

A novel nutritional intervention improves lung function in overweight/obese adolescents with poorly controlled asthma: the Supplemental Nutrition in Asthma Control (SNAC) pilot study

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ABSTRACT: Asthma in the obese is often severe, difficult to treat, and characterized by less eosinophilic inflammation than asthma in the nonobese. Obesity-associated metabolic dysregulation may be a causal factor. We previously reported that a nutrient- and fiber-dense bar [Children's Hospital Oakland Research Institute (CHORI)-bar], which was designed to fill gaps in poor diets, improved metabolism in healthy overweight/obese (OW/OB) adults. In this pilot trial, OW/OB adolescents with poorly controlled asthma were randomized to weekly nutrition/exercise classes with or without twice-daily CHORI-bar consumption. Intent-to-treat analysis did not indicate CHORI-bar-specific effects. However, restricting the analysis to participants with acceptable compliance and a relatively low fraction of exhaled nitric oxide (FENO; <50/ ppb, a surrogate for noneosinophilic asthma; study participants: CHORI-bar, *n* = 16; controls, *n* = 15) indicated that CHORI-bar-specific, significant improvements in lung function (forced vital capacity, percent-predicted forced expiratory volume in 1 s, and percent-predicted forced expiratory flow between 25 and 75% of forced vital capacity), primarily in participants with low chronic inflammation (high-sensitivity C-reactive protein <1.5 mg/L). (We previously observed that chronic inflammation blunted CHORI-bar-induced metabolic improvements in healthy OW/OB adults.) Lung function improvement occurred without weight loss and was independent of improvements in metabolic and anthropometric end points and questionnaire-based measures of asthma control and quality of life. This study suggests that a nutritional intervention can improve lung function in OW/OB adolescents with asthma and relatively low FENO without requiring major changes in dietary habits, lifestyle, or weight loss and that this effect is blunted by chronic inflammation.—Bseikri, M., McCann, J. C., Lal, A., Fong, E., Graves, K., Goldrich, A., Block, D., Gildengoren, G. L., Mietus-Snyder, M., Shigenaga, M., Suh, J., Hardy, K., Ames, B. N. A novel nutritional intervention improves lung function in overweight/obese adolescents with poorly controlled asthma: the Supplemental Nutrition in Asthma Control (SNAC) pilot study. *FASEB J.* 32, 000–000 (2018). www.fasebj.org

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Almost 40% of adults with asthma are obese (1). Asthma in the obese is poorly understood, often severe, and difficult to treat (2–6). Compared with most of the asthma in the

nonobese, asthma in the obese is typically characterized by less-eosinophilic lung inflammation [(often supported by a lower fraction of exhaled nitric oxide (FENO)) (7–12), and a

ABBREVIATIONS: ACT, Asthma Control Test; BMI, body mass index; CHORI, Children's Hospital Oakland Research Institute; FEF25–75, percent-predicted forced expiratory flow between 25 and 75% of forced vital capacity; FENO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume for 1 s; FEV1%, percent-predicted forced expiratory volume in 1 s; FVC, forced vital capacity; FVC%, percent-predicted forced vital capacity; HDL-c, HDL-cholesterol; HOMA-IR, homeostatic model of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-c, LDL-cholesterol; OW/OB, overweight/obese; PAS, physical activity score; PedsQL, Pediatric Quality of Life Inventory; PedsQL-AM, Pediatric Quality of Life Inventory–Asthma Module; TC, total cholesterol; TG, triglycerides; VLDL-c, VLDL cholesterol

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T-helper cell, type 1 (Th1)-favored cytokine profile (7, 11, 13–16).

Poor nutrition and consequent metabolic dysregulation may be causal factors in the development of asthma in the obese

Most of the obese eat so-called Western diets, which are high in calories, sugar, salt, and unhealthy fats but are low in micronutrients (comprising many essential vitamins, minerals, and ω -3 fatty acids), fiber, and plant polyphenols (17–19). Not surprisingly, obesity is often associated with micronutrient deficiencies (20–22). Western diets are major contributors to metabolic dysregulation common in the obese, including chronic inflammation, dyslipidemia, insulin resistance, poor antioxidant defenses, and low vitamin and mineral status (23, 24). A Western diet pattern is also associated with increased prevalence of asthma (25–27), whereas consumption of a Mediterranean diet may be protective (28, 29). It is, therefore, not surprising that metabolic dysregulation (30–36) and low nutrient status (37–42) are also associated with asthma in the obese and have been suggested to be contributing, causal factors.

Nutrition and exercise therapy for obese asthma

To date, only a few clinical trials have examined the effects of diet and exercise on asthma in the obese population. Dietary changes in those studies were part of comprehensive weight-loss programs, some of which included an exercise component. Improved lung function occurred in some (43–46), but not all (47), of those studies and was dependent upon successful weight loss. Improvements in questionnaire-based measures of asthma control and quality of life, but not lung function, were also recently reported in a weight-loss program (48). A clinical trial that tested the effects of supplementation on obese asthmatics with ω -3 fatty acids is in progress (49).

A recent, comprehensive review and meta-analysis by the Cochrane group (50) concluded that exercise alone can improve questionnaire-based assessments of asthma symptoms and quality of life [*e.g.*, the Asthma Control Test (ACT); Optum, Eden Prairie, MN, USA]. The Cochrane group (50) also concluded that there was not convincing evidence that exercise improved lung function, as measured by spirometry in patients with asthma, which is consistent with other reports (51–53). In contrast, a recent report indicated that exercise improved both asthma control and lung function in a randomized trial of obese adults with asthma (54).

A nutrient-rich dietary intervention

The approach taken in this pilot, randomized, controlled clinical trial was to address metabolic abnormalities connected with obese-associated asthma directly through a targeted nutritional intervention [the Children's Hospital Oakland Research Institute (CHORI)-bar, Oakland, CA,

USA], which is known to promote broadscale improvements in the metabolic dysregulation of obesity (55, 56) without requiring wholesale changes in dietary habits. Our hypothesis is that, by directly focusing on improvement of metabolic dysregulation, rather than on weight loss *per se*, it may be possible to improve asthma control, lung function, and quality of life in obese adolescents with asthma.

The CHORI-bar was developed in collaboration with the U.S. Department of Agriculture (USDA; Washington, DC, USA) as a novel, nutrient-dense, high-fiber, fruit-based supplement bar (55, 56). This nutritionally rich bar is intended to fill gaps in Western diets and has important compositional similarities to a Mediterranean diet (55, 56). Consumption of the CHORI-bar twice daily by healthy, lean and overweight/obese (OW/OB) adults, without requiring other dietary/lifestyle changes, favorably shifted metabolic/anthropometric indicators of dysregulation in a healthy direction (55, 56). Statistically significant improvements in lipoprotein profiles as well as markers of oxidative stress in predominantly lean adults were observed at 2 wk (55). Statistically significant decreases in weight, waist circumference, diastolic blood pressure, heart rate, insulin resistance, and insulin; an increase in HDL2b, and realignment of LDL lipid subfractions toward a less-atherogenic profile occurred in 2-mo trials in healthy OW/OB adults. Those changes were observed predominantly in participants with relatively low levels of chronic inflammation (56).

This trial in OW/OB adolescents with poorly controlled asthma consisted of an intensive, 2-mo program, during which the CHORI-bar group ate 2 bars daily, and both the control and CHORI-bar groups attended weekly exercise/nutrition classes and were encouraged to engage in home exercise activities. A small subgroup continued for 4 additional mo, during which they attended monthly classes, and the CHORI-bar group ate 1 bar each day.

MATERIALS AND METHODS

Recruitment and enrollment criteria

Recruitment for this randomized, controlled, nonblinded study was from Children's Hospital and Research Center Oakland (CHRCO) Primary Care, Behavioral Weight-Loss, Pulmonary, Asthma, and Adolescent Medicine clinics. Stratified randomization was based on the ACT, a questionnaire that assigns scores between 5 (most severe symptoms) and 25 (complete control of symptoms). The allocation ratio of participants in the CHORI-bar to the control group was 2:1. The trial was approved by the CHRCO Institutional Review Board. Informed, written consent from parent/guardians and assent from adolescents was obtained before study participation.

As shown in the study flow diagram (Fig. 1), 56 adolescents were enrolled in the study and randomized. Subjects underwent stratified randomization based on their ACT score. Scores of 18–19 were considered mildly uncontrolled, 15–17 moderately uncontrolled, and <14 severely uncontrolled. The allocation ratio of participants in the intervention to control groups was 2:1. Each participant was accompanied by ≥ 1 parent or guardian, who agreed to attend classes with their child. All 56 randomized participants were included in the intent-to-treat analysis. Subgroup analysis was restricted to the 31 participants (CHORI-bar,

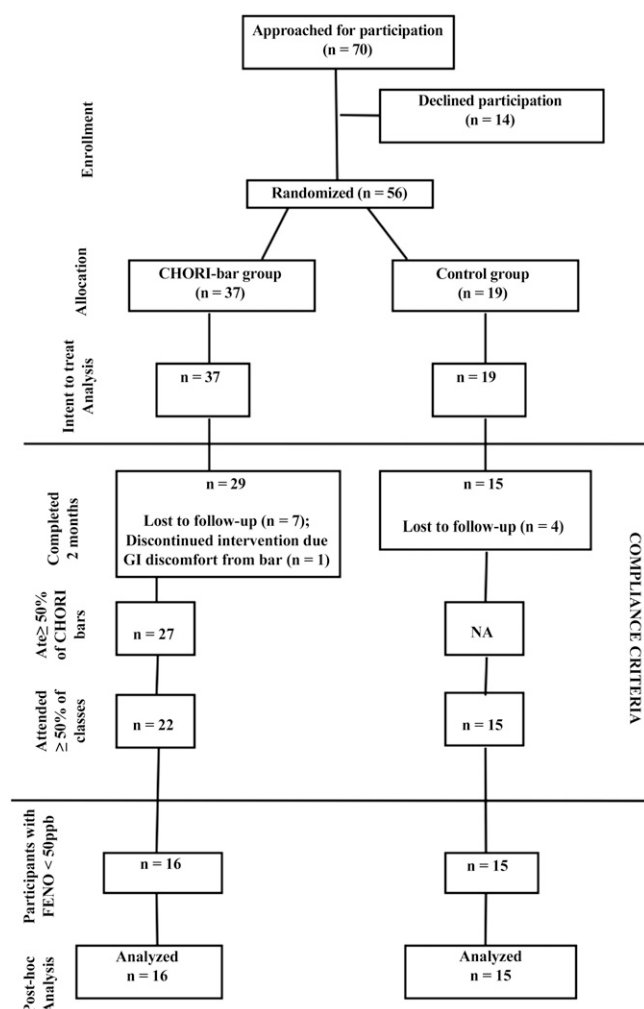


Figure 1. Study flow diagram. For additional information on recruitment, enrollment, and compliance criteria, see Materials and Methods. NA, not applicable.

$n = 16$; controls, $n = 15$) with noneosinophilic asthma [using FENO <50 ppb as a surrogate measure (13, 57)] who had completed the 2-mo trial with acceptable compliance (Fig. 1). Management of the participants' asthma during the study was at the discretion of their physicians.

Inclusion criteria

Inclusion criteria at enrollment included participants who were 14–18 yr old, with a body mass index (BMI) >85th percentile for their age (guidelines from the Centers for Disease Control and Prevention, Atlanta, GA, USA), a reported diagnosis of asthma by a physician, an ACT score ≤ 19 [associated with impaired asthma control (58)], and a willingness to attend, with a parent or guardian, the weekly, family-based nutrition, exercise, and lifestyle counseling classes conducted by a registered dietitian.

Exclusion criteria

Exclusion criteria included a diagnosis of significant comorbid disease, such as diabetes mellitus, rheumatologic or oncologic processes; a significant developmental delay that precluded the ability to perform spirometry testing; or current therapy with antihypertensive medications, lipid-lowering agents, or systemic corticosteroids.

Study design and compliance

Participants were enrolled for studies conducted in the summer of either 2012 or 2013. They were assigned to a CHORI-bar or control group. During the 2-mo study, both groups attended 8 separate, but identical, weekly nutrition and exercise classes. The CHORI-bar group consumed the bar twice daily, after a run-in period of 1 wk, during which 1 bar/d was consumed. Participants were instructed to drink ≥ 8 ounces of water with each bar. The study design included an optional 4-mo extension, during which, the CHORI-bar group ate 1 bar/d, and both the CHORI-bar and control groups attended classes once a month. The number of participants who agreed to participate in the extension was, however, very small, and only limited results are reported for the 4-mo extension.

No specific instruction was given about whether to use the bar as a meal replacement. Participants were given a sufficient supply of CHORI-bars at each class. Acceptable compliance at 2-mo required $\geq 50\%$ class attendance. In addition, acceptable compliance for the CHORI-bar group required at least 50% consumption of bars, as measured by returned bar wrappers, consumption recorded in daily logs, and responses to a questionnaire administered at 2 mo.

Nutrition-education and exercise classes

All classes were taught by a registered dietitian with exercise and coaching experience. Each class was 90 min long and included nutrition education and preplanned physical activity (30–40 min). Systematic baseline assessment and follow-up of effects of the program on diet and physical activity were not included in the protocol. A physician attended all classes and advised participants to follow their asthma-medication regimen as prescribed.

Study visits

Study visits were scheduled at baseline and after the 2- and 6-mo clinical phases. Those visits were performed at the CHRCO Pediatric Clinical Research Center.

Anthropometric measures

Weight was measured using a stand-on scale (ScaleTronix; WelchAllyn, Skaneateles Falls, NY, USA). Height was measured with a digital stadiometer (Seca, Hamburg, Germany). Waist circumference was measured at the umbilicus. Resting heart rate and blood pressure were obtained *via* automated measurement (GE Medical Systems, Tampa, FL, USA).

Lung function

Spirometry testing was performed and interpreted according to American Thoracic Society (New York, NY, USA) standards with a portable, computer-based system (CareFusion, San Diego, CA, USA) that recorded forced expiratory volume for 1 s (FEV1) and forced vital capacity (FVC) (59). Normative values and percentages predicted for spirometry were based on Knudson *et al.* (60). Calculations were made to determine: 1) the percent-predicted FEV1 (FEV1%), the volume of air that is exhaled in the first second during spirometry; 2) the percent-predicted FVC (FVC%), the volume of air that is completely and forcibly exhaled during spirometry; and 3) the percent-predicted forced expiratory flow between 25 and 75% of FVC (FEF25–75) (61). Breath samples were collected, and the FENO was analyzed (GE Analytical Instruments, Boulder, CA, USA) (13). Clinical asthma status, including use of controller

medication, frequency of short-acting β -agonist administration, need for emergency room or urgent primary-care visits for asthma, and need for systemic steroids, was recorded.

Biochemical analyses

Fasting blood glucose, LDL-cholesterol (LDL-c), HDL-cholesterol (HDL-c), triglycerides (TG), total cholesterol (TC), insulin, high-sensitivity C-reactive protein (hsCRP), total IgE, and vitamin D 25-OH were measured by a commercial provider (ARUP Group, London, England). High-MW adiponectin was measured in an ELISA-based assay by a commercial provider (Eurofins Pharma Bioanalytics Services USA, St. Charles, MO, USA). The homeostatic model of insulin resistance (HOMA-IR) was calculated as: fasting insulin (mIU/L) $\times$ glucose (mg/dl)/405 (62).

Questionnaires

Questionnaires were administered at each Pediatric Clinical Research Center study visit, and included the ACT, Pediatric Quality of Life Inventory (PedsQL; Mapi Research Trust, Lyon, France), Pediatric Quality of Life Inventory–Asthma Module (PedsQL-AM; Mapi Research Trust), and the Physical Activity Questionnaire for Adolescents (developed by the University of Saskatchewan, Saskatoon, SK, Canada).

Composition of the CHORI-bar

Characteristics of the CHORI-bar were previously described (55, 56). Composition of the bar used for this study is summarized in **Table 1** (63, 64). Bar composition was from analysis by Medallion Labs (Minneapolis, MN, USA), and calculated from USDA tables (63). Briefly, the CHORI-bar is moderate in calories ($\approx$ 130 kcal/36-g bar), but nutrient dense, with a polyphenolic-rich matrix of fruit, walnuts, and nonalkali-processed dark chocolate, added vitamins, essential minerals, docosahexaenoic acid (a long-chain polyunsaturated fatty acid), soluble and insoluble fibers, protein, and other small molecules intended to benefit gut health (65).

Statistical analyses

Sample-size calculation was based on a *t* test of the difference in experimental groups on the primary outcome (ACT) measured as a continuous variable, with a hypothesized expected effect size of a 4-point change. To obtain a significance level of 0.05 and power of 80% (66, 67) with a 2:1 proportion of intervention to control groups, a total *n* = 33 was determined (22 intervention, 11 control). We aimed to enroll a minimum of 45 subjects to allow for a 35% dropout rate. A total of 70 subjects were approached for participation, and 56 were randomized.

Statistical analyses were performed using SAS software (v.9.4; SAS Institute, Cary, NC, USA). Variables included biochemical and anthropometric measures, questionnaire responses, and spirometry outcomes. Descriptive statistics were calculated for the various subgroups and times to include means and measures of variability. Analyses were conducted from an intent-to-treat perspective, including all randomized participants, regardless of participation in treatment. Data were examined for assumptions of normality using measures of skewness and kurtosis, plots, and the Anderson-Darling test. Log transformations were then performed for highly skewed data (HOMA-IR, insulin, and hsCRP). Initial bivariate analysis using a Student's *t* test for continuous measures and a χ^2 test for categorical measures was conducted to compare baseline values between control and CHORI-bar groups. Regression models were constructed on changes from baseline over 2- and 6-mo time periods. Changes over time compared the control and CHORI-bar groups using general

TABLE 1. CHORI-bar composition

Composition	Amount
Total calories (kcal)	127
Total fat (g)	4.8
Saturated fat (g)	2.4
Trans fat (g)	0.0
DHA, 22:6 ω -3 (mg)	171
Cholesterol (mg)	0.0
Sodium (mg)	35.0
Potassium (mg)	209
Total carbohydrate (g)	19.5
Fiber, total dietary (g)	7.84
Sugars (g)	8.17
Total protein	5.45
β -Carotene (IU)	179
Vitamin A	35.9
Calcium (mg)	276
Vitamin D ₃ (IU)	831
Vitamin K ₁ (μ g)	50.0
Riboflavin (mg)	0.50
Vitamin B ₆ (mg)	0.53
Vitamin B ₁₂ (μ g)	0.70
Pantothenic acid (mg)	1.48
Zinc (mg)	3.16
Copper (μ g)	327
Chromium (μ g)	15.0
Vitamin C (mg)	76.6
Iron (mg)	4.10
Vitamin E (IU)	3.78
Thiamine (vitamin B ₁) (mg)	0.29
Niacin (nicotinic acid) (mg)	7.14
Folate (μ g)	165
Biotin (μ g)	7.70
Phosphorus (mg)	197
Magnesium (mg)	201
Selenium (μ g)	9.4
Manganese (mg)	1.11
Choline (mg)	26.6
Glutamine (g)	1.00
Lactate (mg)	343
Glycerin (g)	1.50
Polyphenols, total (mg)	522
Polyphenols, monomeric (mg)	157

DHA, docosahexaenoic acid. Weight of 1 bar = 36.3 g. Bar composition, unless otherwise indicated below, was from analysis by Medallion Labs. Values were calculated from USDA tables (63) for vitamin A (Medallion Labs reported <18 IU), vitamin K₁, copper (Medallion Labs reported <363 μ g), chromium, biotin, selenium, choline, glutamine, lactate, and glycerine. Polyphenol concentrations were derived from the USDA database for the flavonoid content of selected foods, release 2.1 (64); NDB (nutrient database) numbers 09050, 09078, 97074, and 09279. Estimates of cocoa polyphenols were from personal communication with Dr. Mark Payne (Hershey Center of Health and Nutrition Analysis, Hershey, PA, USA; March 12, 2012). Medallion Labs–reported value was for β -carotene. Vitamin E was added as mixed tocopherols. The value for glutamine does not include glutamine from protein.

linear models with time treated as a repeated measure. For the intent-to-treat change analysis, baseline values for randomized participants who did not complete the trial (Fig. 1) were assumed to also apply at the 2-mo time point. For outcomes of changes from baseline, each model included the baseline value of the dependent variable (change) as a predictor to adjust for regression to the mean effects. The generalized estimating equation, with an exchangeable working-correlation structure, was used to account for within-person correlations in outcomes at different times. Models included group, time, and group-by-time

interactions. A series of models were also examined that included adjustments for gender, waist circumference-to-height ratio, physical activity score (PAS), hsCRP, and FENO. Statistical results of adjusted models were, in general, similar to unadjusted models, and reported statistics reflect results of unadjusted models. Within-group changes were assessed by general linear models with time treated as repeated measures. A value of $P \leq 0.05$ was considered significant for all statistical tests, and $P < 0.10$ indicated trends.

RESULTS

Overall intent-to-treat analysis

Baseline characteristics

The study flow diagram is in Fig. 1. Fifty-six participants were randomized as described in the Materials and Methods: 37 to the CHORI-bar group and 19 to the control group. All randomized participants were included in the intent-to-treat statistical analysis. Age, gender, and race compositions of the CHORI-bar and control groups were similar, except there were significantly fewer females in

the CHORI-bar compared with the control group ($P = 0.046$). Mean $\pm$ SD age was 15.4 ± 1.3 (CHORI-bar) and 15.5 ± 1.6 (control) yr; sex (female) was 13 (35%; CHORI-bar) and 12 (63%, control); and race was white 0 (0%, CHORI-bar) and 1 (5%, control); black, 24 (65%, CHORI-bar) and 10 (53%, control); Hispanic, 11 (30%, CHORI-bar) and 5 (26%, control); Asian 1 (3%, CHORI-bar) and 1 (5%, control); and other 1 (3%, CHORI-bar) and 2 (11%, control).

Baseline values, summary results, and group differences at 2 mo are in Table 2. At baseline, FENO was significantly higher in the CHORI-bar group ($P = 0.045$), ACT was slightly higher in the CHORI-bar group ($P = 0.077$), and heart rate was slightly lower in the CHORI-bar group ($P = 0.066$). There were no other significant or trending significant differences between variables at baseline. At baseline, note that mean $\pm$ SD HOMA-IR, reflective of insulin resistance, was 6.82 ± 4.75 and 7.91 ± 3.88 in CHORI-bar and control participants, respectively. Both of these values are considerably more than the 2.5 commonly used as the cutoff for insulin resistance (68). All participants were either overweight (BMI z score ≥ 1) or obese (BMI z score ≥ 2.0). An ACT score ≤ 19 (58), indicating poorly controlled asthma, was an inclusion criterion for the study,

TABLE 2. All randomized participants: baseline characteristics and results at 2 mo

	CHORI-bar group (<i>n</i> = 37) ^{<i>a</i>}		Control group (<i>n</i> = 19) ^{<i>a</i>}		Group difference (<i>P</i>) ^{<i>b</i>}
Variable	Baseline	2 mo	Baseline	2 mo	Change (2 mo)
Lung function					
FVC%	110.46 ± 14.02	115.86 ± 12.05	113.00 ± 17.44	114.53 ± 18.66	0.79
FEV1%	92.30 ± 15.55	97.48 ± 13.17	97.42 ± 16.10	96.87 ± 16.34	0.69
FEV1/FVC	78.14 ± 6.98	78.69 ± 6.69	81.26 ± 5.84	80.00 ± 6.15	0.68
FEF25–75%	77.59 ± 24.05	82.48 ± 25.57	88.32 ± 23.26	84.07 ± 22.13	0.50
FENO	35.80 ± 23.52	30.48 ± 20.21	24.03 ± 11.53	21.99 ± 13.85	0.94
Questionnaire-based measures					
ACT	15.00 ± 2.95	20.34 ± 3.13***	13.42 ± 3.39	19.73 ± 3.15***	0.89
PedsQL	71.40 ± 14.25	81.48 ± 13.00***	75.18 ± 12.09	80.00 ± 10.00**	0.94
PedsQL-AM	70.80 ± 12.85	82.64 ± 11.49***	72.63 ± 17.81	78.80 ± 12.21**	0.58
PAS	2.33 ± 0.60	2.54 ± 0.73*	2.14 ± 0.74	2.18 ± 0.81	0.12
Anthropometric and other physical measures					
SBP (mmHg)	118.51 ± 7.85	117.41 ± 8.37	115.99 ± 9.41	115.08 ± 9.19	0.81
DBP (mmHg)	66.92 ± 8.27	67.75 ± 8.80	65.71 ± 8.81	65.33 ± 6.54	0.43
Heart rate (bpm)	69.64 ± 11.35	70.94 ± 11.93	75.80 ± 12.20	70.00 ± 8.36**	0.0036
Weight (kg)	99.50 ± 21.26	99.62 ± 22.84	99.51 ± 23.11	101.28 ± 23.03	0.68
Waist circumference (cm)	109.30 ± 15.10	109.54 ± 14.79	111.01 ± 17.15	111.01 ± 17.97	0.83
BMI (<i>z</i> score)	2.14 ± 0.42	2.11 ± 0.42	2.21 ± 0.43	2.20 ± 0.46	0.49
Lipids (mg/dl)					
HDL-c	47.65 ± 12.50	43.45 ± 8.66	44.32 ± 12.58	46.47 ± 15.45	0.12
LDL-c	90.86 ± 18.68	87.31 ± 20.98	87.79 ± 19.01	88.00 ± 21.17	0.86
Total cholesterol	159.27 ± 25.01	149.07 ± 22.67*	153.11 ± 22.06	152.47 ± 21.47	0.64
Non-HDL-c	111.62 ± 22.20	105.62 ± 22.79	108.79 ± 25.16	106.00 ± 28.06t	0.74
TG	104.14 ± 51.02	92.34 ± 46.13**	104.58 ± 55.29	91.00 ± 44.02***	0.61
VLDL-c	20.76 ± 10.22	18.45 ± 9.26**	21.00 ± 10.91	18.00 ± 8.79***	0.53
TG/HDL-c	2.42 ± 1.65	2.29 ± 1.49	2.81 ± 2.31	2.35 ± 1.66***	0.17
Insulin resistance					
Glucose (mg/dl)	93.46 ± 8.22	92.62 ± 6.28	94.00 ± 7.80	92.67 ± 6.61	0.57
Insulin (mU/L)	29.24 ± 19.56	32.07 ± 20.89	33.63 ± 15.28	26.27 ± 11.84*	0.008
HOMA-IR	6.82 ± 4.75	7.25 ± 4.54	7.91 ± 3.88	6.01 ± 2.73*	0.011
Inflammation					
hsCRP (mg/L)	3.85 ± 4.30	4.38 ± 6.14	3.83 ± 5.69	3.47 ± 4.89	0.38
IgE (IU/ml)	518.57 ± 712.17	560.03 ± 734.23	294.32 ± 516.62	247.33 ± 497.21†	0.22

^aMean $\pm$ SD. Statistical significance of changes from 0–2 mo within either the CHORI-bar or the control group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, † $P < 0.10$ and $P \geq 0.050$. ^bSignificance values comparing the CHORI-bar *vs.* control group changes at 2 mo.

which is reflected in the relatively low mean $\pm$ SD baseline ACT scores in both the CHORI-bar and control groups (15.0 ± 2.95 vs. 13.42 ± 3.39 , respectively). Lung function, as measured by spirometry, was similar at baseline in both control and intervention groups, with mean FEV1/FVC ratios in both groups in the abnormal range (69).

Effects at 2 mo

As highlighted in Table 2, group differences in change at 2 mo were significant for only 3 variables. Heart rate decreased 7.7% in controls but did not change in the CHORI-bar group ($P = 0.0036$). Insulin and HOMA-IR each decreased 21.9% in the control group, and increased 9.7% in the CHORI-bar group ($P = 0.008$ and 0.011 , respectively). These control group-specific decreases cannot be explained by the differences in sex ratios between the 2 groups because the changes are independent of gender (data not shown). No other significant or trending significant group differences were observed.

Within-group statistically significant improvements occurred in both CHORI-bar and control groups in 2 TG-dependent metabolic measures [TG and VLDL cholesterol (VLDL-c)], and questionnaire-based measures of asthma control (ACT), quality of life (PedsQL), and asthma (PedsQL-AM) (Table 2). The possibility that these results could have been a consequence of the inclusion of exercise in the protocol is discussed.

Effects on lung function: subgroup analysis of participants with low-eosinophilic asthma who satisfied compliance criteria

The intent-to-treat analysis did not reveal any statistically significant effects of the intervention on the 3 spirometry measures of lung function (FVC, FEV1, and FEF25–75). However, as shown in Table 2, movement of all 3 measures in the direction of improvement occurred in the CHORI-bar, but not the control, group. As shown in the study flow diagram (Fig. 1), the loss of more than one-third of the initially randomized cohort suggested that effects of the intervention might have been blunted in the intent-to-treat analysis. Furthermore, an equal proportion of subjects (8 in the CHORI-bar group and 4 in the control group) were lost to follow-up, suggesting that the burden of participation in the study, rather than consumption of the bar itself, was the reason for attrition. Additionally, although FENO was <50 ppb (suggesting noneosinophilic asthma) in all control participants, FENO was >50 ppb in the 6 compliant participants in the CHORI-bar group who completed the 2-mo study (Fig. 1), raising additional concerns about the blunted effects of the nutritional intervention in the intent-to-treat analysis on noneosinophilic asthma. Therefore, a subgroup analysis was conducted on compliant participants with FENO <50 ppb ($n = 31$; 16 in the CHORI-bar group, and 15 in the control group) who successfully completed the 2-mo protocol.

Baseline characteristics and overall results of the subgroup statistical analysis were similar to that in the intent-to-treat analysis, as shown in Table 3, with the exception

that trends emerged in this analysis suggesting CHORI-bar-specific improvements in lung function. As shown in Fig. 2A, statistically significant ($P < 0.05$) within-group increases (improvements) in 2 spirometry measures, FVC% (+2.84%) and FEV1% (+3.68%) were observed at 2 mo in the CHORI-bar, but not the control, group: FVC% (+0.87%) and FEV1% (–0.26%). The 2-mo change comparison between the CHORI-bar and control groups trended significant ($P = 0.093$) for FEV1%. FEF25–75 increased (+6.27%) in the CHORI-bar group but not in the control group (–2.87%, $P = 0.20$); these changes were not significant at the $P = 0.10$ cutoff. The FEV1/FVC ratio was unchanged in both groups. The 2-mo changes in lung function in the CHORI-bar group were no longer significant if the 6 subjects with baseline FENO >50 ppb were included in the analysis (data not shown).

Chronic inflammation (hsCRP) blunted CHORI-bar-induced improvements in spirometry

hsCRP is a standard measure of chronic inflammation that we previously reported blunted CHORI-bar-induced improvements of both metabolic and anthropometric measures linked to health status in healthy OW/OB adults (56). In that earlier study, hsCRP varied over a wide range and was greater than an informal cutoff of 1.5 mg/L (suggesting chronic inflammation) in about half of the participants. Almost all of the CHORI-bar-induced improvements observed in that study occurred in the less-inflamed subgroup (56). Figure 3 illustrates that baseline hsCRP also varied over a wide range among both CHORI-bar and control OW/OB adolescents in this study, and that hsCRP was also greater than the informal cutoff of 1.5 mg/L (56) for roughly half of the participants.

To determine whether chronic inflammation influenced the responsiveness of spirometry measures to CHORI-bar consumption in this subgroup of OW/OB asthmatics, effects at 2 mo on intervention and control groups were assessed separately in participants with lower and higher hsCRP at baseline.

As shown in Figs. 2B, C, virtually all improvements in lung function occurred in the participants with less inflammation in the CHORI-bar subgroup. Note that increases in all 4 spirometry measures in the CHORI-bar subgroup were more robust statistically in the participants with less inflammation (Fig. 2B) compared with all subgroup participants (Fig. 2A), despite the smaller sample size. As shown, there were no effects on spirometry in the control group, regardless of the degree of inflammation. CHORI-bar vs. control group differences in changes over the 2-mo trial period for the participants with less-inflammation (Fig. 2B) were as follows: FVC, $P = 0.25$; FEV1, $P = 0.055$; FEV1/FVC, $P = 0.20$; FEF 25–75, $P = 0.13$. No significant effects were observed in the participants with greater inflammation (Fig. 2C). In contrast to improvements in spirometry, improvements in the questionnaire-based measures (ACT, PedsQL, and PedsQL-AM) in both the CHORI-bar and control groups were not dependent on the degree of chronic inflammation (data not shown).

TABLE 3. Compliant, low-FENO participants: baseline characteristics and results at 2 mo

Variable	CHORI-bar group (<i>n</i> = 16) ^a		Control group (<i>n</i> = 15) ^a		Group difference (<i>P</i>) ^b
	Baseline	2 mo	Baseline	2 mo	Change (2 mo)
Lung function (spirometry)					
FVC%	110.0 ± 9.48	113.1 ± 11.4*	113.8 ± 18.8	114.5 ± 18.7	0.34
FEV1%	93.2 ± 13.5	96.4 ± 14.2*	97.3 ± 16.8	96.9 ± 16.3	0.093
FEV1/FVC	79.6 ± 7.69	80.2 ± 7.51	80.7 ± 5.66	80.0 ± 6.15	0.27
FEF25–75%	81.9 ± 28.5	86.1 ± 30.0	86.7 ± 22.2	84.1 ± 22.1	0.10
Questionnaire-based measures					
ACT	15.1 ± 3.26	20.9 ± 3.36***	13.3 ± 3.50	19.7 ± 3.15***	0.38
PedsQL	79.2 ± 11.0	83.2 ± 12.6*	73.4 ± 9.29	80.0 ± 10.0*	0.93
PedsQL-AM	74.5 ± 10.0	83.8 ± 12.9***	71.8 ± 16.4	78.8 ± 12.2**	0.32
PAS	2.60 ± 0.55	2.77 ± 0.77	2.21 ± 0.78	2.18 ± 0.81	0.092
Anthropometric and other physical measures					
SBP (mmHg)	117.3 ± 6.48	117.4 ± 6.78	115.5 ± 8.49	115.1 ± 9.19	0.52
DBP (mmHg)	68.0 ± 8.33	68.8 ± 8.15	66.6 ± 8.32	65.3 ± 6.54	0.23
Heart rate (bpm)	71.8 ± 10.6	75.9 ± 11.8	77.5 ± 11.6	70.0 ± 8.4***	0.002
Weight (kg)	93.0 ± 22.4	92.8 ± 22.6	101.3 ± 22.9	101.3 ± 23.0	0.90
Waist circumference (cm)	105.5 ± 16.0	104.6 ± 14.9	111.4 ± 17.5	111.0 ± 18.0	0.59
BMI (z score)	2.06 ± 0.46	2.04 ± 0.44	2.22 ± 0.42	2.20 ± 0.46	0.96
Lipids (mg/dl)					
HDL-c	45.6 ± 12.1	44.7 ± 9.22	44.0 ± 13.5	46.5 ± 15.5	0.17
LDL-c	81.2 ± 14.2	83.8 ± 16.4	90.3 ± 18.6	88.0 ± 21.2	0.74
Total cholesterol	153.0 ± 22.9	145.9 ± 16.9*	156.3 ± 18.7	152.5 ± 21.5	0.36
Non-HDL-c	107.4 ± 18.0	101.2 ± 15.5*	112.3 ± 25.1	106.0 ± 28.1 [†]	0.88
TG	101.2 ± 51.7	87.3 ± 47.7***	109.5 ± 59.7	91.0 ± 44.0**	0.71
VLDL-c	20.2 ± 10.4	17.4 ± 9.53***	21.9 ± 11.8	18.0 ± 8.79***	0.62
TG/HDL-c	2.38 ± 1.39	2.12 ± 1.53 [†]	3.06 ± 2.54	2.35 ± 1.66***	0.35
Insulin resistance					
Glucose (mg/dl)	92.3 ± 6.60	92.8 ± 5.75	94.1 ± 8.55	92.7 ± 6.61	0.57
Insulin (mU/L)	24.9 ± 15.7	30.4 ± 13.4*	34.9 ± 15.9	26.3 ± 11.8*	0.0020
HOMA-IR	5.78 ± 3.97	6.93 ± 6.26 [†]	8.23 ± 4.11	6.01 ± 2.73*	0.003
Inflammation					
hsCRP (mg/L)	2.47 ± 1.91	2.41 ± 2.12	3.71 ± 5.79	3.47 ± 4.89	0.75 ^c
Adiponectin (ng/ml)	1807 ± 564.3	2161 ± 692*	2366 ± 1980	2401 ± 1833	0.061
IgE (IU/ml)	464 ± 912	455 ± 862	334 ± 575	247 ± 497	0.25

^aMean ± SD. Statistical significance of changes from 0–2 mo within either the CHORI-bar or the control group. **P* < 0.05, ***P* < 0.01, *P* < 0.001, [†]*P* < 0.10 and *P* ≥ 0.050. ^bSignificance values comparing the CHORI-bar *vs.* control group changes at 2 mo. ^chsCRP > 10 was excluded from analysis if the change from baseline was >2-fold to exclude the possibility of intercurrent infection.

CHORI-bar-specific improvements in lung function were also observed at 6 mo in the small subset of compliant, low-FENO participants (bar group, *n* = 4; control group, *n* = 7) who continued eating 1-bar/d for 4 mo after the 2-mo intensive phase of the trial (data not shown). In this small subgroup, statistically significant improvements at 6 mo in 3 spirometry measures were observed in the CHORI-bar group (FVC%, *P* = 0.0031; FEV1%, *P* = 0.0055; FEV1/FVC = *P* = 0.034). Differences between the CHORI-bar and control groups in changes during the 6-mo period were significant for FEV1% (*P* = 0.040) and FEV1/FVC (*P* = 0.043).

Some evidence suggests that CHORI-bar-specific metabolic improvements may have begun to emerge during the less-exercise-intensive, 4-mo extension of the program. Assays were conducted on samples from the compliant, low-FENO subgroup for the adipokine adiponectin, a key regulatory protein suggested as an overall biomarker of metabolic health (70). We previously showed that adiponectin responded robustly to CHORI-bar consumption in both lean and OW/OB adults (56). In the current study, as shown in Fig. 4A and Table 3, adiponectin increased at 2 mo only in the CHORI-bar group and continued to increase during the last 4 mo of the trial. Analysis of all

compliant participants indicated significant (*P* < 0.05) group-by-time interactions for 5 variables, all metabolic: HDL-c, TG, non-HDL, TG/HDL, and VLDL. These significant group-by-time interactions were primarily due to within-group changes from 2 to 6 mo in the CHORI-bar group, which were in the direction associated with health benefits (Fig. 4B–F). Results of the 6-mo extension are suggestive, but clearly limited, because of the very few participants that completed the 6-mo phase of the study.

Summary of effects of the intervention on measures of lung function and asthma control

Results presented above suggest CHORI-bar-specific improvements in lung function in low-FENO, compliant participants, but only in those with relatively low levels of chronic inflammation, as measured by hsCRP. In contrast, ACT, the standard questionnaire-based measure of asthma control, presented a strikingly different pattern of results in both the intent-to-treat and the subgroup analyses. Specifically, significant improvements were observed in both the CHORI-bar and control groups. These improvements were not dependent on the degree of

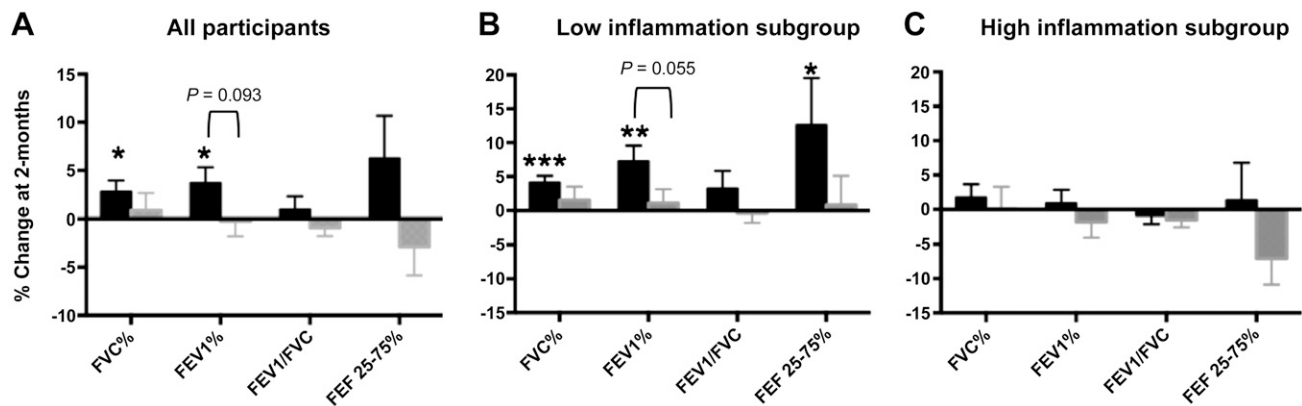


Figure 2. Effects of CHORI-bar consumption for 2 mo on lung function in compliant, low-FENO participants. Plotted is the percentage of change at 2 mo (means $\pm$ SE). Black bars: CHORI-bar group; gray bars: control group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for within-group changes. Between-group significance values that trended significant ($P < 0.10$ and $P \geq 0.05$) are indicated over brackets. FVC% is the percentage of predicted volume of air completely exhaled during the spirometry maneuver; FEV1% is the volume of air exhaled during the first second of the spirometry test; FEV1/FVC is the FEV1 as a fraction of the total lung capacity; FEF 25–75% is the average flow rate during the middle 50% of the FVC (61). A) All participants: CHORI-bar group, $n = 16$; control group, $n = 15$. B) Low baseline inflammation (hsCRP < 1.5) subgroup of A: CHORI-bar group, $n = 7$; control group, $n = 8$. C) High baseline inflammation (hsCRP > 1.5) subgroup of A: CHORI-bar group, $n = 9$; control group, $n = 7$.

chronic inflammation. The discordance between spirometry and ACT measures is further supported by a lack of correlation between changes at 2 mo in any of the 4 spirometry measures, with change in ACT scores, either across the entire low-FENO intervention subgroup ($n = 16$) or only the participants with less inflammation ($n = 7$): low-FENO participants in the CHORI-bar group (ACT vs. FVC: $r = -0.20$, $P = 0.46$; FEV1: $r = -0.26$, $P = 0.34$; FEV1/FVC: $r = +0.25$, $P = 0.34$; and FEF25–75: $r = -0.17$, $P = 0.53$); CHORI-bar subgroup with less inflammation (ACT vs. FVC: $r = -0.12$, $P = 0.64$; FEV1: $r = -0.076$, $P = 0.82$; FEV1/FVC: $r = -0.30$, $P = 0.40$; and FEF25–75: $r = -0.24$, $P = 0.52$).

DISCUSSION

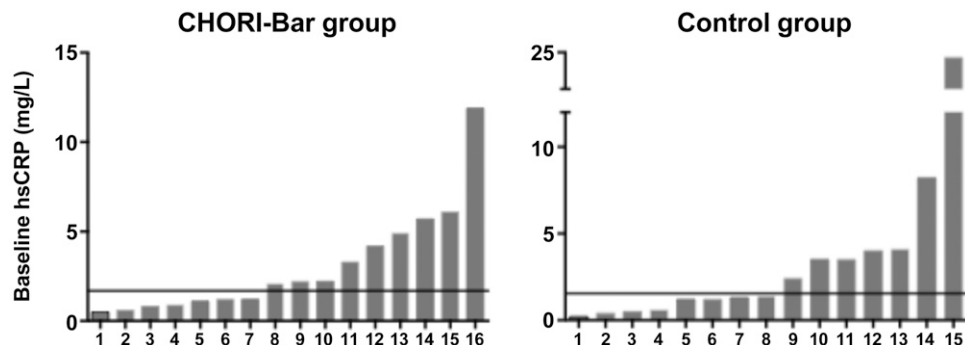
In this pilot, randomized, controlled clinical trial, a nutrient-dense supplement bar designed to fill gaps in poor diets (the CHORI-bar) (55, 56) was tested for its ability to improve lung function (by spirometry), asthma control, quality of life, and metabolic profiles in OW/OB adolescents with poorly controlled asthma. The major finding of this study is that CHORI-bar consumption for 8 wk improved lung function (FVC%, FEV1%, and FEF 25–75%), but only in compliant participants with non-eosinophilic asthma (using FENO < 50 ppb as a surrogate

measure) and relatively low levels of chronic inflammation (by hsCRP) (Fig. 2). No effects on lung function were observed in the control group, regardless of inflammation status (Fig. 2).

Relationships between inflammation and spirometry

In our previous 8-wk study of CHORI-bar effects in otherwise healthy OW/OB adults (56), most metabolic and anthropometric improvements were observed in participants with relatively low chronic inflammation. It is striking that, in this study, CHORI-bar-induced improvements in lung function also occurred only in participants with relatively low levels of chronic inflammation (Fig. 2). Although lung function was reported to improve in some weight loss studies (45) [although not in others (47, 48)], improvement in spirometry measures in this study occurred in the absence of weight loss. There was no significant weight loss in the 8-wk trial, overall in the intent-to-treat analysis (Table 2); in the compliant, low-FENO group (Table 3); or in the subgroup with less inflammation (data not shown). In this regard, it is of possible interest that a recent 10-wk dietary/exercise intervention weight-loss trial in OW/OB asthmatics observed improvements

Figure 3. Range of baseline hsCRP (mg/L) plasma concentrations in the compliant, low-FENO CHORI-bar and control groups. Participants are ordered on the x axis according to baseline concentrations of hsCRP. The horizontal lines indicate the cutoff value of 1.5 mg/L used to subdivide the 2 groups into lower and higher inflammation categories.



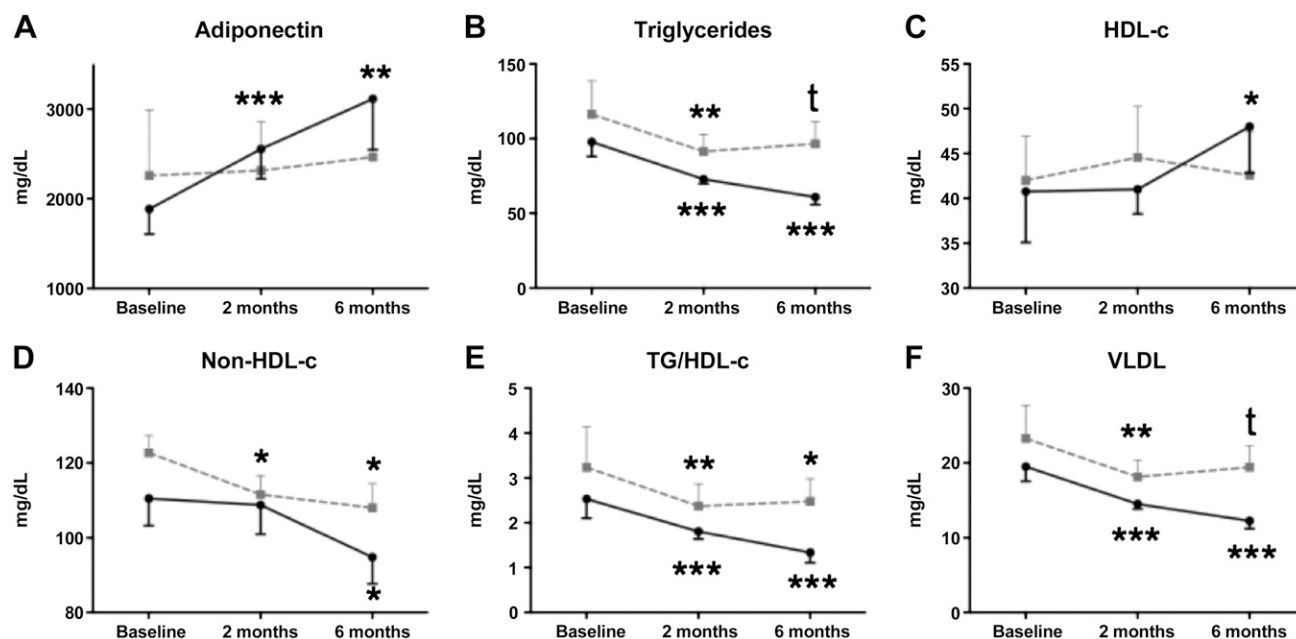


Figure 4. Effects on metabolism at 2 and 6 mo for adiponectin (A), triglycerides (B), HDL-c (C), non-HDL-c (D), TG/HDL-c (E), and VLDL (F). CHORI-bar-specific improvements in metabolism emerge at 6 mo, after 2-mo consumption of 2 bars/d and 4 mo additional consumption of 1 bar/d. Means $\pm$ SE is plotted for compliant, low-FENO participants who completed 6 mo (CHORI-bar group, $n = 4$; control group, $n = 7$). Solid black line: CHORI-bar group; gray line: control group. $P < 0.10$, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ indicate within-group changes from 0–2 to 0–6 mo that were statistically significant or trending significant. Overall group differences were as follows: adiponectin (A): $P = 0.058$ and TG (B): $P = 0.097$. Group differences from 0 to 6 mo were TG (B): $P = 0.052$ and VLDL (F): $P = 0.044$.

in spirometry, but only in participants who lost $>5\%$ of their body weight (45). A similar observation was reported in an earlier study (43). We suggest that the failure of lung function to improve in participants in those 2 studies may not have been because they did not lose weight, but because they had relatively high levels of systemic inflammation, which made it more difficult for them to lose weight in response to the dietary intervention and also more difficult for lung function to improve. In our previous study, CHORI-bar-induced weight loss occurred only among participants with relatively low levels of chronic inflammation (56). We are unaware of any studies that have examined the relationship of chronic inflammation to dietary-induced improvements in spirometry.

Other information in the literature on relationships between chronic inflammation and lung function is limited to cross-sectional comparisons. Inverse relationships between systemic inflammation (e.g., hsCRP) and lung function have been observed in lean, asthmatic children (71) and adults (72), but relationships are less clear in obese patients with asthma. Many investigators have discussed the possibility that there could be a causal link between increased chronic systemic inflammation and the non-eosinophilic form of asthma in obesity (16, 32, 73, 74). Consistent with that suggestion, hsCRP was, overall, higher in obese asthmatic adults compared with obese nonasthmatic controls (75). However, a direct relationship between measures of airway inflammation and systemic inflammation was not observed in adults (76) and there was no relationship observed between obesity and systemic inflammation in asthmatic children (77).

Discordance between lung function and ACT scores

A second major observation in this trial was the apparent lack of relationship between ACT scores and lung function, also noted previously by others (78–80). In this study, baseline spirometry measures and ACT scores were not correlated, whether examined across both CHORI-bar and control groups combined or within each group separately (data not shown). Changes in lung function and ACT scores over the course of the 2-mo trial also appeared to be independent of one another. As indicated above, lung function improved only in the CHORI-bar group with relatively less inflammation (Fig. 2), whereas ACT scores improved in both control and CHORI-bar groups (Tables 2 and 3). Furthermore, greater sensitivity of the low-inflammation subgroup to bar-induced changes in the direction of improved lung function was not paralleled in ACT scores, which increased similarly in both low- and high-inflammation subgroups in the CHORI-bar group and also across all participants (data not shown).

It is not clear why spirometry improved only in the CHORI-bar group, whereas ACT scores improved in both control and bar groups. A possible explanation is that improvements in ACT scores were primarily due to the exercise component of the program and spirometry improvements to the CHORI-bar intervention. This possibility is supported by earlier studies reporting that exercise improved ACT scores but had no effect on lung function (50). It also cannot be ruled out that improvement in ACT scores in both bar and control groups reflected known seasonal fluctuations in asthma symptoms (81). The trial

was conducted during the summer months, a period when need for medical care (e.g., emergency room visits) is known to decline. However, because improvements in lung function occurred only in the CHORI-bar group, it is unlikely that explanation applies to effects on lung function.

The lack of apparent correlation between improvement in spirometry measures and ACT scores may also be related to the fact that, although improvements in spirometry measures were statistically significant, effect size was modest. ACT scores are based on answers to questions that elicit information, including frequency of medication use, interference with school or work, and inability to sleep (82). It is suggested that, although improvements in spirometry indicated movement in a healthy direction, changes were not robust enough over the course of this 2-mo trial to translate into detectable improvements in ACT scores, particularly in the presence of the exercise effect.

Mechanistic considerations

With the exception of adiponectin (Fig. 4A and Table 3), CHORI-bar-specific metabolic improvements were less evident in this study in OW/OB adolescents with asthma than in our previous studies in lean and OW/OB, otherwise healthy, adults (55, 56). It is suggested that the inclusion of exercise in the intensive 2-mo phase of the study limited its sensitivity for detection of CHORI-bar-specific metabolic effects. Exercise is well known to improve metabolism (83), and, indeed, metabolic improvements occurred in both CHORI-bar and control groups during this period. This suggestion is further supported by the emergence of several possible CHORI-bar-specific metabolic improvements among the few participants who ate 1 bar/d in a 4-mo extension of the trial, during which, exercise was likely to be less of a factor (Fig. 4).

It is not clear by what mechanism CHORI-bar consumption resulted in improvements in lung function. The only significant differences in metabolic responses at 2 mo between the CHORI-bar and control groups were for insulin/HOMA-IR (Tables 2 and 3) and adiponectin (Fig. 4A and Table 3), a regulatory adipokine produced in adipose tissue that is inversely associated with obesity, insulin resistance, and inflammation and is a central mediator of metabolic homeostasis involving lipid and glucose metabolism and inflammation (84). Adiponectin and insulin/HOMA-IR increased significantly in the CHORI-bar group, whereas adiponectin did not change, and insulin/HOMA-IR decreased significantly in the control group. It is unlikely that either of these metabolic changes in the CHORI-bar group are related to the observed improvement in spirometry because they occurred predominantly in participants with relatively high chronic inflammation (data not shown), whereas improvement in spirometry occurred exclusively in those with less chronic inflammation (Fig. 2).

Limitations

Interpretation of study results was complicated by several factors: 1) although the inclusion of exercise and nutrition education was applied to intervention and control groups equally, the amount of change that each participant

incorporated into their daily lives was likely to vary and is difficult to quantify, which may have limited the sensitivity of the study for detection of CHORI-bar-induced changes in parameters affected by exercise or dietary habits; 2) small group sizes, which limited the power of the study to detect between-group changes; and 3) inherent difficulties in monitoring compliance in adolescents. Other limitations included the absence of a placebo, although difficulties in applying the same placebo standards used for drug trials to nutritional interventions have been discussed (85), and because multiple statistical tests were conducted, some false-positives may have occurred.

CONCLUSIONS

A common form of asthma in obese patients is non-eosinophilic, which tends to be more severe and more difficult to treat than asthma in nonobese patients. Its association with poor dietary habits and metabolic dysregulation offers an important opportunity for lifestyle therapy. Although this is a pilot study with significant limitations, the results are suggestive and have important implications for the role of exercise and targeted nutritional supplementation in therapy for obese patients with asthma. Future work should be directed toward validating these results and understanding the mechanisms by which chronic inflammation reduces sensitivity to dietary-induced improvements in lung function. [F]

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AUTHOR CONTRIBUTIONS

J. C. McCann, A. Lal, M. Shigenaga, M. Mietus-Snyder, B. N. Ames, K. Hardy, M. Bseikri, and E. Fong developed the overall concept; M. Bseikri, A. Lal, E. Fong, M. Mietus-Snyder, and K. Graves designed the clinical trial; M. Bseikri, E. Fong, K. Graves, A. Goldrich, and D. Block performed the clinical trial; M. Bseikri, E. Fong, J. C. McCann, G. L. Gildengoren, M. Shigenaga, and J. Suh performed the data analysis and assay; and M. Bseikri, J. C. McCann, A. Lal,

E. Fong, M. Shigenaga, K. Graves, G. L. Gildengoren, B. N. Ames, M. Mietus-Snyder, and J. Suh prepared the manuscript.

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