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Dyspnea as predictor of cause-specific heart/lung disease mortality in Bangladesh: a prospective cohort study

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Abstract

Background—The spectrum of mortality outcomes by cause in populations with/without dyspnea has not been determined. The study aimed to evaluate whether dyspnea, a symptom, predicts cause-specific mortality differences between groups. The hypothesis was that diseases that result in chronic dyspnea, those originating from the heart and lungs, would preferentially result in heart and lung disease mortality in those with baseline dyspnea (relative to no dyspnea) when followed over time.

Methods—A population-based sample of 11,533 Bangladeshis was recruited and followed for 11–12 years and cause-specific mortality evaluated in those with and without baseline dyspnea. Dyspnea was ascertained by trained physicians. The cause of death was determined by verbal

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autopsy. Kaplan-Meier survival curves, the Fine-Gray competing risk hazards model and logistic regression models were used to determine group differences in cause-specific mortality.

Results—Compared to those not reporting dyspnea at baseline, the adjusted hazard ratios were 6.4 (3.8-10.7), 9.3 (3.9-22.3), 1.8 (1.2-2.8), 2.2 (1.0-5.1) and 2.8 (1.3-6.2) for greater risk of dying from COPD, asthma, heart disease, tuberculosis and lung cancer, respectively. In contrast, there was a similar risk of dying from stroke, cancer (excluding lung), liver disease, accidents and other (miscellaneous causes) between the dyspneic and nondyspneic groups. In addition, the hazard ratio was 2.1 (1.7-2.5) for greater all-cause mortality in those with baseline dyspnea versus no dyspnea.

Conclusions—Dyspnea, ascertained by a single question with binary response, predicts heart and lung disease mortality. Individuals reporting dyspnea were 2 to 9-fold more likely to die of diseases that involve the heart and/or lungs relative to the nondyspneic individuals. Therefore, in those with chronic dyspnea, work-up to look for the five common dyspneic diseases resulting in increased mortality (COPD, asthma, heart disease, tuberculosis and lung cancer), all treatable, should reduce mortality and improve the public health.

Keywords

Dyspnea and cause-specific mortality; dyspnea and cardiovascular mortality; dyspnea and longitudinal studies; breathlessness predicts mortality outcomes

INTRODUCTION

Dyspnea, an uncomfortable subjective breathing sensation^{1,2}, is reproducible^{1,3}, and has been shown to be associated with an increase in cardiovascular^{4,5,6} and all-cause^{4,7-13} mortality in prospective studies done in developed countries. No studies have evaluated dyspnea as the exposure with mortality as the outcome in an undeveloped country. More importantly, dyspnea as a symptom has been demonstrated to be associated with an approximate 2-fold increase in all-cause and cardiovascular disease mortality⁴⁻¹³ over a decade. In addition, dyspnea is easy to elicit by questionnaire^{1,3,14} and is often detected in subjects without known disease¹⁵. Therefore, from a public health perspective, dyspnea is of great importance since early elicitation of the symptom will result in faster action to determine cause with a subsequent reduction in mortality.

No prospective studies have evaluated dyspnea as the exposure and cause-specific mortality as the outcome with separation of lung and heart diseases and all diseases into multiple separate outcome categories. In addition, cardiovascular disease has always included both heart disease and cerebrovascular disease together^{5,6,12}, instead of evaluating these diseases separately. With dyspnea as the exposure, the separation of cardiovascular disease may be important since heart disease (and not stroke) is more likely to be associated with dyspnea. The question, “What diseases result in death with dyspnea as the exposure (relative to no dyspnea at baseline)?”, is obviously a very important public health question. Delineating the most likely causes of death, when one has dyspnea, allows a focused work-up to look for these diseases, diagnose them early, and reduce subsequent mortality.

The primary objective was to evaluate whether or not dyspnea would be associated with an increase in cause-specific mortality types between groups. A minor objective was determination of all-cause mortality between dyspnea groups.

METHODS

Data source and approvals

Baseline data was obtained from the Health Effects of Arsenic Longitudinal Study (HEALS).¹⁶ This study area is about 183 km² in Araihaazar, Bangladesh, about 25 km southeast of Dhaka, the capital city. The area was picked because it has a homogeneous sociocultural population with an arsenic well water exposure distribution between 0.1 ug and 864 ug/L. Procedures were approved by the Bangladesh Medical Research Council (Dhaka, Bangladesh) and institutional review boards of Columbia University (New York) and the University of Chicago (Chicago, IL). Details of data collection have been previously published.^{16,17}

Participants selection and the exposure variable dyspnea

Baseline data was obtained **from** October of 2000 until May, 2002. The data was collected from adults aged 18-75 years, married since they are more stable and less likely to move out of the study area and resident in Araihaazar, Bangladesh, for 5 years. All of the subjects were selected who were drinking out of one of 5966 wells that had been evaluated for arsenic concentrations. Given the above requirements (adult, married, living in area for 5 years, drinking from wells with measured arsenic concentrations) the goal of sampling was to select 1/3 from wells with arsenic concentrations > 100 ug/L (actual 37.34%), 1/3 from wells with 25 to 100 ug/L (actual 30.49%), and 1/3 from wells with < 25 ug/L (actual 32.16%)¹⁶.

After obtaining consent, a 45 minute in-person interview by trained study physicians collected demographics including age, sex, educational attainment (0-16 years), occupational history, and smoking (past, present, and never). Vital signs including blood pressure, height, and weight were measured and BMI was calculated. A baseline clinical exam included an assessment for arsenic related skin lesions. The baseline data collection instrument was 18 pages.

The exposure variable dyspnea was determined at baseline by trained physicians asking the question "During the last 6 months, have you had dyspnea?" Elicitation of the presence or absence of dyspnea in this population has a reliability of > 90% as previously determined.¹ The subjects were asked this question during the resting state in Bengalese by Bengali doctors. The goal of the study was detection of persistent dyspnea (chronic dyspnea) any time in the last 6 months. Dyspnea was recorded as a simple dichotomous (yes/no) response.

Assessment of cause-specific mortality

A verbal autopsy questionnaire, validated by the International Centre for Diarrheal Disease Research, Bangladesh, was used to evaluate and assign a cause of death.¹⁸ A trained physician interviewed family members and/or informants of the decedents in-person to fill

out the verbal autopsy questionnaire. Autopsies were reviewed by a group of expert physicians, and a cause of death assigned /coded by the International Classification of Diseases (ICD-10). Deaths were attributed to chronic obstructive pulmonary disease (COPD) with ICD-10 J43 and J44, asthma with ICD-10 J45 and J46, lung cancer ICD-10 C34, cancer not lung ICD-10 C00 to D48 (excluding C34); cerebrovascular disease (stroke) ICD-10 I61, I63, I64, and I69; sudden death ICD-10 R96; Tuberculosis ICD-10 A15, A16, A17, A18 and B90; liver disease ICD-10 K 70 to K76; pulmonary heart disease ICD-10 I27.9; ischemic heart disease (IHD) ICD-10 I20 to I25; all heart disease (includes IHD but not pulmonary heart disease) ICD-10 I00 to I25; accidents ICD-10 V01 to V09 and W01 to W87. Other causes of death were ICD-10 coded but included many less common diagnosis such as tetanus, meningitis, obstetric complications, probable assault, suicide, etc.

Pulmonary heart disease or Cor Pulmonale (chronic) was defined as disease of the heart from pulmonary hypertension secondary to diseases of the lungs, or its blood vessels, with right ventricular hypertrophy. Right heart failure in the absence of left heart failure is a common consequence.

Follow-up time was calculated as the number of days between baseline interview and date of death or, if alive, date of the last interview or report of being alive; such participants were censored.

Laboratory Analysis

Arsenic concentrations in well water were analyzed at the Geochemistry Research Laboratory of Columbia University by graphite furnace atomic absorption (GFAA).¹⁹ The limit of detection for GFAA was 5 ug/L. Water concentrations from samples at the detection limit were re-analyzed by inductively coupled plasma mass spectrometry with a detection limit of 0.1 ug/L.²⁰

Study covariates

Sociodemographic factors measured included age, sex, and years of education. Self-reported smoking status was classified as never/ever. Arsenic well water concentrations were measured once at baseline since the cohort was in geographic area with known elevated concentrations of arsenic in groundwater.²¹ The study physicians measured height, weight, and blood pressure at the baseline interview.

Statistical analysis

The Pearson Chi Square test analyzed categorical data and the independent samples t-test evaluated continuous data (table 1).

Kaplan-Meier survival curves were used to display mortality over time in those with and without dyspnea. The logrank test looked for differences between groups.

The **log minus log plot** of the survival curve was **graphed** to check the Cox Proportional Hazards (PH) assumption for different groups of subjects.

For cause-specific mortality the Cox PH model was modified using the Fine-Gray competing risks method^{22,23} to estimate the hazard ratios (HR) between those with dyspnea and those without dyspnea by cause of death if applicable (table 2). Oftentimes, for cause specific mortality a constant hazard between groups was not found and the Cox PH model could not be used. Here, a logistic regression model helped to determine if differences might exist between all thirteen diagnostic groups (table 3).

For all-cause mortality the Cox PH model (table 4) was used to estimate HR between those with dyspnea at baseline and those without dyspnea. Model 1 compared crude mortality between groups using dyspnea presence or absence. Model 2 adjusted for age (years). Model 3 included adjustment for age, gender (female as referent), education (continuous), systolic blood pressure, BMI (dichotomous with normal of 18.5 to 24.99 as referent), smoking (referent as nonsmoker), and arsenic well water concentration (continuous).

Interaction was evaluated between dyspnea and arsenic, gender, hypertension, and smoking. All variables were changed if needed to dichotomous and product terms were used.

A p value less than 0.05 was considered significant. Analysis was performed with SPSS version 21 (SPSS Inc., Chicago, IL). Risks when expressed are as HR with 95% confidence intervals.

RESULTS

Table 1 summarizes baseline demographics of the dyspneic and nondyspneic populations. The average age was 37.0 ± 10.1 years. Those with dyspnea were older, had less education, and were exposed to higher arsenic well water concentrations. The prevalence of dyspnea was 7.9%. The average study follow-up was 11.2 years. There were 11,746 adult subjects enrolled at baseline with 11,533 subjects correctly coded for dyspnea who were included for data analysis in this study. There were 761 deaths during 11.2 years in 11,533 individuals. The distribution of deaths by cause is listed in table 3. The person-years of follow-up was 120,071 in those without dyspnea and 9,864 in those with dyspnea. The median time from death to filling out the verbal autopsy was 2 months.

The Kaplan-Meier survival curve as seen in Figure 1A showed a clear separation between groups. The logrank test found a significant difference between groups ($p < 0.001$). Similar results were found for all eight diagnostic groups in table 2 (data not shown). Figure 1B is the **log minus log plot versus survival time** using all data to test the Cox PH assumption. The difference is consistent with meeting the PH assumption that the hazard between groups is constant over time. This validates the use of the PH model with the data.

Cause specific mortality was compared between those with and without dyspnea in table 2. Causes of death by the COX PH model were limited to those with a significant logrank test as seen in table 2. Subjects with dyspnea at baseline were significantly more likely to die of diseases that affect the heart and/or lungs (COPD, asthma, tuberculosis (TB), heart disease, lung cancer, and pulmonary heart disease) compared to subjects without dyspnea with hazard ratios of two or greater. In addition, sudden death tended toward significance with a HR greater than two but the analysis was limited by small numbers.

Table 3 summarizes all thirteen diagnoses by odds ratio (OR) comparing dyspnea versus no dyspnea. Cancer not involving the lung, stroke, liver disease, renal disease, accidents, and other (mixture of diseases) were not significantly different between groups. Sudden death was also not significant but was suggestive with the large HR (table 2) and/or OR (table 3).

Associations between dyspnea and all-cause mortality from the Cox PH model for all subjects are summarized in table 4A. To eliminate any confounding secondary to smoking, an analysis was done in nonsmokers (table 4B). To eliminate the potential bias of the very sick being included at baseline with a potential weighting favoring the dyspneic group, the data was re-analyzed after eliminating deaths occurring in the same year after enrollment. The adjusted HR was 2.07 (1.71 – 2.51), revealing no difference compared to the total population from table 4A.

Analysis was also stratified by gender with similar results (table 1, online supplementary appendix). Again, both crude and adjusted HRs were consistent with an approximately 2-fold greater all-cause mortality in those with dyspnea.

Interaction was not found between dyspnea and any covariate.

DISCUSSION

Chronic dyspnea was associated with a significant increase in cause-specific mortality from diseases that affect the heart and lungs (table 2). In particular, those with dyspnea at baseline had a 6 to 9-fold greater risk of dying from pulmonary heart disease, COPD, or asthma relative to those without dyspnea. At worst, those with dyspnea had a 1.8 to greater than 2.8-fold risk of death over 11-12 years from heart disease, TB and lung cancer, respectively, compared to those without dyspnea. Two previous studies lumped all chronic respiratory diseases together and found adjusted rate ratios of 7.9 (5.7-11.1) and 4.2 (2.6-6.6), consistent with some of our results but did not specify individual lung diseases.^{6,24} Therefore, comparison between studies was not possible.

There was a 2.56-fold greater risk of sudden death in those with dyspnea. Sudden death, defined as nonviolent death occurring within 24-hours from onset, is felt to be secondary to cardiac disease about 50% of the time.²⁵ Therefore, occult heart disease related dyspnea might be the explanation for the sudden death findings in some cases implying a possible underestimation of the 2-fold greater risk of death in those with dyspnea who die of heart disease. Also, pulmonary heart disease revealed a significant 5.8-fold greater risk of death in those with dyspnea, but results were limited by small numbers. This category could have been combined with all heart disease making heart diseases findings more robust. In contrast, subjects with a stroke, liver disease, cancer not primarily from the lung, accidents, and those with the category of other (a mixture of many diseases), showed no increase in mortality between the dyspneic and nondyspneic groups.

COPD primarily results from smoking and smoking is the number one preventable cause of death in the U.S. and world-wide.²⁶ Converting the COPD deaths to cause-specific mortality per year of follow-up gives **274** deaths per 100,000 per year for those with dyspnea and 27

deaths per 100,000 per year for those without dyspnea. Therefore, if one has dyspnea with COPD in Bangladesh the excess death rate per 100,000 per year would be **247**.

One other study in a developed country evaluated cause-specific mortality related to COPD and found after control for lung function a 3.3-fold greater risk of death¹² in those with severe dyspnea (dyspnea grade 5). This same study found risks of dyspnea without control of lung function of 2.3 (1.5 – 3.6) and 9.3 (3.9 – 14.6) for grade 3/4 and severe dyspnea, respectively.¹² These HRs are similar to the current study with a risk of COPD mortality of 6.4 (3.8 – 10.7). The current study did not control for lung function. Despite this, the HRs of death from COPD in those without adjustment for lung function are similar in both the current and recent study¹², lending credibility to our study findings. In addition, one study in subjects with COPD and an average FEV₁/FVC ratio as percentage of 43.0 ± 10.4 evaluated survival by ATS FEV₁ stages versus dyspnea grades 1 through V.²⁷ The study found a better prediction of survival by dyspnea grade than by staging of disease severity by FEV₁.²⁷ This further suggests that dyspnea is a predictor of mortality in COPD and is consistent with our study results.

Dyspnea has been associated with increased cardiovascular disease mortality.^{4,5,6,12,24,28} Cardiovascular disease is the rubric under which cerebrovascular disease and heart disease are included. Based on the current study findings of a 1.88 (1.24 – 2.84)-fold greater risk of heart disease death in those with dyspnea at baseline and null dyspnea-stroke association, it appears that in previous studies^{5,6,12,24,28} the driving force behind increased cardiovascular disease mortality was heart disease and not stroke. Had previous studies separated cardiovascular disease into stroke and heart disease, undoubtedly the heart disease risk would have been much higher and the stroke risk would not have been significant.^{5,6,12,24,28} Two previous studies detected a weak dyspnea-stroke disease association.^{24,28} However, neither study used competing risk proportional hazards analysis which tends to reduce elevated hazard ratios and one study did not control for hypertension²⁸, a strong stroke risk factor. Therefore, it is unlikely dyspnea is associated with cerebrovascular disease.

Limitations include the observational nature of the study which could always mean that uncontrolled confounding produced the results. Although possible, the biologic plausibility of dyspneic diseases resulting in mortality secondary to diseases of the heart and lungs make this less likely. Another limitation is lack of medical certification of death which occurs for less than one third of the 57 million world-wide annual deaths.²⁹ In less developed countries, the verbal autopsy (a medical questionnaire filled out by a trained expert who goes into the field and interviews those who were close to the subject who died and knew the circumstances leading up to death) is felt to be the “next” best available determination of death, particularly if adjudicated by a panel of physicians (after the verbal autopsy is filled out).²⁹ The validity of a verbal autopsy can be up to 80% for common causes of death when a physician fills out the verbal autopsy which is then compared to a panel of physicians who get more information as done in one cohort study.³⁰ In this study, the verbal autopsy was filled out by a physician and cause of death was then adjudicated by a panel of physicians before an ICD-10 cause of death was determined from the evidence. Therefore, considering the reduced resources in Bangladesh, we feel the most accurate cause of death that could be ascertained was determined in this study. Finally, it is always possible that biomass fuels

were responsible for some of the deaths from COPD as well as smoking.³¹ Since there are 1.1 billion smokers and 3 billion people exposed to biomass fuels world-wide, it is felt a lot of COPD may occur in those exposed to biomass fuels, particularly in developing countries.³² One summary study found a 2.55 (2.06 – 3.15)-fold greater odds of COPD in nonsmokers exposed to biomass fuels, relative to those not exposed to biomass fuels who were not smokers.³¹ The verbal autopsy takes smoking exposure into account when determining cause of death. Therefore, we believe the majority of our COPD deaths were smoking related or less likely smoking and biomass fuel exposure related, and undoubtedly the diagnosis of COPD deaths in nonsmokers was significantly underestimated.

Strengths include the population-based, large sample size and a long follow-up time making it more likely a difference would be found (if present) since the number of deaths is large. A particular strength is the specific blinded determination of cause of death made in all subjects by verbal autopsy¹⁸, adjudicated by physicians and coded by the ICD-10 system. The physicians doing the autopsies were unaware of the study. Another strength is that a general population sample was evaluated, not an occupational cohort, eliminating the healthy worker effect as an issue related to survival. This study was done in a developing country in contrast to all other studies done with dyspnea as the exposure done in developed countries. Despite the setting, the study validates the powerful nature of the symptom of dyspnea as a predictor of both cause-specific and all-cause mortality, no matter how (simple question) or where (undeveloped country) it is elicited. Finally, this study further validates the gender independence of dyspnea as a predictor of all-cause mortality as suggested by smaller studies.^{9,10,12}

There are several novel findings in this study. This is the first study to demonstrate that many lung and heart diseases such as asthma, heart disease separated from cardiovascular disease, lung cancer, TB, and possibly sudden death and pulmonary heart disease that often have dyspnea as part of their disease symptomatology are all associated with an increase in cause-specific mortality. For COPD, this is the second definitive longitudinal study after Figarska's et.al.¹² Previous studies have suggested that dyspnea is associated with cardiovascular mortality^{4,5,6,12,24,28} but either have not separated out heart disease from stroke^{4,5,6,12} or have statistical analytic limitations^{24,28}. Heart disease and not stroke appears to be responsible for the increase in cardiovascular mortality. Finally and re-assuringly, this is the first study to demonstrate that dyspnea is a predictor of all-cause mortality in a developing country. Theoretically, but unlikely with dyspnea, one could have an increase in cause-specific mortality without an increase in all-cause mortality.^{33,34} Those with dyspnea at baseline had an overall mortality rate of 1409 deaths per 100,000 per year relative to those without dyspnea with a mortality rate of 518 deaths per 100,000 per year.

This study should be generalizable to any developing country with limited health resources. The spectrum of increased dyspnea outcomes relative to subjects without dyspnea will probably be similar to those of developing countries with the exception of TB. Developed countries will likely have earlier diagnosed TB and hardly any with chronic dyspnea from TB. Other dyspneic diseases should be similar to all countries, particularly since smoking is common to all countries and is associated with many outcomes in those with dyspnea as seen from table 2.

From a public health standpoint, this study suggests that treating diseases with chronic dyspnea, if diagnosed early, might result in large mortality reductions. Using COPD as an example, in Bangladesh there was an estimated **247** more deaths per 100,000 per year in those with dyspnea compared to no dyspnea. Bangladesh is eighth in the world in terms of total smokers.^{35,36} In addition, it has been estimated that 25% of male deaths and 7% of female deaths in Bangladesh are at least partly smoking related.³⁷ This makes the high COPD death rate in those with dyspnea in Bangladesh understandable.

In conclusion, this study delineates the spectrum of diseases that result in mortality with breathlessness as a chronic symptom. In contrast, individuals without baseline dyspnea are equally likely to die of diseases not related to the heart and lungs. From both a public health and clinical perspective, those with chronic dyspnea should be targeted for early diagnostic evaluation. Most of the chronic diseases associated with dyspnea that result in early mortality are amenable to treatment. Earlier detection and treatment should reduce both heart and lung disease mortality. Specifically, in those with dyspnea, work-up to determine etiology should include a chest imaging study, a measure of oxygenation such as pulse oximetry, and tests of lung function or cardiac function, depending on history.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known on the subject?

Dyspnea is a known predictor of all-cause mortality and has also been associated with an increase in cardiovascular disease mortality which includes stroke.

What this study adds?

The spectrum of disease that dyspnea preferentially predicts for higher mortality has not been previously delineated in any studies until now.

Dyspnea predicts a higher mortality for only one aspect of cardiovascular disease, not all cardiovascular disease.

Knowing the common causes of mortality that occur with chronic dyspnea should help health practitioners screen for and treat dyspneic diseases at an earlier stage. Earlier detection and treatment should reduce mortality.

A.

B.

Figure 1.

A. A Kaplan-Meier survival curve of the total population over 11 to 12 years for all-cause mortality (**expressed as person days**). The logrank test revealed a significant difference between curves with a p value less than 0.001.

B. A **Log minus Log plot versus survival time** to test the Cox Proportional Hazard assumption with all data. The average hazard between groups was approximately constant and consistent with the proportional hazards assumption.

Table 1

Baseline demographic characteristics of subjects with and without dyspnea.

	Dyspnea	No Dyspnea	p value
Subjects	913	10620	
Age (yrs)	40.1 (10.1)	36.7 (10.1)	< 0.01
Sex			
Female	519 (56.8%)	6080 (57.3%)	= 0.81 [#]
Male	394 (43.2%)	4540 (42.7%)	
Smoking			
Nonsmoker	520 (57.0%)	6920 (65.2%)	< 0.01 [#]
Ex-smoker	98 (10.7%)	665 (6.3%)	
Smoker	292 (32.0%)	3028 (28.5%)	
Missing	3 (0.3%)	8 (0.0%)	
Education (yrs)	2.8 (3.6)	3.5 (3.9)	< 0.01
BMI	19.5 (3.6)	19.8 (3.1)	= 0.049
Systolic BP (mm hg)	115.0 (17.9)	114.7 (17.9)	= 0.57
Arsenic Conc. (ug/L)	113.0 (120.0)	100.4 (115.1)	< 0.01

Baseline data in this table was collected between October 2000 and May 2002.

[#] Chi Square, all other comparisons were by the nonpaired t-test. BMI = body mass

Index. BP = blood pressure. % = percent in the column with total number (n). A value in parenthesis () is the standard deviation with the mean preceding it for age,

education, BMI, systolic BP, and arsenic conc.

Table 2

Cause Specific Mortality Hazard Ratios (HR) by Diagnosis at Time of Death comparing Dyspnea versus no Dyspnea.

Disease	Crude HR	*Adjusted HR	p value, adjusted HR	Hazard Rates per 100,000/yr
COPD	9.88 (5.92 – 16.48)	6.39 (3.81 – 10.72)	< 0.001	Dys: 273.7 No Dys: 26.6
Asthma	15.63 (6.58 – 37.08)	9.31 (3.88 – 22.34)	< 0.001	Dys: 121.6 No Dys: 7.5
Heart Disease	2.55 (1.70 – 3.80)	1.88 (1.24 – 2.84)	< 0.01	Dys: 294.0 No Dys: 110.8
Pulmonary Heart Disease	7.76 (2.19 – 27.48)	5.80 (1.60 – 21.03)	< 0.01	Dys: 40.6 No Dys: 5.0
Sudden Death	3.32 (1.09 – 10.09)	2.56 (0.83 – 7.93)	p = 0.10	Dys: 40.6 No Dys: 11.7
Tuberculosis	3.43 (1.56 – 7.55)	2.27 (1.02 – 5.05)	< 0.05	Dys: 81.1 No Dys: 22.5
Lung Cancer	4.01 (1.88 – 8.56)	2.85 (1.32 – 6.16)	< 0.01	Dys: 91.2 No Dys: 21.7
Cancer, not Lung	1.74 (0.95 – 3.18)	1.36 (0.74 – 2.51)	p = 0.33	Dys: 121.7 No Dys: 66.6

* Adjusted for age, gender, arsenic well water concentration, education, blood pressure, BMI, and smoking. Cancer, not lung with significant difference between curves by logrank test but no difference when analyzed by Fine-Gray competing hazards models as seen here. Stroke, renal disease, liver disease, accidents, and other (miscellaneous causes of death) were not included in this table since the log minus log plot did not reveal a constant hazard between groups and the log rank test was not significant for a difference between groups. **Calculated HR from the true hazard rates will be higher than the crude HR seen. This occurs since the Fine-Gray analysis results in lower HRs overall. Dys = Dyspnea, No Dys = No Dyspnea.**

Table 3

Dyspnea and its relation to cause specific mortality – odds ratios (OR)

Diagnosis n=death number; deaths exposed	Crude Odds Ratio	#Adjusted Odds Ratio	p value, adjusted OR
COPD, n =59; 27 with dyspnea	10.08 (6.01 – 16.91)	6.78 (3.97 – 11.58)	< 0.001
Asthma, n=21; 12 with dyspnea	15.70 (6.60 – 37.37)	9.52 (3.92 – 23.11)	< 0.001
Heart Disease, n=162; 29 with dyspnea	2.59 (1.72 – 3.89)	1.97 (1.28 – 3.02)	< 0.01
Pulmonary Heart Disease, n=10; 4 with dyspnea	7.78 (2.19 – 27.64)	5.85 (1.60 – 21.36)	< 0.01
Sudden Death, n=18; 4 with dyspnea	3.33 (1.10 – 10.15)	2.36 (0.75 – 7.41)	p = 0.14
Tuberculosis, n=35; 8 with dyspnea	3.47 (1.57 – 7.66)	2.32 (1.03 – 5.21)	< 0.05
Lung Cancer, n=35; 9 with dyspnea	4.06 (1.90 – 8.68)	2.92 (1.34 – 6.37)	< 0.01
Cancer (not lung), n=92; 12 with dyspnea	1.75 (0.95 – 3.23)	1.37 (0.74 – 2.55)	p = 0.32
Stroke, n=137; 15 with dyspnea	1.44 (0.84 – 2.47)	1.01 (0.57 – 1.80)	p = 0.96
Liver Disease, n=36; 4 with dyspnea	1.46 (0.51 – 4.13)	1.14 (0.40 – 3.28)	p = 0.80
Renal Disease, n=15; 1 with dyspnea	0.83 (0.11 – 6.32)	0.82 (0.11 – 6.38)	p = 0.85
Accidents, n=19; 2 with dyspnea	1.37 (0.32 – 5.94)	0.67 (0.09 – 5.12)	p = 0.70
Other, n=122; 12 with dyspnea	1.27 (0.70 – 2.32)	1.03 (0.56 – 1.88)	p = 0.93

Adjusted for age, gender, arsenic well water concentration, education, blood pressure, BMI, and smoking. Other is the term for the combination of all other diseases ICD-10 coded that were in too small number to be listed as a separate category. The diseases of sudden death, pulmonary heart disease, renal disease and accidents have small numbers with more unstable estimates.

Table 4

Cox Regression Model with the primary exposure variable dyspnea and the primary outcome variable all-cause mortality. Table 4A includes the complete population of 11,533. Table 4B includes the complete nonsmoking population of 7440.

A (n = 11,533)	HR (95% C.I.)	p value
Model 1	2.73 (2.27 – 3.28)	< 0.001
Model 2	2.11 (1.76 – 2.54)	< 0.001
Model 3	2.10 (1.74 – 2.52)	< 0.001

B (n = 7,440)	HR (95% C.I.)	p value
Model 1	2.33 (1.62 – 3.35)	< 0.001
Model 2	1.91 (1.33 – 2.75)	< 0.001
Model 3	1.90 (1.32 – 2.74)	< 0.001

Adjusted for no covariates (Model 1); age only (Model 2); age, sex, water arsenic, education, systolic BP, BMI, and smoking status (Model 3).

Adjusted for no covariates (Model 1); age only (Model 2); age, sex, water arsenic, education, systolic BP, and BMI (Model 3).