Is previous respiratory disease a risk factor for lung cancer?

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Author's contributions to the study

Rachel Denholm conducted the analyses and wrote the first draft and most of the paper. Ann Olsson, Kurt Straif, Paolo Boffetta, and Isabelle Stücker launched this project and have been involved in all steps. Joachim Schüz, Darren Brenner and Sara De Matteis participated in the writing team including revising several drafts. Thomas Brüning, Hans Kromhout, Roel Vermeulen, Susan Peters and Benjamin Kendzia have been involved in the coordination of the SYNERGY project since it started in 2007, Thomas Behrens joined the coordinating team in 2011. All other authors have contributed substantially to the original studies, i.e. designed and directed its implementation, including quality assurance and control. All authors have received drafts of the manuscript and have suggested additional analyses and contributed to the interpretation and discussion.

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Scientific Knowledge on the Subject:

Chronic bronchitis, emphysema, tuberculosis, pneumonia and asthma when examined in isolation have been associated with an increased risk of lung cancer diagnoses.

What This Study Adds to the Field:

Our results from a very large pooled study show that chronic bronchitis and emphysema are positively associated with lung cancer, after accounting for other pulmonary diseases. The positive association between pneumonia and lung cancer was stronger when diagnosed 2 years or fewer prior to lung cancer diagnoses, compared to longer. Co-occurrence of chronic bronchitis, emphysema and pneumonia had a stronger association with lung cancer, compared to any one condition. Asthma diagnosed 5 or more years prior was inversely related to lung cancer, and no association was observed when asthma co-occurred with chronic bronchitis.

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Abstract

Rationale: Previous respiratory diseases have been associated with increased risk of lung cancer. Respiratory conditions often co-occur and few studies have investigated multiple conditions simultaneously.

Objectives: Investigate lung cancer risk associated with chronic bronchitis, emphysema, tuberculosis, pneumonia and asthma.

Methods and Measurements: The SYNERGY project pooled information on previous respiratory diseases from 12,739 cases and 14,945 controls from 7 case-control studies conducted in Europe and Canada. Multivariate logistic regression models were used to investigate the relationship between individual diseases adjusting for co-occurring conditions, and patterns of respiratory disease diagnoses and lung cancer. Analyses were stratified by sex, and adjusted for age, centre, ever-employed in a high-risk occupation, education, smoking status, cigarette pack-years and time-since quitting smoking.

Main Results: Chronic bronchitis and emphysema were positively associated with lung cancer, after accounting for other respiratory diseases and smoking (for example in men OR=1.33; 95% CI 1.20-1.48 and 1.50; 1.21-1.87, respectively). A positive relationship was observed between lung cancer and pneumonia diagnosed 2 or fewer years prior to lung cancer (OR=3.31; 2.33-4.70 for men), but not longer. Co-occurrence of chronic bronchitis, emphysema and pneumonia had a stronger positive association with lung cancer than individual conditions. Asthma had an inverse association with lung cancer, the association being stronger with an asthma diagnosis 5 or more years prior to lung cancer compared to shorter.

Conclusions: Findings from this large international case-control consortium indicate that after accounting for co-occurring respiratory diseases, chronic bronchitis and emphysema continue to have a positive association with lung cancer.

Introduction

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer related deaths worldwide(1). Recent evidence suggests that there is a relationship between previous respiratory disease (PRD), including chronic bronchitis, emphysema, tuberculosis and respiratory, and lung cancer diagnoses(2). Tobacco is a shared risk factor of PRD and lung cancer. Yet, the mechanisms by which PRD may independently influence lung cancer risk are poorly understood, but it has been hypothesised that inflammation caused by PRD may act as a catalyst in the development of lung neoplasms(3).

Much of the existing literature focuses on individual PRD, and do not account for the high level of co-occurrence observed amongst different respiratory diseases. For example, chronic obstructive pulmonary disease (COPD) frequently co-occurs with pneumonia(4) and a medical history of respiratory disease early in life has been related to a later increased risk of asthma, chronic bronchitis and emphysema(5).

The aim of this pooled analysis was to investigate the relationship between multiple PRD and lung cancer risk in a large multinational dataset with detailed information of smoking habits. To further understand the role of PRD in lung cancer aetiology, we investigated the influence of patterns of multiple respiratory diseases and latency of PRD on lung cancer diagnoses.

Some of the results of this study have been previously reported in the form of an conference abstract(6).

Methods

The SYNERGY project is a consortium of international lung cancer case-control studies with information on occupational and lifetime smoking histories(7, 8). More information about the SYNERGY project is available (http://synergy.iarc.fr). Of the participating centers, 13 collected information on PRD. Table 1 describes the characteristics of the studies. Cases and controls were frequency-matched for sex and age in most studies. Interviews were predominantly conducted through face-to-face interviews, with the exception of the Montreal and the Toronto Lung Cancer studies which used telephone-interviews. Individual countries in the International Agency for Research on Cancer (IARC) multicenter lung cancer study in Central and Eastern Europe and the United Kingdom (INCO) are included as individual studies in these analyses. Ethical approvals were obtained in accordance with legislation in each country, and in addition by the Institutional Review Board at IARC.

In all studies PRD was self-reported ('ever had' or 'doctor diagnosed' a disease) and most collected information on 5 PRD (chronic bronchitis, emphysema, tuberculosis, pneumonia and asthma). INCO/LLP-UK study participants reported 'bronchitis' diagnoses. In the Montreal study information on chronic bronchitis was not collected and in the ICARE study emphysema and pneumonia were omitted. The HdA and AUT studies restricted PRD diagnosed ≥2 years prior to lung cancer diagnoses or control interview.

Statistical Analyses

Logistic regression models were fitted to calculate odds ratios (OR) and 95% confidence intervals (CI) of lung cancer associated with PRD diagnoses. All PRD were included in the same model to account for multiple PRD diagnoses. As not all studies collected information on all 5 PRD, 3 models were developed; the first model included all 5 PRD (chronic bronchitis, emphysema, tuberculosis, pneumonia and asthma), the second, 4 PRD (chronic

bronchitis omitted), and the third, 3 PRD (emphysema and pneumonia omitted) (Figure 1). Subjects with asbestosis (n=89) and silicosis (n=110) were omitted, as these diseases are causally associated with known lung carcinogens. Analyses were stratified by sex due to differences in smoking-related exposures observed in men and women. The potential effect of cigarette smoking status was examined by stratifying the analyses; former smokers (stopped ≥5 years prior to lung cancer diagnoses or control interview), current smokers (≥1 cigarette per day for ≥1 year, and participants who quit <5 years prior to lung cancer/interview) and never smokers. Analyses were also stratified by histological subtype to investigate the association between PRD diagnoses and subtypes of lung cancer.

A high level of co-occurrence was observed between all PRD, thus further analyses were restricted to studies and participants with data on all 5 PRD (Figure 1). Patterns of PRD diagnoses with ≥20 cases and ≥20 controls were investigated and a categorical variable for each PRD was created indicating whether participants reported the index respiratory disease only, or other co-occurring PRD. Associations were examined using logistic regression models. Due to the small number of women with specific PRD patterns, only associations in men are reported.

The effect of latency of PRD diagnoses on lung cancer risk was investigated in studies with information on age at PRD diagnoses (Figure 1). Three studies did not collect year of PRD diagnoses (HdA, AUT and INCO/LLP-UK). A latency variable for each PRD was created indicating whether the diagnoses had been made <2, 2-4, 5-9 or ≥10 years prior to lung cancer/interview. Logistic regression models were fitted to categorical latency variables for each PRD, and adjustments were made for additional PRD diagnosed at any age.

Models were adjusted for center, age (continuous), employment in an occupation with an excess risk of lung cancer ('list A' job, Appendix 1 (9, 10); yes/no) and level of education (none, <6, 6-9, 10-13, >13 years). Additional adjustments were made for cigarette smoking

status (current smokers, former smokers; and never-smokers), pack-years (∑duration x average intensity per day/20) and time-since-stopped smoking cigarettes (2-7, 8-15, 16-25, >25 years), where appropriate. Subjects with missing data on any covariates were omitted from analyses.

Meta-analyses and forest plots were used to explore study-specific ORs and extent of heterogeneity. Heterogeneity was assessed using a chi-squared test of the Cochrane Q statistic and I^2 statistic. If there was evidence of heterogeneity between studies, outliers were identified using Galbraith plots and removed in sensitivity analysis.

All analyses were conducted using Stata v.11.0 for Windows (StataCorp LP, College Station, TX). The Stata command 'metan' was used in the meta-analyses.

Results

Study population

A description of the total study population (12,739 cases and 14,945 controls) is shown in Table 2. The median age was 63 years for men and 62 years for women. More cases than controls were current smokers (71% vs. 26% men and 61% vs. 20% women) and the mean cumulative tobacco consumption (cigarette pack-years) was higher in cases compared to controls (42.7 (SD 26.7) vs. 26.0 (SD 23.2) men and 35.2 (SD 23.3) vs. 20.0 (SD 18.5) women). A greater proportion of women, both cases and controls, were never smokers, and, on average consumed less tobacco, compared to men. In cases, squamous cell carcinoma was the most frequently characterised histologic subtype amongst men (41%), compared to adenocarcinoma in women (44%).

PRD prevalence

The most frequently reported PRD were pneumonia (25% of 10,194 cases and 18% of 11,642 controls) and chronic bronchitis (24% of 11,617 cases and 15% of 13,451 controls).

Emphysema was the least frequently reported PRD (5.0% of 10,106 cases and 2.2% of 11,631 controls). There was a high level of PRD co-occurrence; of subjects with any PRD, between 50% and 83% of cases and 40% and 83% of controls reported another, dependent on the index condition (Appendix 2). In particular, a high proportion of participants who reported emphysema (77% of 367 cases and 83% of 206 controls) or asthma (83% of 620 cases and 67% of 535 controls) reported another PRD.

PRD and lung cancer

In all models persons with chronic bronchitis, emphysema and pneumonia had an increased risk of lung cancer, compared to persons with no PRD diagnoses. For men, relationships persisted after further adjustment for 'list A' occupation, level of education, smoking status, pack-years and time-since-stopped smoking (Table 3). There was little difference in the strength of association amongst the PRD models. For women, emphysema and pneumonia remained positively associated with lung cancer after adjustment for confounding factors (not significant for emphysema). Chronic bronchitis was associated with an increased risk of lung cancer in the 3 PRD model only (OR=1.25; 95% CI 1.07-1.47). No relationship between tuberculosis and lung cancer was observed.

An inverse relationship between asthma and lung cancer was observed in all models. Effect estimates weakened and were no longer significant after controlling for additional confounding factors for men, except in the 3 PRD model (OR=0.86; 0.74-0.99). Amongst women, inverse associations remained in the adjusted 5 and 4 PRD models.

In the meta-analysis, there was evidence of heterogeneity ($p<0.05$) across studies in the chronic bronchitis and pneumonia models, and in the emphysema and asthma models in men (Appendix 3). When outliers were removed there was little change in most of the effect estimates (Appendix 4). For men, no association was found between emphysema and lung

cancer (OR=1.05; 0.68, 1.55. I^2 27.9% after outliers removed). For women, no association between pneumonia and lung cancer was found (OR=0.95; 0.62, 1.48. I^2 58.5% after outliers removed).

Results stratified by smoking status showed patterns of association in former and current smokers similar to those observed in the overall results (Appendix 45). In never smokers, numbers were small and no significant risk of lung cancer was found in relation to any of the PRD; an inverse association between asthma and lung cancer was however observed in men in the 4 (OR=0.39; 0.17-0.90) and 3 PRD models (OR=0.49; 0.24-0.98).

Results stratified by lung cancer histological subtype showed that chronic bronchitis and pneumonia were positively associated with all lung cancer subtypes; whilst emphysema was positively related to squamous cell and adenocarcinoma (Appendix 56). Asthma was inversely associated with all lung cancer subtypes among women, and with adenocarcinoma among men.

Patterns of PRD diagnoses

Due to the high level of co-occurrence amongst all PRD and similar findings in all models, the remaining analyses focused on studies with data on all 5 PRD.

The relationship between patterns of PRD diagnoses and lung cancer in men are shown in Table 4. Associations reflected previous patterns observed in all models, and relationships persisted after adjustment for confounding factors (Table 4). Chronic bronchitis 'only' and pneumonia 'only' had a positive relationship with lung cancer (OR=1.39; 1.21-1.59 and OR=1.23; 1.09-1.38, respectively), the strength of association increasing with co-occurring emphysema and pneumonia. A large effect estimate was observed for emphysema 'only' (OR=2.68; 1.71-4.21). An inverse relationship was found between asthma 'only' and lung

cancer (although not significant). There was no association between chronic bronchitis or pneumonia and lung cancer when either co-occurred with asthma or tuberculosis.

Latency of PRD

In men, latency of chronic bronchitis and emphysema had little effect on the relationship with lung cancer (Table 5). Relationships remained consistent for chronic bronchitis after adjustment for potential confounding factors. In the adjusted model, there was little difference in the strength of association between emphysema at different latencies and lung cancer, however only emphysema diagnosed ≥10 years prior to lung cancer/interview remained statistically significant (OR=1.94; 1.29-2.92). In women, chronic bronchitis diagnosed ≥5 years prior to lung cancer/interview and emphysema diagnosed ≤4 years prior were positively associated with lung cancer; relationships attenuated after adjustment for potential confounding factors.

Tuberculosis diagnosed 2-4 years prior had an OR=3.76 (1.05-13.56) for men and OR=5.31 (0.54, 51.77) for women, the effect estimate remaining in the adjusted model (OR=3.26; 0.80-13.25 and OR=5.06; 0.44, 58.33 for men and women, respectively).

For pneumonia, effect estimates were similar in both unadjusted and adjusted models and stronger relationships were observed in the shorter latencies, compared to longer; for example in men OR=3.31; 2.33-4.70 and OR=1.82; 1.19-2.78 for <2 and 5-9 years, respectively.

Asthma diagnosed ≥5 years prior was inversely related to lung cancer among men; a weaker or no association were observed at other latencies. In women, asthma diagnosed ≥2 years prior had an inverse relationship with lung cancer in both unadjusted and adjusted analyses, although 95% CI included the null effect.

Discussion

In this investigation we pooled data from case-control studies in Europe and Canada to examine the association between multiple PRD and lung cancer. A high level of co-occurrence amongst different PRD was observed. Chronic bronchitis and emphysema were positively associated with lung cancer, irrespective of the latency between PRD diagnoses and lung cancer/interview. Pneumonia had a positive association with lung cancer, the relationship being stronger for pneumonia diagnosed ≤2 years prior to lung cancer diagnoses than at those diagnosed later latencies. Asthma had an inverse association with lung cancer, the association being stronger for asthma diagnosed ≥5 years prior to lung cancer compared to <5 years. No association was observed between tuberculosis and lung cancer after accounting for confounding factors. Co-occurrence of chronic bronchitis and either/both emphysema and pneumonia had a stronger positive association with lung cancer than chronic bronchitis 'only', with emphysema diagnoses being particularly important. Chronic bronchitis was not associated with lung cancer when it co-occurred with asthma.

Methodological considerations

The study strengths include the large sample size and detailed information on lifetime smoking history. Data on multiple PRD was collected thus the relationship between patterns of PRD and lung cancer could be investigated. Limitations include some centers using hospital-based control selection, the low response rate among controls in the AUT study (40%), and the small number of never smokers. There was limited detail on the respiratory diseases, for example investigation of atopic and allergic subtypes of asthma was not possible. The comparability of chronic bronchitis between studies may be limited due to differences in the definition of the condition. Most studies reported diagnoses of 'chronic bronchitis', whilst INCO/LLP-UK studies used a broader definition of the disease, asking participants whether they had had 'bronchitis', which includes acute and chronic subtypes.

However, sensitivity analysis excluding the INCO/LLP-UK studies found little difference in the results (data not shown).

Temporality is an important consideration when investigating PRD and lung cancer as some of the conditions resemble the early symptoms of lung cancer. Latency analysis was possible in studies that collected age at PRD diagnoses. Excluding participants without age at PRD diagnoses reduced the sample size by almost 50% and missing data may have influenced the relationship between PRD and lung cancer. However, overall patterns of association were comparable between the full and restricted study sample indicating that missing data may not have influenced the associations (data not shown).

PRD diagnoses were self-reported and participants may have misreported their disease status (11, 12). The lack of medical records or spirometry data limit the validity of the disease definition, and this may have varied by PRD. For example diagnosis of emphysema requires sensitive pulmonary function tests compared to a sputum test for tuberculosis. Studies that have compared self-reported data and medical records of chronic respiratory diseases have found good agreement for the absence or presence of asthma (13, 14), and moderate to poor agreement for COPD, emphysema, pneumonia and tuberculosis(15, 16). However, self-reported COPD has also been shown to have a high level of agreement with spirometry results(17, 18). Recall bias is a potential problem in all case-control studies and it is possible that misclassification may have introduced some bias here. Nevertheless, cases did not report all PRD at a consistently higher level than controls, as shown by the positive association between chronic bronchitis and emphysema with lung cancer, null association for tuberculosis and an inverse relationship for asthma, indicating that recall bias may not have a strong influence on the results(19). Differences in the severity or treatment of the PRD could also mean that participants who report different diseases may differently recall

exposure to other risk factors, such as smoking history. Never smokers were investigated in this study, but due to small numbers, the results are difficult to interpret.

Interpretation of findings and comparison with the literature

Co-occurrence of PRD

Co-occurrence of different pulmonary conditions was common in the SYNERGY consortium, as shown elsewhere. In particular, asthma and emphysema were rarely reported in isolation, compared to other PRD. In an Italian general population study 13% of adults reported a physician's diagnoses of asthma and COPD, the proportion increasing to 20% amongst participants aged 65 and older(20). Clinical record studies have reported high levels of co-occurrence of respiratory diseases(21). An American study found that 47% of patients age >65y hospitalized for pneumonia had a co-morbid chronic pulmonary disease (22, 23). Our estimates of co-occurrence are at the upper end of previously reported figures; of participants who reported one PRD, 31.3% cases and 26.3% controls reported ≥2 PRD. Respiratory diseases often share symptoms, for example COPD and asthma. The overlap of asthma and COPD diagnoses can reach 20% of all patients with chronic respiratory disease(24). A previous diagnosis of a respiratory disease is also associated with an increased risk of future diagnoses of another respiratory disease. Prior tuberculosis infection has been associated with irreversible airway obstruction and an increased risk of COPD, whilst childhood pneumonia is linked to an increased risk of major respiratory diseases in adulthood(25). Given the high proportion of patients with multiple pulmonary diseases, it is important to account for multiple diagnoses when investigating the independent contribution of each respiratory disease to cancer risk.

Chronic bronchitis and emphysema and lung cancer

Findings in this study of a positive association between chronic bronchitis and emphysema and lung cancer are consistent with previous pooled analysis, which also included the AUT, Toronto and INCO/LLP-UK studies. Brenner et al observed an average overall relative risk of 1.47 (1.29-1.68) from 13 studies and 2.33 (1.86-2.94) from 16 studies for chronic bronchitis and emphysema, respectively. Comparable independent associations were observed in this study, irrespective of latency. Often chronic bronchitis and emphysema are grouped together, along with other pulmonary syndromes, into COPD, despite heterogeneity in their clinical presentation, physiology, response to therapy, decline in lung function, and survival(26). It is important to investigate chronic bronchitis and emphysema separately as grouping them may mask differences in their association with lung cancer. As shown here, individual conditions and different patterns of PRD had unique and independent associations with lung cancer.

Emphysema was found to have a stronger association with lung cancer, compared to chronic bronchitis as well as other PRD. Studies which have investigated chronic bronchitis and emphysema separately have reported similar findings (2, 27). A 20 year follow-up study of 448,600 lifelong non-smokers, reported that lung cancer mortality was significantly associated with both emphysema (hazard ratio (HR)=1.7; 1.1–2.6), and emphysema combined with chronic bronchitis (HR= 2.4; 1.2–4.9), but not with chronic bronchitis alone (HR= 1.0; 0.7–1.3)(28).

A potential explanation for the increase in lung cancer risk is the inflammatory response to chronic bronchitis and emphysema which is conducive to tumor initiation(3). Increases in genetic mutations, angiogenesis(29) and anti-apoptotic signalling(30) are potential processes through which inflammation may increase the risk of cancer development.

Pneumonia and lung cancer

Pneumonia had a positive relationship with lung cancer, but there was some indication that the time between pneumonia and lung cancer diagnoses may influence the relationship. A stronger effect was shown between pneumonia with shorter latencies and lung cancer, compared to those diagnosed later. In a prospective UK study of primary care data, the association between pneumonia and lung cancer was influenced by timing of diagnoses; greater effect estimates were observed with pneumonia diagnosed within 6 months prior to lung cancer (OR=13.3) compared to 1-5 years (OR=1.34)(31). People with symptoms or diagnoses of a pulmonary disease are more likely to undergo further clinical investigation than those without, providing greater opportunity for a subsequent diagnoses of lung cancer. The strong association with short latency may also reflect reverse causality, as bronchial suppression or immunosuppression caused by a tumor may make patients more susceptible to infection. The association between pneumonia and lung cancer may therefore be partially explained by the misdiagnoses of early lung cancer symptoms or ascertainment bias due to increased monitoring of patients.

Asthma and lung cancer

Here an inverse association between asthma and lung cancer was observed, with the relationship stronger with longer compared to shorter latencies. A previous meta-analysis of existing studies found a positive relationship between asthma and lung cancer, with a stronger relationship in recent studies and shorter latencies(32). In sub-group analysis, they stratified by other respiratory diseases and found an inverse relationship between asthma and lung cancer in studies that adjusted for co-occurring chronic bronchitis, emphysema or COPD (shown in Supplementary Table V). Rosenberger et al concluded that there was no clear evidence of an independent association between asthma and lung cancer(32). Avoidance of known risk factors, such as tobacco-smoking, and by working in 'clean' industries may partially explain the inverse association and the strong association observed amongst

participants diagnosed with asthma ≥10 years prior to lung cancer/interview. A greater proportion of participants who reported asthma were classified as never smokers (21%), compared to those who reported emphysema (9%), bronchitis (14%) and pneumonia (15%). It has been hypothesized that asthma may reduce the risk of lung cancer, thus counteracting the association with other respiratory diseases, through a more efficient elimination of abnormal cells(33). Long term steroid treatment (inhalers or tablets) can have an important effect of the inflammation pathway and could also biologically explain the inverse relationship. Information on treatment or grade of asthma was not available in these studies and could not be investigated here.

Tuberculosis and lung cancer

The published literature on tuberculosis and lung cancer is mixed. A meta-analysis found that tuberculosis was associated with adenocarcinoma lung cancer, but not squamous or small cell carcinoma(34). Findings from this study, of overall no association between tuberculosis and lung cancer are consistent with a previous investigation of tuberculosis which accounted for co-occurring pulmonary diseases, such as chronic bronchitis and asthma(35) (30). However, the number of tuberculosis cases in this consortium was small and thus results should be interpreted with caution.

Multiple PRD and lung cancer

Our study is one of a few that reports on the relationship between multiple types of pulmonary diseases and lung cancer. There was a stronger association with lung cancer with increasing number of pulmonary diseases (chronic bronchitis, emphysema and pneumonia). Yet, no association was observed between chronic bronchitis and lung cancer when asthma was also reported. Other studies have observed similar results. A Hong Kong longitudinal study that grouped COPD and asthma observed no association with lung cancer mortality in

female never smokers(36). A Chinese occupational cohort study examining chronic bronchitis, asthma and tuberculosis found only prior chronic bronchitis was associated with an increased lung cancer risk, with an adjusted HR of 1.50 (1.24–1.81), after including all respiratory diseases in the same model(35). A general practice study in the UK found no independent association between asthma and lung cancer after excluding all patients with a diagnoses of COPD(31).

Conclusions

Findings from this large international case-control consortium indicate that individual respiratory diseases may be differentially associated with lung cancer, after accounting for co-occurring PRD. The pooling of data provided the power to investigate multiple PRD and different histological subtypes of lung cancer, which was not possible in the individual lung cancer case-control studies. Respiratory diseases, such as chronic bronchitis, emphysema and asthma, are frequent conditions found in the general population, thus identifying those at greater risk would be of clinical importance. PRD frequently co-occur and in this study, the relationship between different patterns of PRD diagnoses and lung cancer varied, with emphysema being particularly important whilst co-occurring asthma and bronchitis were not associated with lung cancer. The different associations found with each PRD may support the hypothesis of a different biological mechanism underlying the etiological pathway from a specific respiratory disease to lung cancer. These findings could be used to identify potentially vulnerable groups, and inform the type and periodicity of clinical surveillance recommended for each PRD. Further investigation of our observed associations is needed to characterise high-risk groups which could then be used to develop opportunities for early disease detection.

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Table 1: Description of the studies included in the pooled analysis

Study Acronym	Country	Cases	Response rate (%)	Controls	Response rate (%)	Data collection	Control type
HdA	Germany	1,004	69	1,002	68	1988-1993	Population
AUT	Germany	3,180	77	3,249	41	1990-1995	Population
INCO-Cz. Rep.	Czech Republic	304	94	452	80	1998-2002	Hospital
INCO-Hungary	Hungary	391	90	305	100	1998-2001	Hospital
INCO-Poland	Poland	793	88	835	88	1998-2002	Population & hospital
INCO-Romania	Romania	179	90	225	99	1998-2001	Hospital
INCO-Russia	Russia	599	96	580	90	1998-2000	Hospital

Study Acronym	Country	Cases	Response rate (%)	Controls	Response rate (%)	Data collection	Control type
INCO-Slovakia	Slovakia	345	90	285	84	1998-2002	Hospital
INCO/LLP-UK	UK	442	78	917	84	1998-2005	Population
Montreal	Canada	1,176	85	1,505	69	1996-2002	Population
EAGLE	Italy	1,921	87	2,089	72	2002-2005	Population
ICARE	France	2,926	87	3,555	81	2001-2006	Population
TORONTO	Canada	455	62	948	60 & 84	1997-2002	Population & hospital

Table 2: Description of the study population

	Men; %/mean (n)		Women; %/mean (n)	
	Cases (n=9,794)	**Controls (n=11,163)**	**Cases (n=2,945)**	**Controls (n=3,782)**
Age (median); years	63	62	61	62
Highest level of education				
None	1.0 (96)	0.6 (72)	0.9 (25)	0.8 (29)
Some primary; <6y	16.9 (1,656)	11.5 (1,284)	16.1 (474)	15.0 (568)
Primary/some secondary; 6-9y	52.0 (5,089)	45.2 (1,330)	43.8 (4,886)	38.5 (1,455)
Secondary/some college; 10-13y	17.6 (1,720)	22.3 (656)	21.9 (2,441)	25.4 (959)
University; >13y	12.6 (1,233)	22.2 (2,480)	15.6 (460)	20.4 (771)
'List A' occupation				
Never	85.2 (8,347)	90.2 (10,073)	94.5 (2,871)	98.7 (3,734)
Ever	14.8 (1,447)	9.8 (1,090)	2.5 (74)	1.3 (48)
Smoking status				
Never	2.4 (233)	23.5 (2,627)	25.4 (749)	59.0 (2,232)
Former (≥5 years)	26.6 (2,601)	43.6 (4,869)	14.0 (413)	18.3 (693)
Current	71.1 (6,690)	32.9 (3,667)	60.5 (1,783)	22.7 (857)
Pack-year; mean	42.7 (9,561)	35.2 (2,196)	26.0 (8,536)	20.0 (1,550)
Time since cessation of smoking				
2-7y	12.6 (1,229)	7.5 (835)	8.9 (263)	4.7 (177)
8-15y	9.6 (944)	10.0 (1,120)	5.3 (156)	4.8 (180)
16-25y	8.2 (806)	13.8 (1,544)	3.8 (113)	5.9 (224)
≥26y	4.8 (469)	16.0 (2,900)	2.0 (59)	5.4 (204)
Centers				

	Men; %/mean (n)		Women; %/mean (n)	
	Cases (n=9,794)	**Controls (n=11,163)**	**Cases (n=2,945)**	**Controls (n=3,782)**
HdA	7.9 (774)	7.2 (804)	5.4 (159)	4.3 (164)
AUT	26.2 (2,562)	23.8 (2,654)	17.5 (514)	14.4 (545)
INCO-Cz. Rep.	2.3 (229)	2.6 (289)	2.3 (68)	4.2 (158)
INCO-Hungary	3.2 (312)	2.2 (247)	2.9 (86)	1.7 (64)
INCO-Poland	5.6 (545)	5.1 (568)	8.2 (241)	6.8 (258)
INCO-Romania	1.4 (139)	1.4 (152)	1.4 (40)	2.0 (76)
INCO-Russia	5.3 (516)	4.5 (501)	2.7 (79)	2.0 (77)
INCO-Slovakia	2.9 (385)	2.1 (234)	2.0 (58)	1.3 (49)
INCO/LLP-UK	2.8 (272)	5.1 (564)	5.4 (158)	9.1 (343)
Montreal	6.5 (634)	7.7 (858)	14.8 (435)	15.9 (601)
EAGLE	15.4 (1,503)	14.3 (1,564)	13.5 (398)	13.1 (497)
ICARE	19.3 (1,888)	22.7 (2,560)	19.0 (558)	18.9 (716)
TORONTO	1.4 (135)	1.5 (168)	1.4 (135)	6.2 (234)
Histologic type*				
Squamous cell carcinoma	40.8 (3,966)		19.1 (560)	
Small cell carcinoma	16.4 (1,594)		17.2 (504)	
Adenocarcinoma	25.9 (2,520)		44.1 (1,291)	

*The remaining cases had other or mixed histology types or information was missing (n=2,304)

Table 3: The association between previous respiratory disease (PRD) diagnoses and risk of lung cancer; odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression models

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
Men	7,023		7,652			7,697		8,535			9,120		10,280		
None	3,938	56.1	5,055	66.1	Ref	5,113	66.4	6,319	74.0	Ref	6,459	70.8	8,182	73.6	Ref
Bronchitis	1,639	23.3	1,176	15.4	1.33(1.20, 1.48)						2,166	23.8	1,442	14.0	1.52(1.39, 1.67)
Emphysema	346	4.9	176	2.3	1.50(1.21, 1.87)	398	5.2	204	2.4	1.68(1.37, 2.05)					
Tuberculosis	349	5.0	323	4.2	1.00(0.83, 1.20)	364	4.7	341	4.0	1.01(0.85, 1.21)	461	5.05	427	4.15	1.10(0.94, 1.29)
Pneumonia	1,750	24.9	1,444	18.9	1.24(1.13, 1.37)	1,945	25.3	1,580	18.5	1.36(1.24, 1.48)					
Asthma	372	5.3	402	5.3	0.89(0.75, 1.07)	424	5.5	468	5.5	0.96(0.81, 1.13)	540	5.9	614	6.0	0.86(0.74, 0.99)
Women	1,864		2,430			2,312		3,041			2,497		3,171		
None	1,056	56.7	1,514	62.3	Ref	1,501	64.9	2,193	72.1	Ref	1,648	66.0	2,340	73.8	Ref
Bronchitis	484	26.0	487	20.0	1.12(0.92, 1.35)						673	27.0	567	17.9	1.25(1.07, 1.47)
Emphysema	65	3.5	43	1.8	1.35(0.85, 2.12)	97	4.2	54	1.8	1.42(0.96, 2.11)					
Tuberculosis	97	5.2	100	4.1	1.16(0.83, 1.60)	108	4.7	111	3.7	1.10(0.80, 1.51)	133	5.3	130	4.1	1.21(0.91, 1.60)

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
Pneumonia	418	22.4	403	16.6	1.20(1.00, 1.44)	605	26.2	536	17.6	1.38(1.18, 1.62)					
Asthma	139	7.5	224	9.2	0.75(0.57, 0.98)	199	8.6	299	9.8	0.74(0.59, 0.93)	233	9.3	286	9.0	0.90(0.73, 1.12)

Participants diagnosed with previous respiratory diseases at any age; participants may be diagnosed with more than 1 respiratory disease. Analyses include; [1]the Montreal study and [2]the ICARE study. All previous respiratory diseases included in the same model; further adjustment made for age and center, 'list A' occupation, level of education, smoking status, pack-years and time-since-stopped smoking.

Table 4: The associations between combinations of previous respiratory disease (PRD) diagnoses and lung cancer in men; odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression models

PRD patterns	Controls		Cases		OR (95% CI)	
	n	%	n	%	Unadjusted	Adjusted
Bronchitis (n=11,808)	5,577		6,231			
None	5,055	81.1	3,938	70.6	Ref	Ref
Bronchitis only	577	9.3	751	13.5	1.81(1.61, 2.04)	1.39(1.21, 1.59)
Bronchitis & Emphysema	37	0.6	77	1.4	2.69(1.81, 4.01)	1.70(1.09, 2.66)
Bronchitis & Tuberculosis	29	0.5	33	0.6	1.62(0.98, 2.70)	1.04(0.59, 1.85)
Bronchitis & Pneumonia	261	4.2	431	7.7	2.26(1.92, 2.66)	1.83(1.52, 2.20)
Bronchitis & Asthma	112	1.8	78	1.4	1.04(0.77, 1.40)	1.03(0.73, 1.46)
Bronchitis & Emphysema & Pneumonia	28	0.5	57	1.0	2.60(1.64, 4.11)	1.69(1.02, 2.80)
Bronchitis & Tuberculosis & Pneumonia	32	0.5	53	1.0	2.25(1.44, 3.52)	1.86(1.13, 3.04)
Bronchitis & Pneumonia & Asthma	43	0.7	73	1.3	2.47(1.68, 3.65)	1.99(1.27, 3.11)
Emphysema (n=9,515)	4,284		5,231			
None	5,055	96.7	3,938	92.0	Ref	Ref
Emphysema only	33	0.6	92	2.2	3.41(2.28, 5.10)	2.68(1.71, 4.21)
Emphysema & Bronchitis	37	0.7	77	1.8	2.69(1.80, 4.00)	1.67(1.07, 2.61)
Emphysema & Bronchitis & Pneumonia	28	0.5	57	1.3	2.64(1.67, 4.18)	1.69(1.02, 2.80)
Pneumonia (n=12,187)	5,688		6,499			
None	5,055	77.8	3,938	69.3	Ref	Ref
Pneumonia only	942	14.5	972	17.1	1.26(1.14, 1.40)	1.23(1.09, 1.38)
Pneumonia & Bronchitis	261	4.0	431	7.6	2.10(1.79, 2.48)	1.73(1.44, 2.07)
Pneumonia & Tuberculosis	57	0.9	58	1.0	1.21(0.84, 1.75)	1.15(0.75, 1.75)
Pneumonia & Asthma	27	0.4	33	0.6	1.59(0.94, 2.68)	1.46(0.80, 2.68)
Pneumonia & Bronchitis & Emphysema	28	0.4	57	1.0	2.68(1.70, 4.24)	1.71(1.03, 2.83)

PRD patterns	Controls		Cases		OR (95% CI)	
	n	%	n	%	Unadjusted	Adjusted
Pneumonia & Bronchitis & Tuberculosis	32	0.5	53	0.9	2.06(1.32, 3.22)	1.74(1.06, 2.85)
Pneumonia & Bronchitis & Asthma	43	0.7	73	1.3	2.27(1.54, 3.34)	1.84(1.18, 2.87)
Asthma (n=9,767)	4,310		5,457			
None	5,055	92.7	3,938	91.4	Ref	Ref
Asthma only	150	2.8	82	1.9	0.76(0.57, 1.01)	0.73(0.53, 1.01)
Asthma & Bronchitis	112	2.1	78	1.8	1.02(0.76, 1.38)	1.01(0.71, 1.43)
Asthma & Pneumonia	27	0.5	33	0.8	1.62(0.96, 2.74)	1.49(0.81, 2.74)
Asthma & Pneumonia & Bronchitis	43	0.8	73	1.7	2.28(1.55, 3.37)	1.87(1.19, 2.93)

Participants diagnosed with index previous respiratory disease and other respiratory diseases at any age; i.e. participants with data on all 5 PRD. Unadjusted models include age and center, adjusted models further adjust for 'list A' occupation and level of education, smoking status, pack-years, time-since-stopped smoking.

Table 5: The association between latency of previous respiratory disease (PRD) diagnoses and lung cancer using logistic regression models; odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression models

Latency of PRD diagnoses*		Men						Women					
		Cases (n=4,448)		Controls (n=4,912)		OR (95%)		Cases		Controls		OR (95%)	
		n	%	n	%	Model 1	Model 2	n	%	n	%	Unadjusted	Adjusted
Bronchitis	None	2,707	77.7	3,125	86.1	Ref	Ref	797	75.8	1,115	81.3	Ref	Ref
(n=7,116)	<2y	110	3.2	48	1.3	2.52(1.78, 3.56)	1.78(1.22, 2.61)	19	1.8	28	2.0	0.81(0.44, 1.49)	0.58(0.30, 1.15)
	2-4y	60	1.7	43	1.2	1.51(1.01, 2.25)	1.10(0.71, 1.72)	24	2.3	30	2.2	0.98(0.56, 1.72)	0.77(0.42, 1.44)
	5-9y	85	2.4	45	1.2	1.92(1.32, 2.80)	1.76(1.16, 2.68)	21	2.0	20	1.5	1.32(0.70, 2.50)	0.98(0.49, 1.96)
	≥10y	524	15.0	369	10.2	1.53(1.31, 1.79)	1.30(1.09, 1.55)	190	18.1	178	13.0	1.33(1.02, 1.73)	1.18(0.88, 1.59)
Emphysema	None	3,332	93.7	3,612	97.7	Ref	Ref	1,063	97.1	1,381	98.6	Ref	Ref
(n=7,252)	<2y	35	1.0	12	0.3	3.04(1.56, 5.94)	1.94(0.96, 3.93)	12	1.1	5	0.4	3.17(1.09, 9.17)	1.99(0.62, 6.42)
	2-4y	37	1.0	15	0.4	2.56(1.39, 4.71)	1.98(0.97, 4.03)	9	0.8	4	0.3	2.31(0.70, 7.67)	1.17(0.31, 4.34)
	5-9y	40	1.1	17	0.5	2.34(1.31, 4.18)	1.60(0.84, 3.04)	3	0.3	4	0.3	0.94(0.21, 4.31)	0.36(0.06, 2.22)
	≥10y	111	3.1	41	1.1	2.42(1.67, 3.51)	1.94(1.29, 2.92)	8	0.7	7	0.5	1.14(0.41, 3.22)	0.81(0.26, 2.56)
Tuberculosis	None	3,380	94.5	3,546	95.8	Ref	Ref	1,038	94.5	1,352	96.6	Ref	Ref

Latency of PRD diagnoses*		Men						Women					
		Cases (n=4,448)		Controls (n=4,912)		OR (95%)		Cases		Controls		OR (95%)	
		n	%	n	%	Model 1	Model 2	n	%	n	%	Unadjusted	Adjusted
(n=7,276)	<2y	12	0.3	5	0.1	2.28(0.79, 6.54)	1.37(0.47, 3.98)	5	0.5	0	0.0		
	2-4y	12	0.3	3	0.1	3.76(1.05, 13.56)	3.26(0.80, 13.25)	3	0.3	1	0.1	5.31(0.54, 51.77)	5.06(0.44, 58.33)
	5-9y	14	0.4	7	0.2	1.79(0.71, 4.54)	1.03(0.40, 2.65)	6	0.6	0	0.0		
	≥10y	158	4.4	139	3.8	1.07(0.84, 1.36)	1.06(0.81, 1.39)	47	4.3	47	3.4	1.16(0.76, 1.78)	1.12(0.70, 1.79)
Pneumonia	None	2,639	74.6	2,939	80.5	Ref	Ref	860	79.3	1,152	83.5	Ref	Ref
(n=7,188)	<2y	167	4.7	53	1.5	3.10(2.25, 4.27)	3.31(2.33, 4.70)	41	3.8	27	2.0	1.63(0.98, 2.71)	1.21(0.70, 2.08)
	2-4y	68	1.9	50	1.4	1.30(0.89, 1.90)	0.94(0.63, 1.43)	20	1.9	26	1.9	0.89(0.49, 1.63)	0.78(0.40, 1.52)
	5-9y	76	2.2	46	1.3	1.61(1.10, 2.34)	1.82(1.19, 2.78)	21	1.9	20	1.5	1.29(0.68, 2.42)	1.07(0.54, 2.14)
	≥10y	588	16.6	562	15.4	1.00(0.88, 1.15)	1.04(0.90, 1.21)	142	13.1	154	11.2	1.00(0.77, 1.30)	0.90(0.68, 1.20)
Asthma	None	3,416	95.9	3,519	95.3	Ref	Ref	1,020	93.2	1,276	91.7	Ref	Ref
(n=7,253)	<2y	28	0.8	21	0.6	1.08(0.60, 1.93)	1.21(0.62, 2.40)	13	1.2	15	1.1	0.99(0.45, 2.15)	1.32(0.58, 3.00)
	2-4y	20	0.6	14	0.4	1.15(0.56, 2.34)	0.82(0.37, 1.79)	11	1.0	20	1.4	0.65(0.30, 1.39)	0.57(0.24, 1.37)
	5-9y	26	0.7	31	0.8	0.60(0.35, 1.03)	0.44(0.24, 0.79)	12	1.1	23	1.7	0.66(0.32, 1.35)	0.64(0.28, 1.43)

Latency of PRD diagnoses*	Men						Women					
	Cases (n=4,448)		Controls (n=4,912)		OR (95%)		Cases		Controls		OR (95%)	
	n	%	n	%	Model 1	Model 2	n	%	n	%	Unadjusted	Adjusted
≥10y	71	2.0	107	2.9	0.51(0.37, 0.70)	0.67(0.47, 0.98)	38	3.5	58	4.2	0.79(0.51, 1.22)	0.83(0.51, 1.35)

*Number of year's index respiratory disease diagnosed prior to lung cancer diagnoses or control interview. Participants restricted to those with age of diagnoses for index respiratory disease and complete data on other 4 respiratory diseases; i.e. participants with data on 5 PRD.

Unadjusted models include age and center, adjusted models further adjust for 'list A' occupation and level of education, smoking status, pack-years, time-since-stopped smoking.

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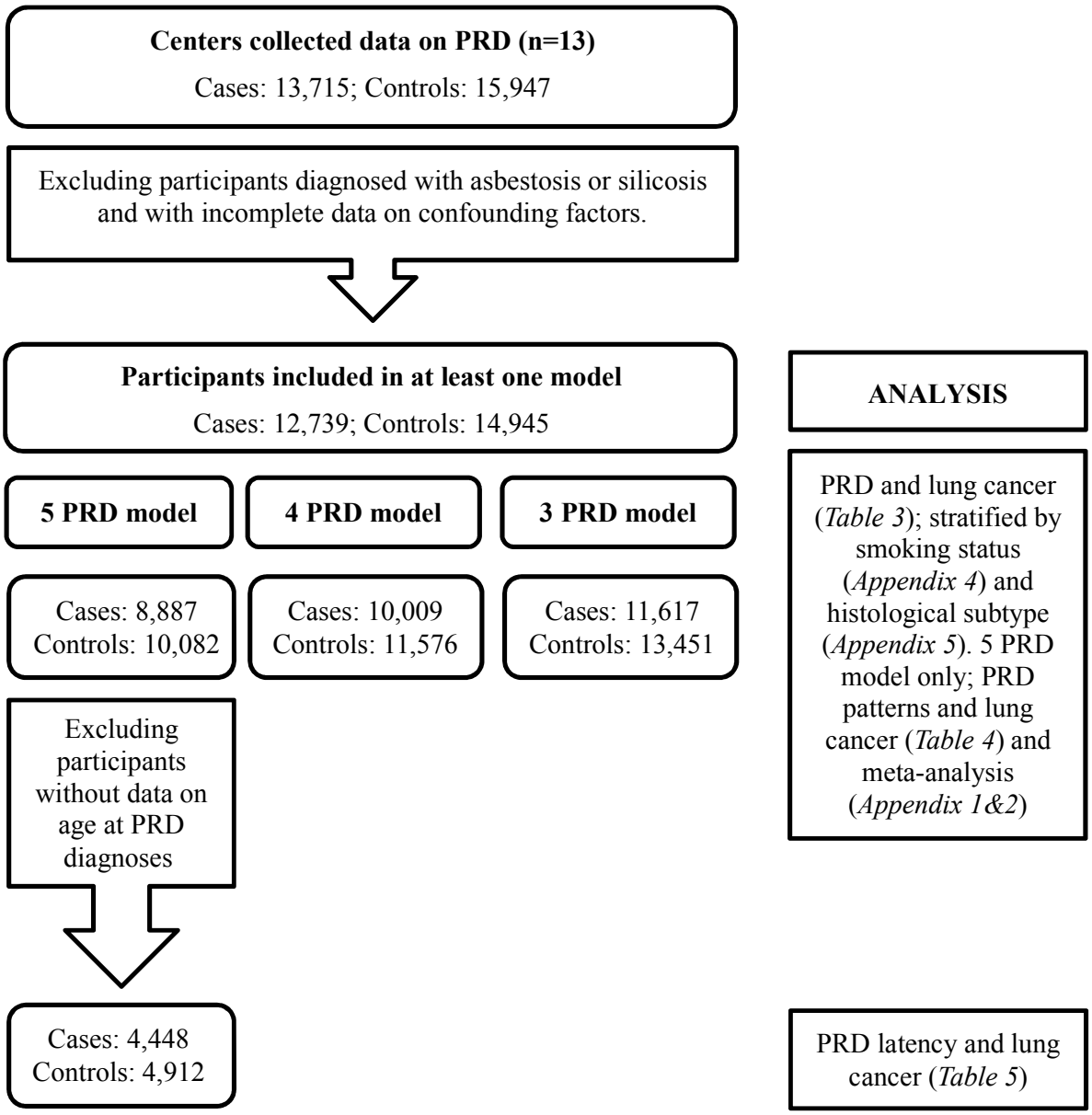


Figure 1: Flowchart of exclusion, participants and analysis

ONLINE DATA SUPPLEMENT

Appendix 1: Industries and occupations that have been classified as having an increased risk of developing lung cancer

ISIC4		International Standard Classification of Occupations	
Code	Industry	Unit groups	Code
2301	Mining of iron ores	Mining technicians	03810; 03890
2302	Mining of uranium & thorium ores	Production supervisors & general foreman; mining, quarrying & well drilling	70020
	Mining of non-ferrous metal ores, except uranium & thorium ores		
2902	Mining of chemical & fertilizer minerals	Miners & quarrymen	71100-71130; 71150-71170; 71190
2909	Mining & agglomeration of peat		
	Mining of gypsum, anhydrite	Mineral & stone treaters	71230-71260; 71290
	Mining & quarrying of asbestos, mica, quartz, gem stones, abrasives, asphalt & bitumen, other non-metallic minerals, n.e.c.	Crane and hoist operators	97345
1110	Growing of cereals & other crops n.e.c	Orchard, vineyard and related tree and shrub crop workers	62330
	Growing of vegetables, horticultural specialities, nursery products		
	Growing of fruit, nuts, beverage & spice crops		
	Farming of cattle, sheep, goats, horses, asses, mules & hinnies; dairy farming		
	Raising domesticated or wild animals n.e.c. (e.g. swine, poultry, rabbits)		
	Growing of crops combined with farming of animals (mixed farming)		
	Landscape gardening		
	Tree nurseries, except forest trees		
2901	Quarrying of building or monumental stone; mining of ceramic or refractory clay, chalk, dolomite; sand & gravel	Miners & quarrymen	71110; 71130; 71190
	Mining of feldspar	Mineral & stone treaters	71220-71240; 71290

ISIC4		International Standard Classification of Occupations	
Code	Industry	Unit groups	Code
3720	Manufacture of primary products of precious & non-ferrous metal (excluding forging & casting operations)	Building caretakers, charworkers, cleaners & related workers	55000
		Launderers, dry-cleaners & pressers	56000
	Casting of non-ferrous metals	Fire fighters	58110
	Forging of precious & non-ferrous metals	Farm machinery operators	62800
	Treatment & specialized operation on precious & non-ferrous metals, on a fee or contract basis	Loggers	63100
		Production supervisors & general foremen	70000
	Recycling of non-ferrous metal waste & scrap	Miners & quarrymen	71100
3841	Manufacture of engines & turbines for marine propulsion	Mineral & stone treaters	71200
	Manufacture of marine capstans, pulleys, tackle, etc	Well drillers, borers & related workers	71300
	Building & repairing of ships (other than sport & pleasure boats) & specialized parts	Metal processers	72000
		Wood preparation workers & paper makers	73000
	Building & repairing of sport & pleasure boats & specialized parts	Chemical processors & related workers not elsewhere classified	74900
3842	Manufacture of railway & tramway locomotives & rolling stock	Spinners, weavers, knitters, dyers & related workers	75000
3610	Manufacture of non-structural non-refractory ceramic ware (pottery, china, & earthenware)	Tanners, fellmongers & pelt dressers	76000
		Food & beverage processors	77000
3691	Manufacture of refractory clay products	Tobacco preparers & tobacco product makers	78000
	Manufacture of structural non-refractory clay & ceramic products	Tailors, dressmakers, sewers, upholsterers & related workers	79000
		Shoemakers & leather goods makers	80000
		Cabinetmakers & related woodworkers	81000
		Stone cutters & carvers	82000
		Blacksmiths, toolmakers & machine tool operators	83000
		Machine fitters, machine assemblers & precision instrument makers (except electrical)	84000
		Electrical fitters & related electrical & electronics workers	85000

ISIC4		International Standard Classification of Occupations	
Code	Industry	Unit groups	Code
		Sound-equipment operators & cinema projectionists	86200
		Plumbers, welders, sheet-metal & structural metal preparers & erectors	87000
		Jewellery & precious metal workers	88000
		Glass formers, potters & related workers	89000
		Rubber & plastics product makers	90000
		Paper & paperboard makers	91000
		Printing pressmen	92200
		Stereotypers & electrotypers	92300
		Printing engravers (except photo-engravers)	92400
		Photo-engravers	92500
		Bookbinders & related workers	92600
		Photographic dark-room workers	92700
		Printers & related workers not elsewhere classified	92900
		Painters	93000
		Musical instrument makers & tuners	94100
		Basketry weavers & brush makers	94200
		Non-metallic mineral product makers	94300
		Other production & related workers	94900
		Bricklayers, stonemasons & tile setters	95100
		Reinforced concreters, cement finishers & terrazzo workers	95200
		Roofers	95300
		Carpenters, joiners & parquetry workers	95400
		Plasterers	95500

ISIC4		International Standard Classification of Occupations	
Code	Industry	Unit groups	Code
		Glaziers	95700
		Construction workers not elsewhere classified	95900
		Stationary engine & related equipment operators	96000
		Material handling & related equipment operators, dockers & freight handlers	97000
		Transport equipment operators	98000
		Labourers not elsewhere classified	99900
3710	Manufacture of primary iron & steel products	Metal casters	72400
	Casting of iron & steel	Metal moulders & coremakers	72500
	Forging of iron & steel		
	Treatment & specialized operation on iron & steel, on a fee or contract basis		
	Manufacture of wheels for railway cars & locomotives		
	Recycling of non-ferrous metal waste & scrap, outside of scrap yard		
3720	Manufacture of primary products of precious & non-ferrous metal (excluding forging & casting operations)	Metal Casters	72440; 72450; 72490
	Casting of non-ferrous metals	Metal platers & coaters	72800
	Forging of precious & non-ferrous metals	Metal cleaner	72940
	Treatment & specialized operation on precious & non-ferrous metals, on a fee or contract basis		
	Recycling of non-ferrous metal waste & scrap		
3841	Manufacture of engines & turbines for marine propulsion	Machinery fitters & machine assemblers	84130
	Manufacture of marine capstans, pulleys, tackle, etc	Plumbers & pipe fitters	87130
	Building & repairing of ships & specialized parts		
	Building & repairing of sport & pleasure boats & specialized parts		

ISIC4		International Standard Classification of Occupations	
Code	Industry	Unit groups	Code
3842	Manufacture of railway & tramway locomotives & rolling stock		
3839	Manufacture of switches, fuses, sockets, plugs, conductors, lightning arresters	Electrical & electronic equipment assemblers	85320
	Manufacture of insulated wire & cable		
	Manufacture of accumulators, primary cells & primary batteries		
	Manufacture of electric lamps, fixtures		
	Manufacture of motor vehicle lighting equipment; carbon & graphite electrodes; other electrical equipment n.e.c.		
3720	Manufacture of primary products of precious & non-ferrous metal	Welders and flame-cutters	87245
	Casting of non-ferrous metals		
	Forging of precious & non-ferrous metals		
	Treatment & specialized operation on precious & non-ferrous metals, on a fee or contract basis		
	Recycling of non-ferrous metal waste & scrap		
3610	Manufacture of non-structural non-refractory ceramic ware	Glass & ceramics kilnmen	89350-89390
3691	Manufacture of refractory clay products	Glass formers, potters & related workers not elsewhere classified	89930; 89940; 89990
	Manufacture of structural non-refractory clay & ceramic products		
3540	Manufacture of briquettes of hard coal, at mining site or from purchased coal	Roofer	95320; 95340
	Manufacture of briquettes of lignite, at mining site or from purchased coal	Earth moving & related machinery operators	97460
	Manufacture of coke oven products		
	Manufacture of petroleum refinery products from purchased materials		
	Manufacture of asphalt products		
	Manufacture of asphalt floor tiles		
4102	Manufacture of gas; distribution of gaseous fuels through mains		
3720	Manufacture of primary products of precious & non-ferrous metal	Crushers, grinders & mixers	74100

ISIC4		International Standard Classification of Occupations	
Code	Industry	Unit groups	Code
	Casting of non-ferrous metals	Cookers, roasters & related heat-treaters	74200
	Forging of precious & non-ferrous metals	Filter & separator operators	74300
	Treatment & specialized operation on precious & non-ferrous metals, on a fee or contract basis	Still & reactor operators	74400
	Recycling of non-ferrous metal waste & scrap	Petroleum-refining workers	74500
3841	Manufacture of engines & turbines for marine propulsion	Chemical processors & related workers not elsewhere classified	74920; 74925
	Manufacture of marine capstans, pulleys, tackle, etc	Painters	93000
	Building & repairing of ship s& specialized parts	Roofers	95330; 95390
	Building & repairing of sport & pleasure boats & specialized parts	Insulators	95600
3842	Manufacture of railway & tramway locomotives & rolling stock	Earth moving & related machinery operators	97450
3540	Manufacture of briquettes of hard coal, at mining site or from purchased coal		
	Manufacture of briquettes of lignite, at mining site or from purchased coal		
	Manufacture of coke oven products		
	Manufacture of petroleum refinery products from purchased materials		
	Manufacture of asphalt products		
	Manufacture of asphalt floor tiles		
4102	Manufacture of gas; distribution of gaseous fuels through mains		
3610	Manufacture of non-structural non-refractory ceramic ware		
3691	Manufacture of refractory clay products		
	Manufacture of structural non-refractory clay & ceramic products		
3699	Manufacture of peat briquettes	Crushers, grinders & mixers	74190
	Manufacture of glass wool	Fibre preparers	75100
	Manufacture of non-clay refractory products	Spinners & winders	75200
	Manufacture of articles of concrete, cement & plaster	Weavers & related workers	75415-75425;

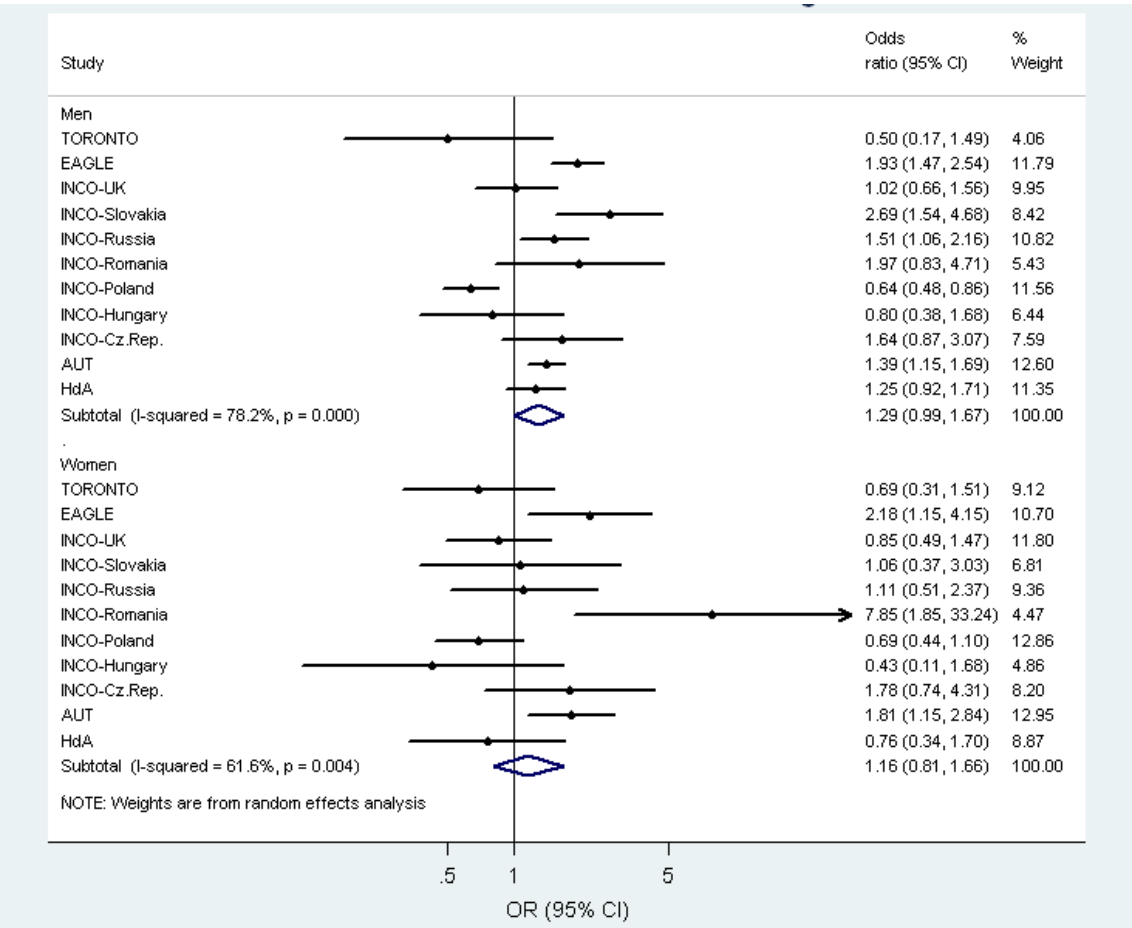
ISIC4		International Standard Classification of Occupations	
Code	Industry	Unit groups	Code
	Cutting, shaping & finishing of stone (not at quarry)		75470-75490
	Manufacture of asbestos products; friction materials; mineral insulating materials; grindstones, abrasive products; articles of mica, graphite or other	Knitters	75500
	Manufacture of cermets	Bleachers, dyers & textile product finishers	75670
	Manufacture of graphite products	Stone cutters & carvers	82020-82050; 82090
	Manufacture of vinyl asbestos floor tiles		
	Retail sale of tombstones & monuments (already engraved)	Non-metallic mineral product makers	94330

Appendix 2: Proportion of participants with an index previous respiratory disease (PRD) who report another condition

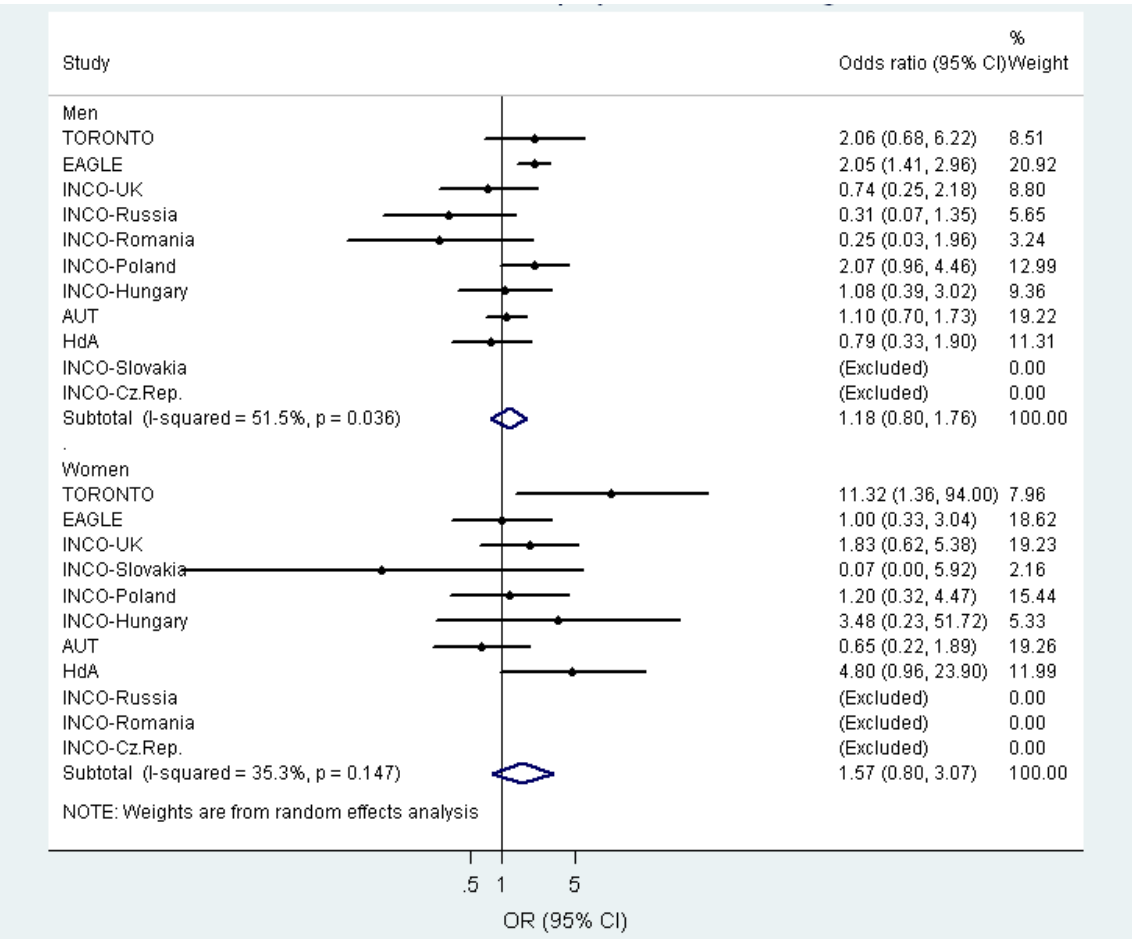
	Co-occurrence PRD; %(n)			
	Men		Women	
	Case	Control	Case	Control
Bronchitis	57.7 (1,023)	54.2 (682)	60.9 (336)	51.8 (266)
Emphysema	76.2 (295)	83.2 (163)	80.0 (72)	82.7 (43)
Tuberculosis	63.3 (254)	50.6 (178)	71.3 (87)	47.0 (54)
Pneumonia	46.6 (847)	36.6 (544)	61.4 (291)	50.9 (226)
Asthma	83.9 (427)	70.7 (362)	80.8 (193)	61.4 (173)

Appendix 3: The association between previous respiratory disease and risk of lung cancer stratified by sex; study specific odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression models and overall effect estimates and heterogeneity calculated using meta-analysis random-effect models

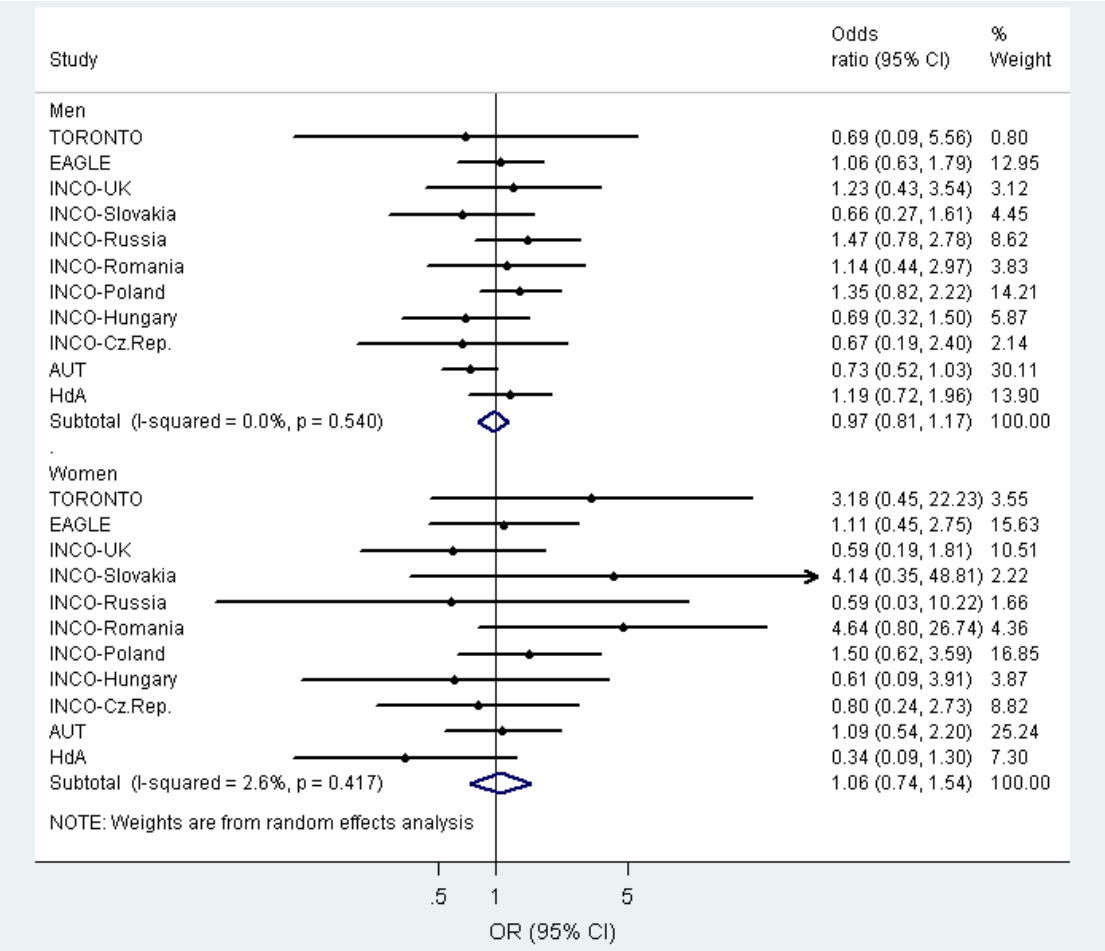
Bronchitis



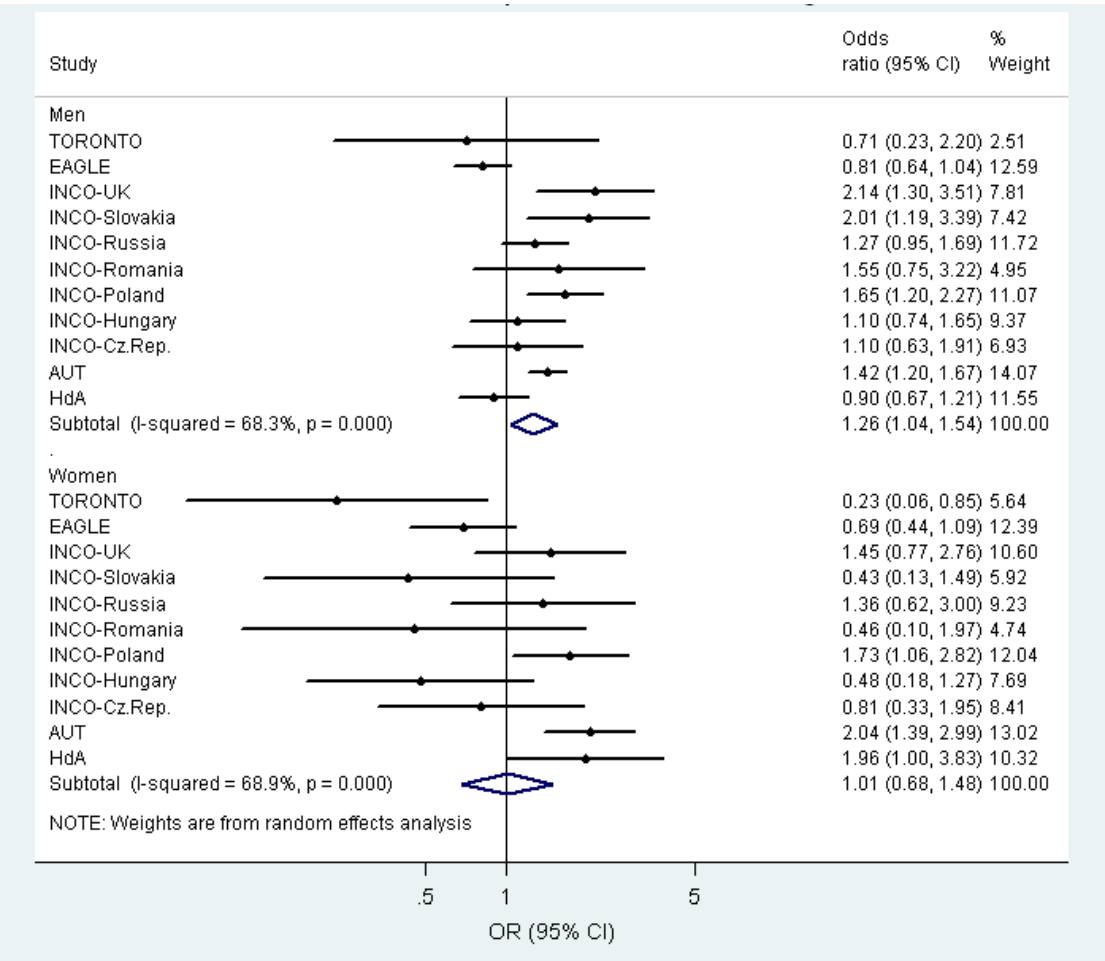
Emphysema


Study
Odds ratio (95% CI)
% Weight
Men
TORONTO 2.06 (0.68, 6.22) 8.51
EAGLE 2.05 (1.41, 2.96) 20.92
INCO-UK 0.74 (0.25, 2.18) 8.80
INCO-Russia 0.31 (0.07, 1.35) 5.65
INCO-Romania 0.25 (0.03, 1.96) 3.24
INCO-Poland 2.07 (0.96, 4.46) 12.99
INCO-Hungary 1.08 (0.39, 3.02) 9.36
AUT 1.10 (0.70, 1.73) 19.22
HdA 0.79 (0.33, 1.90) 11.31
INCO-Slovakia (Excluded) 0.00
INCO-Cz.Rep. (Excluded) 0.00
Subtotal (I-squared = 51.5%, p = 0.036) 1.18 (0.80, 1.76) 100.00
Women
TORONTO 11.32 (1.36, 94.00) 7.96
EAGLE 1.00 (0.33, 3.04) 18.62
INCO-UK 1.83 (0.62, 5.38) 19.23
INCO-Slovakia 0.07 (0.00, 5.92) 2.16
INCO-Poland 1.20 (0.32, 4.47) 15.44
INCO-Hungary 3.48 (0.23, 51.72) 5.33
AUT 0.65 (0.22, 1.89) 19.26
HdA 4.80 (0.96, 23.90) 11.99
INCO-Russia (Excluded) 0.00
INCO-Romania (Excluded) 0.00
INCO-Cz.Rep. (Excluded) 0.00
Subtotal (I-squared = 35.3%, p = 0.147) 1.57 (0.80, 3.07) 100.00
NOTE: Weights are from random effects analysis
.5
1
5
OR (95% CI)

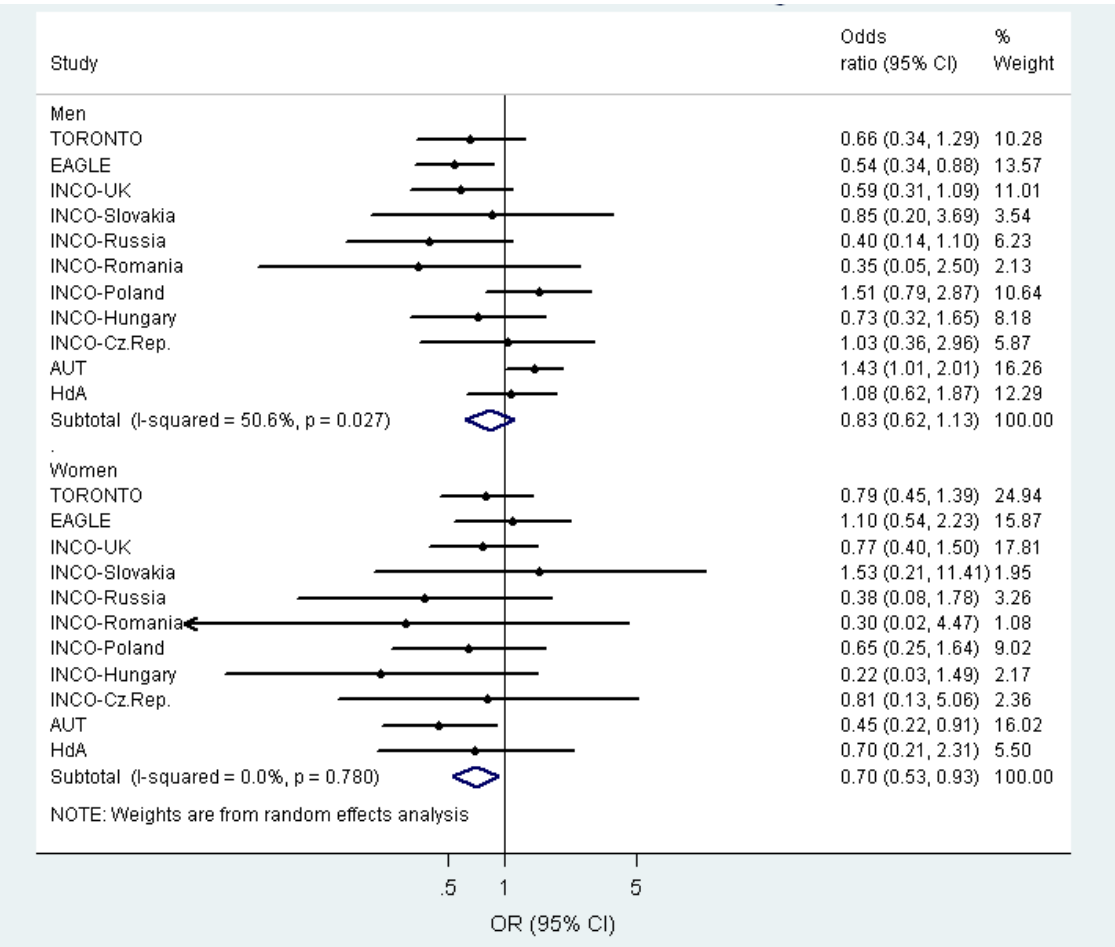
Tuberculosis



Pneumonia


Study
Odds ratio (95% CI)
% Weight
Men
TORONTO 0.71 (0.23, 2.20) 2.51
EAGLE 0.81 (0.64, 1.04) 12.59
INCO-UK 2.14 (1.30, 3.51) 7.81
INCO-Slovakia 2.01 (1.19, 3.39) 7.42
INCO-Russia 1.27 (0.95, 1.69) 11.72
INCO-Romania 1.55 (0.75, 3.22) 4.95
INCO-Poland 1.65 (1.20, 2.27) 11.07
INCO-Hungary 1.10 (0.74, 1.65) 9.37
INCO-Cz.Rep. 1.10 (0.63, 1.91) 6.93
AUT 1.42 (1.20, 1.67) 14.07
HdA 0.90 (0.67, 1.21) 11.55
Subtotal (I-squared = 68.3%, p = 0.000) 1.26 (1.04, 1.54) 100.00
Women
TORONTO 0.23 (0.06, 0.85) 5.64
EAGLE 0.69 (0.44, 1.09) 12.39
INCO-UK 1.45 (0.77, 2.76) 10.60
INCO-Slovakia 0.43 (0.13, 1.49) 5.92
INCO-Russia 1.36 (0.62, 3.00) 9.23
INCO-Romania 0.46 (0.10, 1.97) 4.74
INCO-Poland 1.73 (1.06, 2.82) 12.04
INCO-Hungary 0.48 (0.18, 1.27) 7.69
INCO-Cz.Rep. 0.81 (0.33, 1.95) 8.41
AUT 2.04 (1.39, 2.99) 13.02
HdA 1.96 (1.00, 3.83) 10.32
Subtotal (I-squared = 68.9%, p = 0.000) 1.01 (0.68, 1.48) 100.00
NOTE: Weights are from random effects analysis
.5
1
5
OR (95% CI)

Asthma



Participants diagnosed with a previous respiratory disease at any age; participants may be diagnosed with more than 1 previous pulmonary disease. All five respiratory diseases are included in the same model; further adjustment made for age and center, ever-employed in an occupation with established lung cancer risk, level of education, smoking status, pack-years and time-since-stopped smoking

Appendices 4: Comparison of pooled analyses and meta-analyses investigating the association between previous respiratory disease (PRD) diagnoses and risk of lung cancer; odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression models in the pooled analysis and random-effect models in the meta-analysis

	Pooled data	**Meta-analyses**		**Meta-analyses excluding studies to reduce heterogeneity***		
	OR (95% CI)	**OR (95% CI)**	**I^2**	**Studies excluded**	**OR (95% CI)**	**I^2**
Men; n=14,675						
None	Ref	Ref			Ref	
Bronchitis	1.33(1.20, 1.48)	1.29(0.99, 1.67)	78.2%	INCO-Poland, INCO-Slovakia & EAGLE	1.30(1.10, 1.53)	17.4%
Emphysema	1.50(1.21, 1.87)	1.18(0.80, 1.76)†	51.5%	EAGLE	1.05(0.71, 1.55)	27.9%
Tuberculosis	1.00(0.83, 1.20)	0.97(0.81, 1.17)	0.0%			
Pneumonia	1.24(1.13, 1.37)	1.26(1.04, 1.54)	68.3%	HdA, INCO/LLP-UK & EAGLE	1.39(1.24, 1.57)	0.0%
Asthma	0.89(0.75, 1.07)	0.83(0.62, 1.13)	50.6%	AUT & EAGLE	0.82(0.62, 1.09)	9.1%
Women; n=4,294						
None	Ref	Ref			Ref	
Bronchitis	1.12(0.92,1.35)	1.16(0.81,1.66)	61.6%	INCO-Poland & INCO-Romania	1.16(0.83, 1.61)	43.8%
Emphysema	1.35(0.85,2.12)	1.57(0.80,3.07)‡	35.3%	TORONTO	1.29(0.73, 2.30)	13.8%

Tuberculosis	1.16(0.83,1.60)	1.06(0.74,1.54)	2.6%			
Pneumonia	1.20(1.00,1.44)	1.01(0.68,1.48)	68.9%	AUT, EAGLE & TORONTO	0.95(0.62, 1.48)	58.5%
Asthma	0.75(0.57,0.98)	0.70(0.53,0.93)	0.0%			

Participants diagnosed with a previous respiratory disease at any age; participants may be diagnosed with more than 1 pulmonary disease. All five respiratory diseases are included in the same model; further adjustment made for age and center, ever-employed in an occupation with established lung cancer risk, level of education, smoking status, pack-years and time-since-stopped smoking.

The I^2 index can be interpreted as a percentage of heterogeneity, that is, the part of total variation that is due to between-studies variance

*If there was evidence of heterogeneity between studies, outliers were identified with Galbraith plots and excluded from analysis. †Due to small number of male participants who reported emphysema, INCO-Cz. Rep (cases=2; control=0) and INCO-Slovakia (cases=8; controls=0) excluded from meta-analyses. ‡Due to small number of female participants who reported emphysema, INCO-Cz. Rep (cases=0; control=0), INCO-Romani (cases=0; control=2) and INCO-Russia (cases=2; controls=0) were excluded from meta-analyses.

Appendix 5: The association between previous respiratory disease (PRD) diagnoses and risk of lung cancer stratified by smoking status; odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression models

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
Men															
Former smokers (>5y)	1,709		3,186			1,903		3,650			2,407		4,405		
None	933	54.6	2,044	64.2	Ref	1,218	64.0	2,639	72.3	Ref	1,678	69.7	3,446	78.2	Ref
Bronchitis	396	23.2	524	16.5	1.30(1.09, 1.55)	132					576	23.9	662	15.0	1.49(1.29, 1.73)
Emphysema	116	6.8	84	2.6	1.64(1.18, 2.28)	78	6.9	99	2.7	1.83(1.36, 2.47)					
Tuberculosis	76	4.5	135	4.2	0.98(0.72, 1.35)	499	4.1	145	4.0	0.94(0.69, 1.28)	119	4.9	191	4.3	1.15(0.89, 1.48)
Pneumonia	442	25.9	641	20.1	1.22(1.04, 1.43)	135	26.2	713	19.5	1.34(1.16, 1.55)					
Asthma	117	6.9	201	6.3	0.90(0.68, 1.19)	1,218	7.1	237	6.5	0.95(0.74, 1.22)	180	7.5	300	6.8	0.87(0.70, 1.09)
Current smokers	5,149		2,731			5,616		3,015			6,493		3,383		
None	2,879	55.9	1,781	65.2	Ref	3,757	66.9	2,250	74.6	Ref	4,598	70.8	2,673	79.0	Ref
Bronchitis	1,234	24.0	451	16.5	1.39(1.21, 1.53)						1,568	24.2	525	15.5	1.55(1.37, 1.75)

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
Emphysema	227	4.4	63	2.3	1.45(1.07, 1.97)	263	4.7	73	2.4	1.61(1.21, 2.12)					
Tuberculosis	267	5.2	121	4.4	0.98(0.78, 1.24)	279	5.0	126	4.2	1.02(0.81, 1.27)	333	5.1	138	4.1	1.03(0.83, 1.28)
Pneumonia	1,284	24.9	529	19.4	1.25(1.11, 1.42)	1,417	25.2	568	18.8	1.36(1.21, 1.53)					
Asthma	249	4.8	100	3.7	0.99 (0.76, 1.29)	282	5.0	116	3.9	1.06(0.84, 1.34)	350	5.4	154	4.6	0.91(0.73, 1.13)
Never smokers	165		1,735			178		1,870			220		2,492		
None	126	76.8	1,230	70.9	Ref	138	77.5	1,430	76.5	Ref	183	83.2	2,063	82.8	Ref
Bronchitis	9	5.5	201	11.6	0.48(0.23, 1.00)						22	10.0	255	10.2	1.10(0.68, 1.81)
Emphysema	3	1.8	29	1.7	1.68(0.45, 6.22)	3	1.7	32	1.7	1.17(0.33, 4.15)					
Tuberculosis	6	3.6	67	3.9	1.09(0.85, 2.60)	7	3.9	70	3.7	1.26(0.56, 2.87)	9	4.1	98	3.9	1.23(0.60, 2.52)
Pneumonia	24	14.6	274	15.8	1.04(0.86, 1.66)	29	16.3	299	16.0	1.12(0.73, 1.72)					
Asthma	6	3.6	101	5.8	0.41(0.24, 1.03)	7	3.9	115	6.2	0.39(0.17, 0.90)	10	4.6	160	6.4	0.49(0.24, 0.98)
Women															
Former smokers (>5y)	243		434			318		582			338		545		

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
None	125	51.4	252	58.1	Ref	196	61.6	382	65.6	Ref	208	61.5	375	68.8	Ref
Bronchitis	66	27.2	98	22.6	1.53(0.96, 2.46)						96	28.4	111	20.4	1.54(1.04, 2.27)
Emphysema	13	5.4	11	2.5	1.78(0.65, 4.87)	18	5.7	13	2.2	1.82(0.76, 4.35)					
Tuberculosis	16	6.6	20	4.6	1.15(0.54, 2.45)	18	5.7	23	4.0	1.08(0.53, 2.20)	22	6.5	26	4.8	1.15(0.61, 2.19)
Pneumonia	50	20.6	79	18.2	0.96(0.61, 1.52)	81	25.5	123	21.1	1.13(0.78, 1.68)					
Asthma	31	12.8	60	13.8	0.68(0.38, 1.20)	42	13.2	86	14.8	0.72(0.45, 1.15)	45	13.3	76	13.9	0.79(0.50, 1.24)
Current smokers	1,078		575			1,419		727			1,442		705		
None	566	52.5	329	57.2	Ref	879	62.0	503	69.2	Ref	869	60.3	490	69.5	Ref
Bronchitis	342	31.7	152	26.4	1.21(0.91, 1.61)						482	33.4	170	24.1	1.45(1.14, 1.85)
Emphysema	43	4.0	12	2.1	1.80(0.88, 3.71)	70	4.9	18	2.5	1.71(0.96, 3.05)					
Tuberculosis	61	5.7	21	3.7	1.31(0.75, 2.27)	69	4.9	25	3.4	1.22(0.73, 2.02)	86	6.0	24	3.4	1.66(1.01, 2.71)
Pneumonia	273	25.3	112	19.5	1.26(0.95, 1.67)	419	29.5	148	20.4	1.59(1.25, 2.01)					
Asthma	76	7.1	56	9.7	0.75(0.48, 1.17)	123	8.7	76	10.5	0.73(0.51, 1.04)	143	9.9	66	9.4	1.07(0.74, 1.54)
Never smokers	543		1,421			575		1,732			717		1,921		

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
None	365	67.2	933	65.7	Ref	426	74.1	1,308	75.5	Ref	571	79.6	1,475	76.8	Ref
Bronchitis	76	14.0	237	16.7	0.85(0.61, 1.17)						95	13.3	286	14.9	0.90(0.68, 1.19)
Emphysema	9	1.7	20	1.4	0.99(0.44, 2.26)	9	1.6	23	1.3	0.91(0.41, 2.04)					
Tuberculosis	20	3.7	59	4.2	0.92(0.54, 1.57)	21	3.7	63	3.6	0.94(0.56, 1.59)	25	3.5	80	4.2	0.88(0.55, 1.41)
Pneumonia	95	17.5	212	14.9	1.17(0.88, 1.56)	105	18.3	265	15.3	1.22(0.93, 1.60)					
Asthma	32	5.9	108	7.6	0.71(0.46, 1.11)	34	5.9	137	7.9	0.68(0.45, 1.03)	45	6.3	144	7.5	0.79(0.55, 1.14)

Participants diagnosed with a previous respiratory disease at any age; participants may be diagnosed with more than 1 pulmonary disease. Analyses include; [1]the Montreal study and [2]the ICARE study. All previous pulmonary diseases included in the same model; further adjustment made for age and center, 'list A' occupation, level of education, smoking status, pack-years and time-since-stopped smoking (where applicable).

Appendix 6: The association between previous respiratory disease (PRD) diagnoses and risk of lung cancer with different sample sizes and number of pulmonary diseases stratified by histological subtype; odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression models

	5 PRD models					**4 PRD models[1]**					**3 PRD models[2]**				
	Cases		**Controls**		**OR (95% CI)**	**Cases**		**Controls**		**OR (95% CI)**	**Cases**		**Controls**		**OR (95% CI)**
	n	**%**	**n**	**%**		**n**	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Men															
Squamous cell carcinoma	2,989		7,652			3,228		8,535			3,727		10,280		
None	1,559	52.2	5,055	66.1	Ref	2,043	63.3	6,319	74.0	Ref	2,525	67.8	8,182	79.6	Ref
Bronchitis	775	25.9	1,176	15.4	1.46(1.28, 1.66)						1,001	26.9	1,442	14.0	1.73(1.55, 1.94
Emphysema	147	4.9	176	2.3	1.58(1.20, 2.08)	170	5.3	204	2.4	1.87(1.46, 2.40)					
Tuberculosis	152	5.1	323	4.2	0.95(0.76, 1.20)	160	5.0	341	4.0	0.98(0.78, 1.23)	200	5.4	427	4.2	1.11(0.91, 1.37)
Pneumonia	837	28.0	1,444	18.9	1.35(1.20, 1.52)	915	28.4	1,580	18.5	1.49(1.33, 1.66)					
Asthma	164	5.5	402	5.3	0.96 (0.76, 1.21)	180	5.6	468	5.5	1.01 (0.81, 1.25)	238	6.4	614	6.0	0.94(0.77, 1.14)
Small cell carcinoma	1,200		7,652			1,309		8,535			1,485		10,280		
None	730	60.8	5,055	66.1	Ref	927	70.8	6,319	74.0	Ref	1,085	73.1	8,182	79.6	Ref

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
Bronchitis	262	21.8	1,176	15.4	1.22(1.02, 1.47)						335	22.6	1,442	14.0	1.37(1.17, 1.61)
Emphysema	34	2.9	176	2.3	1.03(0.66, 1.59)	40	3.1	204	2.4	1.10(0.74, 1.64)					
Tuberculosis	56	4.7	323	4.2	0.88(0.63, 1.23)	57	4.4	341	4.0	0.86(0.62, 1.20)	65	4.4	427	4.2	0.88(0.65, 1.20)
Pneumonia	262	22.0	1,444	18.9	1.16(0.98, 1.38)	297	22.7	1,580	18.5	1.27(1.08, 1.49)					
Asthma	61	5.0	402	5.3	1.22(0.87, 1.70)	71	5.4	468	5.5	1.22(0.90, 1.66)	84	5.7	614	6.0	1.03(0.78, 1.36)
Adenocarcinoma	1,581		7,652			1,798		8,535			2,303		10,280		
None	930	58.8	5,055	66.1	Ref	1,235	68.7	6,319	74.0	Ref	1,691	73.4	8,182	79.6	Ref
Bronchitis	323	20.4	1,176	15.4	1.38(1.17, 1.62)						474	20.6	1,442	14.0	1.49(1.30, 1.70)
Emphysema	83	5.3	176	2.3	1.34(0.98, 1.83)	100	5.6	204	2.4	1.54(1.17, 2.04)					
Tuberculosis	77	4.9	323	4.2	1.04(0.78, 1.37)	80	4.5	341	4.0	1.04(0.79, 1.36)	118	5.1	427	4.2	1.16 (0.92, 1.47)
Pneumonia	359	22.7	1,444	18.9	1.15(1.00, 1.34)	412	22.9	1,580	18.5	1.24(1.09, 1.43)					
Asthma	74	4.7	402	5.3	0.86(0.64, 1.14)	92	5.1	468	5.5	0.92 (0.72, 1.19)	120	5.2	614	6.0	0.77(0.61, 0.96)
Women															
Squamous cell	365		2,430			454		3,041			471		3,171		

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
carcinoma															
None	180	49.3	1,514	62.3	Ref	264	58.2	2,193	72.1	Ref	282	59.9	2,340	73.8	Ref
Bronchitis	124	34.0	487	20.0	1.34(0.97, 1.85)						167	35.5	567	17.9	1.64(1.25, 2.15)
Emphysema	14	3.8	43	1.8	1.24(0.59, 2.60)	27	6.0	54	1.8	1.70(0.94, 3.07)					
Tuberculosis	15	4.1	100	4.1	0.78(0.41, 1.47)	17	3.7	111	3.7	0.75(0.41, 1.36)	22	4.7	130	4.1	1.00(0.58, 1.70)
Pneumonia	102	28.0	403	16.6	1.38(1.01, 1.89)	150	33.0	536	17.6	1.85(1.42, 2.40)					
Asthma	29	80	224	9.2	0.64(0.38, 1.08)	43	9.5	299	9.8	0.69(0.45, 1.06)	45	9.6	286	9.0	0.80(0.53, 1.21)
Small cell carcinoma	343		2,430			419		3,041			428		3,171		
None	189	55.1	1,514	62.3	Ref	274	65.4	2,193	72.1	Ref	269	62.9	2,340	73.8	Ref
Bronchitis	98	28.6	487	20.0	1.12(0.78, 1.62)						128	29.9	567	17.9	1.32(0.97, 1.80)
Emphysema	11	3.2	43	1.8	1.81(0.77, 4.25)	14	3.3	54	1.8	1.48(0.71, 3.11)					
Tuberculosis	16	4.7	100	4.1	1.01(0.52, 1.97)	18	4.3	111	3.7	0.99(0.53, 1.84)	25	5.8	130	4.1	1.50(0.86, 2.62)
Pneumonia	87	25.4	403	16.6	1.50(1.07, 2.12)	117	27.9	536	17.6	1.69(1.26, 2.27)					

	5 PRD models					4 PRD models[1]					3 PRD models[2]				
	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)	Cases		Controls		OR (95% CI)
	n	%	n	%		n	%	n	%		n	%	n	%	
Asthma	19	5.5	224	9.2	0.43(0.23, 0.80)	29	6.9	299	9.8	0.53(0.32, 0.88)	39	9.1	286	9.0	0.87(0.55, 1.40)
Adenocarcinoma	731		2,430			945		3,041			1,077		3,171		
None	446	61.0	1,514	62.3	Ref	640	67.7	2,193	72.1	Ref	763	70.8	2,340	73.8	Ref
Bronchitis	148	20.3	487	20.0	1.01(0.78, 1.30)						235	21.8	567	17.9	1.20(0.98, 1.48)
Emphysema	20	2.7	43	1.8	1.38(0.77, 2.49)	30	3.2	54	1.8	1.41(0.85, 2.33)					
Tuberculosis	37	5.1	100	4.1	1.18(0.77, 1.80)	43	4.6	111	3.7	1.13(0.75, 1.68)	52	4.8	130	4.1	1.15(0.81, 1.65)
Pneumonia	146	20.0	403	16.6	1.15(0.91, 1.46)	230	24.3	536	17.6	1.33(1.10, 1.62)					
Asthma	45	6.2	224	9.2	0.62(0.43, 0.90)	66	7.0	299	9.8	0.60(0.44, 0.82)	89	8.3	286	9.0	0.79(0.59, 1.04)

Participants diagnosed with a previous respiratory disease at any age; participants may be diagnosed with more than 1 pulmonary disease. Analyses include; [1]the Montreal study and [2]the ICARE study. All previous pulmonary diseases included in the same model; further adjustment made for age and center, 'list A' occupation, level of education, smoking status, pack-years and time-since-stopped smoking.