Obesity and Asthma: Unveiling Metabolic and Behavioral Pathways
Statistical Analysis Plan
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Data Analyses: We will obtain a HIPAA waiver to use de-identified data to compare non-respondents and those lost to follow-up to study participants by age, gender and ethnicity. Factor Structure of Measures: We will examine the factor structure of key measures (e.g., MARS) and the multi-component structure of the IPQ and BMQ. Measurement Invariance: We will determine whether the key measures are invariant across language using multiple indicator multiple cause models. We will use the chi-square test, ANOVA, or the Kruskal Wallis test to compare the baseline characteristics of obese vs. non-obese patients with early onset and late onset asthma, as appropriate. **Overview**: We will employ latent growth curve modeling (LGCM) approaches using MPLUS 7.3 software to test Aims 1 and 2 hypotheses. LGCM leverages the analytical power of structural equation modeling (SEM) for the intensive analysis of longitudinal data. Similar to classic SEM, LGCM allows for the examination of complex models including those that posit mediation and moderation, as proposed here. Before conducting analyses, we will examine the distribution of dependent variables and, as appropriate, consider transformations (e.g., log, Box-Cox) to reduce non-normality in continuous variables.

Aim 1. Compare the longitudinal relationship between L-arginine/ADMA balance and morbidity (lung function, asthma control, acute resource utilization, and quality of life) between obese adults with late onset asthma vs. (1) obese adults with early onset asthma and non-obese asthmatics with early (2) or late (3) onset disease: The primary asthma morbidity outcomes will be FEV_1 and control (ACQ scores); the primary measure of NO metabolism will be L-arginine/ADMA ratio. All analyses will compare four groups: 1) obese with late onset asthma; 2) obese with early onset asthma; 3) non-obese with late onset asthma; and 4) non-obese with early onset asthma. First, we will compare the levels of plasma L-arginine, ADMA, L-arginine/ADMA ratios, and arginase among these groups, at each time point using the Kruskal-Wallis test. The Wilcoxon signed-rank test will be used to compare levels of NO metabolism biomarkers in periods without vs. during asthma attacks. The analysis will involve longitudinal assessment of asthma morbidity measures across four time points (0, 6, 12, and 18 months). We hypothesize that both time-varying covariates (e.g., NO metabolism biomarkers) assessed at the four time points and time-invariant covariates (e.g., early vs. late asthma onset) will predict asthma morbidity assessed at these time points (Figure 1). We also hypothesize potential lagged effects of covariates at earlier time points. As a first step, we will identify the measurement model for the latent variables at each time point using confirmatory factor analysis. Specifically, we will create latent variables representing random effects intercepts and slopes for NO metabolism (NO_{t0}, NO_{t6}, NO_{t12} and NO_{t18}; where *t0* represents baseline NO metabolism biomarkers) and asthma morbidity measures (AM_{t0}, AM_{t6}, AM_{t12} and AM_{t18}; e.g., FEV_1 at baseline, 6, 12, and 18 months). We will estimate slope and intercept parameters using a Weighted Least Squares Mean-Variance adjusted (WLSMV) estimator, which provides robust estimates for complex models with modest sample sizes and can be employed with dichotomous, ordinal, and/or continuous endogenous variables. We will test this measurement model for absolute fit using Chi-square and RMSEA statistics. In addition, we will consider adjusting the model based on modification indices to improve the overall fit.

Next, an overall unconditional model will be fitted to identify the growth trajectory across time. To that end, we will fit a growth function for NO metabolic biomarkers and asthma morbidity (e.g., FEV_1) using linear, quadratic, and unstructured models. Relative model fit will be evaluated based on various indices of exact and close fit: χ^2 (>.05), the comparative fit index (CFI>.97), the Tucker-Lewis fit index (TLI>.97), the root mean squared error of approximation (RMSEA<.05), and the weighted root mean square residual when using WLSMV (WRMR<.90). The most parsimonious model with the best fit will be retained. Finally, we will fit the full structural model, including the hypothesized relationships. For example, obesity and age of onset will be included as a predictor of NO metabolism-related pathways as well as asthma morbidity. Because we hypothesize that NO metabolism-related pathways are primarily important for obese patients with late onset asthma, we will include an interaction term between obesity and age of asthma onset. The model will also control for sex, age, comorbidities (including OSA), depression, allergic sensitization, and other key baseline covariates. To address the possible mediational effects of NO metabolism-related pathways, we will fit models to estimate both direct and indirect effects, first separately, and then combined. Lagged effects of the time- varying predictors, as well as the effects of the latent growth variables themselves (intercept, slope, and their random effects) will be evaluated as potential mediators (i.e., NO metabolism biomarkers) of the effects of obesity and age of onset on asthma morbidity. We will also be able to compare models of complete vs. partial mediation by comparing constrained models (direct effects constrained to zero) with unconstrained models that allow for partial mediation. Relative fit, as well as estimates of effect size will be calculated, along with Sobel tests and Monte Carlo confidence intervals to evaluate the mediational hypotheses. As indicated above, the interrelationships between gender, obesity, and asthma morbidity is complex, thus, we will explore the potential modifying effects of gender. We will also conduct sensitivity analyses in which we test different thresholds for the definition of good medication adherence (≥70%, 60%, 50%). Once the final model is fitted, we will repeat the analyses freeing the parameters to differ by gender. Comparing these models to a model in which the differential effects of gender are constrained will provide valuable insight into the possible role of

gender in the hypothesized effects.

Note: In addition to data from the 4 scheduled time points, we will also obtain data when patients have asthma exacerbations. Because LGCM is limited in its ability to model effects in which time points are not common throughout patients (as anticipated for exacerbation data), we will use more flexible hierarchical growth models (e.g., linear mixed models or generalized linear mixed models) as needed to explore these data points.

Aim 2. Evaluate the interrelation between obesity- and asthma-related illness beliefs, and the impact of cognitive function, on patients' management of these conditions over time: For asthma, we will compare electronic (primary outcome) and self-reported (secondary outcome) adherence to medications according to obesity/age of onset categories using a chi-square test. For obesity, primary outcomes will be the Connor Diet Habit Survey scores for diet and accelerometer data for exercise. Secondary analyses will assess other SMB.

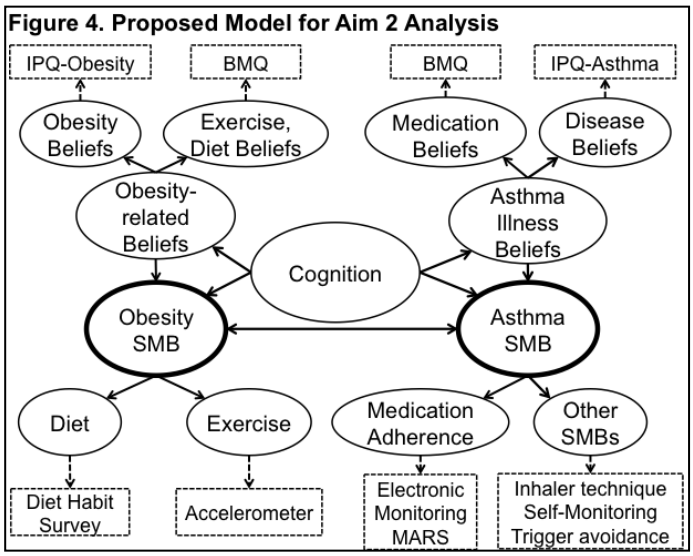

Figure 4. Proposed Model for Aim 2 Analysis

We will use LGCM to examine the interrelationships between asthma- and obesity-related beliefs and self-management of these conditions over time (Figure 4). Latent variables to be investigated include: 1) cognition, as measured by the battery described above; 2) asthma beliefs; 3) obesity beliefs. Asthma and obesity beliefs will constitute a latent variable consisting of two constructs: a) disease beliefs (measured with the IPQ) and b) medication/diet/exercise beliefs (measured with the BMQ); and 3) asthma and obesity SMB, including time-variant medication adherence (electronic and self-report measures following each study time point), diet, exercise and other SMB. We will use LGCM to predict the effects of obesity on these latent behavioral constructs. We will be able to examine the direct and indirect pathways from obesity to cognitive functioning and illness beliefs, to asthma and obesity SMB (intercept, slope, as well as their random effects). We will assess the potential influence of cognition and illness beliefs on SMB separately then test a full model, predicting SMB once individual contributions are identified. As in Aim 1, we will estimate both direct and indirect effects, as well as partial vs. complete mediation. We will include covariates as above. Integrating Biological and Behavioral Pathways: Finally, we will employ LGCM to characterize the interrelation and relative contribution of biological and behavioral pathways linking obesity and asthma morbidity (Figure 1). In addition to the time-variant relationships between SMB and biological markers, we will also explore the possibility of time-lagged relationships between biological markers and SMB. For example, we will assess if SMB at time 1 predict L-arginine/ADMA ratios at time 2, and vice-versa. Comparison of model fit among these lagged analyses will yield critical new data to elucidate the complex interplay between biology and behavior in the maintenance of asthma morbidity. The model will control for other confounders as specified above.

Missing Data: For data missing at random (e.g., data entry errors), we will use multiple imputation methods with PROC MI and PROC MIANALYZE in SAS. For the outcome assessments, we cannot assume data are missing at random, but we will consider pattern-mixture methods to adjust for an occasional missed point in subjects who complete subsequent follow-up. **Power Calculation:** Power calculations for LGCM and sample size based were based on published methods. Effect size in this approach is defined as a null and alternative hypothesis value of the RMSEA index, which we hypothesize to be 0.05 (adequate fit) and 0.03 (good exact fit), respectively. Power in SEM can be conceptualized as a function of sample size and the number of parameters to be estimated in the model, relative to the information provided in the overall variance-covariance matrix of the observed variables. The estimated power is based on a proposed sample size of 400 with an 80% follow-up rate. For Aim 1, the proposed model involves 14 latent variables across all time points, and 34 observed underlying variables, yielding estimated power >0.80 for an average effect of 0.10 with an alpha of 0.05. For the model in Aim 2, there are 13 latent variables (not including the six separate indicators of cognition) and 18 observed variables, yielding >0.80 power for average effects of 0.15. Overall, despite the challenges of estimating *a priori* power for SEM approaches, especially those involving growth models, we believe the proposed study will be adequately powered to address the research aims.

Aim 3. Develop and pilot test three theory-based modules that integrate counseling for asthma and obesity to promote better SMB, including self-monitoring, adherence to asthma medications, and lifestyle changes for weight loss: **Overview:** We will script messages aimed to counter beliefs linked to low adherence to asthma and obesity SMB and to support those that promote better SMB. We will incorporate these messages in 3

counseling modules: a session in which the counselor identifies the patient's beliefs about asthma and obesity and provides education to address them, then 2 sessions in which we integrate these messages with diet and physical activity counseling from the Diabetes Prevention Program (DPP). After pre-testing and refinement, we will conduct a proof-of-concept pilot RCT of the modules in a subset of 80 obese patients who have completed their 18-month participation in the observational cohort portion of this study. We recognize that effective self-management of asthma and obesity requires complex behaviors and thus a more comprehensive intervention than what we propose here. As such, we do not anticipate a major impact of the modules on SMB. However, if the modules are well received by patients and results of the RCT suggest a positive influence on beliefs and behaviors, we will seek additional funding to elaborate this approach to integrated asthma-obesity self-management support and create then test a fully developed intervention.

Translating Aim 2 Findings to an Integrated Asthma-Obesity Self-Management Counseling Strategy: To guide design of the intervention, we will apply the SRM, which has been used to build coping strategies, knowledge, and skills in patients with low adherence to self-management tasks by addressing beliefs that influence SMB.[81] According to the SRM, behavior changes associated with positive health outcomes will counter maladaptive beliefs and provide the positive reinforcement necessary to sustain behavior change. Our quantitative analyses in Aim 2 will link asthma (disease and medication) and obesity-related beliefs, and their interrelationship, to adherence to SMB for both conditions. Illness and medication beliefs having the strongest associations with poor SMB will be addressed in the intervention. Session 1: As in our PCORI-funded intervention for asthma in the elderly, we will develop a practical screening tool based on validated items from the IPQ and BMQ that will be used by a counselor (described below) to identify key disease beliefs held by the patient. The counselor will then address the beliefs that may interfere with effective SMB using motivational interviewing techniques. This targeted counseling will be combined with a discussion of the interaction between asthma and obesity and benefits of integrated management (e.g., better asthma control = greater ability to do exercise = weight loss = reduced risk of asthma; dietary modification = weight loss = reduced asthma risk). Sessions 2 and 3: will be based on modules 2 and 4 of the DPP weight management curriculum, which focus on diet and exercise self-monitoring. We will modify each DPP module to reinforce issues addressed in session 1 and will integrate strategies for co-management of obesity and asthma. For example, in session 2, we might recommend use of controller medication immediately before a meal (e.g., breakfast) or link daily weight and diet self-monitoring tasks with peak flow measurements. We may reinforce use of short acting bronchodilators before exercise and educate patients to differentiate between asthma symptoms and shortness of breath from exertion.

We will use cognitive restructuring methods to address misconceptions about asthma and obesity. For example, patients may feel that asthma or obesity cannot be controlled, even with appropriate treatment, because they compare their functional status to peers without the illness. These views can be "reconstructed" by teaching patients to compare themselves to other patients of the same age with these conditions and to give them realistic and achievable markers for improvement over time (e.g., goal to walk 1 mile in 1 month). We will also focus on refining symptom discrimination for guiding self-regulation feedback loops. According to the SRM, patients interpret symptoms in relation to their mental model of illness and these assessments in turn guide their SMB. Appraisal of the efficacy of their actions serves reinforces or modifies SMB. Thus, in all modules we will work on helping the patient develop accurate perceptual discrimination of symptoms arising from asthma and obesity, thereby creating a process in which patients search for the appropriate signals to initiate and appraise the effects of self-management to generate effective self-regulatory feedback controls. The counselor will also address emotional responses, using normalizing statements (e.g., "Many patients feel that way…"). Finally, we will use strategies to enhance comprehension and retention including teach-to-goal, motivational interviewing, multi-modal communication, and optimized formatting of print materials. To sustain self-regulation, strategies for patients to record, monitor and effectively attribute their outcomes will be reinforced using the aforementioned tools for asthma symptom monitoring in addition to diet and exercise logs.

Refinement of Counseling Modules: We will conduct qualitative interviews with ~10 patients at each site who complete the cohort study before the pilot to evaluate and refine the sessions. A counselor will administer the 3 one-hour sessions at 1-week intervals to each patient. During the audio-recorded sessions, an observer (MC or AF) will periodically assess the patient's understanding of content, language appropriateness, and perceptions of impact using a think-aloud approach and probe for ideas to increase impact. After 2-3 participants complete the sessions, we will discuss their reactions, opinions, and recommendations, then modify script and text as needed. This iterative process will continue until no further modifications are deemed necessary. Dr. Conroy will prepare a procedural manual for the educational sessions and counselor training. Counselors: Certified diabetes educators (CDE) at the participating sites will conduct the sessions. The CDEs at ISMMS and UPMC are trained in motivational interviewing, a core element of the proposed intervention. They will also be trained in asthma self-management support using materials we developed for our PCORI-

asthma study. Drs. Conroy and Federman will train the counselors at each site on all protocols.

Pilot RCT Procedures: We will use data from the 12-month interview to identify obese asthmatics with low adherence to asthma SMB for the pilot (N=80). Eligible patients who agree to participate in the pilot will be randomized (using adaptive randomization to balance the number of participants in each arm) to the intervention vs. attention control group stratifying by site (NY or Pittsburgh). Intervention Group: Counseling will be conducted 1:1 by the CDEs at the study sites and will take place during 1-hour sessions beginning on the day of the patient's 18-month in-person research interview and will continue once a week for a total of 3 sessions. Attention Control: Control patients will undergo three 1-hour educational sessions covering general asthma knowledge, and diet and exercise. Sources for the education will include a general asthma education workbook, Asthma 1-2-3 and the diet and exercise resources on the US Department of Agriculture Website, http://www.choosemyplate.gov/. The CDE will walk the patient through the materials, one topic addressed during each session. Unlike the intervention, the attention control will not follow a theory-based approach to support self-monitoring of asthma or obesity. For the attention control, we considered using the DPP without the integrated asthma education and attention to illness beliefs. However, the DPP component itself might improve diet and exercise behaviors, hampering our ability to observe benefits of the very limited integrated intervention we assess in the pilot. Outcome Assessment: A telephone follow-up survey 4 weeks after the last in-person counseling session will be administered to reassess the patient's asthma and obesity and medication beliefs, their adherence to asthma SMB, and self-monitoring of diet and weight. Data Analysis: 1) Quantitative Assessment: Differences in illness representations (IPQ for asthma and obesity), medication beliefs (BMQ), adherence to asthma medications (MARS), and diet and exercise self-monitoring (DHS) will be assessed using a t-test or Wilcoxon test, as appropriate. 2) Qualitative Feedback: The post-intervention interview will also include open-ended questions for: a) recollection of specific messages from the counseling, b) satisfaction and perceived usefulness, and c) ways of improving the messages and their delivery. Fidelity Assessment: 2 investigators (AF, MC) will observe randomly selected intervention and control sessions to determine CDE fidelity to the educational intervention. Power: The study will have >90% power to identify a clinically meaningful difference of 1 unit in IPQ, BMQ, MARS, or DHS scores for 40 patients in each study arm (n=80).