento sedentário (2 ou mais horas por dia de tempo de tela) foi de 80%, e este estava positivamente associado com o estado nutricional[39]. Similarmente, uma revisão sistemática evidenciou que a prevalência de tempo excessivo de tela em adolescentes brasileiros era de 70,9%[40]. A prática de atividade física, apesar de seus inúmeros benefícios para a saúde, apresenta resultados conflitantes acerca do seu papel como preditor de ganho de peso durante a adolescência[41, 42]. Análises do ERICA demonstraram que a prática de atividade física moderada a vigorosa e o tempo de tela são associados com risco cardiometabólico, independentemente de outros fatores[43]. No entanto, a associação entre tempo de tela e risco cardiometabólico é mais pronunciada em jovens com sobrepeso ou obesidade comparado com aqueles de peso normal, enquanto a associação entre prática de atividade física e risco cardiometabólico permanece a mesma em ambos grupos.

Diversos estudos demonstram relação complexa entre as condições sociais e excesso de peso. De modo geral, indivíduos com maior nível socioeconômico são menos propensas a ter sobrepeso ou obesidade em países de alta renda, mas mais propensas em países de média e baixa renda[44]. No entanto, nos locais em que ocorreu uma rápida transição demográfica, como no Brasil, a prevalência de excesso de peso também vem aumentando nas populações de menor nível socioeconômico, configurando-se uma carga dupla de doenças, com desnutrição e obesidade coexistindo[45]. Isso se deve principalmente à modificação dos padrões alimentares, com maior consumo e disponibilidade de alimentos ultraprocessados, e menor consumo alimentos *in natura*. O custo de manter uma alimentação saudável, rica em frutas e vegetais, também é maior, dificultando o seu consumo por populações de baixo poder aquisitivo. A população de menor nível socioeconômico também tem menor acesso a estratégias de prevenção em saúde, como a prática de exercícios.

Padrões dietéticos não saudáveis também estão fortemente associados com comportamento sedentário, como fazer refeições em frente a telas. De modo geral, crianças e adolescentes que comem enquanto assistem televisão consomem menos frutas e vegetais e mais alimentos ultraprocessados[46]. Em adolescentes brasileiros, aqueles com comportamento sedentário tinham uma prevalência de consumo diário de alimentos ultraprocessados de 42,8%,

comparado a 29,8% naqueles sem comportamento sedentário[47]. Dados do ERICA mostram que existe uma associação positiva entre tempo de tela e síndrome metabólica; contudo, essa associação se mantém significativa somente em adolescentes que reportaram o consumo de lanches não saudáveis em frente a telas[48]. A propaganda de alimentos industrializados voltada para crianças é outra explicação para a ligação entre a exposição a telas e o consumo excessivo de energia – por esse motivo, nos últimos anos diversos países têm restringido a publicidade de alimentos ricos em gordura na televisão voltada para jovens[49].

Consequências do excesso de peso para a saúde

O excesso de peso contribui para o desenvolvimento de diversas doenças crônicas não transmissíveis (DCNT) e outros problemas de saúde[50], listados na **Tabela 2**. Em 2019, as doenças cardiovasculares foram responsáveis por cerca de 30% das mortes mundialmente, das quais a principal causa é a doença cardíaca isquêmica[51]. O estudo de Framingham demonstrou que indivíduos com obesidade apresentam o dobro do risco de desenvolver doença arterial coronariana comparado com aqueles com peso normal[52]. Na coorte de Framingham foi observado que, isoladamente, o excesso de peso foi responsável por 70% e 61% dos casos de hipertensão arterial em homens e mulheres, respectivamente[53]. Da mesma forma, mulheres na 4ª década de vida com obesidade eram sete vezes mais propensas a desenvolver hipertensão arterial do que mulheres de peso normal da mesma idade[54]. Um estudo com mais de 83 mil mulheres identificou o IMC como melhor preditor para incidência de hipertensão arterial[55]. A trajetória de mudança de peso também pode influenciar o risco de desenvolver hipertensão arterial – em homens adultos, a taxa de aumento do IMC em qualquer ponto durante o curso de vida aumentava o risco de hipertensão arterial, independentemente do IMC inicial[56].

O excesso de peso também está intimamente ligado a doenças metabólicas, em especial ao desenvolvimento de diabetes mellitus tipo 2 (DM2) e suas complicações micro e macrovasculares, como neuropatia periférica e dano renal. As dislipidemias, como aumento do colesterol LDL (*low-density lipoprotein*), aumento de triglicérides e diminuição do colesterol HDL (*high-density lipoprotein*), também são associadas ao sobrepeso e à obesidade. A obesidade é o principal fator de risco modificável para o desenvolvimento da resistência insulínica e, por consequência, do DM2[57, 58]. Em uma meta-análise de estudos de coorte prospectivos, foi encontrado que, em indivíduos com obesidade, o risco de DM2 era sete vezes maior em homens e 12 vezes maior em mulheres[50]. Em jovens essa associação também vem ficando cada vez mais evidente - na década de 90, menos de 3% de todos os novos casos de

DM2 em adolescentes estavam associados à obesidade; atualmente, estima-se que 45% dos casos seriam devidos a obesidade[59]. Por outro lado, a perda de peso, mesmo que modesta, leva à melhora do controle glicêmico e reduz o risco de desenvolvimento da doença[58, 60].

Múltiplos problemas de saúde são relacionados com o excesso de peso. Neoplasias de esôfago, estômago, rim, intestino grosso e reto têm como fator de risco a presença de obesidade[50, 61-63]; e a cirurgia bariátrica está associada com diminuição no risco de câncer[64]. Esteatose hepática, cirrose e carcinoma hepatocelular também são associados ao excesso de peso, e o risco de doenças da vesícula biliar (colelitíase, colecistite e colesterolose) é de duas a três vezes maior em indivíduos com obesidade, sendo mais alto em mulheres[65]. Problemas ortopédicos , como osteoartrite de joelhos e de quadril, estão diretamente relacionados com traumas de repetição associados ao excesso de peso[66]. Problemas respiratórios, como asma, são até duas vezes mais comuns em indivíduos com sobrepeso e obesidade[50], e essa relação também é vista na população pediátrica[67]. O excesso de peso também está associado a diversos distúrbios psicológicos e psiquiátricos, como depressão, ansiedade e distúrbios alimentares[68]. Em um estudo australiano, pacientes com obesidade apresentaram prevalência de depressão de 23%, comparado a 11% daqueles com peso normal[69]. O risco de ansiedade e depressão encontrado em crianças suecas era 43% e 33% maior em meninas e meninos com obesidade, respectivamente[70]. Além disso, a crescente discriminação de indivíduos baseada no peso é um fator que gera impactos sociais e psicológicos significativos, e que parece influenciar negativamente no atendimento de saúde dessas pessoas (*weight-bias*)[71, 72].

Além de aumentar individualmente o risco desses problemas de saúde, a obesidade também leva a um risco maior de mortalidade por todas as causas. Nos últimos anos, estima-se que, mundialmente, mais de 4 milhões de pessoas morrem anualmente como resultado direto do sobrepeso e da obesidade[73]. A chance de morte prematura também é elevada nessa população, havendo risco de 50 a 78% maior em indivíduos com obesidade comparado a aqueles com peso normal[74]. Da mesma forma, indivíduos que tiveram obesidade na infância apresentam mortalidade três vezes maior na vida ajuda jovem[75]. Alguns estudos também sugerem que a obesidade durante a vida adulta jovem é um preditor de morte prematura mais importante do que a obesidade na meia idade[74].

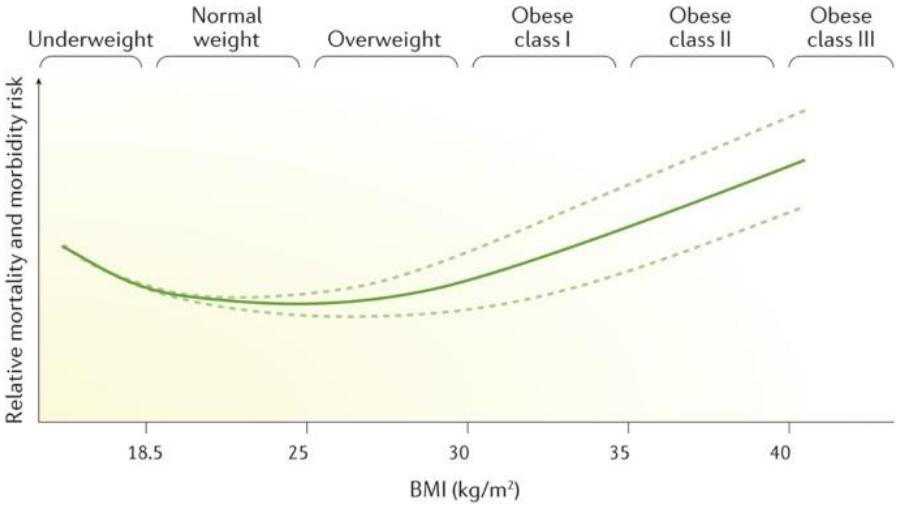
TABELA 2. Condições de saúde associadas com o excesso de peso.

Aterosclerose, Doença arterial coronariana, Insuficiência cardíaca e outras doenças do coração
Hipertensão arterial sistêmica
Acidente vascular cerebral
Diabetes mellitus tipo 2
Dislipidemias (colesterol LDL e triglicerídeos altos, colesterol HDL baixo)
Problemas articulares (osteoartrite)
Câncer (esôfago, estômago, intestino grosso e reto, fígado, etc)
Doenças do fígado (esteatose hepática, cirrose) e da vesícula biliar (colelitíase, colecistite)
Apneia do sono e problemas respiratórios
Distúrbios psicológicos e psiquiátricos (ansiedade, depressão)

Legenda: LDL, low density lipoprotein; HDL, high density lipoprotein.

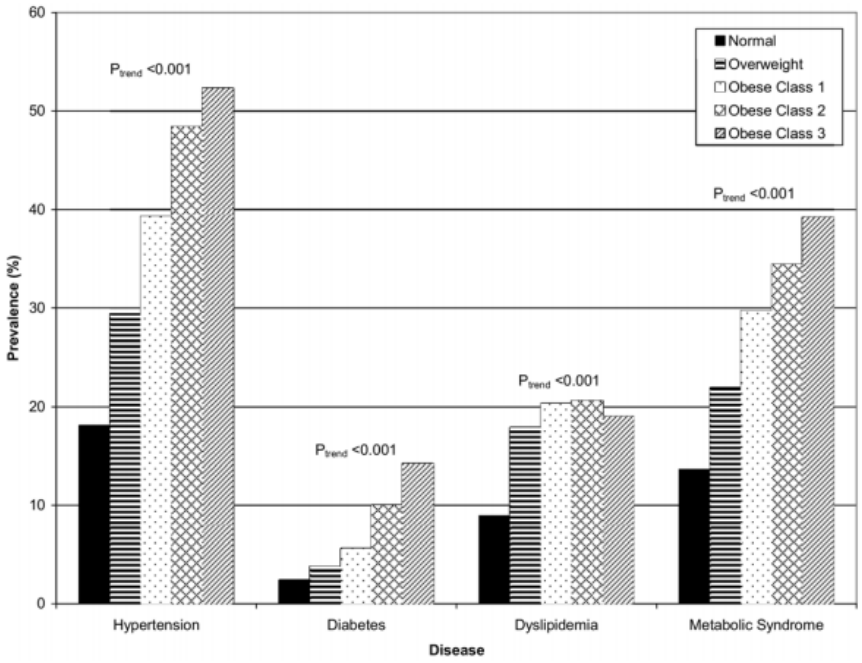
Graus elevados de obesidade aumentam ainda mais o risco de complicações de saúde, como pode ser visto na **Figura 2.** Análises de dados do NHANES demonstraram uma relação positiva linear entre aumento de IMC e complicações como hipertensão arterial, DM2, dislipidemia e síndrome metabólica **(Figura 3)**[76]. Em comparação com indivíduos com peso normal, a razão de chances ajustada de apresentar hipertensão arterial foi de 1,7 (IC95% 1,5-1,8) para sobrepeso, 2.6 (IC95% 2,2-3,1) para obesidade classe I, 3.7 (IC95% 3,1-4,3) para classe II e 4.8 (IC95% 3,8-5,9) para classe III. Valores similares foram encontrados para diabetes mellitus tipo 2. Dentre os casos novos de DM2 entre 1976-1980 e 1999-2004, metade apresentava obesidade classe II ou III[77]. Em pacientes admitidos no hospital com insuficiência cardíaca[78], o risco de eventos adversos (morte, re-hospitalização e visita a emergência) em 60 dias aumentou linearmente a partir de um IMC de 40 kg/m², alcançando mais de 40% em indivíduos com IMC de 50 kg/m². Também foi observado no estudo de Framingham que a pressão arterial sistólica aumenta 4mmHg a cada aumento de peso de 4,5 kg[79]. Em comparação com indivíduos com graus menores de obesidade, aqueles com obesidade severa têm um risco de morte por todas as causas duas vezes maior[80].

FIGURA 2. Relação entre IMC e risco de morbimortalidade.



Legenda: BMI, body mass index (Índice de massa corporal); kg, quilogramas; m², metros quadrados. Fonte: González-Muniesa, P., Mártinez-González, MA., Hu, F. et al. Obesity. Nat Rev Dis Primers. 2017;3:17034.

FIGURA 3. Associação entre grau de obesidade e risco de doenças relacionadas, dados do *National Health and Nutrition Examination Survey* (NHANES).



Fonte: Nguyen NT, Magno CP, Lane KT, Hinojosa MW, Lane JS. Association of Hypertension, Diabetes, Dyslipidemia, and Metabolic Syndrome with Obesity: Findings from the National Health and Nutrition Examination Survey, 1999 to 2004. J Am Coll Surg. 2008;207(6):928-34.

O excesso de peso durante a infância e a adolescência é associado com aumento da incidência de diversas doenças, como diabetes mellitus tipo 2, hipertensão arterial sistêmica,

dislipidemia, doença hepática gordurosa não alcoólica e apneia obstrutiva do sono. Diversos estudos demonstraram que o desenvolvimento da aterosclerose em jovens está fortemente relacionado com a obesidade[81, 82]. Por exemplo, crianças com obesidade apresentam maior rigidez arterial e espessura da camada íntima-média da artéria carótida [83, 84]. No entanto, existem questionamentos acerca da relação entre severidade de obesidade e risco de doenças cardiovasculares em crianças e adolescentes. Até recentemente, a maioria dos estudos considerava a obesidade como uma categoria única, avaliando com o mesmo risco aqueles com IMC equivalente à 30 kg/m² ou de 60 kg/m², por exemplo.

Atualmente, acredita-se que exista uma relação proporcional entre inúmeros problemas de saúde e crescentes graus de obesidade em crianças e adolescentes. Em um estudo com mais de 230 mil jovens israelenses foi observado que, à medida que aumentava a classe de obesidade, maiores eram as chances de existir alguma comorbidade[24]. Utilizando como referência aqueles com sobrepeso, o risco de DM2 foi 5 vezes maior naqueles com obesidade classe I, 19 vezes na classe II e 38 vezes na classe III. O risco para hipertensão arterial também aumenta com crescentes graus de obesidade, sendo aproximadamente três vezes maior naqueles com obesidade classe III. Similarmente, em adolescentes coreanos os riscos de pressão arterial sistólica elevada e hemoglobina glicada (HbA1c) aumentada eram seis vezes maiores naqueles com obesidade classe III em comparação com sobrepeso[85]. Em outro estudo, realizado com jovens norte-americanos com obesidade, a ocorrência de pressão arterial elevada e de tolerância à glicose diminuída estava associada com severidade da obesidade – a cada 5 kg/m² de aumento no IMC, foi observado um aumento de 10% e 15% no risco dos dois fatores, respectivamente[86]. Cerca de 21% dos adolescentes com obesidade severa em uma amostra apresentavam tolerância à glicose diminuída[87]. A prevalência de síndrome metabólica, independente do critério utilizado, também parece aumentar gradualmente com a piora do grau de obesidade. Dados na literatura demonstram que indivíduos com obesidade classe II e III têm três vezes mais chances de apresentar síndrome metabólica do que aqueles com obesidade classe I[88].

Peptídeos natriuréticos

Os peptídeos natriuréticos são marcadores bioquímicos da função cardíaca, estando associados com a presença de hipertrofia de ventrículo esquerdo e insuficiência cardíaca. O principal estímulo para a sua liberação é a distensão dos miócitos cardíacos, que pode ocorrer por aumento no volume ou nas pressões dentro do coração[89]. O pró-peptídeo natriurético tipo

B (proBNP) é a molécula precursora que, durante a sua secreção, é clivada em forma ativa (peptídeo natriurético cerebral, BNP) e inativa (fragmento N-terminal do pró-peptídeo natriurético tipo B, NT-proBNP)[90]. Os principais efeitos cardiovasculares relacionados ao BNP são vasodilatação, aumento da permeabilidade vascular, natriurese e diminuição da secreção de renina e de aldosterona.

Mais recentemente, evidenciou-se que a ação dos peptídeos natriuréticos não está restrita somente ao eixo coração-rim, podendo atuar na regulação metabólica, no funcionamento do tecido adiposo e no desenvolvimento da resistência à insulina[91, 92]. Esses hormônios se ligam a receptores natriuréticos tipo A (NPR-A) localizados no tecido adiposo, aumentando a produção intracelular de monofosfato cíclico de guanosina (cGMP). Essa ligação estimula a lipólise[93], aumenta a biogênese mitocondrial[94], promove o escurecimento de adipócitos[95], regula a distribuição da gordura corporal[94] e aumenta a secreção de adiponectina pelos adipócitos[96].

Diversos estudos transversais relacionam menores níveis de BNP e NT-proBNP com a presença de obesidade, DM2 e síndrome metabólica[97-99]. Um estudo com a prole da coorte do *Framingham Heart Study* mostrou que, em adultos sem insuficiência cardíaca, o IMC era inversamente associado aos níveis de BNP[100]. Um estudo realizado com 1.759 adultos do Japão observou a mesma associação em outro cenário cultural[101]. A relação inversa entre IMC e peptídeos natriuréticos também está presente em indivíduos com insuficiência cardíaca, incitando a necessidade de pontos de corte distintos por IMC no diagnóstico da doença[102, 103]. De forma oposta, a perda de peso (em especial após realização de cirurgia bariátrica) é acompanhada por aumento dos níveis de BNP e NT-proBNP[104, 105].

Um número crescente de estudos sugere que níveis elevados de peptídeos natriuréticos podem proteger contra doenças metabólicas. Camundongos que apresentam superexpressão de BNP ou que são tratados com infusões exógenas de peptídeos natriuréticos exibem massa gorda reduzida, melhor tolerância à glicose e maior gasto energético basal, apesar de receberem dieta rica em gorduras[94]. Essa relação é descrita em humanos em múltiplos estudos, especialmente acerca do desenvolvimento de DM2[106-108]. No *Atherosclerosis Risk in Communities Study* (ARIC), que avaliou cerca de 7 mil indivíduos durante um seguimento de 12 anos, demonstrou que níveis de NT-proBNP estavam inversamente associados com a incidência de DM2 mesmo após ajuste para múltiplas variáveis e na análise de subgrupos[109]. No entanto, são escassos na literatura dados longitudinais sobre risco de obesidade e alterações nos níveis dos peptídeos natriuréticos independentemente de mudanças em outros marcadores de risco cardiometabólico.

JUSTIFICATIVA

O excesso de peso durante a juventude é relevante e comum, e vem apresentando prevalência crescente na última década. O sobrepeso e a obesidade são fatores de risco para inúmeros problemas de saúde, em especial cardiológicos e metabólicos, e sua presença aumenta a ocorrência de complicações e a mortalidade associada. O grau de obesidade é uma informação importante na estratificação de risco, visto que classes maiores estão diretamente associadas com maior presença de fatores de risco cardiometabólicos. Ademais, o estudo de fatores de risco, como níveis de peptídeos natriuréticos, é necessário para o entendimento da etiologia da obesidade e possível prevenção por meio de intervenções precoces.

Desta forma, a escrita desta tese se justifica com base nos seguintes pontos:

- Não há na literatura estimativa atualizada e representativa da prevalência de sobrepeso e obesidade em adolescentes brasileiros ao longo do tempo e por macrorregião do país;
- Existem poucos estudos visando compreender a associação de graus de obesidade com fatores de risco cardiometabólicos em jovens, em especial em adolescentes brasileiros, e nos estudos que existem, os resultados são conflitantes;
- Hormônios como BNP e NT-proBNP têm potencial para auxiliar na investigação das causas e fatores de risco da obesidade.

OBJETIVOS

Objetivo geral:

- Avaliar a associação entre obesidade e fatores de risco cardiovascular em dois estágios distintos - na adolescência e na vida adulta.

Objetivos específicos:

- Artigo 1: Identificar e compilar os dados, por meio de revisão sistemática com metanálise, a prevalência de excesso de peso, sobrepeso e obesidade em adolescentes brasileiros ao longo das últimas décadas.
- Artigo 2: Avaliar a associação entre grau de obesidade e fatores de risco cardiometabólicos em uma amostra representativa de adolescentes brasileiros.
- Artigo 3: Investigar a associação entre níveis de NT-proBNP com o risco de obesidade em uma coorte representativa de adultos norte-americanos.

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ARTIGO 1 - Prevalence of overweight and obesity among Brazilian adolescents over time: a systematic review and meta-analysis.

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ABSTRACT

Objective: To estimate the burden of weight excess in Brazilian adolescents.

Design: Systematic review with meta-analysis.

Setting: We searched the literature in four databases (MEDLINE/PubMed, EMBASE, SciELO and LILACS). Studies were included if they had cross-sectional or cohort design and enrolled Brazilian adolescents. Studies based on self-reported measures were excluded. Random effect models were used to calculate prevalence estimate and its 95% confidence interval (95%CI).

Participants: Brazilian adolescents (10 to 19 years old).

Results: One hundred and fifty-one studies were included. Trend analyses showed a significant increase in the prevalence of excess weight in the last decades: 8.2% (95%CI:7.7-8.7) until year 2000, 18.9 (95%CI:14.7-23.2) from 2000 to 2009, and 25.1% (95%CI:23.4-26.8) in 2010 and after. A similar temporal pattern was observed in the prevalence of overweight and obesity separately. In sensitivity analyses, lower prevalence of excess weight was found in older adolescents and those defined using IOTF cutoff points. The Southeast and South regions had the highest prevalence of excess weight, overweight and obesity. No significant difference in prevalence by sex was found, except for studies before the year 2000.

Conclusions: The prevalence of overweight and obesity in Brazilian adolescents is high and continues to rise. Public policies on an individual level and targeting modifications in the obesogenic environment are necessary.

INTRODUCTION

Obesity in early life has immediate consequences on health, such as hyperlipidemia, hypertension, abnormal glucose tolerance and other cardiovascular risk factors[1, 2]. It is a precursor of adulthood obesity[3], leading to development of cardiometabolic risk factors like atherosclerosis and type 2 diabetes[1, 4]. According to data from the World Health Organization (WHO), in 2012, chronic non-communicable diseases were responsible for 38 million deaths worldwide[5]. From an economic point of view, chronic non-communicable diseases are responsible for high public financial expenditures, with obesity being especially linked to sky-rocketing medical costs[6].

In the last decades, the global prevalence of overweight and obesity in children and adolescents has exponentially increased[7]. In 2008, it was estimated that 170 million people less than 18 years-old were classified as overweight or obese[7]; and projection models show that, by 2030, 30% of children and adolescents will be affected by these conditions in USA[8]. Estimates by WHO show that most overweight and obese youths live in low- and middle-income countries, where the rates have been increasing even faster compared to high-income countries[9].

In Brazil, overweight and obesity among youth is an important public health concern due to its increasing prevalence. Data from the Family Budget Survey (POF), conducted between 1974 and 2009, shows that obesity among adolescents increased from 0.4 to 5.9% in boys and from 0.7 to 4.0% in girls[10]. More recently, the Study of Cardiovascular Risks in Adolescents (ERICA), which evaluated 73,399 Brazilian adolescents aged 12 to 17 years, revealed that 17.1% and 8.4% of adolescents had overweight and obesity, respectively[11].

Differences between Brazilian regions are striking in many ways, with social, demographic, cultural and economic factors particularly influencing nutritional status. The south and southeast are more developed and industrialized regions, midwest is in development trough agribusiness, while the north and northeast regions are characterized by the higher social inequalities in Brazil. Access to health care services is much lower in the north and northeast regions compared to the rest of the country. Despite very different epidemiological profiles, regional information about the trends in prevalence of weight excess among adolescents are scarce. A previous systematic review that included 28 Brazilian studies showed an overall prevalence of obesity among adolescents of 14.1%, but results weren't stratified by region or decades, therefore making it difficult to generalize such rate for the whole country[12]. The

diversity between Brazilian geographical areas highlights the necessity of collecting data from studies conducted in different cities and states of Brazil, in order to obtain a better epidemiological profile of youth obesity across the country during the past decades.

In order to have a better understanding of weight excess trends in Brazilian adolescents, we performed a systematic review and meta-analysis of observational studies that presented data about weight status in this population. Our objective was to estimate the prevalence of overweight and obesity in Brazilian adolescents, considering regional and temporal variations. We hypothesized overweight and obesity would significantly increase over the years in all regions of Brazil.

METHODS

The protocol for this review was registered and published on the Prospero database (Registration number: CRD42018107055). The report of this systematic review follows the PRISMA statement[13, 14].

Search strategy

The search strategy was performed in Portuguese and English languages, without restriction of publication data, by the main investigator. The literature search combined the following keywords: overweight, obesity, adolescents and Brazil. The terms were searched in four databases: MEDLINE (Medical Literature Analysis and Retrieval System Online/PubMed), EMBASE (Elsevier), Scientific Eletronic Library Online (SciELO), *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS). Full search strategy is shown in the supplementary material (Table S1). All potentially eligible studies were considered for review. Duplicate studies were excluded. The software EndNote version X7 (Thomson Reuters, New York, NY) was used for reference selection management. The last search was performed in June 2020.

Study eligibility

Two pairs of reviewers (MS and MRG; JAR and MM) analyzed study eligibility independently. Figure 1 shows the flow diagram of the studies included in the meta-analysis. The studies were selected based on the following criteria: cross-sectional and cohort studies that reported the prevalence of overweight/obesity among Brazilian adolescents (10 to 19 years old). Weight and height had to be measured to calculate the body mass index (BMI); studies based on self-reported data were excluded.

Populations in the studies had to be selected through random sampling or census, and studies that included less than 300 individuals were excluded. A sample size calculation was performed considering the following parameters: prevalence of overweight/obesity 25%[11], power of 80%, and confidence level of 95%. These parameters required a sample of around 300 adolescents. This criterion was adopted for help us in the screening processes, avoiding studies with non-representative sample at local level, at least, or those with a large margin of error.

Additionally, studies that assessed only specific subgroups not representative of its geographical strata were considered ineligible. Systematic reviews, narrative reviews, clinical trials, case-control and case reports studies, as well as studies using overweight/obesity diagnostic criteria for adults were excluded from this review. Studies in English and Portuguese were included. A third investigator (FVC) solved disagreements between reviewers.

Data extraction

Two pairs of reviewers (MS and MRG; JAR and MM) separately evaluated the studies for data extraction. Titles and abstracts were reviewed and publications were selected for reading in full if they presented data according to the inclusion/exclusion criteria or had insufficient information in the abstract to make a decision. Studies from the same population were assessed and the article with more details was included. In relation to studies with insufficient information, a request was sent to the authors; if they did not reply, the study was excluded from this review.

Data were entered in a pretested Microsoft Office Excel™ spreadsheet based on the Strengthening in Epidemiology Statement (STROBE) checklist[15]. The absolute, rather than relative value of each variable, was obtained. Any discordance between the data extracted was discussed until consensus was reached. Captured variables included: study name, date of publication, year of data collection, study design and type (household survey, school-based survey, etc), age range, region, diagnostic criteria for overweight and obesity and estimated prevalence of overweight and obesity (overall and by sex).

Risk of bias

We assessed the risk of bias for each selected study using a 10-item tool that was specifically developed for population-based prevalence studies[16]. The tool is divided in two domains – external validity (four items) and internal validity (six items). After evaluation of the 10 items, each item received a score of 1 (yes) or 0 (no). According to overall scores, a

summary assessment deemed a study to be at low (9-10), moderate (6-8) or high (≤5) risk of bias.

Statistical analysis

Random effect models were used to calculate all pooled estimates of prevalence and their 95% confidence interval (95% CI). Results are presented by decades (before year 2000, years 2000 to 2009, and year 2010 and after). Sensitivity analyses were performed by sex, age group, macroregion and diagnostic criteria. Double arcsine transformation was used to handle distribution asymmetry related to different prevalence measures[17]. Continuity correction was used for adjustment when a discrete distribution was approximated by a continuous distribution. Pooled values were then converted to prevalence. Chi-square test was used to determine differences in prevalence rates among different decades. The Cochran chi-square and I^2 tests were used to evaluate statistical heterogeneity and consistency among the studies. Values of I^2 higher than 50% were considered an indication of high heterogeneity; however, high heterogeneity is expected in meta-analysis of prevalence studies. Statistical analyses were performed using MetaXL (Epi-Gear International, Sunrise Beach, Australia), an Excel-based comprehensive program for meta-analysis.

RESULTS

The search retrieved 10,144 articles in four databases, of which 4,032 were duplicates and were excluded. Additional 5,099 articles were removed based on title and abstracts, and 1,013 full-text articles were assessed for eligibility, of which 151 (9,187,431 individuals) met all the inclusion criteria (Figure 1).

The main characteristics of the included studies are described in Table S2. Most studies had cross-sectional design (146 studies, 97%). Sample sizes varied substantially with a median of 1,009 adolescents. Few studies collected the data before the 2000s (9 studies, 6%). The most used criteria to define overweight or obesity was from the World Health Organization (80 studies, 53%).

A meta-analysis was conducted according to the excess weight category and temporal trends by decades. Changes in the prevalence of excess weight over time and by Brazilian regions are shown in Figure 2. The overall prevalence of overweight/obesity, overweight and obesity was 20.6% (95%CI: 19.6-21.5, I^2 100%), 14.5% (95%CI: 13.5-15.4, I^2 100%) and 6.6% (95%CI: 6.2-7.0, I^2 100%), respectively. In trend analyses, we observed a significant increase

in the prevalence of overweight/obesity in the last decades [8.2% (95%CI: 7.7-8.7, I^2 100%) until 2000s, 18.9 (95%CI: 14.7-23.2, I^2 100%) in the 2000s, and 25.1% (95%CI: 23.4-26.8, I^2 98%) in the 2010s]. Similar results are observed for the trends in the prevalence of overweight and obesity when analyzed separately. Complete forest plots for overweight/obesity, overweight and obesity, showing all studies included, can be found on the Figures S1, S2 and S3.

In relation to regional estimates, only the Northeast and Southeast regions had data available before year 2000 invalidating comparisons among regions at this time. Between years 2000 and 2009 and after 2010, the Northeast had the lowest prevalence of weight excess, overweight and obesity compared to the other regions. A small number of studies from the Midwest and North regions were included in the last two time periods. The highest prevalence of all weight groups in years 2010 and after was found in the Southeast region, followed by the South region (Figure 2).

Prevalence rates of excess weight category and their 95%CI by sex, age group and diagnostic criteria are presented in Table 1. The overall prevalence of overweight and obesity was similar among sexes, except for studies before year 2000, for which females had a higher prevalence of weight excess. Studies that enrolled older adolescents and those adopting International Obesity Task Force (IOTF) cutoff points after year 2000 reported lower prevalence ratios of weight excess compared to other categories. High statistical heterogeneity was identified in all analyses.

Risk of bias assessment is presented in Table S3. Overall risk of bias was considered low in 108 studies (71.5%), moderate in 42 studies and high in 1 study. All studies had data collected using the same mode and directly from the subjects, had an acceptable case definition, measured the parameter of interest with an instrument shown to have validity and reliability, and had appropriate numerators and denominators for the parameter of interest. Most studies selected a population that was nationally representative in the parameters of interest (66.9%) and had a sampling frame representative of the target population (88.7%). A census or a random form of selection were used in 115 studies (76.2%) and the likelihood of nonresponse bias was minimal in 77 studies (51.0%).

DISCUSSION

In this systematic review, we identified 151 studies reporting rates of weight excess in Brazilian adolescents, with data collected from 1974 to 2018. Prevalence of weight excess ranged from to 2.2% to 44.4%, and an increase could be seen when comparing information from more recent to older studies. Populations were included from household surveys, birth cohorts and school-based samples, and only 12 studies included individuals from more than one macroregion in Brazil.

Individual cross-sectional studies have hinted the rising trends of overweight and obesity among this age group in different countries[18, 19], but representative data of trends about the prevalence of overweight and obesity among Brazilian adolescents were limited. To fill this gap, we performed a systematic review focused on adolescents from all regions in Brazil and we show separate data by decades of data collection. In general, we observed an increase in the prevalence of overweight and obesity among Brazilian adolescents since the 70s. The high statistical heterogeneity found was expected, as previous meta-analysis of prevalence studies showed[12, 20]. In our analysis, the heterogeneity can be due to differences between samples of the studies in many characteristics, such as age (some included adolescents from all ages, others only those with 10 to 13 years or 17 and older), ethnic background (some were made with indigenous populations), criteria for excess weight (five different classifications were observed) and type of study (school-based, household survey or cohort).

In the last decades, Brazil and other middle-income countries have experienced a quick transition in food availability and eating habits. Until recently, the most prevalent nutritional problem in Brazilian children and adolescents was underweight/undernutrition, especially in the poorer and less developed regions of the country[21]. However, due to a rapid industrial expansion and changes in lifestyle (such as increase in sedentary time[22] and consumption of ultra-processed foods[23]), a double disease burden can be seen – undernutrition is still present in many areas, but obesity related health problems are higher than ever[24]. Countries like India and China, which also underwent significant socioeconomic changes in a small amount of time, have similar growing trends in weight excess in youth. From the 80s to the last 10 years, for an example, overweight rates increased from 1.8% to over 13% in Chinese children and adolescents[25].

In this systematic review, we present an overall prevalence of weight excess from studies that have adopted different criteria to classify adolescents with overweight and obesity,

two of them specifically made using only Brazilian children[26, 27]. Classification based on WHO references[28] was the most commonly used, especially in studies published since 2009. Criteria by IOTF for overweight/obesity[29] was the preferred before year 2000**.** It is possible to consider that adding prevalence from diverse cutoffs is a limitation and could lead to imprecise results; however, the prevalence for overweight/obesity still exponentially increased in last decades when we analyze separately studies that used WHO reference curves (4.4% until year 2000 to 26.6% in the 2010s) and IOTF criteria (9.2% to 21.7%), despite including a smaller number of articles.

In subgroup analysis, the prevalence of weight excess varied greatly among macroregions, reflecting the health inequalities between them. In the literature, many studies show that associations between socioeconomic status and rates of obesity depend on local characteristics – people with higher socioeconomic status (SES) are less likely to be overweight or obese in high-income countries, but more likely in lower-income countries[30]. In a continental size country such as Brazil, it is important to address how significant differences among regions can influence nutritional patterns. In our study, we found a positive association between SES and rates of weight excess comparing regions – prevalence was lower in the northeast region across all decades and higher in the south and southeast regions in the last decade. States from the northeast region have the lowest Human Development Index (HDI) in the country, and nutritional transition at these places is relatively recent or concurrent, with underweight still being an important public health concern. Conversely, at the south and southeast regions, comprising states that have the highest HDIs of the country, these changes were observed decades ago, and ultra-processed foods are more easily accessible[24, 31]. This dietary pattern has been previously reported in adolescents - in the ERICA study, higher SES was associated with greater consumption of unhealthy foods, such as sugary drinks and snacks[32].

The prevalence of overweight/obesity in this study was similar and increased across decades in both sexes; however, girls had higher rates of weight excess before year 2000 (11.9% *vs* 4.6%). This can be partially explained due to the fact that, in this period, two big studies included only boys at older age (17 to 19 years) from the Brazilian Army database. Similar results by gender are observed in a recent country-wide survey in Brazil[33], supporting that prevention polices against obesity should be conducted independently of sex. Finally, analyses comparing group ages showed that younger adolescents had higher prevalence of weight excess compared to their older counterparts. This can be directly related to puberty and

its effect on acquisition of fat free mass, reaching the highest levels at peak height growth velocity[34].

Treatment of obesity in a health system usually involves recommendation of lifestyle modifications (increase physical activity, decrease sugar and fat consumption), pharmacological therapy and, in selected cases, bariatric surgery. Nevertheless, obesity rates continue to grow alarmingly worldwide. This can be attributed to the fact that the "pressure" from the obesogenic environment is still the same, and therefore interventions should also try to change socioeconomic, political and cultural context involving weight excess. Efforts such as clear nutritional labeling in packages or decrease in percentual of fats are commonly accepted by decision-makers and food industry. However, regulation of food advertising, taxing or banning energy-dense and nutrition-poor foods sold in schools find a barrier for implementation, mostly due to commercial interests[35]. Actions for prevention of obesity during childhood also involve the same modifications in public policies. Only when obesity is approached in an interdisciplinary way beyond the health sector, we will have a real chance of altering its repercussions later in life.

Nonetheless, it is important to consider regional access to healthcare services and economical power when defining prevention strategies, as they vary greatly between Brazilian regions. Populations from the north and northeast regions, especially those with lower SES, have more difficulty in reaching the healthcare system, and when they do, resources are scarce[36]. Additionally, access to healthy foods, such as vegetables and fruits, can be limited, as they have higher prices compared to ultra-processed foods. In contrast, adolescents from the south and southeast regions have higher prevalence of excessive screen[22] and sitting time[37], as well as higher access to physical education classes. These inequity patterns show that there is no simple or single solution to tackle this health problem in Brazil. Public policies need to be specific for each region, considering their strengths and weaknesses, in order to be effective. In the south and southeast, the higher accessibility to infrastructure (sports courts, tracks, swimming pools) can be used to diminish sedentary behavior and to promote physical activity; while in the north and northeast it is essential to improve nutritional composition and overall access to healthcare services.

Our study has some limitations. The number of studies from before the 2000s was much smaller than those from other decades, and more than half were composed by adolescents from the Southeast region of Brazil; therefore, the prevalence from this period may not be accurate.

There was also a low representation of individuals from the North and Midwest regions, especially before 2010. This poor coverage of epidemiological changes in some Brazilian regions restricts the evaluation of national prevalence of weight excess over time. Further studies in these macroregions are required to correctly demonstrate racial, cultural, and socioeconomic diversity of this nation. Differences and changes in diagnosis criteria over time among the studies may also limit the interpretation of our results. High heterogeneity was found in all analyses; however, this is expected when gathering results from more than a hundred studies that used multiple criteria and included individuals from different regions and age groups.

CONCLUSIONS

Despite inherent limitations from gathering data of studies from a continentally sized country such as Brazil, our findings can be considered the most recent trend estimates of weight excess in adolescents, and they clearly show that the prevalence of overweight and obesity are alarmingly increasing in recent years. This situation warrants public health interventions, which should be based mainly on prevention of overweight during the adolescence and its health consequences later in life.

FIGURE LEGENDS

FIGURE 1. Flow diagram of study selection.

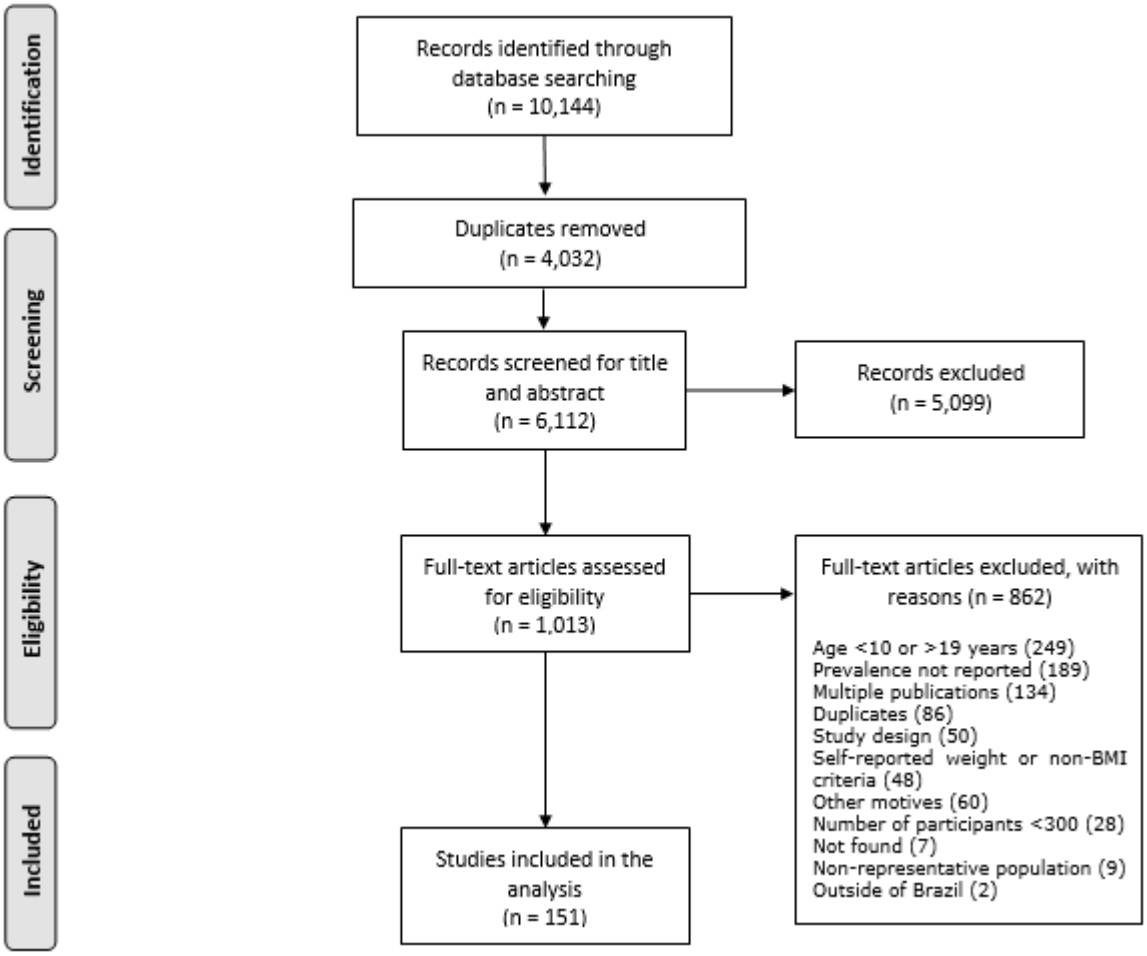


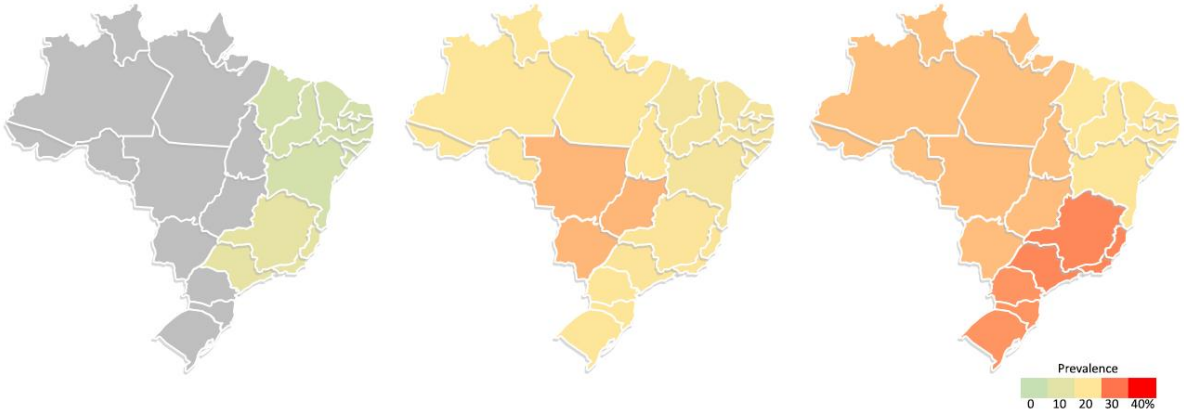
FIGURE 2. Prevalence of weight excess (overweight/obesity), overweight and obesity by time period in Brazilian macroregions. **Weight excess:** a) Before year 2000: Northeast (n=3, 5.3%; 95%CI 2.5-8.9, I^2 99%), Southeast (n=8, 11.9%; 95%CI 6.5-18.1, I^2 99%). b) Years 2000 to 2009: North (n=3, 19.4%; 95%CI 13.5-25.7, I^2 98%), Northeast (n=14, 16.4%; 95%CI 13.9-19.1, I^2 97%), Midwest (n=2, 24.2%; 95%CI 17.9-30.9, I^2 97%), Southeast (n=27, 19.1%; 95%CI 16.7-21.6, I^2 98%), South (n=23, 19.6%; 95%CI 16.5-22.9, I^2 98%). c) Years 2010 and after: North (n=5, 23.3%; 95%CI 21.3-25.5, I^2 82%), Northeast (n=18, 19.6%; 95%CI 17.0-22.5, I^2 97%), Midwest (n=4, 23.6%; 95%CI 22.2-25.1, I^2 51%), Southeast (n=19, 28.2%; 95%CI 25.8-30.6, I^2 95%), South (n=28, 27.1%; 95%CI 24.2-30.0, I^2 97%). **Overweight:** a) Before year 2000: Southeast (n=4, 9.0%; 95%CI 3.5-15.5, I^2 98%). b) Years 2000 to 2009: North (n=2, 17.7%; 95%CI 9.6-26.8, I^2 97%), Northeast (n=10, 11.7%; 95%CI 9.8-13.7, I^2 94%), Midwest (n=2, 16.4%; 95%CI 12.8-20.1, I^2 93%), Southeast (n=21, 13.6%; 95%CI 12.1-15.2, I^2 95%), South (n=13, 16.1%; 95%CI 13.9-18.3, I^2 94%). c) Years 2010 and after: North (n=2, 15.2%; 95%CI 14.7-15.8, I^2 0%), Northeast (n=14, 12.9%; 95%CI 11.1-14.8, I^2 94%), Midwest (n=4, 15.6%; 95%CI 14.3-17.0, I^2 59%), Southeast (n=12, 19.4%; 95%CI 18.1-20.8, I^2 85%), South (n=18, 17.1%; 95%CI 15.3-19.1, I^2 94%). **Obesity:** a) Before year 2000: Southeast (n=3, 2.9%; 95%CI 1.3-4.8, I^2 90%). b) Years 2000 to 2009: North (n=2, 5.2%; 95%CI 4.0-6.5, I^2 59%), Northeast (n=10, 4.5%; 95%CI 2.9-6.3, I^2 97%), Midwest (n=2, 7.8%; 95%CI 5.1-10.7, I^2 93%), Southeast (n=23, 6.6%; 95%CI 5.2-8.1, I^2 97%), South (n=15, 6.7%; 95%CI 5.3-8.3, I^2 95%). c) Years 2010 and after: North (n=3, 6.9%; 95%CI 5.8-8.1, I^2 20%), Northeast (n=15, 6.0%; 95%CI 4.9-7.2, I^2 93%), Midwest (n=5, 8.4%; 95%CI 7.1-9.8, I^2 79%), Southeast (n=12, 9.8%; 95%CI 7.9-11.9, I^2 97%), South (n=19, 8.7%; 95%CI 6.7-10.9, I^2 98%).

WEIGHT EXCESS

BEFORE YEAR 2000
Overall prevalence: 8.2% (95%CI 7.7-8.7)
I^2=100%

YEARS 2000 TO 2009
Overall prevalence: 18.9% (95%CI 14.7-23.2)
I^2=100%

YEARS 2010 AND AFTER
Overall prevalence: 25.1% (95%CI 23.4-26.8)
I^2=98%



OVERWEIGHT

BEFORE YEAR 2000
Overall prevalence: 3.3% (95%CI 3.0-3.7)
I^2=99%

YEARS 2000 TO 2009
Overall prevalence: 14.0% (95%CI 9.9-18.3)
I^2=100%

YEARS 2010 AND AFTER
Overall prevalence: 16.4% (95%CI 15.3-17.4)
I^2=95%

OBESITY

BEFORE YEAR 2000
Overall prevalence: 2.4% (95%CI 2.1-2.6)
I^2=99%

YEARS 2000 TO 2009
Overall prevalence: 6.0% (95%CI 4.6-7.4)
I^2=100%

YEARS 2010 AND AFTER
Overall prevalence: 8.0% (95%CI 7.0-9.0)
I^2=97%

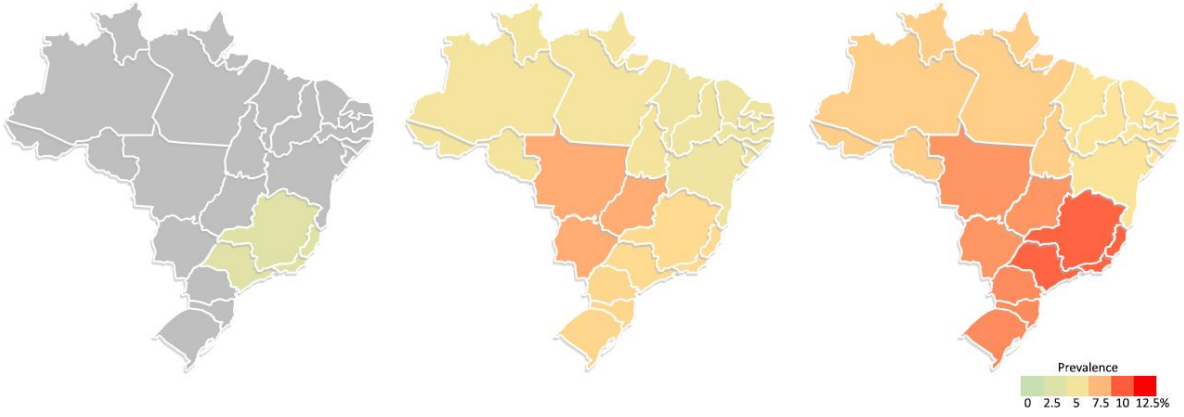


Table 1. Subgroup meta-analyses of weight excess, overweight and obesity by decades.

Variables	Time trends								
	Before 2000			2000 – 2009			2010 and after		
	N	% (95%CI)	I^2%	N	% (95%CI)	I^2%	N	% (95%CI)	I^2%
Weight excess (overweight/obesity)									
Sex									
Female	10	11.9 (8.4-15.7)	99	46	19.2 (17.7-20.7)	96	40	23.8 (22.1-25.5)	95
Male	13	4.6 (4.4-5.0)	99	46	20.7 (14.9-26.8)	100	39	24.8 (22.4-27.1)	97
Age group, years									
10 to 14	1	-	-	26	20.5 (18.1-23.0)	98	17	28.3 (24.6-32.0)	98
15 to 19	5	4.7 (4.4-5.1)	99	19	14.2 (9.0-19.8)	100	12	18.0 (15.3-20.9)	97
Diagnostic criteria									
IOTF	7	9.2 (5.7-13.1)	99	23	17.2 (15.0-19.6)	97	16	21.7 (19.1-24.3)	95
Must	1	-	-	3	21.1 (17.8-24.6)	87	-	-	-
Conde and Monteiro	-	-	-	8	22.3 (18.4-26.4)	98	5	26.1 (14.8-38.4)	99
WHO	4	4.4 (4.1-4.7)	99	33	19.3 (13.0-26.1)	100	45	26.6 (24.3-28.9)	98
CDC	1	-	-	5	16.9 (10.4-24.0)	98	5	21.9 (18.0-26.0)	92
Overweight									
Sex									
Female	3	10.9 (3.9-19.2)	95	28	14.7 (13.3-16.2)	94	22	16.4 (15.2-17.7)	90
Male	6	2.3 (2.1-2.6)	99	29	13.8 (8.3-19.7)	100	22	15.3 (13.7-16.9)	94
Age group, years									
10 to 14	1	-	-	18	15.4 (13.2-17.7)	98	10	17.8 (15.2-20.4)	96
15 to 19	4	1.8 (1.7-2.0)	99	10	10.7 (4.3-18.1)	100	8	12.6 (10.2-15.1)	93
Diagnostic criteria									
IOTF	2	14.5 (11.4-17.8)	72	16	14.2 (12.4-16.1)	92	9	14.5 (12.3-16.8)	92
Must	-	-	-	2	13.6 (12.0-15.2)	46	-	-	-
Conde and Monteiro	-	-	-	6	19.5 (17.5-21.6)	92	2	11.7 (6.0-18.3)	93
WHO	3	1.7 (1.6-1.8)	98	23	13.1 (7.5-19.2)	100	33	17.7 (16.7-18.9)	93
CDC	1	-	-	4	11.5 (4.3-20.0)	98	3	11.1 (10.4-12.1)	0
Obesity									
Sex									
Female	2	4.2 (3.1-5.3)	0	32	6.1 (5.3-6.9)	92	23	6.5 (5.6-7.5)	93
Male	5	2.2 (2.0-2.5)	99	33	6.6 (4.6 -8.8)	100	23	7.8 (6.3-9.3)	97
Age group, years									
10 to 14	1	-	-	19	6.5 (5.0-8.1)	98	11	9.7 (7.2-12.5)	98
15 to 19	4	2.2 (1.9-2.5)	100	10	3.4 (1.9-5.2)	98	9	5.3 (4.0-6.6)	91
Diagnostic criteria									
IOTF	1	-	-	18	4.9 (3.8-6.1)	93	9	4.9 (3.7-6.2)	91
Must	-	-	-	2	7.4 (3.9-11.8)	94	-	-	-
Conde and Monteiro	-	-	-	6	5.3 (3.5-7.4)	97	2	3.3 (2.0-4.9)	64
WHO	3	2.2 (1.9-2.5)	100	24	6.7 (4.4-9.3)	100	33	9.4 (8.3-10.6)	97
CDC	1	-	-	5	6.5 (2.4-11.5)	96	3	7.0 (6.4-7.8)	0

IOTF, International Obesity Task Force; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention.

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ARTIGO 2 - Severity of obesity is associated with worse cardiometabolic risk profile in adolescents: findings from a Brazilian national study (ERICA)

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Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to issues in making them accessible online, such as storage difficulties. However, the datasets are available on reasonable request to the corresponding author.

ABSTRACT

Background: The prevalence of obesity and severe obesity among adolescents has increased dramatically in developing countries. However, the distribution of cardiometabolic risk factors through the severity of obesity continuum is relatively unknown among youth.

Objective: To evaluate the association of weight categories with cardiometabolic risk factors among Brazilian adolescents.

Methods: The Study of Cardiovascular Risk in Adolescents - ERICA, was a multicenter, school-based, cross-sectional study composed of Brazilian adolescents (12-17 years). Severity of obesity was classified according to the IOTF reference values for body mass index (BMI) and several cardiometabolic risk factors were measured after clinical and biochemical exams and categorized using standard definitions of abnormal values.

Results: Among the 37,892 adolescents enrolled, 8,708 had weight excess, being classified with overweight (17.2%), obesity (5.6%) and severe obesity (1.3%). Increasing severity of obesity was associated with a worse cardiometabolic profile in the overall sample. Multivariable models that controlled for age, sex, skin color, socioeconomic status, physical activity and total energy intake, showed that individuals in higher categories of severity of obesity tended to have higher prevalence ratios of most cardiometabolic risk factors compared to the other weight groups; except for high fasting blood glucose among boys.

Conclusions: Progressive degrees of weight excess are positively associated with cardiometabolic risk factors in youth from a middle-income country, indicating the importance in classifying the severity of weight excess among adolescents and considering this to plan prevention programs against early development of obesity related disease.

Introduction

Obesity in children and adolescents has exponentially increased in the last decades, rising from 0.8% in 1975 to over 6.8% in 2016 [1]. The same tendency can be seen in Brazil, where the prevalence of overweight and obesity in adolescents increased six times in boys (4% to 28%) and three times in girls (8% to 23%) since the 70's [2, 3]. Severe obesity is the fastest growing subcategory of excess weight in adolescents, reaching more than 4% of all youth in the United States [4].

Weight excess in youth can lead to the development of many cardiovascular risk factors that, if not early controlled, tend to persist and increase the risk for early cardiovascular disease in adult life [5-7]. Cardiometabolic risk factors such as abnormal glucose levels, dyslipidemia, and hypertension are more prevalent in obese adolescents than in those with normal weight [8, 9]. These conditions are associated with higher risk of coronary heart disease, stroke, diabetes mellitus and all-cause mortality in adulthood [10]. Weight reduction, however, can significantly change these outcomes [11].

Data from a systematic review showed that the risk of mortality by all causes in adults with severe obesity (class II and III) is higher than in those with overweight or class I obesity [12]. In adolescents classified within the obese category, there is a variety of risks accompanying increases in BMI; however, this association is still being investigated [11, 13-17]. In the United States, results from the *National Health and Nutrition Examination Survey* (NHANES) 1999/2012, which included 8.579 children and adolescents with excessive weight, showed that having severe obesity lead to an increased risk of low levels of high-density lipoprotein cholesterol (HDL-c), high systolic and diastolic blood pressure, and high levels of triglycerides and glycated hemoglobin (HbA1c) [13]. Furthermore, differences by age, sex and ethnicity were also observed in the relation between severity of obesity and cardiometabolic risk in youth [13, 16].

In some low- and middle-income countries where quick nutritional transitions were observed in the last decades [18, 19], the severity of obesity and its associated comorbidities among young people were insufficiently explored. Investigating the association between severity of obesity and cardiometabolic risk factors in Brazil can help us identify the individuals at higher risk groups and develop public health strategies against obesity-related outcomes early in life, which would apply to other low and middle-income countries. Thus, the objective of this study was to evaluate the association of severity of obesity and known cardiometabolic risk factors in a representative sample of Brazilian adolescents.

Methods

Design and sample

The Study of Cardiovascular Risk in Adolescents (*Estudo de Riscos Cardiovasculares em Adolescentes, ERICA*) was a multicenter, school-based national cross-sectional study carried out in urban and rural settings in Brazil. The sample was composed of students between 12 and 17 years old enrolled in private and public schools in Brazilian municipalities with at least 100,000 inhabitants. Data were collected between February 2013 and November 2014.

A complex sampling approach was performed. Thus, the population target was divided into 32 geographic strata: all 26 state capitals, the Federal District, and five more strata representing other municipalities with at least 100,000 inhabitants in each region of Brazil. The schools were selected based on probability proportional to size (number of students per school) and inversely proportional to the distance between the school municipality and the state capital. In total, 1,247 schools in 124 municipalities were selected. Three classrooms were randomly selected from each school, and all students in these classes were invited to participate in ERICA. Further details regarding the sampling and design of the ERICA project can be read in previous publications [20, 21]. The participation rate for adolescents who completed the questionnaires, anthropometric measures and blood sampling in ERICA was 52% [22].

In summary, ERICA's sample size calculation was performed considering that the prevalence of metabolic syndrome in adolescents is around 4%, a maximum estimation error of 0.9% and a 95% confidence level, the required size for a simple random sample would be 1,821 students. However, considering that the sample is clustered by school, shift, grade and class, a design effect of 2.97 was considered. In addition, sample size was increased in 15% considering possible non-response and other losses. Finally, the calculation showed that was necessary to enroll 6,219 adolescents in each of the 12 domains (6 ages x 2 sexes), resulting in a total sample size of at least 74,628 adolescents [20].

For this study, we used data from students who attended school during the morning (925 schools), as overnight fasting was mandatory for the blood sampling. The final available sample size for this study was 37,892. The study was approved by the Research Ethics Committees in all 27 federation units in Brazil. All subjects and their legal guardians provided written informed assent/consent to participate in the study.

Severity of obesity

Body mass index [BMI = weight (kg)/height (m^2)] was used to assess the severity of

obesity. Weight and height were measured using a digital scale and a portable stadiometer, respectively. Both measures were taken with adolescents in light clothing and without shoes. The assessed anthropometric measures were performed following standard practices [23]. The severity of obesity was defined according to sex and age-specific cut-off points recommended by the International Obesity Task Force (IOTF) [24]. The BMI IOTF cut-offs for youth were calculated to represent BMI centile corresponding to BMI at age 18 years old (i.e., Overweight ≥ 25kg/m² and < 30kg/m²; Obesity ≥ 30kg/m² and < 35kg/m²; and Severe Obesity ≥ 35kg/m²). The IOTF specific cut-off points of BMI for sex and age were previously published and can be accessed elsewhere [24, 25].

Cardiometabolic risk factors

Blood pressure was verified using a digital monitor (Omron 705-IT) previously validated for use in youth [26]. Blood pressure was taken from each student's right arm using individual cuff sizes after five minutes sitting still, with an interval of at least three minutes between each measure. The average values of the second and third readings were used in the analyses. High blood pressure was defined as values of systolic or diastolic blood pressure ≥ 95th percentile for sex, age, and height [27].

All participants were asked to refrain from eating for at least 10–12 hours before the blood sampling. Compliance with the overnight fast was confirmed by a questionnaire before venipuncture. Fasting blood samples were collected for measuring fasting glucose, HbA1c, insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-c), HDL-c, and triglycerides. The reference values used to determine abnormal values of cardiometabolic variables are shown in Supplementary Table 1, which were in accordance with national and international guidelines [27-31]. All blood samples were analyzed by a single laboratory following a standardized protocol [32].

Metabolic syndrome was defined according to the International Diabetes Federation criteria [33]. These include a high waist circumference as a mandatory component (< 16 years: ≥ 90th percentile; ≥ 16 years, males: ≥ 90 cm; and ≥ 16 years, females: ≥ 80 cm), which was measured at midway between the iliac crest and the lower costal margin, and plus two or more of the following criteria: fasting plasma glucose ≥ 100mg/dl; systolic blood pressure ≥ 130mmHg and/or diastolic blood pressure ≥ 85mmHg; triglycerides ≥ 150mg/dl; HDL-c in adolescents < 16 years: < 40 mg/dl; HDL-c in males ≥ 16 years: < 40 mg/dl; and HDL-c in girls > 16 years: < 50 mg/dl.

Covariates

The covariates included in the analyses were sex, age (12-17 years) and self-reported skin color (white, black, brown or others). The socioeconomic status (SES) was assessed with a similar instrument used by the Brazilian Demographic Census [34], which takes into account possession of specific goods and the presence of a housekeeper at home. Thereafter, for some analyses, this variable was categorized in tertiles.

Statistical analysis

All estimates and their 95% confidence intervals (95%CI) were calculated using the ERICA's sample weights, taking into account the complex sample design and obtaining population-representative findings [20]. All the descriptive analyses were stratified by weight category (normal weight, overweight, obesity and severe obesity). The mean values and 95%CI for cardiometabolic risk factors were estimated for the overall sample. Triglycerides and fasting insulin do not follow a parametric distribution, thus, for this variable, median and interquartile range are presented.

The prevalence of abnormal cardiometabolic risk factors according to the severity of obesity was calculated for overall sample and stratified by sex and age groups (12-14 and 15-17 years old). The adjusted Wald's test for trend was calculated to evaluate the increase or decrease in the prevalence of abnormal cardiometabolic risk factors through the weight categories.

Poisson regression models were used to examine the association of severity of obesity (adolescents with normal weight were the reference group) with abnormal cardiometabolic risk factors. All models were adjusted for sex, age, skin color, socioeconomic status, physical activity and total energy intake; and the inclusion of these variables was decided *a priori* and is in accordance with the literature [13, 14, 16]. These analyses were performed for overall sample and by sex.

All tests were two-tailed, and the analyses were performed in Stata version 14 (Stata Corp., College Station, TX, USA) taking the study design (complex sample) into account. P-values < 0.05 denotes statistical significance. We followed the STROBE statement to prepare this report [35].

Results

Among the sample of 37,892 adolescents, 8,708 had weight excess, being classified with overweight (17.2%), obesity (5.6%) and severe obesity (1.3%). The mean age in the overall sample was 14.6 (standard error=0.01) years and was higher in severe obesity. Regarding to the prevalence of each weight category, we did not observe associations with sex and age group, however adolescents with brown (mixed) skin color showed a slightly lower prevalence of obesity e severe obesity, especially when compared with white (Table 1). Regarding the concentration levels of the cardiometabolic risk factors, HDL-cholesterol decreased and all other increased through the weight categories. Similarly to the observed in the overall sample, when the analysis was stratified by sex, both boys and girls with higher severity of obesity showed a poor cardiometabolic profile (data not shown).

Figure 1 shows the prevalence of abnormal cardiometabolic risk factors according to the severity of obesity. There was an increase in the prevalence of higher levels for blood pressure, total and LDL-c, triglycerides, HbA1c, fasting plasma glucose, fasting insulin and metabolic syndrome with increasing severity of obesity ($p<0.01$ for all). The prevalence of low HDL-c levels was proportional to increase in severity of obesity ($p<0.01$).

Table 2 shows the prevalence of abnormal values for cardiometabolic risk factors by sex and age group. The prevalence of most risk factors increased by severity of obesity in both sexes; however, this association was not significant for high fasting plasma glucose in males. Boys in all weight categories had a significantly higher prevalence of low HDL-c compared with girls. Girls with normal weight and overweight, compared with boys in the same respective weight category, had higher prevalence of abnormal levels of total and LDL cholesterol, but lower of elevated HbA1c and high blood pressure. Difference in prevalence between sexes in the obesity and severe obesity groups were discreet. When the data was analyzed by age, increasing severity of obesity was correlated with higher presence of all cardiometabolic risk factors in both age groups, except for fasting plasma glucose in 12-14 years adolescents.

Excluding adolescents with normal weight (in which less than 0.1% had metabolic syndrome), the prevalence of metabolic syndrome increased along with severity of obesity in both sex and age categories (not shown). Overall the prevalence of metabolic syndrome was 4.7% (95%CI: 3.7% - 5.9%), 23.8 (95%CI: 19.6% – 28.6%), 30.5% (23.3% - 38.8%) among adolescents with overweight, obesity and sever obesity, respectively.

Table 3 shows the prevalence ratios for the abnormal cardiometabolic risk factors adjusted for sex, age, skin color, socioeconomic status, physical activity level and total energy

intake. Prevalence ratios of the majority of cardiometabolic risk factors tended to increase with higher severity of obesity in the overall sample. Among sexes, the same association was found, except for high fasting plasma glucose in boys (p for trend = 0.579). Prevalence of metabolic syndrome, compared to adolescents with overweight, was significantly higher among those with obesity or severe obesity in the overall sample and in both sexes.

Discussion

Our study, involving 37,892 Brazilian youth, showed that severe obesity should be considered a public health concern due to the observed prevalence and suggests that there is a positive association between severity of obesity and worst cardiometabolic profile in this age group. In 2013, the American Heart Association released a scientific statement recommending the division of childhood obesity in three classes (class I, III and III) [15]. It was justified by greater precision for categorizing this population and better identification of individuals with higher number of cardiovascular risk factors. However, the Brazilian Ministry of Health still recommends stratification of childhood obesity in only two classes, following WHO 2007 reference [36, 37].

Our adjusted models show that increasing weight excess severity tends to be accompanied with concomitantly rise in the prevalence of cardiometabolic risk factors. However, in other populations such as in high income countries, the obesity-related cardiometabolic risk factors can differ. A Korean study with 1,326 adolescents showed a correlation with obesity level for all studied variables except fasting plasma glucose and diastolic blood pressure [14]. On the other hand, in North-American children and adolescents, only systolic blood pressure, HDL-c and fasting plasma glucose levels were related to severity of obesity [13]. These divergent results may be explained by different cutoffs for abnormal values used in both studies, a much broader age inclusion criteria (3 to 19 years) in the study from the USA, and differences in the socioeconomic parameters of the populations. It can also be related to specific diet patterns and sugar consumption in each region – countries from the Americas have the highest intake of sugar-sweetened beverages; while those from Asia have the lowest [38].

In ERICA, the prevalence of cardiometabolic risk factors increased with obesity class in both sexes, except for fasting plasma glucose in males. Low HDL-c was more prevalent in males than in females across all weight categories, just as elevated blood pressure and high Hb1Ac. Girls tended to have more elevated insulin than boys. Furthermore, in our study,

differences between sexes were more prominent in the normal weight and overweight groups; whereas in those with obesity and severe obesity they were subtle. Data regarding these associations by sex are still controversial. During puberty, due to changes in hormonal levels, body fat percentage increases in girls and decreases in boys [39]. A study in Italian youth with obesity showed that girls were more insulin resistant, had higher body fat percentage and lower lean body percentage than boys, independently of Tanner stage [40]. Previous studies also showed that Brazilian girls are more physically inactive [41], eat snacks more frequently in front of the television [42] and have diets with higher levels of sugar than boys [43], all factors that could contribute to higher insulin resistance in this group.

A graded relationship between severity of obesity and unfavorable cardiometabolic profile were found in participants on both age groups (12-14 and 15-17 years), without a significant difference between them. Our findings disagree from those of Lambert et al, in which older adolescents were more likely to have higher number of cardiometabolic risk factors in comparison with those younger, especially boys [44] – however, only youths with 9, 13 and 16 years of age were included in the study, and obesity was used as a single category, not divided in classes of BMI. Prior work has also shown that older adolescents were more likely to have metabolic syndrome and its components than their younger counterpart, mostly due to the expected increase of visceral fat deposits with age [45]. Disproportions of pubertal stages among groups, independently of age, could help understanding these differences.

It is important to consider that obesity and its associated comorbidities are a considerable burden for health systems around the world. A systematic review with twelve studies from the United States estimated an annual medical expenditure per person with obesity of $1901 in 2014 USD, reaching nationally almost $150 billion [46]. In Brazil, studies have shown a yearly cost of diseases related with overweight and obesity of $2.1 billion, in which more than 40% were due to cardiovascular diseases and diabetes [47]. Considering that most children and adolescents with obesity remain in the same BMI category in adulthood, early strategies to prevent this disease and its related costs are usually cost-effective and should be stimulated [48, 49].

Treatment options for adolescents with severe obesity are initially based in lifestyle modifications, such as adhering to a healthy diet and increasing physical activity. However, this kind of intervention provides discrete short-term changes in weight, and individuals usually remain in the same BMI category [15]. Other treatments for obesity in adolescents involve

drugs (such as orlistat and sibutramine in Brazil) and bariatric surgery [50]. Although effective in weight loss and improvement of cardiometabolic risk factors, long-term effects of this procedure on morbimortality of adolescents are still unknown, owing to the short follow up time in previous studies. Due to the challenging aspects of treating adolescents with any class of obesity, it is important to establish preventive actions during childhood, finding new ways to promote change of unhealthy habits; or even during intra-uterine life, providing favorable conditions for fetal development [51].

Our study has some potential limitations. As it is a cross-sectional study, it is not possible to establish a causal relationship between severity of weight excess and cardiometabolic risk factors. However, considering previous studies [52], it is acceptable to think that increase of adiposity leads to a worse cardiometabolic profile, rather than the opposite. Smaller number of participants in the obesity and severe obesity groups (5.6% and 1.3% of the sample, respectively) could have led to imprecision, especially when subdividing in sex or age for subgroup analysis. Also, we did not plan to stratify adolescents by pubertal status, which has a known impact in metabolism changes such as glucose homeostasis and could account for differences in cardiovascular variables [16]. Nevertheless, the reliability of this self-referenced information is low, and it is reasonable to assume that age could be used as a surrogate since it accompanies puberty stage.

The main strength of our findings resides in the large, multiethnic and representative national sample of adolescents enrolled from a middle-income country. Data collection, anthropometric measures, and biochemical analysis were standardized and followed a specific protocol [21]. Regression models were adjusted for several possible confounding factors; and maintained the association between severity of obesity and worsening of cardiometabolic profile. Adolescents were also stratified in two classes of obesity rather than one, and results were compared with the normal weight group, further reinforcing the parallel of increasing cardiometabolic risk factors with severity of obesity.

Conclusion

Prevalence of obesity in adolescence is increasing exponentially in the last few years, emerging as an alarming health problem globally. This study is the first representative study with Brazilian adolescents showing that abnormal levels in biomarkers of cardiometabolic risk, such as lipids and glucose profile, appear to increase with severity of obesity. Worsening of

cardiometabolic profile accompanying BMI categories in adolescents from low- and middle-income countries indicate the need to stratify this population further and highlight the importance of public health strategies to stop progression to higher obesity classes and associated health problems.

Figures

Figure 1: Prevalence of abnormal cardiometabolic risk factors according to the severity of obesity. ERICA 2013-2014. Abbreviations: BP, blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin.

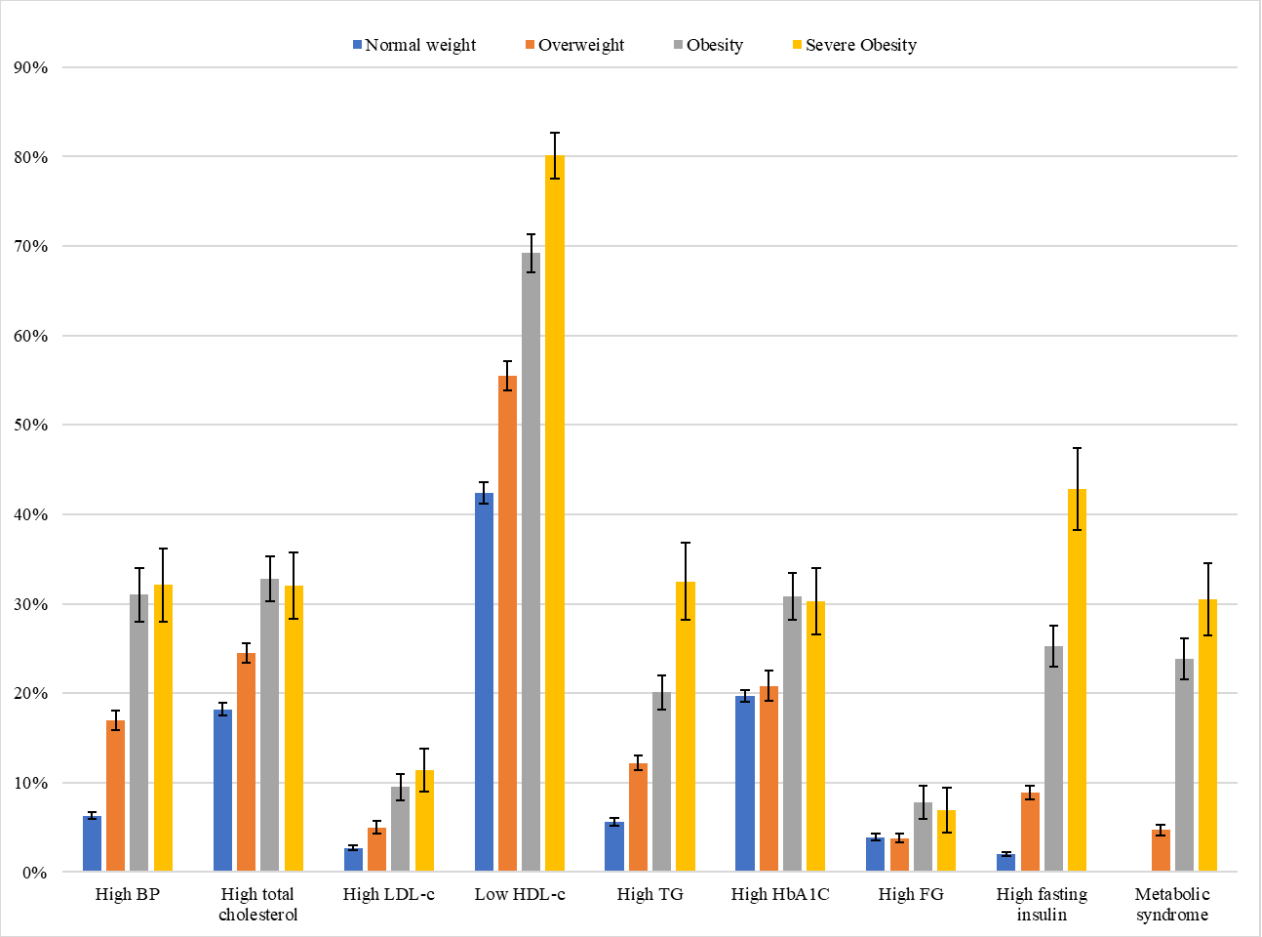

Table 1. Distribution of obesity severity, demographic and clinical characteristics among Brazilian adolescents. ERICA 2013-2014.

Characteristics	Normal weight	Overweight	Obesity	Severe obesity
	Weighted % (95%CI)			
Overall (n=37,892)	75.9 (74.5-77.2)	17.2 (16.2-18.3)	5.6 (5.1-6.2)	1.3 (1.1-1.5)
Sex				
Female	75.9 (74.0-77.8)	17.8 (16.3-19.4)	5.1 (4.5-5.7)	1.2 (0.9-1.5)
Male	75.0 (73.0-77.7)	16.6 (15.0-18.4)	6.1 (5.3-7.0)	1.3 (1.0-1.7)
Age (years)				
12-14	74.0 (71.4-76.5)	18.7 (17.0-20.6)	6.0 (5.2-6.9)	1.2 (0.9-1.6)
15-17	77.6 (75.9-79.1)	15.9 (14.7-17.3)	5.2 (4.4-6.1)	1.3 (1.0-1.6)
Skin color				
White	74.5 (72.5-76.5)	17.3 (16.0-18.7)	6.5 (5.6-7.7)	1.6 (1.2-2.2)
Black	75.3 (69.9-80.0)	17.8 (13.3-23.5)	5.2 (3.9-7.0)	1.6 (1.0-2.6)
Brown (mixed)	77.2 (75.3-79.1)	17.1 (15.6-18.7)	4.7 (4.0-5.5)	1.0 (0.8-1.2)
Others	74.8 (69.3-79.5)	17.0 (14.0-20.4)	7.5 (4.1-13.3)	0.8 (0.5-1.3)
SES (tertiles)				
1st	78.8 (77.0-80.5)	14.7 (13.3-16.3)	5.5 (4.6-6.5)	1.0 (0.7-1.4)
2nd	76.4 (73.6-78.9)	16.8 (15.1-18.6)	5.9 (4.7-7.3)	1.0 (0.8-1.3)
3rd (Higher)	71.9 (68.8-74.8)	20.8 (18.7-23.1)	5.4 (4.3-6.8)	1.9 (1.4-2.5)
Region				
North	79.9 (78.1-81.5)	14.9 (13.6-16.4)	4.1 (3.5-4.8)	1.1 (0.8-1.5)
Northeast	75.6 (72.9-78.2)	18.1 (16.1-20.4)	5.0 (4.3-5.8)	1.2 (0.9-1.6)
Southeast	76.2 (73.9-78.4)	16.8 (15.1-18.7)	6.0 (5.1-7.1)	1.0 (0.7-1.3)
South	71.5 (69.1-73.9)	19.9 (18.4-21.5)	6.0 (5.1-7.1)	2.5 (1.6-3.9)
Midwest	78.0 (76.6-79.3)	15.7 (14.6-16.8)	5.0 (4.3-5.7)	1.4 (0.9-2.1)
	Weighted mean (95%CI)			
Weight (kg)	52.4 (52.1-52.7)	69.1 (68.5-69.8)	83.7 (82.8-84.7)	101.9 (98.6-105.2)
BMI (kg/m²)	19.6 (19.5-19.6)	25.5 (25.4-25.5)	30.3 (30.1-30.5)	37.0 (36.4-37.6)
Waist circumference (cm)	68.1 (67.9-68.3)	81.0 (80.6-81.4)	93.2 (92.5-93.9)	105.8 (104.3-107.3)
SBP (mmHg)	109.2 (108.7-109.7)	117.0 (116.3-117.7)	121.5 (120.4-122.7)	121.7 (119.6-123.8)
DBP (mmHg)	65.5 (65.1-65.9)	68.3 (67.8-68.9)	71.6 (70.8-72.5)	72.6 (71.2-74.0)
Cholesterol (mg/dl)	146.8 (145.7-148.0)	151.2 (149.5-153.0)	156.1 (152.5-159.8)	160.4 (156.4-154.3)
LDL-c (mg/dl)	83.7 (82.9-84.5)	88.9 (87.4-90.4)	94.2 (91.2-97.2)	97.4 (94.3-100.4)
HDL-c (mg/dl)	48.3 (47.6-49.0)	45.2 (44.6-45.9)	41.5 (40.5-42.5)	38.8 (37.6-40.0)
Triglycerides[a] (mg/dl)	67.0 (66.0-68.0)	76.0 (74.0-78.0)	88.0 (81.1-94.9)	113.0 (102.2-123.8)
HbA1c (%)	5.38 (5.36-5.39)	5.39 (5.36-5.41)	5.48 (5.44-5.53)	5.52 (5.46-5.58)
Fasting insulin[a] (mU/L)	7.5 (7.3-7.7))	10.8 (10,5-11.1)	15.8 (15.1-16.5)	18.5 (16.2-20.8)
Fasting plasma glucose (mg/dl)	86.0 (85.5-86.4)	87.2 (86.6-87.8)	88.2 (87.3-89.1)	89.4 (87.7-91.1)

Abbreviations: SES, socio-economic status; BMI, body mass index; SBP, systolic blood pressure, DBP, diastolic blood pressure; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; HbA1c, Glycated hemoglobin; 95%CI, 95% confidence intervals. [a] Weighted median and interquartile range.

Table 2. Prevalence of cardiometabolic risk factors by severity of obesity and stratified by sex and age. ERICA 2013 – 2014.

Characteristics	Normal weight	Overweight	Obesity	Severe obesity	*p-value*
	Weighted % (95% CI)				
High blood pressure					
Sex					
Female	5.0 (4.1-6.2)	12.4 (10.4-14.7)	23.3 (16.5-31.7)	31.0 (20.5-43.9)	*<0.001*
Male	7.5 (6.6-8.6)	22.0 (18.1-26.5)	37.5 (29.7-45.9)	33.0 (22.4-45.6)	*<0.001*
Age (years)					
12-14	6.5 (5.4-7.8)	15.5 (13.2-18.2)	32.2 (25.6-39.6)	28.9 (18.5-42.0)	*<0.001*
15-17	6.1 (5.0-7.4)	18.5 (15.3-22.3)	29.8 (23.1-37.5)	34.7 (24.6-46.5)	*<0.001*
High total cholesterol					
Sex					
Female	23.8 (22.2-25.5)	28.9 (25.3-32.9)	30.4 (23.6-38.2)	30.8 (23.8-38.9)	*<0.001*
Male	12.6 (11.1-14.2)	19.8 (16.5-23.5)	34.8 (28.5-41.7)	32.9 (22.3-45.6)	*<0.001*
Age (years)					
12-14	18.9 (17.1-20.8)	24.6 (21.4-28.1)	32.9 (27.0-39.5)	33.6 (22.1-47.4)	*<0.001*
15-17	17.6 (15.9-19.6)	24.5 (21.6-27.7)	32.7 (26.3-39.7)	30.5 (23.1-39.1)	*<0.001*
High LDL-c					
Sex					
Female	3.5 (2.8-4.5)	6.5 (4.6-9.3)	8.1 (5.3-12.1)	10.5 (6.5-16.4)	*<0.001*
Male	2.0 (1.4-2.7)	3.4 (2.6-4.4)	10.7 (7.3-15.5)	12.1 (6.3-21.9)	*<0.001*
Age (years)					
12-14	2.8 (2.0-3.9)	5.0 (3.5-7.2)	10.2 (6.7-15.2)	11.2 (5.5-21.4)	*<0.001*
15-17	2.7 (2.2-3.3)	5.0 (3.6-7.0)	8.8 (6.0-12.8)	11.5 (7.3-17.8)	*<0.001*
Low HDL-c					
Sex					
Female	32.9 (30.4-35.6)	48.0 (44.8-51.2)	59.4 (51.2-67.1)	71.9 (63.5-78.9)	*<0.001*
Male	51.9 (49.4-54.3)	63.6 (58.8-68.1)	77.3 (71.3-82.4)	86.9 (78.0-92.5)	*<0.001*
Age (years)					
12-14	38.9 (35.8-42.1)	55.3 (50.1-60.3)	74.4 (68.6-79.5)	83.3 (74.0-89.8)	*<0.001*
15-17	45.3 (42.4-48.2)	55.7 (51.9-59.6)	63.9 (57.1-70.1)	77.3 (69.6-83.4)	*<0.001*
High triglycerides					
Sex					
Female	6.7 (5.8-7.8)	11.1 (9.3-13.1)	15.5 (11.7-20.4)	27.9 (20.2-37.1)	*<0.001*
Male	4.4 (3.3-5.7)	13.5 (11.2-16.3)	23.9 (19.2-29.3)	36.3 (24.7-49.8)	*<0.001*
Age (years)					
12-14	5.7 (4.8-6.7)	12.8 (10.8-15.1)	19.7 (14.9-25.6)	39.4 (26.3-54.2)	*<0.001*
15-17	5.4 (4.4-6.7)	11.6 (9.5-14.2)	20.6 (16.0-26.0)	26.4 (19.0-35.3)	*<0.001*
High HbA1c					
Sex					
Female	16.6 (15.0-18.4)	17.3 (14.8-20.1)	29.4 (23.0-36.8)	29.0 (21.3-38.3)	*<0.001*
Male	22.7 (20.8-24.8)	24.5 (20.1-29.5)	32.0 (24.7-40.3)	31.3 (20.9-44.2)	*0.010*
Age (years)					
12-14	22.1 (20.0-24.3)	22.6 (18.5-27.2)	35.8 (29.3-42.8)	32.2 (21.4-45.3)	*<0.001*
15-17	17.7 (16.1-19.4)	18.9 (14.8-23.8)	25.9 (19.5-33.4)	28.6 (20.6-38.3)	*0.002*
High fasting plasma glucose					
Sex					
Female	2.2 (1.7-2.9)	2.7 (1.8-3.8)	8.7 (4.1-17.6)	9.3 (3.4-22.9)	*<0.001*
Male	5.5 (4.3-7.2)	5.1 (3.5-7.4)	7.1 (3.7-13.0)	4.7 (2.0-11.0)	***0.802***

Age (years)					
12-14	4.7 (3.7-6.0)	3.4 (2.4-4.7)	8.5 (3.7-16.1)	8.4 (3.7-18.1)	***0.179***
15-17	3.1 (2.4-4.1)	4.3 (2.9-6.4)	7.1 (3.5-14.0)	5.6 (2.3-12.9)	*0.015*
High fasting insulin					
Sex					
Female	2.6 (2.0-3.4)	11.0 (8.9-13.6)	27.2 (21.7-33.5)	48.4 (37.4-59.6)	*<0.001*
Male	1.4 (1.0-2.0)	6.7 (5.0-8.8)	23.8 (18.3-30.3)	38.2 (26.7-51.2)	*<0.001*
Age (years)					
12-14	2.3 (1.8-3.0)	10.6 (8.4-13.1)	25.7 (19.5-32.9)	41.4 (28.8-55.3)	*<0.001*
15-17	1.8 (1.3-2.5)	7.2 (5.5-9.4)	25.0 (19.8-31.0)	44.0 (33.5-55.0)	*<0.001*

Wald's test for trends was used to obtain the p-values presented

Abbreviations: HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; HbA1c, Glycated hemoglobin.

Table 3. Adjusted* prevalence ratios for cardiometabolic risk factors by severity of obesity and sex in adolescents. ERICA 2013-2014.

Risk factors	Overall	Girls	Boys
	PR (95% CI)	PR (95% CI)	PR (95% CI)
High blood pressure	*p <0.001*	*p <0.001*	*p <0.001*
Normal weight	Reference	Reference	Reference
Overweight	2.8 (2.3-3.5)	2.5 (2.0-3.3)	3.0 (2.3-3.9)
Obesity	4.8 (3.9-6.0)	4.7 (3.3-6.8)	4.9 (3.9-6.3)
Severe obesity	5.2 (3.7-7.1)	6.3 (3.0-10.1)	4.5 (3.0-6.8)
High total cholesterol	*p <0.001*	*p <0.001*	*p <0.001*
Normal weight	Reference	Reference	Reference
Overweight	1.3 (1.2-1.5)	1.2 (1.1-1.4)	1.5 (1.3-1.9)
Obesity	1.8 (1.6-2.1)	1.3 (1.0-1.6)	2.8 (2.2-3.4)
Severe obesity	1.7 (1.4-2.2)	1.3 (1.0-1.7)	2.4 (1.6-3.5)
High LDL-c	*p <0.001*	*p <0.001*	*p <0.001*
Normal weight	Reference	Reference	Reference
Overweight	1.8 (1.3-2.6)	2.0 (1.3-3.1)	1.8 (1.2-2.6)
Obesity	3.5 (2.5-4.8)	2.4 (1.5-3.8)	5.3 (3.5-8.1)
Severe obesity	4.1 (2.6-6.4)	3.3 (1.9-5.8)	5.9 (3.0-11.8)
Low HDL-c	*p <0.001*	*p <0.001*	*p <0.001*
Normal weight	Reference	Reference	Reference
Overweight	1.3 (1.3-1.4)	1.5 (1.3-1.6)	1.3 (1.2-1.3)
Obesity	1.6 (1.5-1.8)	1.8 (1.6-2.1)	1.5 (1.4-1.7)
Severe obesity	2.0 (1.8-2.1)	2.2 (1.9-2.5)	1.8 (1.6-2.0)
High triglyceride	*p <0.001*	*p <0.001*	*p <0.001*
Normal weight	Reference	Reference	Reference
Overweight	2.2 (1.8-2.7)	1.6 (1.2-2.1)	3.2 (2.3-4.3)
Obesity	3.7 (3.0-4.6)	2.4 (1.8-3.2)	5.7 (4.2-7.9)
Severe obesity	5.9 (4.4-7.9)	4.4 (3.1-6.1)	8.7 (5.6-13.9)
High HbA1c	*p <0.001*	*p <0.001*	*p=0.008*
Normal weight	Reference	Reference	Reference
Overweight	1.1 (0.9-1.2)	1.0 (0.9-1.2)	1.1 (0.9-1.2)
Obesity	1.6 (1.4-1.9)	1.8 (1.4-2.2)	1.5 (1.2-2.0)
Severe obesity	1.6 (1.2-2.0)	1.8 (1.3-2.5)	1.4 (0.9-2.0)
High fasting plasma glucose	*p=0.003*	*p <0.001*	*p=0.579*
Normal weight	Reference	Reference	Reference
Overweight	1.0 (0.8-1.4)	1.2 (0.8-1.7)	1.0 (0.7-1.5)
Obesity	2.0 (1.2-3.4)	3.8 (1.8-8.0)	1.3 (0.7-2.7)
Severe obesity	1.9 (0.9-3.9)	4.4 (1.7-11.4)	1.0 (0.4-2.3)
High fasting insulin	*p <0.001*	*p <0.001*	*p <0.001*
Normal weight	Reference	Reference	Reference
Overweight	4.4 (3.5-5.6)	4.1 (3.1-5.5)	4.8 (3.1-7.3)
Obesity	12.7 (9.9-16.3)	10.2 (7.8-13.4)	17.7 (11.6-26.8)
Severe obesity	21.5 (15.6-29.6)	17.8 (11.6-27.4)	27.9 (17.2-45.2)
Metabolic syndrome	*p <0.001*	*p <0.001*	*p <0.001*
Normal weight	NI	NI	NI
Overweight	Reference	Reference	Reference
Obesity	5.20 (3.78-7.14)	3.91 (2.33-6.57)	6.21 (4.09-9.44)
Severe obesity	6.85 (4.82-9.72)	6.33 (3.65-10.9)	7.88 (4.65-13.4)

*Weighted Poisson regression models adjusted for sex, age, skin color, socioeconomic status, physical activity and total energy intake; Wald's test for trends was used to obtain the p-values presented. Abbreviations: PR, prevalence ratios; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; HbA1c, Glycated hemoglobin; NI, not informed.

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ARTIGO 3 – Six Year Changes in N-terminal pro-Brain Natriuretic Peptide and Changes in Weight and Risk of Obesity

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Author contributions: MS. ML and ES designed the study and drafted the manuscript. MS and ND conducted the analyses. MS, ML, ND, OT, BS, CB, CN, and ES provided data interpretation and meaningful contributions to the revision of the manuscript. MS and ES are the guarantors of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Abstract

Objective: We aim to study the prospective association between N-terminal pro-Brain natriuretic peptide (NT-proBNP), and changes in weight and obesity risk in a community-based population.

Methods: We analyzed data from 9,681 participants from the Atherosclerosis Risk in Communities Study, at two time points 6-years apart. Among people without obesity at baseline, we used multivariable logistic regression models to examine the association between baseline levels of NT-proBNP (serum at Visit 2, plasma at Visit 4) and incident obesity. We used multivariable linear regression model to examine the association between changes in NT-proBNP and changes in weight.

Results: The prevalence of obesity increased from 28% to 35% in the 6-year follow up period. Compared with individuals in the highest NT-proBNP quartile, those in the lowest were more likely to have obesity at baseline (OR 1.25; 95%CI 1.08-1.45) and, among people who were not obese at baseline, more likely to develop obesity at follow-up (OR 1.35; 95%CI 1.07-1.69). Changes in NT-proBNP were inversely associated with weight change.

Conclusions: In this prospective study, lower levels of NT-proBNP were associated with higher risk of obesity, and changes in NT-proBNP were inversely associated with changes in weight. This suggests that NPs or their pathways may be potential targets in the treatment of obesity.

Introduction

Natriuretic peptides (NPs) are biochemical markers of cardiac function, which correlate with the severity of heart failure (HF) and also strongly predict future HF development (1). The main stimulus for NP release is distension of cardiac myocytes, which can occur in situations of increased ventricular wall stress caused by processes such as hypertension and volume overload (2). These hormones have well established protective cardiovascular effects. Neprilysin inhibitors (Entresto) are widely used in the treatment of congestive HF, promoting vasodilation, natriuresis, and decreased renin and aldosterone secretion (3). The action of NPs, however, is not restricted to the heart-kidney axis. They also may play a role in metabolic pathways and the development of insulin resistance. In adipose tissue, NPs are known to stimulate lipolysis, mitochondrial biogenesis and browning of adipocytes (4).

Cross-sectional studies have demonstrated that diabetes and obesity are inversely associated with lower levels of BNP and NT-proBNP. Wang et al (5) found that, among 3389 participants of the Framingham Heart Study offspring cohort without HF, body mass index (BMI) was inversely associated with NP levels. Compared to those with a normal BMI, obese men and women had 40% and 38% lower plasma BNP levels, respectively. In the setting of HF, NT-proBNP is widely used to aid diagnosis, stratify cardiovascular risk and monitor therapy effect. This inverse association of BMI with NP levels is also present in those with HF, and BMI-specific cutoff-points for HF diagnosis and prediction have been proposed in the literature (6-8). Possible explanations for the low levels of NPs in obesity are impaired synthesis and release from the cardiomyocytes or, less likely, increased clearance by NP receptor-C (9-12).

A growing number of studies suggest that NPs are not only associated with but may also protect against metabolic diseases. Transgenic mice overexpressing BNP were protected against diet-induced obesity and insulin resistance, despite being fed a high fat diet (13). Preclinical studies have also shown that BNP treatment in obese mice improves glucose tolerance and insulin sensitivity (14,15). Similar observations have been seen in human studies. In a subsample of 3,019 participants from the Jackson Heart Study, a cohort of African-American adults from Mississippi, BNP levels had a U-shape association with the incidence of metabolic syndrome (16). The Atherosclerosis Risk in Communities Study (ARIC) also demonstrated that NT-proBNP levels were inversely associated with diabetes risk, even after multivariable adjustments (17). Likewise, the Women's Health Study (18), the Cardiovascular Health Study (19) and the Multi-Ethnic Study of Atherosclerosis (20) have additionally provided support for an inverse association between NPs levels and incident diabetes.

However, longitudinal data regarding the direct association of changes in NPs with weight change and risk of obesity, independently of changes in other cardiometabolic risk markers, are limited.

We hypothesized that lower baseline levels and decreases in NT-proBNP over time would be independently associated with increases in weight and a higher risk of obesity in the community-based population of the ARIC Study.

Methods

Study population

The ARIC Study is an ongoing prospective cohort of 15,792 middle-aged adults designed to investigate the etiology of atherosclerosis and its clinical outcomes. Participants were recruited from four communities in the United States (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland). Participants were enrolled from 1987 to 1989 and underwent clinical examinations approximately every three years thereafter for 3 more visits (1990-1992, 1993-1995, 1996-1998). Subsequent visits also occurred in 2011-2013, 2016-2017 and 2018-2019. In this analysis, we used data on NT-proBNP available from visits 2 (1990-92) and 4 (1996-98). More information about data collection is published elsewhere (21).

A total of 11,449 participants attended both visits. We excluded participants with race/ethnicity other than black or white (n=31) and black individuals from Minneapolis and Washington County centers (n=38); those with missing data for variables of interest (n=745); and those missing NT-proBNP levels (n=954). The final sample size was composed of 9,681 adults. For the analyses examining the incidence of obesity, individuals with obesity at baseline were excluded (n=2,741).

The ARIC study has been approved by the Institutional Review Boards (IRB) at all participating institutions: University of North Carolina at Chapel Hill IRB, Wake Forest University IRB, Johns Hopkins University IRB, University of Minnesota IRB and University of Mississippi Medical Center IRB. Written informed consent was obtained from all study participants. All methods were carried out in accordance with the relevant guidelines and regulations for human subject research, in accordance with the Declaration of Helsinki (22).

Measurements

All covariates were assessed at baseline following standard protocols. BMI was calculated from measured weight and height at both visits and obesity was defined as a BMI ≥

30 kg/m^2. Diabetes was defined as fasting (≥8 hours) blood glucose ≥126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL, self-reported physician diagnosed diabetes or "sugar in blood", or use of medication for diabetes in the past two weeks. Hypertension was defined as mean systolic blood pressure (BP) ≥ 140 mmHg, mean diastolic BP ≥ 90 mmHg, or use of medication for high blood pressure in the past 2 weeks. Atherosclerotic cardiovascular disease (ASCVD) was defined as history of coronary heart disease and/or stroke.

Assays of NT-proBNP levels were conducted in serum (visit 2) and plasma (visit 4) samples that had been stored at -70ºC. Measurements were made using a sandwich immunoassay method on a Roche Elecsys 2010 Analyzer at visit 2, and an ECLIA immunoassay on an automated Cobas e411 analyzer at visit 4. The lower detection limit for both assays was 5 pg/mL, and participants with unmeasurable levels were assigned a value of 2.5 pg/mL. NT-proBNP, glucose, total cholesterol, HDL- and LDL-cholesterol, triglycerides and hs-CRP were re-calibrated based on published equations to minimize any systematic differences across study visits (23).

Statistical Analyses

We compared the characteristics of the study participants by quartiles of NT-proBNP at baseline. We used multivariable logistic regression models to estimate the association of NT-proBNP quartiles with prevalence of obesity at baseline. Among those who were non-obese at baseline, we examined the risk of developing obesity at 6 years according to baseline quartiles of NT-proBNP. Two adjustment models were used: Model 1 included age, sex, race-center, smoking status, eGFR, hypertension, diabetes, heart failure and ASCVD (coronary heart disease or stroke); Model 2 included the variables in model 1 plus total cholesterol, HDL-cholesterol and use of lipid lowering medication. We analyzed the associations of baseline deciles of NT-proBNP with 6-year change in weight. The reference category for change in NT-proBNP was the one with values crossing zero. We also used linear regression to evaluate weight change as a linear spline which was regressed on log-transformed change in NT-proBNP (knots located at deciles of change in log-NT-proBNP). We conducted sensitivity analyses excluding patients with HF prior to visit 4. All statistical analyses were performed using Stata v15.1 software, and a p value < 0.05 was considered statistically significant.

Results

Baseline data

Mean age at baseline (1990-1992) was 57 years, 56% were women and 78% were white. The prevalence of obesity was 28%. NT-proBNP levels were almost 12% lower in participants with obesity compared to those without obesity at baseline (77.0 ± 135.3 pg/mL in obese and 87.1 ± 439.5 pg/mL in non-obese). The prevalence of coronary heart disease generally increased with increasing quartiles of NT-proBNP levels at baseline, while the prevalence of diabetes, levels of BMI, glucose, triglycerides, total cholesterol, and eGFR decreased (**Table 1**, P for trend <0.0001). Individuals in the lowest quartile of NT-proBNP levels at baseline were less likely to have hypertension, HF and coronary heart disease compared to those in the highest quartile (**Table 1**).

Outcomes

Obesity

In cross-sectional analyses, individuals in the lowest quartile of NT-proBNP (≤ 27.2 pg/mL) were more likely to have obesity at baseline than those in the highest quartile (OR 1.37, 95%CI 1.18-1.58; Model 1; **Table 2**). After additional adjustment for lipids (Model 2), the association was slightly attenuated, but remained significant and strong (OR 1.25, 95%CI 1.08-1.45).

During the 6-year follow up period, the overall prevalence of obesity increased from 28% to 35%. The risk of developing obesity during the 6-year period was highest among individuals in the lowest quartile of NT-proBNP in both models (**Table 3**).

Change in weight

We found an inverse association between change in weight and change in NT-proBNP level (**Figure 1**). Participants who had an increase in NT-proBNP between the two visits greater than or equal to the 90th percentile of change in NT-proBNP (≥126.2 pg/mL), decreased their weight by an average of ~1.3 kg (mean weight change -1.33; 95%CI -1.86 to -0.80). Statistically significant decreases in weight were observed when NT-proBNP levels increased by more than 59.1 pg/mL in the 6-year follow up (**Figure 2A**). Decreases in NT-proBNP levels of more than 22.3 pg/mL over the same period were associated with statistically significant increases in weight (decrease in NT-proBNP -22.3 to -42.3, mean weight change 0.55 kg, 95% CI (0.03, 1.07); decrease in NT-proBNP <-42.3, mean weight change 0.60 kg, 95% CI (0.09, 1.12)). Results were similar in sensitivity analysis excluding participants with HF (**Figure 2B**).

Discussion

In this prospective cohort of 9,681 adults, we found that lower NT-proBNP levels at baseline were associated with an increased risk of obesity, and changes in NT-proBNP levels over a 6-year follow-up period were inversely associated with changes in weight. This relationship was not driven by incident HF, which is known to directly affect NT-proBNP levels. Consistent with other cross-sectional studies, individuals with obesity also had lower levels of NT-proBNP compared to their non-obese counterparts. To our knowledge, this is the first study to show the prospective association of baseline levels and changes in NT-proBNP with the incidence of obesity and changes in weight over time.

NPs and obesity

Several mechanisms have been proposed to explain the inverse relation between NPs and obesity. In the adipose tissue, BNP has a lipolytic effect via stimulation of GC-A and GC-B. Activation of these receptors induce a rise in cyclic guanosine monophosphate (cGMP) levels and subsequent activation of cGMP-dependent protein kinase 1 (cGK1), which in turn modify the lipid droplet surface to facilitate lipolysis (3). The existence of this pathway is supported by *in vitro* studies on isolated human fat cells (13,24-26). Notably, the impact of NPs on adipose tissue may be altered in individuals with obesity or insulin resistance, with attenuation or loss of the protective lipolytic effect of NPs (27,28).

NPs and hormones

Natriuretic peptides are also linked with modulated expression of numerous hormones, and may indirectly influence food intake. In a randomized clinical trial with 10 healthy men, acute intravenous infusion of BNP decreased circulating ghrelin concentrations, an important hormone that stimulates appetite (29). Participants reported decreased hunger and increased feeling of satiety, demonstrating an induced anorexic effect of BNP infusion. However, this study only evaluated the acute effect of infusion with BNP, and changes in other variables affected by NPs (for example, insulin) could be responsible for the decrease in ghrelin. In contrast, adiponectin, which is responsible for the regulation of various metabolic pathways, has a positive association with NT-proBNP levels. Higher levels of adiponectin are associated with decreased BMI and lower risk of metabolic syndrome and diabetes. Fully understanding the link between NPs and the endocrine system is essential to interpret the interplay of these peptides with obesity.

Directionality of the relationship between NPs and adiposity

Low levels of NPs are also proposed to be a consequence of obesity (5). Several mechanisms have been suggested, such as reduced synthesis and release from the heart. Substances released by the adipose tissue could be involved in suppressing production of NPs by the myocytes. Higher glycosylation of proBNP, seen in individuals with obesity, leads to impaired conversion of this molecule and, consequently, to lower plasma concentrations of BNP and NT-proBNP. Individuals with obesity also appear to have increased expression of neprilysin, an endopeptidase that degrades NPs. Taking into account these investigations along with our findings, it is possible to assume that the relationship between NPs and adiposity is bidirectional, with each factor influencing the levels of the other. Previous work has demonstrated inverse associations of NT-proBNP with the development of metabolic syndrome (18,30) and diabetes (31). While this study does not directly address metabolic syndrome and diabetes, it is likely that an increase in weight, and thus lower levels of NPs, contribute to a greater likelihood of these metabolic abnormalities.

Study limitations

Our study has some limitations. We had only one measure of NT-proBNP at each visit, and this peptide is known to vary within individuals over short periods of time, similar to other neuro-hormones (32). We did not have measures of BNP; however, NT-proBNP and BNP are secreted in equimolar amounts after cleavage of proBNP, and previous studies have shown that their levels are closely correlated. Nevertheless, the biological variation of NT-proBNP is much less than that of BNP (33). We also did not have information on lean and fat body mass, which could be useful since some studies suggest that the percentage of fat body mass may be more closely associated with BNP levels than BMI (34). It is also possible that differences in other factors which were not evaluated in this analysis could influence the associations of NPs with weight change. Due to the observational nature of the study, we cannot exclude the possibility of residual confounding.

Study strengths

Nonetheless, our study has important strengths. We used data from the ARIC study, a prospective cohort that follows a biracial community-based sample since 1987 using standardized and rigorous data collection methods. Our large sample and availability of serial measurements of multiple cardiometabolic markers allowed us to investigate, over a 6-year follow up period, the relationship between natriuretic peptides and weight. We were able to

show the prospective association of baseline levels and changes in NT-proBNP with incident obesity controlling for other risk factors.

Conclusion

In conclusion, we found inverse associations of baseline and longitudinal NT-proBNP levels with weight change and incidence of obesity. Our results suggest that NPs or their pathways may be potential targets in the treatment of obesity. However, the molecular networks involving the natriuretic system are complex and additional research, especially interventional studies, is needed to address the clinical relevance of our findings.

Acknowledgements

The authors thank the staff and participants of the ARIC study for their important contributions.

Table 1. Characteristics of participants according to NT-proBNP quartiles at baseline (visit 2, 1990-1992), the Atherosclerosis Risk in Communities (ARIC), n=9681

	Q1 (≤ 27.17 pg/mL)	Q2 (27.19 – 50.79 pg/mL)	Q3 (50.81 – 90.58 pg/mL)	Q4 (≥ 90.63 pg/mL)	P for trend
N	2,422	2,419	2,421	2,419	
Age, years	55.0 (5.3)	56.3 (5.4)	57.2 (5.7)	58.3 (5.7)	<0.0001
Female (%)	838 (34.6%)	1270 (52.5%)	1611 (66.5%)	1727 (71.4%)	<0.0001
Race (%)					
White	1644 (67.9%)	1908 (78.9%)	2004 (82.8%)	2029 (83.9%)	<0.0001
Black	778 (32.1%)	511 (21.1%)	417 (17.2%)	390 (16.1%)	<0.0001
Current smokers (%)	474 (19.6%)	431 (17.8%)	466 (19.2%)	492 (20.3%)	<0.0001
Hypertension (%)	727 (30.0%)	709 (29.3%)	755 (31.2%)	1003 (41.5%)	<0.0001
Diabetes (%)	393 (16.2%)	320 (13.2%)	274 (11.3%)	258 (10.7%)	<0.0001
History of coronary heart disease or stroke (%)	62 (2.6%)	87 (3.6%)	124 (5.1%)	289 (11.9%)	
Prevalent heart failure (%)	74 (3.1%)	88 (3.6%)	72 (3.0%)	140 (5.8%)	<0.0001
Use of medication for hypertension, diabetes or lipid lowering (%)	779 (32.2%)	762 (31.5%)	784 (32.4%)	1061 (43.9%)	<0.0001
Weight, kg	84.1 ± 15.3	80.6 ± 16.0	76.7 ± 16.8	75.6 ± 17.1	<0.0001
BMI, kg/m^2	28.7 ± 4.9	28.2 ± 5.0	27.5 ± 5.5	27.3 ± 5.5	<0.0001
Obesity [BMI≥30 kg/m^2] (%)	781 (32.2%)	716 (29.6%)	622 (25.7%)	622 (25.7%)	<0.0001
Waist circumference, cm	100.3 ± 12.4	98.8 ± 13.3	96.1 ± 14.6	95.4 ± 15.2	<0.0001
Glucose, mg/dL	102.1 (94.4, 112.6)	99.2 (92.5, 107.8)	97.3 (90.6, 104.9)	96.3 (90.6, 104.9)	<0.0001
Glycated hemoglobin, %-point	5.5 (5.2, 5.9)	5.4 (5.2, 5.8)	5.4 (5.2, 5.7)	5.4 (5.2, 5.7)	<0.0001
Triglycerides, mg/dL	126.1 (90.5, 178.8)	117.9 (85.5, 166.7)	112.9 (82.4, 160.6)	111.8 (82.4, 156.5)	<0.0001
HDL-cholesterol, mg/dL	20.1 (17.9, 23.0)	20.9 (17.9, 23.8)	21.6 (18.7, 26.0)	22.3 (18.7, 26.7)	<0.0001
Total cholesterol, mg/dL	204.7 (180.8, 231.5)	203.7 (179.8, 228.5)	202.7 (180.8, 227.5)	201.7 (178.8, 227.5)	0.001
CRP, mg/L	2.0 (1.0, 4.0)	2.1 (1.0, 4.4)	2.3 (1.1, 4.9)	2.6 (1.2, 5.7)	<0.0001
eGFR, mL/min/1.73 m²	99.1 (91.3, 107.6)	97.7 (89.5, 105.3)	96.9 (89.0, 104.8)	95.6 (86.1, 103.3)	<0.0001

Data is presented as number (%), mean ± standard deviation or median (interquartile range).
BMI=Body mass index; CRP=C-Reactive Protein; eGFR=Estimated glomerular filtration rate; HDL=High-density lipoprotein

Table 2. Odds ratios (95% confidence intervals) of prevalent obesity at baseline according to quartiles of NT-proBNP at baseline, N=9,681

	NT-proBNP categories (pg/mL)			
	Q1 (≤ 27.17)	**Q2 (27.19 – 50.79)**	**Q3 (50.81 – 90.58)**	**Q4 (≥ 90.63)**
Model 1	1.37 (1.18-1.58)*	1.26 (1.10-1.45)*	1.05 (0.91—1.21)	1 (reference)
Model 2	1.25 (1.08-1.45)*	1.17 (1.02-1.35)*	1.03 (0.89 – 1.18)	1 (reference)

Model 1: Adjusted for age, sex, race-center, smoking status, eGFR, hypertension, diabetes, heart failure, ASCVD (coronary heart disease or stroke). Model 2: Model 1 plus total cholesterol, HDL-cholesterol and lipid lowering medication.

*$p<0.05$

ASCVD= atherosclerotic cardiovascular disease; eGFR=Estimated glomerular filtration rate; HDL=High-density lipoprotein

Table 3. Odds ratios (95% confidence intervals) of incident obesity at the 6-year follow up visit (visit 4, 1996-1998) among those participants who were non-obese at baseline (visit 2, 1990-1992), N=6,940

	NT-proBNP categories (pg/mL)				
	Q1 (≤ 27.17)	**Q2 (27.19 – 50.79)**	**Q3 (50.81 – 90.58)**	**Q4 (≥ 90.63)**	**P for trend**
Model 1	1.51 (1.21-1.89)*	1.49 (1.21-1.83)*	1.09 (0.89-1.35)	1 (reference)	<0.0001
Model 2	1.35 (1.07-1.69)*	1.37 (1.11-1.69)*	1.06 (0.85-1.30)	1 (reference)	0.002

Model 1: Adjusted for age, sex, race-center, smoking status, eGFR, hypertension, diabetes, heart failure, ASCVD (coronary heart disease or stroke). Model 2: Model 1 plus total cholesterol, HDL-cholesterol and lipid lowering medication.

*p<0.05

ASCVD= atherosclerotic cardiovascular disease; eGFR=Estimated glomerular filtration rate; HDL=High-density lipoprotein

Figure Legends

Figure 1. Adjusted six-year change in log-transformed NT-proBNP with change in weight (β coefficient, 95%CI), the Atherosclerosis Risk in Communities (ARIC) Study (1990-1992 to 1996-1998). The association between weight change as a linear spline with log-transformed change in NT-proBNP. The dashed line is the β coefficient and the shaded region is the 95% confidence interval. Knots are located at deciles of change in log NT-proBNP. This model is adjusted for age, sex, race-center, smoking status, estimated glomerular filtration rate, hypertension, diabetes, heart failure, atherosclerotic cardiovascular disease (coronary heart disease or stroke), total cholesterol, high-density lipoprotein-cholesterol and lipid lowering medication. We found an inverse association between change in weight and change in NT-proBNP level.

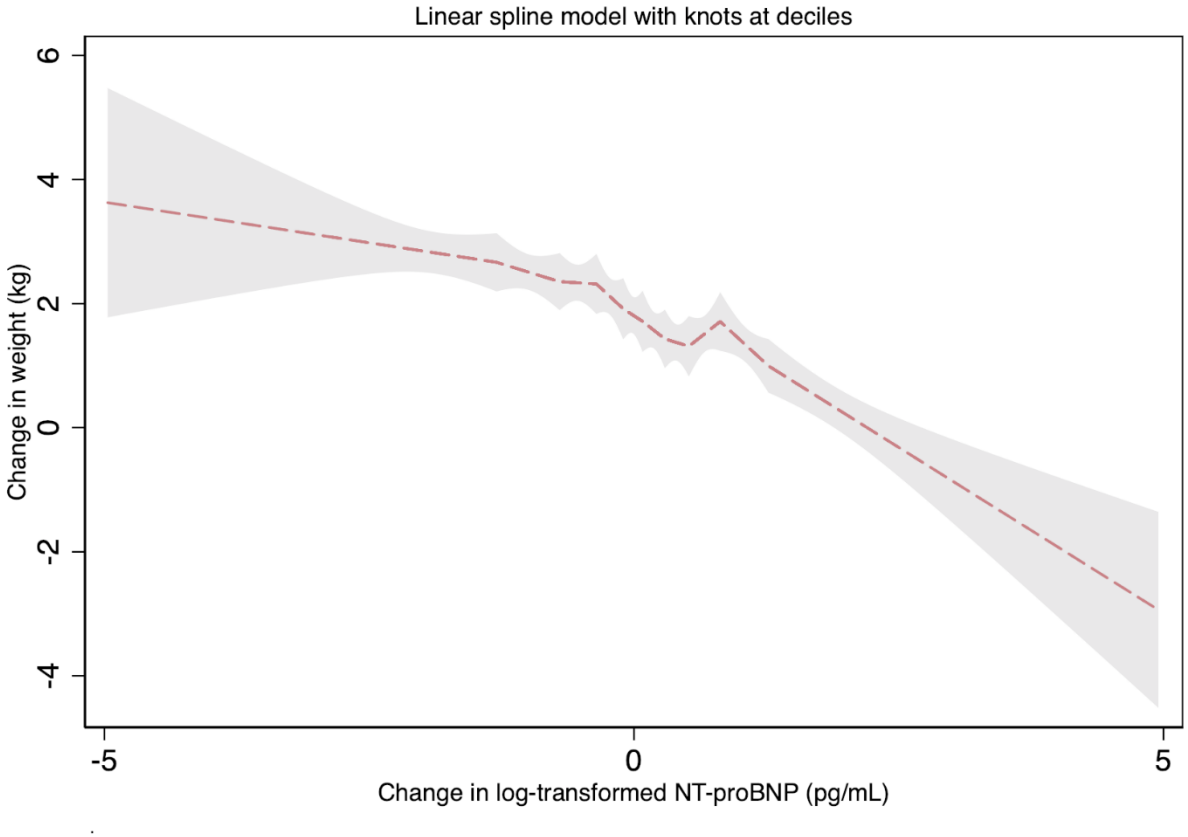
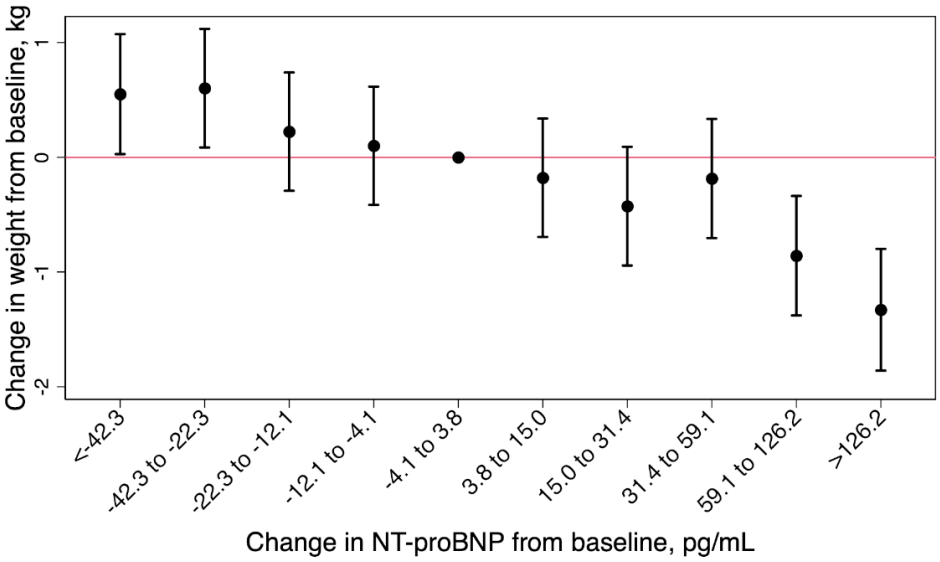
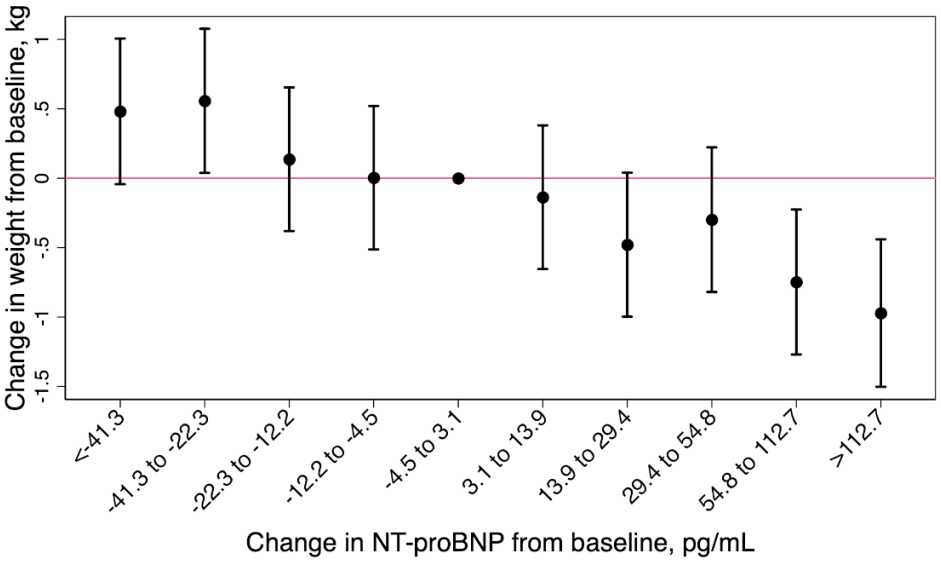


Figure 2. Change in weight by deciles of change in NT-proBNP over the 6-year follow up period (A) and after exclusion of participants with heart failure occurring at or prior to visit 4 (B), the Atherosclerosis Risk in Communities (ARIC) Study (1990-1992 to 1996-1998). (A) and (B) are adjusted for age, sex, race-center, smoking status, estimated glomerular filtration rate, hypertension, diabetes, heart failure, atherosclerotic cardiovascular disease (coronary heart disease or stroke), total cholesterol, high-density lipoprotein-cholesterol and lipid lowering medication. Statistically significant decreases in weight were observed when NT-proBNP levels increased by more than 59.1 pg/mL (A) and 54.8 pg/mL (B) in the 6-year follow up. Decreases in NT-proBNP levels of more than 22.3 pg/mL over the same period were associated with statistically significant increases in weight (A).



(A)



(B)

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CONCLUSÕES E CONSIDERAÇÕES FINAIS

O excesso de peso é um problema de saúde pública mundial cuja prevalência vem aumentando de forma alarmante. Considerando a importância desse tema, o objetivo desta tese foi avaliar a associação entre obesidade e fatores de risco cardiovascular na adolescência e na vida adulta. Para isso, foram realizados três estudos com delineamentos e fontes de dados distintos.

Nossos achados demonstram que as prevalências de excesso de peso, sobrepeso e obesidade em adolescentes brasileiros aumentaram expressivamente nas últimas décadas. É importante destacar que, devido a expressivas desigualdades entre as regiões brasileiras, as mudanças temporais de prevalência também foram distintas. As regiões Sul e Sudeste, que possuem os melhores indicadores de status socioeconômico e de saúde do país, apresentaram as maiores taxas de excesso de peso nos últimos anos; enquanto a região Nordeste, menos desenvolvida, foi a que apresentou as menores taxas. Acreditamos que esses dados possam ser considerados as estimativas de tendência de excesso de peso em adolescentes brasileiros mais recentes na literatura.

A estratificação da obesidade em diferentes graus é uma informação essencial na avaliação de risco cardiometabólico. Utilizando dados de adolescentes brasileiros, observamos que, à medida que aumentava a severidade de obesidade, maior era a prevalência de valores anormais de diversos fatores de risco, como pressão arterial elevada e aumento dos níveis de colesterol, triglicerídeos e glicose. Sendo oriundos de uma amostra multiétnica representativa de adolescentes de todas as regiões do Brasil, esses achados são relevantes para guiar a criação de políticas públicas de prevenção à obesidade em jovens no país.

Os peptídeos natriuréticos tiveram seu papel na regulação do metabolismo descoberto recentemente. Por meio de dados de uma coorte de adultos norte-americanos, demonstramos que níveis baixos de NT-proBNP estavam associados com um risco aumentado de desenvolver obesidade. Essa associação se manteve mesmo após exclusão de participantes com insuficiência cardíaca, condição que influencia diretamente os níveis dos peptídeos natriuréticos. Além disso, em concordância com estudos prévios, indivíduos com obesidade apresentavam níveis de NT-proBNP mais baixos em relação a aqueles sem obesidade. Esses achados sugerem que os peptídeos natriuréticos podem ser alvos potenciais no tratamento da obesidade; no entanto, estudos adicionais, especialmente intervencionais, são necessários para o melhor entendimento do seu mecanismo de ação.

ANEXO 1 – Produção científica adicional

Além dos artigos que compõem esta tese, outras produções científicas foram realizadas durante o período de doutorado e ajudam a ilustrar a minha trajetória e processo de formação.

Artigos completos

1. Schaan CW, Cureau FV, Sbaraini M, Sparrenberger K, Kohl III HW, Schaan BD. Prevalence of excessive screen time and TV viewing among Brazilian adolescents: a systematic review and meta-analysis. Jornal de Pediatria. 2019, 95(2):155-165.
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Apresentações em congressos internacionais

1. Sbaraini M, Wallace A, Selvin E, Burns A, Tcheugui JBE, Gerstenblith G, Hoogeveen RC, Ballantyne CM, Coresh J, Ndumele CE. Variation in NT-proBNP levels after bariatric surgery and its association with body fat percentage. American Heart Association EPI|Lifestyle Scientific Sessions, 2020.
2. Sbaraini M, Lazo M, Daya NR, Tang O, Ballantyne CM, Ndumele CE, Selvin E. Weight Variation and Change in N-terminal pro-Brain Natriuretic Peptide (NT-proBNP). American Heart Association EPI|Lifestyle Scientific Sessions, 2020.
3. Sbaraini M, Cureau F, Sparrenberger K, Teló GH, Schaan B. Increasing Values of Cardiometabolic Risk Markers Are Associated with Severity of Obesity in Adolescents: Findings from the ERICA Study. ENDO – Endocrine Society Meeting, 2019.

Capítulo de livro

1. Teló G, Sbaraini M, Schaan BD. Complicações cardiovasculares do diabetes. In: Agnes Nogueira Gossenheimer; Beatriz D'Agord Schaan; Gabriela Heiden Teló. Diabetes Melito - Uma visão interdisciplinar. Porto Alegre, Pubblicato editora - 1ª edição. 2021, 1:65-72.

Participação em ações de extensão

1. Oficineiro e apoio técnico com contato aluno/público. LIDIA: Liga Interdisciplinar de Diabetes, 2019-2020.

APÊNDICES

Material suplementar artigo 1

Table S1. Search strategy by database.

PUBMED: "Overweight" [Mesh] OR "Overweight" [Title/Abstract] OR "Obesity" [Mesh] OR "Obesity" [Title/Abstract] OR "Pediatric Obesity" [Mesh] OR "Pediatric Obesity" [Title/Abstract] OR "Obesity, Pediatric" [Title/Abstract] OR "Childhood Obesity" [Title/Abstract] OR "Obesity, Childhood" [Title/Abstract] OR "Childhood Onset Obesity" [Title/Abstract] OR "Obesity, Childhood Onset" [Title/Abstract] OR "Child Obesity" [Title/Abstract] OR "Obesity, Child" [Title/Abstract] OR "Childhood Overweight" [Title/Abstract] OR "Childhood Overweights" [Title/Abstract] OR "Overweight, Childhood" [Title/Abstract] OR "Obesity in Childhood" [Title/Abstract] OR "Infant Obesity" [Title/Abstract] OR "Obesity, Infant" [Title/Abstract] OR "Infant Overweight" [Title/Abstract] OR "Overweight, Infant" [Title/Abstract] OR "Infantile Obesity" [Title/Abstract] OR "Obesity, Infantile" [Title/Abstract] OR "Adolescent Obesity" [Title/Abstract] OR "Obesity, Adolescent" [Title/Abstract] OR "Obesity in Adolescence" [Title/Abstract] OR "Adolescent Overweight" [Title/Abstract] OR "Overweight, Adolescent" [Title/Abstract] OR "Body Mass Index" [Mesh] OR "Body Mass Index" [Title/Abstract] OR "Index, Body Mass" [Title/Abstract] OR "Quetelet Index" [Title/Abstract] OR "Index, Quetelet" [Title/Abstract] OR "Quetelet's Index" [Title/Abstract] OR "Quetelets Index" [Title/Abstract] **AND** Brazil [Mesh] OR Brazil* [Title/Abstract] OR Brazil [Title/Abstract] OR "Minas Gerais" [Title/Abstract] OR "São Paulo" [Title/Abstract] OR "Espirito Santo" [Title/Abstract] OR "Rio de Janeiro" [Title/Abstract] OR Bahia [Title/Abstract] OR Pará [Title/Abstract] OR "Mato Grosso" [Title/Abstract] OR "Mato Grosso do Sul" [Title/Abstract] OR Goiás [Title/Abstract] OR "Rio Grande do Sul" [Title/Abstract] OR Ceará [Title/Abstract] OR Pernanbuco [Title/Abstract] OR "Santa Catarina" [Title/Abstract] OR Amazonas [Title/Abstract] OR Maranhão [Title/Abstract] OR Tocantins [Title/Abstract] OR Piauí [Title/Abstract] OR Rondônia [Title/Abstract] OR Roraima [Title/Abstract] OR Paraná [Title/Abstract] OR Acre [Title/Abstract] OR Amapá [Title/Abstract] OR Paraíba [Title/Abstract] OR "Rio Grande do Norte" [Title/Abstract] OR Alagoas [Title/Abstract] OR Sergipe [Title/Abstract] OR "Distrito Federal" [Title/Abstract] **AND** "Child"[Mesh] OR "Child"[Title/Abstract] OR "Children"[Title/Abstract] OR "Adolescent"[Mesh] OR "Adolescent"[Title/Abstract] OR "Adolescents"[Title/Abstract] OR "Adolescence"[Title/Abstract] OR "Teens"[Title/Abstract] OR "Teen"[Title/Abstract] OR "Teenagers"[Title/Abstract] OR "Teenager"[Title/Abstract] OR "Youth"[Title/Abstract] OR "Youths"[Title/Abstract] OR "Adolescents, Female"[Title/Abstract] OR "Adolescent, Female"[Title/Abstract] OR "Female Adolescent"[Title/Abstract] OR "Female Adolescents"[Title/Abstract] OR "Adolescents, Male"[Title/Abstract] OR "Adolescent, Male"[Title/Abstract] OR "Male Adolescent"[Title/Abstract] OR "Male Adolescents"[Title/Abstract] ***AND** Prevalence [Mesh] OR Prevalence.

EMBASE: 'obesity'/exp/mj OR 'adolescent obesity'/exp/mj OR 'childhood obesity'/exp/mj OR 'paediatric obesity':ab,ti OR 'pediatric obesity':ab,ti OR 'adiposity':ab,ti OR 'alimentary obesity':ab,ti OR 'body weight, excess':ab,ti OR 'nutritional obesity':ab,ti OR 'overweight':ab,ti OR 'body mass'/exp/mj OR 'BMI (body mass index)':ab,ti OR 'body ban mass':ab,ti OR 'body mass index':ab,ti OR 'Quetelet index':ab,ti AND Brazil/exp/mj OR Brazil:ab,ti OR 'Minas Gerais':ab,ti OR 'São Paulo':ab,ti OR 'Espirito Santo':ab,ti OR 'Rio de Janeiro':ab,ti OR Bahia:ab,ti OR Pará:ab,ti OR 'Mato Grosso':ab,ti OR 'Mato Grosso do Sul':ab,ti OR Goiás:ab,ti OR 'Rio Grande do Sul':ab,ti OR

Ceará:ab,ti OR Pernanbuco:ab,ti OR ‘Santa Catarina’:ab,ti OR Amazonas:ab,ti OR Maranhão:ab,ti OR Tocantins:ab,ti OR Piauí:ab,ti OR Rondônia:ab,ti OR Roraima:ab,ti OR Paraná:ab,ti OR Acre:ab,ti OR Amapá:ab,ti OR Paraíba:ab,ti OR ‘Rio Grande do Norte’:ab,ti OR Alagoas:ab,ti OR Sergipe:ab,ti OR ‘Distrito Federal’:ab,ti AND 'child'/exp/mj OR ‘children’:ab,ti OR 'adolescent'/exp/mj OR ‘teenager’:ab,ti *AND Prevalence/exp OR Prevalence:ab,ti

LILACS:

ENGLISH: a) **Title -** (ti:("Overweight" OR "Obesity" OR "Pediatric Obesity" OR “Childhood Obesity” OR “Child Obesity” OR “Childhood Overweight” OR “Obesity in Childhood” OR “Infant Obesity” OR “Infant Overweight” OR “Infantile Obesity” OR “Adolescent Obesity” OR “Obesity in Adolescence” OR “Adolescent Overweight” OR "Body Mass Index")) **AND** (ti:(Brazil)) **AND** (ti:("Child" OR “Children” OR "Adolescent" OR “Adolescents” OR “Adolescence” OR “Teens” OR “Teen” OR “Teenagers” OR “Teenager” OR “Youth” OR “Youths” OR “Female Adolescent” OR “Female Adolescents” OR “Male Adolescent” OR “Male Adolescents”))]. b) **Abstract -** (ab:("Overweight" OR "Obesity" OR "Pediatric Obesity" OR “Childhood Obesity” OR “Child Obesity” OR “Childhood Overweight” OR “Obesity in Childhood” OR “Infant Obesity” OR “Infant Overweight” OR “Infantile Obesity” OR “Adolescent Obesity” OR “Obesity in Adolescence” OR “Adolescent Overweight” OR "Body Mass Index")) **AND** (ab:(Brazil)) **AND** (ab:("Child" OR “Children” OR "Adolescent" OR “Adolescents” OR “Adolescence” OR “Teens” OR “Teen” OR “Teenagers” OR “Teenager” OR “Youth” OR “Youths” OR “Female Adolescent” OR “Female Adolescents” OR “Male Adolescent” OR “Male Adolescents”)).

PORTUGUESE: a) **Title -** (ti:(Sobrepeso OR Obesidade OR “Obesidade pediátrica” OR “Obesidade infantil” OR “Sobrepeso infantil” OR “Sobrepeso pediátrico” OR “Obesidade na adolescência” OR “Sobrepeso na adolescência” OR “Indice de massa corporal”)) **AND** (ti:(Criança OR Crianças OR Adolescente OR Adolescentes OR Adolescência OR Juvenil OR Jovem OR Jovens OR Infância)) **AND** (ti:(Brasil)). b) **Abstract -** (ab:(Sobrepeso OR Obesidade OR “Obesidade pediátrica” OR “Obesidade infantil” OR “Sobrepeso infantil” OR “Sobrepeso pediátrico” OR “Obesidade na adolescência” OR “Sobrepeso na adolescência” OR “Indice de massa corporal”)) **AND** (ab:(Criança OR Crianças OR Adolescente OR Adolescentes OR Adolescência OR Juvenil OR Jovem OR Jovens OR Infância)) **AND** (ab:(Brasil)).

SCIELO:

ENGLISH: (ti:((ab:("Overweight" OR "Obesity" OR "Pediatric Obesity" OR “Childhood Obesity” OR “Child Obesity” OR “Childhood Overweight” OR “Obesity in Childhood” OR “Infant Obesity” OR “Infant Overweight” OR “Infantile Obesity” OR “Adolescent Obesity” OR “Obesity in Adolescence” OR “Adolescent Overweight” OR "Body Mass Index")) **AND** (ab:((Brazil))) **AND** (ab:("Child" OR “Children” OR "Adolescent" OR “Adolescents” OR “Adolescence” OR “Teens” OR “Teen” OR “Teenagers” OR “Teenager” OR “Youth” OR “Youths” OR “Female Adolescent” OR “Female Adolescents” OR “Male Adolescent” OR “Male Adolescents”))))

PORTUGUESE: (ti:((ab:(Sobrepeso OR Obesidade OR “Obesidade pediátrica” OR “Obesidade infantil” OR “Sobrepeso infantil” OR “Sobrepeso pediátrico” OR “Obesidade na adolescência” OR “Sobrepeso na adolescência” OR “Indice de massa corporal”)) **AND** (ab:(Criança OR Crianças OR Adolescente OR Adolescentes OR Adolescência OR Juvenil OR Jovem OR Jovens OR Infância)) **AND** (ab:(Brasil))))

Table S2. Summary and characteristics of included studies (n=151).

Study	Type of study	First year of data collection	Age range (years)	City, state or region	Criteria of diagnosis	Sample size	Number of girls (%)
Da Veiga et al., 2004* [38]	CS, household survey	1974	10-19	Southeast and Northeast regions	IOTF	40493	20681 (51)
De Vasconcelos Chaves et al., 2010* [39]	CS, Army database	1980	17-19	26 Brazilian states and Federal District	WHO 95	3,705,984	0
Da Veiga et al., 2004* [38]	CS, household survey	1989	10-19	Southeast and Northeast regions	IOTF	6469	3173 (49)
De Vasconcelos Chaves et al., 2010* [39]	CS, Army database	1990	17-19	26 Brazilian states and Federal District	WHO 95	3,318,628	0
Sawaya et al., 1995 [40]	CS, household survey	1990	10-18	São Paulo (SP)	WHO 83	682	308 (45)
Caliman et al., 2006* [41]	CS, Army database	1995	17-19	Viçosa (MG)	CDC 2000	1324	0
Chiara et al., 2003 [42]	CS, household survey	1995	12-18	Rio de Janeiro (RJ)	IOTF	502	238 (47)
Da Veiga et al., 2004* [38]	CS, household survey	1996	10-19	Southeast and Northeast regions	IOTF	3934	1948 (50)
Peres et al., 2008 [43]	CO, birth cohort	1997	15	Pelotas (RS)	WHO 95	888	408 (46)
Silva and Malina, 2003 [44]	CS, school-based survey	1997	14-15	Niterói (RJ)	Himes e Dietz, 1994	323	200 (62)
Anjos et al., 2003 [45]	CS, school-based survey	1999	10-17	Rio de Janeiro (RJ)	IOTF	1913	954 (50)
Lancarotte et al., 2010 [46]	CS, school-based survey	1999	10-19	São Paulo (SP)	Must	1861	NI
De Vasconcelos Chaves et al., 2010* [39]	CS, Army database	2000	17-19	26 Brazilian states and Federal District	WHO 95	1,745,871	0
Caliman et al., 2006* [41]	CS, Army database	2000	17-19	Viçosa (MG)	CDC 2000	1289	0

Frainer et al., 2011 [47]	CS, household survey	2000	10-18	Salvador (BA)	Conde e Monteiro	426	207 (49)
Freitas Junior et al., 2008 [48]	CS, school-based survey	2000	10-18	Presidente Prudente (SP)	IOTF	951	439 (46)
Nobre et al., 2006 [49]	CS, school-based survey	2000	10-14	São Paulo (SP)	Must	2125	1073 (50)
Farias Júnior et al., 2003 [50]	CS, school-based survey	2001	15-18	Florianópolis (SC)	IOTF	1832	925 (50)
De Souza Ferreira et al., 2008 [51]	CS, school-based survey	2001	12-19	Metropolitan area, Rio de Janeiro (RJ)	IOTF	561	383 (68)
Terres et al., 2006 [52]	CS, household survey	2001	15-18	Pelotas (RS)	IOTF	960	497 (52)
Campagnolo et al., 2008 [53]	CS, household survey	2002	10-19	São Leopoldo (RS)	WHO 95	722	429 (59)
Del Duca et al, 2010 [54]	CS, school-based survey	2002	15-19	Santa Catarina	IOTF	5028	2984 (59)
Kuschnir et al., 2009 [55]	CS, school-based survey	2002	13-14	Nova Iguaçu (RJ)	CDC 2000	2858	1433 (50)
Rodrigues et al., 2006 [56]	CS, school-based survey	2003	10-14	Vitória (ES)	IOTF	380	203 (53)
Amorim et al., 2006 [57]	CS, school-based survey	2003	11-14	Minas gerais (MG)	IOTF	1719	861 (50)
Barros et al., 2014 [58]	CS, school-based survey	2003	15-19	Niterói (RJ)	WHO 07	530	353 (67)
Campos et al., 2006 [59]	CS, school-based survey	2003	10-19	Fortaleza (CE)	Must	1158	555 (48)
Costa et al., 2007 [60]	CS, school-based survey	2003	14-19	Toledo (PR)	WHO 95	2562	1423 (56)
Dutra et al., 2006 [61]	CS, household survey	2003	10-19	Pelotas (RS)	WHO 95	810	403 (50)
Gomes et al., 2009 [62]	CS, household survey	2003	10-19	Niterói (RJ)	WHO 07	523	NI

Rosa et al., 2006 [63]	CS, school-based survey	2003	12-17	Niterói (RJ)	CDC 2002	456	253 (55)
Pereira et al., 2018* [64]	CS, household survey	2003	12-19	São Paulo (SP)	WHO 07	360	NI
Pelegrini et al., 2010 [65]	CS, school-based survey	2004	10-17	Chapecó, Concórdia e Saudades (SC); Erval Grande (RS)	IOTF	1415	695 (49)
Araujo et al., 2010 [66]	CO, birth cohort	2004	11	Pelotas (RS)	WHO 95	4452	2260 (51)
Barbiero et al., 2009 [67]	CS, school-based survey	2004	10-18	Porto Alegre (RS)	WHO 95	511	282 (55)
Cintra et al., 2014 [68]	CS, school-based survey	2004	10-15	São Paulo (SP)	WHO 07	8019	4317 (55)
Detsch et al., 2007 [69]	CS, school-based survey	2004	14-18	São Leopoldo (RS)	IOTF	495	495 (100)
Thomaz et al., 2010 [70]	CS, school-based survey	2004	12-15	Salvador (BA)	WHO 07	2060	1168 (57)
Suñe et al., 2007 [71]	CS, school-based survey	2004	11-13	Capão da Canoa (RS)	IOTF	719	361 (50)
Goldani et al., 2013 [72]	CO, birth cohort	2004	10-11	Ribeirão Preto (SP)	IOTF	790	388 (49)
Toral et al., 2007 [73]	CS, school-based survey	2004	10-17	Piracicaba (SP)	CDC 2000	390	209 (54)
Aerts et al., 2010 [74]	CS, school-based survey	2005	10-18	Gravataí (RS)	IOTF	1442	707 (49)
Vanzelli et al., 2008 [75]	CS, school-based survey	2005	10-18	Jundiaí (SP)	IOTF	662	336 (51)
Santana et al., 2017* [76]	CS, household survey	2005	12-19	Duque de Caxias (RJ)	WHO 07	511	259 (51)
Fanhani et al., 2011 [77]	CS, school-based survey	2005	12-16	Maringá (PR)	Must	1212	NI
Flores et al., 2013* [78]	CS, school-based survey	2005	11-14	26 Brazilian states and Federal District	Conde e Monteiro	14069	6498 (46)

Oliveira et al., 2009 [79]	CS, household survey	2005	10-19	Gameleira (PE) and São João do Tigre (PB)	WHO 95	645	NI
Silva and Lopes, 2008 [80]	CS, school-based survey	2005	10-12	João Pessoa (PB)	IOTF	692	NI
Stabelini Neto et al., 2012 [81]	CS, school-based survey	2006	12-18	Curitiba, São Matheus and Jacarezinho (PR)	CDC 2000	582	295 (51)
Coelho et al., 2012 [82]	CS, school-based survey	2006	10-14	Ouro Preto (MG)	WHO 07	414	NI
Fernandes et al., 2007 [83]	CS, school-based survey	2006	11-17	Presidente Prudente (SP)	IOTF	807	445 (55)
Kac et al., 2012 [84]	CS, household survey	2006	15-19	26 Brazilian states and Federal District	WHO 06	1529	1529 (100)
Leal et al., 2012 [85]	CS, household survey	2006	10-19	Pernambuco (PE)	WHO 07	735	NI
Tassitano et al., 2009 [86]	CS, school-based survey	2006	14-19	Recife (PE)	IOTF	4210	2517 (60)
Flores et al, 2013* [78]	CS, school-based survey	2007	11-14	26 Brazilian states and Federal District	Conde e Monteiro	8327	3589 (43)
Pelegrini et al., 2007 [87]	CS, school-based survey	2007	14-18	Florianópolis (SC)	IOTF	653	418 (64)
Benedet et al., 2013 [88]	CS, school-based survey	2007	11-14	Florianópolis (SC)	IOTF	1590	837 (53)
Christofaro et al., 2014 [89]	CS, school-based survey	2007	10-17	Londrina (PR)	IOTF	1021	528 (52)
Da Silva et al., 2009 [90]	CS, school-based survey	2007	10-17	Rio grande do Norte (RN)	Conde e Monteiro	1701	801 (47)
Lourenço Silva et al., 2018 [91]	CS, school-based survey	2007	13-19	Rio de Janeiro (RJ)	WHO 07	1628	898 (55)
Fernandes et al., 2009 [92]	CS, school-based survey	2007	11-17	Presidente Prudente (SP)	IOTF	1779	824 (46)
Guedes et al., 2011 [93]	CS, school-based survey	2007	10-18	Vale do Jequitinhonha (MG)	WHO 07	3261	NI

Guerra et al., 2013 [94]	CS, household survey	2007	10-19	Legal Amazonia (BR)	WHO 06	524	276 (53)
Pinto et al., 2010 [95]	CS, school-based survey	2007	10-14	Recife (PE)	IOTF	1405	800 (57)
Laus et al., 2013 [96]	CS, school-based survey	2007	14-19	Ribeirão Preto (SP); Pequeri, Goianá, Tabuleiro and Belmiro Braga (MG)	WHO 07	788	419 (53)
Vieira Cunha Lima et al., 2011 [97]	CS, school-based survey	2007	10-19	Natal (RN)	IOTF	432	209 (48)
Pereira et al., 2018* [64]	CS, household survey	2008	12-19	São Paulo (SP)	WHO 07	378	NI
Caran et al., 2018 [98]	CS, school-based survey	2008	15-19	Niterói (RJ)	WHO 07	487	299 (61)
Bispo et al., 2015 [99]	CS, household survey	2008	11-17	Belo Horizonte (MG)	WHO 07	1030	489 (47)
Souza et al., 2010 [100]	CS, school-based survey	2008	10-14	Salvador (BA)	WHO 95	694	366 (53)
Castro et al., 2012 [101]	CS, school-based survey	2008	10-19	Guarita, Iraí, Monte Caseros, Carreteiro, Ventarra, Nonoai, Cacique Doble, Carreteiro, Inhacorá, Ligeiro, Rio da Várzea and Serrinha (RS)	WHO 07	1803	872 (48)
Cunha et al., 2018 [102]	CS, household survey	2008	10-19	26 Brazilian states and Federal District	WHO 07	5266	2673 (51)
Cureau et al., 2012 [103]	CS, school-based survey	2008	14-18	Santa Maria (RS)	Conde e Monteiro	424	192 (45)
de Moraes et al., 2014 [104]	CS, school-based survey	2008	14-17	Maringá (PR)	IOTF	991	540 (54)
Silva et al., 2011 [105]	CS, school-based survey	2008	14-17	Midwest of Santa Catarina (SC) and North of Minas Gerais (MG)	IOTF	1065	599 (56)
Silva et al., 2013 [106]	CS, school-based survey	2008	14-19	Ponta Grossa (PR)	Conde e Monteiro	653	378 (58)
Polderman et al., 2011 [107]	CS, school-based survey	2008	12-17	Aracaju (SE)	IOTF	1002	560 (56)
Krinski et al., 2011 [108]	CS, school-based survey	2008	12-17	Vilhena (RO)	Conde e Monteiro	3118	1725 (55)

Becker da Silva et al., 2019 [109]	CS, school-based survey	2008	12-14	São José (SC)	WHO 07	2042	1115 (55)
Flores et al., 2013* [78]	CS, school-based survey	2009	11-14	16 Brazilian states	Conde e Monteiro	2196	1039 (47)
Fiuza et al., 2017 [110]	CO, birth cohort	2009	10-17	Cuiabá (MT)	WHO 07	1716	846 (49)
Romero et al., 2015 [111]	CS, school-based survey	2009	10-14	Piracicaba (SP)	WHO 07	454	243 (54)
Araujo et al., 2010 [112]	CS, school-based survey	2009	11-19	26 Brazilian states and Federal District	WHO 07	58971	32316 (55)
Farias et al., 2012 [113]	CS, school-based survey	2009	14-18	Rio Branco (AC)	CDC 2000	741	401 (54)
Santana et al., 2013 [114]	CS, school-based survey	2009	11-17	Salvador (BA)	WHO 07	1494	852 (57)
Miranda et al., 2014 [115]	CS, school-based survey	2009	10-19	Goianá, Tabuleiro, Belmiro Braga e Pequeri (MG)	WHO 07	445	255 (57)
Leal et al., 2020 [116]	CS, school-based survey	2009	13-19	São Paulo (SP)	WHO 07	1156	565 (49)
Lock et al., 2020 [117]	CS, school-based survey	2009	12	Porto Alegre (RS)	WHO 07	1528	758 (50)
Santana et al., 2017* [76]	CS, household survey	2010	12-19	Duque de Caxias (RJ)	WHO 07	301	154 (51)
Neto et al., 2015 [118]	CS, school-based survey	2010	10-17	Vitória de Santo Antão (PE)	CDC 2000	2866	1554 (54)
Castilho et al., 2014 [119]	CS, school-based survey	2010	11-18	Campinas (SP)	WHO 07	2011	NI
Cecon et al., 2017 [120]	CS, school-based survey	2010	10-19	Viçosa (MG)	WHO 07	2123	1411 (66)
Raphaelli et al., 2011 [121]	CS, school-based survey	2010	10-18	Barão do Triunfo (RS)	WHO 95	377	177 (47)
da Cruz et al., 2013 [122]	CS, school-based survey	2010	11-15	Alegre (ES)	WHO 07	524	277 (53)

de Oliveira et al., 2016 [34]	CS, school-based survey	2010	10-14	Juiz de Fora (MG)	WHO 07	403	218 (54)
Souza et al., 2017 [123]	CS, school-based survey	2010	11-19	Palmeira das Missões (RS)	WHO 06	3662	NI
Vasconcellos et al., 2013 [124]	CS, school-based survey	2010	10-18	Niterói (RJ)	WHO 07	4546	3082 (68)
de Moraes et al., 2019 [125]	CO, school-based survey	2010	10-19	Rio de Janeiro (RJ)	WHO 07	809	374 (46)
Franceschin et al., 2020 [126]	CS, school-based survey	2010	13-19	Rio de Janeiro (RJ)	WHO 07	1015	542 (53)
Monteiro et al., 2016 [127]	CS, household survey	2011	13-19	Caracol (PI)	WHO 07	1088	569 (52)
Carneiro et al., 2017 [128]	CS, school-based survey	2011	12-18	Goiânia (GO)	WHO 07	1169	621 (53)
Christofaro et al., 2016 [129]	CS, school-based survey	2011	14-17	Londrina (PR)	IOTF	1231	716 (58)
Coutinho et al., 2014 [130]	CS, school-based survey	2011	10-19	São Paulo (SP)	WHO 07	1618	814 (50)
Cureau et al., 2014 [131]	CS, school-based survey	2011	14-19	Santa Maria (RS)	IOTF	1132	610 (54)
Guedes et al., 2014 [132]	CS, school-based survey	2011	15-18	Francisco Sá (MG)	WHO 07	1538	1036 (67)
de Pinho et al., 2014 [133]	CS, school-based survey	2011	11-17	Montes Claros (MG)	WHO 07	535	364 (68)
Finato et al., 2013 [134]	CS, school-based survey	2011	11-14	Caxias do Sul (RS)	Conde e Monteiro	1230	606 (49)
Fortes et al., 2013 [135]	CS, school-based survey	2011	10-15	Juiz de fora (MG)	WHO 07	562	299 (53)
Graup et al., 2014 [136]	CS, school-based survey	2011	10-17	Uruguaiana (RS)	IOTF	1455	741 (51)

Guedes et al., 2013 [137]	CS, local program survey	2011	11-17	Montes Claros (MG)	IOTF	1560	811 (52)
Sousa Júnior et al., 2013 [138]	CS, school-based survey	2011	14-17	Floriano (PI)	IOTF	395	201 (51)
Oliveira et al., 2018 [139]	CS, school-based survey	2011	14-19	Pernambuco (PE)	IOTF	6264	3737 (60)
Rosini et al., 2015 [140]	CS, school-based survey	2011	11-14	Guabiruba (SC)	WHO 07	419	NI
Pitanga et al., 2019 [141]	CS, household survey	2011	15-18	Camaçari (BA)	IOTF	613	338 (55)
Anjos et al., 2017 [142]	CS, school-based survey	2012	10-17	15 Brazilian states	WHO 07	2681	1338 (50)
Cavalcanti et al., 2016 [143]	CS, school-based survey	2012	15-19	Campina Grande (PB)	CDC 2000	559	330 (59)
D'Avila et al., 2015 [144]	CS, school-based survey	2012	11-14	Florianópolis (SC)	WHO 07	962	574 (60)
Neves et al., 2015 [145]	CS, school-based survey	2012	10-14	Juiz de Fora (MG)	WHO 07	411	220 (54)
Lopes et al., 2018 [146]	CS, school-based survey	2012	10-17	Itaipu Lake region (PR)	IOTF	3849	2027 (53)
Guimarães et al., 2013 [147]	CS, school-based survey	2012	12-17	Curitiba (PR)	IOTF	572	326 (57)
Iepsen et al., 2014 [148]	CS, school-based survey	2012	13-19	Canguçu, São Lourenço do Sul, Pelotas, Piratini, Cerrito (RS)	IOTF	510	301 (59)
Rodrigues et al., 2015 [149]	CS, school-based survey	2012	10-19	Picos (PI)	WHO 07	320	192 (60)
Almeida Santana et al., 2017 [150]	CS, school-based survey	2012	10-13	Recife (PE)	CDC 2000	392	193 (49)
Aranha et al., 2020 [151]	CS, school-based survey	2012	10-17	Barcelos (AM)	WHO 07	745	NI

Costa et al., 2020 [152]	CS, school-based survey	2012	12-18	Cuiabá (MT)	WHO 07	1335	NI
Silva et al., 2020 [153]	CS, school-based survey	2012	10-17	26 Brazilian states and Federal District	WHO 07	6843	2705 (40)
Bloch et al., 2016 [11]	CS, school-based survey	2013	12-17	26 Brazilian states and Federal District	WHO 07	73399	40675 (55)
Vieira et al., 2015 [154]	CS, school-based survey	2013	12-18	Natal (RN)	WHO 07	347	250 (72)
D'Avila et al., 2017 [155]	CS, school-based survey	2013	12-19	Palmeira das Missões (RS)	WHO 95	784	450 (57)
Enes et al., 2018 [156]	CS, school-based survey	2013	10-19	Piracicaba (SP)	WHO 07	525	318 (61)
Paes-Silva et al., 2018 [157]	CS, school-based survey	2013	12-19	Recife (PE)	WHO 07	411	251 (61)
Guilherme et al., 2015 [158]	CS, school-based survey	2013	10-14	Paranavaí (PR)	Conde e Monteiro	566	279 (49)
Alberti et al., 2019 [159]	CS, school-based survey	2013	10-19	Joaçaba (SC)	WHO 07	2172	1166 (54)
da Silva et al., 2019 [160]	CS, household survey	2013	12-17	Curitiba (PR)	Conde e Monteiro	495	251 (51)
Pereira et al., 2017 [161]	CS, school-based survey	2014	10-17	Imperatriz (MA)	WHO 06	473	260 (55)
Silva et al., 2016 [162]	CS, school-based survey	2014	10-19	26 Brazilian states and Federal District	Conde e Monteiro	2162	635 (29)
de Araujo et al., 2017 [163]	CS, school-based survey	2014	11-17	Fortaleza (CE)	WHO 07	1182	573 (48)
Carmo et al., 2018 [164]	CS, school-based survey	2014	17-18	São Luís (MA)	WHO 07	405	225 (56)
Fradkin et al., 2018 [165]	CS, school-based survey	2014	10-13	Acopiara, Cachoeirinha, Camocim, Crato, Florianópolis, Iguacu, Manaus, Porto Alegre, Quezada, and Ubajar	CDC 2000	1738	881 (51)

Gemelli et al., 2016 [166]	CS, school-based survey	2014	10-18	Porto Velho (RO)	CDC 2002	727	727 (100)
Pozza et al., 2018 [167]	CS, school-based survey	2014	10-15	Itatiba (SP)	WHO 07	2964	1500 (51)
Reuter et al., 2018 [168]	CS, school-based survey	2014	12-17	Santa Cruz do Sul (RS)	WHO 07	1200	679 (57)
Silva et al., 2018 [169]	CS, school-based survey	2014	14-19	São José (SC)	WHO 07	1132	613 (54)
Ulbricht et al., 2018 [170]	CS, school-based survey	2014	11-18	Curitiba (PR)	Conde e Monteiro	675	203 (30)
Guimarães et al., 2019 [171]	CS, school-based survey	2014	10-19	Picos (PI)	WHO 07	357	225 (63)
Moura et al., 2019 [172]	CS, school-based survey	2014	10-14	João Pessoa (PB)	WHO 07	1138	591 (52)
Marques et al., 2016 [173]	CS, school-based survey	2015	13-19	Itaqui (RS)	WHO 07	654	364 (56)
Ripka et al., 2017 [174]	CS, school-based survey	2015	12-17	South region	WHO 06	374	NI
Pereira et al., 2018* [64]	CS, household survey	2015	12-19	São Paulo (SP)	WHO 07	377	NI
Da Silva et al., 2018 [175]	CS, school-based survey	2015	11-17	Criciúma (SC)	WHO 07	583	300 (51)
Lourenço et al., 2018 [176]	CS, school-based survey	2015	14-19	Uberaba (MG)	IOTF	1009	555 (55)
Tebar et al., 2018 [177]	CS, school-based survey	2015	10-17	Presidente Prudente (SP)	IOTF	1011	557 (55)
Urbano da Silva et al., 2018 [178]	CS, school-based survey	2015	13-17	26 Brazilian states and Federal District	WHO 07	10926	5430 (50)
Farias et al, 2019 [179]	CS, school-based survey	2015	14-18	Porto Velho (RO)	WHO 07	2694	1482 (55)
Guttier et al, 2019 [180]	CO, birth cohort	2015	11	Pelotas (RS)	WHO 07	3182	1545 (49)

Ramos et al., 2019 [181]	CS, school-based survey	2015	10-14	Londrina (PR)	IOTF	394	207 (53)
da Silva et al., 2020 [182]	CS, school-based survey	2015	11-17	Curitiba (PR)	WHO 07	862	441 (51)
Cesar et al., 2020 [183]	CS, school-based survey	2015	10-19	Lapa (PR)	WHO 07	492	262 (53)
Schwertner et al., 2020 [184]	CS, school-based survey	2015	15-18	Florianópolis (SC)	IOTF	330	244 (74)
de Souza Dantas et al., 2018 [185]	CS, school-based survey	2017	12-18	Dourados (MS)	IOTF	578	392 (68)
Lima et al., 2020 [186]	CS, school-based survey	2017	14-19	Vale do Capibaribe (PE)	IOTF	1242	690 (56)

CS, Cross-sectional; CO, Cohort; IOTF, International Obesity Task Force; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention; NI, not informed. ***Studies that included individuals from more than one time period are presented separately in this table.**

Table S3. Risk of bias assessment using tool by Hoy et al[†].

Study	1. Was the study's target population a close representation of the national population in relation to relevant variables?	2. Was the sampling frame a true or close representation of the target population?	3. Was some form of random selection used to select the sample, OR was a census undertaken?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects (as opposed to a proxy)?	6. Was an acceptable case definition used in the study?	7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	8. Was the same mode of data collection used for all subjects?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	11. Summary item on the overall risk of study bias
Da Veiga, 2004	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Chaves, 2010	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Sawaya, 1995	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Caliman, 2006	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Chiara, 2003	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Peres, 2008	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Silva, 2003	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Anjos, 2003	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Lancarotte, 2010	NO	YES	NO	YES	YES	YES	YES	YES	YES	YES	Moderate
Frainer, 2011	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Junior, 2008	NO	NO	NO	NO	YES	YES	YES	NO	YES	YES	High
Nobre, 2006	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Farias Júnior, 2003	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Ferreira, 2008	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Terres, 2006	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Campagnolo, 2008	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Del Duca, 2010	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Kuschnir, 2009	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Amorim, 2006	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate

Barros, 2014	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Campos, 2006	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Costa, 2007	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Dutra, 2006	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Gomes, 2009	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Pereira, 2018	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Rodrigues, 2006	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Rosa, 2006	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	Low
Barbiero, 2009	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Cintra, 2014	NO	NO	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Detsch, 2007	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Goldani, 2013	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Luiza Araujo, 2010	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Pelegrini, 2010	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Sune, 2007	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Thomaz, 2010	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Toral, 2007	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Aerts, 2010	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Fanhani, 2011	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Flores, 2013	YES	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Oliveira, 2009	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Santana, 2017	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Silva, 2008	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Vanzelli, 2008	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Coelho, 2012	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Fernandes, 2007	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Kac, 2012	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low

Leal, 2012	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Stabelini Neto, 2012	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Tassitano, 2009	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Benedet, 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Christofaro, 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
da Silva, 2009	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
de Moraes, 2014	YES	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Fernandes, 2009	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Guedes, 2011	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Guerra, 2013	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Laus, 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Lima, 2011	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Lourenço da Silva, 2018	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Pelegrini, 2007	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Pinto, 2010	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Becker da Silva, 2019	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Bispo, 2015	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Caran, 2018	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Castro, 2012	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Cunha, 2018	YES	NO	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Cureau, 2012	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Krinski, 2011	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Polderman, 2011	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Silva, 2011	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Silva, 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Souza, 2010	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Araujo, 2010	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low

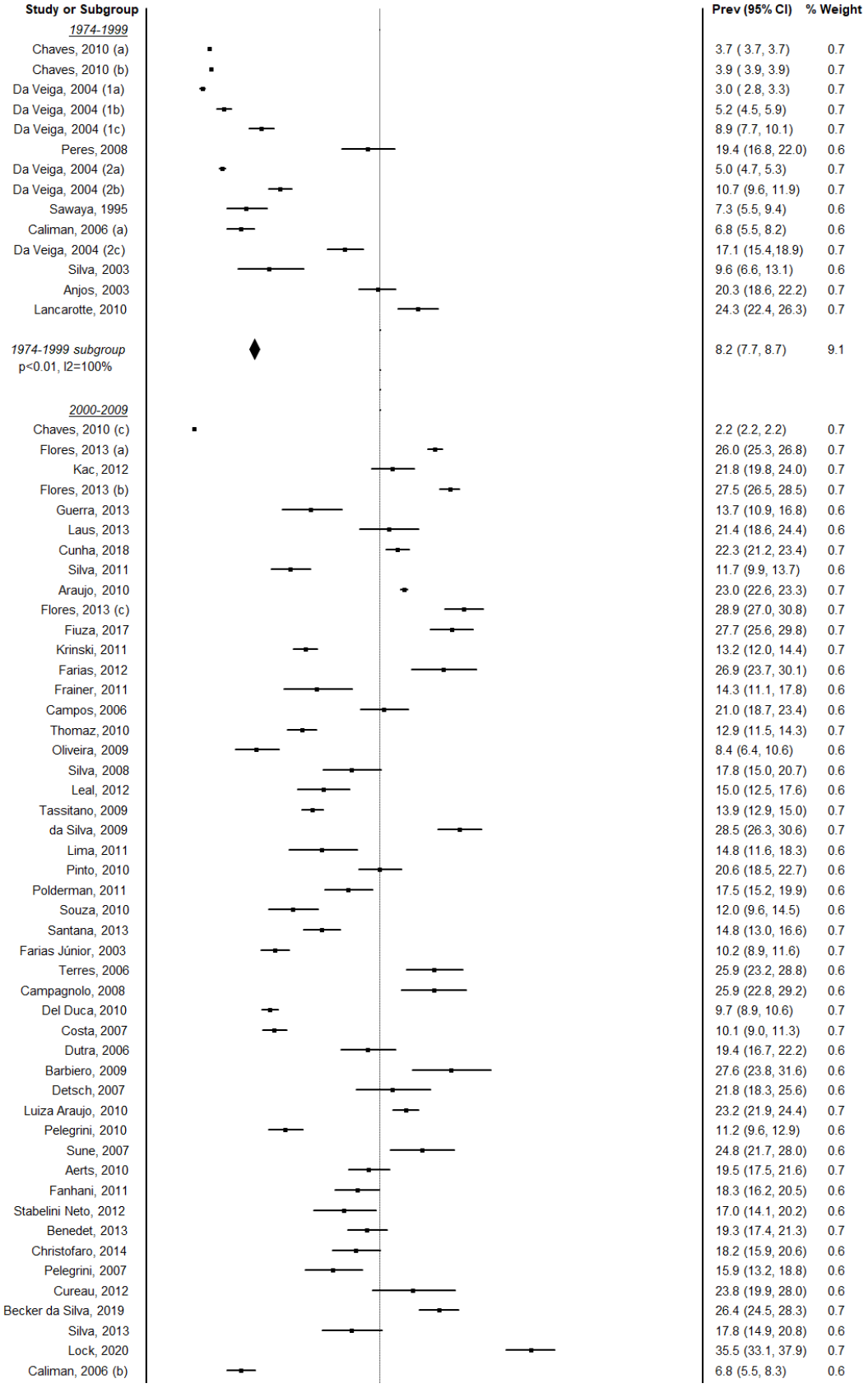
Farias, 2012	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Fiuza, 2017	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Leal, 2020	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Lock, 2020	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Miranda, 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Romero, 2015	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Santana, 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Castilho, 2014	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Cecon, 2017	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
da Cruz, 2013	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
de Moraes, 2019	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
de Oliveira, 2016	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Franceschin, 2020	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Neto, 2015	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Raphaelli, 2011	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Souza, 2017	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Vasconcellos, 2013	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Carneiro, 2017	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Christofaro, 2016	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Coutinho, 2014	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Cureau, 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
de Pinho, 2014	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Finato, 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Fortes, 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Graup, 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Guedes, 2013	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate

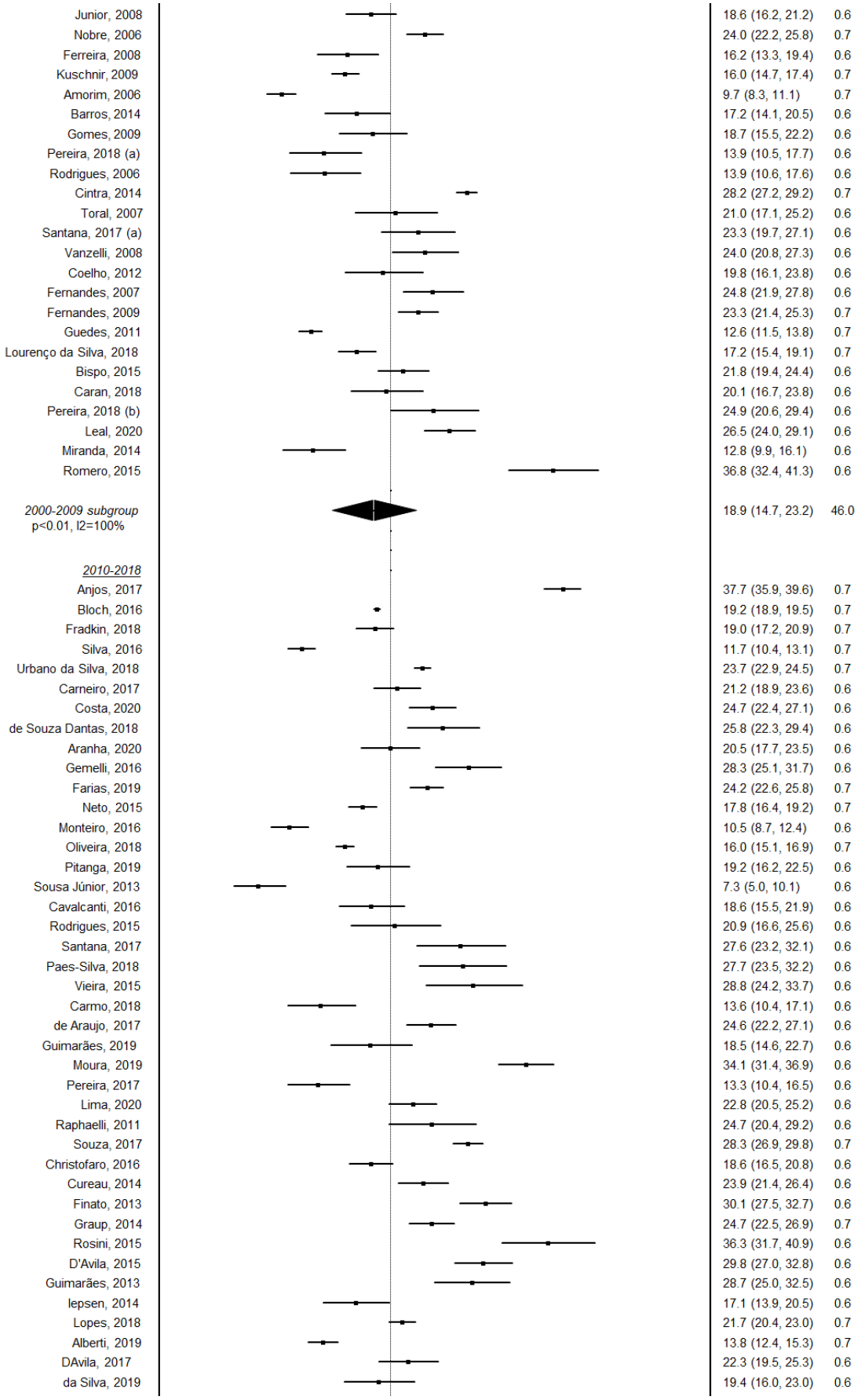
Guedes, 2014	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Monteiro, 2016	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Oliveira, 2018	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Pitanga, 2019	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Rosini, 2015	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Sousa Júnior, 2013	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Anjos, 2017	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Aranha, 2020	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Cavalcanti, 2016	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Costa, 2020	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
D'Avila, 2015	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Guimarães, 2013	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Iepsen, 2014	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Lopes, 2018	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Neves, 2015	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Rodrigues, 2015	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Santana, 2017	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Silva, 2020	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Alberti, 2019	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Bloch, 2016	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
D'Avila, 2017	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
da Silva, 2019	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Enes, 2018	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Guilherme, 2015	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Paes-Silva, 2018	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Vieira, 2015	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Carmo, 2018	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low

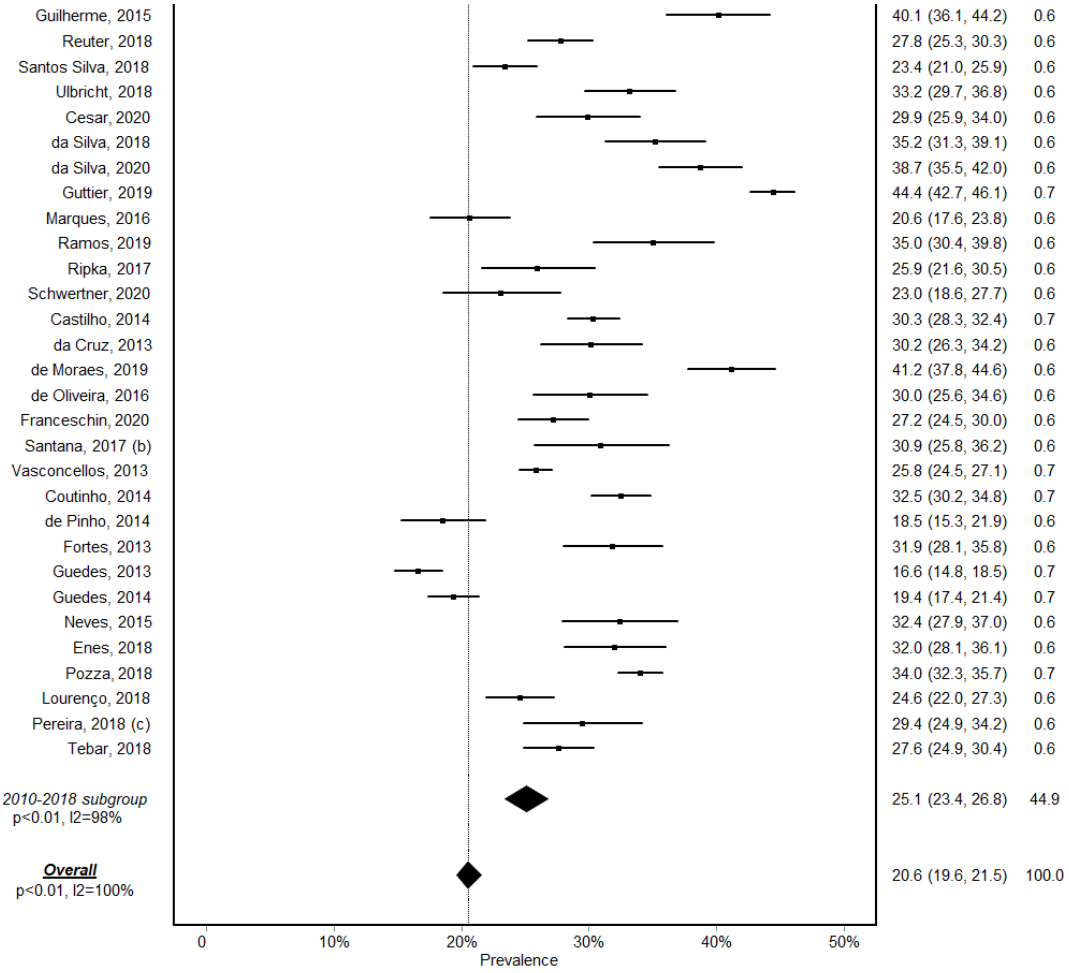
de Araujo, 2017	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Fradkin, 2018	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Gemelli, 2016	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Guimarães, 2019	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Moura, 2019	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Pereira, 2017	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Low
Pozza, 2018	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES	Moderate
Reuter, 2018	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES	Moderate
Santos Silva, 2018	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Silva, 2016	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Ulbricht, 2018	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Cesar, 2020	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
da Silva, 2018	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
da Silva, 2020	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Farias, 2019	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Guttier, 2019	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Lourenço, 2018	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Marques, 2016	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Ramos, 2019	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Ripka, 2017	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Schwertner, 2020	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	Moderate
Tebar, 2018	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Urbano da Silva, 2018	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
de Souza Dantas, 2018	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Moderate
Lima, 2020	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES	Moderate

†10-item tool divided in two domains – external validity (items 1-4) and internal validity (items 5-10). Each item receives a score of 1 (yes) or 0 (no). According to overall scores, a summary assessment deems a study to be at low (9-10), moderate (6-8) or high (≤5) risk of bias. Reference: Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. Journal of Clinical Epidemiology 2012;65:934-9.

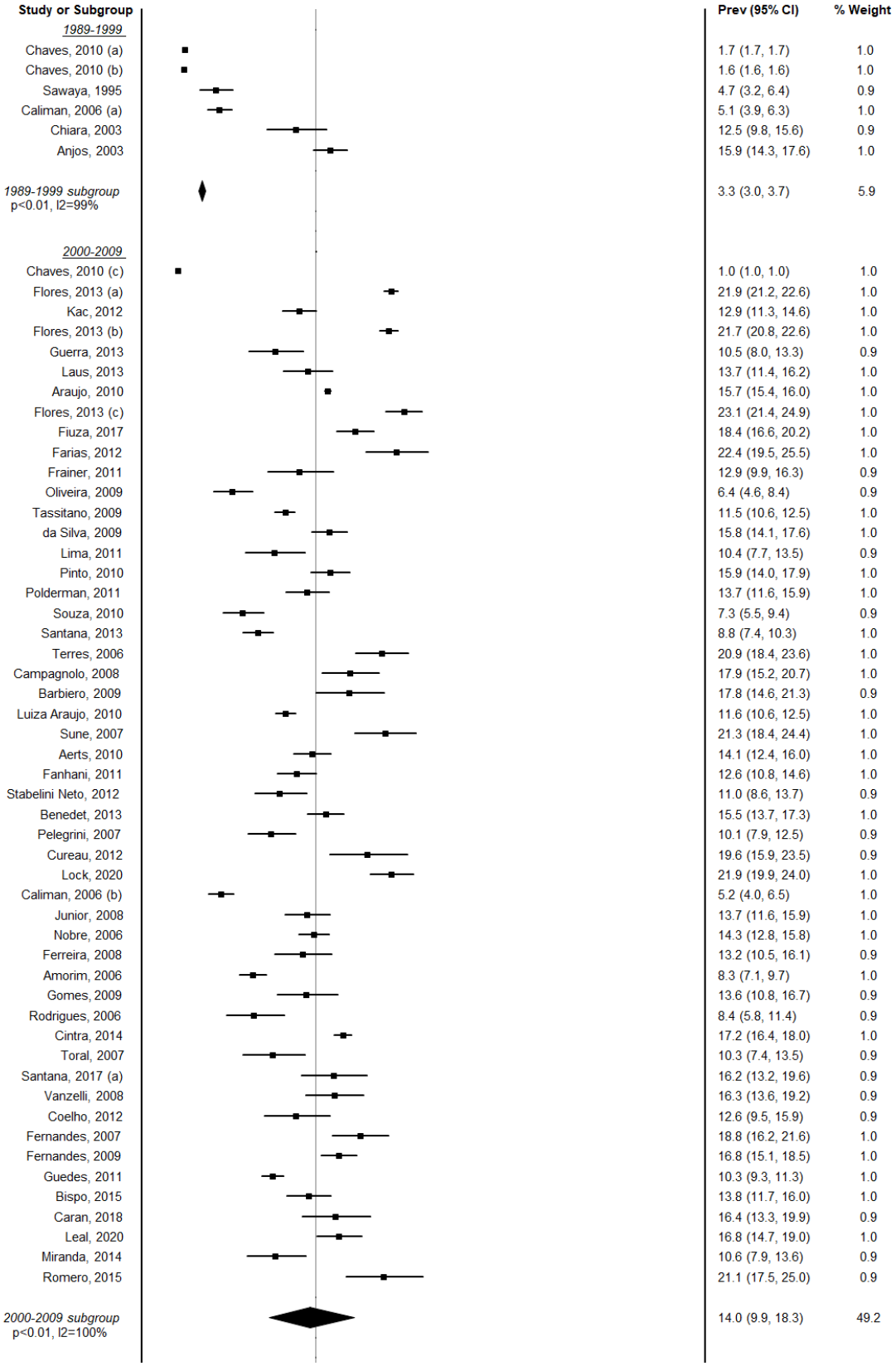
Supplementary Figure 1.

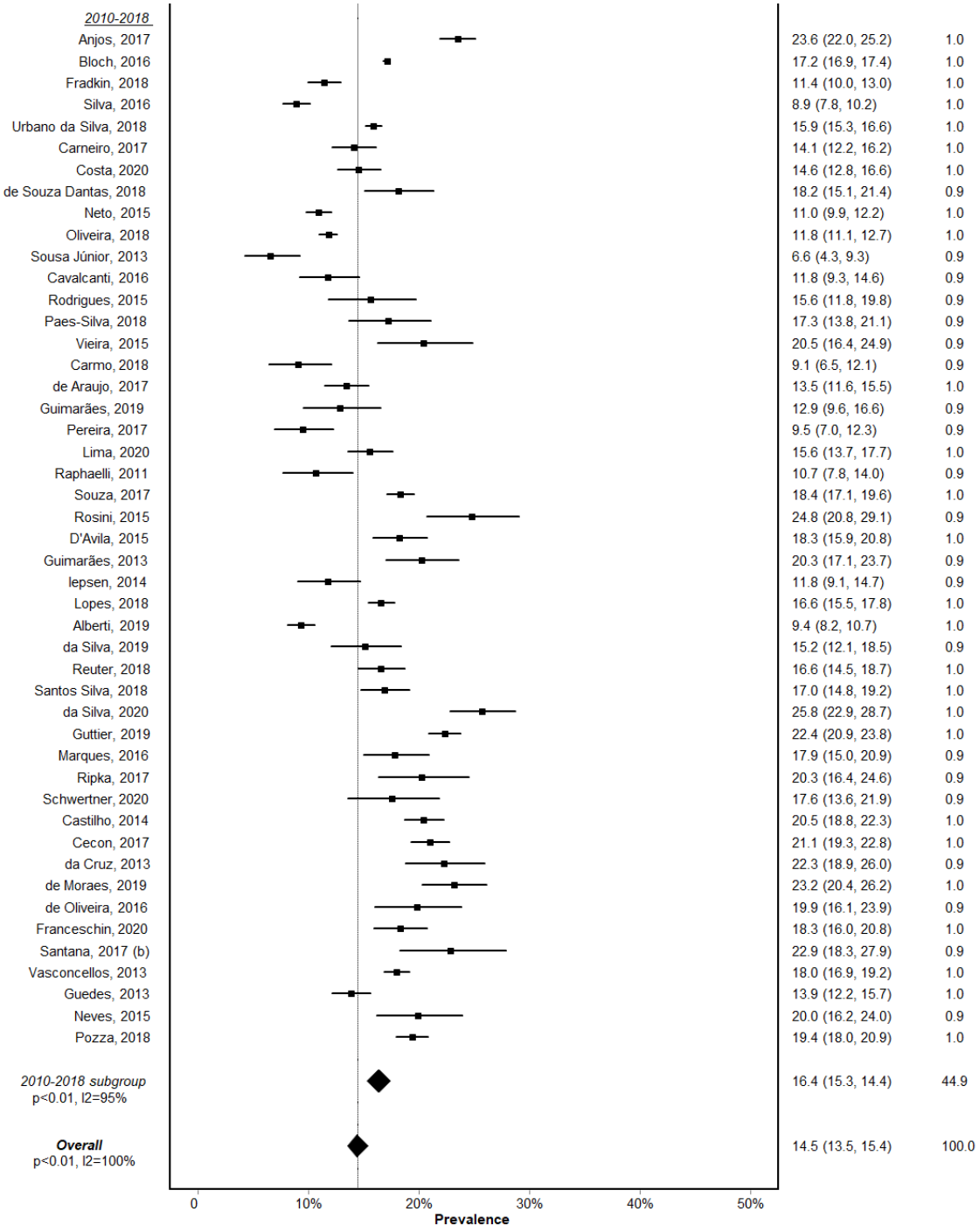



Junior, 2008 18.6 (16.2, 21.2) 0.6
Nobre, 2006 24.0 (22.2, 25.8) 0.7
Ferreira, 2008 16.2 (13.3, 19.4) 0.6
Kuschnir, 2009 16.0 (14.7, 17.4) 0.7
Amorim, 2006 9.7 (8.3, 11.1) 0.7
Barros, 2014 17.2 (14.1, 20.5) 0.6
Gomes, 2009 18.7 (15.5, 22.2) 0.6
Pereira, 2018 (a) 13.9 (10.5, 17.7) 0.6
Rodrigues, 2006 13.9 (10.6, 17.6) 0.6
Cintra, 2014 28.2 (27.2, 29.2) 0.7
Toral, 2007 21.0 (17.1, 25.2) 0.6
Santana, 2017 (a) 23.3 (19.7, 27.1) 0.6
Vanzelli, 2008 24.0 (20.8, 27.3) 0.6
Coelho, 2012 19.8 (16.1, 23.8) 0.6
Fernandes, 2007 24.8 (21.9, 27.8) 0.6
Fernandes, 2009 23.3 (21.4, 25.3) 0.7
Guedes, 2011 12.6 (11.5, 13.8) 0.7
Lourenço da Silva, 2018 17.2 (15.4, 19.1) 0.7
Bispo, 2015 21.8 (19.4, 24.4) 0.6
Caran, 2018 20.1 (16.7, 23.8) 0.6
Pereira, 2018 (b) 24.9 (20.6, 29.4) 0.6
Leal, 2020 26.5 (24.0, 29.1) 0.6
Miranda, 2014 12.8 (9.9, 16.1) 0.6
Romero, 2015 36.8 (32.4, 41.3) 0.6
2000-2009 subgroup
p<0.01, I2=100% 18.9 (14.7, 23.2) 46.0
2010-2018
Anjos, 2017 37.7 (35.9, 39.6) 0.7
Bloch, 2016 19.2 (18.9, 19.5) 0.7
Fradkin, 2018 19.0 (17.2, 20.9) 0.7
Silva, 2016 11.7 (10.4, 13.1) 0.7
Urbano da Silva, 2018 23.7 (22.9, 24.5) 0.7
Carneiro, 2017 21.2 (18.9, 23.6) 0.6
Costa, 2020 24.7 (22.4, 27.1) 0.6
de Souza Dantas, 2018 25.8 (22.3, 29.4) 0.6
Aranha, 2020 20.5 (17.7, 23.5) 0.6
Gemelli, 2016 28.3 (25.1, 31.7) 0.6
Farias, 2019 24.2 (22.6, 25.8) 0.7
Neto, 2015 17.8 (16.4, 19.2) 0.7
Monteiro, 2016 10.5 (8.7, 12.4) 0.6
Oliveira, 2018 16.0 (15.1, 16.9) 0.7
Pitanga, 2019 19.2 (16.2, 22.5) 0.6
Sousa Júnior, 2013 7.3 (5.0, 10.1) 0.6
Cavalcanti, 2016 18.6 (15.5, 21.9) 0.6
Rodrigues, 2015 20.9 (16.6, 25.6) 0.6
Santana, 2017 27.6 (23.2, 32.1) 0.6
Paes-Silva, 2018 27.7 (23.5, 32.2) 0.6
Vieira, 2015 28.8 (24.2, 33.7) 0.6
Carmo, 2018 13.6 (10.4, 17.1) 0.6
de Araujo, 2017 24.6 (22.2, 27.1) 0.6
Guimarães, 2019 18.5 (14.6, 22.7) 0.6
Moura, 2019 34.1 (31.4, 36.9) 0.6
Pereira, 2017 13.3 (10.4, 16.5) 0.6
Lima, 2020 22.8 (20.5, 25.2) 0.6
Raphaelli, 2011 24.7 (20.4, 29.2) 0.6
Souza, 2017 28.3 (26.9, 29.8) 0.7
Christofaro, 2016 18.6 (16.5, 20.8) 0.6
Cureau, 2014 23.9 (21.4, 26.4) 0.6
Finato, 2013 30.1 (27.5, 32.7) 0.6
Graup, 2014 24.7 (22.5, 26.9) 0.7
Rosini, 2015 36.3 (31.7, 40.9) 0.6
D'Avila, 2015 29.8 (27.0, 32.8) 0.6
Guimarães, 2013 28.7 (25.0, 32.5) 0.6
Iepsen, 2014 17.1 (13.9, 20.5) 0.6
Lopes, 2018 21.7 (20.4, 23.0) 0.7
Alberti, 2019 13.8 (12.4, 15.3) 0.7
DAvila, 2017 22.3 (19.5, 25.3) 0.6
da Silva, 2019 19.4 (16.0, 23.0) 0.6

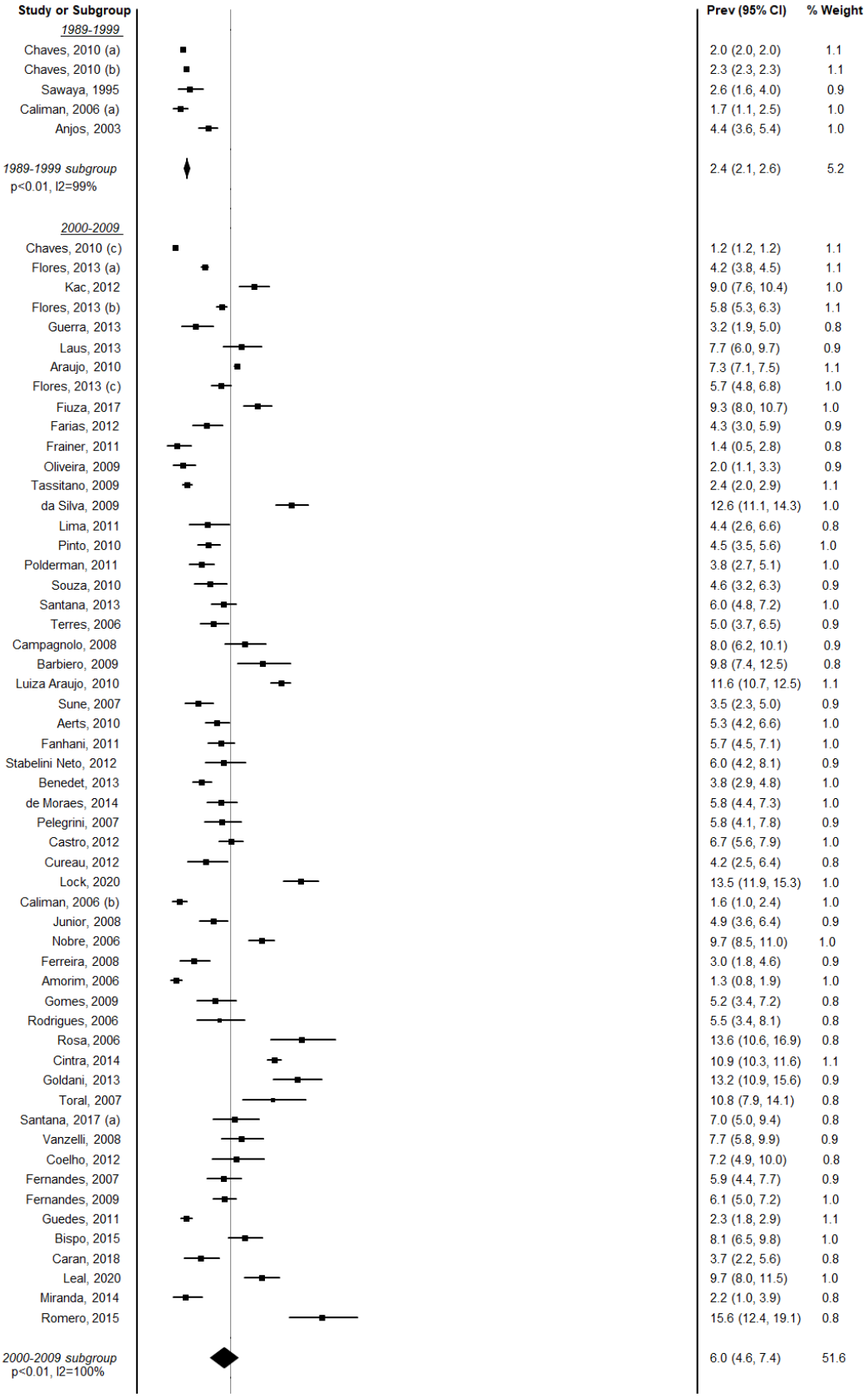

Guilherme, 2015 40.1 (36.1, 44.2) 0.6
Reuter, 2018 27.8 (25.3, 30.3) 0.6
Santos Silva, 2018 23.4 (21.0, 25.9) 0.6
Ulbricht, 2018 33.2 (29.7, 36.8) 0.6
Cesar, 2020 29.9 (25.9, 34.0) 0.6
da Silva, 2018 35.2 (31.3, 39.1) 0.6
da Silva, 2020 38.7 (35.5, 42.0) 0.6
Guttier, 2019 44.4 (42.7, 46.1) 0.7
Marques, 2016 20.6 (17.6, 23.8) 0.6
Ramos, 2019 35.0 (30.4, 39.8) 0.6
Ripka, 2017 25.9 (21.6, 30.5) 0.6
Schwertner, 2020 23.0 (18.6, 27.7) 0.6
Castilho, 2014 30.3 (28.3, 32.4) 0.7
da Cruz, 2013 30.2 (26.3, 34.2) 0.6
de Moraes, 2019 41.2 (37.8, 44.6) 0.6
de Oliveira, 2016 30.0 (25.6, 34.6) 0.6
Franceschin, 2020 27.2 (24.5, 30.0) 0.6
Santana, 2017 (b) 30.9 (25.8, 36.2) 0.6
Vasconcellos, 2013 25.8 (24.5, 27.1) 0.7
Coutinho, 2014 32.5 (30.2, 34.8) 0.7
de Pinho, 2014 18.5 (15.3, 21.9) 0.6
Fortes, 2013 31.9 (28.1, 35.8) 0.6
Guedes, 2013 16.6 (14.8, 18.5) 0.7
Guedes, 2014 19.4 (17.4, 21.4) 0.7
Neves, 2015 32.4 (27.9, 37.0) 0.6
Enes, 2018 32.0 (28.1, 36.1) 0.6
Pozza, 2018 34.0 (32.3, 35.7) 0.7
Lourenço, 2018 24.6 (22.0, 27.3) 0.6
Pereira, 2018 (c) 29.4 (24.9, 34.2) 0.6
Tebar, 2018 27.6 (24.9, 30.4) 0.6
2010-2018 subgroup
p<0.01, I2=98%
25.1 (23.4, 26.8) 44.9
Overall
p<0.01, I2=100%
20.6 (19.6, 21.5) 100.0
0
10%
20%
30%
40%
50%
Prevalence

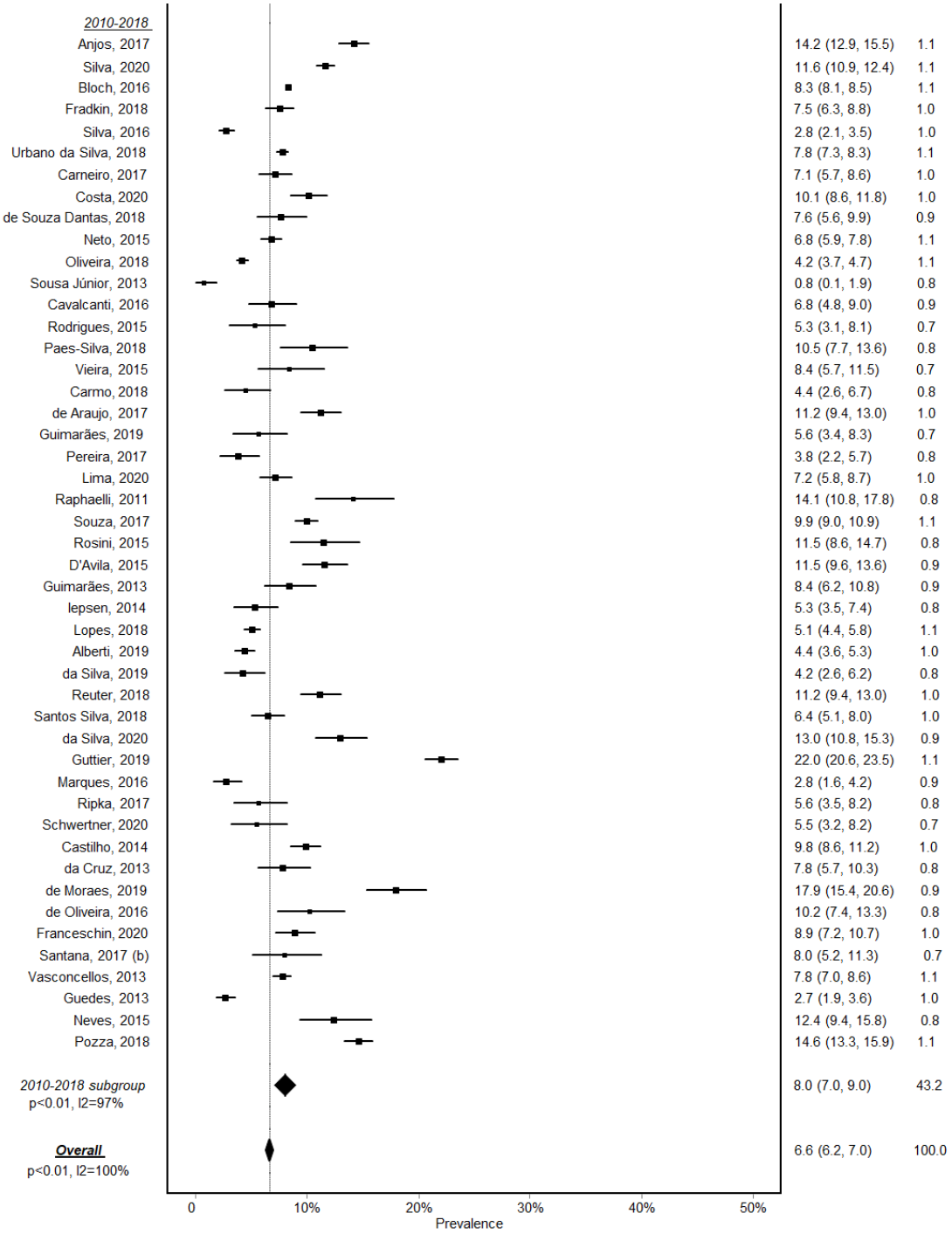
Supplementary Figure 2.




2010-2018
Anjos, 2017 23.6 (22.0, 25.2) 1.0
Bloch, 2016 17.2 (16.9, 17.4) 1.0
Fradkin, 2018 11.4 (10.0, 13.0) 1.0
Silva, 2016 8.9 (7.8, 10.2) 1.0
Urbano da Silva, 2018 15.9 (15.3, 16.6) 1.0
Carneiro, 2017 14.1 (12.2, 16.2) 1.0
Costa, 2020 14.6 (12.8, 16.6) 1.0
de Souza Dantas, 2018 18.2 (15.1, 21.4) 0.9
Neto, 2015 11.0 (9.9, 12.2) 1.0
Oliveira, 2018 11.8 (11.1, 12.7) 1.0
Sousa Júnior, 2013 6.6 (4.3, 9.3) 0.9
Cavalcanti, 2016 11.8 (9.3, 14.6) 0.9
Rodrigues, 2015 15.6 (11.8, 19.8) 0.9
Paes-Silva, 2018 17.3 (13.8, 21.1) 0.9
Vieira, 2015 20.5 (16.4, 24.9) 0.9
Carmo, 2018 9.1 (6.5, 12.1) 0.9
de Araujo, 2017 13.5 (11.6, 15.5) 1.0
Guimarães, 2019 12.9 (9.6, 16.6) 0.9
Pereira, 2017 9.5 (7.0, 12.3) 0.9
Lima, 2020 15.6 (13.7, 17.7) 1.0
Raphaelli, 2011 10.7 (7.8, 14.0) 0.9
Souza, 2017 18.4 (17.1, 19.6) 1.0
Rosini, 2015 24.8 (20.8, 29.1) 0.9
D'Avila, 2015 18.3 (15.9, 20.8) 1.0
Guimarães, 2013 20.3 (17.1, 23.7) 0.9
Iepsen, 2014 11.8 (9.1, 14.7) 0.9
Lopes, 2018 16.6 (15.5, 17.8) 1.0
Alberti, 2019 9.4 (8.2, 10.7) 1.0
da Silva, 2019 15.2 (12.1, 18.5) 0.9
Reuter, 2018 16.6 (14.5, 18.7) 1.0
Santos Silva, 2018 17.0 (14.8, 19.2) 1.0
da Silva, 2020 25.8 (22.9, 28.7) 1.0
Guttier, 2019 22.4 (20.9, 23.8) 1.0
Marques, 2016 17.9 (15.0, 20.9) 0.9
Ripka, 2017 20.3 (16.4, 24.6) 0.9
Schwertner, 2020 17.6 (13.6, 21.9) 0.9
Castilho, 2014 20.5 (18.8, 22.3) 1.0
Cecon, 2017 21.1 (19.3, 22.8) 1.0
da Cruz, 2013 22.3 (18.9, 26.0) 0.9
de Moraes, 2019 23.2 (20.4, 26.2) 1.0
de Oliveira, 2016 19.9 (16.1, 23.9) 0.9
Franceschin, 2020 18.3 (16.0, 20.8) 1.0
Santana, 2017 (b) 22.9 (18.3, 27.9) 0.9
Vasconcellos, 2013 18.0 (16.9, 19.2) 1.0
Guedes, 2013 13.9 (12.2, 15.7) 1.0
Neves, 2015 20.0 (16.2, 24.0) 0.9
Pozza, 2018 19.4 (18.0, 20.9) 1.0
2010-2018 subgroup
p<0.01, I2=95%
16.4 (15.3, 14.4) 44.9
Overall
p<0.01, I2=100%
14.5 (13.5, 15.4) 100.0
0
10%
20%
30%
40%
50%
Prevalence

Supplementary Figure 3.




2010-2018
Anjos, 2017 14.2 (12.9, 15.5) 1.1
Silva, 2020 11.6 (10.9, 12.4) 1.1
Bloch, 2016 8.3 (8.1, 8.5) 1.1
Fradkin, 2018 7.5 (6.3, 8.8) 1.0
Silva, 2016 2.8 (2.1, 3.5) 1.0
Urbano da Silva, 2018 7.8 (7.3, 8.3) 1.1
Carneiro, 2017 7.1 (5.7, 8.6) 1.0
Costa, 2020 10.1 (8.6, 11.8) 1.0
de Souza Dantas, 2018 7.6 (5.6, 9.9) 0.9
Neto, 2015 6.8 (5.9, 7.8) 1.1
Oliveira, 2018 4.2 (3.7, 4.7) 1.1
Sousa Júnior, 2013 0.8 (0.1, 1.9) 0.8
Cavalcanti, 2016 6.8 (4.8, 9.0) 0.9
Rodrigues, 2015 5.3 (3.1, 8.1) 0.7
Paes-Silva, 2018 10.5 (7.7, 13.6) 0.8
Vieira, 2015 8.4 (5.7, 11.5) 0.7
Carmo, 2018 4.4 (2.6, 6.7) 0.8
de Araujo, 2017 11.2 (9.4, 13.0) 1.0
Guimarães, 2019 5.6 (3.4, 8.3) 0.7
Pereira, 2017 3.8 (2.2, 5.7) 0.8
Lima, 2020 7.2 (5.8, 8.7) 1.0
Raphaelli, 2011 14.1 (10.8, 17.8) 0.8
Souza, 2017 9.9 (9.0, 10.9) 1.1
Rosini, 2015 11.5 (8.6, 14.7) 0.8
D'Avila, 2015 11.5 (9.6, 13.6) 0.9
Guimarães, 2013 8.4 (6.2, 10.8) 0.9
Iepsen, 2014 5.3 (3.5, 7.4) 0.8
Lopes, 2018 5.1 (4.4, 5.8) 1.1
Alberti, 2019 4.4 (3.6, 5.3) 1.0
da Silva, 2019 4.2 (2.6, 6.2) 0.8
Reuter, 2018 11.2 (9.4, 13.0) 1.0
Santos Silva, 2018 6.4 (5.1, 8.0) 1.0
da Silva, 2020 13.0 (10.8, 15.3) 0.9
Guttier, 2019 22.0 (20.6, 23.5) 1.1
Marques, 2016 2.8 (1.6, 4.2) 0.9
Ripka, 2017 5.6 (3.5, 8.2) 0.8
Schwertner, 2020 5.5 (3.2, 8.2) 0.7
Castilho, 2014 9.8 (8.6, 11.2) 1.0
da Cruz, 2013 7.8 (5.7, 10.3) 0.8
de Moraes, 2019 17.9 (15.4, 20.6) 0.9
de Oliveira, 2016 10.2 (7.4, 13.3) 0.8
Franceschin, 2020 8.9 (7.2, 10.7) 1.0
Santana, 2017 (b) 8.0 (5.2, 11.3) 0.7
Vasconcellos, 2013 7.8 (7.0, 8.6) 1.1
Guedes, 2013 2.7 (1.9, 3.6) 1.0
Neves, 2015 12.4 (9.4, 15.8) 0.8
Pozza, 2018 14.6 (13.3, 15.9) 1.1
2010-2018 subgroup
p<0.01, I2=97%
8.0 (7.0, 9.0) 43.2
Overall
p<0.01, I2=100%
6.6 (6.2, 7.0) 100.0
0
10%
20%
30%
40%
50%
Prevalence

Material suplementar artigo 2

Supplementary Table 1. Definitions of abnormal values for evaluation of cardiometabolic risk factors.

Variables	Abnormal Value Definition	Reference
Glycated hemoglobin	≥5.7%	American Diabetes Association, 2019
Fasting plasma glucose	≥100 mg/dl	American Diabetes Association, 2019
High blood pressure	≥95th percentile	National High Blood Pressure Education Program, 2004
Total cholesterol	≥170 mg/dl	V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis, 2013
LDL-cholesterol	≥130 mg/dl	V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis, 2013
HDL-cholesterol	≤45 mg/dl	V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis, 2013
Triglycerides	≥130 mg/dl	V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis, 2013
Fasting insulin	≥20 mU/L	Brazilian Guidelines of Prevention of Atherosclerosis in Childhood and Adolescence, 2005
Metabolic Syndrome	Abdominal obesity plus at least 2 more components: low HDL-cholesterol, high triglycerides, high plasma glucose or high blood pressure	International Diabetes Federation, 2007[b]

[a] Adolescents with excess weight (BMI ≥ 85th); [b] International Diabetes Federation criteria: abdominal obesity - mandatory component (< 16 years: ≥ 90th percentile; ≥ 16 years males: ≥ 90 cm and females: ≥ 80 cm) and at least two of the following criteria: fasting plasma glucose ≥ 100 mg/dl; systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg; triglycerides ≥ 150 mg/dl; HDL-cholesterol in adolescents < 16 years: < 40 mg/dl; HDL-cholesterol in males ≥ 16 years: < 40 mg/dl; and HDL-cholesterol in girls > 16 years: < 50 mg/dl.

Material suplementar artigo 3

Table S1. Beta coefficient (95% confidence interval) of BMI (kg/m^2) at baseline according to quartiles of NT-proBNP at baseline, N=9,681

	NT-proBNP categories (pg/mL)			
	Q1 (≤ 27.17)	**Q2 (27.19 – 50.79)**	**Q3 (50.81 – 90.58)**	**Q4 (≥ 90.63)**
Model 1	1.16 (0.86-1.46)*	0.92 (0.64-1.20)*	0.36 (0.08-0.63)*	1 (reference)
Model 2	0.83 (0.53-1.12)*	0.66 (0.38-0.94)*	0.25 (-0.02-0.52)	1 (reference)

Model 1: Adjusted for age, sex, race-center, smoking status, eGFR, hypertension, diabetes, heart failure, ASCVD (coronary heart disease or stroke). Model 2: Model 1 plus total cholesterol, HDL-cholesterol and lipid lowering medication. *p<0.05.
ASCVD= atherosclerotic cardiovascular disease; eGFR=Estimated glomerular filtration rate; HDL=High-density lipoprotein