American Lung Association
Airways Clinical Research Centers

Pilot of Lifestyle and Asthma Intervention (PLAN)

Protocol

Version 1.4

NCT03291808

PI at University of Vermont: Anne Dixon, MD
PI at Johns Hopkins: Robert Wise, MD

Supported by NIH grants: R34 HL136755

27 Mar 2020

Table of contents

1. Introduction

The purpose of this protocol is to pilot test a weight loss intervention in obese patients with poorly controlled asthma.

1.1. Background

Obesity is a risk factor for the development of asthma (approximately 250,000 cases per year of asthma in the U.S. are related to obesity).[1] Obese patients often have poorly controlled asthma (with a nearly 5-fold risk of hospitalization compared with lean asthmatics) and do not respond as well to conventional controller therapy.[2-6] Obesity particularly affects minority populations[7]: non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%). This is thought to account in part for the disparities of asthma in minority populations. There is a pressing public health need to develop interventions specifically for obese asthmatics.

One obvious intervention to consider for treatment of obese asthmatics is weight loss. Weight loss surgery significantly improves asthma-related outcomes.[8-10] However, uncontrolled asthma increases surgical risk, and is an expensive, complex intervention only appropriate for a small subset of patients.[11,12] Life-style interventions to promote weight loss in asthma may provide a simple, less expensive alternative, with the potential to reach a broader range of patients. Single center studies suggest that diet-induced weight loss might improve asthma,[13-16] but there have been no large multicenter clinical trials addressing the efficacy of weight loss in patients with poorly controlled asthma.[17]

Our ultimate purpose is to test the hypothesis that weight loss through an intensive life style intervention will improve asthma control. But we first need to establish whether our weight loss intervention is effective in patients with asthma.

1.2. Primary objective

The primary objective of this study is to determine the effectiveness of an internet-based weight loss intervention in producing weight loss in obese patients with poorly controlled asthma.

1.3. Secondary objective

The ultimate purpose is to implement a multi-center weight loss intervention trial for obese patients with poorly controlled asthma.

1.4. Overview of study design

This will be a pilot study of a weight loss intervention at two centers, the University of Arizona and the University of Vermont. The primary outcome of interest will be the percent of participants achieving a 5% weight loss, which is the amount of weight loss that prior studies suggest is required to improve asthma control.

This will be a single arm-phase II futility trial; the "futility" to be assessed is the ability to produce weight loss. Such designs are widely used in efficiently informing decisions to proceed to Phase III clinical trials. This trial design is appropriate when the effect of the placebo arm can reasonably be estimated (weight loss is likely to be close to 0), and the toxicity of the treatment is minimal (no toxicity is anticipated related to weight loss).[18] Therefore, this will be a single arm 6-month study of 40 participants (20 at each site). All participants will be assigned to the weight loss intervention, which is described in detail below.

2. Methods

2.1. Eligibility criteria

2.1.1. Inclusion criteria

- Physician diagnosis of asthma on regular controller therapy for at least the past 3 months
- Age: ≥18 years of age
- Obese: BMI > 30 kg/m^2
- Poorly controlled asthma
  - Asthma Control Test Score ≤ 19,[19,20] or
  - use of rescue inhaler on average > 2 uses/week for preceding month, or
  - nocturnal asthma awakening on average 1 or more times / week in preceding month, or
  - ED/hospital visit or prednisone course for asthma in past six months
- Ability and willingness to provide informed consent
- Ability to access internet weight loss program for a trial period
- Completion of asthma, food and weight diary entries for same 3 consecutive days between visits 1 and 2

2.1.2. Exclusion criteria

- History of bariatric surgery
- Participant currently on weight loss drugs
- Any condition that puts the participant at risk from participation in a weight loss study or a condition that precludes participation in regular exercise as judged by the site physician
- Pregnancy (by patient self-report)
- Participation in another weight loss intervention within the last month
- Weight loss of ≥ 10 pounds in the last 6 months by self-report
- Intention to move out of area within the next 6 months

2.1.3. Rationale for eligibility criteria

Our goal is to enroll obese adults with asthma on asthma controller drugs. Enrollment criteria are purposely broad to ensure that the study population broadly reflects individuals who may be eligible for a weight loss intervention in a general medical setting. We are not excluding people who have co-morbid conditions or who smoke insofar as these individuals may benefit from the weight loss.

2.2. Asthma clinical assessments

Patients will undergo spirometry with post-bronchodilator reversibility testing at 0 weeks and 24 weeks, spirometry at all other visits will be done without bronchodilator administration. Questionnaires and diary entries will be available in English and Spanish.

- Asthma diaries on the PLAN website will be completed by participants throughout the study to record daily morning peak expiratory flow (PEF), daily asthma symptom scores, beta-agonist use, nocturnal asthma awakenings, and health care use. Diary data are used to identify episodes of poor asthma control and days with no asthma symptoms (asthma-free days).
- The Asthma Control Test (ACT) is a 4-week recall questionnaire that measures asthma control.[19]
- The Asthma Symptom Utility Index (ASUI) is a 2-week utility-weighted asthma symptom questionnaire.[21]
- The Marks Asthma Quality of Life Questionnaire (Marks AQLQ) assesses asthma specific quality of life.[22]
- Medical Outcomes Study (SF36v1) is a measure of general health related quality of life which correlates with asthma outcomes.
- The IWQOL-lite is used to measure the effect of weight loss on QOL.[23]
- Food Frequency,[24] activity[25] and motivation to lose weight[26], will be assessed using validated questionnaires.
- Anthropometrics will include height, weight, waist, hip circumference per NHANES III.
- For subjects who have not been seen in the pulmonary clinic in the last 12 months will have a brief physical exam at visit 2.
- Spirometry will be performed in accordance with ATS/ERS guidelines.[27]
- Adverse effects will be assessed by open-ended questions at each visit and rated in severity.
- Interval health history will be recorded at each clinic visit. Records of all hospitalizations and, if necessary, deaths are obtained for verification of diagnoses and assessment of safety issues.
- Participants will be asked if they are pregnant at every visit, and if they become pregnant, they will be withdrawn from the study.
- Baseline questionnaires and exam will be administered to ascertain demographics Including self-reported ethnicity and race, general health, co-morbid conditions, asthma symptoms, and medication use. Medical clearance for diet and moderate exercise will be provided by the study site physician.
- Exit questionnaires will be administered at the last visit to determine global assessments of treatment, adequacy of informed consent procedures, satisfaction with study procedures and personnel, and opinions about the intervention.
- Blood specimens will be collected for fasting blood glucose and analysis of metabolic and oxidative markers related to asthma. Excess blood specimens will be used for future asthma research with the patient's consent. Fasting blood draw may take place within 7 days of rest of the procedures scheduled for visit 2 or visit 6.

2.3. Schedule of visits

Visit Number	V1	V2	N	-	P1‡	V3	V4	V5	V6
Time (week)		-2		0	2	6	12	18	24
Informed Consent	•								
Medical History	•	•				•	•	•	•
Interim Body Weight Measurement			•						
Orientation to weight loss program	•	•							
Start Weight Loss Program				•					
Provision of Chromebook computer		•							
Addressing website login issues and exercise strategies/concerns at home; facilitator contact					•				
Assessment of compliance with food, asthma and weight diaries		•							
Assessment of diary entry compliance		•				•	•	•	•
Spirometry	•	•¥				•	•	•	•¥
Asthma Control (ACT and ASUI)	•	•				•	•	•	•
Marks Asthma Quality of Life	•	•				•	•	•	•
Quality of Life (SF36v1)	•	•							•
Arizona Food Frequency Questionnaire	•								•
Stanford Brief Activity Questionnaire	•								•
Impact of Weight on Quality of Life	•								•
Motivation to lose weight (Tre-MORE)	•								
Height (V1 only), Weight, Hip and Waist Circumference	•	•				•	•	•	•
Blood draw (fasting)		•							•
End of Study Questionnaire									•

‡The purpose of P1 is to check in the participant to make sure they have made contact with the weight loss facilitator, and are not having technical problems with the website, or with MyFitnessPal.
¥Spirometry at V2 and V6 will be pre and post bronchodilator, all other visits spirometry without bronchodilator.

2.4. Weight loss intervention

The weight loss intervention will be implemented under the direction of Dr. Jean Harvey (Chair of Nutrition at UVM). Participants will be introduced to the weight loss program during visit 1. A research coordinator will show participants how to access the weight loss website, the MyFitnessPal program, and provide information to contact the assigned weight loss coach. The participant's picture will be taken to display on the chat page and on the biography page for their group when they use the study web site. Participants may opt out of this feature if they are uncomfortable having their picture displayed.

After visit 1, participants will be asked to enter information on the weight loss website and the MyFitnessPal program to display that they understand how to use the programs. Participants will have a 3-day trial period to enter daily asthma symptoms, food intake and exercise information online. The research team will assess completion of this trial period; only participants who enter complete diaries for same 3 consecutive days will be eligible to enroll in the study.
We will attempt to enroll participants into this study in groups of 5-10 to provide an adequate group for the weight loss intervention.

2.4.1. Basic components of the weight loss program

This 6-month intervention will include restricted calorie intake and increased physical activity. Key behavioral strategies to facilitate changes in dietary habits and activity patterns will be introduced, promoted and reinforced throughout the program. Weekly "group meetings" in a synchronous chat (i.e., in real time) led by a facilitator will be the venue for the group process. Extensive web-based resources to support behavior changes will be offered. The online groups will be "closed" such that those individuals who start the group remain in that group for the duration of their participation. Group chat sessions will meet online weekly for 6 months.

1. *Diet*
   A balanced reduced calorie deficit diet will be prescribed. All participants will be given an individualized calorie goal. Emphasis will be placed on consuming a diet high in fruits, vegetables, and whole grains, and low in fat, sugar, salt and alcohol. Participants are asked to target fat intake to 25% of their overall calorie goal because a number of studies [28,29] suggest superior weight loss when fat and calories are both controlled.

   Participants will record their daily calorie and fat intake daily electronically. They will have access on the study website to calorie and fat gram guides which use pull down menus and personally customized calorie/fat counters to facilitate ease of recording. The interventionist will reviews this diaries weekly and provide feedback to reinforce or shape new behaviors.

2. *Exercise*
   Participants will be provided with graded goals to reach the recommended weekly minimum of 200 minutes of moderate intensity exercise by week 9 of the program. We will recommend brisk walking as in our previous studies. At visit 1, we will verify they have a safe place to exercise as in our previous studies, other forms of aerobic exercise will also be encouraged should the participant prefer. All exercise will be monitored using electronic diaries that include pull down menus for a wide range of activities.

3. *Behavioral strategies*
   The major features of the behavior modification strategies in the program are based on Social Cognitive Theory[30] and are described below. Dr. Thomson and Vega-Lopez will be involved in training the bilingual lifestyle coach in cultural adaptation for Hispanic participants.

2.4.2. Internet delivery of behavioral weight control program

Participants will have access to behavioral lessons weekly. The standard version of the lesson is very visual, capitalizing on the capabilities of the internet delivery. We will be notified over the Web site when participants have completed lessons and we will, therefore, be able to electronically assess compliance with this program component

All potential participants will be given an orientation to the website and MyFitnessPal at Visit 1 prior to entering the weight loss program. We will assess compliance with asthma and food diary entries at Visit 2, only participants who have completed diary requirements (same 3 days of asthma and food diaries) will be considered eligible to continue in study.

Participants will be enrolled into a "group" at Visit 2, although they will not meet in-person and this "group" will be maintained throughout an individual's study participation. Groups will be homogenous with respect to language (English of Spanish). Participants will have access to the Internet site and will be assigned a group on-line chat time. The group facilitator will e-mail them weekly, and they will be encouraged to use various components of the Web site. Individual usage of the site will be tracked by username through server activity logging and the use of WebTrends (NetIQ Corporation, San Jose, CA) log analysis software.

Participants will have access to new behavioral lessons each week. Participants will be provided with a computer. We will provide them with a data plan or hot-spot for internet access if they do not have internet access.

2.4.3. Promoting adherence to the online weight control intervention

We encourage adherence by tailoring the intervention expectations to shape an individual's behavior such that it approaches the intervention goals. For example, individuals who are having difficulty self-monitoring are given options to make it easier, walking them through how to develop their own shortcuts to self-monitoring (the "my pantry" option on the website), having a short term goal of recording just a few days a week or only specific meals of the day, etc. Individuals who miss a group chat session will be contacted by email promptly. Lesson materials are available for those who miss the chat, and summaries of the missed session. We use a problem-solving approach to barriers to attendance. We have found this comprehensive and proactive approach to adherence promotion to be effective in maintaining high levels of study participation.

2.4.4. Online weight control facilitator

Dr. Harvey has trained a cadre of experienced facilitators who have conducted the online weight control program. Online weight control interventionists on our research team at present include registered dieticians, masters-level health behavior experts, and doctoral level psychologists. Thus, our online intervention team is multi-disciplinary, skilled in conducting behavioral weight loss treatment programs, and ethnically diverse. The interventionist will be directly supervised by Dr. Harvey.

2.4.5. Intervention training and fidelity monitoring

Our previous experience in obesity treatment outcome research suggests that the following quality procedures will help ensure treatment fidelity:

1. Development of detailed intervention protocols;
2. Careful training, certification, and periodic re-training;
3. Periodic observation of intervention delivery to ensure protocol adherence and to provide corrective feedback;
4. Documentation of all intervention contacts to monitor participant exposure to treatment; and
5. Regular project meetings to review overall conformity to structured protocols and prevent any drift between interventionists.

2.4.6. Assembling weight control cohorts

The intervention requires that 5-10 participants form a group to participate in the weekly group chat sessions. A group may include participants from both sites. The group will essentially be a cohort of participants starting and ending the study at the same time. Because it is essential that the V1 and V2 visits be conducted close together, the cohorts need to be assembled prior to starting the study. Individuals who are interested in the study will be directed to the PLAN website to complete a study registrations form. The form will include individuals' names, contact information, basic eligibility information, information on the days of the week and times that a person will be consistently available for group chat sessions, preferred language (English or Spanish), and the center. These data may be collected prior to an individual providing consent for the study. The registration form will include text briefly describing study and how the information provided on the registration form will be used. Clinical center personnel will only be able to see the data from individuals who selected their center for attending study visits. The central coordinator will be able to view registration data from both sites in order to assemble the cohorts of 5-10 individuals who can participate in group chats at the same time. Once there are sufficient individuals who can participate in group chats at the same or similar times, the central coordinator will contact the clinical center coordinator to schedule V1 and V2 visits for these individuals. If the individual has not provided consent, consent will be obtained at the V1 visit before screening. Once all the cohort has completed V2, the coaches will contact cohort members to schedule the first chat. The goal is for the first chat session to take place in the 2 weeks following V2.

2.5. Statistical considerations

2.5.1. Data analysis

The appropriateness of the human, technological and systems components of the data acquisition and management procedures will be analyzed including practicality of data acquisition, estimation of likely participant characteristic and outcome distributions, suitability and functionality of paper and electronic forms, and resources required for participants contact and follow up, and to anticipate rates for missing data. Secondary analyses will include adjustments for different degrees of self-reported exercise.

2.5.2. Sample size

The decision to proceed to the full scale trial will be based on a futility design analysis, which guided our sample size estimates. We will determine this study as futile if we cannot produce a clinically significant weight loss in a significant proportion of participants. A clinically significant weight loss is set at 5% (which is the amount of weight that appears to be necessary to improve asthma control based on previous studies, and also the amount of weight loss required for FDA approval of a weight loss medication). A significant proportion of the population is set at 35% (FDA recommend that a weight loss medication must produce a 5% weight loss in 35% of participants to be considered effective).[31]

A straightforward way to test for futility with a binary outcome is based on the binomial distribution[32]. For a given minimum sufficient efficacy (p_1) and level that would indicate the intervention was ineffective (p_o), the threshold for continuing, *c*, can be determined for any sample size, *n*, as follows: the largest value of *c* such that $P(X \geq c | p_o) \leq \alpha$, type I error, and $P(X \geq c | p_1) \geq 1\text{-}\beta$, power, i.e. minimize the type II error. Ineffective thresholds of 5% and 10% were considered (Table 2). To be conservative, drop-outs will count as weight loss failures. With 40 patients, we have 94% power and $\alpha < 0.001$ using a threshold of 9 and assuming p_o.= 0.1 vs p_1 = 0.35, i.e. if ≥9 individuals have clinically significant weight loss we would reject futility and continue on to a larger trial. For the 12 Hispanics, we would need ≥3 (α = 0.026, 1-β = 0.87) and ≥2 (α = 0.02, 1-β = 0.85) individuals to achieve 5% weight loss reject futility assuming p_o.= 0.1 vs p_1 = 0.45 and p_o.= 0.05 vs p_1 = 0.35, respectively.

Table 2: Power, type I error, and threshold for rejecting futility for a variety of futility, p_0, and minimum efficacy, p_1, thresholds

p_o	p_1	*c*	**N = 40** α, 1-β	p_o	p_1	*C*	**N = 12** *C*, α, 1-β
0.1	0.25	6 7 8	0.013, 0.96 0.003, 0.90 < 0.001, 0.82	0.10	0.40	2 3 4	0.11, 0.92 0.026, 0.77 0.004, 0.56
	0.30	7 8 9	< 0.001, 0.94 < 0.001, 0.89 < 0.001, 0.80		**0.45**	2 **3** 4	0.11, 0.96 **0.026, 0.87** 0.004, 0.70
	0.35	**9** 10 11	**< 0.001, 0.94** < 0.001, 0.88 < 0.001, 0.79	0.05	0.35	1 **2** 3	0.12, 0.96 **0.020, 0.85** 0.002, 0.65

2.5.3. Statistical methods

Descriptive statistics will be generated for all study parameters (e.g. SD of change in ACT). Cross-sectional comparisons will be made using Kruskall-Wallis and Fisher's exact tests. We will determine the proportion of participants achieving a 5% weight loss with exact 95% confidence intervals. Mixed effects models will be used to analyze repeated measures.

3. Monitoring

3.1. Composition of the Data and Safety Monitoring Plan (DSMB)

Significant changes or amendments to the protocol or consent form will be submitted to the DSMB, and included in the DSMB reports.

The American Lung Association appoints a DSMB to oversee trials conducted by the ACRC. The primary responsibility of the DSMB is to protect participants but may also have recommendations regarding the scientific conduct of the study to optimize the risk-benefit ratio for participants. The DSMB is typically composed of a pulmonary specialist, an ethicist, a statistician, a patient representative, and specific content experts which in this case would likely be a nutritionist or health psychologist.

3.2. Medical Monitor

Dr. Wise at Johns Hopkins serves as the medical monitor for the ALA-ACRC research group and reviews all serious adverse event or unusual event reports to determine whether any immediate local or study-wide actions are indicated. Interim serious adverse events or adverse events related to study procedures are transmitted to the DSMB by the DCC with concurrent notification of the clinical site IRBs and, if appropriate, NIH.

3.3. Monitoring procedures, frequency of monitoring, contents of DSMB report

Typically, the DSMB would have an initial meeting to review and approve the protocol, and then meet every six months or more frequently to review the progress of the trial. The investigators present the DSMB study performance data including screening and enrollment data, and measures of data quality and timeliness. Safety data will include reporting of adverse events, protocol deviations, and unexpected or unanticipated problems that may affect the safety or scientific validity of the study.

At the end of each DSMB meeting, the board will vote whether to continue the study as planned or whether to recommend changes to the study. The DSMB may recommend that the study be stopped early if there is evidence that the risk-benefit ratio does not warrant continuation of the trial.

3.4. Adverse event and unanticipated event reporting

The site PI will submit a completed serious adverse event report to the DCC and the IRB, and then the DCC will report to the NIH, and Chair of the DSMB within 7 days of the report of a potentially life-threatening (grade 4) or severe (grade 3) serious adverse event that is possibly, probably or definitely related to the study.

The PI will report to the DCC and the IRB, and the DCC will report to the NIH, FDA and DSMP within 15 days of any other event or condition regardless of grade, which in their judgment represents an event reportable to the IRB, NIH, FDA and DSMP.

A summary of all adverse events will be reported to the DSMP, NIH, and IRB at least annually.

3.5. Changes/amendments to protocol or consent

Significant changes or amendments to the protocol or consent form will be submitted to the DSMB, and included in the DSMB reports.

3.6. Risks

Participation in this research protocol requires routine clinical procedures that entail more than minimal risk. The registration database will contain personal identifiers and be stored at the DCC. Access to those data will be restricted to the database manager and the coordinator(s) responsible for assembling cohorts. Data are stored on servers that are maintained behind an institutional firewall. All portions of the data system will be password-protected using a standard challenge/response system coupled with a second user-specific identity system requiring users to log in with their personal PIN and strong password, which are checked before the login is completed. Once the user is logged in, all subsequent activities are stamped with the user's PIN and date-time stamp.

3.6.1. Pulmonary function testing

Pulmonary function testing requires deep and forceful respiratory efforts. It is a commonly performed and safe examination that is widely performed in patients with lung disorders. Some patients report chest soreness the day following the procedure. Some patients may experience light-headedness during the forced expiration. The risk of syncope is mitigated by having the patient perform the test in the seated rather than standing position. Spirometry will also be performed with a bronchodilator on visits 2 and 7. On rare occasions (less than 5% of the time), bronchodilators may cause nervousness, a rapid heartbeat or headache at the doses used in this study. If you develop any of these problems, we will monitor you closely until the problem goes away (typically in 30 minutes).

3.6.2. Venipuncture

Venipuncture may cause bruising and minor discomfort. Abnormal fasting blood glucose levels will be communicated to participants and, with their permission, their primary care physician.

3.6.3. Psychological and financial risks

Psychological or financial risks are unlikely, but there may be unforeseen psychological or financial risks for participants in this trial. For example, patients may have unrealistic expectations of benefit from treatment received in a trial, or may have psychological distress from having a diagnosis of asthma or other concomitant diseases discovered during screening evaluation. Patients may also have financial loss from their occupations to attend clinic visits. Many patients, however, receive psychological benefit from participating in a study that may help others, and the financial costs are mitigated by small honoraria for participation in the study.

3.6.4. Exercise program

Exercise Program potential risks may include the participant not being able to identify a safe place to exercise, or having physical impediments to exercise. We will try to help participants identify a safe place to exercise. We will exclude participants who the site physician determines are physically unable to participate in a regular (typically walking-based) exercise program.

Participation in a weight loss program: The participant might not be able to identify a safe place to exercise, or have physical impediments to exercise. We will try to help participants identify a safe place to exercise. We will exclude participants who the site physician determines is physically unable to participate in a regular (typically walking-based) exercise program.

3.6.5. Management of SAEs or other study risks

We will follow our standard IRB procedures for following SAE's, and reporting procedures as outlined above.

3.7. Potential benefits of the proposed research to human subjects and others

Patients will benefit from asthma education and attention to their asthma care program. Some obese patients may achieve weight loss which is generally considered healthy. If this program is successful, it will provide evidence to support a new approach to the treatment of poorly controlled asthma in obese patients with particular emphasis on minorities. Moreover, some participants in research studies report that they enjoy participation because they have the opportunity to assist in the development of new knowledge that may be helpful to others and that the relationship with the research staff is rewarding.

3.8. IND/IDE information

Not applicable

3.9. Conflicts of interest

We will follow the ALA ACRC annual reporting requirements for management of conflict of interest.

3.10. Data acquisition and transmission

The research team at the study site will collect information directly from the participant, recorded with full Identifiers. Data collected at study visits will be identified with a study ID and alpha code, assigned by the clinic coordinator so that personal identifiers are not keyed into the study database. However, the registration database, which will be used to assemble the cohorts, will have personal identifiers. The registration database will not contain the study ID's assigned to enrolled participants so that the personal identifiers cannot be linked with the study data at the DCC.

3.11. Stopping rules, interim analysis

Patients may withdraw from the study at any time.

There are no plans for interim outcome data analysis for this pilot study.

3.12. Inclusion of women

Both women and men will be enrolled in these studies. Asthma is more prevalent among female adults, and so we anticipate a slight majority of participants will be women.

3.13. Inclusion of minorities

We anticipate Vermont and Arizona will reflect the demographics of these two regions, and anticipate recruiting a high proportion of Hispanics at the Arizona site.

3.14. Inclusion of children

We will not include children under 18 years of age, as weight loss in children will require a specific family-centered intervention, and so differ from the type of intervention that we will be using in adults. Asthma and obesity are obviously important medical issues in younger children, and so our network is working to develop a separate study specifically to target obesity in younger asthmatics.

4. References

1. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *American journal of respiratory and critical care medicine.* 2007;175(7):661-666.
2. Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax.* 2008;63(1):14-20.
3. Vortmann M, Eisner MD. BMI and health status among adults with asthma. *Obesity.* 2008;16(1):146-152.
4. Mosen DM, Schatz M, Magid DJ, Camargo CA, Jr. The relationship between obesity and asthma severity and control in adults. *The Journal of allergy and clinical immunology.* 2008;122(3):507-511 e506.
5. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *The European respiratory journal.* 2006;27(3):495-503.
6. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respiratory medicine.* 2007;101(11):2240-2247.
7. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA : the journal of the American Medical Association.* 2014;311(8):806-814.
8. Dixon AE, Pratley RE, Forgione PM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *The Journal of allergy and clinical immunology.* 2011;128(3):508-515 e501-502.
9. Maniscalco M, Zedda A, Giardiello C, et al. Effect of bariatric surgery on the six-minute walk test in severe uncomplicated obesity. *Obesity surgery.* 2006;16(7):836-841.
10. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respiratory medicine.* 2012;106(5):651-660.
11. Avriel A, Warner E, Avinoach E, et al. Major respiratory adverse events after laparascopic gastric banding surgery for morbid obesity. *Respiratory medicine.* 2012;106(8):1192-1198.
12. Dorman RB, Miller CJ, Leslie DB, et al. Risk for hospital readmission following bariatric surgery. *PloS one.* 2012;7(3):e32506.
13. Hernandez Romero A, Matta Campos J, Mora Nieto A, et al. [Clinical symptom relief in obese patients with persistent moderate asthma secondary to decreased obesity]. *Revista alergia Mexico.* 2008;55(3):103-111.
14. Johnson JB, Summer W, Cutler RG, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free radical biology & medicine.* 2007;42(5):665-674.
15. Scott HA, Gibson PG, Garg ML, et al. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology.* 2013;43(1):36-49.
16. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *Bmj.* 2000;320(7238):827-832.
17. Adeniyi FB, Young T. Weight loss interventions for chronic asthma. *The Cochrane database of systematic reviews.* 2012;7:CD009339.

18. Koch MW, Korngut L, Patry DG, et al. The promise of futility trials in neurological diseases. *Nature reviews. Neurology.* 2015;11(5):300-305.
19. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *The Journal of allergy and clinical immunology.* 2006;117(3):549-556.
20. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *The Journal of allergy and clinical immunology.* 2009;124(4):719-723 e711.
21. Revicki DA, Leidy NK, Brennan-Diemer F, Sorensen S, Togias A. Integrating patient preferences into health outcomes assessment: the multiattribute Asthma Symptom Utility Index. *Chest.* 1998;114(4):998-1007.
22. Marks GB, Dunn SM, Woolcock AJ. An evaluation of an asthma quality of life questionnaire as a measure of change in adults with asthma. *Journal of clinical epidemiology.* 1993;46(10):1103-1111.
23. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care.* 1994;32(1):40-66.
24. Thomson CA, Giuliano A, Rock CL, et al. Measuring dietary change in a diet intervention trial: comparing food frequency questionnaire and dietary recalls. *Am J Epidemiol.* 2003;157(8):754-762.
25. Taylor-Piliae RE, Norton LC, Haskell WL, et al. Validation of a new brief physical activity survey among men and women aged 60-69 years. *American journal of epidemiology.* 2006;164(6):598-606.
26. Cresci B, Castellini G, Pala L, et al. Motivational readiness for treatment in weight control programs: the TREatment MOtivation and REadiness (TRE-MORE) test. *Journal of endocrinological investigation.* 2011;34(3):e70-77.
27. Standardization of Spirometry, 1994 Update. American Thoracic Society. *American journal of respiratory and critical care medicine.* 1995;152(3):1107-1136.
28. Pascale RW, Wing RR, Butler BA, Mullen M, Bononi P. Effects of a behavioral weight loss program stressing calorie restriction versus calorie plus fat restriction in obese individuals with NIDDM or a family history of diabetes. *Diabetes Care.* 1995;18(9):1241-1248.
29. Schlundt DG, Hill JO, Pope-Cordle J, Arnold D, Virts KL, Katahn M. Randomized evaluation of a low-fat ad libitum carbohydrate diet for weight reduction. *International Journal of Obesity and Related Metabolic Disorders.* 1993;17(11):623-629.
30. Bandura A. *Social foundations of thought and action: A social congitive theory.* Englewood Cliffs, New Jersey: Prentice-Hall; 1986.
31. Colman E. Food and Drug Administration's Obesity Drug Guidance Document: a short history. *Circulation.* 2012;125(17):2156-2164.
32. A'Hern RP. Sample size tables for exact single-stage phase II designs. *Statistics in medicine.* 2001;20(6):859-866.