1

Online Supplement

Participant Selection for Original Cohort

Children between 10 and 17 years of age with asthma, receiving daily controller therapy, and fitting the

age- and sex-adjusted body mass index (BMI) parameters for lean (20-65th percentile) and

overweight/obese (BMI $\geq$ 85th percentile) were enrolled through the Nemours multispecialty pediatric

asthma clinic in Jacksonville, FL. We used common BMI-percentile conventions for overweight/obesity[1,

2], and selected from a narrower BMI-percentile range among normal weight individuals to avoid

misclassification. Asthma was defined by accepted convention: physician-diagnosis of asthma and either

a ≥12% improvement in forced expiratory volume in 1 second (FEV1) following bronchodilator or FEV1

methacholine PC20 ≤ 16 mg/ml[3, 4].   Participants were excluded if they had any smoking history, been

on controller daily oral steroids, had a change in controller therapy in the previous 8 weeks, had any

interval illness in the past 4 weeks, or had another significant chronic disease.

Clinical Data

Two to three clinic visits within 3 weeks were conducted, with no two visits occurring on successive days.

At visit 1, participants signed an IRB-approved parental permission form and minor assent. Participants

completed staff-directed, structured interviews and questionnaires providing past asthma and medical

history, family and environmental history, quality-of-life information and a comprehensive interview of

asthma symptoms, controller treatment and past healthcare utilization. Each participant's controller step

prescribed by his/her asthma physician was determined[5]. Participants underwent a physical

examination, anthropometric measurements, and spirometry (before and after bronchodilator). Highest

parental education level, median household incomes, and poverty index (percent below poverty level)

was determined for each patient's household. Participants completed a methacholine challenge test and

exhaled nitric oxide (FENO) at visits 2 and 3, respectively, adhering to recommended guidelines[6, 7].

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Symptom and Quality-of-Life Analyses

Participants and parents answered structured interview questions regarding symptom patterns, common

asthma triggers and the primary symptom experienced with loss of control.   The structured interviews

also documented asthma symptom frequency and severity, digestive symptoms, and sleep

characteristics. Asthma symptom control was assessed at visit 1 using multiple questionnaires (Asthma

Control Questionnaire (ACQ)[8], Asthma Control Test (ACT)[9, 10], and childhood ACT (c-ACT)[11]) to

measure the broad array of symptoms that asthmatic children experience and report. Symptoms were

measured using the Asthma Symptom Utility Index (ASUI)[12].

Asthma-related quality-of-life was measured using the Paediatric Asthma Quality of Life

Questionnaire (PAQLQ)[13, 14] and the Paediatric Caregiver's Asthma Quality of Life Questionnaire

(PACQLQ)[15]. Properties of the asthma control scores, symptom scores, and asthma quality of life

scores can be found in the repository.

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Digestive Symptoms assessed from the GSAQ

Digestive symptoms were measured using the Pediatric Gastroesophageal Reflux (GER) Disease

Symptom Assessment Questionnaire (GSAQ) which is a 10-item tool[40] that has been validated in

children in the assessment of gastroesophageal reflux disease and digestive symptoms such as

chest/abdominal pain, pain/choking with eating, swallowing dysfunction, regurgitation and nausea. It

assesses symptom severity from the previous 7-days on an 8-point scale with 0 and 7 indicating the least

and greatest severity, respectively.

49

Lung Function Testing

Participants completed spirometry (Jaeger MasterScreen, San Diego, CA) adhering to recommended

ATS standards[16, 17]. Participants also completed fractional exhaled nitric oxide (FENO) (Sievers 280

NOA analyzer, Boulder, CO) maneuvers according to recommended standards[18]. Participants

54 completed a methacholine challenge by experienced staff using the ten Provacholine® concentrations

55 dosing scheme with a five-breath dosimeter protocol[6].

56

57 **Participant Selection for Replicate Cohort**

58 The replicate cohort was taken from a study conducted by the American Lung Association Asthma

59 Clinical Research Centers (ALA-ACRC). The study design has been published[3]. All participants

60 signed written informed consents for the Study of Acid-Reflux in Childhood Asthma (SARCA) study,

61 which was approved by the Nemours Florida IRB (82404-29) and by all other ALA-ACRC IRBs, and

62 registered at ClinicalTrials.gov (NCT00604851). We included baseline data from 306 participants age

63 6-17 years with inadequately controlled persistent asthma. For inclusion, participants required

64 physician diagnosis of asthma, prescription of an asthma controller medication, and either ≥12% post-

65 bronchodilator FEV1 improvement or methacholine PC20 < 16mg/ml. Inadequate control was defined

66 by poor ACQ score (≥1.25), frequent bronchodilator use or exacerbations. Participants required a

67 recent absence of GERD symptoms that would require treatment with a proton pump inhibitor (PPI) at

68 the time of enrollment. Medications for treatment of gastrointestinal symptoms in the past month

69 (including PPI, H2 blockers, bethanechol, and metoclopramide) were exclusionary. Participants with

70 history of anti-reflux or peptic ulcer surgery were excluded. 2453 participants were screened in order

71 to randomize 306 participants into the 24-week multicenter clinical trial assessing the efficacy of daily

72 oral lansoprazole versus placebo for patients with inadequately controlled asthma.

73

74 **Data Collected**

75   We collected demographics, body mass index percentiles, spirometry (before and after

76 bronchodilator), Asthma Control Questionnaire (ACQ) and GERD Symptom Assessment Questionnaire

77 (GSAQ) at baseline. We grouped participants as underweight, normal weight, overweight or obese by

78 CDC classification[20] based on age and sex-adjusted BMI-percentile. Since we were primarily

79 interested in serving as a replicate to the original study, we included only participants with a BMI-

80 percentile between the 20th and 65th percentile (leans) and ≥95th percentile (obese).   Asthma

81 symptoms were assessed using the ACQ[8] and modified ACQ6[21]. Spirometry with bronchodilator

82 challenge testing was performed using ATS/ERS standard procedures.

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Supplement Figures

Figure E1 Impulse oscillometry among lean, overweight and obese adolescents measured by respiratory system resistance (A) and reactance (B). Error bars denote standard deviations. No differences were seen based on body habitus at any hertz.
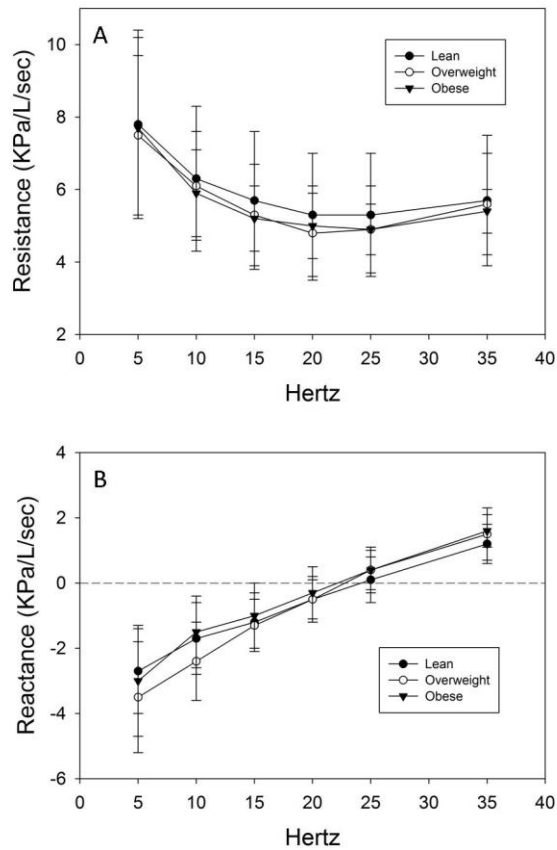
Table E1: Patient Characteristics by GSAQ Score Tertiles				
Variables, mean (SD)	GSAQ Tertiles			p-value
	T1	T2	T3	
n	124	74	108	
GER Score range	0-4	6-15	16-223	
Female, n (%)	42 (34)	27 (36)	49 (45)	.184
Race, n (%)				.191
White	45 (36)	26 (35)	47 (44)	
Black	64 (52)	38 (51)	51 (47)	
Other	15 (12)	10 (14)	10 (9)	
Hispanic/Latino, n (%)	25 (20)	11 (15)	17 (16)	.571
Birth weight < 2.5 kg, n (%)	12 (10)	3 (4)	3 (3)	.078
Age of asthma diagnosis, years	3.1 (2.8)	3.5 (3.2)	3.6 (3.5)	.194C
BMI ≥95th percentile, n (%)C	38 (31)	21 (28)	35 (32)	.846
Anthropometric measures T				.225
BMI-percentile	75.5 (25.8)	68.4 (30.1)	72.9 (29.0)	
Environment				.928
ETS exposure at home, n (%)	21 (17)	14 (19)	19 (18)	
Co-morbidities				
GER disease	0 (0)	0 (0)	0 (0)	--
Allergic rhinitis	68 (55)	51 (69)	62 (57)	.130
Neuropsychiatric disorder	0 (0)	0 (0)	0 (0)	--
Controller treatments, n (%)				
ICS-LABA	75 (60)	48 (65)	51 (47)	.035
LTRA	69 (56)	32 (43)	60 (56)	.514
Utilization for Asthma				
Urgent care visits in past year	2.3 (2.6)	3.0 (3.4)	3.4 (5.4)	.042T
Steroid bursts in past year	1.6 (1.6)	2.0 (2.3)	1.8 (2.1)	.377
Values are means (SD) unless noted, SD – standard deviation, GSAQ – GERD symptom assessment questionnaire, GERD – gastroesophageal reflux disease, BMI – body mass index, ETS – environmental tobacco smoke, IQR – intraquartile range, ICS – inhaled corticosteroids, LABA – long acting Beta-agonists, LTRA – leukotriene receptor antagonist, T - ANOVA test for linear trend used for continuous variables, C - Cochran-Armitage Trend test for categorical variables, K – Kruskal-Wallis test.				

	ACQ	Woken	morning	activities	SOB	Wheeze	SABA	FEV1	FEV1%	FEV1/FVC
Table E2a: Correlation Coefficients between Asthma and GSAQ score subscales in Obese Children (BMI≥95th percentile)										
GER score	**.474** **(<.0001)**	0.325 (0.0013)	0.392 (<.0001)	**0.437** **(<.0001)**	**0.460** **(<.0001)**	0.385 (0.0001)	.344 (0.0006)	-0.001 (0.9925)	.017 (.864)	.028 (.784)
Abdominal pain	0.355 (0.0004)	
Chest pain / heartburn	0.259 (0.0112)	
Difficulty swallowing	0.288 (0.0046)	
Night-time pain / awakening	0.307 (0.0025)	
Nausea	**0.439** **(<.0001)**	
Vomiting / Regurgitation	0.150 (0.1467)	
Burping / belching	.373 (.0002)	
Choking when eating	.384 (<.0001)	
Pain after eating	.238 (0.0201)	

Measures are Pearson's correlation coefficients (p-values), GSAQ – GERD symptoms assessment questionnaire, GERD – gastroesophageal reflux disease, ACQ – asthma control questionnaire score, FEV1% – Forced expiratory volume in 1 second (percent predicted), SOB – shortness of breath, SABA – short acting beta-agonist use, FEV1% – forced expiratory volume in 1 second percent predicted, FVC – forced vital capacity (liters), Dark grey boxes indicate p-value significance <0.01, Light grey boxes indicate p-value significance < 0.05. **BOLDED** values represent R values ≥ 0.400. Woken – "on average, during the past week, how often were you woken by your asthma during the night?" Morning – "on average, during the past week, how bad were your asthma symptoms when you woke up in the morning?" Activities – "In general, during the past week, how limited were you in your activities because of your asthma?" SOB – "In general, during the past week, how much shortness of breath did you experience because of your asthma?" Wheeze – "In general, during the past week, how much time did you wheeze?" SABA – "On average, during the past week, how many puffs/inhalations of short-acting bronchodilator have you used each day? FEV1 – FEV1 percent predicted subscale of ACQ represented by a 7-point ordinal scale, FEV1% - FEV1 percent predicted, FVC – forced expiratory volume.

Table E2b: Correlation Coefficients between Asthma and GSAQ score subscales in Lean Children (BMI 20-65th percentile)										
	ACQ	Woken	Morning	Activities	SOB	Wheeze	SABA	FEV1	FEV1%	FEV1/FVC
GER score	0.354 (0.0011)	0.28866 (0.0085)	**0.44623** **(<.0001)**	0.24140 (0.0289)	0.36542 (0.0007)	0.22239 (0.0446)	0.12055 (0.2807)	-0.04071 (0.7165)	0.0508 (0.6143)	0.1660 (0.0970)
Abdominal pain	0.135 (0.2263)	Measures are Pearson's correlation coefficients (p-values), GSAQ – GERD symptoms assessment questionnaire, GERD – gastroesophageal reflux disease, ACQ – asthma control questionnaire score, FEV1% – Forced expiratory volume in 1 second (percent predicted), SOB – shortness of breath, SABA – short acting beta-agonist use, FEV1% – forced expiratory volume in 1 second percent predicted, FVC – forced vital capacity (liters), Dark grey boxes indicate p-value significance <0.01, Light grey boxes indicate p-value significance < 0.05. **BOLDED** values represent R values ≥ 0.400. Woken – "on average, during the past week, how often were you woken by your asthma during the night?" Morning – "on average, during the past week, how bad were your asthma symptoms when you woke up in the morning?" Activities – "In general, during the past week, how limited were you in your activities because of your asthma?" SOB – "In general, during the past week, how much shortness of breath did you experience because of your asthma?" Wheeze – "In general, during the past week, how much time did you wheeze?" SABA – "On average, during the past week, how many puffs/inhalations of short-acting bronchodilator have you used each day? FEV1 – FEV1 percent predicted subscale of ACQ represented by a 7-point ordinal scale, FEV1% - FEV1 percent predicted, FVC – forced expiratory volume.								
Chest pain / heartburn	0.254 (0.0211)									
Difficulty swallowing	0.179 (0.1076)									
Nausea	0.217 (0.0506)									
Vomiting / Regurgitation	0.082 (0.4624)									
Burping / belching	0.072 (0.5224)									
Choking when eating	0.127 (0.2538)									
Pain after eating	0.189 (0.0884)									

Table E3: Impulse Oscillometry Measures by BMI-percentile grouping				103
Variables, mean (SD)	BMI-percentile groups			p-value[T] 104
	20-65%	85-94%	95-100%	105
n	21	12	23	106
Impedance (KPa/L/sec), mean (SD)				
Z5	8.3 (2.8)	8.6 (2.5)	7.7 (2.1)	.478
Resistance (KPa/L/sec), mean (SD)				
R5	7.8 (2.6)	7.5 (2.2)	7.7 (2.5)	.851
R10	6.3 (2.0)	6.1 (1.5)	5.9 (1.2)	.433
R15	5.7 (1.9)	5.3 (1.4)	5.2 (0.9)	.314
R20	5.3 (1.7)	4.8 (1.3)	5.0 (0.9)	.382
R25	5.3 (1.7)	4.9 (1.2)	4.9 (0.7)	.339
R35	5.7 (1.8)	5.6 (1.4)	5.4 (0.6)	.534
Reactance (KPa/L/sec) [1], mean (SD)				
X5	-2.7 (1.3)	-3.5 (1.7)	-3.0 (1.7)	.527
X10	-1.7 (1.1)	-2.4 (1.2)	-1.5 (1.1)	.715
X15	-1.2 (0.9)	-1.3 (0.8)	-1.0 (1.0)	.612
X20	-0.5 (0.7)	-0.5 (0.6)	-0.3 (0.8)	.309
X25	0.1 (0.7)	0.4 (0.7)	0.4 (0.6)	.178
X35	1.2 (0.6)	1.5 (0.8)	1.6 (0.5)	.053
AX (KPa/L)	25.0 (17.3)	29.4 (16.3)	21.9 (16.9)	.558
F res (L/sec)	23.5 (5.9)	23.9 (5.5)	20.9 (5.7)	.159
SD – standard deviation, T – ANOVA test for linear trend, R – resistance, X – reactance, AX – area of reactance, F res – Resonant frequency				