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Respiratory symptom clusters and cause-specific mortality by sex in a general Swedish adult population

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Background: Respiratory symptoms – such as wheezing, chronic cough, and dyspnea – are frequently reported in the general adult population and associated with adverse outcomes. Previous reports have found sex differences in reporting of respiratory symptoms, but it is unclear if these differences are reflected in long-term outcomes. The aim with the present study was to identify clusters based on respiratory symptoms in adults, and to investigate associated cause-specific mortality by sex.

Methods: Respiratory symptoms and background characteristics were obtained from questionnaire data from two Swedish population-representative adult cohorts (N = 56,206). Linkage was done to the national Cause-of-Death register to obtain mortality register data (6-21 years follow-up). Based on the presence or absence of 28 respiratory symptoms, subjects with at least one respiratory symptom were clustered using the CLustering LARge Applications algorithm. The hazard ratio, using asymptomatic subjects as reference, for respiratory, lung cancer, and cardiovascular mortality was calculated separately for men and women with the Fine-Gray model.

Results: In total, 63% of the study population reported ≥1 respiratory symptom, among which five unique clusters were identified (Table 1). Adjusted cause-specific mortality analyses by sex are presented in Table 2.

Conclusions: A general trend was seen in which clusters with more respiratory symptoms were associated with increased cause-specific mortality, with the strongest association seen for respiratory mortality among both men and women in the two clusters with the highest respiratory symptom frequencies. Clusters with rhinitis symptoms were generally associated with higher risk of cause-specific mortality compared to clusters without rhinitis symptoms among women, whereas among men, the opposite was seen, with generally higher risk of cause-specific mortality in clusters without rhinitis than in clusters with rhinitis. This was also reflected in lung cancer mortality, which was only significantly higher among men, in the cluster with non-allergic respiratory symptoms.

Figures

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Table 1. Selected respiratory symptoms in the clusters.

Variable n (%) affirmative response	**Cluster 1** Low-symptomatic with nocturnal breathing disturbance *n* = 13,320	**Cluster 2** Intermittent rhinitis and conjunctivitis *n* = 9,025	**Cluster 3** Intermittent attacks of breathlessness *n* = 7,313	**Cluster 4** Non-allergic respiratory symptoms *n* = 2,770	**Cluster 5** Allergic respiratory symptoms with chronic rhinitis *n* = 2,743
Attacks of breathlessness, in last 10 years	851 (6.4%)	1,390 (15%)	1,086 (15%)	2,291 (83%)	2,496 (91%)
Attacks of breathlessness, in last 12 months	388 (2.9%)	629 (7.0%)	586 (8.0%)	2,099 (76%)	2,268 (83%)
Attacks of breathlessness during physical strain	804 (6.0%)	1,415 (16%)	4,504 (62%)	2,112 (76%)	2,156 (79%)
Attacks of breathlessness from dust, tobacco, fume, or cold	1,362 (10%)	2,757 (31%)	5,502 (75%)	2,220 (80%)	2,485 (91%)
Wheezing, in last 12 months	2,224 (17%)	1,202 (13%)	1,338 (18%)	2,748 (99%)	2,556 (93%)
Rhinitis, in last 12 months	9 (<0.1%)	7,845 (87%)	52 (0.7%)	49 (1.8%)	2,591 (94%)
Rhinitis for ≥5 days / week	6 (<0.1%)	6,919 (77%)	26 (0.4%)	8 (0.3%)	2,320 (85%)
Rhinitis for ≥5 days / week for ≥5 weeks	0 (0%)	3,386 (38%)	7 (<0.1%)	1 (<0.1%)	1,490 (54%)
Rhinitis with conjunctivitis	7 (<0.1%)	7,622 (84%)	57 (0.8%)	38 (1.4%)	2,406 (88%)
Woken by shortness of breath, cough, or chest tightness	6,309 (47%)	2,276 (25%)	1,209 (17%)	2,110 (76%)	2,069 (75%)

Higher prevalence compared to the whole respiratory symptomatic group (p <0.001)

Lower prevalence compared to the whole respiratory symptomatic group (p <0.001)

Table 2. Adjusted cause-specific mortality analyses by sex.

	All-cause mortality ICD-10 codes = any *n* = 3,576 (men: 2,027; women: 1,549)	**Cardiovascular mortality** ICD-10 codes = I00-99 *n* = 1,002 (men: 633; women: 369)	**Respiratory mortality** ICD-10 codes = J00-99 *n* = 205 (men: 103; women: 102)	**Lung cancer mortality** ICD-10 codes = C34 *n* = 178 (men: 90; women: 88)
Cluster 1 (low-symptomatic with nocturnal breathing disturbance)				
Men	0.96 (0.80-1.13)	0.74 (0.52-1.06)	0.80 (0.31-2.07)	0.44 (0.13-1.45)
Women	0.87 (0.72-1.06)	1.03 (0.69-1.53)	1.00 (0.37-2.71)	0.63 (0.24-1.66)
All	1.09 (0.99-1.19)	0.86 (0.66-1.12)	0.88 (0.44-1.74)	0.55 (0.26-1.16)
Cluster 2 (intermittent rhinitis and conjunctivitis)				
Men	1.12 (0.99-1.25)	**1.39 (1.14-1.69)**	0.98 (0.53-1.81)	0.89 (0.49-1.64)
Women	1.06 (0.92-1.21)	1.06 (0.80-1.40)	1.04 (0.52-2.05)	1.65 (0.96-2.83)
All	1.21 (1.09-1.34)	**1.27 (1.08-1.49)**	1.02 (0.64-1.60)	1.28 (0.87-1.91)
Cluster 3 (intermittent attacks of breathlessness)				
Men	1.32 (1.15-1.51)	**1.42 (1.12-1.80)**	1.33 (0.69-2.58)	1.81 (0.99-3.27)
Women	1.09 (0.93-1.27)	1.21 (0.88-1.66)	**2.14 (1.12- 4.09)**	0.53 (0.21-1.31)
All	0.92 (0.81-1.05)	**1.33 (1.10-1.61)**	**1.68 (1.06-2.67)**	1.14 (0.70-1.86)
Cluster 4 (non-allergic respiratory symptoms)				
Men	**1.51 (1.29-1.77)**	**1.52 (1.13-2.03)**	**5.35 (3.09-9.27)**	**3.11 (1.75-5.54)**
Women	**1.38 (1.14-1.66)**	1.39 (0.95-2.04)	**6.66 (3.69-11.99)**	1.66 (0.79-3.48)
All	**1.44 (1.28-1.62)**	**1.46 (1.16-1.84)**	**5.90 (3.96-8.80)**	**2.37 (1.51-3.73)**
Cluster 5 (allergic respiratory symptoms with chronic rhinitis)				
Men	**1.38 (1.09-1.74)**	1.35 (0.87-2.11)	**4.67 (2.21-9.86)**	0.34 (0.05-2.44)
Women	**1.56 (1.27-1.92)**	**1.79 (1.20-2.69)**	**4.68 (2.33-9.39)**	1.68 (0.74-3.81)
All	**1.51 (1.30-1.76)**	**1.64 (1.22-2.19)**	**4.65 (2.81-7.68)**	1.19 (0.59-2.44)

Plots of hazard ratio (HR) with 95% CI for each cluster, using respiratory asymptomatic subjects as reference, for all subjects and for men and women separately. Adjusted for age, smoking status, body mass index (BMI), educational level, socio-economic status, occupational vapor, gas, dust, and fumes exposure, and comorbidity burden. **Bold HR (95% CI)** indicates statistically significant 95% CI.

ICD: International Classification of Diseases (10) main cause-of-death codes used to define outcome. ***n***: number of events.