Exposure to coal dust and the risk of developing anthracosis and lung fibrosis

[1,2] Beer C, [2]Kolstad HA, [3]Søndergaard K, [4]Olsen KE, [5]Omland Ø, [1]Sigsgaard T, [6]Bendstrup E, [7]Sherson D, [1,2] Schlünssen V

Affiliations

[1] Department of Public Health, Section for Environment, Occupation and Health, Danish Ramazzini Centre, Aarhus University, Aarhus, Denmark

[2] Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark

[3] Department of Dermatology and Venereology, Aarhus University Hospital, Aarhus, Denmark

[4] Department of Pathology, University of Southern Denmark, Odense, Denmark

[5] Department of Health Science and Technology, The Faculty of Medicine, Aalborg University Hospital, Aalborg, Denmark

[6] Department of Pulmonary Medicine, Aarhus University Hospital, Aarhus, Denmark

[7] Department of Occupational and Environmental Medicine, University of Southern Denmark, Odense, Denmark

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Foreword

The authors received a research grant from the Danish Work Environment Fund in December 2013 following an open call of the funding agency. The title of the call was "Exposure to coal dust and the risk of developing anthracosis and lung fibrosis". Pulmonary fibrosis (PF) is more commonly used term and is therefore used in the report. Anthracosis is regarded as part of "coal workers pneumoconiosis" the term used for PF among coal workers.

The reference document follows the special guidelines for preparation and quality approval of reviews in the form of reference documents in the field of occupational diseases provided by the Danish Work Environment Fund November 2010.

The working group consisted of a core group and a working group including the following members and responsibilities:

Core group, responsible for literature database search, literature selection for data analysis, data extraction, and drafting the report:

Vivi Schlünssen (VS), Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, and Department of Public Health, Danish Ramazzini Centre, Aarhus University Denmark

Henrik Albert Kolstad (HK), Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark

Klaus Søndergaard (KS), Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark

David Sherson (DS), Department of Occupational and Environmental Medicine, University of Southern Denmark, Odense, Denmark

Christiane Beer (CB), Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, and Department of Public Health, Danish Ramazzini Centre, Aarhus University Aarhus, Denmark

Working group for data extraction:

Karen Ege Olsen (KO), Department of Pathology, Odense University Hospital, Denmark

Øyvind Omland (ØO), Department of Occupational Medicine, Danish Ramazzini Centre, Aalborg University Hospital, Denmark

Torben Sigsgaard (TS), Department of Public Health, Danish Ramazzini Centre, Aarhus University, Denmark

Elisabeth Bendstrup (EB), Department of Pulmonary Medicine, Aarhus University Hospital, Aarhus, Denmark

Main conclusions were agreed on during a two days meeting where all participants were present together with two external reviewers:

Professor Dick Heederik (DH), Institute for Risk Assessment Science, Utrecht University, the Netherlands

Professor Edward L. Petsonk (EP), Section of Pulmonary and Critical Care Medicine, West Virginia University School of Medicine, Morgantown, WV, USA.

After the meeting the external reviewers as well as all co-authors commented on the report, and their comments are included in the final version of the report.

Aarhus, March 27, 2015

The authors

Dansk resume

Lungefibrose er en sjælden og oftest alvorlig lungesygdom med en dårlig prognose. Det er veldokumenteret at eksponering for kulstøv ved minearbejde kan forårsage lungefibrose, også kaldet coal workers pneumoconiosis. Det er derimod mindre klart hvilke komponenter i kulstøvet som forårsager disse lungelidelser. Kul indeholder almindeligvis kvarts i varierende koncentrationer afhængig af kulkvaliteten med det laveste kvartsindhold i højkvalitetskul som for eksempel antracit. På grund af kvarts' kendte fibrinogene egenskaber har kvarts været anset for en vigtig årsag til lungefibrose blandt kulminearbejdere. Der forekommer også eksponering for kul ved en række andre arbejdsopgaver, herunder lastning og lodsning af kul ved skibsfart samt håndtering af kul i kulfyrede kraftvarmeværker, arbejdsopgaver som også finder sted i Danmark, og hvor kvartsudsættelsen formentlig er lav sammenlignet med ved minearbejde på grund af brugen af høj kvalitets kul med højt energiindhold og de meget forskellige eksponeringsforhold. Formålet med dette systematiske review er at vurdere om kulstøv uden kvarts kan forårsage lungefibrose. Inklusionskriterier var studier der:

1) Havde informationer om kulstøvsudsættelse og havde en ekstern ikke eksponeret kontrolgruppe eller eksponeringskontrast indenfor den eksponerede gruppe
2) Tog højde for kvartsindholdet i deres analyser
3) Havde lungefibrose, pneumokoniose, coal workers pneumoconiosis eller antrakose som outcome.

Vi fulgte PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) kriterierne i vores søgestrategi og efterfølgende data ekstraktion. Vi foretog litteratursøgning i 4 databaser, (Pubmed, Embase, the Cochrane libary og SveMed+) og inkluderede artikler på dansk, engelsk, norsk og svensk. Derudover gennemgik vi alle referencelister i de inkluderede artikler samt referencelister fra tidligere reviews.

Vi fandt 2945 artikler i den primære søgning, hvoraf 280 var dubletter som blev fjernet. De efterfølgende trin blev foretaget af hele projektgruppen som blev opdelt i

hold på to som fordelte artiklerne mellem sig. Disse to personer skulle ved konsensus blive enige om artikelvalg i de efterfølgende faser i søgning og dataekstraktion.

Ved at læse artikel overskrifter fandt vi 1878 ikke relevante artikler. Vi gennemlæste 787 abstracts, og ekskluderede 562 artikler som ikke levede op til inklusionskriterierne. 225 artikler blev gennemlæst, og af disse var der kun 9 studier blandt minearbejdere, heraf en fundet ved gennemsøgning af referencelister, som levede op til alle inklusionskriterier. Centrale karakteristika blev ekstraheret og systematiseret i tabeller. Vi inkluderede 7 studier fra Storbritannien, ét studie fra Tyskland og ét fra USA. Af disse var 5 tværsnitsstudier, 2 followup studier og 2 case-kontrol studier med mellem 21 og 8829 deltagere.

Ud af disse 9 studier var der 2 som ikke understøttede en sammenhæng mellem kulstøv uden kvarts og udvikling af lungefibrose. Et studie var inkonklusivt og de resterende 6 studier tydede på en selvstændig effekt af kulstøv uden kvarts eller andre mineraler (herefter kaldet rent kul) og udvikling eller forværring af lungefibrose. Der var en række metodologiske problemer i de inkluderede studier. Det største problem var, at alle deltagerne i et eller andet omfang var eksponeret for kvarts, hvilke gør det meget vanskeligt at udtale sig om effekten af eksponering for rent kul, også selvom alle studierne på forskellig vis forsøgte at tage højde for kvartsindholdet i deres analyser.

Man kunne i studierne ikke vurdere selektionen ud af studiepopulationerne, og det er svært at vurdere hvordan dette har påvirket resultatet. Tre af studierne havde som formål at undersøge sammenhængen mellem kvarts og lungefibrose, hvorfor de kun indirekte gav information om den eksponering for rent kul. Der var kun justeret for rygning i 3 studier, hvilket er et betydeligt potentielt problem, da rygning er en risikofaktor for udvikling af lungefibrose. Da der sandsynligvis er en sammenhæng mellem hvor meget man har røget og den kumulerede eksponering for kulstøv blandt rygerne vil det tendere til at overvurdere kuls betydning for udvikling af lungefibrose. I de fleste studier blev lungefibrose defineret ud fra konventionelle røntgen billeder af lungerne, hvilket er en upræcis måde at diagnosticere lungefibrose på, og langt fra den praksis som bruges i dag. Det er ikke muligt at sige i hvilken retning dette har påvirket

studiernes resultater. Studierne inkluderede kun mænd, så disse resultater kan ikke umiddelbart overføres til kvinder.

Der er en række toksikologiske studier i forsøgsdyr som understøtter at rent kul kan forårsage lungefibrose, men dog ikke i samme grad som kvarts.

Vi konkluderer, at de fleste studier i dette review understøtter at kul kan forårsage eller forværre lungefibrose. Der er generelt betydelige metodologiske svagheder i studierne.

Alt i alt er det forfatternes vurdering, at der er en begrænset dokumentation (+) for en årsagssammenhæng mellem rent kul og udvikling eller forværring af lungefibrose i henhold til de kriterier som er defineret af Arbejdsskadestyrelsen og Erhvervssygdoms-udvalget.

Baseret på de inkluderede studier har det ikke været muligt at udregne et samlet estimat for den mulige effekt at rent kulstøv, ej heller at komme med et bud på dosis-respons sammenhænge mellem rent kul og lungefibrose.

For at afdække om kul eksponerede personer der ikke er minearbejdere men som eksponeres for kul med intet eller lavt kvartsindhold har en øget risiko for lungefibrose vil det være nødvendigt med velgennemførte studier af en kohorte af eksponerede (f.eks. ansatte på kulfyrede kraftvarmeværker) hvor informationer om lungefibrose fås fra landpatientregistre og fra specifikke lungefibroseregistre som findes i eksempelvis Danmark.

Abstract

Objectives

Exposure to coal dust is causally associated with development of PF (PF), also known as coal worker pneumoconiosis (CWP). It is unclear which constituents of coal dust are responsible for the excess risk, but quartz has been considered an important explanatory factor. Workers that handle coal during shipping and loading of coal and at combined heat and power plants in Denmark are exposed to dusts from coal that likely is comprised of mainly the non-quartz/non-mineral part of the coal. We aimed at systematically reviewing the relation between exposure to the non-quartz fraction of coal dust and PF.

Methods

In a systematic review based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria and involving searches in 4 databases 2945 articles were identified. However, our eligibility criteria led to an inclusion of only 9 studies from Great Britain (n=7), Germany (n=1) and the US (n=1) which provided information on the relation between exposure to the non-quartz part of coal and PF. Five cross sectional studies, two follow-up studies and two nested case control studies were included with study populations between 21 and 8829 participants.

Results

From these nine studies two did not demonstrate a relation between the non-quartz part of coal and the development and progression of PF, one was inconclusive and the other six studies indicated an independent direct or indirect effect of the non-quartz or non-mineral part of PF. The major limitation was that quartz exposure was present to some degree in all studies. Smoking was not taken into account in most studies, and the diagnosis of PF was not based on current clinical definitions.

Conclusion

Most of the included studies support an independent effect of non-quartz or non-mineral coal dust on the development of PF. However, due to major methodological limitations, the evidence is mostly graded low. The available data does not allow calculation of a general hazard ratio or odds ratio. In order to improve the evidence studies on subjects working solely with the carbon part of coal are needed.

Introduction

Development of lung diseases caused by exposure to coal dust and coal impurities like quartz and iron has been studied over the last century, and it is well documented that exposure to coal dust is causally associated with respiratory disorders (1-3). The major focus has been on interstitial lung diseases (ILD), although chronic airflow obstruction is also widely recognized as a health outcome related to coal mine dust exposures (4, 5). ILD comprises a group of uncommon and often severe lung diseases characterized by pulmonary inflammation and pulmonary fibrosis (PF). In only around one-third of ILD patients the causal factor is known Quartz exposure is a well-documented cause of PF (also known as silicosis). Other causal risk factors are asbestos (asbestosis), specific drugs, radiation, connective tissue disease as well as biological and chemical agents (allergic alveolitis) (6). The prognosis for most cases of ILD is poor (7) and lung transplantation is the only effective cure. Lung diseases associated to coalmine dust are named according to the exposure suspected to cause the disease, i.e. coal workers' pneumoconiosis (CWP), silicosis and mixed dust pneumoconiosis. Anthracnosis is used both as a synonym for CWP or as massive carbon deposits seen in the lung at autopsy. Recently, dust-related diffuse fibrosis has also been described (3). Risk factors for CWP are primarily related to airborne dust concentration, exposure duration, and coal characteristics, e.g., coal rank, quartz and iron content. However, genetic predisposition might also play a role (8, 9). Coal rank describes the degree of maturation of coal from peat to anthracite. Low-rank coals include peat, lignite and sub-bituminous coals. These coals have lower energy content due to the low carbon content. As time, heat, and burial pressure all increase, the rank does as well. High-rank coals, including bituminous and anthracite coals, contain more carbon than lower-rank coals, which results in much higher energy content. (10). Depending on the rank of coal it contains variable amounts of hydrogen, oxygen, nitrogen, trace metals, e.g., cadmium, copper, nickel, lead and iron as well as inorganic minerals. Some of the most common inorganic minerals that are present in coal dust are kaolin, mica, titanium, magnesium, iron and quartz (10).

Although the association of coal mine dust exposure and the development of lung diseases have been investigated for decades it is still not clear which characteristics of

the dust are actually responsible for disease development. Previously there has been a particular interest in quartz as an important fibrogenic component because it is known that quartz itself can also cause PF (silicosis) (11). However, some epidemiological and experimental evidence suggests a minor fibrogenic role for quartz (8). A convincing exposure-response relationship has been shown for coalmine dust exposure and CWP, and lung pathology studies among workers exposed to coal dusts with little or no silica have documented extensive CWP, without silicosis (3). An inverse relationship between quartz and CWP has also been described (12), and hard coal rank with increased iron may correlate with CWP risk (13). Experimental evidence has linked coal iron content with the formation of reactive oxygen species (14).

Despite the increasing demand for alternative energy sources, coal is still an important energy source in the world. Around 30% of the global primary energy needs are covered by coal generating 41% of the world's electricity. It is used in 70% of the world's steel production (http://www.worldcoal.org/resources/coal-statistics/). Based on statistics from the World Coal Association the total world coal production reached a record level of 7831Mt in 2012, which is a 2.9% increase in comparison to 2011 suggesting an increasing coal demand.

Exposure of workers to coal dust is seen in coal mining but also when handling coal, e.g. at combined heat and power plants and during shipping and loading of coal. These occupational exposures are the relevant for Denmark, due to the lack of coal mining industry. I Denmark, handling of coal is done as follows. Coal is loaded by crane from ship directly into the pit of the heat and power plant. From there the coal is transported directly to the furnace via a conveyor belt. Employees who maintain and repair these systems are exposed to coal dust and fly ash. High rank coal with a low content of minerals and other contaminants are used (Personal communication Nicolai Dam, Trefor, a large Danish energy company).

There are presently no systematic reviews on the non-quartz / non-mineral part of coal and development of lung diseases. The aim of our study was to systematically review and investigate what is in particular known about the relation between exposure to the non-quartz part of coal dust and the risk of PF.

Methods

Search strategy

The systematic review is based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria (15) a revision of the QUOROM (quality of reporting of meta-analysis) guidelines developed by an international group (16).

For the literature search the the National Library of Medicine (PubMed), Embase, and the Cochrane Library was used. In addition, searches were performed in the Scandinavian databases bibliotek.dk and SveMed+. The literature search was performed by CB based on the search terms shown in supplement I. Depending on the database, we included papers published in English, Danish, Swedish and Norwegian in the search (see supplement I). However, only articles in English passed the pre-selection by the core group (VS, HK, KS, DS, and CB). The search results were imported into a database (RefWorks). Duplicates were subsequently removed. All articles in the database were reviewed by two members of the core group. Both reviewers had to agree on an article before it was included for data extraction. In addition to the mentioned languages, the pre-selection of articles were based on the following eligibility criteria: Epidemiologic peer-reviewed studies on relevant exposure and outcome including case-control, cross-sectional and follow-up studies with an external control group or exposure contrast in the exposed group. Case studies, meta-analyses and reviews were excluded. After pre-selection of the articles the remaining articles were divided between all members of the project group. All articles were searched for relevant literature citations (snowball articles) that did not appear in the original literature search. In addition, the RefWorks database was systematically searched for review articles and meta-analyses. These articles were searched for snowball articles as well.

Data that were extracted from the articles are given in table 1 and include publication year, country where the study was performed, study design, study period and study population, number of exposed and controls, age and age range, exposure levels and duration, how the exposure assessment was performed, the presence or absence of exposure response analysis, outcome, covariates accounted for, and results.

Furthermore, a systematic search for systematic reviews, meta-analysis or Cochrane-reviews was performed in the PubMed and EMBASE database. The search term was "coal" and the search was limited to systematic reviews, meta-analysis, and Cochrane-reviews in English that were officially categorized as these article types by the used databases.

Definition of exposure

As the objective of this rapport was to investigate the relation between the non-quarts part of coal exposure and PF it was a prerequisite for inclusion that the quartz content of the measured dust was known, that the quartz content was taken into consideration in the analyses or that the mineral content of the lung in autopsy studies was known.

Definition of outcome

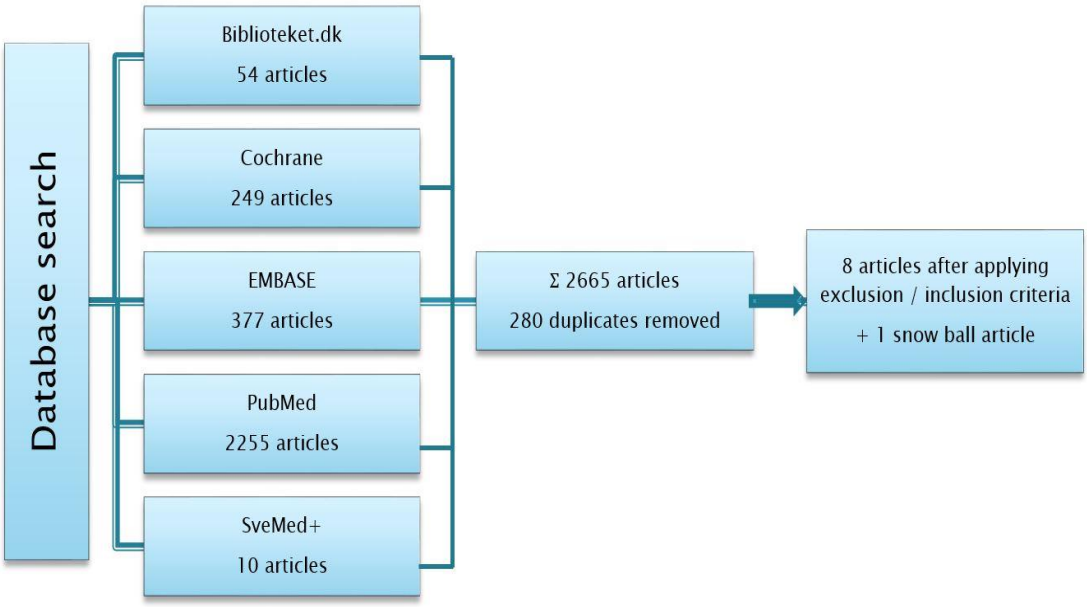
PF (including pneumoconiosis and CWP) were the relevant outcomes. The specific used search terms or search histories are listed in supplement I. As the retrieved literature covered several decades, the diagnostic criteria varied over time. The diagnosis was either clinical or based on death certificates. The clinical diagnosis of PF was based on analysis of X-ray films, lung function measures or a combination of both.

Results

Selection of papers

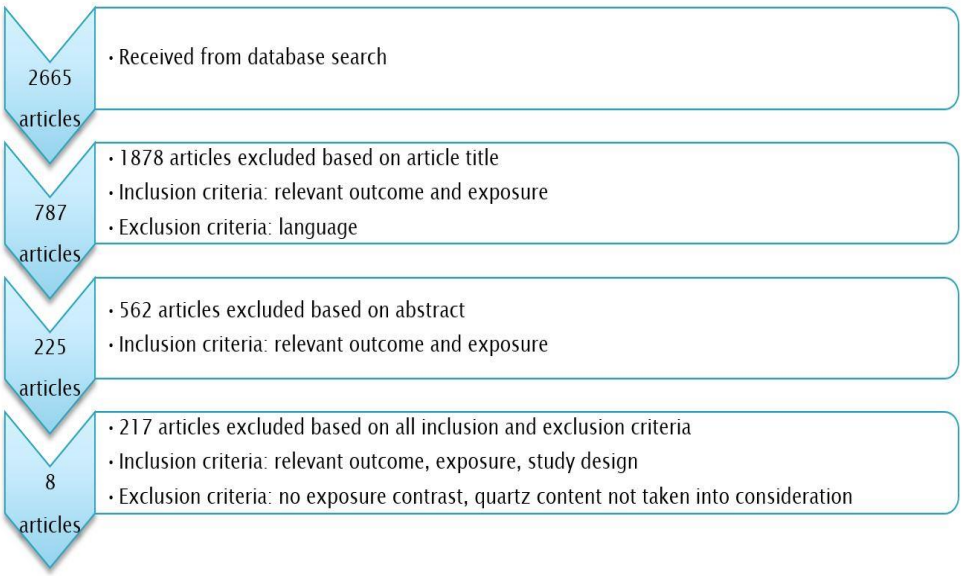
The literature search resulted in 2945 articles with 54 from the Danish database biblioteket.dk; 10 from the Swedish database SveMed+; 249 from the Cochrane library; 377 from EMBASE; and 2255 from PubMed using the search terms given in supplement I. After removing of 280 duplicates 2665 articles were evaluated based on our inclusion and exclusion criteria by 2 reviewers (Fig. 1).

Fig 1: Results from database search



From the article title 1878 articles were regarded as not suitable and excluded (Fig. 2).

Fig 2: Exclusion of articles found by the systematic database search



The inclusion criteria for this step were relevant outcome and exposure. The resulting 787 articles were evaluated on abstract level. Due to the inclusion criteria of relevant outcome and exposure 562 articles were excluded leaving 225 articles to be evaluated using all inclusion and exclusion criteria as mentioned in the method chapter. Nine articles, including one snowball article, were found to meet all the criteria and were used for data extraction.

Description of included papers

The results of the studies are summarized in table 1. Seven of these studies were from Great Britain (17-23); one was performed in Germany (24) and one in US (25). The study design included mostly cross sectional studies (18-23) but also two follow-up studies with follow up periods of 9.3 (24) and 38 years (25) and two nested case control studies (17, 19) were included. The study populations varied between 21 (17) and 8829 subjects (24, 25) (median number of participants 371). The mean age was between 43 years (19) and 52 years (19, 23, 26) and the age range in the studies was between 35 (23) and 74 years (20). In most of the studies in table 1 neither the mean age nor age range was specified (17, 18, 21, 22, 24). The study population in all studies was solely males. All follow up and cross sectional studies compared exposure levels within coal miners and did not have any external exposure group (18, 20-25).

Exposure measurements

The exposure measurements were performed with gravimetric personal or area dust sampling in all studies and are given as mg/m^3 or gh/m^3 for coalmine dust and quartz, respectively (Table 1). The quartz content varied between 1% (19) and 13% (17). The exposure duration was between >10 years (19) and up to 44 years (21). In two studies, the exposure duration was not stated (18, 22). The study population described by Seaton *et al.* was exposed between 30,000 and 70,000 hours (17) and in the study of Buchanan *et al.* the exposed individuals were on average exposed to coalmine dust for 8000 hours (20). Cumulative exposure to respirable dust and respirable quartz respectively was in most studies assessed based on work duration in specific tasks or jobs times the average measured exposure in each of the tasks/jobs (17-25). In two studies among deceased coal miners' exposure was assessed as coal dust and quartz content in the lung tissue using infrared spectrophotometry, X-ray diffractometry or fluorescence analysis (18, 22). Covariates that were accounted for included quartz (19, 20, 23, 25, 27), age (17, 20, 25), and smoking (19, 20, 25). In three studies, no covariates were taken into consideration (18, 21, 22). Except for three studies (18, 19, 22), exposure-response analyses were performed in all studies.

Adjustment for quartz content

The quartz dust content was taken into consideration in different ways. Buchanan *et al.* adjusted for cumulative quartz exposure using general exposure index (GEI) models. The GEI for quartz exposure was based on the mean quartz concentration for each period, the number of hours worked, and the time from exposure period to follow up. Work hours and periods were collected from exposure history questionnaires (20). A detailed analysis of the coal dust samples by infrared spectro-photometry using the KBr disc methods were performed by Seaton *et al.* and Jacobsen *et al.* (17, 19). They report precise information on the carbon and quartz content that allowed for a direct comparison of x-ray progression index and carbon and quartz content (17, 19). In their study from 1997, Morfeld *et al.* used Cox regression modeling with time-dependent covariates including quartz to estimate the relative risk of opacities in relation to the non-quartz component (24). Hurley *et al.* used a

micro-infrared technique and infrared spectroscopy for samples that were taken during the last 10 years of the study (23). The assessment of the quartz concentration by Douglas *et al.* and Ruckley *et al.* was done after pathological examination on autopsies and the dust composition (coal, quartz etc.) was determined on samples of whole dried lung tissue by calculating the weight loss after ashing (coal) and infrared spectrophotometry (quartz) (21, 22) or in the case of Casswell *et al.* by using X-ray diffractometry and fluorescence analysis (18). Graber *et al.* used data from the Mine Safety and Health Administration to estimate the amount of respirable quartz dust exposure for job groups and assigned an individual cumulative quartz exposure estimate to each study participant (25).

Diagnostic criteria

The studies were performed between 1981 and 2010, covering nearly 30 years, and different diagnostic criteria have been used in the different studies. Except for Douglas *et al.* who based the diagnosis on autopsies (21), the evaluation of lung opacities and diagnosis of PF was based on the most recent International Labour Organization (ILO) classification scheme that were valid at the time of publishing (17-20, 22, 23, 25, 27). The ILO classification system is used for diagnosing PF including CWP and silicosis. The guidelines were updated in 2011 (28). Most versions uses four categories (0, 1, 2 and 3) that are based on profusion of small opacities, where 0 indicates an absence of opacities or opacities less than for category 1. There are 12 subcategories. Examples of categorization are 0/1, 1/0, 1/1, etc., where the first figure denotes the category which best matches the x-ray image and the second figure indicates the subcategory that has been considered as an alternative; for example, 0/1. Category 1/1 means that the x-ray-image has been classed as category 1 and that no other category has been considered. The studies included between 1 reader (17) and up to the mean of 11 readers (18) evaluating development or progression of opacities. In one study consensus was reached between 2-3 readers (27), and one study defined a progression if at least 3 out of 5 readers agreed on this (19).

Associations between coal dust and PF

Buchanan *et al.* found no significant association between cumulative respirable dust and opacities 2/1+ after adjustment for quartz. However, the absolute risk for

opacities 2/1+ after 15 years exposure to non-quartz respirable dust was 0.8%. Seaton *et al.* found that cases (change in opacities progression of at least 1+) had been exposed to higher % quartz but lower % coal and concluded that quartz might be an important factor in the development and rapid progression of opacities (17). Jacobsen *et al.* came to the same conclusion (19). They reported a mean difference between cases (change in opacities progression of at least 2 categories2+) and controls of respirable mixed dust of 5.2 gh/m^3 and quartz of 0.75 gh/m^3. The mean difference of quartz % in mixed dust was 1%. However, they also found that not all cases with progressive massive fibrosis had higher exposures to quartz than corresponding controls (19). Morfeld *et al.* did not find a relationship between cumulative coalmine dust exposure and abnormal radiological findings. However, they report a strong mine effect on the development of opacities 1+ that could not be explained by dust or quartz concentration (24). Hurley *et al.* report a strong effect of cumulative dust exposure on the occurrence of opacities 2/1 even after stratifying by cumulative quartz exposure, and the effect of dust on the opacities could not be explained by quartz or ash. However, high quartz concentrations had an effect on rapid progression of opacities (23). Douglas *et al.* found that lung lesions increased with whole dust and ash deposits; however, it was not possible to evaluate the quartz effect properly (21). For exposure to low rank coal Ruckley *et al.* showed that the increase in radiologic profusions was most closely related to the ash component (mineral part of the coal) whereas for exposure to high rank coal both coal dust and ash content were each associated to radiological profusions (19). This is in agreement with the findings of Casswell *et al.* who showed that both coal and mineral dust in lung tissue were associated to the radiological findings. Graber *et al.* found hazard ratios between 1.17 and 2.58 for respirable coal dust and pneumoconiosis mortality after adjustment for quartz. In addition, the effect depended on the mine and was highest for hard coal mines (25).

Discussion

Overall findings

The objective of this review was to investigate specifically the role the non-quartz part of coal dust plays on the risk to develop PF, also known as CWP. Our criteria led to an inclusion of only nine studies (17-25) with PF as outcome that were suitable for our review and gave directly or indirectly information on the relation between exposure to the non-quartz /non-mineral part of coal and PF. Two studies did not demonstrate a relation between the non-quartz part of coal and the development and progression of PF (17, 24), one study did not allow for a conclusion in this matter (21), whereas six studies indicated an independent effect of the non-quartz or non-mineral part of coal dust (18-20, 22, 23, 25).

The importance of quartz exposure in coal dust

As the quartz content has been considered an important risk factor for PF (also known as silicosis) (11) we have focused on quartz in our in- and exclusion criteria, and articles were only included when either information on the quartz level were available or when the data were adjusted for the quartz or the non-mineral fraction of the coal. However, several authors have questioned the importance of quartz, as quartz has been found to be a minor contributor to PF (8, 29). There are studies where quartz could not be attributed either to CWP or progressive massive fibrosis (30-35) unless the quartz concentration exceeds 10% as, e.g. shown in *in vivo* animal studies of rats where coal dust was supplemented with different concentrations of quartz (8, 36-38). This was supported by the studies by Hurley *et al.* (23) and Jacobsen *et al.* (19). Both found that a rapid progression of opacities was associated to high quartz concentrations only.

The level of bioavailable iron has been associated with the cytotoxic ability of coal dust in *in vitro* studies, and also in recent epidemiological studies among workers in high rank coal anthracite mines (13, 39-41). Among bituminous coal miners Huang *et al.* found an ecologic (analyzed on region level) association between the prevalence of CWP and bioavailable iron ($r=0.94$, $p<0.0015$), total iron ($r=0.85$, $p<0.016$), and pyritic sulfur ($r=0.91$, $p<0.0048$) but not with coal rank ($r=0.59$, $p<0.16$) or silica ($r=0.28$,

p<0.54) (13). This is in contrast to the study of Casswell *et al.* (18) who investigated the impact of the composition of lung tissue on radiological appearance of opacities, and iron did not add much. Casswell *et al.* stated that the iron content of the lung itself is well correlated with the category of simple pneumoconiosis; however, they subscribe this to the high correlation of the iron content with the coal and mineral content of the lung (18).

Three studies had the objective to investigate the effect of the quartz on the occurrence of opacities and thereby indirectly stating the effect of the non-quartz part of the mixed coal mine dust (17, 19, 23). In Hurley *et al.*, a large study with a high quality exposure assessment they excluded an effect of ash. As ash is the mineral part of coal mine dust they thereby stated that the carbon part was responsible for the development of opacities (23). The study by Jacobsen *et al* investigated progression and not development of opacities (19). Their results suggested that rapid progression of opacities was due to high quartz content but also supported that exposure to quartz was not the sole factor responsible for progressive massive fibrosis (19). The objective of Seaton *et al.* was to explore the effect of quartz on CWP, and they only accounted for the quartz part of mixed coalmine dust. In addition, although their objective was to look at the progression of PF most cases were healthy at the start of the study (17).

In a well-conducted study, Buchanan *et al.* explored the effect of coalmine dust. When the quartz effect was removed in their models the predicted risk of develop opacities 2/1+ after 15 years exposure was 0.8% (20). In the follow-up study by Graber *et al.* they found a hazard ratio for cumulative respirable coal dust after adjustment for quartz between 1.17 and 2.58, depending on the mine (25). Furthermore, Ruckley *et al.* and Casswell *et al.* showed an effect of the carbon part of the mixed coalmine dust on the appearance of opacities (18, 22). Both studies were performed directly on the lungs of deceased coal miners and measured the characteristics and concentrations of the recovered lung dust. Ruckley *et al.* found that both the coal dust and the ash concentration increased in the lungs in relation to radiological profusion. However, this effect was only seen for high rank coal. The study of Casswell *et al.* showed as well that the coal dust but also the mineral dust increased in the lungs in relation to the

radiological score. The strength of both studies is that the depositions of the mixed coalmine dust are directly measured. However, both studies did not give any details on the exposure level, exposure duration and did not account for any confounders. Seaton *et al.* and Morfeld *et al.* did not show a relation between the non-quartz part of coalmine dust and the appearance of opacities (17, 24). In Morfeld *et al.*, they used a different methodology using small size films that are not compatible with ILO standards (24). From the study performed by Douglas *et al.* it was not possible to evaluate the effect of the non-quartz part of the mixed coal mine dust (21). However, an increasing amount of mixed coal dust and ash deposits increased the observed lesions in the lungs.

The studies by Seaton *et al.* and Buchanan *et al.* investigated the same mine however in different subpopulations and with different study designs and setups (17, 20). The same is true for the studies by Jacobsen *et al.* and Hurley *et al.* (19, 23). Furthermore, a study by Morfeld *et al.* (42) has been excluded as a subset of the study population was already included in Morfeld *et al.* 1997 (24).

Strength and limitations

There are no systematic differences in the studies supporting or refuting an independent effect of non-quartz/non-mineral coal dust on development of PF with regard to study design, or exposure assessment. Though, Morfeld *et al.* (27) was the only study who partly used small size films for some of the mines, and this might have underestimated the number of opacities and could be an explanation for the strong mine effect reported by the authors. The only three studies who adjusted for age, smoking and quarts supported an independent effect of non-quartz/non-mineral coal dust on development of PF (19, 20, 25).

There are several limitations in the included studies. Most of the studies are cross sectional studies and information about dropout rates was not given (18-23). Due to the comprehensive objective quantitative exposure assessment in most studies, information bias is probably not a serious problem. However, selection out of the cohort is likely, also in the two follow-up studies, and its effect on the measures of association presented in the different studies cannot be evaluated.

All study populations consisted solely of males. Thus, this review provides no information about particular risks of these exposures for females caused by possible gender specific susceptibility as smaller airway calibers (43) or hormonal factors (44). Three of the included studies had another objective than the one defined in this review and investigated the effect of the quartz and only indirectly the effects of the non-quartz /non-mineral component of coal (17, 19, 23). Two of these studies were aiming at exploring the impact of quartz on progression and not on the development of opacities (17, 19).

Smoking was only taken into account in few studies (19, 20, 25). Smoking is regarded a risk factor for most subtypes of PF, including idiopathic pulmonary fibrosis (45, 46), also for parenchymal opacities (>1/0), and it is suggested that smoking is a true risk factor as well as an effect modifier (47). As most studies are not adjusted for neither smoking nor age or person-year the results may in general overestimate the effect of coal dust as cumulative exposure to coal dust and cumulative exposure to smoking is probable correlated.

Another limitation might be associated with the diagnosis of PF, in the included papers stated as CWP. CWP and silicosis are subtypes of PF defined by the type of exposure (coal and quartz respectively) which is an obstacle when aiming at investigating these associations. All included papers, though, have used these terms, and therefore they are also used in this review. Although early CWP does not usually cause symptoms, it is associated with FEV_1 losses and decline in single breath diffusing capacity for carbon monoxide (48). Most pulmonary symptoms are associated with advanced PF or other conditions like chronic bronchitis and chronic airflow limitation. The identification and diagnosis of CWP is in the literature based on exposure history and respiratory symptoms in combination with radiological changes (opacities) in chest radiographs (3, 49). In a current clinical setting for diagnosing PF lung function test and conventional radiological findings are combined with HRCT scanning and in uncertain cases lung biopsy, which is not the case in the included studies. The presence and the severity of CWP is classified using the ILO classification system where CWP is classified according to the number, size, and shape of small opacities using standard reference films developed by the ILO (50). The used ILO

criteria differed between the studies, and included between 1 reader (17) and up to 11 readers (18) with a variable agreement. In addition, the limitations of film-based chest radiographs have to be noted as the sensitivity of radiographs is limited. Pathologic abnormalities have to be moderate to severe before they can be detected with certainty in comparison to current digital radiological techniques. In addition, progressive massive fibrosis might be confused with carcinoma, tuberculosis, or bacterial infectious lesions (50), and it is difficult to foreseen how this impact the findings in the included studies.

PF in coal dust exposed workers may be complex. Lesions typical for silicosis were found in conjunction with CWP in 8% of autopsied lungs from coal workers employed in modern United States conditions, and in 28% of lungs from those who had worked before regulation of dust exposure (51). Classical chest radiography is not able to distinguish between CWP and silicosis, and tissue examinations is preferable for a reliable determination of the diagnosis as done in the studies by Ruckley *et al.* and Casswell *et al.* that both showed an effect of the carbon part of the mixed coal mine dust on the appearance of opacities (18, 22).

The pathogenic mechanisms of quartz and/or coal dust in lungs are presumably similar and involve direct cytotoxicity, activation of oxidant generation by alveolar macrophages, stimulation of the secretion of inflammatory cytokines and chemokines from alveolar macrophages and/or alveolar epithelial cells, stimulation of secretion of fibrogenic factors from alveolar macrophages and/or alveolar epithelial cells (51). Although severe responses (massive fibrosis, cor pulmonale, and respiratory failure) can occur from either dust when exposures are excessive, silica seems to be more cytotoxic and to induce stronger responses than coal dust (51).

There has been no study that addresses the pure carbon part of coal dust and it is a general obstacle that in all studies quartz exposure is present to some degree. Different methods have been used in all the studies to take quartz into account by modelling, adjustment or by simple subtraction. Though, it is an important drawback that studies with populations exposed to pure carbon alone is not available.

Toxicity of pure coal dust

It is biologically plausible that the pure carbon part of coal dust can induce lung opacities. Important factors for the uptake and fate of coal dust particles in the lungs include the chemical and morphological properties of the dust particles as well as lung volume, breathing rate and depth (52). The particle toxicity itself is dependent on factors like particle durability and leaching, deposition and translocation, and particle clearance via mucus-ciliary and interstitial lymphatic routes. After deposition of the particles in the lung, the particles interact with macrophages and epithelial cells as the two main target cells (52). After phagocytosis of the coal dust particles, activated macrophages are producing and releasing increased amounts of reactive oxygen species (ROS) and cytokines. The coal dust particles might produce ROS directly at the particle surface through surface radicals and ions. Increased formation of ROS has been associated with a number of diseases and has been shown to induce damage to cell membranes, increased lipid peroxidation, oxidation of proteins, and DNA damage (52). Epithelial cells also produce ROS and cytokines after stimulation. Cytokine release from macrophages might recruit additional phagocytic cells like neutrophils and monocytes. This recruitment may lead to an amplification of the local formation of ROS and cytokines. These excessive amounts of ROS and cytokines may cause damage and affect lung tissue morphology, cell turnover and deposition of components of the extracellular matrix (52).

Cytokines like tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1) that are important in lung inflammation and fibrosis, are released after exposure to coal dust. Coal miners with CWP have elevated levels of these cytokines in their serum and broncho-alveolar lavage (53, 54). Elevated levels of markers for oxidant injury like superoxide dismutase, glutathione peroxidase, and catalase suggest a role for oxidative stress due to free radical formation and have also been found in animal models for lung inflammation (55, 56). In connection with these suggested mechanisms of coal dust induced toxicity genetic susceptibility has been investigated. Some studies found an association between the frequency of the TNF-α-308 variant (deletion of a nucleotide in the promoter region of the TNF- α gene) and the development of CWP (57-59) another study found no association of single nucleotide

polymorphisms in genes involved in inflammatory and fibrotic processes and progressive massive fibrosis (60). [1]

Dust from anthracite coal has been associated with higher cytotoxicity and pathogenicity than dust from bituminous coal. This has been explained by the higher amount of free radicals at the surface of anthracite coal dust particles (51, 61, 62). In addition, the porous surface of the coal dust particles leads to a large surface area where compounds like benzene, phenol, and methylene that are present in the coal mining atmosphere can be adsorbed. The presence of such chemicals at the surface of the coal particles may change the biological activity of the particles as well (51). The stronger toxicity of high rank coal was supported by Graber *et al.* and Ruckley *et al.* (22, 25). This is in agreement with other studies that found higher rates of CWP for anthracite coal compared to bituminous coal (63, 64). Graber *et al.* and Ruckley *et al.* also found this stronger effect for the non-quartz part of the mixed coal mine dust in high rank coal mines (22, 25) suggesting that the higher amount of free radicals at the surface of anthracite coal dust particles plays an important role in the toxicity of mixed coal mine dust. However, in a recent review Mo *et al.* on several Chinese studies showed similar CWP risk for anthracite (5.38; 95% CI 2.11, 10.04) and bituminous coal (5.88; 95% CI 2.21, 11.16) (65).

Exposure levels

Publication of the Interim Standards Study of the British Pneumoconiosis Field Research (6) was the basis for regulation of coal dust exposure of coalmine workers. In 1969, the average level of respirable coalmine dust in underground coalmines was limited to a maximum of 3 mg/m^3 in the U.S.A. by the United States Federal Coal Mine Health and Safety Act (66). In 1972 the occupational exposure limit (OEL) was further reduced to 2 mg/m^3 (66), which is the current OEL for respirable coal dust in Denmark.

Based on four of the included studies the cumulative coal dust exposure level was calculated to 48.6 gh/m^3 with exposure duration between 3.8 and 33 years (17, 19, 20, 23). In average exposure levels for respirable coal dust were reported to be 1.8 mg/m^3 and average exposure levels for respirable quartz 0.18 mg/m^3 (27). In Denmark the current OEL limit for respirable quarts is 0.1 mg/m^3. The total dust concentration on

Danish power plants using oil, gas and coal was recently measured to be below, 0.1 mg/m^3 (67). We are not aware of any quarts measurements from Danish or European power plants. In a US study among power plant workers from bituminous- and subbituminous-fired plants were revealed concentrations of quartz in fly ash from non-detectable to 0.18 mg/m^3 with a mean value of 0.05 mg/m^3 during normal production activities (68). Taken together we assume Danish workers to be substantially lower exposed compared to the subjects in the present review.

Conclusion

In conclusion, most of the included studies suggest an independent effect of non-quartz /non-mineral coal dust on the development of PF. Due to major methodological limitations, the evidence is in general graded low. Some of the included studies had different objectives than the one defined in this review and were focusing on quartz and thereby only indirectly provided information on the relation between the non-quartz /non mineral part of coal and PF. The major limitation is that none of the studies addresses the pure carbon part of coal dust; in all studies quartz exposure was present to some degree. Smoking is not taken into account in most studies. The diagnosis of PF is not based on current clinical definitions. Finally, none of the s*t*udies included women in their investigations, so no conclusions can be made for women exposed to coal dust.

Taken together we find that the degree of evidence of a causal association between pure coal dust exposure and pulmonary fibrosis is limited (+) according to the up-to-data criteria.

Danish workers are probably exposed to substantially lower concentrations of coal dust compared to the subjects included in the present review.

The available data does not allow a calculation of an overall effect of the non-quartz content of coal dust on health in the form of a meta-hazard ratio or meta-odds ratio. In order to strengthen the evidence, well conducted studies on non-coal miners exposed to coal dust with no or very low mineral content are needed.

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Table 1: Characteristics and main results of 9 epidemiologic studies of lung function and pneumoconiosis among coal exposed individuals under consideration of the quartz content of the coal

Author Year Country (ref.)	Study design (Study period)	Study population Exposed /control	Age (range)	Exposure assessment	Exposure levels Exposure duration	Exposure-response analysis	Outcome (Measure)	Covariates Accounted for	Result
Casswell 1970 UK (18)	Cross sectional study among deceased coal miners	98/0*	No data	Measurement of recovered lung dust; X-ray diffractometry or fluorescence analysis of mineral matter, including quartz and iron	No data	No	Full sized chest radiograph: Modelled mean of 11 readings between 0/- and 3/4. ILO classification 1959.	Non	Both coal dust and mineral dust increased in the lungs in relation to radiological score: Coal: β = 0.126 (SD 0.01). Mineral: β = 0.533 (SD 0.04).Correlation between mineral and quartz: r = 0.96.
Seaton 1981 UK (17)	Nested case control from one British colliery. Same mine as in Buchanan *et al.* 2003	21 cases; 21 controls	No data	Thermal precipitator and MRI Gravimetric dust sampling from 1954 to 1978. Cumulative exp. 1974-78 by occupational group times duration within each group.	Cases: resp. dust 11478 mgh/m^3 Controls: resp. dust 7173 mgh/m^3 Range exp. duration: appr. 30,000 – 70,000 h	Yes	Full sized posterior-anterior chest radiograph: One reader: 1+ change in opacities 1974 to 1978. ILO classification 1972.	Age matched controls	Cases vs controls: % coal in resp. dust: 57 vs 63%, $p < 0.05$ % quartz in resp. dust: 13 vs 8%, $p < 0.05$
Hurley 1982 UK (23)	Cross sectional study, 10 British coal mines	2600	52 (35-65)	Thermal precipitator and MRI Gravimetric dust sampling from 1954 to 1978. Cumulative exp. by occupational group times duration within each group.	Mean resp. dust 183 gh/m^3 Mean quartz 8.8 gh/m^3 Mean duration 33 years	Yes	Full sized posterior-anterior chest radiograph, mean of 5 readers: Opacities 2/1+ (ILO classification 1968).	Quartz	Strong effect of cumulative dust exp. when stratified by cumulative quartz exp. Coal dust has an effect on opacities that cannot be explained by quartz or ash More rapid progression at very high quartz content

Author Year Country (ref.)	Study design (Study period)	Study population Exposed /control	Age (range)	Exposure assessment	Exposure levels Exposure duration	Exposure-response analysis	Outcome (Measure)	Covariates Accounted for	Result
Jacobsen 1982 UK (19)	Nested case control study among 4333 miners from 10 British coal mines. Same mines as in Hurley *et al.* 1982	45 cases; 41 controls	Cases 43 Controls 44	Thermal precipitator and MRI Gravimetric dust sampling from 1954 to 1978. Cumulative exp. by occupational group times duration within each group.	Cases: resp. dust 43 gh/m^3 Controls: resp. dust 38 gh/m^3 Exp. duration >10 years	No	Full sized posterior-anterior chest radiograph: Change: 2+ step (ILO classification 1968)	Smoking, quartz	Mean difference cases vs. controls: Resp. mixed coal dust 5.2 gh/m3 Quartz 0.75 gh/m3 Quartz % of mixed coal dust 1% Quartz-related unusually rapid progression of opacities
Ruckley 1984 UK (22)	Cross sectional study among deceased coal miners	261/0*	No data	Measurement of recovered lung dust and infrared spectrophotometry of residual ash, including quartz	No data	No	Full size posterior-anterior chest radiograph: Opacities ILO classification 1971) 3 Gradings of pathological findings: O; 1 (< 1.5 mm); 2 (1.5 - 3 mm); 3 (> 3 mm). > 10 mm excluded.	Non	Low rank coal: the increase in profusion was most closely related to the ash component of the total dust High rank coal: both coal dust and ash increased in the lungs in relation to radiological profusion
Douglas 1986 UK (21)	Cross sectional study among deceased coal miners	430/0* Autopsied lung pairs. (1972-74).	No data	Thermal precipitator and MRI Gravimetric dust sampling from 1954 to 1980. Average level by occupational group times duration within each group.	resp. dust 136.9-303.1 gh/m^3 Carbon 81.1-94% Quartz 2.8-5.4 % Exp. duration 27-44 years	Yes	3 Gradings of pathological findings: 1: < 1mm ; 1-9mm and 10+ mm lesions	No	Increasing lesions with increased whole dust and ash deposits in the lungs. Not possible to evaluate the quartz effect properly.

Author Year Country (ref.)	Study design (Study period)	Study population Exposed /control	Age (range)	Exposure assessment	Exposure levels Exposure duration	Exposure-response analysis	Outcome (Measure)	Covariates Accounted for	Result
Morfeld 1997 Germany (24)	Follow up (mean follow-up time 9.3 year), 3 German coal mines	5778/0*	No data	43,842 gravimetric dust sampling, individual and area measurements.	Mean resp. dust 1.8 mg/m^3 Mean quartz 0.18 mg/m^3 Between 1.7 – 12.5% quartz Mean exp. duration 21.1 years	Yes	Full and small sized anterior-posterior chest radiograph: Opacities 0/1+ (ILO classification 1980)	Quartz	1 mg/m3 versus 3 mg/m3 resp. dust adjusted for quartz dust: RR=0.98 (p = 0.98) No relationship between coal dust and abnormal radiological finding. Strong "mine" effect not explained by dust or quartz concentration
Buchanan 2003 UK (20)	Cross-sectional study, 1990 -91, one British colliery. One of the 10 mines included in Hurley 1982	371/0*	50-74	Thermal precipitator and MRI Gravimetric dust sampling from 1954 to 1980. Average level by occupational group times duration within each group.	Mean non quartz resp. dust 53.1 gh/m^3 Mean quartz 4.48 gh/m^3 Mean exp. duration 8000 h	Yes	Full size posterior-anterior chest radiograph: Opacities 2/1+ (ILO classification 1980)	Smoking, age, quartz	OR, resp. dust gh/m3 pre 1964 adjusted for quartz: 0.996 (0.971-1.022) OR, resp. dust gh/m3 post 1964 adjusted for quartz: 1.025 (0.974-1.079) Absolut risk for15 years exp. to non-quartz resp. dust: 0.8%
Graber 2014 USA (25)	Follow-up mortality study 1969-2007, underground coal mine workers	8829/0*	Mean 45 at start of follow-up.	Mine safety and health administration compliance data from 1982-2002. Gravimetric sampling. Average level by occupational group times duration within each group.	Mean Coal dust 64.6 mg/m^3-yr Quartz 2.6 mg/m^3-yr Mean duration 20.8 years	Yes	Pneumoconiosis from death certificates Full size anterior-posterior chest radiograph, (ILO classification 1980	Smoking, age, coal rank, race, calendar year, quartz	Cox proportional hazard analysis. Resp. dust HR adjusted for quartz between 1.17 and 2.58 depending on mine, highest for hard coal mines. Interaction between dust and mine. Quartz HR adjusted for resp. dust: 1.33 (0.94-1.90)

*No internal control group

PMF – Progressive massive fibrosis
FEV1 – Forced expiratory volume in one second
FVC – Forced vital capacity
FEV1/FVC – ratio FEV1/FVC

ILO – International Labour Organization
RR – Relative risk
OR – Odds ratio
Resp. – Respirable

Exp.-exposure

Supplementary 1. Search terms coal and pulmonary fibrosis

Search bibliotek.dk

Included: journal articles, e-articles, e-journal articles, e-documents, free accessible e-documents

Languages: English, Danish, Norwegian, Swedish, German

Search terms: kul* (free text) and lunge* (free text)

Search dato: 15.04.2014

Search The Cochrane Library

Included: Cochrane reviews, reviews, trials

Search terms: coal

Search dato: 15.04.2014

Search Embase

Languages: English

Search terms: coal, coal worker, coal miner, coal loading, coal shipping, anthracosis, anthracosilicosis, coal, worker pneumoconiosis, pneumoconiosis, black lung, silicosis, bronchial anthracofibrosis, pneumofibrosis, lung fibrosis, pulmonary fibrosis, fibrosing alveolitis, hamman rich syndrome, parenchymal lung diseases, parenchyma lung diseases, interstitial lung disease (MeSH terms)

Search dato: 15.04.2014

Search PubMed

Included: all article types

Languages: English

Search terms: *Exposure:* coal, coal worker, coal miner, coal loading, coal shipping, coal power plant, coal CHP, coal combined heat and power, coal heating plant, coal dust (all fields); *Outcome:* anthracosis, anthracosilicosis, anthracosis, black lung, anthracosis pneumoconiosis, coal worker pneumoconiosis, coal worker's pneumoconiosis, coal miners lung, black lung disease, coalworkers pneumoconiosis, coal mine dust lung disease, silicosis) OR pneumoconiosis, bronchial anthracofibrosis, pneumofibrosis, lung fibrosis, pulmonary fibrosis, pulmonary fibrosis, fibrosing alveolitis, fibrosing alveolitides, hamman rich syndrome, interstitial lung disease, parenchymal lung diseases

Search dato: 15.04.2014

Search SveMed+

Included: all article types

Languages: English, Danish

Search terms: coal (free text search), coal, kul, kuleksponering

Search dato: 14.04.2014