Longitudinal changes in airway hyperresponsiveness and COPD mortality

To the Editor:

Airway hyperresponsiveness (AHR) is associated with an increased mortality risk among males [1] and chronic obstructive pulmonary disease (COPD) patients [2]. However, this association is largely based on cross-sectional studies using a single measurement of AHR to predict mortality; inherently ignoring the longitudinal variability of AHR. AHR is variable regardless of disease or medication status, and is linked with changes in smoking habits, seasonal variations and exposure to pollutants [3–5]. Considering this, it remains unclear how changes in AHR affect mortality, specifically from causes such as COPD, cardiovascular disease (CVD) and cancer.

We used data from the Vlagtwedde–Vlaardingen study (1965–1990) [6], a general population-based cohort of two communities in the Netherlands followed-up every 3 years. At all visits, AHR was measured using histamine biphosphate administered in increasing doses of 1, 4, 8, 16 and 32 mg·mL^{-1} for 30 s followed by lung function measurements. The provocation concentration (PC_{10}) which caused a steady reduction in inspiratory vital capacity (IVC) or forced expiratory volume in 1 s (FEV_1) of >10% compared to baseline was then considered as the threshold value. Data on weight, height, eosinophil count, smoking habits and respiratory symptoms were also collected at each follow-up period. Vital status of all participants including specific causes of death was updated on December 31, 2016 at Statistics Netherlands (The Hague, the Netherlands). The causes of death were coded according to the International Classification of Diseases (versions 7–10).

We classified AHR based on histamine threshold, with ⩽8 mg·mL^{-1} indicating positive AHR (responders) and >8 mg·mL^{-1} indicating negative AHR (non-responders) [7]. We then included subjects who had a minimum of two AHR measurements and categorised changes in AHR from baseline (first available measurement) to the last available measurement for each subject as: "never AHR" (if subjects were non-hyperresponsive at baseline and during follow-up), "persistent AHR" (if subjects were hyperresponsive at baseline and during follow-up), "remitting AHR" (if subjects were hyperresponsive at baseline, but became non-hyperresponsive during follow-up), "developing AHR" (if subjects were non-hyperresponsive at baseline but became hyperresponsive during follow-up) and "variable AHR" (if subjects did not have a specific trend in AHR, constituting all remaining subjects). We calculated subject-specific annual change estimates for continuous variables (body mass index (BMI), FEV_1, FEV_1/IVC ratio and eosinophil count) by taking the difference between the last and first available measurements and standardising this based on the number of years of follow-up. Changes in smoking and dyspnoea were used as defined previously [8, 9]. Asthma attacks were self-reported attacks of shortness of breath with wheezing in any of the visits.

The association between changes in AHR and all-cause and cause-specific mortality was estimated using a Cox proportional-hazards model. The time to event was defined from the last available AHR measurement until the date of death or censoring on December 31, 2016. We adjusted for lung function by including both baseline FEV_1 and the yearly change estimate of FEV_1 in the model. We also adjusted for other fixed (sex, place of residence, baseline age) and changing (BMI, eosinophil count, smoking status, dyspnoea and asthma attacks) covariates. For cause-specific mortality, subjects who died from causes other than the cause of interest were censored at the age of death and a competing risk analysis was performed [10]. Subjects who died due to external causes of death such as accidents and suicides were excluded from the analysis (n=18).

In total, 1464 subjects had at least two AHR measurements. Among these, 702 (47.9%) had died by the end of December 31, 2016 and only nine (0.6%) were lost to follow-up (table 1). Among those who died,

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TABLE 1 Characteristics of the participants classified by changes in airway hyperresponsiveness (AHR)

	Never AHR	Always AHR	Remitting AHR	Developing AHR	Variable AHR
Subjects	850 (58.1)	41 (2.8)	41 (2.8)	357 (24.4)	175 (12.0)
Male	479 (56.4)	25 (61.0)	23 (56.1)	215 (60.2)	104 (59.4)
Baseline age years	35.5±10.9	43.9±10.1	42.4±12.1	38.8±10.7	37.7±10.7
Baseline BMI kg·m^{-2}	24.9±3.5	26.4±4.1	26.3±3.9	25.6±3.3	25.6±2.7
Baseline FEV_1 L	3.38±0.75	2.52±0.67	2.67±0.80	3.13±0.66	3.08±0.76
Baseline FEV_1/IVC %	79.94±6.73	67.57±11.61	72.29±6.57	76.32±7.63	75.31±8.92
Baseline smoking status					
Never-smoker	272 (33.3)	8 (20.5)	12 (29.3)	93 (27.0)	54 (31.6)
Ex-smoker	130 (15.9)	5 (12.8)	5 (12.2)	47 (13.6)	16 (9.4)
Current smoker	415 (50.8)	26 (66.7)	24 (58.5)	205 (59.4)	101 (59.1)
Annual change in BMI kg·m^{-2}	0.1±0.2	0.1±0.2	0.1±0.3	0.1±0.2	0.1±0.2
Annual change in FEV_1 mL·year^{-1}	−19.3±39.2	−34.7±31.0	5.8±107.6	−30.7±28.7	−22.7±22.9
Annual change in FEV_1/IVC %·year^{-1}	−0.22±0.70	−0.49±0.88	0.08±1.04	−0.34±0.58	−0.17±0.45
Change in smoking status					
Persistent never-smoker	229 (27.3)	7 (17.9)	11 (26.8)	77 (22.0)	45 (25.9)
Persistent ex-smoker	139 (16.6)	5 (12.8)	6 (14.6)	47 (13.4)	22 (12.6)
Persistent current smoker	247 (29.4)	13 (33.3)	15 (36.6)	135 (38.6)	52 (29.9)
Quitter	136 (16.2)	9 (23.1)	8 (19.5)	52 (14.9)	38 (21.8)
(Re-)starter	34 (4.1)	2 (5.1)	0 (0.0)	14 (4.0)	6 (3.4)
Unstructured	54 (6.4)	3 (7.7)	1 (2.4)	25 (7.1)	11 (6.3)
Vital status					
Alive	479 (56.4)	9 (22.0)	14 (34.1)	169 (47.3)	82 (46.9)
Dead	365 (42.9)	32 (78.0)	27 (65.9)	185 (51.8)	93 (53.1)
Unknown	6 (0.7)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)
Causes of death					
COPD	8 (2.2)	6 (18.8)	3 (11.1)	5 (2.7)	6 (6.5)
CVD	120 (32.9)	11 (34.4)	9 (33.3)	64 (34.6)	31 (33.3)
Cancer	139 (38.1)	6 (18.8)	9 (33.3)	71 (38.4)	30 (32.3)
Other	98 (26.8)	9 (28.1)	6 (22.2)	45 (24.3)	26 (28.0)
Hazard ratios#					
All	1.00	0.96 (0.63–1.46)	0.95 (0.62–1.45)	0.95 (0.78–1.17)	1.18 (0.91–1.51)
COPD	1.00	6.07 (1.23–29.92)	1.35 (0.23–7.83)	1.05 (0.26–4.15)	4.56 (1.20–17.24)
CVD	1.00	1.09 (0.53–2.24)	0.80 (0.38–1.72)	1.07 (0.75–1.50)	0.85 (0.60–1.19)
Cancer	1.00	0.47 (0.19–1.14)	0.90 (0.44–1.84)	0.85 (0.60–1.19)	0.92 (0.59–1.42)

Data are presented as n (%), mean±SD or hazard ratio (95% CI). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; IVC: inspiratory vital capacity; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease. #: never AHR (referent).

28 (3.9%) died of COPD, 235 (32.6%) died of CVD and 255 (35.4%) died due to cancer. Deceased subjects had a higher prevalence of AHR, were more often smokers and had lower lung function levels at baseline. Subjects who died of COPD had more AHR at baseline (35.7%) than those who died of CVD (13.6%) or cancer (10.2%).

In the adjusted model, none of the four AHR-change categories, compared to never AHR, showed a statistically significant association with all-cause mortality. However, the adjusted cause-specific survival analysis showed a statistically significant association between changes in AHR and COPD mortality. Subjects with persistent AHR or variable AHR had a higher risk of dying of COPD compared to those who were never hyperresponsive. Specifically, throughout the observation period, subjects with persistent AHR were six times more likely to die of COPD (hazard ratio (HR) 6.07, 95% CI 1.23–29.92) and those with variable AHR were four times more likely to die of COPD (HR 4.56, 95% CI 1.2–17.24), both compared to those who never had AHR (table 1). We did not observe a significant association between changes in AHR and CVD or cancer mortality.

Cockcroft and Davis [11] classified components of AHR as persistent and transient, reflecting airway remodelling and airway inflammation, respectively. In our study, subjects with persistent AHR probably had irreversible airway remodelling. Repetitive stimuli and a constant activation of the repair process are mechanisms behind airway remodelling in COPD leading to airway wall thickening, decrease in airway lumen size and reduced airflow [12, 13]. These mechanisms can accelerate the progress of COPD and lead to premature death. Individuals with variable AHR probably present the transient component of AHR

characterised by airway inflammation [11]. This independence of airway restructuring and airway inflammation in COPD [14] suggests potentially distinct pathophysiological mechanisms behind individuals with persistent AHR and variable AHR.

Clinical management of airway inflammation may possibly "normalise" AHR and lower long-term mortality risk from COPD, but future studies should be performed to investigate this. In our study, subjects with remitting AHR did not have a higher risk of COPD mortality compared to the never AHR. This suggests that "losing" AHR over time can have a favourable outcome on the risk of COPD death, and possibly indicates the gradual attenuation of airway inflammation in some individuals [15]. This improvement of AHR can also be related to lifestyle changes including smoking cessation and use of medications to manage asthmatic symptoms. Compared to those who died of CVD or cancer, subjects who died from COPD had a higher prevalence of asthmatic symptoms (wheezing and asthma attack) at baseline.

A major strength of our study is the extensive follow-up with minimal attrition and the use of objective and standardised measurements. People with low lung function levels (FEV_1 <1.5 L) were excluded from AHR measurements. This is important to note since reduced FEV_1 is related to mortality and AHR, indicating that the results are best generalisable to those with good lung health. Although histamine provocation is no longer commonly used due to its adverse effects, it is very similar to a methacholine bronchoprovocation test [16]. A PC_{10} $\leqslant$8 mg·mL^{-1} in the 30-s protocol used in our study is comparable to a PC_{20} $\leqslant$4 mg·mL^{-1} in the 2-min protocol, which is the recommended cut-point for positive AHR [17]. We were not able to control for other possible confounders such as medication status and use of inhaled corticosteroids (which are shown to influence both AHR and COPD mortality), clinical data on lung phenotypes, airway calibre, occupational exposure and ambient air pollution. Finally, the use of administrative data for outcome assessment might have introduced some misclassification bias on the causes of death.

With a longitudinal cohort accruing 51 years of follow-up, repeated AHR measurements and control for previously suggested confounders such as lung function and smoking [18], we show that AHR that is present at all occasions (persistent) or some occasions but not always (variable) is associated with a higher risk of COPD mortality. Early targeting of individuals who display AHR on multiple occasions or those with varying AHR measurements could be an important step in reducing COPD related deaths.

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