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Childhood obesity in relation to poor asthma control and exacerbation: a meta-analysis

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Table S1: Search strategy for the systematic review

Domain	·	Determinant (s)			Outcome	e (s)
Children OR		BMI OR		Asthma control		Asthma exacerbation OR
Childhood AND	AND	Body mass index	AND		OR	Asthma severity AND
Adolescents OR	-	Obesity OR	_			Hospitalization OR
Pediatrics	_	Overweight				Oral corticosteroid use



Fig S1: Flow diagram of study selection



Fig S2: Funnel plots for publication bias in the association overweight/obesity and poor asthma control (p-value=0.81) and asthma exacerbations (p-value=0.80)

Association body mass index (BMI) and poor asthma control/exacerbations in BREATHE, PACMAN and PAGES

Methods and data analysis:

Association BMI and poor asthma control/exacerbations was tested in BREATHE, PACMAN and PAGES databases. For this cross-sectional analysis, the study sample consisted of asthmatic children and adolescents who participated in three North-European pediatric cohorts including the BREATHE cohort (Scotland, UK, age: 4–18 years) [1,2], the Pharmacogenetics of Asthma Medication in Children study (PACMAN) cohort (The Netherlands, age: 4–12 years) [3] and the Pediatric Asthma Gene Environment Study (PAGES) cohort (Scotland, UK, age: 4–17 years) [4]. All three studies are retrospective cohort studies. In BREATHE, children and adolescents with physician-diagnosed asthma were recruited either through primary or secondary clinics. In PACMAN paediatric users of asthma medication were selected through Dutch community pharmacies. In this cohort, children aged 4-12 years with at least 2 years of medication history available and at least 3 prescriptions for any asthma drug within the last 2 years and at least 1 prescription in the last 6 months were selected from pharmacies in different regions in the Netherlands. In PAGES physician-diagnosed asthmatic children were recruited through primary and secondary care. A detailed clinical history including e.g. information on asthma symptoms, treatment, asthma control and exacerbations was obtained from the parents and children. In PACMAN, BMI at the time of recruitment was calculated using weight and height measures for

each child at the time of recruitment in pharmacy or the values were obtained from parental questionnaire. In BREATHE and PAGES weight and height were measured using the calibrated equipment in each hospital's clinic and BMI calculated. Data on asthma control were available in PACMAN and PAGES. In PACMAN the Asthma Control Questionnaire score (ACQ) was used to measure asthma control. An ACQ 20.75 was considered as poor asthma control [5]. For children and adolescents in PAGES, asthma control was assessed using the 7-item childhood Asthma Control Test scores (ACT). An ACT score of ≤ 19 was considered poor asthma control [6]. Two measures of asthma exacerbations were applied [7]; 1) asthma-related visits to an emergency department (ED) in the past 12 months from the date of completion of the questionnaire (PACMAN) and asthma-related hospitalization in the past 6 months (BREATHE and PAGES) 2) prescribed courses of oral corticosteroids (OCSs) in the past 12 months (PACMAN) and in the past 6 months (BREATHE and PAGES). We used SAS version 9.1 for Windows to calculate age- and gender-adjusted BMI percentiles for children using height and weight measures as defined by the CDC standardized sexand age-specific growth charts (http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm). Children were classified as follows: a) non-obese: either normal weight (BMI >5th to <85th percentile) or overweight (BMI≥85th to <95th percentile) and b) obese (BMI≥95th percentile) [8]. Underweight children were not included in the logistic regression analyses. The differences in baseline characteristics of children with and without missing values in the three cohorts were compared. The frequency of baseline characteristics in the different BMI percentile categories were stratified by gender. The associations of obesity with poor asthma control and/or risk of exacerbations among obese girls and boys versus non- obese peers was estimated using binary logistic regression in univariate and multivariate ways to calculate crude and adjusted odd ratios (ORs) with 95% confidence intervals (CIs). In subgroup analysis, the effect of age on this association was tested in stratified analyses in three different age categories 4-6, 6.01-12.99 and 13-18 years. In a sensitivity analysis, the associations between obesity versus normal weight and poor asthma control and/or risk of exacerbations among obese girls and boys were also evaluated. Age, eczema, hay fever, pet's exposure, breast feeding, family history of asthma and family history of allergy, asthma in sibling and race/ethnicity were considered as potential confounders in these associations.

P-values of 0.05 were used to assess the statistical significance of main effect associations. We used SPSS 23.0 to analysis the data.

Results:

Data were available for 1,318 children and adolescents ages 4-18 years of the BREATHE cohort, 648 children ages 4-12 year of the PACMAN cohort and 422 children and adolescents ages 4-17 years of the PAGES cohort. The baseline characteristics of the three study populations are presented in **Table S2**. The incidence of obesity was 13% in BREATHE, 11% in PACMAN and 15% in PAGES. Poor asthma control was higher in PAGES (64%) compared with PACMAN (40%). Asthma exacerbations (either ED visits/asthma related hospitalization or OCSs dispensing) rates were higher in BREATHE (27%) and PAGES (40%) compared with PACMAN (10%).

We found statistically significant differences in baseline characteristics of the patients with and without data on BMI which was more pronounced in BREATHE and PAGES. Children in BREATHE and PAGES cohorts with missing data on BMI have remarkably less asthma exacerbations (both hospitalization due to asthma and OCSs use) compared with those that have data on BMI (Table S3).

The frequency of the baseline characteristics in the different BMI percentile categories was shown in **Table S4**. As shown, no significant differences between obese vs. non-obese children in different baseline characteristics were observed neither in girls nor in boys in the BREATHE cohort. In the PACMAN cohort, there were statistically significant differences between obese and non-obese peers in different baseline characteristics e.g. age (p=0.003), race (p=0.03) and exacerbations (p<0.001) in girls and family history of asthma in boys (p=0.01). In the PAGES cohort, significant difference between obese and non-obese children was shown only in girls with eczema (p=0.05) and in boys with poor asthma control (p=0.04).

As shown in **Table S5**, when boys and girls were combined, there was no association between obesity and poor asthma control in either population with an opposite direction in PACMAN and PAGES cohorts (OR: 0.95, 95% CI: 0.54-1.67 and OR: 1.66, 95% CI: 0.70-3.94, respectively). Obese girls in the PACMAN cohort were more likely to have poor asthma control compared to non-obese girls while in the PAGES cohort obese boys were at increased risk of poor asthma control than non-obese boys. No asthma control data was available for the BREATHE cohort.

There was an increased risk for exacerbations (both ED visits and OCSs use) among obese girls compared to non-obese girls in the PACMAN population (OR: 4.03, 95% CI: 1.06-15.38 and OR: 5.66, 95% CI: 1.37-23.31, respectively) but not in the other populations. When boys only and when

boys and girls were combined, there was no significant association between obesity and risk for exacerbations (**Table S5**).

When stratifying logistic regression analysis by age, the results showed no difference between different age categories (**Table S6**).

A sensitivity analysis was conducted to evaluate the association between obesity and outcomes in obese versus normal-weight children and the results showed no significant differences compared with the results for these associations in obese versus non-obese peers (data not shown).

Actual confounders in the association between obesity and asthma severity were the following:

in BREATHE, age, rhinitis, and family history of asthma, in PACMAN, age, eczema, breast feeding, ethnicity/race, family history of asthma and allergy, and in PAGES, age, eczema, rhinitis and family history of allergy.

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		BREATHE (n=1,318)	PACMAN (n=648)	PAGES (n=422)
Gender (girls), n (%)		534 (40.5)	242 (37.3)	179 (42.4)
Age, mean (SD), years		10.1 (3.7)	8.4 (2.4)	9.8 (3.3)
	4-6	230 (17.5)	145 (22.4)	71 (16.8)
Age groups, years	6.01-12.99	777 (59.0)	503 (77.6)	271 (64.2
	13-18	311 (23.6)	-	80 (19.0)
Race/ethnicity	White in UK Caucasian [*] in Netherlands	-	564 (87.0)	313 (74.2)
	Others	-	68 (10.5)	15 (3.6)
BMI (kg/m ²), mean (SD)		19.0 (4.1)	16.9 (2.7)	19.1 (4.8)
	Underweight (<5th percentile)	43 (3.3)	63 (9.7)	14 (3.3)
BMI percentile category, n	Normal weight ((≥5th to 85th percentile)	877 (66.5)	438 (67.6)	280 (66.4)
(%)	Overweight (≥85th to 95th percentile)	221 (16.8)	80 (12.3)	63 (14.9)
	Obese (≥95th percentile)	177 (13.4)	67 (10.3)	65 (15.4)
Asthma control $n(\%)$	Well-controlled	-	368 (56.8)	93 (36.2)
Asuma control, if (70)	Poor-controlled	-	258 (39.8)	164 (63.8)
ED visits/hospitalization due to asthma, n (%)		200 (15.2)	40 (6.2)	57 (14.3)
OCSs use, n (%)		342 (25.9)	33 (5.1)	157 (39.4)
Asthma exacerbations ^o , n (%)		357 (27.1)	62 (9.8)	170 (40.3)
	Step 1	249 (18.9)	62 (9.7)	33 (7.9)
Medication used based on	Step 2	706 (53.6)	383 (59.8)	93 (22.2)
BTS ^a treatment step, n (%)	Step 3	198 (15.0)	107 (16.7)	237 (56.6)
	Step 4	165 (12.5)	31 (4.8)	56 (13.4)
	Eczema	706 (53.6)	387 (59.7)	167 (39.6)
Atopy, n (%)	Hay fever	348 (26.7)	256 (39.5)	165 (39.1)
	Food allergy	-	309 (47.7)	148 (35.1)
	Breast feeding	-	462 (71.3)	-
Environmental factors, n (%)	Pets exposure	829 (64.5)	273 (42.1)	230 (54.5)
Family history of asthma ^b , n (%)		541 (41.0)	287 (44.3)	315 (74.6)
Family history of allergy ^c , n (%)		643 (48.8)	497 (76.7)	148 (35.1)
Asthma in sibling d , n ($\%$)		398 (30.2)	184 (28.4)	-

Table S2: Baseline characteristics of children with asthma (with available BMI)

Abbreviations: BMI, body mass index; SD, standard deviation; ED, emergency department visit for asthma; OCSs, oral corticosteroids; BTS, British Thoracic Society.

*Caucasian including Dutch, Turkish and Moroccan.

^a The treatment step was modified from BTS guidelines as follows: step 1 is use of short-acting beta agonists (SABAs) as needed; step 2 is the step 1 plus regular inhaler corticosteroids (ICSs); step 3 is the step 2 plus regular long-acting beta agonists (LABAs); and step 4 is the step 3 plus oral leukotriene receptor antagonists (LTRAs).

^b At least one asthmatic parent.

^c At least one allergic parent.

^d At least on asthmatic sibling.

[®] Asthma exacerbations defined as either ED visits/hospitalization due to asthma or OCSs use

Table S3: Differences in baseline characteristics of children with and without data on BMI

		Missing BMI	Non- missing BMI		Missing BMI	Non- missing BMI		Missing BMI	Non- missing BMI	
		BREATHE (n=162)	BREATHE (n=1,318)	P-value	PACMAN (n=347)	PACMAN (n=648)	P-value	PAGES (n=340)	PAGES (n=422)	P-value
Gender, n (%)	Girls	69 (11.4)	534 (86.6)	0.61	137(36.1)	242 (63.9)	0.51	145 (44.8)	179 (55.2)	0.95
	Boys	93 (10.6)	784 (89.4)	0.01	210 (34.1)	406 (65.9)	0.51	195 (44.5)	243 (55.5)	0.75
	4-6	56 (19.6)	230 (80.4)		68 (31.9)	145 (68.1)	0.31	19 (21.1)	71 (78.9)	_
Age groups, years	6.01-12.99	25 (7.5)	310 (92.4)	<0.001	279 (35.7)	503 (64.3)	0.51	222 (45.0)	271 (55.0)	<0.001
	13-18	25 (7.4)	311 (92.6)		-	-		99 (55.3)	80 (44.7)	
Race/ethnicity	White in UK Caucasian [*] in Netherlands	-	-	-	317 (36.0)	564 (64.0)	0.01	63 (16.8)	313 (83.2)	0.07
Asthma control, n (%)	Poor controlled	-	-	-	148 (44.6)	258 (41.2)	0.32	88 (62.4)	164 (63.8)	0.78
ED visits/hospitalizati on due to asthma, n (%)		67 (41.4)	200 (15.2)	<0.001	21 (6.2)	40 (6.5)	0.87	14 (4.6)	57 (14.3)	<0.001
OCSs use, n (%)		78 (48.1)	342 (25.9)	<0.001	27 (7.9)	33 (5.2)	0.09	45 (14.8)	157 (39.4)	<0.001
Asthma exacerbations, n (%)		87 (53.7)	357 (27.1)	<0.001	39 (11.4)	62 (9.7)	0.39	46 (15.1)	170 (42.6)	<0.001
	Eczema	96 (59.3)	706 (53.6)	0.17	232 (69.3)	387 (60.9)	0.01	116 (37.7)	167 (39.6)	0.60
Atopy, n (%)	Hay fever	67 (41.4)	348 (26.7)	<0.001	155 (47.1)	256 (40.8)	0.06	111 (36.0)	165 (39.1)	0.40
	Food allergy	-	-	-	177 (53.0)	309 (48.8)	0.22	74 (24.0)	148 (35.1)	0.001
Environmental factors, n (%)	Pets exposure	92 (57.1)	829 (64.5)	0.07	112 (33.1)	273 (42.9)	0.003	196 (57.6)	230 (54.5)	0.39
Family history of asthma ^{**} , n (%)		82 (50.6)	541 (41.0)	0.02	161 (50.5)	287 (45.9)	0.19	247 (80.2)	315 (74.6)	0.08
Family history of allergy ^{***} , n (%)		112 (69.1)	643 (48.8)	<0.001	271 (83.9)	497 (79.1)	0.08	153 (45.0)	148 (35.1)	0.005

Abbreviations: BMI, body mass index; ED, emergency department visit for asthma; OCSs, oral corticosteroids; *Caucasian including Dutch, Turkish and Moroccan. **At least one asthmatic parent. ***At least one allergic parent.

Table S4: Frequency of baseline characteristics in different BMI percentile categories, stratified by gender

				BRI	EATHE					PAC	MAN					PAG	ES		
		(Girls (n=534)		Boys (n=784)		(Girls (n=242)		F	Boys (n=406)			Girls (n=179)		B	oys (n=243)	
BMI percentile categories		Obese	Non obese	P-value	Obese	Non obese	P-value	Obese	Non obese	P- value	Obese	Non obese	P-value	Obese	Non obese	P-value	Obese	Non obese	P- value
N (%)		68 (12.7)	443 (83.0)		109 (13.9)	655 (83.5)		31 (12.98)	191 (78.9)		36 (8.9)	327 (80.5)		30 (16.8)	143 (79.9)		35 (14.4)	200 (82.3)	
	4-6	16 (18.0)	73 (82.,0)		25 (17.9)	115 (82.1)		14 (26.4)	39 (73.6)		11 (14.9)	63 (85.1)		5 (17.2)	24 (82.8)		6 (14.3)	36 (85.7)	
Age groups, years	6.01-12.99	35 (12.5)	245 (87.5)	0.36	61 (13.0)	408 (87.0)	0.35	17 (10.1)	152 (89.9)	0.003	25 (8.7)	264 (91.3)	0.11	18 (16.5)	91 (83.5)	0.89	19 (12.8)	130 (87.2)	0.26
	13-18	17 (12.0)	125 (88.0)		23 (14.8)	132 (85.2)		-	-		-	-		7 (20.0)	28 (80.0)	_	10 (22.7)	34 (77.3)	-
Race /ethnicity	White in UK Caucasian [*] in Netherlands	-	-		-	-		22 (11.4)	171 (88.6)	0.03	28 (8.8)	290 (91.2)	0.21	23 (17.3)	110 (82.7)	0.32	27 (15.5)	147 (84.5)	0.72
Asthma control, n (%)	Not-well controlled	-	-		-	-		13 (44.8)	79 (42.7)	0.83	14 (9.9)	127 (90.1)	0.89	12 (63.2)	66 (70.2)	0.54	17 (81.0)	68 (56.7)	0.04
ED visits/hospita lization due to asthma, n (%)		9 (13.2)	67 (15.1)	0.68	19 (17.4)	97 (14.8)	0.48	5 (17.2)	8 (4.4)	0.008	2 (5.9)	20 (6.9)	0.91	4 (14.3)	19 (13.8)	0.94	5 (15.2)	28 (14.8)	0.96
OCSs use, n (%)		12 (17.6)	113 (25.5)	0.16	33 (30.3)	175 (26.7)	0.44	5 (16.1)	7 (3.7)	0.005	3 (8.3)	18 (5.6)	0.50	9 (32.1)	45 (32.6)	0.96	15 (45.5)	87 (46.3)	0.93
Exacerbations, n (%)		12 (17.6)	116 (26.2)	0.13	35 (32.1)	183 (27.9)	0.37	9 (29.0)	12 (6.4)	<0.001	4 (11.1)	32 (9.8)	0.81	11 (18.3)	49 (81.7)	0.70	16 (14.7)	93 (85.3)	0.94
	Eczema	34 (50.0)	233 (52.6)	0.69	52 (47.7)	365 (55.5)	0.12	17 (56.7)	124 (66.7)	0.29	16 (44.4)	189 (58.5)	0.11	7 (23.3)	61 (42.7)	0.05	12 (34.3)	84 (42.0)	0.39
Atopy, n (%)	Hay fever	19 (28.4)	107 (24.3)	0.48	37 (34.3)	171 (26.4)	0.09	7 (24.1)	81 (43.8)	0.046	10 (28.6)	138 (43.1)	0.10	7 (23.3)	57 (39.9)	0.09	15 (42.9)	78 (39.0)	0.67
	Food allergy	-	-		-	-		15 (51.7)	85 (46.4)	0.60	14 (38.9)	160 (49.2)	0.24	6 (20.0)	51 (35.7)	0.10	10 (28.6)	78 (39.0)	0.24
Environment	Breast feeding	-	-		-	-		18 (62.1)	135 (72.6)	0.25	26 (72.2)	231 (72.0)	0.97	-	-		-	-	
al factors, n (%)	Pets exposure	45 (66.2)	295 (68.9)	0.65	65 (60.2)	394 (61.7)	0.77	9 (30.0)	93 (49.7)	0.04	12 (33.3)	136 (42.1)	0.31	16 (53.3)	81 (56.6)	0.74	21 (60.0)	106 (53.0)	0.44
Family history of asthma ^{**} , n (%)		29 (43.3)	189 (43.1)	0.90	40 (37.0)	270 (41.8)	0.37	17 (56.7)	101 (54.9)	0.86	7 (20.0)	133 (42.1)	0.01	23 (76.7)	116 (81.1)	0.58	27 (77.1)	142 (71.0)	0.46
Family history of atopy ^{***} , n (%)		35 (52.2)	219 (50.0)	0.76	48 (44.4)	311 (48.1)	0.51	23 (76.7)	149 (81.0)	0.58	20 (57.1)	255 (80.2)	0.002	9 (30.0)	58 (40.6)	0.28	12 (34.3)	65 (32.5)	0.84
Asthma in sibling ^{*****} , n (%)		24 (35.8)	142 (32.3)	0.57	34 (31.5)	189 (29.3)	0.65	8 (40.0)	57 (36.3)	0.75	11 (34.4)	91 (34.2)	0.99	-	-		-	-	

Abbreviations: BMI, body mass index; ED, emergency department visit for asthma; OCSs, oral corticosteroids;* Caucasian including Dutch, Turkish and Moroccan, **At least one asthmatic parent

At least one atopic parent, * At least one asthmatic sibling.

Table S5: Association obesity and poor asthma control/exacerbations by gender (obese vs. non-obese children)

		BREATHE			PACMAN	PAGES			
		OR (9:	5%CI)		OR (9	OR (95%CI)			
	Subjects	Crude	Adjusted*	Subjects	Crude	Adjusted*	Subjects	Crude	Adjusted*
	included,			included			included,		
	n			, n			n		
Poor asthma control									
Girls	-	-	-	213	1.08 (0.49-2.37)	1.28 (0.53-3.08)	113	0.73 (0.26-2.04)	0.88 (0.23-3.39)
Boys	-	-	-	351	0.96 (0.47-1.94)	0.89 (0.41-1.92)	141	3.25 (1.03-10.24)	2.78 (0.84-9.20)
Total	-	-	-	564	1.02 (0.60-1.72)	0.95 (0.54-1.67)	254	1.57 (0.75-3.32)	1.66 (0.70-3.94)
ED visits/asthma-									
related hospitalization									
Girls	511	0.86 (0.41-1.81)	0.80 (0.38-1.71)	210	4.51 (1.36-14.90)	4.03 (1.06-15.38)	166	1.04 (0.33-3.34)	1.26 (0.38-4.17)
Boys	764	1.21 (0.71-2.08)	1.27 (0.73-2.21)	344	0.91 (0.20-4.06)	0.70 (0.15-3.24)	222	1.03 (0.37-2.88)	1.29 (0.44-3.81)
Total	1275	1.07 (0.69-1.66)	1.08 (0.69-1.68)	554	2.07 (0.86-4.95)	1.91 (0.76-4.83)	388	1.03 (0.48-2.23)	1.17 (0.53-2.56)
OCSs use									
Girls	511	0.63 (0.32-1.21)	0.57 (0.29-1.12)	221	5.03 (1.49-17.01)	5.66 (1.37-23.31)	166	0.98 (0.41-2.34)	1.06 (0.42-2.69)
Boys	764	1.19 (0.76-1.86)	1.27 (0.80-2.00)	361	1.55 (0.43-5.54)	1.47 (0.39-5.56)	221	0.97 (0.46-2.03)	0.90 (0.40-2.02)
Total	1275	0.96 (0.67-1.38)	0.94 (0.65-1.38)	582	2.66 (1.15-6.16)	2.04 (0.79-5.25)	387	0.95 (0.55-1.67)	0.93 (0.51-1.71)

*Adjusted for age, hay fever, eczema, family history of asthma and allergy, breast feeding, pet's exposure and race/ethnicity by stepwise logistic regression model. Data on breast feeding was not available in BREATHE and PAGES cohorts.

Data on race/ethnicity was not available in BREATHE cohort.

Table S6: Association obesity and poor asthma control/exacerbations stratified by age, obese versus non-obese children

	· ·	BREATHE		PACMAN	PAGES			
	Subjects	OR (95%CI)	Subjects	OR (95%CI)	Subjects	OR (95%CI)		
	included, n		included, n		included, n			
Poor asthma control								
4-6 year	-	-	124	0.83 (0.30-2.31)	21	-		
6.01-12.99 year	-	-	440	0.98 (0.49-1.95)	158	1.32 (0.45-3.88)		
13-18 year	-	-	-		75	1.35 (0.34-5.42)		
ED visits/asthma-related								
hospitalization								
4-6 year	229	0.84 (0.35-1.97)	124	3.13 (0.90-10.92)	69	1.69 (0.26-11.16)		
6.01-12.99 year	749	1.05 (0.59-1.88)	430	1.40 (0.31-6.35)	243	1.42 (0.53-3.81)		
13-18 year	297	1.46 (0.45-4.70)	-	-	76	0.40 (0.05-3.43)		
OCSs use								
4-6 year	229	0.89 (0.43-1.87)	127	2.72 (0.61-12.12)	69	1.45 (0.29-7.11)		
6.01-12.99 year	749	0.90 (0.54-1.49)	455	2.04 (0.55-7.56)	242	0.91 (0.40-2.07)		
13-18 year	297	1.17 (0.49-2.80)	-	-	76	0.86 (0.27-2.72)		

*Adjusted for gender, hay fever, eczema, family history of asthma and allergy, breast feeding, pet's exposure and race/ethnicity by stepwise logistic regression model. Data on breast feeding was not available in BREATHE and PAGES cohorts.

Data on race/ethnicity was not available in BREATHE cohort.