J Bras Pneumol. 2022;48(6):e20220222
https://dx.doi.org/10.36416/1806-3756/e20220222

The bidirectional association between wheezing and obesity during adolescence and the beginning of adulthood in the 1993 birth cohort, Pelotas, Brazil

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Submitted: 14 June 2022
Accepted: 30 August 2022

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ABSTRACT

Objective: To analyze the bidirectional association between wheezing and obesity during adolescence and the beginning of adulthood in a cohort in southern Brazil. **Methods:** This prospective longitudinal study used data from the 1993 birth cohort in Pelotas, Brazil. The following outcome variables were measured at 22 years of age: self-reported wheezing during the last 12 months and obesity (BMI ≥ 30 kg/m^2). The following exposure variables were measured at ages 11, 15, and 18: self-reported wheezing (no wheezing or symptom presentation in 1, 2, or 3 follow-ups) and obesity (non-obese or obese in 1, 2, or 3 follow-ups). Crude and adjusted logistical regression stratified by sex were used in the analyses. The reference category was defined as participants who presented no wheezing or obesity. **Results:** A total of 3,461 participants had data on wheezing and 3,383 on BMI. At 22 years of age, the prevalence of wheezing was 10.1% (95%CI: 9.1; 11.2), and obesity, 16.2% (95%CI: 15.0; 17.6). In females, the presence of wheezing in two follow-ups revealed a 2.22-fold (95%CI: 1.36; 3.61) greater chance of developing obesity at 22 years of age. Meanwhile, the presence of obesity in two follow-ups resulted in a 2.03-fold (95%IC: 1.05; 3.92) greater chance of wheezing at 22 years of age. No associations were found between wheezing and obesity in males. **Conclusions:** The obtained data suggest a possible positive bidirectional association between wheezing and obesity, with greater odds ratios in the wheezing to obesity direction in females and in the category of occurrence of exposure in two follow-ups.

Keywords: Asthma, BMI, Respiratory Sounds, Wheezing, Body Weight.

INTRODUCTION

In recent years, the literature has shown a positive association between wheezing and obesity.[1-3] Furthermore, the Global Initiative for Asthma (GINA) annually reiterates the importance of research in this field, given that asthmatic obese patients display worse disease control and a greater burden and frequency of symptoms, interfering with their quality of life.[4]

A systematic review proposed the possibility of obesity being a risk factor or effect modifier for wheezing status.[5] However, the literature is inconsistent in assuming a direction for the association or the possibility of common causes between asthma and obesity.[6,7] In order to clarify the relationship between these diseases and propose strategies for management and prevention, it is necessary to understand the contribution of each disease in the association in different populations with distinct socioeconomic and environmental aspects.[8,4]

The bidirectional analysis of the association between wheezing and obesity in longitudinal studies may be considered a recent approach in the literature. Some bidirectional longitudinal studies[9-11] indicated that obesity probably precedes the onset of asthma. Granell et al.[11] proposed that for each increment of 1 kg/m^2 in the Body Mass Index (BMI), the risk of developing asthma during infancy increases by 55%. In contrast, Zhang et al.[12] found that children diagnosed with asthma in any follow-up study had an approximately 40% greater chance of becoming obese in the subsequent follow-up. Therefore, the association directionality between these diseases remains uncertain.[6,7]

Thus, the aim of the present study was to explore the bidirectional association between wheezing and obesity in a cohort in southern Brazil, investigating the associations between a) the presence of wheezing during adolescence (11, 15, and 18 years of age) and the presence of obesity at age 22, and b) the presence of obesity during adolescence (11, 15, and 18 years of age) and the presence of wheezing at age 22.

METHODS

This was a longitudinal, prospective, and population-based study of the 1993 birth cohort in Pelotas, Brazil. In 1993, all live births whose families resided in the

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urban area of Pelotas were eligible for the study and, subsequently, followed up at different ages for 22 years. The analyses included: a) participants who answered questions about wheezing in the follow-ups conducted at 11, 15, and 18 years of age and with anthropometric measurements at age 22, and b) participants with anthropometric measurements at 11, 15, and 18 years of age and with information on wheezing collected in the follow-up at age 22. More details concerning the cohort's methodology may be found in previous publications.[13-15]

In order to investigate the bidirectional association, the variables of interest herein were wheezing (chest wheezing) and BMI. The wheezing variable was defined according to the "International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee"[16] and measured using a questionnaire validated for the Brazilian population.[17] Treated as a binary variable, participants were considered to present wheezing after an affirmative response to the question related to the 12 months leading up to the follow-up visit: *"Since <month> of last year, have you experienced any chest wheezing?"*. The variable BMI (weight/height^2) was dichotomized using the cutoff points that characterize the presence of obesity. Participants who presented with a BMI ≥ + 2 z-scores at ages 11 and 15 and BMI ≥ 30.0 kg/m^2 at ages 18 and 22 were considered obese.[18] In the follow-ups at 11 and 15 years of age, the participants' weight was measured twice using a digital scale (Tanita, accuracy of 100 grams), while at ages 18 and 22, weight was obtained using the BOD POD® body composition tracking system (BOD POD® Composition System; COSMED, Albano Laziale, Italy). Height was measured with a stadiometer.

For the bidirectional analysis, the following combinations were used: a) presence of wheezing at ages 11, 15, and 18 as exposure and "obesity at 22 years of age" as the outcome, and b) obesity at ages 11, 15, and 18 as exposure and "wheezing at the 22-year follow-up" as the outcome. Exposure variables were generated for the presence of wheezing and obesity and were categorized as follows: absence of exposure in all three follow-ups, 1 follow-up (presence of exposure in one of the three follow-ups); 2 follow-ups (presence of exposure in two of the three follow-ups); always presenting exposure (presence of exposure in all three follow-up visits).

The covariates collected in the perinatal follow-ups were: sex (male/female), skin color (white/black/other), birthweight (grams), gestational age at birth (weeks), maternal schooling during pregnancy (years), maternal smoking during pregnancy (yes/no), family history (father and/or mother) of asthma (yes/no), and family income (minimum wages). At the 11-year follow-up, the covariates of interest were: family income (in Reais) and parental smoking (never/ex-smoker/smoker). In order to characterize the sample at the 22-year follow-up, the following covariates were evaluated: schooling (years), asset index (quintiles), smoking (never smoked/ex-smoker/smoker), total physical activity (leisure and commuting) ≥ 150 min/week (yes/no), and the use of corticosteroids in the last three months (yes/no).

The categorical variables were described as relative frequencies and the respective 95% confidence intervals (95%CI). According to the perinatal follow-up variables, Pearson's chi-square test was used to compare the original cohort sample and the samples included in the analyses. The prevalence of obesity and wheezing at 22 years of age was described according to the demographic, socioeconomic, behavioral, and health variables, and either Pearson's chi-square test or a Chi-square test for linear trends was used according to the independent variables.

In order to test the crude and adjusted association between the outcomes wheezing and obesity at 22 years of age according to exposure (obesity and wheezing from ages 11 to 18, respectively), logistical regressions stratified by sex were used, regardless of the significance of the test of interaction. Confounders were determined *a priori* and included simultaneously in the analytical models. The confounding variables were defined as: skin color, birthweight, gestational age, maternal schooling during pregnancy, maternal smoking during pregnancy, family history of asthma, and family income and parental smoking at the 11-year follow-up. The p-value of the association analyses was given by the Wald Test. A 5% significance level was adopted, and the analyses were performed using the Stata 16.0 software (Stata Corp. LP, College Station, TX, USA).

The 1993 cohort follow-ups were approved by the Ethics Committee of the Federal University of Pelotas, with the most recent protocol being No. 1.250.366, at 22 years of age. All participants or guardians were informed regarding the objectives of the study and signed a term of free and informed consent prior to the beginning of data collection, in accordance with the Declaration of Helsinki.

RESULTS

The 1993 cohort consisted of 5,249 live births, with follow-up rates of 87.5%, 85.7%, 81.4%, and 76.3% at ages 11, 15, 18, and 22, respectively. The present study's sample included 3,461 participants with complete wheezing information from 11 to 18 years of age, and 3,383 participants with BMI data from 11 to 18 years of age. No differences were observed in the distribution of perinatal characteristics between the original cohort sample and the samples included in the analyses (Table 1).

The prevalence of obesity and wheezing over the last 12 months at the 22-year follow-up according to demographic, socioeconomic, behavioral, and health variables is shown in Table 2. The prevalence of obesity was 16.2% (95%CI: 15.0; 17.6). The highest prevalence of obesity with statistical significance was observed in female participants as opposed to males (18.5% versus 13.7%), black skin color (19.1% versus

15.1% with white skin color), family history of asthma (18.6% versus 15.1% without a family history), and participants whose parents were ex-smokers at the 11-year follow-up (17.9% compared to 13.5% in those whose parents were non-smokers). The prevalence of obesity was 17.9% in the poorest asset index quintile at 22 years of age, whereas, in the wealthiest quintile, it was 10.8%. Also, participants with 12 or more years of schooling showed a lower prevalence of obesity (12.1%) when compared to the other categories.

The prevalence of wheezing in the last 12 months was 10.1% (95%CI: 9.1; 11.2). The highest prevalence of wheezing, with statistical significance, was observed in participants whose mothers had the least schooling (11.9% versus 8.9% of mothers with more years of schooling), smoked during pregnancy (12.1% versus 9.2% in non-smokers), and in participants with a parental history of asthma (14.7% versus 7.8% without parental history of asthma). Regarding the variables pertaining to the participants themselves, a larger prevalence of wheezing at the 22-year follow-up was found in those with fewer years of schooling (18.3% versus 8% with more years of schooling), in the poorest quintile compared to the richest (12.9% versus 7.7%), among smokers (20.1% versus 7.7% in non-smokers), among the obese (14% versus 9.5% in the non-obese), and among those who reported using corticosteroids in the last three months compared to those who did not use such medications (19.3% versus 8.5%) (Table 2).

During the period from 11 to 18 years of age, three follow-ups were carried out in the 1993 birth cohort. While the overall prevalence of wheezing in at least one of the follow-up visits was 23.2% (95%CI: 21.8; 24.6), 2.4% (95%CI: 1.9; 2.9) always reported the presence of the symptom. As for obesity, the overall prevalence in at least one follow-up was 11.4% (95%CI: 10.3; 12.5), and 3.7% (95%CI: 3.2; 4.4) were obese in all follow-ups. In the stratification by sex,

Table 1. Baseline characteristics of the original cohort and the samples included in the analyses. The 1993 Birth Cohort, Pelotas, Brazil.

		Included in the analyses[a]			
	Original Cohort (n = 5,249)	Wheezing from age 11 to 18 (n = 3,461)		Obesity from age 11 to 18 (n = 3,383)	
	% (95% CI)	% (95% CI)	p-value*	% (95% CI)	p-value*
Sex			0.098		0.249
Male	49.6 (48.2;51.0)	47.8 (46.1;49.5)		48.3 (46.6;50.0)	
Female	50.4 (49.0;51.7)	52.2 (50.5;53.9)		51.7 (50.0;53.3)	
Birthweight (grams)			0.521		0.277
< 2,500	10.3 (9.5;11.1)	9.5 (8.5;10.5)		9.5 (8.6;10.6)	
2,500 - 2,999	26.4 (25.2;27.6)	26.0 (24.6;27.5)		25.6 (24.1;27.1)	
3,000 - 3,499	38.8 (37.5;40.1)	39.0 (37.4;40.6)		38.8 (37.1;40.4)	
≥ 3,500	24.5 (23.4;25.7)	25.5 (24.0;26.9)		26.1 (24.7;27.7)	
Gestational age (weeks)			0.222		0.178
≤ 36	11.5 (10.6;12.4)	10.2 (9.2;11.3)		10.1 (9.1;11.3)	
37 - 38	20.0 (18.9;21.2)	20.1 (18.7;21.5)		20.1 (18.6;21.5)	
≥ 39	68.5 (67.1;69.8)	69.7 (68.0;71.3)		69.8 (68.1;71.4)	
Maternal schooling during pregnancy (years)			0.262		0.121
0 - 4	28.0 (26.8;29.2)	26.6 (25.2;28.1)		26.1 (24.6;27.6)	
5 - 8	46.2 (44.9;47.6)	47.9 (46.2;49.6)		48.0 (46.3;49.7)	
≥ 9	25.8 (24.6;26.9)	25.4 (24.0;26.9)		25.9 (24.4;27.4)	
Maternal smoking during pregnancy			0.590		0.406
No	66.6 (65.3;67.9)	67.2 (65.6;68.7)		67.5 (65.9;69.0)	
Yes	33.4 (32.1;34.7)	32.8 (31.3;34.4)		32.5 (31.0;34.1)	
Family income (minimum wages)			0.407		0.064
≤ 1	18.8 (17.8;19.9)	18.1 (16.8;19.4)		16.9 (15.7;18.2)	
1.1 - 3	41.8 (40.5;43.2)	41.5 (39.8;43.1)		42.1 (40.4;43.8)	
3.1 - 6	23.5 (22.3;24.6)	25.2 (23.8;26.7)		25.7 (24.2;27.2)	
6.1 - 10	8.4 (7.7;9.2)	8.0 (7.2;9.0)		8.3 (7.4;9.4)	
≥ 10	7.5 (6.8;8.2)	7.2 (6.4;8.1)		7.0 (6.2;7.9)	

[a]Sample wheezing from 11 to 18 years of age: participants with information on wheezing in the last 12 months in the follow-ups at ages 11, 15, and 18 and information on obesity (BMI ≥ 30 kg/m²) at 22 years of age; Sample obesity from 11 to 18 years of age: participants with information on obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) at ages 11, 15, and 18 and information on wheezing in the last 12 months at the 22-year follow-up.*Pearson's chi-square test; significance level of 5% - comparison between original cohort and the samples included in the analyses.

Table 2. Prevalence of obesity (BMI ≥ 30 kg/m²) and wheezing in the last 12 months at the 22-year follow-up according to demographic, socioeconomic, behavioral, and health variables in the 1993 Birth Cohort, Pelotas, Brazil.

	Obesity at 22 years of age[a] (n = 3,461)		Wheezing at 22 years of age[b] (n = 3,383)	
	% (95% CI)	p-value*	% (95% CI)	p-value*
Sex		<0.001		0.154
Male	13.7 (12.1;15.5)		10.9 (9.5;12.6)	
Female	18.5 (16.8;20.5)		9.4 (8.1;10.9)	
Skin color		0.029		0.111
White	15.0 (13.5;16.6)		9.5 (8.3;10.9)	
Black	19.1 (15.9;22.8)		12.7 (10.0;15.9)	
Other	18.2 (15.5;21.2)		10.1 (8.1;12.5)	
Maternal schooling during pregnancy (years)		0.007		0.035
0 - 4	17.4 (15.1;20.2)		11.9 (10.0;14.3)	
5 - 8	17.5 (15.7;19.5)		9.8 (8.4;11.4)	
≥ 9	12.6 (10.5;15.0)		8.9 (7.1;11.1)	
Maternal smoking during pregnancy		0.100		0.011
No	15.5 (14.1;17.1)		9.2 (8.1;10.5)	
Yes	17.8 (15.6;20.2)		12.1 (10.2;14.2)	
Family history of asthma		0.011		<0.001
No	15.1 (13.6;16.7)		7.8 (6.8;9.1)	
Yes	18.6 (16.4;21.0)		14.7 (12.8;17.0)	
Parental smoking at the 11-year follow-up		0.024		0.126
Never	13.5 (11.4;15.9)		9.1 (7.4;11.2)	
Ex-smoker	17.9 (15.5;20.6)		9.2 (7.5;11.4)	
Smoker	17.1 (15.3;19.2)		11.3 (9.8;13.1)	
Schooling at 22 years of age		0.001		<0.001
0 - 4	15.2 (8.8;24.9)		18.3 (11.3;28.1)	
5 - 8	18.5 (16.0;21.2)		14.4 (12.2;17.0)	
9 - 11	17.8 (15.8;19.9)		8.4 (7.1;10.0)	
≥ 12 years	12.1 (10.1;14.3)		8.0 (6.5;9.9)	
Asset index at 22 years of age (quintiles)		<0.001		0.020
First (poorest)	17.9 (15.1;21.1)		12.9 (10.6;15.8)	
Second	18.7 (15.8;21.9)		9.6 (7.6;12.2)	
Third	17.8 (15.1;20.1)		9.2 (7.2;11.6)	
Fourth	15.9 (13.3;18.9)		11.3 (9.1;14.0)	
Fifth (richest)	10.8 (8.6;13.5)		7.7 (5.9;10.0)	
Smoking at 22 years of age		0.080		<0.001
Never	15.4 (14.0;16.9)		7.7 (6.7;8.9)	
Ex-smoker	19.6 (15.7;24.3)		11.7 (8.7;15.5)	
Smoker	17.9 (14.9;21.3)		20.1 (16.9;23.7)	
Total physical activity ≥ 150 min/week (leisure and commuting) at age 22		0.089		0.120
No	17.7 (15.6;19.9)		9.1 (7.6;10.8)	
Yes	15.4 (13.9;17.0)		10.8 (9.5;12.2)	
Obesity (BMI ≥ 30 kg/m²) at age 22		-		0.002
No	-		9.5 (8.4;10.7)	
Yes	-		14.0 (11.3;17.2)	
Wheezing in the last 12 months at 22 years of age		0.011		-
No	15.6 (14.3;17.0)		-	
Yes	20.9 (17.0;25.5)		-	
Corticoid use in the last three months at the 22-year follow-up		0.783		<0.001
No	16.1 (14.7;17.5)		8.4 (7.4;9.5)	
Yes	16.7 (13.2;20.8)		19.3 (15.6;23.7)	
Total	16.2 (15.0;17.6)		10.1 (9.1;11.2)	

* Pearson's chi-square test or Chi-square test for linear trends. Significance level of 5%. [a] Sample wheezing from 11 to 18 years of age: participants with information on wheezing in the last 12 months in the follow-ups at ages 11, 15, and 18 and information on obesity (BMI ≥ 30 kg/m²) at 22 years of age. [b] Sample obesity from 11 to 18 years of age: participants with information on obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) at ages 11, 15, and 18 and information on wheezing in the last 12 months at the 22-year follow-up.

the prevalence of obesity in the two aforementioned categories was higher in men (13.8% and 4.7%, respectively). The same was not observed among women (Figure 1).

The association between the presence of wheezing from age 11 to 18 and obesity at 22 years of age according to sex may be observed in Table 3. There were no associations between wheezing and obesity in males. Conversely, in females, the presence of wheezing from age 11 to 18 was positively associated with obesity at 22 years of age in the crude analysis. Later, in the adjusted analyses, the wheezing category in two follow-ups maintained this association with a 95%CI that did not cross one. Women who presented wheezing in two follow-ups had 2.22 times (95%CI: 1.36; 3.61) more chances of developing obesity at 22 years of age when compared to participants who had not wheezed in previous follow-ups (p = 0.002).

In Table 4, we observed an association between obesity from 11 to 18 years of age and the presence of wheezing at age 22 according to sex. No associations were observed for males. In females, the presence of obesity in two follow-ups was positively associated with the presence of wheezing reported at 22 years of age, although without statistical significance. Female participants also showed 2.03 times (95%CI: 1.05; 3.92) greater chances of developing wheezing at age 22 than those who did not present obesity in the follow-ups of interest (p = 0.101).

DISCUSSION

The aim of this study was to analyze the bidirectional association between wheezing and obesity during adolescence and early adulthood. According to our analyses, approximately one-third of the participants presented wheezing in at least one of the adolescence follow-ups, and around 10% presented wheezing during early adulthood. On the other hand, nearly one-fifth of the participants were classified as obese in at least one follow-up between the ages of 11 and 18, and close to 16% were obese at 22. Additionally, a positive bidirectional association between wheezing and obesity was observed even after adjustment for confounding variables. In female participants, the presence of self-reported wheezing in two follow-ups between 11 and 18 years of age increased the chances of being obese at age 22. In turn, the presence of obesity in two follow-ups increased the female participants' chances of presenting wheezing at 22 years of age.

When analyzing the distribution of demographic, socioeconomic, behavioral, and health variables in participants who presented with wheezing or obesity at 22 years of age, demographic and social inequalities were observed. There was a greater prevalence of outcomes among participants with less schooling, who belonged to the poorest quintiles of the asset index, and who were of black skin color. Malta et al.[19] reported similar results when analyzing socioeconomic inequalities in the prevalence of chronic non-communicable diseases in Brazilian adults using data from the 2019 National Health Survey, reinforcing the importance of monitoring health inequality indicators and implementing public policies that address this issue.

Regarding behavioral variables, the largest prevalence of wheezing or obesity at 22 years of age was tied to the exposure category of smoking. Several studies have demonstrated positive associations between exposure to smoking and obesity or wheezing.[20,21] A meta-analysis involving 79 studies showed that exposure to smoking during pregnancy or in the

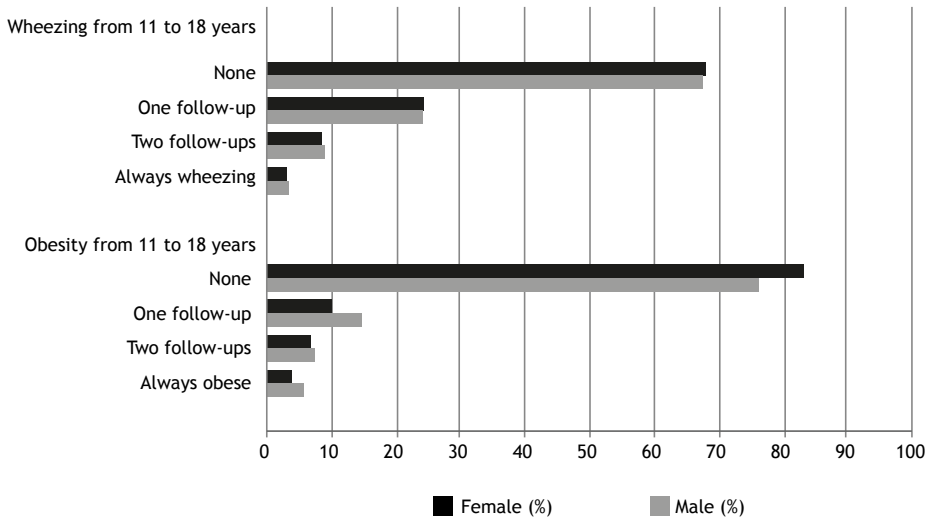

Figure 1. Prevalence of wheezing in the last 12 months and obesity during adolescence in the 1993 Birth Cohort, Pelotas, Brazil. Sample wheezing from 11 to 18 years of age: participants with information on wheezing in the 12 months prior to the follow-ups at ages 11, 15, and 18 and information on obesity (BMI ≥ 30 kg/m²) at the 22-year follow-up. Sample obesity from 11 to 18 years of age: participants with information on obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) at ages 11, 15, and 18 and information on wheezing in the 12 months prior to the 22-year follow-up.

Table 3. Association between wheezing from 11 to 18 years of age and obesity at age 22. 1993 Birth Cohort, Pelotas, Brazil.

	Obesity at 22 years of age[b]			
	Crude		Adjusted	
	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Wheezing from 11 to 18 years[a]				
Males (n=1,533)		0.807		0.357
None	1.00		1.00	
One follow-up	0.87 (0.59;1.28)		0.80 (0.52;1.23)	
Two follow-ups	0.98 (0.54;1.76)		0.80 (0.42;1.53)	
Always wheezing	1.10 (0.42;2.88)		0.89 (0.30;2.63)	
Females (n=1,709)		0.001		0.002
None	1.00		1.00	
One follow-up	1.34 (1.00;1.80)		1.28 (0.91;1.79)	
Two follow-ups	1.89 (1.21;2.96)		2.22 (1.36;3.61)	
Always wheezing	2.04 (0.93;4.50)		1.64 (0.68;3.99)	

OR: Odds Ratio; 95% IC: 95% confidence interval; Significance level of 5%.* p-value by Wald's test. [a] Wheezing in the 12 months prior to the follow-ups at ages 11, 15, and 18; [b] Obesity: BMI ≥ 30 kg/m². Adjusted by skin color, birthweight, gestational age, maternal schooling during pregnancy, maternal smoking during pregnancy, family history of asthma, family income at 11 years of age, parental smoking at the 11-year follow-up.

Table 4. Association between obesity from 11 to 18 years of age and wheezing at age 22. 1993 Birth Cohort, Pelotas, Brazil.

	Wheezing at 22 years of age[b]			
	Crude		Adjusted	
	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Obesity from 11 to 18 years[a]				
Males (n=1,545)		0.553		0.308
None	1.00		1.00	
One follow-up	0.87 (0.51;1.47)		0.88 (0.49;1.56)	
Two follow-ups	1.03 (0.50;2.12)		1.33 (0.61;2.90)	
Always obese	1.44 (0.69;2.99)		1.55 (0.70;3.40)	
Females (n=1,708)		0.054		0.101
None	1.00		1.00	
One follow-up	1.56 (0.92;2.64)		1.41 (0.77;2.58)	
Two follow-ups	1.88 (1.03;3.42)		2.03 (1.05;3.92)	
Always obese	1.10 (0.39;3.14)		0.98 (0.29;3.31)	

OR: Odds Ratio; 95% IC: 95% confidence interval; Significance level of 5%.* p-value by Wald's test. [a] Obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) assessed in the follow-ups at ages 11, 15, and 18; [b] Wheezing in the 12 months prior to the 22-year follow-up. Adjusted by skin color, birthweight, gestational age, maternal schooling during pregnancy, maternal smoking during pregnancy, family history of asthma, family income at 11 years of age, parental smoking at the 11-year follow-up.

postnatal period (father, mother, or a relative) increased the risk of wheezing during childhood and adolescence.[21]

A document containing global strategies for asthma management and prevention (GINA) suggests the possibility of a phenotype for asthma, known as "asthma with obesity," since asthmatic obese individuals exhibit more severe respiratory symptoms and greater difficulty in disease control.[4] Our results showed that the largest prevalence of obesity was among participants who reported wheezing in the last 12 months and that had a family history of asthma. In addition, there was a larger prevalence of wheezing in obese participants when compared to those who were not obese.

The literature shows a possible positive association between asthma and obesity, though mostly in cross-sectional studies,[1,22,23] which are subject to reverse causality bias. Longitudinal studies are necessary to verify the direction of the association;[3,10,24] however, few studies have documented the bidirectional association, indicating that this approach needs to be further explored.[9-12,25]

In this study, we found that the presence of wheezing in two follow-ups increased the chance of being obese at 22 years of age by approximately 120% when compared to participants without wheezing (Table 3, females). Zhang et al.[12] also observed that children diagnosed with asthma in any given follow-up had 1.38 times (95%CI: 1.12; 1.71) more chances of becoming obese in the subsequent follow-up of their study when compared to children without asthma. The literature is uncertain regarding possible causal mechanisms associated with exposure to asthma and

the incidence of obesity. In general, the hypotheses point to reduced physical activity,[26] continuous use of asthma-control medication,[27] a potential metabolic disorder related to insulin and leptin resistance,[28] and exposure to smoking.[29] It should be noted that there are possible genetic factors common to both diseases associated with genes with pleiotropic effects, such as β2-adrenergic receptors (ADRB2), vitamin D (VDR), leptin (LEP), protein kinase C alpha (PRKCA), and tumor necrosis factor alpha (TNFα).[30]

Our results also showed that obesity increases the chance of the occurrence of wheezing and are supported by the longitudinal bidirectional studies with Mendelian randomization by Granell et al.[11] and Xu et al.,[9] who found that for each increment from 1 to 4.8 kg/m^2 in BMI, individuals had from 1.18 (95%CI: 1.11; 1.25) to 1.55 (95%CI: 1.16; 2.07) times greater risk of developing asthma. In general, the direction of the association from obesity to asthma has already been studied and described in the literature. Once again, the mechanisms related to the plausibility of the association are not well defined, but the literature points to systemic inflammation in obesity as a causal factor for the inflammation of the respiratory tracts and, consequently, wheezing. In other words, adipocytes would be a possible source of pro-inflammatory cytokines.[31]

In the same population included in this study, at 11 and 15 years of age, Noal et al.[2] found that the risk of persistent wheezing was 80% greater in obese adolescents when compared to those who were eutrophic at age 11, and among those who were in the upper tertile of the skinfold sum. From ages 18 to 22, Menezes et al.[3] found that obese individuals had 2 times (95%CI: 1.32; 3.03) more chances of developing wheezing at 22 years of age. The previously evaluated ages in this same cohort only referred to two follow-ups (ages 11 and 15 in Noal's study and 18 and 22 in Menezes'); it is possible that the bidirectionality observed in the present study was due to the longer period of analysis (11, 15, 18, and 22 years).

In a prospective population-based study performed with teenagers and young adults in Norway, Egan et al.[25] also found a possible positive bidirectional association between asthma and obesity. However, it was only significant for males, in which adolescents who presented with obesity had 1.80 times (95%CI: 1.02; 3.18) more chances of self-reported asthma diagnosis or symptoms in 11 years of follow-up, and adolescents who reported symptoms or diagnosis of asthma had 1.90 times (95%CI: 1.12; 3.24) greater chances of developing obesity. In our study, despite observing a statistically significant association between wheezing and obesity in females only, it is not possible to infer that sex is an effect modifier of the association, due to the lack of significance, which may be related to the sample size of the exposure categories and the power of the analysis for males; the other point is that males have a lower percentage of fat tissue than women, a fact that can distort the effect measure toward a null effect. Corroborating our findings, a meta-analysis of prospective longitudinal studies conducted by Beuther et al.[32] on overweightness, obesity, and the incidence of asthma showed that the association wasn't modified by sex.

When analyzing the effect measurements between the exposure categories for wheezing and obesity from ages 11 to 18, in some cases there was an increase in the effect measurement values as the exposure increased. However, it is not possible to state that there were dose-response effects in all tested associations. Meanwhile, a meta-analysis of longitudinal studies showed that the incidence of asthma increased by around 50% when subjects presented with overweightness/obesity with dose-response effects.[32]

Some limitations may be pointed out in this study, such as the use of the symptom wheezing as a "proxy" for asthma diagnosis; however, in epidemiological studies with large samples, this measurement is commonly used.[16] It is possible that wheezing in the last 12 months could be subject to information bias; nevertheless, consequent underestimation would not have a substantial effect. [17] According to the SAPALDIA study (Swiss Study on Air Pollution and Lung Diseases in Adults), respiratory symptoms are reliable predictors of asthma; wheezing as a single symptom showed the best sensitivity (74.7%), negative predictive value (99.3%), and Youden index (0.62). As for the symptom combinations, the association of wheezing with two of the three symptoms (nocturnal dyspnea, chest tightness, and cough) was the best tool for diagnosing asthma.[33] Moreover, the periods between follow-ups (approximately 3 years) and the variables' evaluation time (wheezing in the last 12 months and BMI at the moment of data collection) would lead to fluctuations in outcomes, and some information may have been lost; thus, it is not possible to state that the occurrence and effect measurements were not underestimated.

On the other hand, strong points include the prospective design of 22 years of follow-up in a population-based sample. The extended follow-up period allows the cumulative effect of the exposures over the studied outcomes to be observed. The high follow-up rates, with the smallest being 22 years (approximately 75%), reduce the possibility of selection bias, confirmed by the results in Table 1.

In conclusion, this study demonstrated a possible positive bidirectional association between wheezing and obesity, with larger effect measurement values in the wheezing to obesity direction, even after adjustments for confounders. This association appears to be more evident in females and for the category presence of wheezing/obesity in two follow-ups during adolescence. Future studies should evaluate if there are any critical points for specific ages that lead to the outcomes, to clarify the still obscure aspects of this wheezing/obesity association.

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