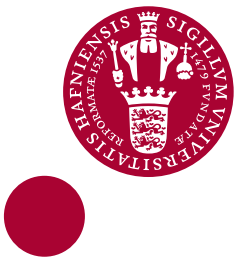

Two-fold risk of pneumonia and respiratory mortality in individuals with myeloproliferative neoplasm

A population-based cohort study

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Research Paper

Two-fold risk of pneumonia and respiratory mortality in individuals with myeloproliferative neoplasm: A population-based cohort study

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ABSTRACT

Background: High cardiovascular comorbidity contributes to excess mortality in patients with myeloproliferative neoplasm, while less is known about respiratory comorbidity and mortality. We tested the hypothesis that individuals with myeloproliferative neoplasm have increased risk of pneumonia and respiratory mortality.
Methods: Of 249 294 invited individuals aged ≥20 from the Danish general population from 2003−2015, 107 900 participated and were included in the Copenhagen General Population Study (response-rate: 43%). We examined lung function and respiratory symptoms at baseline examination and followed individuals prospectively from baseline examination through 2018 to determine risk of pneumonia and respiratory mortality using Cox proportional hazard regression. Among 351 individuals with myeloproliferative neoplasm, 131 (37%) were diagnosed at baseline examination and 220 (63%) were diagnosed during follow-up. The follow-up cases were entered in the regression analysis by using a time-varying variable.
Findings: In total, 125 (36%) individuals had essential thrombocythaemia, 124 (35%) had polycythaemia vera, and 102 (29%) had myelofibrosis/unclassifiable myeloproliferative neoplasm. During follow-up we observed 5979 pneumonias and 2278 respiratory deaths. Compared to individuals without myeloproliferative neoplasm, multivariable adjusted hazard ratios in individuals with myeloproliferative neoplasm were 2·18 (95% CI: 1·60-2·96) for pneumonia and 2·27 (1·46-3·53) for respiratory mortality. Corresponding hazard ratios were 1·26 (0·71-2·30) and 0·96 (0·31-2·94) for essential thrombocythaemia, 2·50 (1·57-3·98) and 3·58 (1·94-6·59) for polycythaemia vera, and 3·03 (1·86-4·93) and 2·40 (1·11-5·19) for myelofibrosis/unclassifiable myeloproliferative neoplasm, respectively. Results were similar in those with and without airflow limitation, and in never-smokers and ever-smokers separately.
Interpretation: Individuals with myeloproliferative neoplasm had two-fold increased risk of pneumonia and respiratory mortality, mainly due to polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm. These are novel findings.

1. Introduction

Philadelphia chromosome-negative myeloproliferative neoplasm (myeloproliferative neoplasm), encompassing essential thrombocythaemia, polycythaemia vera, and myelofibrosis, are clonal stem cell neoplasms characterized by chronic inflammation, clonal myeloproliferation, and myeloaccumulation leading to elevated peripheral blood cell counts [1,2]. Myeloproliferative neoplasms are heterogeneous but very closely related neoplasms with different but overlapping cellular, molecular, and clinical alterations [1,2]. These alterations are also believed to be the reason for the high comorbidity observed in patients with myeloproliferative neoplasm [2]. Indeed, patients with myeloproliferative neoplasm more often have e.g. cardiovascular and thromboembolic diseases, autoimmune disorders, and osteoporotic fractures compared to individuals without such neoplasm [3,4,5−8]. Importantly, the high comorbidity also contributes to excess mortality and reduced life expectancy [9,10]. Whether patients with myeloproliferative neoplasm also have increased risk of respiratory comorbidity and mortality is unknown.

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Research in context

Evidence before this study

We searched PubMed for previous human studies published in English until June 1, 2019, using the following MeSH terms: "lung disease", "pneumonia", and "death" in combination with "myeloproliferative disorders". Previous studies were mainly case-reports. No studies examined risk of pneumonia or respiratory mortality in patients with myeloproliferative neoplasm.

Added value of this study

Using a Danish contemporary population-based cohort of 107 900 individuals followed for up to 14 years, we found that individuals with myeloproliferative neoplasm had a two-fold increased risk of pneumonia and respiratory mortality. Increased risks were mainly in those with polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm. These increased risks were observed in those with and without normal lung function and in ever-smokers and never-smokers alike.

Implications of all the available evidence

Patients with myeloproliferative neoplasm have two-fold increased risk of pneumonia and respiratory mortality, mainly due to polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm.

We therefore investigated risk of pneumonia and respiratory mortality in individuals with myeloproliferative neoplasm from a Danish contemporary population-based cohort totalling 107 900 individuals with up to 14 years of follow-up. We tested the hypothesis that individuals with myeloproliferative neoplasm have increased risk of pneumonia and respiratory mortality.

2. Methods

2.1. Study population

Of 249 294 invited individuals aged ≥20 from the Danish general population in the time period from 2003 to 2015, 107 900 participated and were included in the Copenhagen General Population Study (response rate: 43%) [11,12]. Non-participants were more often men (48% versus 45%) and slightly younger (median age: 56 versus 58). Individuals were invited via the national Danish Civil Registration System [13], which records all individuals living in Denmark with a unique identification number (Civil Registration Number) since birth or immigration, to reflect the adult Danish population. At enrolment, all participants completed a comprehensive questionnaire, underwent a physical examination, and gave blood.

2.2. Ethics

The study was approved by Herlev and Gentofte Hospital and a Danish ethical committee (approval number: H-KF-01-144/01) and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.3. Myeloproliferative neoplasms

Information on myeloproliferative neoplasm was obtained from the national Danish Patient Registry, which records medical diagnoses from all public- and private hospitals in Denmark since 1977 [14]. Cases of myeloproliferative neoplasm included essential thrombocythaemia (International Classification of Diseases [ICD]−8: 287·29 and ICD-10: D47·3, D75·2), polycythaemia vera (ICD-8: 208·99 and ICD-10: D45), myelofibrosis (ICD-8: 209 and ICD-10: D47·4, C94·5), and unclassifiable myeloproliferative neoplasm (ICD-10: D47·1) and were defined as hospital contacts recorded at haematological departments with the mentioned ICD codes as main underlying cause, recorded until April 10, 2018 (see Fig. S1 for a flowchart of case ascertainment). Both individuals with myeloproliferative neoplasm at baseline examination, i.e. prevalent cases, and during follow-up, i.e. incident cases, were included in the statistical analyses. Date of diagnosis was defined as the initial day of hospital contact at the haematological department with a diagnosis of myeloproliferative neoplasm for incident cases. Of the 351 cases included, 349 cases (99·4%) had a primary diagnosis of myeloproliferative neoplasm from a haematological department, and two cases (0·6%) had a secondary diagnosis and were included due to persistent contact to a haematological department. In total, 17 cases (four with a primary diagnosis and 13 with a secondary diagnosis of myeloproliferative neoplasm) were registered at non-haematological departments and not included as cases. Denmark used the ICD-8 codes until January 1, 1994 and proceeded directly to ICD-10 codes after this date. All included cases first recorded with a myeloproliferative neoplasm diagnosis using ICD-8 codes also had an ICD-10 code recorded. The subtype of myeloproliferative neoplasm was determined at diagnosis and was not changed during follow-up in the statistical analyses.

In Denmark, all patients with myeloproliferative neoplasm are diagnosed according to the World Health Organization criteria based on clinical information together with pathological diagnosis using bone marrow biopsy and aspiration; such patients are exclusively followed and treated at specialized haematological departments, as healthcare utilization including treatment for these patients are free of charge [15]. The national Danish Patient Registry has previously shown high validity of recorded ICD codes for haematological neoplasms [16].

2.4. Respiratory characteristics

Lung function was determined using spirometry at baseline examination with measurements of pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) [11,12,17]. Predicted values of FEV_1 and FVC were calculated using internally derived reference values based on a subsample of healthy asymptomatic never-smokers with age and height as covariates separately for men and women [17,18]. Airflow limitation was defined as FEV_1/FVC < 0·70. Information on respiratory symptoms was obtained from the questionnaire at baseline examination and included chronic mucus hypersecretion, dyspnea, wheezing, and cough. Severity of dyspnea was determined using the modified Medical Research Council (mMRC) dyspnea scale [19].

2.5. Outcomes

Pneumonia (ICD-10: J12-J18) was defined as acute emergency department visit and/or hospital admission with the mentioned ICD codes as main underlying cause. This information was obtained from the national Danish Patient Registry, recorded from baseline until April 10, 2018.

Information on vital status was obtained from the national Danish Civil Registration System, which contains date of death for all individuals resident in Denmark [13], recorded from baseline until April 10, 2018. Information on cause of death was obtained from the national Danish Causes of Death Registry, which contains causes of death for all individuals resident in Denmark [20], recorded from baseline until December 31, 2016. Death due to respiratory disease (ICD-10: J00-J99) was defined as one of up to five main contributing causes of

death with the mentioned ICD codes. Since the national Danish Causes of Death Registry lags the national Danish Civil Registration System by approximately one year, not all deaths could be classified by cause (n = 1906).

As follow-up was done by combining the nationwide health registries with the national Danish Civil Registration System through the unique Civil Registration Number, no person was lost to follow-up, and individuals who emigrated were censored at the date of emigration (n = 447). All diagnoses recorded in the registries are strictly made by a medical doctor according to national Danish law using the World Health Organizations ICD codes.

2.6. Covariates

All covariates were determined at baseline examination. Date of birth and sex was obtained from the national Danish Civil Registration System. Information on other covariates was acquired from the questionnaire, physical examination, and the national Danish Patient Registry. Body mass index was measured weight divided by measured height squared (kg/m^2). Smoking status was defined as never, former, or current smoker. Cumulative tobacco consumption was calculated in pack-years based on information on age at smoking initiation and cessation, duration of tobacco consumption, and amount of consumed tobacco (number of daily consumed cigarettes, cheroots, and cigars and grams of weekly consumed pipe tobacco); one pack-year was 20 cigarettes or equivalent smoked daily for a year. Ischaemic heart disease (ICD-8: 410-414 and ICD-10: I20-I25) was defined as a previous hospital contact with the mentioned ICD codes. Socioeconomic status was based on education reported as years attending school and income reported as annual household income. Physical activity was based on leisure-time physical activity reported as type of activity in hours per week.

2.7. Statistical analyses

STATA/SE 13·1 (StataCorp, College Station, Texas, US) was used. Wilcoxon rank-sum test and Pearson's χ^2 test were used for comparison of baseline characteristics. Lung function and respiratory symptoms determined at baseline examination were compared using multiple linear and logistic regression. Risks of pneumonia and respiratory mortality were prospectively determined by using Cox proportional hazard regression. Proportional-hazards assumption was assessed visually using Schoenfeld residuals, without major violations. We used age as the underlying timescale with delayed entry (=left truncation). Individuals who developed myeloproliferative neoplasm during follow-up, i.e. incident cases, were included in the reference group before date of diagnosis and in the myeloproliferative neoplasm group thereafter. Thus, these cases were entered in the regression analysis by using a time-varying variable; however, estimates were similar when incident cases were excluded from the reference group and the myeloproliferative neoplasm group. Risk was also investigated using a Fine-Gray competing risk regression model with death and emigration as competing events [21]. Analyses were stratified according to type of myeloproliferative neoplasm; myelofibrosis and unclassifiable myeloproliferative neoplasm were combined. Analyses were also stratified according to presence and absence of airflow limitation and smoking, as these are heavily associated with respiratory outcomes. Analyses were adjusted for age (as timescale), sex, body mass index, smoking status, cumulative tobacco consumption, baseline ischaemic heart disease, poor socioeconomic status, and physical activity. For comparison, we also investigated risk of pneumonia and respiratory mortality in individuals with other chronic diseases; rheumatoid arthritis (ICD-8: 712.1, 712.2, 712.3 and ICD-10: M05-M06), ischaemic heart disease, and diabetes mellitus (ICD-8: 249-250 and ICD-10: E10-E14). Furthermore, to assess whether risk of pneumonia was a manifestation of confounding by indication, we investigated risk of urinary tract infection (ICD-10: N109A-N109C, N110-N118B, N118D, N119, N12, N300, N308A-N308C, N309, N390) in those with and without myeloproliferative neoplasm, as urinary tract infection is another frequent reason for infection-related hospitalization. Information on ICD codes was obtained from the national Danish Patient Registry. Information on covariates was 99·4% complete and missing values were imputed with multiple imputation using chained equations [22]; however, results were similar without using imputation.

3. Results

Among 107 900 individuals in the Copenhagen General Population Study, 351 had myeloproliferative neoplasm, of whom 131 (37%) were present at baseline (prevalent) and 220 (63%) were diagnosed during follow-up (incident), distributed among essential thrombocythaemia (40 prevalent and 85 incident), polycythaemia vera (62 and 62), myelofibrosis (2 and 33), and unclassifiable myeloproliferative neoplasm (27 and 40), respectively. Of all myeloproliferative neoplasm, 36% had essential thrombocythaemia, 35% polycythaemia vera, and 29% myelofibrosis or unclassifiable myeloproliferative neoplasm. In general, individuals with myeloproliferative neoplasm were older, more often had ischaemic heart disease and poor socioeconomic status, and more often reported a history of smoking (Tables 1 and S1). However, after adjusting for age, neither smoking history nor poor socioeconomic status remained statistically significant.

3.1. Lung function and symptoms

Compared to individuals without myeloproliferative neoplasm, individuals with myeloproliferative neoplasm (prevalent and incident myeloproliferative neoplasm together) did not differ after multivariable adjustment with regard to lung function (FEV_1: 2·5 L versus 2·9 L; FVC: 3·4 L versus 3·8 L), airflow limitation (24% versus 17%), or respiratory symptoms (48% versus 43%) (Table 2). However, individuals with prevalent myeloproliferative neoplasm more often reported respiratory symptoms (65% versus 43%), including chronic mucus hypersecretion (19% versus 8·8%), dyspnea (33% versus 8·2%), and cough (20% versus 12%) compared to those without myeloproliferative neoplasm (Table S2).

Table 1
Baseline characteristics of individuals with and without myeloproliferative neoplasm in the Copenhagen General Population Study.

	Myeloproliferative neoplasm		
	No (n = 107 549)	Yes[a] (n = 351)	p-value
Age – years	58 (48–67)	65 (59–73)	<0.0001
Men – no. (%)	48 208 (45)	168 (48)	0.25
Body mass index – kg/m^2	25.6 (23.2–28.4)	25.7 (23.2–28.3)	0.93
Never-smokers – no. (%)	45 169 (42)	115 (33)	0.00046
Former smokers – no. (%)	43 983 (41)	170 (48)	0.0041
Current smokers – no. (%)	18 397 (17)	66 (19)	0.40
Cumulative tobacco consumption – pack-years[b]	15 (6–30)	21 (10–36)	0.00050
Ischaemic heart disease – no. (%)	6168 (5.7)	53 (15)	<0.0001
Poor socioeconomic status – no. (%)	6302 (6.0)	43 (13)	<0.0001
Physically inactive – no. (%)	6645 (6.2)	21 (6.1)	0.89

Data presented as median (25th and 75th percentiles), or number (%). p-values for comparison are calculated using Wilcoxons rank-sum test or Pearson's χ2 test.

[a] Included both prevalent and incident cases of myeloproliferative neoplasm.

[b] Included only former and current smokers.

Table 2
Baseline lung function and respiratory symptoms of individuals with and without myeloproliferative neoplasm in the Copenhagen General Population Study.

	Myeloproliferative neoplasm		
	No (n = 107 549)	Yes[a] (n = 351)	Adjusted p-value
Lung function			
FEV_1 – L	2·9 (2·4–3·6)	2·5 (2·0–3·3)	0.24
FEV_1 predicted –%	96.7 (86.5–106)	93.5 (82.2–105)	0.23
FVC – L	3.8 (3.1–4.6)	3.4 (2.8–4.2)	0.081
FVC predicted –%	99.3 (89.7–109)	96.1 (84.9–107)	0.048
FEV_1/FVC	0.77 (0.73–0.82)	0.76 (0.70–0.81)	0.27
Airflow limitation: FEV_1/FVC <0.70 – no. (%)	17 903 (17)	83 (24)	0.96
Degree of airflow limitation			
FEV_1% predicted ≥80 – no. (%)	91 742 (85)	278 (79)	0.54
FEV_1% predicted <80 – no. (%)	15 770 (15)	73 (21)	0.53
Respiratory symptoms			
Any respiratory symptom – no. (%)	45 840 (43)	169 (48)	0.64
Chronic mucus hypersecretion – no. (%)	9476 (8.8)	44 (13)	0.41
Dyspnea, mMRC ≥2 – no. (%)	8857 (8.2)	61 (17)	0.00072
Wheezing – no. (%)	18 140 (17)	62 (18)	0.94
Cough – no. (%)	12 982 (12)	50 (14)	0.29

Data presented as median (25th and 75th percentiles), or number (%). Adjusted p-values for comparison are from multivariable adjusted analyses using multiple linear regression or logistic regression adjusted for age, sex, smoking status, cumulative tobacco consumption, body mass index, baseline ischaemic heart disease, poor socioeconomic status, and physical activity. FEV_1 = forced expiratory volume in 1 s. FVC = forced vital capacity. mMRC = modified Medical Research Council dyspnea scale.
[a] Included both prevalent and incident cases of myeloproliferative neoplasm.

3.2. Pneumonia and respiratory mortality

During up to 14 years of follow-up (median 8·7 years), we observed 5979 pneumonias and 10 267 deaths (92 died among individuals with myeloproliferative neoplasm, and 10 175 died among those without myeloproliferative neoplasm), of which 2278 were categorized as respiratory deaths. For the whole cohort, incidence rate per 10 000 years was 66 (95% confidence interval [CI]: 64–67) for pneumonia and 24 (23–25) for respiratory mortality. Individuals with myeloproliferative neoplasm had an increased risk of pneumonia and respiratory mortality compared to individuals without myeloproliferative neoplasm (Figs. 1 and S2). Compared to individuals without myeloproliferative neoplasm, multivariable adjusted hazard ratios (HRs) in individuals with myeloproliferative neoplasm were 2·18 (95% CI: 1·60–2·96) for pneumonia and 2·27 (1·46–3·53) for respiratory mortality (Fig. 1). Increased risks were driven by those with polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm (Figures S3 and S4). Corresponding HRs were 1·26 (0·71–2·30) and 0·96 (0·31–2·94) for essential thrombocythaemia, 2·50 (1·57–3·98) and 3·58 (1·94–6·59) for polycythaemia vera, and 3·03 (1·86–4·93) and 2·40 (1·11–5·19) for myelofibrosis/unclassifiable myeloproliferative neoplasm, respectively (Figs. S3).

For comparison, individuals with chronic disease including rheumatoid arthritis, ischaemic heart disease, and diabetes mellitus also had an increased risk of pneumonia and respiratory mortality, as expected. Nominally, however, the risk estimates seemed even higher for individuals with myeloproliferative neoplasm (Fig. S5). In contrast, individuals with myeloproliferative neoplasm did not have increased risk of urinary tract infection (Fig. S6).

3.3. Myeloproliferative neoplasm, airflow limitation, and smoking

Compared to individuals without myeloproliferative neoplasm and with normal lung function, risk of pneumonia and respiratory mortality were increased in individuals with myeloproliferative neoplasm in those with and without airflow limitation separately (Figs. 2, and S7 left panel). Corresponding results were also similar in never-smokers and ever-smokers with myeloproliferative neoplasm separately (Figures S7 right panel, and S8).

The risk of pneumonia and respiratory mortality in never-smokers with myeloproliferative neoplasm corresponded to the risk of ever-smokers without myeloproliferative neoplasm who had smoked approximately 80 pack-years (Fig. 3). Compared to never-smokers without myeloproliferative neoplasm, HRs for pneumonia were 2·79 (95% CI: 1·65–4·71) in never-smokers with myeloproliferative neoplasm and 3·09 (2·63–3·62) in those without myeloproliferative neoplasm who had smoked ≥80 pack-years. Corresponding HRs for respiratory mortality were 4·71 (2·15–10·3) and 4·16 (3·32–5·20), respectively.

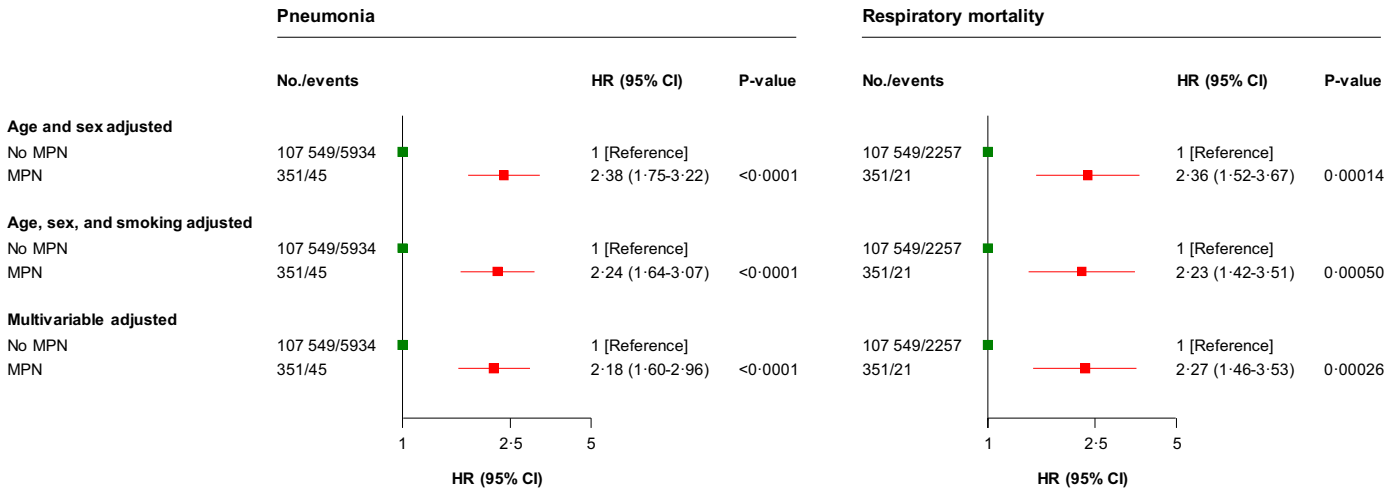

Fig. 1. *Risk of pneumonia and respiratory mortality in individuals with and without myeloproliferative neoplasm.* Risk estimates were obtained using Cox regression analysis. Smoking adjustment included smoking status and cumulative tobacco consumption. Analyses were multivariable adjusted for age, sex, smoking status, cumulative tobacco consumption, body mass index, baseline ischaemic heart disease, poor socioeconomic status, and physical activity. CI = confidence interval. HR = hazard ratio. MPN = myeloproliferative neoplasm.

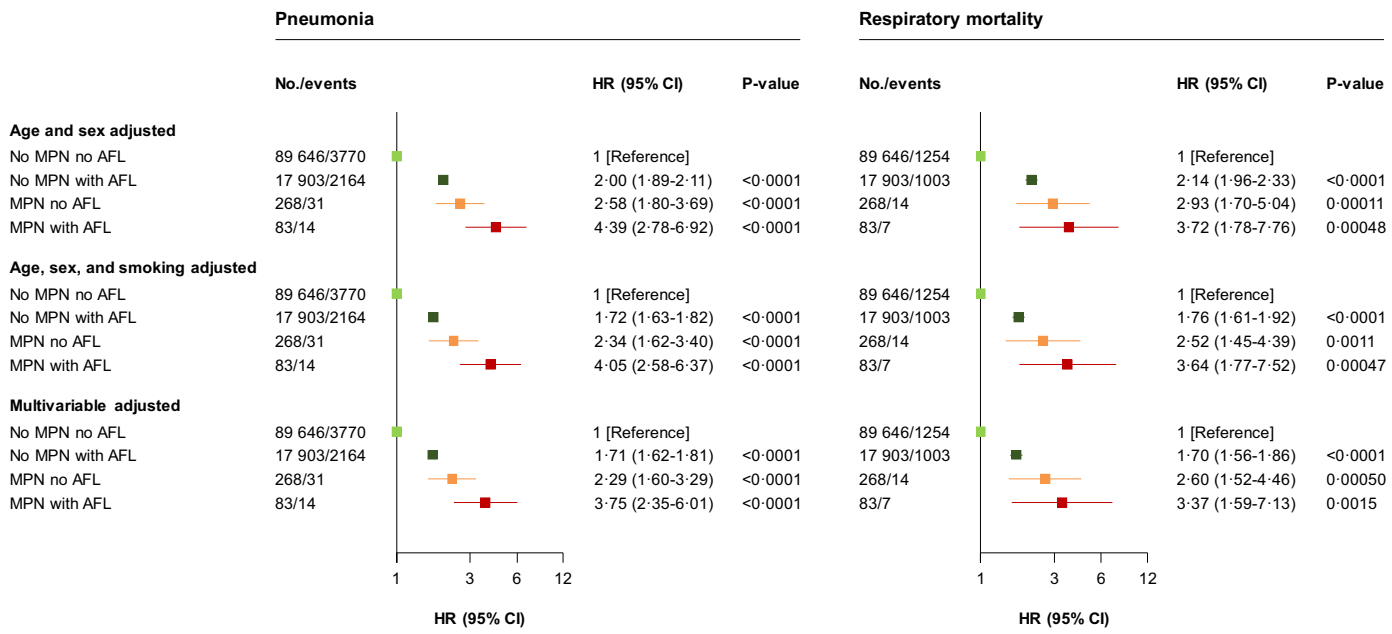

Fig. 2. *Risk of pneumonia and respiratory mortality stratified by airflow limitation in individuals with and without myeloproliferative neoplasm.* Risk estimates were obtained using Cox regression analysis. Airflow limitation was defined as $FEV_1/FVC<0{\cdot}70$. Smoking adjustment included smoking status and cumulative tobacco consumption. Analyses were multivariable adjusted for age, sex, smoking status, cumulative tobacco consumption, body mass index, baseline ischaemic heart disease, poor socioeconomic status, and physical activity. AFL = airflow limitation. CI = confidence interval. FEV_1 = forced expiratory volume in 1 s. FVC = forced vital capacity. HR = hazard ratio. MPN = myeloproliferative neoplasm.

4. Discussion

In 107 900 individuals from a Danish contemporary population-based cohort with a follow-up time of up to 14 years, we found that individuals with myeloproliferative neoplasm had two-fold increased risk of pneumonia and respiratory mortality. Increased risks were mainly driven by those with polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm. These increased risks were observed in those with and without normal lung function and in ever-smokers and never-smokers alike. These are novel findings.

Possible mechanisms and explanations for the present findings may be related to the disease itself and/or to side-effects of treatment. For disease related mechanisms, the fact that patients with myeloproliferative neoplasm have alterations in their bone marrow niche should be considered [23]. Since most stem and progenitor cells are usually present in the bone marrow and less of them in the blood circulation, a less functional bone marrow may lead to displacement and mobilization of stem and progenitor cells, including megakaryocytes, to the blood circulation [24]. In the blood circulation, these stem and progenitor cells may be deposited and activated in different organ systems [24]. Activation of stem and progenitor cells may lead to release of cytokines and growth factors, e.g. pro-inflammatory and pro-fibrotic cytokines, which may lead to chronic low-grade inflammation.[25] Such stem and progenitor cells can be deposited and activated in the pulmonary compartment affecting the lungs and/or pulmonary defence mechanisms against microorganisms [25]. Certainly, such a scenario may help explain the increased risk of pneumonia and respiratory mortality in those with myeloproliferative neoplasm as shown in the present study.

For treatment related mechanisms, patients with myeloproliferative neoplasm are treated with cytoreductive agents, which may have toxic effects in different organ systems. Although adverse pulmonary events for these cytoreductive agents are described to be very rare, patients with myeloproliferative neoplasm are treated for many years, and information on long-term adverse events is scarce. In addition, treatment with cytoreductive and immunomodulatory agents could increase risk of infections in patients with myeloproliferative neoplasm [26,27]. We cannot exclude that side-effects from treatment could be part of the explanation for the increased risk of pneumonia and respiratory mortality shown in our study. Certainly, the presence of respiratory symptoms at baseline examination in those with prevalent and not incident myeloproliferative neoplasm suggest that these symptoms could be due to either treatment or disease *per se*, or a combination of the two. A limitation for interpretation of the mechanistic pathways is lack of information on type of treatment for myeloproliferative neoplasm and on mutation status e.g. *JAK2*V617F and *CALR*. Alternatively, reverse causation may explain some of the findings, as individuals with more severe infections are more likely to undergo blood testing which in turn could lead to diagnosis of myeloproliferative neoplasm. However, in this case we would expect a higher frequency of respiratory symptoms in individuals with incident myeloproliferative neoplasm compared to those without, and this was not the case.

Myeloproliferative neoplasm encompasses essential thrombocythaemia, polycythaemia vera, and myelofibrosis, which are related but still heterogeneous neoplams with varying prognoses [9,10]. Thus, we stratified according to type of myeloproliferative neoplasm and found that individuals with polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm had increased risk of pneumonia and respiratory mortality, whereas those with essential thrombocythaemia did not. This corresponds well with previous studies showing more severe comorbidity in those with polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm, and less severe comorbidity in those with essential thrombocythaemia [9,10]. However, due to a low number of cases and events in these subgroup analyses, results should be interpreted with caution, as we cannot exclude a false negative finding in those with essential thrombocythaemia.

We also stratified the analyses according to presence of airflow limitation and smoking status, which are strongly associated with respiratory comorbidities, and potentially could explain some of our positive findings in individuals with myeloproliferative neoplasm. However, increased risks were also observed in those with normal lung function and in never-smokers.

A potential limitation is how pneumonia outcomes were determined through hospitalization records. Although previous studies have shown

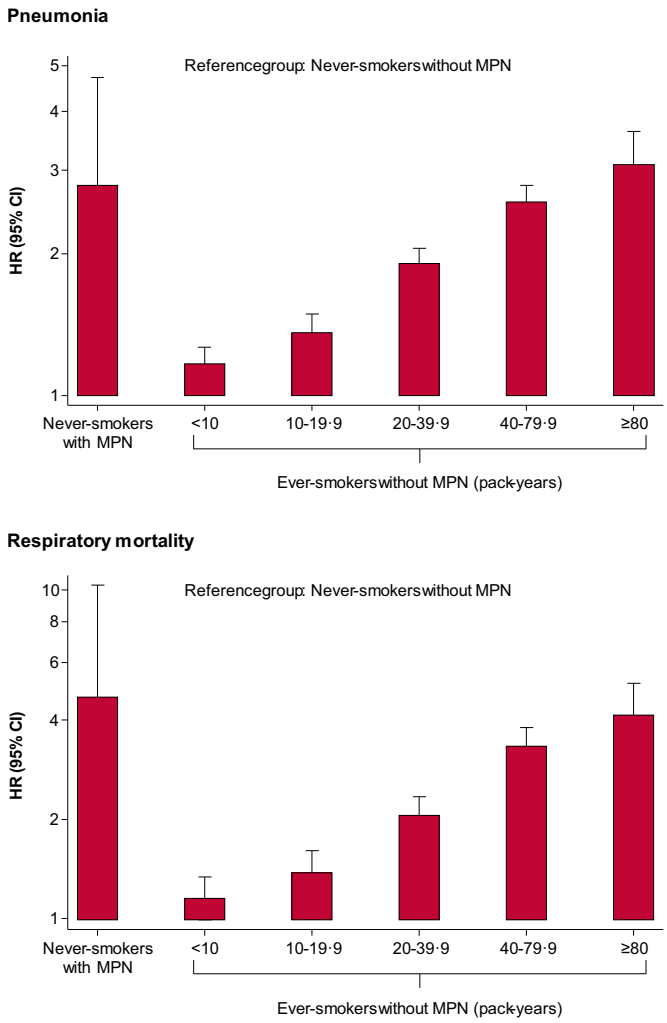

Fig. 3. *Risk of pneumonia and respiratory mortality in never-smokers with myeloproliferative neoplasm versus smokers without myeloproliferative neoplasm.* Risk estimates were obtained using Cox regression analysis. Risk estimate for never-smokers with myeloproliferative neoplasm was obtained from Fig. S8. Risk estimates for ever-smokers stratified according to cumulative tobacco consumption were obtained from a separate analysis with never-smokers without myeloproliferative neoplasm as the reference group, multivariable adjusted for age, sex, body mass index, baseline ischaemic heart disease, poor socioeconomic status, and physical activity. Please note different *y*-axes. CI = confidence interval. HR = hazard ratio. MPN = myeloproliferative neoplasm.

high validity of recorded ICD codes for acute medical hospitalizations including pneumonia in the national Danish Patient Registry [28–30], most pneumonia cases are treated in primary care and not in hospitals. Since patients with myeloproliferative neoplasm are already treated in hospitals, they may be more frequently hospitalized due to pneumonia instead of being treated in primary care. Thus, we cannot completely exclude the possibility of confounding by indication, i.e. that individuals with myeloproliferative neoplasm have automatically an increased risk of pneumonia hospitalization compared to those without. To investigate potential confounding by indication, we chose urinary tract infection, which is another type of infection that is mostly treated in primary care and not in hospitals. If confounding by indication was present, we would also expect an increased risk of urinary tract infection in individuals with myeloproliferative neoplasm compared to those without; however, this was not the case.

Confounding by indication cannot explain the positive findings related to respiratory mortality, as medical doctors both inside and outside hospital settings are reporting to the national Danish Causes of Death Registry. Yet we cannot exclude potential misclassification due to low autopsy rates in Denmark. [20]. Such a misclassification is believed to be non-differential and thus cannot explain our positive findings in the present study.

Another potential limitation is that lung function, respiratory symptoms, and covariates were only assessed at baseline examination. Thus, individuals with incident myeloproliferative neoplasm may have differed with regard to some characteristics at date of diagnosis. Nonetheless, risk estimates were similar after exclusion of individuals with incident myeloproliferative neoplasm from the analyses.

Strengths of the present study include a large number of randomly selected individuals from a contemporary general population cohort, a long observational period without any losses to follow-up, and detailed information on lung function, covariates, and clinical outcomes from nationwide health registries. That essentially all cases with myeloproliferative neoplasm have the diagnosis confirmed using bone marrow biopsy and aspiration in Denmark is clearly a strength as well.

Clinical implications of the present study relate to the importance of prevention, early diagnosis, and treatment of comorbidities in patients with myeloproliferative neoplasm, as the high comorbidity in myeloproliferative neoplasm contributes significantly to excess mortality and reduced life expectancy [9,10]. Vaccines could potentially reduce risk of pneumonia and subsequently respiratory mortality and could be an inexpensive intervention with very few adverse effects. As such recommendations already exist for certain other chronic diseases, e.g. for individuals with chronic obstructive pulmonary disease [31], a similar approach regarding vaccines should be considered in the management of patients with myeloproliferative neoplasm. The present study also highlights that the increased risk of respiratory complications should be considered when choosing optimal medical treatment in patients with myeloproliferative neoplasm, as we cannot exclude that some of our findings could be related to side-effects of treatment given to these patients.

In conclusion, individuals with myeloproliferative neoplasm had two-fold increased risk of pneumonia and respiratory mortality, mainly due to polycythaemia vera and myelofibrosis/unclassifiable myeloproliferative neoplasm. These novel findings were observed in those with and without normal lung function and in ever-smokers and never-smokers alike.

Declaration of competing interest

KMP reports grants from the Danish Karen Elise Jensen Foundation during the conduct of the study. YÇ reports grants from the Lundbeck Foundation and personal fees from Boehringer Ingelheim, AstraZeneca, and Sanofi Genzyme outside the submitted work. HCH reports grants from Novartis Denmark and personal fees from AOP Orphan Pharmaceuticals AG and PharmaEssentia outside the submitted work. CE, SEB, and BGN have nothing to disclose in relation to this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100295.

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