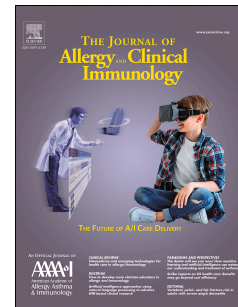


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Quantitative CT metrics are associated with longitudinal lung function decline and future asthma exacerbations: results from SARP-3

James G. Krings, MD, Charles W. Goss, PhD, Daphne Lew, PhD MPH, Maanasi Samant, MD, Mary Clare McGregor, MD, Jonathan Boomer, PhD, Leonard B. Bacharier, MD, Ajay Sheshadri, MD, Chase Hall, MD, Joshua Brownell, MD, Ken B. Schechtman, PhD, Samuel Peterson, MS, Stephen McEleney, BSE, David T. Mauger, PhD, John V. Fahy, MD, Sean B. Fain, PhD, Loren C. Denlinger, MD PhD, Elliot Israel, MD, George Washko, MD, Eric Hoffman, PhD, Sally E. Wenzel, MD, Mario Castro, MD MPH, for the National Heart Lung and Blood Institute's (NHLBI's) Severe Asthma Research Program (SARP) Investigators



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**Quantitative CT metrics are associated with longitudinal lung function decline
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James G. Krings, MD¹, Charles W. Goss, PhD², Daphne Lew, PhD MPH², Maanasi Samant, MD¹, Mary Clare McGregor, MD¹, Jonathan Boomer, PhD³, Leonard B. Bacharier, MD⁴, Ajay Sheshadri, MD⁵, Chase Hall, MD³, Joshua Brownell, MD⁶, Ken B. Schechtman, PhD², Samuel Peterson, MS⁷, Stephen McEleney, BSE⁷, David T. Mauger, PhD⁸, John V. Fahy, MD⁹, Sean B. Fain, PhD¹⁰, Loren C. Denlinger, MD PhD⁶, Elliot Israel, MD¹¹, George Washko, MD¹¹, Eric Hoffman, PhD¹², Sally E. Wenzel, MD¹³, and Mario Castro, MD MPH³, for the National Heart Lung and Blood Institute's (NHLBI's) Severe Asthma Research Program (SARP) Investigators

Institutional Affiliations:

¹Division of Pulmonary and Critical Care Medicine, Department of Medicine, and

²Division of Biostatistics, Washington University in Saint Louis School of Medicine, Saint Louis, MO, ³Division of Pulmonary, Critical Care and Sleep Medicine, Department of

Medicine, University of Kansas School of Medicine, Kansas City, KS, ⁴Department of

Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, ⁵Division of

Pulmonary and Critical Care Medicine, Department of Medicine, The University of

Texas MD Anderson Cancer Center, Houston, TX, ⁶Division of Allergy, Pulmonary, and

Critical Care Medicine, Department of Medicine, University of Wisconsin, Madison, WI,

⁷VIDA Diagnostics, Coralville, IA, ⁸Division of Statistics and Bioinformatics, Department

of Public Health Sciences, Pennsylvania State University, Hershey, PA, ⁹Division of

Pulmonary and Critical Care Medicine, Department of Medicine, University of California
San Francisco, San Francisco, CA ¹⁰Department of Radiology and Biomedical
Engineering, University of Wisconsin, Madison, WI, ¹¹Division of Pulmonary and Critical
Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA,
¹²Department of Radiology, Biomedical Engineering, and Medicine, University of Iowa,
Iowa City, IA, ¹³Division of Pulmonary, Allergy, and Critical Care, Department of
Medicine, University of Pittsburgh, Pittsburgh, PA.

Corresponding Author:

Mario Castro, MD, MPH
Division of Pulmonary, Critical Care and Sleep Medicine
Department of Medicine
University of Kansas School of Medicine
3901 Rainbow Boulevard
Telephone number: +1.913.588.7529
Email: mcastro2@kumc.edu

Conflict of Interest

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Author contributions:

J.G.K. and M.C. are the guarantors of the paper, taking responsibility for the integrity of the work from inception to publication. J.G.K. and M.C. conceived of and designed the study in its entirety. J.G.K., C.W.G., D.L., K.B.S., and M.C. did the primary statistical analysis and made significant contributions to the design of the study and interpretation of the data. J.G.K., M.S., A.S., C.H., S.P., S.M., J.V.F., G.W., E.H., and M.C. were responsible for the interpretation of the imaging analysis. J.G.K. prepared the first draft of the manuscript and all authors revised the draft critically for intellectual content. All authors provided approval of the final manuscript version.

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Running Title: qCT metrics are associated with lung function decline and asthma exacerbations

ABSTRACT:

BACKGROUND: Currently there is limited knowledge of what imaging assessments of asthma are associated with accelerated longitudinal lung function decline.

OBJECTIVES: We aimed to assess whether quantitative computerized tomography (qCT) metrics are associated with longitudinal lung function decline and morbidity in asthma.

METHODS: We analyzed 205 qCT scans of adult asthma patients, and calculated baseline markers of airway remodeling, lung density, and pointwise regional change in lung volume (Jacobian measures) for each participant. Using multivariable regression models, we then assessed the association of qCT measurements with the outcomes of future lung function change, future exacerbation rate, and changes in validated measurements of morbidity.

RESULTS: Greater baseline wall area percent (WA%) ($\beta=-0.15$, 95% CI -0.26 to -0.05, $P<0.01$), hyperinflation% ($\beta=-0.25$, 95% CI -0.41 to -0.09, $P<0.01$), and Jacobian gradient measurements (cranial-caudal $\beta=10.64$, CI 3.79 to 17.49, $P<0.01$; posterior-anterior $\beta=-9.14$, CI -15.49 to -2.78, $P<0.01$) were associated with more severe future lung function decline. Additionally, greater WA% (rate ratio=1.06, CI 1.01 to 1.10, $P=0.02$), air-trapping% (rate ratio=1.01, CI 1.00 to 1.02, $P=0.03$), and lower Jacobian determinant mean (rate ratio=0.58, CI 0.41 to 0.82, $P<0.01$) and Jacobian determinant standard deviation (rate ratio=0.52, CI 0.32 to 0.85, $P=0.01$) were associated with a

greater rate of future exacerbations. However, imaging metrics were not associated with clinically meaningful changes in scores on validated asthma morbidity questionnaires.

CONCLUSIONS: Baseline qCT measures of more severe airway remodeling, more small airways disease and hyperinflation, and less pointwise regional change in lung volumes were associated with future lung function decline and asthma exacerbations.

This study was registered with www.clinicaltrials.gov (NCT01716494).

CLINICAL IMPLICATIONS:

Quantitative imaging metrics were associated with important asthma outcomes including longitudinal lung function decline and future exacerbations. Quantitative imaging may be one tool that helps prognosticate future outcomes in asthma.

CAPSULE SUMMARY:

Currently if imaging characteristics are associated with asthma outcomes is unknown. In this study, asthmatics with more airway remodeling and less regional change in lung expansion had more lung function decline and exacerbations.

KEY WORDS:

Asthma, severe asthma, CT imaging, asthma morbidity, asthma exacerbations, longitudinal, lung function.

ABBREVIATIONS USED:

ACT, asthma control test; ATS, American Thoracic Society; AQLQ, asthma quality of life questionnaire; BMI, body mass index; CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; DPM, disease probability mapping; ERS, European Respiratory Society; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FEV₁%, forced expiratory volume in 1 second % predicted; FRC, functional residual capacity; GINA, Global Initiative for Asthma; NHLBI, National Heart Lung and Blood Institute; PRM, parametric response mapping; qCT, quantitative analyses of multidetector computerized tomography scan; SAD, small airway disease; SARP-3, Severe Asthma Research Program-3; SPIROMICS, Subpopulations of Intermediate Outcome Measures in Chronic Obstructive Pulmonary Disease; TLC, total lung capacity; WA%, wall area percent; WT%, wall thickness percent.

INTRODUCTION

Asthma is a heterogeneous disorder that is characterized by chronic airway inflammation, airway hyperresponsiveness, and variable airway obstruction. Asthma is estimated to affect approximately 300 million people worldwide and is expected to only increase in prevalence in the future.^{1, 2} Prior studies have shown that when compared to healthy controls, a subset of adults with asthma experience an accelerated rate of the longitudinal decline in lung function.³⁻⁶ For example, in one large epidemiologic study of 17,506 participants, adults with asthma experienced an average decline in forced expiratory volume in 1 second (FEV₁) of 38mL per year as compared to 22mL per year in adults without asthma.⁷ In a subset of patients with asthma, this accelerated rate of lung function decline can lead to irreversible, fixed airway obstruction and marked morbidity.⁸

Despite recent advances in the understanding and treatment of asthma, novel biomarkers that can reliably predict which patients with asthma will experience an accelerated decline in lung function have not yet been identified. Prior studies have shown that a more rapid decline in lung function in asthma is associated with prior tobacco abuse, a history of frequent asthma exacerbations, a low baseline FEV₁, exposure to ambient air pollution, low serum 25-hydroxyvitamin D levels, and an elevated fractional exhaled nitric oxide (FeNO).^{7, 9-17} In addition, recent work from our NHLBI-sponsored Severe Asthma Research Program (SARP) group demonstrated that, in moderate-to-severe asthma, insensitivity to systemic steroids is associated with greater longitudinal loss of lung function.¹⁸ However, whether or not objective measures

of airway remodeling are associated with future lung function changes remains unknown.

Results of quantitative analysis of multidetector computerized tomography (qCT) scans have previously been proposed as potential biomarkers that could prognosticate outcomes in chronic obstructive pulmonary disease (COPD),¹⁹ asthma,²⁰ and interstitial lung disease.²¹⁻²³ qCT analysis objectively quantifies airway, parenchymal, and pulmonary vascular characteristics,^{20, 24} and its use has previously led to the successful identification of novel phenotypes in both COPD and asthma.^{19, 25-29} Parametric response mapping (PRM), a relatively new qCT methodology that uses voxel-by-voxel image co-registration of inspiratory and expiratory scans, was recently shown to be a novel biomarker in post-lung transplant recipients.³⁰ In that study, small airways disease, characterized by PRM analysis, was associated with future spirometric lung function decline post-transplant and was the single greatest predictor of post-transplant survival in multivariable modeling. Similarly, in COPD, the degree of small airways disease and emphysema defined using PRM analysis was found to be predictive of future lung function decline.³¹ To date no one has examined if qCT measurements could be used to predict future asthma outcomes.

In this study, we examined a well-characterized multicenter longitudinal cohort of adult asthma patients (SARP-3) in an attempt to determine if qCT metrics are associated with future asthma outcomes including changes in lung function. We first determined baseline markers of airway remodeling, small airways disease, and regional changes in lung expansion using qCT analyses in adults with asthma. We then determined longitudinal changes in both lung function and future asthma morbidity for

280 each participant. We hypothesized that baseline markers of airway remodeling as
281 determined by qCT would be associated with future lung function decline and greater
282 subsequent asthma morbidity.

METHODS

Included Participants

SARP-3 participants were enrolled and characterized from 2012-2015 as previously published³² and included in this study if they were age ≥ 18 at the time of initial spirometry, had a baseline interpretable CT scan, and had ≥ 3 visits with spirometry in order to assess for post-CT longitudinal lung function changes. A total of 205 adult participants met our study inclusion criteria (**Figure 1**). All SARP-3 participants provided written informed consent and the institutional review boards from each of the 14 enrollment sites approved of this study.

CT Image Acquisition and Analyses

SARP-3 used a qCT analysis protocol similar to other large multicenter studies, which has been described in detail by the SPIROMICS group.^{24, 25, 33, 34} Analyses were done with Apollo 2.0 software (VIDA Diagnostics, Inc., Coralville, IA, USA). CT integrity and all automated airway segmentations were manually confirmed by two trained analysts. Our primary predictor variables were wall area % (WA%) and wall thickness percent (WT%) defined as $([\text{wall area}/\text{total area}] * 100\%)$ and $([\text{wall thickness}/\text{outer diameter}] * 100\%)$ respectively. These measurements were calculated at the third generation, or segmental airways, along five airway pathways (RB1, RB4, RB10, LB1, and LB10) as previously described.³⁵⁻³⁷ Pi10 (airway wall area associated with a hypothetical inner perimeter of 10mm) and lumen area were also explored as predictor variables in secondary analyses.³⁸

The effects of lung density measurements on asthma outcomes were evaluated using the following lung density measurements: hyperinflation% (% voxels $\leq$ -950 Hounsfield units [HU] at total lung capacity [TLC]), air-trapping% (% voxels $\leq$ -856HU at functional residual capacity [FRC]), and PRM and disease probability measures (DPM). PRM and DPM are measures that use image co-registration to quantify small airway disease as previously described.^{27, 31, 39-41} Finally, the Jacobian determinant and Jacobian determinant gradient measurements were explored to describe pointwise changes in lung volume characteristics.^{42, 43}

Assessment of Longitudinal Lung Function Change and Asthma Morbidity

All SARP-3 participants were followed longitudinally and, in order to be included in this study, ≥ 3 annual follow-up visits with valid spirometry were required. The primary outcome variable was the per year (slope) change in post-bronchodilator FEV₁ percent predicted (FEV₁%), which was calculated using individual linear regression models for each participant. Changes in asthma morbidity were assessed as the annual rate of asthma exacerbations adjusted for time on study, the yearly change (slope) in asthma control test (ACT) scores, and the yearly change (slope) in asthma quality of life questionnaire (AQLQ) scores.

Statistical Analyses

Study participants were categorized based on their per year rate of lung function change with: *severe decline* defined as FEV₁% loss of $>2\%$ per year; *mild decline*, 0.5 to 2% loss/year; *no change*, 0.5% loss/year to 1% gain/year; and *improvement*, $>1\%$

gain/year.¹⁸ Characteristics of each lung function change group were described and compared using analysis of variance (ANOVA), Kruskal-Wallis, chi-square, or Fisher's exact tests as appropriate. Univariable regression models were then constructed to determine the association between qCT measurements and the individual outcomes of slope change in post-bronchodilator FEV₁% predicted, ACT, AQLQ, and annual exacerbation rate (with each outcome treated as a continuous variable). All univariable and multivariable models controlled for biologic use, baseline post-bronchodilator FEV₁%, as well as baseline ACT score, baseline AQLQ score, or 12-month prior-to-enrollment exacerbation rate as appropriate. Multivariable regression models were constructed separately for each qCT predictor variable and were conducted using a backward elimination model building process. All potential covariates with *P*-values less than 0.2 on univariate analysis were assessed for inclusion in the multivariate models. Only covariates with *P*-values < 0.05 in the multivariate analysis were maintained in the final models. In addition, the variables of baseline FEV₁% response to triamcinolone, body mass index (BMI), exacerbation frequency in the year prior to SARP-3 enrollment, and blood eosinophil count were forced into all multivariable models used to predict longitudinal lung function change.

For exacerbations, a negative binomial distribution was assumed. Time on study was included as an offset term to account for the fact that not all participants had the same number of follow-up visits. All other models assumed a normal distribution and were weighted by the inverse of the mean-squared error of the individual-level linear regression models. Sensitivity analyses were conducted wherein we repeated the models with specific exclusion of those on biologics. We also assessed whether the

351 association between the outcomes and qCT measures varied according to total time
352 that a participant was on study (i.e., a qCT x total follow-up time interaction). Results
353 from these analyses are included in the electronic supplement. A two-sided *P*-value of
354 <0.05 was used to denote statistical significance. All statistical analyses were performed
355 using SAS version 9.4 (Cary, NC, USA).

RESULTS

Demographics and Baseline Asthma and Imaging Characteristics

The demographic and clinical characteristics of the 205 participants who had a baseline CT scan and longitudinal follow-up are described and compared by subsequent change in lung function grouping in **Table 1**. SARP participants in this study were overall comparable to excluded adult SARP participants; however, included participants did have more severe disease (see **Electronic Supplemental Table E1**). The overall cohort represented a demographically diverse sample but consisted primarily of participants with ATS/ERS-defined severe asthma ($n=138$; 67%).⁴⁴ In this study, 75 participants (36.6%) experienced future mild or severe lung function decline. The median length of follow-up in this study was 4.3 years (interquartile range [IQR] 3.9 to 5.1 years). Most baseline demographic and clinical characteristics were similar across future lung function decline group. However, biologic use did vary across change in lung function groups ($P = 0.04$) wherein participants with more severe future lung function decline were more likely to be on a biologic therapy. In addition, the exacerbation rate in the year prior to SARP-3 enrollment ($P < 0.01$) and exacerbation rate during the duration of the SARP-3 study ($P = 0.049$) varied across groups with a higher rate of exacerbations found in the severe lung function decline group. Baseline quantitative imaging results are described and compared by lung function groups in **Table 2**.

Imaging Predictors of Longitudinal Lung Function Decline

In this study, we found that participants with more severe airway remodeling, more hyperinflation, and certain lung volume expansion gradation patterns on qCT were more likely to experience future lung function decline. The consolidated results of the effect of qCT variables on the outcome of lung function decline are presented in **Table 3 and Figure 2** (as well as **Electronic Supplemental Table E2** with use of standardized beta coefficients and **Electronic Supplemental Tables E3-E16** showing results of all covariates included in individual models). On multivariable analyses, which included adjustment for covariates including baseline post-bronchodilator FEV₁% predicted, biologic use, body mass index (BMI), FEV₁% response to triamcinolone, exacerbation frequency in the year prior to SARP-3 enrollment, and baseline blood eosinophil count, greater WA% ($\beta=-0.15$, 95% CI -0.26 to -0.05, $P < 0.01$) was associated with more severe future lung function decline. However, WT% ($\beta=-0.12$, 95% CI -0.37 to 0.12, $P = 0.32$) did not have an association with lung function decline. Our findings indicate that a participant who had a 5% greater WA% at baseline would be expected to have an absolute FEV₁% predicted decline of 0.75% more each year.

When looking at lung density measurements, only hyperinflation% was predictive of longitudinal lung function decline on multivariable analysis ($\beta=-0.25$, 95% CI -0.41 to -0.09, $P < 0.01$). Most lung deformation metrics were not associated with lung function decline on primary analysis; however, Jacobian determinant gradient patterns (cranial-caudal $\beta=10.64$, 95% CI 3.79 to 17.49, $P < 0.01$; posterior-anterior $\beta=-9.14$, CI -15.49 to -2.78, $P < 0.01$) were strongly associated with lung function changes. However, when patients on biologics were excluded, greater amounts of small airway disease (whether measured as AT%, PRM_{SAD}, or DPM_{SAD}) and less lung deformation (Jacobian

determinant mean) were also associated with longitudinal lung function decline (**Electronic Supplemental Table E17**). Interestingly, the effect of several qCT variables on future lung function changes did vary based on the length of longitudinal follow-up. In cases with comparatively longer longitudinal follow-up, participants who had a greater Pi10 or lower Jacobian determinant mean had greater future lung function decline (**Electronic Supplemental Table E18**).

Imaging Predictors of Asthma Morbidity

The association of baseline qCT metrics with future asthma morbidity outcomes is presented in **Table 4** (and **Electronic Supplemental Table E19** with use of standardized beta coefficients and **Electronic Supplemental Tables E20-E33** showing results of all covariates included in individual models). While airway measurements were not associated with ACT scores, several lung density measurements including hyperinflation% ($\beta = -0.01$, 95% CI 0 to 0.02, $P < 0.01$) and air-trapping% ($\beta = -0.004$, 95% CI 0 to 0.01, $P < 0.01$) were significantly associated with AQLQ changes, but markedly below the minimal clinically important difference of 0.5⁴⁵. The Jacobian cranial-caudal gradient was also associated with changes in AQLQ scores ($\beta = 1.28$, 95% CI 0.58 to 1.98, $P < 0.001$).

Finally, in this study, imaging metrics that showed more severe airway remodeling, more small airways disease, and less lung deformation were associated with a greater future rate of asthma exacerbations (**Table 4 and Figure 2**). Even after adjustment for covariates including frequency of prior exacerbations and baseline eosinophil count, participants that had a greater baseline WA% (rate ratio=1.06, 95% CI

1.01 to 1.10, $P = 0.02$) had a higher future rate of asthma exacerbations. In addition, participants that had more small airways disease, assessed via simple voxel thresholding (air-trapping%, rate ratio=1.01, 95% CI 1.00 to 1.02, $P = 0.03$) or either image co-registration method (PRM_{SAD}, rate ratio 1.01, 95% CI 1.00 to 1.03, $P = 0.02$; DPM_{SAD}, rate ratio=1.01, 95% CI 1.00 to 1.02, $P = 0.01$) were more likely to experience exacerbations in the future even after controlling for prior exacerbations. Lastly, participants that had less lung deformation (Jacobian determinant mean, rate ratio=0.58, 95% CI 0.41 to 0.82, $P < 0.01$) and less heterogeneity in lung deformation (Jacobian determinant standard deviation, rate ratio=0.52, 95% CI 0.32 to 0.85, $P = 0.01$) had a greater number of future exacerbations.

DISCUSSION

This study showed that certain quantitative imaging metrics were associated with future lung function decline and asthma exacerbations. Specifically, adults with asthma who had more severe baseline airway remodeling, more hyperinflation, and certain lung deformation patterns were more likely to experience accelerated lung function decline. Similarly, participants with more severe airway remodeling, more air trapping, and less lung deformation were more likely to have future asthma exacerbations. However, qCT metrics were generally not associated with clinically meaningful changes in asthma control or quality of life.

Although investigators have known for decades that a subset of asthma patients have an accelerated decline in lung function, little progress has been made at predicting which patients with asthma will experience a more rapid lung function decline.^{7, 46} The current inability to predict future lung function decline in asthma limits our ability to research treatment paradigms specifically aimed at minimizing the risk of future lung function decline.⁴⁷ If lung function decline and asthma morbidity could be more accurately predicted, it is possible that treatments (such as biologic therapies) could be explored at an earlier timepoint in “high risk” patients to potentially prevent or impede accelerated lung function loss. In this study, several qCT characteristics were predictive of future lung function decline. However, we should point out that these results represent prediction of average outcomes for the entire cohort. Based on these results, qCT metrics alone could not predict individual-level outcomes with enough accuracy to select patients for a personalized medicine treatment approach. Possibly, in the future,

qCT metrics in combination with other biomarkers could predict future adverse outcomes in asthma with enough accuracy to guide individualized therapies however.

Illustrated in **Figure 3** are representative coronal and axial CT images from a SARP-3 participant who suffered severe lung function decline and had numerous exacerbations during the duration of the study, which is directly contrasted with a CT from another participant who had improvement in lung function and had no exacerbations. These contrasting images show the differences in qCT metrics between these two participants who were otherwise clinically similar at baseline, but experienced drastically different subsequent clinical courses. Currently, qCT analyses are primarily used in research studies and require human verification and adjustment. However, complete automation and reporting of qCT values is likely on the horizon. Furthermore, with improved image reconstruction methods that reduce a patient's radiation exposure and with further standardization of imaging acquisition protocols, qCT has the potential to have an increasingly important role in routine clinical care in the future.⁴⁸

In the SARP-3 cohort, more severe airway remodeling, as assessed by WA%, was associated with an increased rate of future lung function decline and a greater frequency of asthma exacerbations after controlling for relevant confounders including baseline FEV₁%, prior exacerbations, and eosinophil count. These results confirmed our primary hypothesis, which predicted that more severe airway remodeling, as reflected by a greater baseline WA%, would be predictive of future lung function decline and asthma morbidity. Prior studies have shown that patients with severe asthma, when compared to those with mild disease, have an increased WA% and WT% on qCT.¹³ Furthermore, both WA% and WT% have been shown to be directly correlated with

response to bronchodilators as well as epithelial thickness from endobronchial biopsies.⁴⁹⁻⁵¹ Our finding that an increased WA% is associated with future accelerated longitudinal lung function decline supports the pathobiological concept that underlying airway remodeling has future detrimental consequences including long-term loss of lung function and increased risk of exacerbations. While an association between increased airway remodeling and future loss of lung function has been previously hypothesized, prior studies have never clearly demonstrated this association.^{52, 53}

In addition, this study demonstrated that greater hyperinflation, as assessed by qCT, was associated with greater future loss of lung function. Of note, in this study, hyperinflation% was used to describe the radiologic findings of hyperinflation (% voxels $\leq$ 950 HU at TLC) rather than the often-described clinical phenomenon of “dynamic hyperinflation” in asthma. While this finding has not been reported before in asthma, prior studies have demonstrated that the equivalent imaging metric (termed emphysema-like lung) is associated with future lung function decline in moderate-to-severe COPD.^{54, 55} Prior studies in COPD and post lung transplantation have demonstrated that PRM measurements were predictive of future lung function decline.^{30, 31} Surprisingly in the current study, small airways disease measurements obtained using PRM and DPM analysis were not predictive of lung function decline. However, when patients on biologics were excluded from the analysis, baseline qCT markers of small airway disease were associated with greater future lung function decline.

Finally, in this study we demonstrated that lung deformation measurements (Jacobian determinant values), as well as lung deformation spatial heterogeneity

(Jacobian gradient values), were independently associated with several asthma-related outcomes. The Jacobian determinant is a biomechanical measurement calculated from image co-registration and reflects the local volume change that occurs at a point from expiration to inspiration.⁵⁶⁻⁵⁸ While lung deformation measurements are less intuitive, Jacobian measurements have previously been found to be of importance in both COPD and asthma.^{56, 57, 59-62} In asthma, low Jacobian determinant values are associated with disease severity and believed to reflect less regional lung expansion, possibly secondary to air trapping and hyperinflation.^{56, 59} In COPD, lower Jacobian determinant values in the penumbra surrounding emphysematous areas of the lung have been found to be prognostic of future lung function decline.⁶¹ In asthma we found that less lung deformation (Jacobian determinant mean) and less lung deformation heterogeneity (Jacobian determinant standard deviation) were independently predictive of future exacerbations, but were not associated with lung function changes. However, as shown in the electronic supplement, in patients not on biologics or who had comparatively longer longitudinal follow-up, a lower baseline Jacobian determinant value was associated with greater longitudinal lung function decline. This finding indicates that with longer longitudinal follow-up, associations between baseline qCT variables and asthma outcomes may become even more apparent. Furthermore, in this study Jacobian spatial heterogeneity predicted lung function decline, with relatively greater caudal and relatively greater posterior Jacobian determinant values having associations with future lung function decline. To our knowledge Jacobian gradients have not been explored in predicting disease outcomes, and this finding should be viewed as hypothesis generating.

We believe this study has a number of strengths. To our knowledge, this study represents the first time qCT measurements have been evaluated in a longitudinal asthma cohort and shown to predict clinically meaningful asthma outcomes. Furthermore, all data in this study were collected from a well-characterized cohort of asthma patients from diverse racial and ethnic backgrounds and with a broad range of disease severity. However, limitations of this study must be considered. First, in this study airway remodeling was assessed via qCT analysis. Although qCT metrics of airway remodeling are correlated with endobronchial measurements, limitations of measuring airway remodeling in this way exist. For example, wall area cannot be normalized by basal membrane length wherein an increase in baseline airway smooth muscle tone could be incorrectly interpreted for airway remodeling using qCT. Additionally, the findings of air-trapping were postulated to primarily represent underlying small airways disease. However, the exact contribution that larger airways or other abnormalities have on the finding of air-trapping cannot be certain. In this study, our only primary hypothesis was that qCT markers of airway remodeling, specifically an elevated WA% and WT%, would be predictive of the individual outcomes of lung function decline and asthma morbidity. As such, all further exploration of associations between other imaging metrics and study outcomes should be considered exploratory, and were not corrected for multiple comparisons. Finally, a subset of participants in this study were on biologic therapies, which have been shown to improve lung function.^{63, 64} However, all univariable and multivariable models in this study corrected for biologic use, and repeat exploratory analyses excluding these 24 participants on biologics were performed and showed similar or stronger associations.

549

550 **CONCLUSIONS**

551 In conclusion, in this study we found that adult asthma patients with more severe
552 airway remodeling, more hyperinflation, and certain lung deformation gradation
553 patterns, discerned from qCT analyses, were more likely to experience future lung
554 function decline. While qCT measurements were generally not associated with clinically
555 meaningful changes in asthma morbidity on questionnaires, more severe airway
556 remodeling, more small airways disease, and less lung deformation were each
557 associated with a greater future rate of asthma exacerbations. Based on results from
558 this study, qCT metrics may be useful to prognosticate clinical outcomes in adult
559 asthma.

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Table Legends

Table 1. Characteristics of adult SARP-3 participants who had a baseline qCT and longitudinal follow-up categorized by future change in lung function. Lung function groups were classified based on their rate (slope) of lung function change with severe decline defined as FEV₁% loss of >2% per year; mild decline, 0.5 to 2% loss/year; no change 0.5% loss/year to 1% gain/year; and improvement, more than 1% gain/year. Lung function groups were compared using chi-square, Fisher's exact test, ANOVA, or Kruskal-Wallis tests as appropriate. SD: standard deviation; BMI: body mass index; IQR: interquartile range; ICS: inhaled corticosteroids; OCS: oral corticosteroids; ACT: asthma control test; AQLQ: asthma quality of life questionnaire; and FeNO: fractional exhaled nitric oxide. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.0001$.

Table 2. Quantitative computerized tomography (qCT) characteristics of SARP-3 participants categorized by future change in lung function. Lung function groups were classified based on their rate (slope) of lung function change with: severe decline defined as FEV₁% loss of >2% per year; mild decline, 0.5 to 2% loss/year; no change 0.5% loss/year to 1% gain/year; and improvement, more than 1% gain/year. Lung function groups were compared using ANOVA or Kruskal-Wallis tests as appropriate. WA%: wall area percent; WT%: wall thickness percent; Pi10: inner perimeter of 10 mm; PRM: parametric response mapping; SAD: functional small airway disease; DPM: disease probability measure; PA: posterior – anterior; CC: cranial – caudal. * $P < 0.05$; † $P < 0.01$.

Table 3. Univariable and multivariable predictors of lung function change over time. Univariable comparisons were adjusted for baseline post-bronchodilator FEV₁% predicted and use of biologics. Multivariable models were adjusted for baseline post-bronchodilator FEV₁% predicted, biologic use, body mass index (BMI), FEV₁% response to triamcinolone, exacerbation frequency in the year prior to SARP-3 enrollment, baseline blood eosinophil count, and other significant covariates. WA%: wall area percent; WT%: wall thickness percent; Pi10: inner perimeter of 10 mm; FRC: functional residual capacity; PRM: parametric response mapping; SAD: functional small airway disease; TLC: total lung capacity; DPM: disease probability measure; PA: posterior – anterior; CC: cranial – caudal. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

Table 4. Multivariable predictors of future asthma morbidity. All multivariable models controlled for biologic use as well as baseline number of exacerbations in the year prior to SARP-3 enrollment, baseline ACT score, and baseline AQLQ score respectively. Other significant covariates were entered into the model, which was formed using a backwards elimination model selection process. ACT: asthma control test; AQLQ: asthma quality of life questionnaire; WA%: wall area percent; WT%: wall thickness percent; Pi10: inner perimeter of 10 mm; PRM: parametric response mapping; SAD: functional small airway disease; DPM: disease probability measure; PA: posterior – anterior; CC: cranial – caudal; * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

Figure Legends:

Figure 1. Study flow diagram.

Figure 2. Predicted (A) annual change in post-bronchodilator FEV₁% and (B) predicted annual asthma exacerbation rate according to baseline wall area % (WA%), hyperinflation %, and air-trapping % (AT%). Solid black lines indicate the predicted annual change (unadjusted for covariates) in FEV₁% and the predicted rate of asthma exacerbations (unadjusted for covariates) based on the baseline qCT variable with gray shaded areas representing 95% confidence intervals around the regression lines. Parameter estimates reported in the inset are from the multivariable models. Individual adult SARP participants are color coded according to the classification of their lung function change grouping with severe decline (red circle) defined as an FEV₁% loss of >2% per year; mild decline (gold diamond), 0.5 to 2% loss/year; no change (blue square), 0.5% loss/year to 1% gain/year; and improvement (green triangle), more than 1% gain/year. After adjustment for covariates, baseline WA% and hyperinflation% were interpedently associated with future lung function decline, while baseline WA% and AT% were independently associated with a greater rate of future asthma exacerbations. * $P < 0.05$; † $P < 0.01$.

Figure 3. Coronal and axial views of (A-C) a SARP-3 participant who did not suffer lung function decline (post-BD FEV₁% = 2.7% per year improvement) and had no exacerbations during the duration of SARP-3 as compared to (D-F) a participant who suffered severe lung function decline (post-BD FEV₁% = 3.8% per year

812 **decline) and had 7 exacerbations (1.75 exacerbations per year) during the**
813 **duration of SARP-3.** A representative axial image from these two participants (A and
814 D) is shown focused on RB9, which demonstrates an increased WA% in the participant
815 who suffered greater lung function decline and asthma morbidity. In addition, coronal
816 sections for the same two participants are shown demonstrating more small airways
817 disease (B and E) and less lung deformation (C and F) in the participant who had more
818 lung function decline and asthma exacerbations during the study period.

819 **Table 1**

	Improvement in Lung Function (N=58)	No Change in Lung Function (N=72)	Mild Lung Function Decline (N=52)	Severe Lung Function Decline (N=23)	P-value
Baseline clinical characteristics:					
Age, year, mean $\pm$ SD	46.6 $\pm$ 14.6	46.2 $\pm$ 13.8	48.5 $\pm$ 14.1	51.7 $\pm$ 12.2	0.36
Female, n (%)	36 (62%)	48 (67%)	35 (67%)	15 (65%)	0.94
Non-white race, n (%)	20 (34%)	23 (32%)	21 (40%)	11 (48%)	0.50
BMI, kg/m ² , median (IQR)	30.3 (26 to 38.7)	30.5 (26.1 to 35.8)	30.0 (27.3 to 38.3)	34.6 (29.8 to 39.4)	0.09
History of nasal polyps, n (%)	15 (26%)	10 (14%)	10 (19%)	9 (39%)	0.06
Baseline asthma characteristics:					
Age of asthma onset, years, median (IQR)	14 (4 to 32)	11 (3 to 27)	11 (5 to 29)	12 (3 to 30)	0.90
Duration of asthma symptoms, year, mean $\pm$ SD	28.0 $\pm$ 15.6	29.5 $\pm$ 14.0	31.3 $\pm$ 15.9	35.0 $\pm$ 17.7	0.28
Exacerbations in the prior 12 months, median (IQR)	1 (0 to 2)	0 (0 to 2)	1 (0 to 3)	2 (0 to 5)	<0.01[†]
ATS/ERS severe classification, n (%)	41 (71%)	43 (60%)	38 (73%)	16 (70%)	0.39
On high dose ICS + 2nd controller, n (%)	42 (72%)	45 (63%)	37 (71%)	16 (70%)	0.62
On biologics in the last 12 months, n (%)	6 (10%)	9 (13%)	9 (17%)	8 (35%)	0.04*
Received OCS in the last 12 months, n (%)	34 (59%)	36 (50%)	32 (62%)	16 (70%)	0.33
ACT score, median (IQR)	19 (13 to 21)	18 (14 to 21)	16 (13 to 20)	14 (10 to 20)	0.08
AQLQ score, median (IQR)	5.1 (4.2 to 5.9)	5.1 (4.3 to 6.3)	5.2 (4.1 to 5.9)	4.8 (4.1 to 6.1)	0.65
Blood eosinophil, %, median (IQR)	3 (2 to 5)	3.2 (2 to 5)	2.9 (1.7 to 6.9)	2.9 (1.5 to 6.4)	0.83
Sputum eosinophil, %, median (IQR)	0.8 (0 to 4.3)	0.5 (0.2 to 3.5)	0.3 (0 to 1.1)	1 (0.7 to 1.4)	0.18
FeNO, ppb, median (IQR)	25.5 (13 to 39)	22 (13.5 to 36)	17 (10 to 33)	18 (12 to 42)	0.32
Serum IgE, kU/L, median (IQR)	174 (67 to 362)	150 (43 to 303)	154 (46 to 345)	139 (17 to 640)	0.91
Baseline spirometry characteristics:					
Pre-bronchodilator FEV ₁ % predicted, mean $\pm$ SD	70.4 $\pm$ 20.4	76.6 $\pm$ 17.9	68.9 $\pm$ 19.7	72.5 $\pm$ 23.7	0.15
Pre-bronchodilator FVC% predicted, mean $\pm$ SD	82.5 $\pm$ 18.8	87.3 $\pm$ 15.1	83.3 $\pm$ 16.8	84.3 $\pm$ 18.1	0.38
Pre-bronchodilator FEV ₁ /FVC ratio (%predicted), mean $\pm$ SD	84.3 $\pm$ 12.1	86.8 $\pm$ 11.1	81.3 $\pm$ 12.6	84.4 $\pm$ 14.1	0.10
Triamcinolone-induced difference from baseline in FEV ₁ % predicted, mean $\pm$ SD	5.0 $\pm$ 9.2	2.6 $\pm$ 6.2	1.6 $\pm$ 8.6	6.8 $\pm$ 11.2	0.04*
Longitudinal characteristics:					
Length of follow-up, years, median (IQR)	4.0 (3.1 to 5.0)	4.4 (4.0 to 5.1)	4.9 (4.0 to 5.1)	4.3 (4.1 to 5.0)	0.03*
Slope of yearly change in post-bronchodilator FEV ₁ % predicted, median (IQR)	2.2 (1.8 to 3.0)	0.1 (-0.2 to 0.5)	-1.1 (-1.5 to -0.8)	-2.9 (-4.0 to -2.2)	<0.0001[†]
Slope of yearly change in ACT score, median (IQR)	0.5 (0.1 to 1.1)	0.3 (-0.1 to 0.8)	0.1 (-0.6 to 0.9)	0.2 (-0.2 to 0.9)	0.08
Slope of yearly change in AQLQ score, median (IQR)	0.1 (0 to 0.3)	0.1 (-0.1 to 0.2)	0.1 (-0.1 to 0.2)	0 (0 to 0.3)	0.06
Exacerbations per year of follow-up, median (IQR)	0.6 (0 to 1.4)	0.3 (0 to 1)	0.5 (0 to 1.3)	1 (0 to 2)	0.049*

820 **Table 2**

Baseline qCT characteristics	Improvement in Lung Function	No Change in Lung Function	Mild Lung Function Decline	Severe Lung Function Decline	P-value
Airway Measurements					
WA%, mean $\pm$ SD	61.3 $\pm$ 3.2	60.9 $\pm$ 2.9	61.6 $\pm$ 2.9	63.4 $\pm$ 3.5	<0.01[†]
WT%, mean $\pm$ SD	16.5 $\pm$ 1.3	16.3 $\pm$ 1.2	16.6 $\pm$ 1.1	17.4 $\pm$ 1.6	<0.01[†]
Lumen area, mm ² , mean $\pm$ SD	20.0 $\pm$ 6.1	19.4 $\pm$ 4.6	19.2 $\pm$ 5.4	17.0 $\pm$ 4.6	0.15
Pi10, mm, mean $\pm$ SD	3.8 $\pm$ 0.1	3.7 $\pm$ 0.1	3.7 $\pm$ 0.1	3.8 $\pm$ 0.1	0.46
Lung Density Measurements					
Air trapping, %, median (IQR)	5.8 (2.3 to 12.7)	4.0 (2.1 to 11.7)	8.7 (4.3 to 16.0)	10.9 (3.6 to 15.4)	0.05
PRM _{SAD} , %, median (IQR)	5.8 (2.3 to 12.7)	4.0 (2.0 to 11.0)	8.8 (4.3 to 16.2)	10.2 (3.8 to 15.3)	0.05*
DPM _{SAD} , %, median (IQR)	22.0 (14.3 to 36.1)	19.2 (9.9 to 27.3)	24.4 (17.3 to 38.2)	27.9 (17.6 to 33.7)	0.02*
Hyperinflation, %, median (IQR)	1.7 (0.8 to 2.7)	1.6 (0.6 to 3.1)	1.9 (0.8 to 3.4)	1.7 (0.8 to 3.6)	0.84
PRM _{hyperinflation} , %, median (IQR)	0.2 (0 to 0.6)	0.1 (0 to 0.4)	0.2 (0 to 0.8)	0.2 (0.1 to 0.8)	0.32
DPM _{hyperinflation} , %, median (IQR)	0.8 (0.1 to 2.8)	0.4 (0.1 to 1.9)	1.2 (0.3 to 3.6)	1.1 (0.4 to 3.4)	0.28
Lung Deformation (Jacobian) Measurements					
Mean $\pm$ SD	2.0 $\pm$ 0.5	2.1 $\pm$ 0.4	1.8 $\pm$ 0.3	1.9 $\pm$ 0.4	<0.01[†]
SD, median (IQR)	0.6 (0.4 to 0.9)	0.7 (0.5 to 0.9)	0.6 (0.4 to 0.7)	0.6 (0.4 to 0.8)	0.03*
Gradient _{CC} , mean $\pm$ SD	0 $\pm$ 0.05	-0.02 $\pm$ 0.05	-0.01 $\pm$ 0.04	-0.01 $\pm$ 0.06	0.15
Gradient _{PA}	0.05 $\pm$ 0.05	0.06 $\pm$ 0.04	0.05 $\pm$ 0.03	0.05 $\pm$ 0.04	0.26

821 **Table 3**

Imaging characteristic	Univariable Analysis		Multivariable Analysis	
	Parameter Estimate (95% CI)	P-Value	Parameter Estimate (95% CI)	P-value
Airway Measurements				
WA%	-0.13 (-0.23 to -0.04)	<0.01[†]	-0.15 (-0.26 to -0.05)	<0.01[†]
WT%	-0.09 (-0.32 to 0.14)	0.45	-0.12 (-0.37 to 0.12)	0.32
Lumen area, mm ²	0.09 (0.04 to 0.15)	<0.01[†]	0.10 (0.04 to 0.15)	<0.001[‡]
Pi10, mm	-0.54 (-3.27 to 2.19)	0.70	0.11 (-3.33 to 3.55)	0.95
Lung Density Measurements				
Air trapping, % voxels ≤-856HU at FRC	0.001 (-0.03 to 0.03)	0.97	-0.01 (-0.04 to 0.02)	0.55
PRM _{SAD} , %	0.002 (-0.03 to 0.03)	0.89	-0.01 (-0.04 to 0.02)	0.58
DPM _{SAD} , %	0.004 (-0.02 to 0.02)	0.71	0 (-0.02, 0.02)	0.71
Hyperinflation, % voxels ≤-950HU at TLC	-0.29 (-0.46 to -0.13)	<0.001[‡]	-0.25 (-0.41 to -0.09)	<0.01[†]
PRM _{Hyperinflation} , %	-0.21 (-0.52 to 0.1)	0.19	-0.13 (-0.40 to 0.15)	0.38
DPM _{Hyperinflation} , %	-0.03 (-0.15 to 0.08)	0.56	0 (-0.11, 0.10)	0.94
Lung Deformation (Jacobian) Measurements				
Mean	0.05 (-0.76 to 0.86)	0.90	0 (-0.74 to 0.74)	0.99
SD	-0.55 (-1.77 to 0.68)	0.38	-0.26 (-1.41 to 0.89)	0.66
Gradient _{CC}	10.4 (3.32 to 17.49)	<0.01[†]	10.64 (3.79 to 17.49)	<0.01[†]
Gradient _{PA}	-8.12 (-14.75 to -1.49)	0.02*	-9.14 (-15.49 to -2.78)	<0.01[†]

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823 **Table 4**

Imaging characteristic	Exacerbation Rate		Slope ACT		Slope AQLQ	
	Rate Ratio (95% CI)	P-Value	Parameter Estimate (95% CI)	P-value	Parameter Estimate (95% CI)	P-value
Airway Measurements						
WA%	1.06 (1.01 to 1.10)	0.02*	-0.02 (-0.06 to 0.02)	0.32	0.004 (-0.01 to 0.01)	0.39
WT%	1.09 (0.97 to 1.23)	0.13	-0.07 (-0.17 to 0.03)	0.19	0.001 (-0.02 to 0.02)	0.96
Lumen area, mm ²	0.98 (0.96 to 1.01)	0.17	0.01 (-0.02 to 0.03)	0.56	-0.002 (-0.01 to 0)	0.28
Pi10, mm	2.78 (0.84 to 9.26)	0.10	-0.39 (-1.53 to 0.75)	0.50	-0.003 (-0.18 to 0.18)	0.98
Lung Density Measurements						
Air trapping, % voxels ≤-856HU at FRC	1.01 (1.00 to 1.02)	0.03*	-0.01 (-0.02 to 0)	0.11	0.004 (0 to 0.01)	<0.01[†]
PRM _{SAD} , %	1.01 (1.00 to 1.03)	0.02*	-0.01 (-0.02 to 0)	0.11	0.01 (0 to 0.01)	<0.01[†]
DPM _{SAD} , %	1.01 (1.00 to 1.02)	0.01*	-0.01 (-0.02 to 0)	0.16	0.002 (0 to 0.004)	0.13
Hyperinflation, % voxels ≤-950HU at TLC	1.00 (0.96 to 1.05)	0.86	-0.04 (-0.09 to 0.01)	0.16	0.01 (0 to 0.02)	<0.01[†]
PRM _{Hyperinflation} , %	1.04 (0.97 to 1.12)	0.25	-0.04 (-0.12 to 0.04)	0.35	0.02 (0 to 0.05)	0.07
DPM _{Hyperinflation} , %	1.02 (0.99 to 1.05)	0.16	-0.02 (-0.05 to 0.01)	0.25	0.01 (0 to 0.02)	0.02*
Lung Deformation (Jacobian) Measurements						
Mean	0.58 (0.41 to 0.82)	<0.01[†]	0.25 (-0.10 to 0.59)	0.16	0.04 (-0.03 to 0.11)	0.21
SD	0.52 (0.32 to 0.85)	0.01*	0.30 (-0.19 to 0.79)	0.23	0.06 (-0.03 to 0.15)	0.17
Gradient _{CC}	1.13 (0.04 to 30.57)	0.94	-0.03 (-3.05 to 2.99)	0.98	1.28 (0.58 to 1.98)	<0.001[‡]
Gradient _{PA}	0.27 (0.01 to 11.13)	0.49	-0.18 (-3.66 to 3.30)	0.92	-0.5 (-1.13 to 0.13)	0.12

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