RESEARCH ARTICLE

Findings on Thoracic Computed Tomography Scans and Respiratory Outcomes in Persons with and without Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study

Wan C. Tan¹*, Cameron J. Hague², Jonathon Leipsic², Jean Bourbeau³, Liyun Zheng¹, Pei Z. Li³, Don D. Sin¹, Harvey O. Coxson¹, Miranda Kirby¹, James C. Hogg¹, Rekha Raju², Jeremy Road³, Denis E. O’Donnell³, Francois Maltais⁶, Paul Hernandez⁷, Robert Cowie⁸, Kenneth R. Chapman³, Darcy D. Marciniuk¹⁰, J. Mark FitzGerald⁴, Shawn D. Aaron¹¹, Canadian Respiratory Research Network and the CanCOLD Collaborative Research group

¹ Center for Heart Lung Innovation, St. Paul’s Hospital, University of British Columbia, Vancouver, BC, Canada, 2 Department of Radiology, St. Paul’s Hospital, University of British Columbia, Vancouver, BC, Canada, 3 Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montréal, QC, Canada, 4 University of British Columbia, Vancouver General Hospital, Institute for Heart and Lung Health, Vancouver, BC, Canada, 5 Division of Respiratory & Critical Care Medicine, Queen’s University, Kingston, ON, Canada, 6 Hospital Laval, Centre de Pneumologie, Institute Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Quebec, QC, Canada, 7 Division of Respirology, QEII Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia, Canada, 8 Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada, 9 Asthma & Airway Centre, University Health Network, Toronto, ON, Canada, 10 Division of Respirology, Critical Care and Sleep Medicine, and Airway research Group, University of Saskatchewan, Saskatoon, SK, Canada, 11 Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

¶ Membership of the CanCOLD Collaborative Research Group is listed in the Acknowledgments.
* wan.tan@hli.ubc.ca

Abstract

Background
Thoracic computed tomography (CT) scans are widely performed in clinical practice, often leading to detection of airway or parenchymal abnormalities in asymptomatic or minimally symptomatic individuals. However, clinical relevance of CT abnormalities is uncertain in the general population.

Methods
We evaluated data from 1361 participants aged ≥40 years from a Canadian prospective cohort comprising 408 healthy never-smokers, 502 healthy ever-smokers, and 451 individuals with spirometric evidence of chronic obstructive pulmonary disease (COPD) who had thoracic CT scans. CT images of subjects were visually scored for respiratory bronchiolitis (RB), emphysema(E), bronchial-wall thickening(BWT), expiratory air-trapping(AT), and bronchiectasis(B). Multivariable logistic regression models were used to assess associations of CT features with respiratory symptoms, dyspnea, health status as determined by

OPEN ACCESS

Citation: Tan WC, Hague CJ, Leipsic J, Bourbeau J, Zheng L, Li PZ, et al. (2016) Findings on Thoracic Computed Tomography Scans and Respiratory Outcomes in Persons with and without Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study. PLoS ONE 11(11): e0166745. doi:10.1371/journal.pone.0166745

Editor: Konstantinos Kostikas, National and Kapodistrian University of Athens, SWITZERLAND

Received: August 18, 2016
Accepted: November 2, 2016
Published: November 18, 2016

Copyright: © 2016 Tan et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The Canadian Cohort Obstructive Lung Disease (CanCOLD) study is currently funded by the Canadian Respiratory Research Network (CRRN); and industry partners Astra Zeneca Canada Ltd, Boehringer Ingelheim Canada Ltd, GlaxoSmithKline Canada Ltd, and Novartis. The project is led by researchers at RI-MUHC Montreal and the UBC Center for Heart Lung Innovation,
COPD assessment test, and risk of clinically significant exacerbations during 12 months follow-up.

Results
About 11% of life-time never-smokers demonstrated emphysema on CT scans. Prevalence increased to 30% among smokers with normal lung function and 36%, 50%, and 57% among individuals with mild, moderate or severe very severe COPD, respectively. Presence of emphysema on CT was associated with chronic cough (OR, 2.11; 95% CI, 1.4–3.18); chronic phlegm production (OR, 1.87; 95% CI, 1.27–2.76); wheeze (OR, 1.61; 95% CI, 1.05–2.48); dyspnoea (OR, 2.90; 95% CI, 1.41–5.98); CAT score ≥10 (OR, 2.17; 95% CI, 1.42–3.30) and risk of ≥2 exacerbations over 12 months (OR, 2.17; 95% CI, 1.42–3.0).

Conclusions
Burden of thoracic CT abnormalities is high among Canadians ≥40 years of age, including never-smokers and smokers with normal lung function. Detection of emphysema on CT scans is associated with pulmonary symptoms and increased risk of exacerbations, independent of smoking or lung function.

Introduction
Chronic obstructive pulmonary disease (COPD) is a complex heterogeneous disease with a spectrum of overlapping clinical subtypes ultimately leading to chronic airflow limitation[1]. However, spirometry is not sensitive enough to detect early changes in lung structure or function and is not specific enough to determine underlying pathophysiologic processes responsible for airflow limitation[1–3]. Increasingly, clinical diagnosis and assessment of COPD have become multidimensional[1, 4] with the use of clinical, physiological, radiological phenotyping with multidimensional computed tomography (MDCT) scans[5] and inclusion of patient-related outcomes, including health status and exacerbation risk, in an attempt to improve assessment of the disease and its severity, thus guiding management[1, 6].

Many Canadians receive thoracic CT scans for a variety of indications, whence airway and/or parenchymal abnormalities are often detected. However, clinical relevance of these abnormalities, especially in never-smokers and those with normal lung function, is unknown. The primary aim of this study was to: 1) ascertain the prevalence of emphysema and airway abnormalities (e.g. bronchiolitis, bronchiectasis, etc) in the general Canadian population ≥40 years of age, including never-smokers and those with normal lung function; 2) determine the relationship of detected CT abnormalities with pulmonary symptoms, health status, and clinical outcomes, such as risk of exacerbations in the general population.

Materials and Methods
Study population
Methodology of the prospective Canadian Cohort of Obstructive Lung Disease (CanCOLD) observational study (ClinicalTrials.gov:NCT00920348) has been reported previously[7]. Briefly, we enrolled subjects from a core sample of 6,592 persons randomly recruited from 9 sites across Canada[7–9]. Participants included individuals ≥40 years who were: 1) healthy...
persons who never smoked (never-smokers) ( \( \leq 1/20 \) pack year of tobacco-smoking history, 
\( FEV_1/FVC \geq 5^{th} \) percentile [LLN]); ii): smokers (ever-smokers) with post-bronchodilator 
\( FEV_1/FVC \geq LLN \); iii) mild COPD (post-bronchodilator \( FEV_1/FVC < LLN \) & 
\( FEV_1/pred \geq 80\% \)); iv) moderate COPD (\( FEV_1/FVC < LLN \) & \( 50\% \leq FEV_1/pred < 80\% \)); and v) 
severe to very severe COPD (\( FEV_1/FVC < LLN \) & \( FEV_1/pred < 50\% \)) [10, 11].

The study was approved by the respective university and institutional ethical review boards 
at each participating site. All participants gave written informed consent.

Methods

We obtained data which included responses to interviewer-administered questionnaires on 
smoking and occupational exposures, respiratory symptoms and comorbidities, spirometry 
measurements made before and 15 minutes after inhalation of 200mcg albuterol, full lung 
function measurements, thoracic CT scans, and 1 year prospective follow-up data on exacerba-
tion-like respiratory events (see below for definition) captured via 3-monthly telephone 
administered questionnaires [12].

Computed tomographic lung scans

Scanning was performed using a standard low dose protocol without bronchodilation within 
one day of lung function testing [13]. All CT scans were acquired using multidetector-row CT 
(MDCT) scanners with a minimum of 16 rows at suspended full inspiration without adminis-
tration of intravenous contrast (details in S1 Text).

CT image analysis

Images 1 mm thick were assessed and graded by two thoracic radiologists with >10 years expe-
rience in chest CTs, who were blinded to the characteristics and group assignment of partici-
pants. Bronchiolitis was defined as ill-defined centrilobular micronodules (S1 Fig) [5, 14–16] 
and graded based on the quartile system according to the following scale: none = 0, trivial = 1, 
mild = 2, moderate = 3, and severe = 4 [16, 17]. Study definition for the presence of respiratory 
bronchiolitis was a score of \( \geq 2 \).

For grading emphysema, each lung was divided into 6 zones ([upper-left and upper-right 
above the carina; mid (middle-left and middle-right) between carina and inferior pulmonary 
veins; and lower (lower-left and lower-right) zones]. The extent of zonal emphysema was 
scored on a 5 point scale as follows: 0 = no emphysema, 1 = 1–25\% (trivial), 2 = 26–50\% 
(mild), 3 = 51–75\% (moderate), 4 = 76–100\% (severe-very severe) (S2 Fig) [14]. Presence of 
emphysema was a summation emphysema score of \( \geq 1 \). Presence of expiratory air-trapping, 
bronchial wall thickening, and bronchiectasis were assessed based on morphological criteria 
from the Fleishner glossary of terms for thoracic imaging [15].

We initially evaluated inter-observer agreement in a subset of 50 subjects. As the weighted 
kappa scores for all variables were comparable to or higher than previously reported [14, 18], 
the remaining scans were read randomly and singly by one of the two radiologists (details in 
S1 Text).

Patient-reported outcomes

Outcomes of interest here consisted of respiratory symptoms including chronic cough, 
chronic phlegm, wheeze, dyspnea scale \( \geq 2 \) according to the modified Medical Research Coun-
cil (mMRC) scale [19], CAT score \( \geq 10 \) [20] and exacerbation frequency \( \geq 2 \) in the following 12 
months [12, 21]. Chronic cough and chronic phlegm were defined as cough/phlegm on most
days for at least 3 months in two consecutive years[8, 11]. Wheeze was defined as wheezing in the chest at any time in the last 12 months[8, 11]. Exacerbation data were collected prospectively through subject telephone interviews conducted tri-monthly; only subjects completing the 12 months follow-up were included. An episode of exacerbation was defined as increased dyspnea, sputum volume, or sputum purulence for at least 2 days that might have affected work, and/or required utilization of antibiotics, corticosteroids, doctor visits, emergency room visits, or hospitalizations[1, 11, 22].

Statistical Analyses
All analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

Descriptive statistics are shown as counts and percentages for categorical data, and means and standard deviations for continuous variables, unless otherwise stated. Non-parametric Kruskall-Wallis test was used to compare continuous variables with post-hoc comparisons using Mann-Whitney test, and chi-squared test with CompProp procedure for comparison of proportions. A two-sided p < 0.05 was considered statistically significant. For multiple comparisons, p values were adjusted by Holm-Bonferroni correction.

Sensitivity analyses were performed: 1) to address the effect of a more stringent threshold for emphysema, and the caveat of regional heterogeneity of emphysema in the lung, we conducted sensitivity testing by repeating analyses for the emphysema threshold emphysema score > 2; and different definitions (mean score, maximum score). 2) To address confounders caused by asthma and restrictive diseases in COPD and non-COPD subgroups respectively, we repeated the prevalence of all CT abnormalities after excluding: a) those with a history of asthma (confounder for COPD); and b) those with preserved ratio, low FEV₁ and low FVC (restrictive physiology, confounder for non-COPD)[23].

To address the association of CT parameters (independent variable) with patient-reported outcomes (dependent variables), multivariable logistic regression models were constructed using each of the CT variables separately with adjustment for age, sex, BMI, pack years, and FEV₁.

Results
We evaluated baseline data of 1361 participants, aged ≥40 years who had thoracic CT scans. The study cohort consisted of 408 never-smokers with normal lung function, 502 ever-smokers with normal lung function, and 451 individuals with COPD of different grades of severity.

Patient characteristics
Table 1 shows baseline demographic characteristics: smoking status, pack years, history of asthma, and spirometry and lung physiological measurements for the whole cohort, stratified into 5 study subgroups. There was no difference in demographic characteristics, occupational exposures, or asthma history between never-smokers and ever-smokers with normal lung function. Subjects with mild COPD were younger than all other subgroups (all p < 0.0003). Moderate-to-severe COPD comprised more current smokers with greater pack-year consumption of tobacco compared to mild COPD (all p < 0.0025). A self-reported history of asthma was more frequent in COPD subgroups compared to non-COPD individuals (all p < 0.001). Pulmonary physiological measurements discriminated COPD of all severity from never-smokers and ever-smokers without COPD (all p < 0.01), although smokers without COPD had slightly increased residual volume (RV) and functional residual capacity (FRC) compared with never-smokers (p < 0.001, 0.0042).
Prevalence of CT features by subgroups

Respiratory bronchiolitis was more frequent in ever-smokers with normal lung function (16%) compared to those with mild (9%) and moderate-severe (9%) COPD (p = 0.016, p = 0.0141). Air-trapping was more frequent in smokers without COPD (35%) compared to...
the normal (25%) (p = 0.0011) or moderate COPD (24%) subgroups (p = 0.0029). Prevalence of bronchial wall thickening increased in smokers without COPD (58%) compared to ‘normal’ subjects (31%) (p = 0.0003), and further increased in COPD of all severity grades (mild 64%, moderate 78%, severe 95%), (p = 0.0004, 0.0005, 0.006, respectively). Similarly, the proportion of individuals with emphysema was elevated in ever-smokers with normal lung function (30%) compared to the normal group (11%) (p = 0.0007) and stepwise increases with increasing severity of COPD (mild 36%, moderate 50%, severe 57%). Bronchiectasis prevalence was only significantly elevated in severe COPD (Table 2, Fig 1).

Sensitivity tests. We consistently observed that emphysema increased in smokers, which further increased in a stepwise fashion with increasing severity of COPD, regardless of the emphysema definition used (e.g. summation score of 1 vs. summation score of 2 vs. mean score vs. maximal score). The p values for comparisons using mean score were: p = 0.0003 for smokers vs. normal; p = 0.0004 for mild COPD vs. normal; and p = 0.0005 for moderate/severe COPD vs. smokers.

When subjects with a) asthma (a self-reported history of asthma: confounder for COPD) or b) restrictive disease (subnormal FEV1 and FVC, but preserved FEV1/FVC ratio: confounder for non-COPD) [23] were excluded from the whole cohort, prevalence for each of the 5 CT features were similar to results computed using the whole cohort (S1 Table, S3 Fig; S2 Table, S4 Fig).

Association between CT features and patient-reported outcomes

Fig 2 and Table 3 show results from multivariable logistic regression models shown as adjusted Odds Ratio, aOR(95% CI) adjusted for age, sex, BMI, pack years, and FEV1. Emphysema was most consistently associated with chronic cough, chronic phlegm, wheeze, dyspnea ≥ 2 mMRC grade, CAT score ≥ 10, exacerbation frequency ≥ 2 within the 12 month follow-up and hospitalized (severe) exacerbation frequency ≥ 1 within the 12 month follow-up (Table 3). Bronchial wall thickening was associated with wheeze and CAT score ≥10; bronchiectasis
with wheeze, dyspnea (mMRC scale ≥2) and CAT score ≥10. No association was found between respiratory bronchiolitis or air–trapping and respiratory outcomes.

Subgroup analyses in the ‘normal’ (never-smokers with normal lung function) and ‘at-risk’ (ever-smokers with normal lung function) showed that bronchiectasis was associated with reduced quality of life (CAT score ≥ 10) in both these subgroups while bronchial wall thickening was associated with chronic phlegm in ‘at-risk’ smokers. While there appeared to be a trend, there was no significant association between emphysema and clinical outcomes in these two non-COPD subgroups. (S3 and S4 Tables).
Discussion

Eleven percent of Canadians aged ≥40 years who never smoked, and 30% of smokers with normal lung function, have evidence of emphysema on CT scans. More importantly, the presence of emphysema was related to poor outcomes as reported by patients, including chronic cough, chronic phlegm, wheeze, dyspnea, reduced health status, and increased risk of exacerbations and hospitalizations for exacerbations during 12 month follow-up.

CT emphysema and bronchial wall thickening performed best at discriminating between subjects with and without airflow limitation and between levels of severity, as previously described in patient studies. These two CT features were also increased in smokers without spirometric evidence of airway obstruction. These findings underscore the usefulness of CT features as radiological markers of COPD in ‘at risk’ smokers and in patients with mild or conceivably early COPD, and support the increasing practice of using CT-based emphysema measurements to identify patients with early COPD in clinical practice who do not demonstrate abnormal spirometry. We extend the findings of previous work, which were largely performed in selected smokers or COPD patients (e.g. ECLIPSE[13] COPDgene[14] and
SPIROMICS studies, by demonstrating the added value of this approach in the general population. Additionally, data could be employed to strengthen anti-smoking efforts as it added population-specific evidence to previous studies of convenient samples of selected smokers. Another application was that radiological markers could be used to define individuals for future early interventional trials, reemphasizing the continued relevance of traditional, population-based epidemiological studies in an era of ‘mega-cohorts’ comprising administrative databases, selected participants, and consortia of cohorts.

The second key finding was the validation of CT features of COPD against clinically relevant health outcomes. To our knowledge, this is the first study that systematically evaluated the influence of the various discrete CT phenotypes on a wide range of clinical outcomes that matter to patients. The most clinically important CT feature was emphysema that was widely associated with symptoms, and severe dyspnea, as well as to reduced health status, and was a significant predictor of future exacerbations, including severe exacerbations requiring hospitalization. The non-significant trend of association between emphysema and outcomes in the normal and at risk non-COPD subgroups would suggest that the extent of emphysema in these two subgroups was mild. Overall, these findings underscore the role of emphysema in furthering our understanding of COPD as imaging findings of emphysema can provide

### Table 3. The risk of visual CT variables on developing of patient-reported outcomes (data for Fig 2 in manuscript).

|                      | Chronic Cough | Chronic Phlegm | Wheeze ≥2 | Dyspnea ≥2 | CAT Score ≥10 | Exacerbation Frequency ≥2 in 1-year follow-up | Hospitalization Frequency for Exacerbation ≥1 in 1-year follow-up |
|----------------------|---------------|----------------|-----------|-------------|--------------|-----------------------------------------------|--------------------------------------------------------------------|
| Emphysema Score ≥1   | aOR = Adjusted Odds Ratios. |                 |           |             |              |                                               |                                                                     |
|                      | 2.11          | 1.87           | 1.61      | 2.90        | 2.17         | 2.54                                          | 5.94                                                               |
| 95% CI               | 1.40–3.18     | 1.27–2.76      | 1.05–2.48 | 1.41–5.98   | 1.42–3.30    | 1.26–5.11                                     | 1.32–26.73                                                        |
| P-value              | < .001*       | 0.002*         | 0.029*    | 0.004*      | < .001*     | 0.009*                                        | 0.020*                                                            |
| Bronchial wall thickening |            |               |           |             |              |                                               |                                                                     |
| aOR                  | 1.15          | 1.29           | 1.81      | 1.05        | 1.42         | 1.35                                          | 1.86                                                               |
| 95% CI               | 0.84–1.56     | 0.92–1.82      | 1.39–2.34 | 0.60–1.83   | 1.08–1.87    | 0.75–2.45                                     | 0.38–9.15                                                         |
| P-value              | 0.392         | 0.141          | < .001*   | 0.871       | 0.012*       | 0.316                                         | 0.446                                                             |
| Bronchiolitis Score ≥2 |                |               |           |             |              |                                               |                                                                     |
| aOR                  | 1.11          | 1.37           | 1.14      | 0.93        | 1.17         | 0.53                                          | -#                                                                |
| 95% CI               | 0.77–1.61     | 0.92–2.03      | 0.83–1.57 | 0.48–1.82   | 0.84–1.63    | 0.20–1.38                                     | -                                                                  |
| P-value              | 0.566         | 0.118          | < .001*   | 0.871       | 0.012*       | 0.316                                         | 0.195                                                             |
| Air trapping         |                |               |           |             |              |                                               |                                                                     |
| aOR                  | 1.03          | 0.83           | 0.92      | 1.39        | 0.97         | 0.92                                          | 0.63                                                              |
| 95% CI               | 0.75–1.41     | 0.59–1.18      | 0.71–1.19 | 0.82–2.36   | 0.73–1.27    | 0.51–1.66                                     | 0.13–3.03                                                        |
| P-value              | 0.851         | 0.311          | 0.507     | 0.218       | 0.806        | 0.782                                         | 0.566                                                             |
| Bronchiectasis       |                |               |           |             |              |                                               |                                                                     |
| aOR                  | 1.43          | 1.45           | 1.57      | 1.90        | 1.89         | 1.47                                          | 0.86                                                              |
| 95% CI               | 0.99–2.06     | 0.97–2.17      | 1.14–2.17 | 1.05–3.42   | 1.36–2.63    | 0.76–2.83                                     | 0.16–4.58                                                        |
| P-value              | 0.056         | 0.069          | 0.006*    | 0.033*      | < .001*     | 0.253                                         | 0.860                                                             |

The outcomes were modeled using each of the CT variables separately with adjustment for age, sex, BMI, pack years, FEV$_1$, aOR = Adjusted Odds Ratios.

* Significant association between visual CT variables and respiratory outcomes.
# Due to small exposed cases, ORs were not computable. Dyspnea (MMRC scale) ≥2.

[doi:10.1371/journal.pone.0166745.t003]
information beyond FEV1 in terms of patient-related health outcomes. For instance, the presence of emphysema may tell us something about disease activity (e.g. having emphysema predicts rapid decline in lung function over time) and about poor gas exchange or gas trapping that are not captured in FEV1. CT based emphysema also provides information about heterogeneity of disease and which lobes are most affected by the disease. All of these factors may relate to patient-related symptoms and outcomes.[32]

Bronchial wall thickening and bronchiectasis were also clinically pertinent as they were related to symptoms and health status. Interestingly, presence of air trapping and bronchiolitis was not associated with any of these outcomes.

However, it is unclear why the prevalence of CT respiratory bronchiolitis and expiratory air trapping (surrogates for ‘small airways disease’) [15] was increased in smokers without COPD but not in those with established COPD, yet were not associated with clinical outcomes. A potential explanation for the lack of clinical association could be that these CT features were the earliest pathological processes occurring in the physiologically ‘silent zones’ of the lungs before more advanced destructive changes that drive airflow limitation detectable on spirometry occurred[33]. The lack of presence of bronchiolitis and air-trapping in COPD can be explained by the subsequent destruction of terminal respiratory units at sites of respiratory bronchiolitis, leaving behind changes of centrilobular emphysema in COPD [34], thus confounding the assessment of bronchiolitis and air trapping. Finally, bronchiectasis was increased in individuals with established moderate and severe COPD compared to mild COPD, suggesting it was marker of severity of disease in COPD.

**Strengths**

This study involved a large prospective cohort of unselected individuals from a random sample in the general population with extensive phenotyping[7, 9], providing data that included a wide range of self-reported patient outcomes and physiological lung function measurements used for linkage to CT features from CT scans that were systematically evaluated and scored according to validated protocols by two dedicated, experienced chest radiologists. The collection of prospective exacerbation data was a definite strength. We also examined various parameters and their relationship with exacerbations requiring hospitalization. CanCOLD participants were selected randomly and not based on symptoms or “disease”, unlike previous large studies such as ECLIPSE[13], COPDgene[14], or SPIROMICS[24]. Thus, the relationship of the CT abnormalities with health status and outcomes of the subjects in the present study was likely free of ascertainment or sampling bias. Moreover, the findings here extend previously published data by demonstrating the high burden of emphysema and airway abnormalities in the general population, even among lifetime non-smokers and those with normal lung function, highlighting the importance of imaging (in addition to lung function measurements) in diagnosing early lung disease in symptomatic individuals.

**Limitations**

A potential limitation in the study was that in our stratification of subject subgroups we did not exclude individuals with asthma from the analysis of chronic airflow limitation, hence some never-smokers labeled as COPD may have fixed airflow limitation and remodeling due to long-standing asthma and some may have poorly controlled asthma which was not fully reversed with bronchodilators. Finally the results here were based on analysis of the baseline CT scans assessment. Findings and changes over time would need to be confirmed by further longitudinal data.
In summary, this study defined the burden of radiological abnormalities in the lungs of the general population, from health to disease, and confirmed the clinical relevance by their associations with multiple clinical outcomes. Our study, which focused on individuals in the population, extended the generalizability of current literature on CT scans in patients to the broader population and provided fundamental data on the occurrence of structural lung changes in disease and early subclinical disease in the general population. It remains to be shown in clinical trials if these findings could be used to guide early therapy and reduce the burden of disease.

Supporting Information
S1 Fig. Noncontrast transaxial CT to represent severe respiratory bronchiolitis. (TIF)
S2 Fig. Noncontrast transaxial CT image showing severe centrilobular emphysema. (TIF)
S3 Fig. Prevalence of CT parameters in five study subgroups (cohort without asthma). (TIF)
S4 Fig. Prevalence of CT parameters in five study subgroups (cohort without restrictive disease). (TIF)
S1 Table. Prevalence of CT parameters in five study subgroups (cohort without asthma). (DOC)
S2 Table. Prevalence of CT parameters in five study subgroups (cohort without restrictive disease). (DOC)
S3 Table. The risk of visual CT variables on developing of patient-reported outcomes for Normal group. (DOC)
S4 Table. The risk of visual CT variables on developing of patient-reported outcomes for healthy smokers (At risk) group. (DOC)
S1 Text. Online text supplement. (DOC)

Acknowledgments
The authors thank the men and women who participated in the study and individuals in the CanCOLD Collaborative research Group. Executive Committee- Jean Bourbeau, (Mcgill University, Montreal, QC, Canada); Wan C Tan, J. Mark FitzGerald; D.D. Sin. (UBC, Vancouver, BC, Canada); Darcy D. Marciniuk (University of Saskatchewan, Saskatoon, SK, Canada); D.E. O'Donnell (Queen’s University, Kingston, ON, Canada); Paul Hernandez (Dalhousie University, Halifax, NS, Canada); Kenneth R Chapman (University of Toronto, Toronto, ON, Canada); Robert Cowie (University of Calgary, Calgary, AB, Canada); Shawn Aaron (University of Ottawa, Ottawa, ON, Canada); F Maltais (University of Laval, Quebec City, QC, Canada). International Advisory Board- Jonathon Samet (the Keck School of Medicine of USC, CA, USA); Milo Puhan (John Hopkins School of Public Health, Baltimore, USA); Qutayba Hamid
Author Contributions

Conceptualization: WCT JB JH.

Data curation: WCT JB PZL LZ JCH HOC MK JL CJH.

Formal analysis: WCT DDS PZL LZ MK.

Funding acquisition: JB WCT.

Investigation: WCT JB JMF RC KRC PH SDA DDM DEO FM CJH JL RR MK HOC JR.

Methodology: WCT JB JCH HOC.

Project administration: WCT JB HOC.

Resources: WCT JB HOC JL CJH JCH.

Software: HOC.

Supervision: WCT JB.

Validation: WCT JB JCH.

Visualization: WCT LZ PZL DDS.

Writing – original draft: WCT DDS.

Writing – review & editing: WCT JB JMF RC KRC PH SDA DDM DEO FM CJH JL RR PZL LZ MK HOC JR JCH DDS.
References

1. GOLD. Global Strategy for Diagnosis, Management, and Prevention of COPD. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. Available from: http://www.goldcopd.org/. 2011.

2. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010; 11:122. Epub 2010/09/14. 1465-9921-11-122 [pii] doi: 10.1186/1465-9921-11-122 PMID: 20831787.

3. Hogg JC, Chu F, Utkoparch S, Woods R, Elliott WM, Buzatu L, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med. 2004; 350(26):2645–53. Epub 2004/06/25. doi: 10.1056/NEJMoa032158 PMID: 15215480.

4. Vestbo J, COPD: definition and phenotypes. Clin Chest Med. 2014; 35(1):1–6. Epub 2014/02/11. doi: 10.1016/j.ccm.2013.10.010 PMID: 24507832.

5. Lynch DA, Austin JH, Hogg JC, Grenier PA, Kauczor HU, Bankier AA, et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. Radiology. 2015; 277(1):192 –205. Epub 2015/05/12. doi: 10.1148/radiol.2015141579 PMID: 25961632.

6. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010; 182(5):598 –604. Epub 2010/06/05. doi: 10.1164/rccm.200912-1843CC PMID: 20522794.

7. Bourbeau J, Tan WC, Benedetti A, Aaron SD, Chapman KR, Coxson HO, et al. Canadian Cohort Obstructive Lung Disease (CanCOLD): Fulfilling the Need for Longitudinal Observational Studies in COPD. COPD. 2012. Epub 2012/03/22. doi: 10.3109/15412555.2012.655520 PMID: 22439011.

8. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007; 370(9589):741–50. Epub 2007/06/25. doi: 10.1016/S0140-6736(07)61377-4 PMID: 17765523.

9. Tan WC, Bourbeau J, FitzGerald JM, Cowie R, Chapman K, Hernandez P, et al. Can age and sex explain the variation in COPD rates across large urban cities? A population study in Canada. Int J Tuberc Lung Dis. 2011; 15(12):1691–8. Epub 2011/11/29. doi: 10.5588/ijtld.11.0211 PMID: 22118181.

10. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. Chest. 2011; 139(4):752 –63. doi: 10.1378/chest.10-1253 PMID: 20884729; PubMed Central PMCID: PMC3168866.

11. Hansell DM, Bankier AA, MacMahon H, McCloud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008; 246(3):697–722. Epub 2008/01/16. 2462070712 [pii] doi: 10.1148/radiol.2462070712 PMID: 18195376.

12. Sayiner A, Hague C, Aljan A, Leipsic J, Wierenga L, Krowchuk NM, et al. Bronchiolitis in young female smokers. Respir Med. 2013; 107(5):732–8. Epub 2013/01/29. S0954-6111(13)00004-8 [pii] doi: 10.1016/j.rmed.2012.12.023 PMID: 23352225.

13. Hague CJ, Krowchuk N, Alhassan D, Ho K, Leipsic J, Sin DD, et al. Qualitative and quantitative assessment of smoking-related lung disease: effect of iterative reconstruction on low-dose computed tomographic examinations. J Thorac Imaging. 2014; 29(6):350–6. doi: 10.1097/RTI.0000000000000118 PMID: 25314025.

14. Grenier P, Mourey-Gerosa I, Benali K, Brauner MW, Leung AN, Lenoir S, et al. Abnormalities of the airways and lung parenchyma in asthmatics: CT observations in 50 patients and inter- and intraobserver variability. Eur Radiol. 1996; 6(2):199–206. PMID: 8797980.
19. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988; 93(3):580–6. PMID: 3342669.

20. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009; 34(3):648–54. doi: 10.1183/09031936.00120509 PMID: 19720809.

21. Xu W, Collet JP, Shapiro S, Lin Y, Yang T, Wang C, et al. Negative impacts of unreported COPD exacerbations on health-related quality of life at 1 year. Eur Respir J. 2010; 35(5):1022–30. doi: 10.1183/09031936.00117909 PMID: 19897555.

22. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J. 2008; 31(4):689–73. Epub 2008/01/25. 09031936.0011707 [pii] doi: 10.1183/09031936.0011707 PMID: 18216052.

23. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med. 2000; 160(11):1683–9. PMID: 10847262.

24. Woodruff PG, Barr RG, Bleeker E, Christensen SA, Couper D, Curtis JL, et al. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. N Engl J Med. 2016; 374(19):1811–21. doi: 10.1056/NEJMoa1505971 PMID: 27168432.

25. Gietema HA, Edwards LD, Coxson HO, Bakke PS, Investigators E. Impact of emphysema and airway wall thickness on quality of life in smoking-related COPD. Respir Med. 2013; 107(8):1201–9. doi: 10.1016/j.rmed.2013.04.016 PMID: 23711580.

26. Hasegawa M, Nasuha Y, Onodera Y, Makita H, Nagai K, Fuke S, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006; 173(12):1309–15. doi: 10.1164/rccm.200601-037OC PMID: 16556695.

27. Kitaguchi Y, Fujimoto K, Kubo K, Honda T. Characteristics of COPD phenotypes classified according to the findings of HRCT. Respir Med. 2006; 100(10):1742–52. doi: 10.1016/j.rmed.2006.02.003 PMID: 16549342.

28. McAllister DA, Ahmed FS, Austin JH, Henschke CI, Keller BM, Lemeshow A, et al. Emphysema predicts hospitalisation and incident airflow obstruction among older smokers: a prospective cohort study. PLoS One. 2014; 9(4):e93221. doi: 10.1371/journal.pone.0093221 PMID: 24699215; PubMed Central PMCID: PMC3974731.

29. Mohamed Hoessein FA, Schmidt M, Mets OM, Gietema HA, Lammers JW, Zanen P, et al. Discriminating dominant computed tomography phenotypes in smokers without or with mild COPD. Respir Med. 2014; 108(1):136–43. doi: 10.1016/j.rmed.2013.08.014 PMID: 24035313.

30. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, et al. Clinical and Radiologic Disease in Smokers With Normal Spirometry. JAMA Intern Med. 2015; 175(9):1539–49. Epub 2015/06/23. doi: 10.1001/jamainternmed.2015.2735 PMID: 26098755; PubMed Central PMCID: PMC4564354.

31. Sorlie P, Wei GS. Population-based cohort studies: still relevant? J Am Coll Cardiol. 2011; 58(19):2010–3. doi: 10.1016/j.jacc.2011.08.020 PMID: 22032715.

32. Coxson HO, Leipsic J, Parraga G, Sin DD. Using pulmonary imaging to move chronic obstructive pulmonary disease beyond FEV1. Am J Respir Crit Care Med. 2014; 190(2):135–44. doi: 10.1164/rccm.201402-0256PP PMID: 24873985.

33. Macklem PT, Mead J. The physiological basis of common pulmonary function tests. Arch Environ Health. 1967; 14(1):5–9. PMID: 6017097.

34. McDonough JE, Yuan R, Suzuki M, Seyedian N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med. 2011; 365(17):1567–75. Epub 2011/10/28. doi: 10.1056/NEJMoai1106955 PMID: 22029978; PubMed Central PMCID: PMC3238466.