# Mortality by level of emphysema and airway wall thickness

**Journal:** *American Journal of Respiratory and Critical Care Medicine*

**Manuscript ID:** Blue-201209-1722OC.R2

**Manuscript Type:** OC - Original Contribution

**Date Submitted by the Author:** 19-Dec-2012

**Complete List of Authors:**
- Johannessen, Ane; Haukeland University Hospital, Centre for Clinical Research
- Skorge, Trude; Haukeland University Hospital, Department of Occupational Medicine
- Bottai, Matteo; Karolinska Institutet, Unit of Biostatistics, Institute of Environmental Medicine
- Grydeland, Thomas; Haukeland University Hospital, Department of Thoracic Medicine; University of Bergen, Institute of Medicine
- Nilsen, Roy; Haukeland University Hospital, Centre for Clinical Research
- Coxson, Harvey; University of British Columbia, Department of Radiology; Vancouver General Hospital, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research
- Dirksen, Asger; Gentofte Hospital, Pulmonary Department
- Omenaas, Ernst; Haukeland University Hospital, Centre for Clinical Research; University of Bergen, Institute of Medicine
- Gulsvik, Amund; Haukeland University Hospital, Department of Thoracic Medicine; University of Bergen, Institute of Medicine
- Bakke, Per; University of Bergen, Institute of Medicine; Haukeland University Hospital, Department of Thoracic Medicine

**Keywords:** COPD, Quantitative CT imaging, Mortality predictors
Mortality by level of emphysema and airway wall thickness

Ane Johannessen¹, Trude Duelien Skorge², Matteo Bottai³, Thomas Blix Grydeland⁴,⁵, Roy Miodini Nilsen¹, Harvey Coxson⁶,⁷, Asger Dirksen⁸, Ernst Omenaas¹,⁵, Amund Gulsvik⁴,⁵, Per Bakke⁴,⁵.

¹ Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway.
² Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway.
³ Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.
⁴ Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway.
⁵ Institute of Medicine, University of Bergen, Bergen, Norway.
⁶ Department of Radiology, University of British Columbia, Vancouver, British Columbia, Canada.
⁷ James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver General Hospital, Vancouver, British Columbia, Canada.
⁸ Pulmonary Department, Gentofte Hospital, Copenhagen, Denmark.

Corresponding author:
Ane Johannessen, Centre for Clinical Research, Haukeland University Hospital, 5021 Bergen, Norway. Phone: +47 55 97 55 56, Fax: +47 55 97 60 88.
E-mail address: ane.johannessen@helse-bergen.no

Author contributions:
AJ took part in the data collection, performed the statistical analyses, drafted and revised the paper. TDS, HC, EO, and AG took part in the data collection and revised the draft paper.
MB provided statistical guidance and revised the draft paper. PSB took part in the data collection, drafted and revised the paper. TBG and AD revised the draft paper. RMN revised the draft paper and constructed Figures #2 and 3.

Current scientific knowledge:
Chest CT makes it possible to subgroup COPD patients into predominantly emphysematic and airways disease phenotypes. So far, however, most COPD patients are assessed through spirometry alone. No data is available as to how level and distribution of emphysema predicts mortality in subjects with moderate or no COPD, and no data is available on mortality prediction of airway wall thickness.

What this study adds to the field:
Level of emphysema predicts all-cause mortality, as well as respiratory and cardiovascular mortality in a population based sample of subjects with and without COPD. Airway wall thickness is associated with respiratory mortality in those with severe emphysema. Given the magnitude of CT examinations performed worldwide each year, predictive effects of such measures on mortality risks are of substantial importance.

Descriptor number: 9.12 COPD: outcomes.
Manuscript word count: 3 504
This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.
ABSTRACT

Rationale: There is limited knowledge of the prognostic value of quantitative computed tomography (CT) measures of emphysema and airway wall thickness (AWT) on mortality. Objectives: To examine 8-yrs mortality in relation to CT-measured emphysema and AWT, and assess if potential impact of these predictors remained after adjustment for lung function. Methods: In the Norwegian GenKOLS study 2003-05, 947 ever-smokers (49% with COPD) aged 40-85 years performed spirometry and CT examination. Mortality data from 2003-11 were gathered from the Norwegian Cause of Death Registry. CT emphysema % low-attenuation areas (LAA) and standardized measure for airway wall thickness (AWT-Pi10) were main predictors. We performed Laplace regression for survival data, estimating survival time for specified population percentiles within each emphysema category. Models were adjusted for sex, FEV₁, COPD status, age, BMI, smoking, inflation level. Measurements and main results: During 8 years follow-up all-cause mortality rate was 15%. While 4% of the subjects with %LAA<3 died, 18% with %LAA 3-10 and 44% with %LAA>10 died. After adjustment, the comparable percentile subjects with medium and high emphysema had 19 months shorter survival than subjects who died in the lowest emphysema category. Subjects with %LAA>10 had 33/37 months shorter survival than the lowest emphysema category with regard to respiratory/cardiovascular mortality, respectively. No significant associations were found between %LAA and cancer/lung cancer mortality. AWT did not predict mortality independently, but a positive interaction with emphysema was observed.

Conclusions: AWT affected mortality with increasing degree of emphysema, whereas CT measure of emphysema was a strong independent mortality predictor.

Abstract word count: 250
INTRODUCTION

Computed tomography (CT) of the thorax is increasingly used to assess subjects with chest symptoms, patients suffering from various lung diseases as well as coronary heart disease, and in lung cancer screening programs. In chronic obstructive pulmonary disease (COPD) spirometry is crucial in both diagnosis and staging. Yet, it is well known that spirometry far from explains the whole picture of COPD (1). Chest CT offers an anatomical correlate of the disease, enabling subgrouping the disease into predominantly emphysematic and airways disease phenotypes.

In USA some 10 million chest CTs were taken in 2007, representing a huge increase since 1980 (2). Little is known of the prediction of CT derived emphysema in subjects with and without normal lung function. In heavy ever-smoking men (3-5) and women (5) it has recently been shown that emphysema predicts increased decline in lung function (3, 4).

Even more scarce data are available on the ability of emphysema to predict mortality (6, 7). One study was based on a sample of predominantly male ever-smokers with extreme smoking consumption (6) and the other was based on patients with alpha-1 antitrypsin deficiency (7). Martinez and co-workers found no association between level of emphysema and risk of death in a large study of patients with severe COPD (8). Emphysema has been related to increased mortality in cancer screening cohorts (9). However, their representativity to the population at large may be questioned.

No data are available as to how level and distribution of emphysema predicts mortality in subjects with moderate or no COPD, and no data are available on mortality prediction of
airway wall thickness. Such data would enhance the risk assessment of subjects examined with chest CT.

We therefore examined the extent of emphysema and airway wall thickness versus total and cause specific mortality in the GenKOLS study which is a large Norwegian community based cohort of subjects including patients with and without COPD followed for 8 years. We hypothesized that a greater level of emphysema and airway wall thickness would predict total mortality as well as respiratory, cardiovascular and lung cancer mortality. We further hypothesized that these associations would be independent of gender, age, lung function, smoking and body mass index.

Some of the results of this study have been previously reported in the form of an abstract at the European Respiratory Society annual congress (10).

**METHODS**

The GenKOLS study has been described in details elsewhere (11). Briefly, the study is a community based study of 462 COPD cases and 485 subjects without COPD examined with a quantitative computed tomography scan. All were aged 40 to 85 years at study start in 2003-04 and had ≥ 2.5 pack years of smoking history. They answered extensive questionnaires and performed spirometry before and after inhaling 400 µg salbutamol (11). COPD cases had post-bronchodilator FEV₁/FVC <0.70 and FEV₁ <80% predicted. Subjects without COPD had post-bronchodilator FEV₁/FVC >0.70 and FEV₁ >80% predicted.

**Quantitative computed tomography**
CT scans were performed using a GE LightSpeed Ultra CT scanner (120 kVp, 200 mA; GE Healthcare, Milwaukee, WI, USA), at suspended full inspiration (apex to base) using 1-mm slice thickness at 20-mm intervals. Details of the CT assessment have been presented elsewhere (11). Briefly, the extent of emphysema was assessed using the percentage of lung voxels with X-ray attenuation values less than (low attenuation areas; %LAA) -950 Hounsfield units (HU) (%LAA950). Percent emphysema for the whole lung was calculated, as was the difference between the upper and lower lung regions in percent emphysema (8). To reduce technical errors associated with very small airways, only airways with an internal perimeter > 6 mm were included. Airway wall thickness (AWT) is presented as the square root of the wall area for a standardized airway with an internal perimeter of 10 mm (11-13). To correct for effects of lung inflation on our CT measurements, CT derived total lung volume was divided by the predicted total lung capacity to obtain a proxy for inflation level (14).

**Outcome variables**

We obtained permission from the Regional Ethics Committee in Western Norway. Information on all-cause mortality as well as on four cause-specific mortality outcomes (respiratory mortality, cardiovascular mortality, cancer mortality and lung cancer mortality) was obtained from the National Cause of Death Registry in Norway from 2003 through June 2011 (91 months). For details of the definitions, see online supplement.

**Statistical analyses**

The main predictors of interest in our analyses were emphysema measured as percentage low attenuation areas (%LAA) and airway wall thickness (AWT-Pi10). We categorized degree of emphysema after inspecting the distribution in a quantile plot, in which it was clear that the majority (60%) had very low %LAA, while a rise in %LAA occurred between the 60th and
the 80\textsuperscript{th} percentile, followed by a sharp rise from the 80\textsuperscript{th} percentile upwards (E-figure 1 in the online supplement). Thus we categorized degree of emphysema into three categories in our analyses: low (less than 3 %LAA), medium (3 – 10 %LAA) and high (above 10 %LAA). When looking at non-COPD cases who remained alive throughout the study period, the upper limit of normal %LAA (95\textsuperscript{th} percentile) was 4 (95% CI 3.5, 6.0). Subsequently, all subjects in the less than 3 %LAA group were considered well within the normal range. Medium and high emphysema are both considered emphysematous categories, although we acknowledge that subjects with %LAA >3 and <4 in the medium category are below the upper limit of normal in the study population. Airway wall thickness (AWT-Pi10) was analyzed as a continuous variable.

Other covariates that were considered as adjustment factors were sex, age, case/control status, post-bronchodilator FEV\textsubscript{1}, smoking status, age of smoking onset, pack years, body mass index and inflation level. All variables that were significant in univariate analyses were adjusted for in the multivariate analyses.

We constructed Kaplan-Meier plots for all mortality outcomes and we performed Laplace regression to examine associations between risk factors and mortality. Laplace regression is an alternative to Cox regression for analysis of survival data (15, 16). It models survival percentiles, instead of hazard ratios. While the Kaplan-Meier curves tell us the proportion of subjects who are still alive at the end of follow-up in each emphysema category, the Laplace regression estimates tell us how many months it took before a specified percentile proportion of the study population died within each emphysema category.

Evaluating percentiles of survival time has numerous advantages. Survival percentiles are easier to interpret than hazard ratios, whose limitations are well known (17). The percentiles measure the time it takes for any given proportion of individuals to die and allow
comparisons across groups of individuals while adjusting for potential confounders. Easy interpretability may help conveying research finding to lay readers.

When interpreting Laplace results, we compared the same percentile across groups. For example, when 4% died in the lowest-degree emphysema category (<3 %LAA), we examined the 4th percentile also in the middle (≥3 – <10 %LAA) and high (≥10 %LAA) emphysema categories, even if more subjects died in the middle and high categories. This ensured a valid comparison across groups. We used the bootstrap to estimate the standard errors of the Laplace regression coefficients. In addition, we estimated Harrell’s C concordance statistic, which assesses the prognostic ability of a variable (18).

Finally we tested for interactions between sex and degree of emphysema on the various mortality outcomes, and for interactions between FEV₁ and degree of emphysema. We also tested for interaction between airway wall thickness and degree of emphysema. The significance level for the interaction effects was set to 0.01 in order to avoid type 2 error.

RESULTS

The study population consisted of 947 subjects (Table 1). Male gender, COPD, lower FEV₁, increasing age, being an ex-smoker, increasing pack years, lower BMI, and increasing emphysema severity were risk factors associated with mortality status (Table 1). While a vast majority of the subjects who remained alive throughout the study period had low %LAA, only a minority of those who died during the follow-up period had equally low %LAA. And while only 13% of those who were still living at the end of the follow-up period had %LAA ≥10, as many as 58% of those who died during the study period had high %LAA. Also, there
was a statistically non-significant tendency for increasing airway wall thickness to be related to mortality risk.

Of the subjects without COPD, 90% (n=434) had %LAA below 3%, 9% (n=45) had %LAA between 3% and 10%, and 1% (n=6) had %LAA 10 and above. The corresponding figures for COPD cases were 29% (n=134), 31% (n=145), and 40% (n=183), respectively.

Of the 144 deaths that occurred in the study population from baseline through June 2011, 28% were respiratory deaths; 10% died of cardiovascular causes; 11% died of cancer other than lung cancer, and 17% died of lung cancer.

Kaplan Meier plots show survival estimates by degree of emphysema for respiratory mortality, cardiovascular mortality, cancer mortality, lung cancer mortality and all-cause mortality (Figure 1). While 4% of the subjects in the lowest emphysema category died, the corresponding figure was 18% for subjects in the middle emphysema category and 44% in the highest emphysema degree category (Figure 1e). The tendency was the same for all cause-specific outcomes as well, in that mortality increased with increasing degree of emphysema, being most pronounced for respiratory mortality (Figure 1a).

**Univariate risk factors for mortality**

Figure 1E shows that 4% of those with low %LAA, 18% of those with medium %LAA and 44% of those with high %LAA died (all-cause mortality) during the follow-up period. Correspondingly, Table 2 for all-cause mortality shows that while the 4% who died in the low %LAA category all died within 79 months of follow-up, the first 4% who died in the medium %LAA category died within 23 months (79 minus 56), and the first 4% who died in the high %LAA category died within 12 months of follow-up (79 minus 67). E-Figure 1 in the online
supplement further illustrates these survival estimates. A similar trend was present when looking at GOLD severity stages and number of survival months (E-Figure 2). While the first 4% who died of all causes in GOLD stage 0 died within the first 91 months, the first 4% who died in GOLD stage 2 died within the first 21 months of follow-up, and the first 4% who died in GOLD stages 3 and 4 died within the first 11 months (E-Figure 2). Airway wall thickness did not influence all-cause mortality. Other significant risk factors in the univariate analyses of all-cause mortality were having COPD, decreased FEV$_1$ % predicted, increased age and being an ex-smoker versus a current smoker.

Emphysema was a significant predictor of all the cause specific mortalities (Table 2, E-Figure 1), with increasing level of emphysema being related to shorter survival. The greatest gradient by emphysema was seen for respiratory mortality, the lowest for cancer mortality. The same pattern was observed for GOLD severity stages (E-Figure 2). Post-hoc estimations of Harrell’s C concordance statistic for %LAA and for GOLD severity classification with regard to the different mortality outcomes (Table 3) showed that emphysema predicted respiratory mortality with excellent discrimination (C = 0.85) and all-cause mortality, cardiovascular mortality and cancer mortality with acceptable discrimination (C between 0.7 and 0.8). Emphysema predicted both respiratory and cardiovascular mortality more accurately than what the GOLD severity classification did. Airway wall thickness predicted none of the cause specific mortalities in the crude analyses.

Of the other predictors examined increasing age and having COPD were related to all the specific outcomes, while decreased FEV1 in percent predicted was related to all the outcomes except cancer mortality. Being a current as compared to an ex-smokers
was related to increased respiratory and cardiovascular survival, earlier onset of smoking was related to reduced respiratory and cardiovascular survival, while increasing pack years of smoking was related to reduced survival in the cancer and lung cancer mortality (Table 2). In addition, inflation level was significantly related to all-cause mortality and lung cancer mortality, but not to respiratory, cardiovascular or cancer mortality.

**CT measures of emphysema in multivariate analyses of mortality**

In the multivariate analyses of all-cause mortality both the middle and the high emphysema groups had 19 months shorter survival than the lowest emphysema group, after adjustment for other significant risk factors (Table 4). Similarly, increasing degree of emphysema was associated with higher respiratory mortality and higher cardiovascular mortality (Table 4). CT measures of emphysema were not significantly associated with cancer and lung cancer mortality in the multivariate analyses (Table 4).

The multivariate analyses were then repeated excluding those with GOLD stadium 3 and 4, and also repeated once more excluding those without COPD (E-Table 1 in the online supplement). The regression coefficients remained unchanged; emphysema was associated with shorter survival time for both the healthier part of the population (non-COPD and GOLD stage 2) and the COPD-subjects (GOLD stage 2-4) with regard to both respiratory mortality and cardiovascular mortality.

**Interaction analyses**
We then tested the *a priori* decided interactions. The only one that reached level of significance in the multivariate analyses was airway wall thickness and degree of emphysema on respiratory mortality. Although airway wall thickness was not associated with respiratory mortality in itself, increased airway wall thickness reduced survival time in subjects with more severe emphysema (Figure 2).

We also examined the association between emphysema and GOLD stages on all-cause mortality (Figure 3). Although not statistically significant as an interaction term, there was a clear pattern that for those in the lowest emphysema category, GOLD severity stage influenced survival time. And for subjects without COPD and also subjects with COPD in GOLD stage 2, degree of emphysema affected survival time.

**DISCUSSION**

This study has shown that level of emphysema predicts all-cause mortality, as well as respiratory and cardiovascular mortality in a population based sample of subjects with and without COPD. There also seemed to be an association between airway wall thickness and respiratory mortality, but only in those with severe emphysema. These associations are independent of gender, age, smoking, lung function and BMI. To our knowledge this is the first study to examine the predictive ability of emphysema on mortality in a community based sample, and also the first study to examine the association between airway wall thickness and mortality. Given the magnitude of CT examinations performed worldwide each year, predictive effects of such measures on mortality risks are of substantial importance. The fact that our study comprised also subjects without COPD and that it focused on several mortality outcomes, makes the results from this study relevant across medical disciplines.
Emphysema and mortality

Our data on mortality by emphysema extend previous findings in male COPD cases with extreme smoking consumption (6) or subjects suffering from alpha-1 antitrypsin deficiency (7). Our results contradict those of the NETT study showing no relationship between emphysema level and mortality (8). The discrepancy between our and the NETT study could be due to the latter comprising highly selective subjects of severe COPD without significant co-morbidities, while the current was a community based study of mostly moderate or none COPD.

There may be several explanations why emphysema predicts respiratory mortality. First, recent longitudinal studies of COPD cases with GOLD stage II-IV have shown a relationship between increased level of emphysema and subsequent greater FEV₁ decline (3-5). The mechanisms behind this association are yet to be clarified. Emphysema may be the cause of the FEV₁ decline, but could also be part of the disease process. Second, level of emphysema is related to both lung specific inflammatory markers, such as surfactant protein D (19), as well as systemic inflammatory markers including C-reactive protein, total white blood count, and neutrophils which all in turn are predictors of mortality. Hence, lung specific and systemic inflammation may cause disease progression and increased mortality. Third, we and others have shown cross-sectionally that emphysema is related to low muscle mass and osteoporosis which are related to increased mortality (20-22). However, it is yet to be determined if emphysema proceeds low skeletal muscle mass and osteoporosis or vice versa (20).
Emphysema independently predicted cardiovascular mortality. It has long been known that terminal stages of COPD are associated with cor pulmonale (23, 24). However, we observed an impact of emphysema on cardiovascular mortality also when excluding those with severe and very severe COPD. This is in line with recent findings of a population based study of 2816 subjects aged 40-86 years, in which emphysema were linearly related to impaired left ventricular filling, reduced stroke volume, and lower cardiac output without changes in the ejection fraction (25). Potential mechanisms in early, mild emphysema may be the subclinical loss of lung parenchyma and the pulmonary capillary bed (26). Another mechanism may be endothelial and microvascular dysfunction of both the pulmonary and systemic capillary system observed cross-sectionally in subjects with mild emphysema (27). To date it is not known if endothelial damage may contribute to emphysema or vice versa. Experimental data indicate both directions (28). Finally, the emphysema-cardiovascular mortality association may work through common risk factors not adjusted for, for instance airborne pollutants other than smoking (29).

Increased level of emphysema and impaired lung function in terms of FEV₁ in percent predicted were both univariately related to increased mortality of lung cancer. However, after including them in a multivariate model together with smoking habits (Table 4), only lung function remained a significant predictor. This is in line with a recent meta-analysis finding that quantitative emphysema assessment was not a predictor while qualitative emphysema assessment predicted mortality from lung cancer (30).

**Airway wall thickness and mortality**

We observed that increased AWT was associated with respiratory mortality in those with severe emphysema. This is in line with a recent microCT examination of lung specimen from
COPD GOLD stage 4 patients showing that narrowing and loss of terminal bronchioles were related to emphysematous destruction (31). This study also found by multidetector CT that number of airways 2-2.5 mm in diameter was increasingly reduced with increasing GOLD stage (31). Our study expands these results by showing that the burden of airway remodeling as reflected by AWT on the respiratory system may be enough to affect mortality, but only in those with severe emphysema. While respiratory mortality in the highest emphysema category ranged from 13% in those with low AWT to 22% in those with high AWT (Figure 2), AWT did not affect mortality rate in the mild and medium emphysema groups. However, it is difficult to fully disentangle the meaning of the observed interaction between airway wall thickness and emphysema on respiratory mortality. We need studies with more statistical power and more robust airway wall thickness measurements to examine this association further.

**Strengths and limitations**

There are several methodological strengths in this study. First, the study population is large and includes subjects both with and without COPD. Second, all CT scans were performed with the same scanner. Third, the present study had a long follow-up period (8 years) which is of the essence when examining mortality in a middle-aged population such as this. Fourth, a thorough validation of all the death certificates was undertaken. Certain methodological weaknesses need further discussion. First, the method for measuring airway wall thickness prevented us from measuring airways smaller than 2 mm in diameter. Given that COPD is mainly a small-airway disease, this is suboptimal. However, it has been shown that measurements of larger airways can be used as a surrogate for the processes in the smaller airways (32), and that the inflammatory response in smaller airways can also be
seen in larger airways (33). Second, the extent of emphysema is represented as the percentage of the lung occupied by low X-ray attenuating regions. However, level of inspiration during the scan, cardiac congestion, fibrosis and increased phlegm production will reduce %LAA, while image noise will increase the level of %LAA thereby influencing the specificity of %LAA as an indicator of emphysema. However, subjects with severe fibrosis were excluded from analysis, and the level of inspiration was taken into account by adding the ratio of CT assessed lung volume to predicted TLC. We also adjusted for phlegm production without this affecting the observed coefficients overtly (additional analyses, results not shown). The large number of subjects in this study will work to decrease the effect of outliers on the associations between emphysema and mortality.

**Implication of the findings**

Chest CT is increasingly used in the clinical evaluation of subjects with and without COPD (34). Emphysema is frequently observed also in subjects with moderate COPD and in ever-smokers without COPD (11). The present study offers the first data on how emphysema level predicts mortality in these groups, and may be used in their risk assessment. Accurate prediction of mortality is important because it helps identify patients in whom the implementation of specific therapeutic measures may improve outcome.

In conclusion, this population based study of subjects with and without COPD has shown that level of emphysema is related to increased as all-cause, respiratory and cardiovascular mortality. Also, increased airway wall thickness is related to increased respiratory mortality in those with severe emphysema, although further studies are needed to examine this association more closely.
REFERENCES


34. Sin DD, Leipsic J, Man SF. Ct in copd: Just a pretty picture or really worth a thousand words (or dollars)? *Thorax* 2011;66:741-742.
Mortality by level of emphysema and airway wall thickness

Ane Johannessen, Trude Duellen Skorge, Matteo Bottai, Thomas Blix Grydeland, Roy Miodini Nilsen, Harvey Coxson, Asger Dirksen, Ernst Omenaa, Amund Gulsvik, Per Bakke.

Tables and figures

Table 1. Baseline characteristics by mortality status of participants in the GenKOLS study 2003-05. N = 947.

<table>
<thead>
<tr>
<th></th>
<th>Alive N = 803</th>
<th>Deceased N= 144</th>
<th>Sig.*</th>
<th>Total N=947</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>352 (44)</td>
<td>40 (28)</td>
<td>&lt;0.01</td>
<td>392 (41)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>451 (56)</td>
<td>104 (72)</td>
<td></td>
<td>555 (59)</td>
</tr>
<tr>
<td>Subjects without COPD, (%)</td>
<td>468 (58)</td>
<td>17 (12)</td>
<td></td>
<td>485 (51)</td>
</tr>
<tr>
<td>COPD cases, GOLD Stage II (%)</td>
<td>228 (28)</td>
<td>49 (34)</td>
<td>&lt;0.01</td>
<td>277 (29)</td>
</tr>
<tr>
<td>COPD cases, GOLD Stage III (%)</td>
<td>83 (10)</td>
<td>46 (32)</td>
<td>&lt;0.01</td>
<td>129 (14)</td>
</tr>
<tr>
<td>COPD cases, GOLD Stage IV (%)</td>
<td>24 (3)</td>
<td>32 (22)</td>
<td></td>
<td>56 (6)</td>
</tr>
<tr>
<td>FEV1(\dagger), mean (SD)</td>
<td>82 (24)</td>
<td>51 (23)</td>
<td>&lt;0.01</td>
<td>77 (26)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>58 (10)</td>
<td>70 (8)</td>
<td>&lt;0.01</td>
<td>60 (10)</td>
</tr>
<tr>
<td>Ex-smokers (%)</td>
<td>425 (53)</td>
<td>92 (64)</td>
<td>0.02</td>
<td>517 (55)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>378 (47)</td>
<td>52 (36)</td>
<td></td>
<td>430 (45)</td>
</tr>
<tr>
<td>Age of smoking onset, mean (SD)</td>
<td>18 (5)</td>
<td>19 (6)</td>
<td>0.03</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Pack years, mean (SD)</td>
<td>23 (15)</td>
<td>34 (21)</td>
<td>&lt;0.01</td>
<td>25 (17)</td>
</tr>
<tr>
<td>Body mass index BMI, mean (SD)</td>
<td>26.2 (4.4)</td>
<td>24.8 (4.6)</td>
<td>&lt;0.01</td>
<td>26.0 (4.4)</td>
</tr>
<tr>
<td>%LAA &lt; 3</td>
<td>542 (68)</td>
<td>26 (18)</td>
<td></td>
<td>568 (60)</td>
</tr>
<tr>
<td>%LAA (\geq 3) - &lt; 10</td>
<td>155 (19)</td>
<td>35 (24)</td>
<td>&lt;0.01</td>
<td>190 (20)</td>
</tr>
<tr>
<td>%LAA (\geq 10)</td>
<td>106 (13)</td>
<td>83 (58)</td>
<td></td>
<td>189 (20)</td>
</tr>
<tr>
<td>AWT-Pi10, mm, mean (SD)</td>
<td>4.84 (0.3)</td>
<td>4.88 (0.3)</td>
<td>0.23</td>
<td>4.85 (0.3)</td>
</tr>
</tbody>
</table>

* Two-sided p-value from Monte Carlo permutation test after 100 random permutations.
\(\dagger\) Percent of predicted post-bronchodilator
Table 3. Estimations of Harrell’s C concordance statistic for %LAA and for GOLD severity classification with regard to mortality outcomes from baseline through June 2011 (all-cause, respiratory, cardiovascular, cancer, lung cancer) after univariate Laplace regression analyses. N = 947 subjects from the GenKOLS study 2003-05.

<table>
<thead>
<tr>
<th></th>
<th>C statistic %LAA</th>
<th>C statistic GOLD severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.76</td>
<td>0.77</td>
</tr>
<tr>
<td>Respiratory mortality</td>
<td>0.85</td>
<td>0.72</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.77</td>
<td>0.71</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>0.70</td>
<td>0.63</td>
</tr>
<tr>
<td>Lung cancer mortality</td>
<td>0.66</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Table 4. Associations between %LAA and mortality outcomes (all-cause, respiratory, cardiovascular, cancer, lung cancer) from baseline through June 2011, adjusted for univariate significant predictors*. Laplace regression. N = 947 subjects from the GenKOLS study 2003-05.

<table>
<thead>
<tr>
<th>Mortality Outcome</th>
<th>%LAA &lt; 3</th>
<th>%LAA ≥3 - &lt;10</th>
<th>%LAA ≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Reference</td>
<td>-19 (-40, 2)</td>
<td>-19 (-37, 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Respiratory mortality</td>
<td>Reference</td>
<td>-60 (-83, -38)</td>
<td>-33 (-56, -11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>Reference</td>
<td>-39 (-82, 5)</td>
<td>-37 (-64, -9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>Reference</td>
<td>-23 (-67, 22)</td>
<td>-13 (-50, 23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.32</td>
<td>0.48</td>
</tr>
<tr>
<td>Lung cancer mortality</td>
<td>Reference</td>
<td>-12 (-48, 24)</td>
<td>9 (-27, 44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
<td>0.63</td>
</tr>
</tbody>
</table>

* The model for all-cause mortality is adjusted for sex, interaction between sex and %LAA, COPD status, post-bronchodilator FEV1 % predicted, age, smoking status, and inflation level. The model for respiratory mortality is adjusted for COPD status, post-bronchodilator FEV1 % predicted, smoking status, and BMI. The model for cardiovascular mortality is adjusted for COPD status, post-bronchodilator FEV1 % predicted, and age. The model for cancer mortality is adjusted for COPD status, age, and post-bronchodilator FEV1 % predicted. The model for lung cancer mortality is adjusted for COPD status, post-bronchodilator FEV1 % predicted, age, pack years and inflation level.

† Coefficient estimated for 4 percentile (all-cause mortality), 0.3 percentile (respiratory and cardiovascular mortality), and 1.5 percentile (cancer and lung cancer mortality). Numbers in bold font type differ from reference categories with statistical significance (p<0.05).
Figure 1. Kaplan Meier survival estimates* by %LAA tertiles, N = 947 subjects from the GenKOLS study 2003-05: (A) respiratory mortality, (B) cardiovascular mortality, (C) cancer mortality, (D) lung cancer mortality, and (E) all-cause mortality from baseline through June 2011.

*Blue line: low %LAA (< 3); red line: medium %LAA (3-10); green line: high %LAA (>10).
Figure 2. Respiratory mortality (%) according to airway wall thickness tertiles and %LAA categories. N = 947 subjects from the GenKOLS study 2003-05.
Figure 3. Number of months survival for estimated population percentiles* in all-cause mortality from baseline through June 2011 according to GOLD stages and %LAA categories, N = 947 subjects from the GenKOLS study 2003-05.

*Estimated percentile: 4 percentile for all-cause mortality
Table 2. Univariate analyses of predictors for all-cause, respiratory, cardiovascular, cancer and lung cancer mortality from baseline through June 2011, Laplace regression. N = 947 subjects from the GenKOLS study 2003-05. Coefficients (95% CI) represent the change in the number of survival months for the estimated percentile* corresponding to one-unit increase of the predictors.

*Estimated percentiles: 4 percentile for all-cause mortality, 0.3 percentile for respiratory and cardiovascular mortality, and 1.5 percentile for cancer and lung cancer mortality. For reference categories in categorical variables, coefficient represents number of months survival and for the other categories, coefficients represent number of months more/less survival relative to the reference category. For continuous variables, coefficients represent number of months survival with every increase in the continuous variable. Numbers in bold font type differ from reference categories with statistical significance (p<0.05).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>All-cause (95% CI)</th>
<th>Respiratory (95% CI)</th>
<th>Cardiovascular (95% CI)</th>
<th>Cancer (95% CI)</th>
<th>Lung cancer (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>37 (21, 52)</td>
<td>11 (-8, 30)</td>
<td>11 (-26, 48)</td>
<td>30 (10, 50)</td>
<td>43 (3, 83)</td>
</tr>
<tr>
<td>Men</td>
<td>-9 (-25, 8)</td>
<td>-6 (-28, 16)</td>
<td>1 (-43, 45)</td>
<td>3 (-27, 34)</td>
<td>-12 (-49, 25)</td>
</tr>
<tr>
<td>Subjects without COPD</td>
<td>93 (84, 101)</td>
<td>92 (43, 142)</td>
<td>93 (84, 102)</td>
<td>72 (49, 95)</td>
<td>99 (77, 122)</td>
</tr>
<tr>
<td>COPD cases</td>
<td>-73 (-83, -63)</td>
<td>-88 (-141, -36)</td>
<td>-86 (-93, -79)</td>
<td>-49 (-76, -21)</td>
<td>-76 (-103, -50)</td>
</tr>
<tr>
<td>FEV1 % predicted (post-bd)</td>
<td>1.3 (1.0, 1.6)</td>
<td>1.6 (0.7, 2.5)</td>
<td>1.6 (1.1, 2.2)</td>
<td>0.8 (0.0, 1.6)</td>
<td>1.1 (0.6, 1.7)</td>
</tr>
<tr>
<td>Age</td>
<td>-3 (-4, -3)</td>
<td>-2 (-4, -1)</td>
<td>-5 (-6, -3)</td>
<td>-3 (-4, -2)</td>
<td>-3 (-5, -2)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>24 (18, 31)</td>
<td>4 (-3, 11)</td>
<td>7 (-18, 32)</td>
<td>31 (23, 39)</td>
<td>31 (11, 51)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>12 (3, 21)</td>
<td>25 (7, 43)</td>
<td>14 (-11, 40)</td>
<td>17 (-9, 42)</td>
<td>1 (-31, 34)</td>
</tr>
<tr>
<td>Age of smoking onset</td>
<td>0 (-1, 1)</td>
<td>1 (1, 2)</td>
<td>1 (1, 2)</td>
<td>1 (-1, 2)</td>
<td>1 (-2, 4)</td>
</tr>
<tr>
<td>Pack years</td>
<td>-0.6 (-1.1, -0.1)</td>
<td>0.1 (-0.5, 0.7)</td>
<td>0 (-1, 1)</td>
<td>-0.6 (-1.1, -0.3)</td>
<td>-0.9 (-1.5, -0.3)</td>
</tr>
<tr>
<td>Body mass index BMI</td>
<td>1 (-1, 3)</td>
<td>5 (2, 9)</td>
<td>3 (-1, 7)</td>
<td>3 (-0, 7)</td>
<td>1 (-4, 6)</td>
</tr>
<tr>
<td>%LAA &lt; 3</td>
<td>79 (63, 95)</td>
<td>78 (58, 97)</td>
<td>76 (57, 96)</td>
<td>75 (56, 93)</td>
<td>79 (67, 92)</td>
</tr>
<tr>
<td>%LAA ≥3 - &lt;10</td>
<td>-56 (-71, -41)</td>
<td>-69 (-90, -48)</td>
<td>-67 (-94, -41)</td>
<td>-47 (-77, -17)</td>
<td>-52 (-85, -18)</td>
</tr>
<tr>
<td>%LAA ≥10</td>
<td>-67 (-88, -46)</td>
<td>-78 (-102, -54)</td>
<td>-72 (-91, -53)</td>
<td>-52 (-72, -31)</td>
<td>-56 (-83, -30)</td>
</tr>
<tr>
<td>AWT-P10, mm</td>
<td>-71 (-312, 170)</td>
<td>211 (-134, 556)</td>
<td>154 (-2, 309)</td>
<td>-107 (-481, 267)</td>
<td>-240 (-508, 28)</td>
</tr>
</tbody>
</table>

**In addition, inflation level was significantly related to all-cause mortality and lung cancer mortality, but not to respiratory, cardiovascular or cancer mortality.**
Mortality by level of emphysema and airway wall thickness

Ane Johannessen, Trude Duellen Skorge, Matteo Bottai, Thomas Blix Grydeland, Roy Miodini Nilsen, Harvey Coxson, Asger Dirksen, Ernst Omenaaas, Amund Gulsvik, Per Bakke.

ONLINE SUPPLEMENT

Regarding the classification of mortality outcomes and validation of the death certificates (in the Methods section):

Respiratory mortality was defined as main or underlying cause of death by International Classification of Disease, 10th revision (ICD-10) codes J40-47. Cardiovascular mortality ICD-10 codes I20-25. Cancer mortality ICD-10 codes beginning with the letter C, and lung cancer mortality ICD-10 code C34. All the death certificates were validated in a standardized way through comparison with the hospitals' patient files and other hospital records including laboratory, pathology and radiology data {McGarvey, 2012 #211}. Two subjects with death (ICD-10 code R98) and left ventricular failure (ICD-10 code I501) were corrected to COPD with acute lower respiratory infection (ICD-10 code J440) and COPD unspecified (J449), respectively, and thus were categorized as respiratory deaths. One subject listed with lung cancer was corrected to mesothelioma (ICD-10 code C450) and consequently removed from the lung cancer mortality group in the analyses.

Regarding the descriptive analyses in Table 1:
Table 1 describes baseline characteristics by mortality status of participants in the GenKOLS study 2003-05, N = 947 subjects. Usually we would have performed chi square tests for categorical variables and t tests for continuous variables in this kind of table. However, since subjects are not randomly assigned to the alive or deceased categories, this would not be appropriate here. Instead, we performed Monte Carlo permutation tests to obtain the p-values listed in Table 1, using the “permute” procedure in Stata, following univariate logistic regression analyses to assess if mortality status depended on the value of each of the covariates.
E-TABLES

E-Table 1. Associations between %LAA and mortality outcomes (all-cause, respiratory, cardiovascular, cancer, lung cancer) from baseline through June 2011, adjusted for univariate significant predictors*. Laplace regression, subanalyses based on the GenKOLS study 2003-05. N = 762 subjects without COPD or with COPD in GOLD stage 2, and 462 subjects with GOLD severity stage 2 or more severe.

<table>
<thead>
<tr>
<th></th>
<th>Non-COPD + GOLD stage 2</th>
<th>COPD GOLD stages 2 - 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival difference months (95% CI) †</td>
<td>Survival difference months (95% CI) †</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>%LAA &lt; 3: Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥3 - &lt;10: -8 (-34, 18)</td>
<td>-19 (-45, 7)</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥10: -10 (-40, 20)</td>
<td>-15 (-34, 4)</td>
</tr>
<tr>
<td>Respiratory mortality</td>
<td>%LAA &lt; 3: Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥3 - &lt;10: -63 (-96, -31)</td>
<td>-36 (-72, 0)</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥10: -43 (-87, 2)</td>
<td>-20 (-44, 3)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>%LAA &lt; 3: Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>mortality</td>
<td>%LAA ≥3 - &lt;10: -36 (-79, 6)</td>
<td>-33 (-64, -2)</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥10: -24 (-80, 33)</td>
<td>-47 (-86, -8)</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>%LAA &lt; 3: Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥3 - &lt;10: -10 (-49, 30)</td>
<td>-7 (-47, 32)</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥10: -8 (-48, 32)</td>
<td>-3 (-34, 27)</td>
</tr>
<tr>
<td>Lung cancer mortality</td>
<td>%LAA &lt; 3: Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥3 - &lt;10: -6 (-52, 40)</td>
<td>-7 (-42, 28)</td>
</tr>
<tr>
<td></td>
<td>%LAA ≥10: 31 (-35, 96)</td>
<td>0 (-31, 32)</td>
</tr>
</tbody>
</table>

* The model for all-cause mortality is adjusted for sex, interaction between sex and %LAA, COPD status, post-bronchodilator FEV1 % predicted, age, smoking status and inflation level. The model for respiratory mortality is adjusted for COPD status, post-bronchodilator FEV1 % predicted, smoking status, and BMI. The model for cardiovascular mortality is adjusted for COPD status, post-bronchodilator FEV1 % predicted, and age. The model for cancer mortality is adjusted for COPD status, age and post-bronchodilator FEV1 % predicted. The model for lung cancer mortality is adjusted for COPD status, post-bronchodilator FEV1 % predicted, age, pack years and inflation level.
† Coefficient estimated for 4 percentile (all-cause mortality), 0.3 percentile (respiratory and cardiovascular mortality), and 1.5 percentile (cancer and lung cancer mortality). Numbers in bold font type differ from reference categories with statistical significance (p<0.05).
E-FIGURES

**E-figure 1.** Quantile plot of the distribution of % LAA in the study population, with reference lines illustrating the cut-offs defining low, medium and high %LAA. N = 947 subjects from the GenKOLS study 2003-05.

![Quantile plot](image)

**E-Figure 2.** Number of months survival for estimated population percentiles* in all-cause mortality, respiratory mortality and cardiovascular mortality from baseline through June 2011 according to %LAA categories, N = 947 subjects from the GenKOLS study 2003-05.

![Survival graph](image)

*Estimated percentiles: 4 percentile for all-cause mortality, 0.3 percentile for respiratory mortality, 0.3 percentile for cardiovascular mortality.
**E-Figure 3.** Number of months survival for estimated population percentiles* in all-cause mortality, respiratory mortality and cardiovascular mortality from baseline through June 2011 according to GOLD stages, N = 947 subjects from the GenKOLS study 2003-05.

*Estimated percentiles: 4 percentile for all-cause mortality, 0.3 percentile for respiratory mortality, 0.3 percentile for cardiovascular mortality.*