Systematic review of the association between exposure to asbestos and the development of asbestosis

Report to The Danish Working Environment Research Fund

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1. Background

Asbestos is a general term for a group of naturally occurring minerals with extraordinary strength and resistance. Because of these properties, asbestos has been used extensively in around 3000 different products mainly in the construction industry (World Health Organization. Regional Office for Europe, 2000). During 1920-2000, the amount of asbestos traded in Europe was approx. 50% of all asbestos traded globally. During 2001-2012 it decreased; particularly in Europe and North America; due to several national asbestos bans (Kameda et al., 2014). The bans on the use of asbestos was a result of the concern regarding the health effects (World Health Organization, 2014), as exposure to asbestos causes several different diseases including mesothelioma, lung cancer and asbestosis (Prüss-Üstün et al., 2011; World Health Organization, 2014). However, asbestos continues to be used in many countries and according to the WHO, it is considered one of the major chemical hazards at work by the ILO (*Exposure to hazardous chemicals at work and resulting health impacts: A global review*, 2021), and about 125 million people are currently exposed to asbestos in the workplace worldwide (World Health Organization, 2018). Some 255,000 deaths are estimated to be caused annually by asbestos exposure; of these 233,000 are due to work-related cancers (Furuya *et al.*, 2018).The number of deaths from asbestosis is lower than from cancer. However, the incidence of asbestosis has been increasing globally over the past decades with higher increases in incidence rates in Australia, high-income North-America, and Southeast Asia (Yang *et al.*, 2020).

Systematic reviews on the relationship between asbestos fibre exposure and the risk of asbestosis are scarce. Since major reports in the 1980s (Doll & Peto, 1985; The Royal Commission, 1984) there does not appear to have been published any systematic reports on the topic. In 2011 a meta-analysis was published on lung function among asbestos-exposed workers (Wilken *et al.*, 2011). Some non-systematic expert-based revisions of diagnostic criteria were published in 1997 (Finnish Institute of Occupational Health, 1997) and revised in 2015 (Wolff et al., 2015), by the American Thoracic Society (ATS) in 2004 (Guidotti *et al.*, 2004), and by an international committee of pathologists in 2010 (Roggli *et al.*, 2010). None of these papers include systematic attempts to unravel the exposure-response relations or to identify lowest accumulated asbestos exposure level required to produce parenchymal lung fibrosis.

Even though new evidence has gathered over the last decades, the associations described in the 1980s still form the basis for the diagnosis of asbestosis today and for how it is compensated in many countries. Thus, an updated systematic review addressing exposure-response relations is critically warranted.

This review was made on request from the Board of Labour Insurance in Denmark. The call asked for a review on existing literature between occupational exposure to asbestos and the risk of asbestosis with a particular emphasis on dose-response associations in the more recent literature, and a grading of the evidence.

1.1 Asbestosis

Several medical papers on what was to become known as asbestosis appeared in the decades prior to 1930 (Greenberg, 1994) when Merewether and Price (Merewether and Price, 1930) published a survey performed among asbestos textile workers (also referred to in the Annual Report of the Chief Inspector of Factories and Workshops for the Year 1929 in Great Britain). The survey revealed signs of fibrosis in 95 out of 363 workers (26%) exposed to asbestos for 0 to 20+ years and chest x-ray (CXR) confirmed the disease in 62 in a subset of 133 of the workers.

The early cases were observed despite the limited use of asbestos with at most 8000 workers exposed in Great Britain at the time (Waldron, 2021). Thus, asbestosis has been a significant occupational disease for more than a century even though statutory controls began to be introduced after the pioneering reports in the 1930ies. The definition of the disease has changed over time. For decades it was a diagnosis based on clinical findings possibly missing milder cases. In the most recent decades, it has become independent of symptoms and has relied on typical radiological (or histological) findings by standardized methods and a documented history of asbestos exposure (Finnish Institute of Occupational Health, 1997).

Asbestosis is a diffuse, interstitial lung fibrosis caused by the inhalation of asbestos fibres. The disease is usually attributed to occupational exposure to asbestos and the fibrotic changes develop slowly over years and decades, and progress even after the end of exposure (The Royal Commission, 1984). The ICD-10 diagnosis code is J61 "pneumoconiosis due to asbestos and other mineral fibres". The combination of radiological verification of typical interstitial fibrosis suggestive of asbestosis and a history of exposure to asbestos is essential for making the diagnosis (Guidotti *et al.*, 2004; Baur *et al.*, 2016). In addition, a mineralogical analysis for asbestos fibres in the lungs can be conducted, although lung biopsy is seldom performed, and no standardized method exists. The presence of asbestos fibres or multiple asbestos bodies in cytological or histological samples from the lungs can prove previous exposure to asbestos when in doubt, but due to clearance of fibres over time, absence of fibres cannot exclude past exposure (European Commission, 2009; Guidotti et al., 2004).

The prevalence of interstitial fibrosis suggestive of asbestosis depends on the intensity and duration of exposure (Guidotti *et al.*, 2004). The latency i.e., time since first exposure (TSFE), also plays a role for the observed prevalence both because the disease may continue to develop (increasing the chances of being detected radiologically) and because fibres may continue to be cleared from the lungs (lowering chances of histopathological detection). No evidence-based threshold for the duration or intensity of exposure in relation to the development of asbestosis exist. In addition, no commonly agreed upon threshold of cumulative exposure or dose exist. We will be using the terms exposure and exposure-response in relation to cumulative exposure, reserving the term dose to studies of internal uptake of asbestos fibres.

Routine readings of CXR tend to have a low sensitivity in detecting low-moderate grade of diffuse parenchymal changes compatible with asbestosis (Albin *et al.*, 1992). In the diagnostics of asbestosis, chest high-resolution computed tomography (HRCT) is superior to plain CXR, as it is more specific and sensitive (Ross, 2003; Guidotti *et al.*, 2004; Paris *et al.*, 2004).

However, HRCT abnormalities similar to asbestosis can be observed in cases of idiopathic pulmonary fibrosis (IPF) and other fibrotic interstitial lung diseases (ILD) (Paris *et al.*, 2004) and these are important differential diagnoses to consider. In case of typical radiology, a history of heavy occupational asbestos exposure reduces, but does not completely exclude the likelihood of an IPF diagnosis (Guidotti *et al.*, 2004; Baur *et al.*, 2017a). The presence of pleural plaques increases the likelihood of asbestosis (Guidotti *et al.*, 2004; Akira and Morinaga, 2016). If a multidisciplinary team does not reach a conclusive diagnosis, e.g. if there are no pleural plaques and no history of sufficient occupational exposure to asbestos, a lung biopsy and histology may be considered (Baur et al., 2017; Raghu et al., 2018). Crackles at lung auscultation is a characteristic and early sign of asbestosis (al Jarad *et al.*, 1993). As the development of asbestosis is exposure-dependent it is fundamental to assess whether the asbestos exposure has had a sufficient duration, intensity, and latency to cause the disease (Dement *et al.*, 1983; Guidotti *et al.*, 2004). In the 1980s the Royal Commission on Asbestos and other authors (Doll and Peto, 1985) proposed a cumulative exposure of 25 fibre-years (fibres per mL air*full time work yrs: fibre-yrs) as a threshold for the development of asbestosis. These opinions have formed the basis of the criteria for recognition of the disease in some countries, whereas other countries use different recognition criteria (Lee *et al.*, 2021). The so-called Helsinki criteria, updated in 2014 (Wolff et al., 2015) using a similar threshold, are still controversial and under debate (Baur et al., 2017). Previously the diagnosis of asbestosis commonly included clinical manifestations (European Commission, 2009; The Royal Commission, 1984). However, the Helsinki and other more recent criteria emphasize the use of radiological findings and exposure using clinical findings as supportive evidence only (Wolff et al., 2015).

From 1990 to 2017, according to Global Burden of Disease (GBD) data, the estimated annual global incidence of asbestosis doubled to approximately 9400 cases with incidence rates increasing particularly in North America and Australasia and decreasing in Western Europa where asbestos bans were first introduced (Yang *et al.*, 2020). Data om global mortality from asbestosis were estimated to increase from 21,000 to 24,100 between 1990 and 2013 (GBD 2013 Mortality and Causes of Death Collaborators, 2015). Later GBD publications have not reported detailed mortality data for asbestosis, but the GBD Results tool (at http://ghdx.healthdata.org/gbd-results-tool; accessed July 13th 2023) estimates global mortality at approximately 3,600 deaths annually; a figure more compatible with the estimated incidence. Mortality rates vary between countries. For example, between 1994-2010 the age-adjusted mortality rate for asbestosis per million people was 1.91, 0.79 and 2.07 in Denmark, France and Norway, respectively (Kameda et al., 2014). The proportion of asbestos use and import in a country has been shown to correlate well with the subsequent number of men with asbestosis (Lin *et al.*, 2007; Barber *et al.*, 2016). However, due to the latency in the development of asbestosis, the disease-burden depends on the time of the introduction of bans in different countries, and therefore the disease-burden reflects previous high levels of asbestos use (Kameda et al., 2014). Nevertheless, the variation in the reported mortality rates and figures suggest that diagnostic efforts and criteria vary with time and between countries.

1.2 Asbestos

There are six types of minerals split into two main classes of asbestos: serpentine (chrysotile) or amphiboles (crocidolite, amosite, actinolite, tremolite and anthophyllite) (World Health Organization. Regional Office for Europe, 2000). The type, size and dose of the asbestos fibres has a bearing on the development of asbestos-related diseases (International Agency for Research on Cancer, 2012), but all types are capable of causing asbestosis (European Commission, 2009). Asbestos fibres appear as bundles of thinner fibres consisting of fibrils. Under industrial handling the fibres tend to decompose into its smaller components and become respirable. Chrysotile can partly dissolve in the lungs due to its ability to split into fibrils (Churg, 1994; Visonà *et al.*, 2021). The amphiboles have longer residence in the lungs because they do not split into fibrils and are less soluble in the lung (World Health Organization. Regional Office for Europe, 2000). These properties make it even more difficult to rely on the detection of asbestos bodies in the lung tissue, if the main exposure has been chrysotile (Baur et al., 2017). The most widely used asbestos type was and still is chrysotile which is now mainly used in the developing countries (World Health Organization, 2014). The use of all types of asbestos is banned in European and some other countries, but there is still a risk of occupational asbestos exposure e.g. in the maintenance of older asbestos-containing buildings and elements (World Health Organization, 2014). The highest asbestos exposure levels have been reported in manufacturing facilities, mining and milling industries (Institute Of Medicine (US) Committee On Asbestos: Selected Health Effects, 2006), while the majority of workers were and still are exposed in the construction sector to varying levels of asbestos.

Different methods and practices have been used to measure the fibre concentrations in the air. The filter-based method using phase-contrast light microscopy (LM) to measure asbestos fibre concentrations is still the most widely used method. It was proposed by WHO in 1976 after having been widely used for some years. The method counts fibres >5µm long and <3µm wide with a length to width aspect ratio of at least 3:1 (World Health Organization, 1997).

However, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) methods have become the gold standard methods of fibre counting. The number of fibres are underestimated with LM compared with EM methods (Cherrie, Addison and Dodgson, 1989). This is especially true regarding the thinnest fibres that are potentially the more hazardous ones when fibres are long. On the other hand, EM more readily detect shorter fibres.

Before the 1970s most studies used particle mass measurements in airborne dust collected by different methods (National Research Council (US) Committee on Nonoccupational Health Risks of Asbestiform Fibers., 1984), although in, e.g. South African studies, fibre rather than mass concentrations had been measured for many years (Sluis-Cremer, 1991). It has proven to be very difficult to reliably translate particle mass concentrations into fibre counts with at least an order of magnitude in difference between proposed translation factors between studies even within similar industries (National Research Council (US) Committee on Nonoccupational Health Risks of Asbestiform Fibers., 1984). Therefore, in our review studies relying on mass only were excluded or graded as low-quality studies.

1.3 Co-factors

By definition, asbestos is the only risk factor for developing asbestosis. However, smoking and age may affect the risk of being diagnosed with asbestosis because of their association with radiological changes that resemble those associated with asbestosis as discussed later. Importantly, the radiological and histological features of unequivocal asbestosis are specific and differ from those seen in other pneumoconioses (Guidotti *et al.*, 2004) and the main differential diagnosis: idiopathic pulmonary fibrosis (IPF) (Roggli *et al.*, 2010). These features are elaborated on in paragraph 3.6.

1.4 Objectives of the study

The objective was to systematically review the risk of asbestosis according to occupational cumulative exposure to asbestos taking intensity, latency, duration, fibre types, type of job or task, smoking, and age into account. A specific aim was to explore the exposure-response relationship, particularly in studies with low cumulative levels of exposure.

2. Methods

This review was conducted in accordance with Special guidelines for preparation and quality approval of reviews in the form of reference documents in the field of occupational diseases according to the Labour Market Insurance in Denmark. The review was also conducted in accordance with Guidelines for preparation of reference documents on the causal association between an occupational exposure and disease outcome according to The Danish Working Environment Research Fund (Arbejdsmiljøforskningsfonden, no date) (documents currently unavailable on the internet, Nov 23rd 2022). Furthermore, the review was conducted in accordance with The Navigation Guide methodology (Lam et al., 2016; Woodruff & Sutton, 2014) and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page *et al.*, 2021) (Appendix 3).

2.2 Working group

The working group consisted of ten experts in occupational medicine, pulmonology, pathology, and epidemiology with significant clinical and scientific expertise in asbestos related diseases.

2.3 Eligibility criteria

The eligibility criteria: Population, Exposure, Comparator and Outcome (PECO) (Woodruff & Sutton, 2014) are described below according to the Navigation Guide Methodology.

2.3.1 Types of population

Studies on workers and former workers with occupational exposure to asbestos were included.

2.3.2 Types of exposure

Studies on exposure to any of the six commonly accepted types of asbestos were included.

2.3.3 Types of comparators

Higher relative to lower/no cumulative asbestos exposure.

2.3.4 Types of outcomes

Studies with asbestosis as the outcome defined by CXR, CT, histo-pathology, or death certificate were included. We also included studies investigating exposure to asbestos without significant exposure to other known fibrogenic agents (e.g. silica) in which only the broader diagnosis pneumoconiosis was used.

2.3.5 Types of studies

Original studies were included irrespective of the design if they quantitated asbestos exposures occurring prior to the diagnosis of the disease. Reviews, meta-analyses, and case studies were excluded.

2.3.6 Types of effect measures

Studies reporting mortality, prevalence, as well as incidence of the disease were included.

2.4 Searches and information sources

Searches were performed from April to May 2020 with librarian assistance. Searches were carried out in PubMed, Embase and Cochrane Libraries for relevant literature published anytime in English, French, German, Italian or a Scandinavian language. The searches included combinations of the terms “asbestos”, “serpentine”, “amphiboles”, “chrysotile”, “crocidolite”, “amosite”, “anthophyllite”, “actinolite”, “tremolite”, “asbestosis”, “interstitial lung disease”, “pneumoconioses” and “pulmonary fibrosis”.

2.4.1 Pubmed

The literature search in PubMed yielded 5,054 citations.

Full search from PubMed: (((((((("Asbestos"[MeSH Terms] OR "asbestos*"[Title/Abstract]) OR "serpentine"[Title/Abstract]) OR "chrysotile"[Title/Abstract]) OR "amphibole*"[Title/Abstract]) OR "crocidolite"[Title/Abstract]) OR "amosite"[Title/Abstract]) OR "anthophyllite"[Title/Abstract]) OR "actinolite"[Title/Abstract]) OR "tremolite"[Title/Abstract]) AND ((((((((("Asbestosis"[MeSH Terms] OR "lung diseases, interstitial"[MeSH Terms]) OR "Pneumoconiosis"[MeSH Terms]) OR "Pulmonary Fibrosis"[MeSH Terms]) OR "Asbestosis"[Title/Abstract]) OR "Asbestosis"[Title/Abstract]) OR "interstitial lung disease*"[Title/Abstract]) OR "Pneumoconiosis"[Title/Abstract]) OR "pneumoconioses"[Title/Abstract]) OR "Pulmonary Fibrosis"[Title/Abstract])

2.4.2 Embase

The literature search in Embase yielded 2,722 after excluding duplicates.

2.4.3 Cochrane Libraries

An additional literature search in the Cochrane Libraries yielded 40 citations.

2.4.4 Other sources

Eight studies were identified through other sources, e.g. by references from other studies, and considered for inclusion. This included studies published until March 2021.

2.5 Study selection

Included articles were selected at two levels. First, all 7,824 titles were screened independently by two researchers and included for further selection, when the two researchers agreed separately or after

a discussion. Then all abstracts of the included titles were read independently by the two researchers and studies were included after discussion of relevance. Full-text articles were then each distributed to two of the ten expert panel members who rated them independently, then reaching consensus. Based on the eligibility and inclusion criteria the final articles were selected for inclusion (Figure 1). When more than one paper included data from a particular cohort, we included the study with the longest follow-up time. In case a cohort was extended with new participants, when a cohort was mixed with previously unstudied cohorts for grouped analysis, or when a cohort was analysed in significantly different ways in separate papers (e.g., by histology in one and radiology in another paper), we included both papers despite the overlap in populations. All information on the eligibility criteria listed previously were sought in each study.

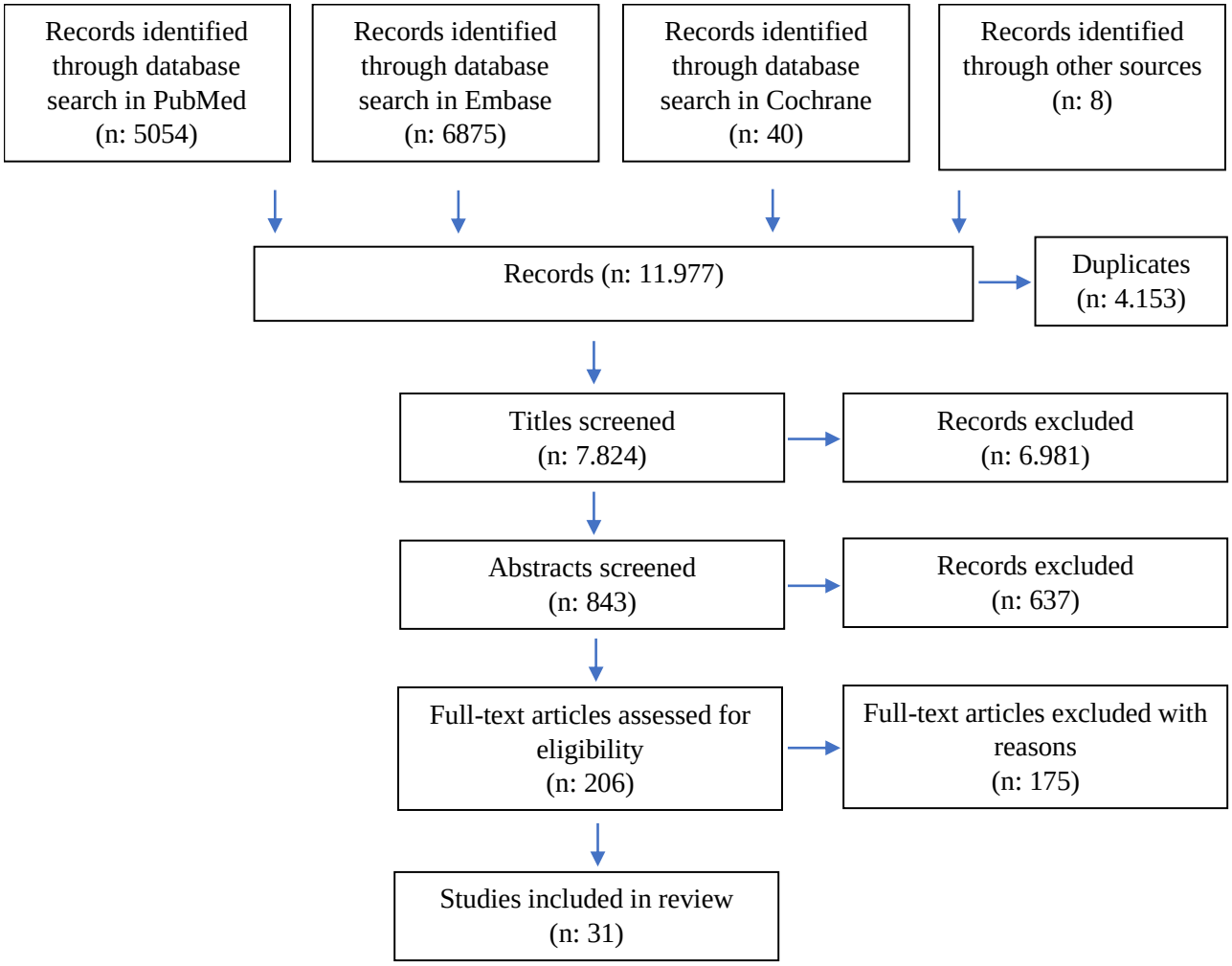

Figure 1. *Flow chart of the study selection in the different stages.*

2.6 Assessment of risk of bias

The criteria for the assessment of risk of bias (RoB) for each individual paper were based on the relevant aspects concerning the aim of this study and scored independently by at least two readers. No existing assessment tool was found to fit the aim perfectly. We thus modified an existing validated tool by Lam *et al*. with added focus on exposure inspired by the recently published RoB-SPEO toll by Pega *et al*. (Lam *et al.*, 2016; Pega *et al.*, 2020) into a tailored RoB tool with added domains concerning accuracy of exposure assessment and of outcomes (see appendix 3). The assessment of the RoB of the studies was performed according to the following score including 9 domains: *disease outcomes (e.g. radiology, histopathology, or cause of death) assessed independently of exposure* (no: 0, yes:1); *design* (cross-sectional: 0, follow-up or case-control: 1); *self-reported job-history* (yes: 0, no: 1); *adjustment for the effect of age* (no: 0, yes: 1); *adjustment for the effect of smoking* (no: 0, yes: 1); *conflict of interest* (yes: 0, no: 1); *diagnosis of high quality (i.e. by accepted definitions and reached by at least two independent evaluators separately (or side-by-side reading) then reaching consensus, or death records verified by reassessing data used for the death certificates)* (no: 0, yes: 1); *fibre exposure measured in a reliable, standardized, accurate way?* (no: 0, yes: 1); *blinding of assessors in relation to exposure (i.e. readers of CXR/CT, pathologist, or clinicians blinded to the exposure) or previous diagnosis of the patient (i.e. assessors of exposure blinded to the clinical assessment)?* (no: 0, yes: 1). If no information was reported or the information was incomplete the score was 0. Highest possible score was 9, representing the highest quality. Regarding the conflict-of-interest domain, we assumed no conflict only if the research was performed exclusively by researchers without any affiliation with or funding from the asbestos industry (including the companies under investigation) and data availability did not depend on companies or claimants. Regarding quality of diagnosis and blinding we scored "0" if the information listed above was unavailable. Regarding fibre measurements we scored "1" if the methods claimed the use of such methods even without describing them in detail.

2.7 Assessment of quality of the evidence

Grading of the overall evidence was performed according to the Navigation Guide methodology as described by (Lam *et al.*, 2016) and graded according to the criteria in appendix 6 as requested by AMF. The following 8 domains were included in the grading: RoB, indirectness of evidence, inconsistency of evidence, imprecision of evidence, publication bias, large magnitude of effect, exposure-response gradient, and residual confounding likely increases confidence in results. See appendix 3.

3. Results

A total of 31 studies were included in this review as shown in the flow-chart Figure 1. The quality score of the studies varied from 2 to 8 as depicted in Figure 2. The review included one cross-sectional study, three case-control studies, 11 cross-sectional studies with historical exposure data, and 16 cohort studies. No lower limit of Quality Score was set, allowing inclusion of studies with a relatively low score. A total of 11 studies were given a score of 6 or higher.

Relevant data on the methods and results of the 31 studies are presented in Table 1. Table 2 provides details on quality, strengths, and weaknesses of the studies. A more detailed description of each study is presented in appendix 1.

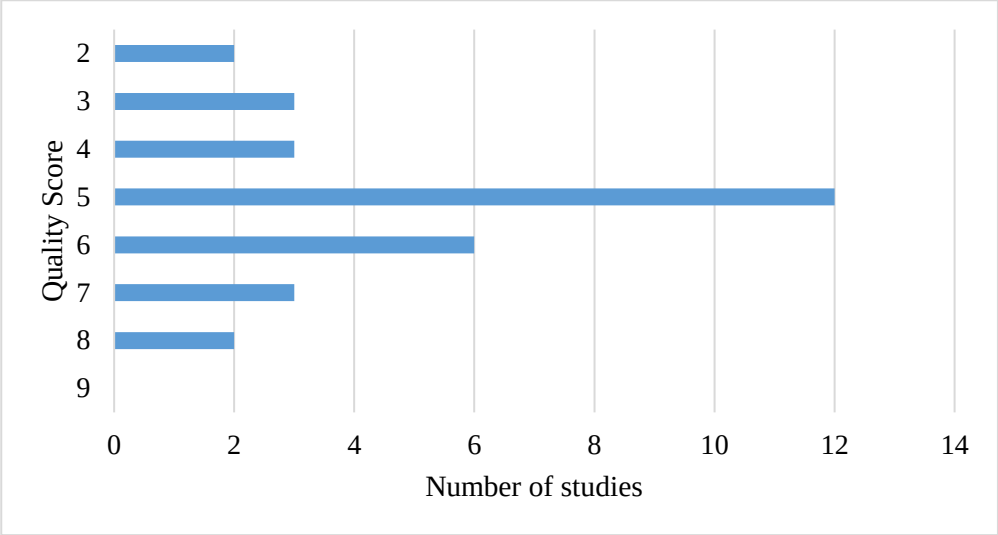

***Figure 2**. Distribution of quality score.*

The included studies are from Europe (Berry et al., 1979; Eisenhawer et al., 2014; Feder et al., 2018; Fischer et al., 2002; Franko et al., 2007; Ghezzi et al., 1972; Jakobsson et al., 1995; Johansson et al., 1987; Magnani et al., 2020; Mastrangelo et al., 2009; Paris et al., 2008; Satta et al., 2020), USA (Ehrlich et al., 1992; Hein et al., 2007; Jones et al., 1989; Larson et al., 2010; A. D. McDonald et al., 1982; Murphy et al., 1971; Rohs et al., 2008), Australia (Armstrong et al., 1988; De Klerk et al., 1991; Harris et al., 2021), South Africa (Irwig et al., 1979; Sluis-Cremer et al., 1990), Asia (Chen et al., 1992; Courtice et al., 2016; Huang, 1990), Canada (Cordier et al., 1984; Finkelstein & Vingilis, 1984; J. C. McDonald et al., 1980) and one study from Brazil (Terra-Filho et al., 2015).

3.1 Intensity and duration

Nine studies reported on the association with intensity of exposure. Of these, three observed a statistically significant increased prevalence of asbestosis with higher intensity exposures (De Klerk et al., 1991; Jones et al., 1989; Paris et al., 2008; Satta et al., 2020), and four a non-significant increased prevalence (De Klerk et al., 1991; Ehrlich et al., 1992; Jones et al., 1989; Mastrangelo et al., 2009). One study did not find an effect (Jakobsson et al., 1995; Mastrangelo et al., 2009) and one observed decreased incidence of asbestosis with increased exposure intensities (Cordier et al., 1984). The difference in exposure varied one order of magnitude between these studies from an increased risk observed in the interval between 0.15 and 0.3 f/ml (Satta et al., 2020) to a non-significant increase >13.5 f/ml (Mastrangelo et al., 2009).

Eighteen studies reported on the association with duration of exposure. Of these, nine studies found a significantly increased incidence, prevalence, or mortality of asbestosis with increased duration of exposure (Eisenhawer et al., 2014; Franko et al., 2007; Irwig et al., 1979; Jakobsson et al., 1995; Jones et al., 1989; A. D. McDonald et al., 1982; Murphy et al., 1971; Terra-Filho et al., 2015) whereas 8 studies reported a non-significant association (Cordier et al., 1984; Ehrlich et al., 1992; Johansson

et al., 1987; Mastrangelo et al., 2009; Paris et al., 2008; Satta et al., 2020) and one did not observe an effect (Courtice et al., 2016). Duration of exposure varied between studies from <1 month to >30 yrs. The shortest duration of exposure with increased population risk of asbestosis was 12(15)-33 months (Cookson et al., 1986; De Klerk et al., 1991; Larson et al., 2010; Sullivan, 2007). Some cases of pneumoconiosis or asbestosis were observed in subjects employed ≤1 yr (Irwig et al., 1979; A. D. McDonald et al., 1982).

3.2 Latency (time since first exposure)

Latency from time of first exposure to onset of disease or death was reported in seventeen studies. It varied substantially between studies from 1 to 66 yrs (Feder et al., 2018; Johansson et al., 1987). Several studies reported mean or median latencies before onset of asbestosis without modelling any exposure-response functions. Although short latencies of a few years were reported, by e.g. (Armstrong et al., 1988; Johansson et al., 1987) mean or median latencies mostly varied between approximately 15 and 40 yrs (Armstrong et al., 1988; Courtice et al., 2016; Eisenhawer et al., 2014; Jakobsson et al., 1995; Johansson et al., 1987; Larson et al., 2010). Five studies reported statistically significant associations between latency and asbestosis (Eisenhawer et al., 2014; Harris et al., 2021; Jakobsson et al., 1995; Jones et al., 1989; Paris et al., 2008). Three studies did not find a significant association between time since first exposure and asbestosis (Cordier et al., 1984; Mastrangelo et al., 2009; Terra-Filho et al., 2015). However, the studies by Terra-Filho *et al*. and by Cordier *et al*. had very limited follow-up times of approximately 11 and yrs not allowing for a complete analysis of latency. These studies and the studies by Armstrong *et al*., Berry *et al*., Chen *et al*., and Cordier, Theriault & Provencher which had latencies of <25 yrs most likely missed a significant proportion of cases of asbestosis due to short latencies.

3.3 Onset and prognosis

In early studies conducted when exposure to asbestos was still heavy in some jobs, asbestosis was often diagnosed at the onset of clinical signs, e.g. crepitations. Profusions on CXR of grade 2/1 or higher (Murphy et al., 1971; Weill et al., 1973) was not uncommon. As described above, onset after just a few years were sometimes reported but latencies of more than 10-20 yrs usually observed (Peto *et al.*, 1977). Cases were often reported to have a poor prognosis. In more recent studies of less heavily exposed workers a favourable prognosis and longer latencies were typically reported (in some cases above 50 yrs (Eisenhawer et al., 2014; Girardi et al., 2020) although mortality from asbestosis was still observed (Girardi *et al.*, 2020; Larson, Williamson and Antao, 2020).

3.4 Exposure-response relationship below 50 fibre-yrs

A total of 17 studies either reported RR, OR, or included figures allowing for estimation of some kind of exposure-response relationship below 50 fibre-yrs. Of these, 9 were followed cohorts either prospectively or retrospectively (Courtice et al., 2016; Ehrlich et al., 1992; Eisenhawer et al., 2014; Finkelstein & Vingilis, 1984; Hein et al., 2007; Irwig et al., 1979; Jakobsson et al., 1995; Larson et al., 2010). One study was a case-control study with historical exposure data. Eight were considered high quality studies with a score of 6 or higher in our grading. Asbestosis was diagnosed using CXR, CT or histology. The mortality studies used death certificates.

In comparison with the group with the lowest cumulative asbestos exposure, the relative risk of asbestosis for cumulative exposure above a reference interval but below 50 fibre-yrs ranged between 1.1 (95% CI 0.5-2.6) and 10.8 (95% CI 1.5-75.7) for asbestosis disease and between 1.2 (95% CI 0.6-2.5) and 8.0 (95% CI 3.2-19.5) for mortality from asbestosis or pneumoconiosis. The percentiles of exposure varied widely, as did risk estimates. Variation in study size, outcome definition, exposure assessment methods, and statistical methods all may have contributed to variation in results. Three high quality studies provided models or figures showing increased risk of asbestosis without a lower limit of cumulative exposure (Courtice et al., 2016; Ehrlich et al., 1992; Hein et al., 2007). An earlier study by Paris *et al*. that received a high quality score showed a non-significantly increased risk from <100 fibre-yrs (OR (95% CI) 3.4 (0.8-15.2), but in order to avoid including data more than once from the same study, we replaced it by a later study with more subjects from the same group, showing an OR of 1.03 (without 95% CI) for each 10 fibre-yrs without a threshold (Paris et al., 2004, 2008). Possibly, earlier papers from other cohorts that were excluded because we selected the latest studies, could have contributed additional information on the exposure-response relationship. Papers difficult to interpret included one that did not provide risk estimates for the groups with lowest exposure (Terra-Filho et al., 2015) and one where cause of death included other respiratory diseases (Hein et al., 2007).

Studies with risk estimates of less than 25 fibre-yrs

Two studies with a high-quality score and providing confidence intervals reported an increased prevalence of asbestosis below 25 fibre-yrs (Ehrlich et al., 1992; Hein et al., 2007). Ehrlich *et al*. reported OR of 1.06 or 1.07 (two readers) per 10 FY without reporting on a threshold for this. Hein *et al*. with a mean cumulative exposure of 5.5 fibre-yrs observed and modelled a not statistically significant increased risk of "pneumoconiosis and other respiratory diseases" (42% asbestosis) as the cause of death below 25 fibre-yrs. A power model without lower threshold fitted the data best.

An additional two studies with a lower quality score provided confidence intervals for an increased prevalence below 25 fibre-yrs (Larson et al., 2010; Satta et al., 2020) and two lower quality rated studies reported statistically significant elevated prevalence of asbestosis below 25 fibre-yrs without confidence intervals (Armstrong et al., 1988; Rohs et al., 2008).

When focusing on the severity of asbestosis rather than on quality score, eight studies reported on grade 2+ asbestosis below 25 fibre-yrs (Armstrong et al., 1988; Ehrlich et al., 1992; Feder et al., 2018; Hein et al., 2007; Larson et al., 2010; Rohs et al., 2008; Satta et al., 2020; Sluis-Cremer et al., 1990). Of these, five provided statistical evidence or exposure response models with an increased prevalence below 25 fibre-yr (Ehrlich et al., 1992; Hein et al., 2007; Larson et al., 2010; Rohs et al., 2008; Satta et al., 2020). Satta *et al*. reported a statistically significant risk for grade 2 asbestosis by HRCT and Larson *et al*. for asbestosis as the cause of death. In fact, most studies – in addition to studying risk of low grade asbestosis (e.g., as defined by ILO CXR grade 1/0) - also investigated higher grades or more severe asbestosis or were cause of death studies. In the studies with exposures higher than 25 fibre-yrs by Jakobsson *et al*. and by Finkelstein and Vingilis the RR for higher grades were elevated compared with the risk for lower grade asbestosis. As mentioned previously, grade 2 asbestosis was observed below 25 fibre-yrs without statistical tests in other studies e.g., by Feder *et al*., Hein *et al*.,

Ehrlich *et al*., and Sluis-Cremer *et al*. Also, Harris *et al*. observed a high prevalence of ILA by HRCT sum grade ≥2 below 25 fibre-yrs. Finally, when focusing on latencies longer than 25 yrs, evidence of asbestosis below 25 fibre-yrs was reported in seven studies(Ehrlich et al., 1992; Feder et al., 2018; Harris et al., 2021; Hein et al., 2007; Larson et al., 2010; Rohs et al., 2008; Sluis-Cremer et al., 1990), being reported as statistically significant in three of these (Harris et al., 2021; Hein et al., 2007; Larson et al., 2010; Rohs et al., 2008). Table 1 and 2 provide details on these findings.

Six studies reported asbestosis below 10 fibre-yrs, two of them reporting statistically significant associations with confidence intervals (Larson et al., 2010; Satta et al., 2020) (Table 2). Satta *et al*. reported significantly increased risk above 5.3 fibre-yrs (OR (95% CI) 8 (1.2-54.5)), however without specifying an upper limit of the exposure group. We calculated the risk of asbestosis in the 5.3 to 10 fibre-yrs interval to be 2.1 (OR (95% CI) 1.4-51.3). Larson *et al*. reported an increased RR for asbestosis as the cause of death among those exposed to less than 8.6 fibre-yrs of 2.8 (RR (95% CI) (1.0-7.6)).

A number of studies reported single cases or groups of cases of asbestosis occurring below exposures of 10 or 5 fibre-yrs without testing statistically or comparing with other groups (Chen et al., 1992; Eisenhawer et al., 2014; Harris et al., 2021; Mastrangelo et al., 2009). Of these, two German studies on highly selected patients from insurance cases or who had had lung biopsies taken found that 27 of 103 cases of asbestos had been exposed to less than 25 fibre-yrs (most of them were below 10 fibre-yrs) (Feder et al., 2018) or that 42% of patients with a pathologic-anatomical diagnosis of asbestos-associated lung fibrosis (ie. >1000 asbestos bodies/cm^3) did not attain 25 fibre-yrs (Fischer et al., 2002).

Studies with risk estimates for higher exposure levels or for particle-based cumulative exposures

A number of studies provided risk estimates or alternative measures of association for asbestosis at cumulative asbestos exposure levels above 50 fibre-yrs, (Courtice et al., 2016; De Klerk et al., 1991; Ghezzi et al., 1972; Huang, 1990; Magnani et al., 2020) and four studies only addressed asbestosis or mortality using cumulative particle exposure rather than fibre exposure (Jones et al., 1989; A. D. McDonald et al., 1982; J. C. McDonald et al., 1980; Murphy et al., 1971). These studies are included in the tables but were not included in the evaluation of the risk of asbestosis.

3.5 Accuracy of measurement methods

The studies varied greatly in the methods used for collecting job history, measuring asbestos fibres in the air, and in the radiological and pathological methods applied.

Most of the published studies were follow-up studies spanning several decades and relying on company records for employment history and a varying number of personal fibre measurements and job-exposure matrices for the quantification of exposure using fibre-yrs as the metric of cumulative exposure. In these, there was a loss of subjects due to employees who could not be traced or who did not want to participate in follow-up investigations. A few studies obtained job history data from insurance or regional surveillance registers.

The most common exposure measurement method was fibre counting on membrane filter by light microscopy according to published standards and used directly in 16 studies and a further 5 studies

counting fibres from precipitators. Indirectly, such fibre counts were behind the data in a smaller number of studies applying job-exposure matrices. A handful of studies combined fibre counting with data from gravimetric methods from older periods that had been translated into fibre counts usually by parallel measurements. Some older studies relied solely on gravimetric methods and in a couple of cases converted these to fibre-yrs despite the well-documented lack of a reliable conversion factor. These differences in methods complicated comparisons of exposure levels between studies. Several studies based their calculations on a very limited number of fibre measurements compared to the number of employees and years that were covered by the investigations. However, the vast majority of studies used comparable filter LM methods and fibre definitions.

Of the 20 studies basing the diagnosis on radiology, 13 used CXR, 5 HRCT or low-dose CT scans and 2 CXR and CT scans. The International Labour Organization (ILO) criteria for CXR reading were almost uniformly applied although a few studies were based on readings performed before these criteria were created, describing changes similar to those endorsed by the ILO. Most studies divided cases into ILO categories, allowing us to exclude cases of pleural plaques only and to consider as asbestosis all cases of ILO grade 1/0 or greater. This grade was considered to be showing asbestosis in the majority of studies using CXR. According to the ILO Guidelines the grade is used for radiographs with opacities but where grade 0 without opacities was considered as an alternative (ILO, 2011). The criteria for diagnosing asbestosis on CT scans appeared sound but differed between studies. In one study applying both methods, the results were similar, albeit with less statistical significance when based on CXR than when based on CT (Terra-Filho et al., 2015). The prevalence of interstitial abnormalities was higher on CXR compared to the thin-section CT. Many studies relied on existing CXR readings performed for surveillance purposes although some were able to apply their own reading by independent investigators of existing radiographs. Only a couple of studies described using gold standard methods of using 2 or more readers independently.

3.5.1 Autopsy and mortality studies

It is not clear whether the 6 studies, that used death register data to study mortality of asbestosis, relied solely on pathology from autopsies or if in some cases radiological findings were also used. Several of the studies relying on death certificates demonstrated increased mortality below 25 fibre-yrs (and also below 10 fibre-yrs), even the single study on pneumoconiosis rather than asbestosis. In addition, three studies applied pathoanatomical counting of asbestos bodies in biopsy or autopsy material in order to make the diagnosis, confirming several cases of asbestosis below 25 fibre-yrs (Feder et al., 2018; Fischer et al., 2002; Johansson et al., 1987). Mortality ratios were often reported as extremely elevated (as they must be when mortality among unexposed by definition is zero), but this information was not used in our review, because the focus was on exposure-response for incidence and prevalence of asbestosis.

3.6 Competing causes of being diagnosed with asbestosis

3.6.0 Environmental asbestos exposure

Radiological interstitial lung abnormalities (ILA) are present in up to 9% of the general population with the highest prevalence among smokers > 60 yrs (Hatabu *et al.*, 2020), compared to approxi-

mately 32% in a population with low-level asbestos exposure in Australia (Harris et al., 2021). Environmental exposure to asbestos is rarely considered of sufficient intensity to cause asbestosis although studies suggest that this may indeed sometimes be the case (Magnani *et al.*, 1998; Larson, Williamson and Antao, 2020; Kwak, Zoh and Paek, 2021) and was probably of importance in two of the included studies (Harris et al., 2021; Magnani et al., 2020). However, it was outside the scope of this report to review the literature on environmental exposure. In cases where environmental exposure was significant e.g., when workers lived close to mining areas as in Wittenoom, Australia, the cumulative occupational exposure estimates may be underestimated, though probably only to a minor extent. In general, environmental exposures probably were orders of magnitude lower than occupational exposures as suggested by exposure intensities of 0.01 - 1.0 f/ml among former residents of Wittenoom (Hansen *et al.*, 1998) compared with maximum intensities surpassing 1000 f/ml in the mines (Armstrong et al., 1988).

3.6.1 Smoking

While by definition, asbestos is the only cause of asbestosis, an increased risk of being diagnosed with asbestosis among smokers compared to non-smokers has been reported elsewhere (Harding and Darnton, 2010; Markowitz *et al.*, 2013; Bledsoe, Christiani and Kradin, 2014) and in several of the studies we included (Berry et al., 1979; Cordier, Theriault and Provencher, 1984; Finkelstein and Vingilis, 1984; Jakobsson et al., 1995; Rohs et al., 2008; Eisenhawer et al., 2014; Terra-Filho et al., 2015; Courtice et al., 2016) whereas other studies investigated and did not observe an effect of smoking (De Klerk et al., 1991; Ehrlich et al., 1992; Franko et al., 2007; Hein et al., 2007; Johansson et al., 1987; Jones et al., 1989; Mastrangelo et al., 2009; Satta et al., 2020). In one well-powered study, an apparent effect of smoking disappeared when controlling for workplace, age at first exposure, time since first exposure, duration and average exposure (Jones et al., 1989). It has been speculated that the observed effect of smoking may be due to reduced elimination of fibres or due to effects of tobacco smoke itself that radiologically may resemble early-stage asbestosis (Johansson et al., 1987). In a study applying both MDCT and CXR, it was concluded that some of the changes observed on CXR, but not CT, probably reflected smoking (Eisenhawer et al., 2014). One of the included studies that applied both CXR and CT found a higher risk of asbestosis with smoking using both methods (Terra-Filho et al., 2015) that disappeared in a multivariate model. In other studies applying CT no association between asbestosis and smoking habits (Mastrangelo et al., 2009) or pack years (Paris et al., 2008) were observed. It was suggested that smoking may affect CXR-based diagnosis of asbestosis more than CT-based. Only few studies adjusted for both age and smoking (Ehrlich et al., 1992; Franko et al., 2007; Jakobsson et al., 1995; Paris et al., 2008). Of these, only one observed an increased risk of being diagnosed with asbestosis with smoking and the risk was observed only among subjects with profusion grade 0/1 but not among those graded 1/0 (Jakobsson et al., 1995). Clearly, pack-years are associated with age and thus with heavier exposures among the older subjects as observed in e.g., (Terra-Filho et al., 2015).

3.6.2 Age

Age has previously been found to be related to an increase in several pathological radiological signs including fibrosis score, independent of smoking and asbestos exposure (Paris *et al.*, 2004; Vehmas *et al.*, 2005). Only seven of the included studies addressed age. Of these, three reported significant

effect of age on the risk of asbestosis (Ehrlich et al., 1992; Hein et al., 2007; Irwig et al., 1979). The observed associations with age could be due to increased latency e.g., in studies by (Irwig et al., 1979; Johansson et al., 1987). Although Irwig *et al*. observed that in general, parenchymal "abnormality was significantly associated with age within each duration of exposure category", when adjusting for age they found only slight attenuations of the effects of asbestos exposure (Irwig et al., 1979). In the remaining four studies, confounding by age was unlikely (Paris et al., 2008; Rohs et al., 2008) or significant effects of cumulative asbestos exposure were observed after adjustment for age (Franko et al., 2007; Jakobsson et al., 1995).

Detailed results on smoking and age in the included studies are described in appendix 2.

3.7 Contributions from other occupational exposures than asbestos

Several studies considered possible concurrent or previous mineral dust exposure, mostly silica from mining. As typical radiological changes from these exposures differ in appearance from asbestosis such exposures did not appear to increase the likelihood of being diagnosed with asbestosis. Such exposures are important in the few studies that investigated pneumoconiosis rather than asbestosis. Frequency of pneumoconiosis increased with asbestos exposure also in studies of textile workers with no suspected silica exposure probably reflecting increased risk of asbestosis (Hein et al., 2007; A. D. McDonald et al., 1982).

3.8 Pre-existing conditions

A few older studies considered if subjects had radiological changes from tuberculosis (J. C. McDonald et al., 1980) or partly corrected for the risk by performing analyses stratified for age or race, still finding increased prevalence of asbestosis at levels below 10 fibre-yrs (Irwig et al., 1979; Sluis-Cremer et al., 1990). Other than this, pre-existing conditions were not considered.

4. Discussion

An extensive scientific literature search identified 31 studies that met our inclusion criteria. We limited the review to the most recent paper including most cases of asbestosis from the several cohorts that had been subjected to repeated analyses. Earlier publications that may have contained limited additional evidence on the included study populations were not systematically identified and read. Some additional information was, however, included for discussion..

The bulk of studies was more than 20 years old, typically addressing asbestosis in workers that were more heavily exposed than in the more recent studies. However, a number of studies had been published in recent years, allowing for inclusion of less heavily exposed workers.

In addition to the included studies and earlier papers from the same cohorts, the literature search identified a larger number of case series, some of which suggested asbestosis at low exposures. As these were excluded a priori, we cannot rule out that some were performed with a high quality of exposure assessment and diagnostic criteria.

It was outside the scope of the review to cover prolonged environmental or household exposures.

The studies were graded by quality based on RoB and additional criteria by published standard methods, modified for the purpose of the review. We presented results according to these. However, only using these criteria proved insufficient for the evaluation of the evidence. Several other issues emerged as important. These included the latency (time since first exposure), the grade of radiological or histological changes, the quality and coverage of fibre measurements, and the use of data collected for other purposes (e.g., legal purposes). Furthermore, some good studies presented results without statistics e.g., only as graphs or did not calculate fibre-yrs, but presented data allowing for the calculation of fibre-yrs. Similarly, the difference in methods used for radiological or histopathological diagnosis of asbestosis was of importance. These issues have been mentioned when deemed necessary for interpretation in the sections presenting the results. Ideally for the purpose of identifying at what level of cumulative exposure asbestosis occurs, studies should have been on ILA rather than on asbestosis, which by definition includes exposure, and have included non-exposed subject, but none fulfilled this. For the purpose of determining the nature of the exposure-response relationship among exposed, the inclusion of subjects with limited exposure was of greater importance than the inclusion of completely unexposed.

4.1 Exposure-response relationship of cumulative exposure

In more than 20 of the 31 studies some type of a cumulative exposure-response relationship was observed; in 17 of these with exposures below 50 fibre-yrs. Observational and statistical methods differed tremendously – precluding a meaningful meta-analysis and, to some extent, quantitative conclusions. Major differences were in outcomes that differed being mostly prevalence of asbestosis by varying definitions and methods (e.g., with or without clinical signs) or cause of death studies with mortality rates; risk estimates being calculated as OR, HR, RR, slopes, or simply visualized; two- or three-fold differences in latencies; and differences in exposure calculation methods. Inclusion of covariates age and smoking also varied. The results suggested both linear and other exposure-response curves and did not allow for conclusion on the shape and whether the curve is steeper or less steep below 50 fibre-yrs. Three high quality studies provided models or figures showing increased risk of asbestosis without a lower limit of cumulative exposure (Courtice et al., 2016; Ehrlich et al., 1992; Hein et al., 2007)and most studies investigating the exposure-response relationship allowed for a non-threshold relationship extrapolated to some extent from cumulative exposures higher than 25 fibre-yrs. High RR or OR of 4 to 20 were typically reported from approx. 40 fibre-yrs and upwards compared with lower exposures. RR or OR of 2-3 were reported around 10 fibre-yrs. Calculations of slopes suggested a risk of asbestosis of approx. 1.004/fibre-yrs. A few studies calculated a 1% risk of asbestosis around 10-22 fibre-yrs.

Few studies observed a statistically significant risk of asbestosis below 25 fibre-yrs and some of these observed a risk of asbestosis below 10 fibre-yrs. No studies compared the risk at very low exposures with that of non-exposed controls. In the studies using low grade asbestosis, e.g., as defined by ILO grade 1/0 or similar grades by CT or histology grade 1, the lack of unexposed controls is a major limitation. Because of this, what was described as prevalence or observed cases of asbestosis at low levels in these studies could be similar to that of the general population. Whether radiological or

histological changes typical of asbestosis at the lowest cumulative exposure levels reflected diffuse changes caused by age or smoking, were caused by low level environmental exposure to asbestos or other inorganic dusts, or were caused by misclassification of exposures, could not be elucidated.

When considering all studies irrespective of their quality score, an elevated risk of asbestosis below 25 fibre-yrs was statistically significant in four studies; an elevated risk was present also for grade 2+ asbestosis in five studies (with two other studies suggesting higher RR at higher than at lower grades); and an elevated risk was present in three studies with a latency longer than 25 yrs.

4.2 Intensity, duration, and latency

Detailed results on the association of asbestosis with intensity or duration of exposure were reported in 18 studies and on differences in time since first exposure (latency) in 17 studies.

The intensity studies did not have enough observations to allow for separating the effect of high peak exposures and continuous lower exposure intensities. A limited number of studies observed exposure-response relationships between intensity and/or duration alone and risk of asbestosis. Duration and latency of exposure causing asbestosis may be very short at extremely intense exposures. Latencies as short as 2-3 years were reported under heavy exposures with the longest latencies reported exceeding 60 yrs (Feder et al., 2018; Johansson et al., 1987). The shortest duration of exposure with statistically significant increased population risk of asbestosis was 12(15)-33 months (Cookson et al., 1986; De Klerk et al., 1991; Larson et al., 2010; Sullivan, 2007). Interestingly, five of the eight studies that calculated risk by fibre-yrs with latencies (TSFE in Table 2) of 30 yrs or longer, found an increased risk of either asbestosis at autopsy or of radiological fibrosis in the range from 4.4 to16 fibre-yrs (Sluis-Cremer, Hnizdo and du Toit, 1990; Hein et al., 2007; Rohs et al., 2008; Larson, Antao and Bove, 2010; Harris et al., 2021). Studies on latency differed in methods, preventing more detailed conclusions about the relationship.

It is reasonable to assume no minimal or maximal duration or latency before the diagnosis of asbestosis can be made, in case of very high or low intensities of exposure. Importantly however, it is questionable whether intensity, duration, or latency used separately without calculation of a cumulative index are of any interest as predictors of the development of asbestosis. As reported by Ehrlich et al., no association could be detected with duration alone without data on concentration (Ehrlich et al., 1992).

4.3 Assessment of fibres

Definition of length and width of fibres for these to be classified as asbestos and distinguished from particles and from other fibre types, and the methods used to collect and identify asbestos fibres changed over time. However, these changes only affected the interpretation of some of the older studies. Excluding results from these older studies did not affect our conclusions.

We included studies using LM as well as EM methods for quantification of the fibre exposure. Because EM methods can identify smaller asbestos fibres, they potentially result in higher cumulative exposures than LM unless some correction is used, rendering comparisons with the LM-based studies difficult. The proportion of long to short fibres or of fibres with varying length to width aspect ratios

is known to vary between industries and jobs. These differences were not captured by the cumulative fibre exposures in any of the studies no matter which assessment method was used.

4.4 Other pneumoconioses

Only few studies were on the less specific diagnosis of pneumoconiosis, which in addition to asbestosis includes interstitial lung disease caused by other agents (McDonald et al., 1980, 1982; Armstrong et al., 1988; Hein et al., 2007). We speculate that asbestosis was probably more commonly misdiagnosed as "unspecified" or among other types of pneumoconioses in earlier studies relying on CXR for screening of workers, than in later studies, applying CT and more rigorous radiological methods. When exposures were mixed (e.g., in mines, where there was also quartz exposure) or if radiographs were potentially less rigorously assessed such as what might be the case in employer initiated annual studies of CXR of hundreds of workers, there might be a risk of confusing asbestosis with other pneumoconioses. To our knowledge, this has not been described as a major limitation in studies of asbestosis. The proportion of pneumoconioses made up by asbestosis differ substantially between countries (Yang *et al.*, 2020), suggesting varying degrees of misdiagnosis, variation in diagnostic activity (e.g., due to differences in the possibilities for workers to be compensated for the disease) as well as variation in previous uses of asbestos between countries. The limited number of studies precluded conclusions about exposure-response relationship for pneumoconiosis.

4.5 Autopsy studies

Most likely, the probability of being diagnosed with asbestosis at death i.e., by autopsy, differed with time and location and may also have been affected by changes in diagnostic criteria and in awareness or legal considerations in earlier studies. This could have diminished chances of less exposed subjects being diagnosed with asbestosis, in theory limiting the ability of such studies to detect any increased mortality of asbestosis among individuals with a low cumulative exposure.

4.6 Bias

Of particular concern in relation to a possible risk of developing asbestosis at very low cumulated exposures was the lack of unexposed controls or reference subjects in almost all the studies. As per definition, asbestosis does not occur among unexposed. However, radiologists and pathologists blinded to the history of asbestos exposure might have classified some unexposed subjects as probably having asbestosis. We speculate that there is a high risk that estimates of asbestosis prevalence among workers with low cumulative exposures were overestimated because this lack of unexposed reference subjects. A few, mostly older studies, collected exposure information simultaneously with data on the disease and there might be a risk of bias e.g., in the studies using death certificate data in which awareness of asbestos exposure may have determined and possibly skewed which cases were labelled as asbestosis. Many studies, however, collected exposure and disease information separately, and often relied on at least two separate readers or pathologists for the evaluation of the disease, minimizing the risk of bias stemming from readers' information on exposures.

Another bias of particular concern was bias from short latencies, i.e., short time since first exposure, in some studies. Insufficient follow-up time would cause a bias in the direction of a lower incidence of asbestosis at the time of observation than what would have been observed had the cohort been

followed longer. On the other hand, a prevalence study with a long latency would miss early more severe cases of asbestosis due to deaths occurring. Low intensity exposures could be associated with bias from poorer recall or poorer recording of exposure, less likelihood of being clinically investigated, or with death resulting from cancer or other diseases before the diagnosis of asbestosis was made.

Cancers and asbestosis are competing causes of death in exposed workers. Thus, the incidence and mortality of asbestosis could be affected by the fact that a proportion of exposed workers died from asbestos related cancers before developing asbestosis. This may be especially true with increasing latency of asbestosis e.g., with low cumulative exposures. None of the included studies accounted for any such effects.

Most of the published studies were follow-up studies based on company records or similarly standardised documents. The risk of information bias was thus low. A few studies used qualitative categories for exposure or metrics such as the unit based on particle measurement mpcf-yrs. Some of these documented the existence of asbestosis in the low range of exposure to particles but this metric did not allow for inclusion in our review on the exposure-response effect of asbestos fibres. Compared with other types of follow-up studies the loss to follow-up appeared minor. Possibly, the loss could have been highest at the extremes of exposure: among the oldest employees with historically higher exposures and among short term employees with low exposures, limiting the confidence in exposure-response functions at these extremes. The few studies based on insurance or surveillance registers probably incurred a high risk of being less representative for asbestos exposed workers in general and of being based on data of varying quality. This would cause a high risk of biased exposure-response relationships but did not severely incriminate the qualitative observation that some cases of asbestosis occurred at very low exposures.

4.7 Exposure misclassification

The risk of non-differential misclassification of exposure decreasing the likelihood of detecting effects at low exposure levels was high in all studies, even the most comprehensive ones. The lifetime individual cumulative exposure calculated from employment did not allow for detailed study of specific tasks held that likely differed between workdays and over the years and were based only on fibre measurements performed a few times, usually lacking data from earlier more heavily polluted periods and sometimes based on different methods. The use of a group-based exposure assessment approach may lead to non-differential misclassification as there is no within-group (e.g., job title) exposure variation. However, this will mainly lead to Berkson-type error, resulting in increased uncertainty of risk estimates but unbiased exposure-response association.

A related problem is the question whether participants in the studies had been exposed to asbestos in jobs that were not included in the exposure estimates of each study. This question was specifically addressed in some studies by relevant though not perfect methods of data sampling (often personal information, sometimes supported by company records or similar). In many more studies, the relevance of such exposures unaccounted for in the main analyses were of negligible importance since the results were driven mainly from long-term employment in the cohort of study, leaving little time for other employment of the participants. It is not unlikely that asbestosis in some subjects with low

cumulative exposures after a short duration of employment was caused by undetected higher exposures elsewhere. This lowers confidence in the results for low cumulative exposures, but there was a sufficient number of high-quality studies with good exposure data to support our conclusions. Inversely, in a few studies, the risk of asbestosis in a control group was increased due to the existence of other industries handling asbestos in the area.

4.8 Smoking and age

The effect of smoking was addressed in some studies and the issue to what extent smoking may contribute to interstitial fibrosis that could falsely be classified as asbestosis is not yet solved as studies point in different directions. Similarly, the separate effect of aging was included in only few studies. Overall, the studies suggest that both smoking and age increase the likelihood of being diagnosed with low grade asbestosis as early radiological changes may resemble changes associated with smoking and high age. Smoking rates have changed over time, and some of the radiological changes on CXR, especially at low grades of profusion, associated with smoking and age could be due to higher levels of asbestos exposure among smokers and among the oldest workers, and not to smoking and age itself.

4.9 Outcome misclassification

As suggested in the literature and as observed by Harris et al. ILA can be rather common in a population with limited (or no known) exposure to asbestos. ILA are defined as incidental radiological findings including radiological patterns such as minor areas with ground-glass opacities but also more severe fibrotic patterns due to reticulation, tractions bronchiectasis, and honeycombing compatible with usual interstitial pneumonia (UIP) (Hatabu *et al.*, 2020). ILA appears without clinical symptoms and without affecting pulmonary function or diffusion capacity. If both symptoms and ILA are present, the patient is highly suspicious for having interstitial lung disease (ILD) rather than just ILA. UIP constitutes the predominant radiological pattern in asbestosis together with pleural thickening or plaques. As the Helsinki (Wolff et al., 2015) and the ATS (Guidotti *et al.*, 2004) criteria do not include symptoms or reduced lung function in their definitions, asbestosis by these definitions does not necessarily comply with the above criteria for ILD but could in fact comply only with ILA, However, asymptomatic HRCT changes in subjects examined for known occupational exposure is currently considered as subclinical ILD and not ILA (Hatabu *et al.*, 2020). Fibrotic ILA is correlated with worsened clinical outcomes (Hata *et al.*, 2021). Similarly, an increased mortality risk among asymptomatic patients with asbestosis is likely because patients with ILA of UIP type had a 2.7-4.5 times higher mortality risk compared to patients without ILA (Putman *et al.*, 2016, 2019). Based on the literature that we reviewed, the question whether typical bilateral evidence of fibrosis among asymptomatic subjects with low or unknown levels of asbestos exposure does in fact represent asbestosis does not seem to be resolved.

4.10 Prognosis

Early onset of asbestosis, i.e., with a short latency, could likely be the result of either more heavy exposure or genetically elevated susceptibility, or both. We did not identify studies investigating the plausible assumption that such early onset defines a poorer prognosis. If followed by a complete

exposure termination, early onset of asbestosis caused by heavy exposure and detected by, e.g., routine CXR might also predict a better prognosis than among workers exposed for longer periods.

4.11 Definition of outcome

The definitions of asbestosis and other fibrotic lung diseases have changed over time. In the earliest studies, the definition of asbestosis was purely clinical but with the introduction of the ILO CXR grading criteria these quickly came into universal use in the medical studies. Still, it is evident from our review that until the 1980s, the diagnosis usually included some degree of symptoms or clinical findings other than radiology or pathology. From the mid-1980s the definition as e.g., described in the Helsinki criteria, is based solely on typical radiological or pathological findings combined with sufficient exposure. Symptoms are used only to describe severity, not in the definition (Finnish Institute of Occupational Health, 1997). The introduction of CT in the 1970's allowed for better and more detailed visualization of interstitial changes, clearly increasing the chances of detecting the disease when applied. CT scans are more sensitive in the detection of interstitial abnormalities and many cases in these studies were probably milder than in CXR only studies. However, CT scans may have been applied less – especially compared with workplaces where regular CXRs were performed on all exposed workers - with the risk of not detecting all cases. Similarly, the diagnostic criteria of other fibrotic lung diseases including IPF have evolved with the use of HRCT as well as other methods (Travis *et al.*, 2013; Raghu *et al.*, 2018). It cannot properly be determined to what extent cases of asbestosis may have been missed or confounded with other interstitial lung diseases in the studies that relied on earlier methods of detection and definitions. Diagnostic advances likely mean that less cases of what is currently defined as asbestosis were missed or misdiagnosed in later studies especially those applying CT scanning.

4.12 Strengths and imitations

The literature search was comprehensive and included three databases and several languages and the risk of missing important studies was minimal. Included studies were published between 1971 and 2021 originating from North and South America, Asia, Australia, and Europe. Several studies were comprehensive, largely covering entire industries except for very early periods with few highly exposed workers of little relevance to the review. The broad perspective enabled the inclusion of studies with both very high and very low exposure levels, reflecting the change in the use of asbestos products with time.

Some large cohorts have been reinvestigated repeatedly over time, extending the follow-up time and with several publications over the years. We did our best to identify and use only those studies with the longest follow-up and/or the largest number of subjects included. However, some later studies also added more workers or even workplaces to the cohort or lost other subjects due to changed criteria or information available, and the distinction between what was merely an extension of follow-up and what was a new study population, was sometimes difficult. Most likely, only a very limited number of workers may also by coincidence be included in more than one separate study from the same area and period because they moved between industries during their lifetime. We do not think that it has had any major influence on our review.

It was a limitation that large numbers of workers were lost to follow-up in some studies, e.g., Italians and other foreign workers leaving the Wittenoom mines in Australia. If these were predominantly workers with short employments, this loss decreased the number of workers with low exposures and the ability to detect any effects in the low end of cumulative exposure. Further the different measurement methods and lack of fibre measurements in older studies may have resulted in highly uncertain estimates of the actual exposure levels especially at earlier times. If smoking and age affect the risk of being diagnosed with asbestosis and further is unequally distributed between individuals with different exposure levels, the lack of data on these two co-factors in most studies is a limitation. Of studies including age as a covariate, few investigated to what extent age affected the associations independently of duration and latency. No studies included calculations of how high mortality of cancers affected the rates of asbestosis.

The large heterogeneity of the studies especially regarding exposure assessment and outcome definitions significantly limited the possibility of drawing firm conclusions and precluded a meta-analysis. Another concern precluding a meaningful meta-analysis, often spuriously accounted for in the conclusions of the included studies, was limited follow-up time, not allowing for investigation during the entire latency period of a lifetime. In our view, comparing different ways of assessing exposure, has limited value if the latency from first exposure differ substantially between studies, as was often the case.

5. Conclusion

In this systematic review of 31 scientific papers, eleven studies were considered of high quality. Two studies with a high-quality score reported an increased prevalence of asbestosis or "pneumoconiosis and other respiratory diseases" below 25 fibre-yrs.

When focusing on other criteria than the quality score, an elevated risk of asbestosis below 25 fibre-yrs was statistically significant in four studies, was present also for grade 2+ asbestosis in five studies and was present in three studies with a latency longer than 25 yrs. Statistically significant risks were reported from 5.3 fibre-yrs for asbestosis. Asbestosis with symptoms or clinical signs was reported only above 25 fibre-yrs and asbestosis diagnosis reported on death certificates was observed below 8.6 fibre-yrs.

Because of large differences in the methods, and the fact that few studies tested for effects below 25 fibre-yrs, the review was suggestive of, but provided limited evidence that an increased risk of parenchymal lung fibrosis (and thus of being diagnosed with asbestosis according to current criteria) occurs below 25 fibre-yrs.

The question whether typical bilateral evidence of fibrosis among asymptomatic subjects with low or unknown levels of asbestos exposure does in fact represent asbestosis does not seem to be resolved. Earlier estimates of a threshold for asbestosis of approximately 25 fibre-yrs have been related to definitions of asbestosis that included clinical symptoms or signs of disease rather than the current definition of radiological or histological changes combined with a history of asbestos exposure. After

lower cumulative exposures the disease may develop with a latency of several decades, in some cases more than 60 years, occurring at an age where respiratory symptoms from other causes are common.

No lower threshold of cumulative exposure for the risk of asbestosis could be determined in papers investigating an exposure-response relationship. Three high quality studies provided models or figures showing increased risk of asbestosis without a lower limit of cumulative exposure. These findings were reported in both old and recent studies and by both radiological and pathological methods.

The effects of age and smoking were addressed in a minority of the studies. High age was associated with radiological changes and even though the typical fibrosis of asbestosis at advanced stages is more specific, early radiological changes due to asbestosis appear to be difficult to differentiate from other fibrotic lung diseases. It was impossible to completely separate the effects of age and asbestos exposure on the radiological findings. Age did not in any study appear to be causative.

The role of smoking was conflicting as the no. of high-quality studies that suggested associations with smoking was similar to the no. that did not observe such an association. The findings suggest that smoking historically increased the risk of being diagnosed with asbestosis, especially of low radiological grades, whereas it is not clear whether the risk is currently increased with CT-based methods (or histology). The observations could be due to heavier asbestos exposures among smokers, poorer clearance of asbestos fibres from the lungs of smokers, or to a low-grade fibrogenic effects of smoking itself.

The risk of developing asbestosis was demonstrated in relation to all types of asbestos fibres and in all major types of jobs with significant exposure. If there are differences in the exposure-response associations, as has been suggested in the past, the literature did not allow for quantification of such differences, especially not when looking at the risk of asbestosis over extended follow-up periods.

Grading of the evidence

1. Low intensities of exposure may be associated with the development of asbestosis (if duration is long) even below 1 f/ml. Good evidence +++
2. Short duration of exposure, possibly just a few months, may be associated with the development or mortality of asbestosis (if intensity of exposure is high). Some evidence ++
3. A cumulative exposure of 25 fibre-yrs or less increases the risk of developing asbestosis. Limited evidence +
4. There is a threshold for the cumulative exposure to asbestos and the risk of developing asbestosis. Insufficient evidence 0
5. Smoking is associated with radiological changes that may increase the risk of being diagnosed with asbestosis. Limited evidence +
6. High age is associated with radiological changes that may increase the risk of being diagnosed with asbestosis. Some evidence ++
7. All types of asbestos fibres are associated with a risk of developing asbestosis. Good evidence +++

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Table 1. Summary of the design, material, and outcome of the studies on asbestosis with exposure informations.

Reference, country	Study design	Study population	Jobs/tasks	Type of fibre	Exposure assessment method	Exposure contrast	Outcome	Measure of association
Irwig et al. 1979, South Africa	Cohort study	N: 1692 Male: 100%	Asbestos miners	Crocidolite and amosite	Not described in detail, but standard method of counting f/ml by LM.	Average exposure level (f/ml): **A: ≤ 10** **B: 10-20** **C: >20-**	Parenchymal fibrosis by CXR (ILO). (agreement between at least 2 out of 3 readers.)	Prevalence (%) (approx.) After two years: A or B: 0 C: 5 After five years: A or B: 0 C: 12 **After 10 years:** **A: 5** **B: 8** **C: 24**
Sluis-Cremer, Hnizdo & DuToit 1990, South Africa	Cross-sectional study with longitudinal exposure assessment	N: 807 Male: 100%	Miners	Amphibole asbestos	1940-65: Konimeter 1965-75: Thermal precipator From 1975: Membrane filter method All used for f/ml by LM.	Cum. exp. (f/ml-y): A: ≤1 (n:33) B: >1-2 (n:29) C: >2-5 (n:64) D: >5-10 (n:73) E: >10-20 (n:68) F: >20-50 (n:105) G: >50-200 (n:125) H: >200-300 (n:175) I: >300- (n:135)	Three degrees of asbestosis at autopsy (standards from 1973) 1. slight 2. moderate 3. marked	No cases of asbestosis was observed ≤ 2 f/ml-y. Slight asbestosis occurred in C Moderate asbestosis occurred in D
Ehrlich et al. 1992, USA	Cohort study; median 25 yrs	N: 386 Male: 100%	Asbestos factory workers	Amosite	Membrane filter method (f/ml by LM).	Quartiles of cum. exp. (f/ml-y): 1Q: ≤5 (n: 85) 2Q: 5.1-25 (n: 87) 3Q: 25.1-125 (n: 119) 4Q: >125- (n: 49)	Parenchymal fibrosis by CXR (ILO). Profusions ≥1/0 (2 independent readers)	Prevalence with abnormalities ≥20 yrs after first employment: 1Q: 12% 2Q: 14% 3Q: 25% 4Q: 59% OR (95% CI) parenchymal abnormalities (10 f/ml-y): Reader 1: 1.06 (1.04-1.09) Reader 2: 1.07 (1.04-1.10)
Hein et al. 2007, USA	Cohort	N: 3072 Male: 59%	NIOSH cohort of South Carolina textile workers (11-	Chrysotile (extremely	JEM combined with detailed work history and converted	6 categories of cum. exposure (f/ml-y): C1: <3 (n: 1125)	Asbestosis mortality. Pneumoconiosis and	SMR (95% CI) for asbestosis: 232.5 (162.8 to 321.9) (p<0.001)

			year update on earlier paper)	small quantities of crocidolite)	particle measurements and f/ml by LM.	**C2: 3 <16 (n: 997)** **C3: 16 <60 (n: 491)** C4: 60 <100 (n: 181) C5: 100 <150 (n: 155) C6: ≥ 150- (n: 123)	other respiratory diseases mortality. (death records)	RR for pneumoconiosis and other respiratory diseases mortality: C1: ref. **C2: 1.20 (0.57-2.52)** **C3: 2.14 (1.00-4.58)** C4: 5.61 (2.65–11.9) C5: 6.89 (3.15–15.1) C6: 15.6 (7.51–32.5) (p<0.0001)
Rohs et al. 2008, USA	Cohort study; 25 yrs follow-up	N: 280 Male: 94%	Vermiculite miners, millers and processors	Tremolite	Different measurements at different time periods: Membrane filters, industrial hygienist who followed worker with sampling device, personal breathing zone sampling (f/ml by LM).	Quartiles of cum. exposure (f/ml-y): 1.Q.: 0.01-0.28 (n: 70) 2.Q.: 0.29-0.85 (n:72) 3.Q :.0.86-2.20 (n: 68) 4.Q.: 2.21-19.03 (n: 70)	Parenchymal fibrosis by CXR (ILO). Profusion of 1/0 or greater.	Eight (2.9%) participants had interstitial changes, seven of which were profusion 1/1 or greater after mean (SD) 11.86 (6.46) f/ml-y exposure compared with control group (p<0.001)
Satta et al. 2020, Italy	Cross-sectional study with longitudinal exposure assessment (case-control approach for one calculation)	N: 115 Male: 100%	Textile workers (acrylic and polyester fiber)	NA	From databases based on job description	Quartiles of cum. exp. (f/ml-y): 1.Q: ≤ 1.09 (n: 18) 2.Q: 1.1-2.59 (n: 19) 3.Q: 2.5-5.25 (n: 13) 4.Q: ≥ 5.26- (n: 11) Extra category: ≥10: (n: 6)	Parenchymal fibrosis by HRCT (grade I and grade II-VI fibrosis.	OR (95% CI) for grade I: 1.Q: ref. **2.Q: 1.2 (0.36-4.37)** **3.Q: 2.1 (0.59-7.76)** **4.Q: 2.5 (0.68-9.01)** **(p=0.165)** **>10: 1.6 (0.32-7.96)** OR (95% CI) for grade II-VI: 1.Q.: ref. **2.Q: 0.5 (0.04-6.75)** **3.Q: 5.8 (0.84-40.6)** **4.Q: 8 (1.18-54.5)** **(p=0.009)** **≥10: 10.8 (1.54-75.7).**
Armstrong et al. 1988, Australia	Cohort study	N: 6916 Male: 94%	Miners and millers, Wittenoom Gorge	Crocidolite	Casella Long Running Thermal Precipitator (f/ml by LM) and converted historical particle measurements.	Mean cum. exp. (f/ml-y): Men: <10: 55.8% 10-100: 29.1% >100-: 4.7% Unknown: 10.4% Women:	Pneumoconiosis mortality (death certificates).	Exposure-related increase in mortality from pneumoconiosis in all exposure groups, including the lowest with < 10 f/ml-y. SMR (95% CI) for pneumoconiosis (censored at time last known to be alive): 25.5 (18.2-35.7).

						<10: 88.1% 10-100: 4.1% >100-: 0% Unknown: 7.8%		Graphically increased mortality rate of appr. 75/100,000 was found 17½ year after exposure for <10 f/ml-y
Johansson et al. 1987, Sweden	Case-control study	N: 89 Male: 94% (89 matched controls with unknown exposure)	Asbestos cement workers	Chrysotile, (small amounts of crocidolite/amosite)	Before 1969: impinger or gravimetric determinations (particles). From 1969: The membrane filter method (f/ml by LM)	Mean cum. exp. (f/ml-y): A: <1 (n: 11) **B: 1-10 (n: 31)** **C: 11-20 (n: 16)** **D: 21-30 (n: 9)** **E: 31-40 (n: 6)** F: >40- (n: 16)	Pulmonary fibrosis by histology (severity graded in 5 categores)	Prevalence with higher degree of fibrosis compared to matched controls: A: 27% **B: 39%** **C: 31%** **D: 67%** **E: 50%** F: 50% Proportions with fibrosis of grade 2 or worse were: 40% with cum. expo.<10 f-y/ml 35% with 11-40 f-y/ml 62% with >40 f-y/ml (p = 0.07)
Larson, Antao & Bove 2010, USA	Cohort	N: 1862 Male: NA	Vermiculite workers (The Agency for Toxic Substances and Disease Registry)	Tremolite, actinolite and other amphibole fibers	JEM based on historical air sampling (f/ml by LM).	Quartiles of cum. exp. for subjects with asbestosis (f/ml-y): 1.Q: <1.4 (n: 4) **2.Q: 1.4<8.6 (n: 8)** **3.Q: 8.6<44 (n: 25)** 4.Q: >44- (n: 32)	Asbestosis mortality (death certificate)	RR (95% CI): 1.Q: ref. **2.Q: 2.8 (1.0-7.6)** **3.Q: 8.0 (3.2-19.5)** 4.Q: 11.8 (4.9-28.7) Parameter estimates (SD) for increasing hazard for each f/ml-y: 0 lag: 0.00136 (0.00020) 20-yr lag: 0.00162 (0.00024
Feder, Theile & Tannapfel 2018, Germany	Cross-sectional study with longitudinal exposure assessment	N: 1038 Male: NA	Insured workers from the German Mesothelioma Registry	NA	Questions in relation to insurance cases, i.e. exposures assessed by job history.	Less than or more than 25 fibre-yrs	Pathologic-anatomical methods in accordance with the Helsinki criteria	27 cases of asbestosis well below 25 fibre years in records from the German Mesothelioma Register
Eisenhawer et al. 2014, Germany	Cohort study	N: 4446 Male: NA	Former power industry workers (welders, insulators, mechanics, electricians, technicians,	NA	Data of airborne asbestos fibre concentrations at defined workplaces and the typical occupational tasks and time periods, i.e. JEM type assessment.	F/ml-y: ≤1 ≥25-	Parenchymal fibrosis by CXR or MDCT (ILO). Profusion of grade ≥1/1 in both	Depending on model (MDCT): OR (95% CI) for >1&<25 f/ml-y: 1.68-1.85 (0.56-5.52) OR for ≥25 f/ml-y vs. ≤1: 1.06-1.27 (0.34-3.91)

			plant operators, others)				lower fields (consensus between two readers) or CT grade 1.	For CXR: OR 0.3-1.2 (0.11-2.7)
Fischer, Günther & Müller 2002, Germany	Cross-sectional study with longitudinal exposure assessment	N: 366 Male: NA	Patients of the German Mesothelioma Register	NA	Questions in relation to insurance cases, i.e. exposures assessed by job history.	Patients without elevated pulmonary asbestos burden: (n: 193) Patients with relevant higher pulmonary asbestos burden and asbestos-associated lung fibrosis: (n: 64)	Patho-anatomical diagnosis of asbestos-associated lung fibrosis and asbestosis	42% of patients with asbestos-associated lung fibrosis or asbestosis (ie. >1000 asbestos bodies/cm3) did not attain 25 fibre-years.
Harris et al. 2021, Australia	Cross-sectional study with longitudinal exposure assessment	N: 1513	Mining and manufacturing	Crocidolite, mixed	Casella Long Running Thermal Precipitator (f/ml by LM) and JEM	Overall mean cum. exp. (f/ml-y): 0.7 (IQR 0.025-4.37)	Parenchymal fibrosis by HRCT grade 2 on LDCT by Helsinki criteria	32% with asbestosis Asbestosis: IQR 0.09-2.32 f/ml-y No asbestosis: IQR: 0.09-3.15 f/ml-y
Chen et al. 1992, Taiwan	Cross sectional study	N: 459 Male: 100 %	33 cement factories: - 21 manufacturing asbestos cement - 10 in friction material - 1 in textiles - 1 in insulation material	Mainly chrysotile	NIOSH 7400 membrane filter method (f/ml by LM).	Mean cum. exposure (f/ml-y): A: <5 (n: 298) B: 5-9.9 (n: 80) C: ≥10-: (n: 81)	Parenchymal fibrosis by CXR (ILO). FVC	No cases of asbestosis observed in any groups. Regression analysis of decline in FVC was 9.85 ± 2.87 ml per f-y/ml and decline in FEV1 was 8.46 ± 2.47 ml per f-y/ml. Statistically significant effect on FVC >=10 fibre-yr.
Mastrangelo et al. 2009, Italy	Cross-sectional study with longitudinal exposure assessment	N: 772 Male: 100%	Workers manufacturing asbestos-cement products, railway rolling stock fabrication and repair, or insulators in shipyards or elsewhere	NA	Internationally established questionnaire that permits estimation of past asbestos exposure using job-specific modules	Quartiles of cum. exp. (f/ml-y): 1.Q: ≤ 8 0 (n: 0) **2.Q: 8-42 (n: 2)** 3.Q: 43-159 (n: 4) 4.Q: ≥ 160- (n: 8)	Parenchymal fibrosis by LDCT	OR (95% CI): 1.Q: ref. **2.Q: 2.41 (0.18-INF)** 3.Q: 5.22 (0.65-INF) 4.Q: 11.6 (1.77+INF) (p=0.004)
Terra-Filho et al. 2015, Brazil	Cross-sectional study with longitudinal exposure assessment	N: 1418 Male: 94%	Miners and millers	Chrysotile (small amounts of amosite)	From 1976: Membrane filter method (f/ml by LM). Before 1976: based on questionnaires	Groups of cum. exposure (f/ml-y): Grp.1: 110.9 ± 140.3 **Grp. 2: 44.1 ± 49.4** **Grp. 3: 7.6 ± 5.4** **Grp. 4: 3.6 ± 4.4**	Parenchymal fibrosis by CXR and thin-section CT (ILO)	OR (95% CI) by CT: Grp. 1: ref. **Grp. 2: 0.21 (0.10-0.44)** **Grp. 3: 0.07 (0.03-0.19)** Grp. 4: NA OR (95% CI) by CXR: Grp. 1: ref.

								Grp. 2: 0.49 (0.27-0.89) **Grp. 3: 0.31 (0.16-0.61)** **Grp. 4: 0.14 (0.05-0.41)** IRR (95% CI) by CXR: **Grp. 1: ref.** **Grp. 2: 1.08 (0.14-8.36)** **Grp. 3: 0.76 (0.09-6.33)** **Grp. 4: 0.84 (0.05-13.49)**
Jakobsson et al. 1995, Sweden	Cohort	N: 203 Male: 100 %	Asbestos cement plant workers	95 % chrysotile, small amounts of amosite and crocidolite	Before 1969: Impinger or gravimetric determinations (particles). From 1969: The membrane filter method (f/ml by LM). Owing to insufficient information, the estimates for 1947-51 have been used for the whole period before 1942.	Cum. exposure (f/ml-y): A: ≤ 10 **B: 10-30** C: >30-	Parenchymal fibrosis by CXR (ILO). Model 1: profusion ≥1/0 Model 2: profusion ≥1/1	OR (90% CI) adjusted for smoking and age. Model 1: A: ref. **B: 1.1 (0.46-2.6)** C: 2.8 (1.2-6.7) Model 2: A: ref. **B: 5.9 (0.98-36)** C: 13 (2.1-77)
Cordier, Theriault & Provencher 1984, Canada	Cohort study	N: 342 Male: 100 %	Asbestos miners in Thetford Mines, Quebec	Chrysotile	Membrane filter method (f/ml by LM). Converted particle measurements by midget impinger.	Cum. exp. (f/ml-y): <30: (n: 42) 30-89: (n: 155) ≥90-: (n: 134)	Parenchymal fibrosis by CXR (ILO).	No association between cumulative exposure index and radiographic changes. Prevalence of small irregular opacities ≥1/0: 2.1 % with < 300 f/ml-y Depending on reader 0-22% cases <30 FY
Franko et al. 2007, Slovenia	Case-control study	N: 2080 Sex distribution unknown	Employees of one asbestos cement factory	Mostly chrysotile, some amphibole	Initially gravimetric (particles), later membrane filter (f/ml by LM).	Asbestosis cases: 38 f/ml-y Controls without asbestosis: 11 f/ml-y (means)	Parenchymal fibrosis by HRCT acc. to Helsinki criteria	OR (95% CI) 3.21 (2.43– 4.23) in cases vs. controls
Finkelstein & Vingilis 1984, Canada	Cohort study, 32 yrs	N: 181 Male: 100 %	Workers manufacturing asbestos-cement pipe and board (same cohort as in Finkelstein 1982)	Chrysotile, crocidolite	From 1969: Personal measurements by membrane filter method (f/ml by LM). Before 1969: Based on questionnaires	Cum. exp. (f/ml-y): A: 0-49.9: (n: 32) B: 50-99.9: (n: 68) C: 100-149.9: (n: 41) D: 150-199.9: (n: 25) E: ≥ 200-: (n: 15)	Parenchymal fibrosis by CXR (ILO). Grades ≥0/1 ≥1/1 ≥2/1	RR for ≥0/1: A: 0.26 B: 0.42 C: ref. D: 0.94 E: 2.24

								(p<0.001). RR for ≥1/1: A: 0.29 B: 0.52 C: ref. D: 1.09 E: 2.57 (p<0.001) RR for ≥2/1: A: 0 B: 0.31 C: ref. D: 2.19 E: 6.01 (p<0.001)
Berry et al. 1979, UK	Cohort study	N: 379 Male: 100 %	Asbestos textile factory workers	Chrysotile, crocidolite	Job histories combined with fiber counting (f/ml by LM; method not specified and changed over years)	Mean cum. exp. (f/ml-y): <50: (n: 41) 50-99: (n: 120) 100-149: (n: 88) 150-199: (n: 58) 200-249: (n: 39) 250-549: (n: 33)	Asbestosis grouped into: 1) crepitations, 2) possible, or 3) certified (symptoms, parenchymal fibrosis by CXR (ILO) and lung function)	For crepitations, possible and certified asbestosis, the 1% prevalence are estimated at 43, 55, and 72 f-y/cc respectively. Similarly, the 1 % prevalence correspond to 50 years' exposure to 0.13, 0.19, and 0.37 f/cc respectively for the three groups. Other mathematical models suggested 1% prevalence at lower exposures.
Magnani et al. 2020, Italy	Cohort study	N: 51801	Pool of workers from many industries	All types	Collected from several previous studies. Asbestos CEI calculated was fibre-type corrected and calculated as mean exposure / workplace / yr * years worked	Fibre-type-weighted cum. exp. index differed between industries, e.g. <54.0 to >620.0 in asbestos cement and <0.8 to >3.2 in industrial ovens	Mortality from asbestosis (death certificates and registers)	8 of 348 cases were in lowest but wide exposure group <146.6 fibre-type weighted CEI. SMR approx. 50000 in asbestos cement but different in other industries
Paris et al. 2008, France	Cross-sectional study with longitudinal exposure assessment	N: 1011 Male: 100 %	Asbestos factory workers. Mainly asbestos textile and friction materials	NA	For some subjects JEM was elaborated from airborne measurements. For all other subjects, estimation was assessed using published air-	Mean cum. exp. (f/ml-y): Healthy subjects: 88.9 (n: 476) Fibrosis: 143.3 (n: 61)	Parenchymal fibrosis by HRCT (consensus by three readers)	OR (10 f/ml-y): 1.03 (95% CI: 1.01-1.04) without threshold

			fabrication, insulation and energy production		borne measurements available in the French database Evalutil.			
Courtice et al. 2016, China.	Cohort (37 yrs follow-up)	N: 586 Male: 100 %	Asbestos factory workers: - Raw materials - Carding and spinning - Weaving - Rubber and cement	Chrysotile	Converted historical total dust measurements in mg/m^3 to fibre concentrations in f/ml.	Quartiles of cum. exposure (f/ml-y) 1.Q: 0 - <89 2.Q: 89 - <133 3.Q: 133- <548 4.Q: ≥548-	Asbestosis from job-history, parenchymal fibrosis by CXR (ILO) and clinical signs.	HR (95% CI): 1.Q: ref. 2.Q: 2.26 (2.14-2.38) 3.Q: 2.71 (2.57-2.85) 4.Q: 3.09 (2.94-3.25). HR for every 100 f-y/ml was 1.055 (1.052–1.058)
Huang JQ 1990, China	Cross-sectional study with longitudinal exposure assessment	N: 776 Male: 100%	Factory workers	Chrysotile	Chinese-standard membrane filter method f/ml by LM) and converted historic gravimetric dust concentrations)	Mean cum. exp. (f/ml-y): Gr.1: 0-99 (n: 385) Gr.2: 100-199 (n:181) Gr.3: 200-399 (n:113) Gr.4: 400-599 (n: 41) Gr.5: 500-799 (n:34) Gr.6: 800-999 (n: 9) Gr.7: 1000-1199 (n: 7) Gr.8: 1200-1549 (n: 6)	Asbestosis (grade I) (Pneumoconioses Diagnostic Panel of Shanghai, CXR)	Prevalence (n (%)): Gr.1: 101 (26) Gr.2: 42 (23) Gr.3: 55 (49) Gr.4: 27 (66) Gr.5: 22 (65) Gr.6: 5 (56) Gr.7: 6 (86) Gr.8: 1 (17) Correlation coefficient between exposure and response: 0.99. Predicted 1% prevalence corresponding to 22 f/ml-y
De Klerk et al. 1991, Australia	Case-control study	N: 2400 Sex distribution unknown	Mining employees	Crocidolite	Casella Long Running Thermal Precipitator (f/ml by LM).	Mean cum. exposure (f/ml-y): 71	Parenchymal fibrosis by CXR (ILO).	RR of asbestosis 1.033 (1.021-1.045) pr f-y/ml
Ghezzi, Aresini & Vigliani 1972, Italy	Cross-sectional study with longitudinal exposure assessment	N: 998 Male: 99,9%	Former and current miners	Chrysotile	Cellulose filter collection (f/ml by LM).	A calculated risk index (0-100) divided into 5 groups without any fibre-yr calculations	Parenchymal fibrosis by CXR (ILO).	Lowest exposure group appear to be 75 fibre-yrs or less with a 16.1% prevalence of asbestosis.
Jones et al. 1989, USA	Cohort study	N: 165 Male: 100 %	Asbestos cement plant workers	Mainly chrysotile, small amounts of crocidolite	Midget Impinger (particles)	Quartiles of cum. exp. (mppcf-y): 1.Q: <110 2.Q: 110-264 3.Q: 265-439 4.Q: ≥440-	Parenchymal fibrosis by CXR (ILO). Profusion ≥1/0	Prevalence (%): 1.Q: 6.1 2.Q: 10.8 3.Q: 26.2 4.Q: 26.3 ($p<0.05$)

McDonald et al. 1982, USA	Cohort study	N: 1392 Male: 100%	Asbestos textile factory workers	Mainly chrysotile (small amounts of crocidolite and amosite)	Impinger method (particles)	Quintiles of cum. exp. (mpcf-y): 1.Q: <10 (n: 470) **2.Q: 10<20 (n: 86)** **3.Q: 20<40 (n: 130)** 4.Q: 40<80 (n: 105) 5.Q: ≥80- (n: 104)	Pneumoconiosis as cause of dead (death certificates)	RR (accumulated up to 10 years before death): 1.Q: ref. **2.Q: 4.04** **3.Q: 13.72** 4.Q: 14.93 5.Q: 37.90
Murphy et al. 1971, USA	Cross-sectional study with longitudinal exposure assessment	N: 101 (94 matched controls) Male: 100 %	Pipe coverers in new ship construction	Amosite, chrysotile	Midget Impinger and Konimeter particle measurements	Employed pipe coverers (exposed) vs. controls (employed ship fitters and pipe fitters)	Asbestosis (3 out of 5 symptoms; dyspnoea, basilar rales in >=2 sites, clubbing of the fingers, vital capacity <80% of predicted, CXR consistent of moderately advanced/advanced asbestosis)	No clinical asbestosis occurred in men exposed to less than 60 mppfc-y. 20% of men exposed to 75-100 mppfc-y had asbestosis, and 38% of those exposed to >100 mppfc-y.
McDonald et al. 1980, Canada	Cohort study	Birth cohort 1891-1920. N: 10.939 Male: 96 %	Asbestos miners and millers in Asbestos and Thetford mines, Quebec (minimal overlap with Cordier et al.)	Chrysotile	Particles concentration with midget impinger. Before 1949 estimates were based on interviews with long-service employees.	Cum. exposure (mpcf-y) accumulated to age 45: A: <30 (n: 1668) B: 30 <300 (n: 1138) C: ≥300 (n: 642) D: ≥1000-	Pneumoconiosis mortality (death registers, ICD7)	RR of dying from pneumoconiosis in relation to dust exposure accumulated up to nine years before death of case: A: ref. B: : 1.65 C:: 5.57 D: 30.6

CEI: cumulative exposure index. CI: confidence interval. CXR: Chest x-ray. FVC: forced vital capacity at lung function test. ILO: International labour organization. INF: infinite. JEM: job-exposure-matrix. HRCT: High resolution CT scanning. LDCT: Low-dose Ct scanning. LM: light microscopy. mpcf:. millions of dust particles per cubic foot. MDCT: multidetector-row thorax CT scanning. OR: Odds ratio. RR: relative risk.

Table 2. Details on exposure, outcome, and quality in the studies on asbestosis with and without asbestos fibre exposure information.

Reference	Lowest exposure group studied (FY)	Longest TSFE studied (yrs)	Most severe grade of asbestosis studied	Effect in most severe outcome group	Most likely direction of estimation error	Effect of age	Effect of smoking	Weaknesses (other than short TSFE/lack of age or smoking data)	RoB score
Irwig et al. 1979	<25	na	ILO 1/0	<10 FY: 2.2% Visually increased risk >40 FY	Uncertain	No change in estimate	na	No FY given, can be estimated from figures. Readers aware that subjects were exposed. Poor control for previous exposures. Very few cases <25 FY.	6
Sluis-Cremer, Hnizdo & DuToit 1990	<25	30.4	Histology grade 2 moderate marked	<10 FY grade 2 cases <200 FY grade 3 case	Underestimate (missing mild cases)	na	na	No unexposed subjects. Readers unlikely to be blinded.	6
Ehrlich et al. 1992	<25	26.5 (20-42)	ILO 1/1	OR 1.04-1.1/10 FY	Underestimate (missing mild cases)	?	No change in estimate	No unexposed controls. Readers aware that subjects were exposed.	6
Hein et al. 2007	<25	40	Cause of death (pneumoconioses and other, 42% asbestosis)	<16 FY: RR 1.2 (0.6;2.5)	Underestimate (missing mild cases)	na	No change in estimate	No blinding. No unexposed controls. Few subjects at low levels.	8
Rohs et al. 2008	<25	~37	ILO 1/1	<11.9 FY: 2.5% (p<0.001)	Overestimate, missing some work time	na	Smoking increased risk	Possible confounding by age. Few subjects at low levels.	8
Satta et al. 2020	<25	na	CT grade II+ (Gamsu grading)	OR 2.4 (1.4;51.3)	Underestimate (missing mild cases by selection)	na	No change in estimate	Surveillance data with many readers, old CT protocol. Exposure from literature/JEM. Selective reporting.	5
Armstrong et al. 1988	<25	5-25	Cause of death: pneumoconiosis	<10 FY visually: MR 75/100,000	Underestimate (missing mild cases, short TSFE)	na	na	No DR below 100 FY. No unexposed controls. Readers aware that subjects were exposed.	6
Johansson et al. 1987	<25	26 (1-63)	Grade 2-5 histology	<40 vs. >40 FY: ~35% vs. 62% with grade 2+	Underestimate (missing mild cases)	No change in estimate	No change in estimate	Surprisingly high prevalence among controls (undetected exposure?). No DR < 30 FY.	6
Larson, Antao & Bove 2010	<25	40.5	Cause of death	< 8.6 FY: RR 2.8 (1.0;7.6)	Underestimate (missing mild cases)	na	na (model suggest little or no change)	Main result not adjusted for smoking (probably minor effect of this). Only crude RR used. Based on few cases at low exposure.	3
Feder, Theile & Tannapfel 2018	<25	27 (1-66)	Grade II+ histology (Helsinki criteria)	No estimate per FY Visual cases <10 FY	Uncertain, possibly large variation in exposure assessment (missing mild cases)	na	na	No unexposed controls. Readers aware that subjects were exposed. Study is based upon a highly selected mesothelioma material.	2

Eisenhawer et al. 2014	<25	(10 yr intervals)	ILO 1/1 CT grade 1	<25 FY: CXR OR 0.3 (0.1-0.8); CT OR 1.7-1.9 (0.6-5.5)	Uncertain, probably large due to use of JEM	na	Smoking increased risk only for CXR	No DR	3
Fischer, Günther & Müller 2002	<25	na	Asbestosis in insurance cases & >1000 asbestos bodies/ccm	<25 FY: 42% of cases	Uncertain, probably large due to use of JEM	na	na	Methods are insufficiently described. Probably lack of blinding.	2
Harris et al. 2021	<25	53.5	HRCT grade 2	<25 FY: 32% cases	Uncertain (JEM) overestimate (sensitive CT without unexposed controls)	na	na	False positives possible as no comparison with completely unexposed. Lack of DR. Only 1 reader.	5
Chen et al. 1992	<25	na (probably few > 20)	ILO 2/1 + symptoms	No cases	Underestimate (missing mild cases, short TSFE)	na	na		5
Mastrangelo et al. 2009	<25 (1 case; else 42 FY)	34	CT grade I? (Remy-Jardin)	No case <8 FY OR 2.4 <42 FY (ns)	Uncertain, possibly large due to use of JEM	No change in estimate	No change in estimate	Not informative <25 FY	5
Terra-Filho et al. 2015	<25 (informative from 44FY only)	~11.5	ILO 1/0 CT "definite"	No estimate per FY Visual increase >44 FY with long TSFE	Underestimate (short TSFE), possibly large due to use of JEM	na	Smoking increased risk	Cohorts differed in time and exposure. Early cohorts without exposure measurements. Variable no. of readers – blinded? CoI? Not informative <25 FY due to statistics chosen.	5
Jakobsson et al. 1995	<30	30	ILO 1/1	OR 5.6 (ns)	Underestimate (missing mild cases)	Adjusted Effect?	No effect in ILO 1/1 group		5
Cordier, Theriault & Provencher 1984	<30	~20 §	ILO 1/0	<30 FY 0-22% cases depending on reader	Underestimate (short TSFE)	na	Smoking increased risk	High variability between readers	7
Franko et al. 2007	<38	na	CT Helsinki/ATS criteria	<38 FY: OR 3.2 (2.4– 4.3)	Overestimate (sensitive CT without unexposed controls)	na	No change in estimate	No unexposed controls. Readers probably aware that subjects were exposed. Possible selection and information bias.	5
Finkelstein & Vingilis 1984	<50	na	ILO 1/1 ILO 1/2	<50 FY: 9.4% in 1/1 group 0% in 1/2 group	Underestimate (missing mild cases)		Smoking increased risk in ILO 1/1 group		7
Berry et al. 1979	<50	na (probably short)	Disease with symptoms or certified	<72 FY: certified asbestosis in 1%	Underestimate (short TSFE)	na	Smoking increased risk		5
Magnani et al. 2020	<54	na	Cause of death	<54 FY: 3 cases No statistics	Underestimate with large uncertainty due to braod JEM (missing mild cases)	na	na	Use of CEI differs from FY. Very rough and broad JEM.	5
Paris et al. 2008	< 100	38.5	CT	OR not given.	Uncertain (missing cases, sensitive CT) but large due to use of JEM	Age increased risk	Smoking increased risk	Different CT methods combined. Exposures based on JEM/literature. Obscure sampling frame: selection bias? Not investigated if age effect could be a TSFE effect.	5

Courtice et al. 2016	<100	49	Disease with symptoms	<133 FY: HR 2.3 (2.1-2.4)	Underestimate (missing mild cases)	na	Smoking increased risk	Outcome not independent of exposure assessment.	7
Huang JQ 1990	<100	na	Chinese ILO 1/0	<100 FY: 26% cases <22 FY: 1% cases estimate	Overstimate (missing some exposure at low end)	na	na		3
De Klerk et al. 1991	<100	na	Claimed cases	Per FY: RR 1.03 (1.02-1.05)	Underestimate (missing mild cases)	na	No change in estimate		6
STUDIES WITHOUT QUANTIFIED CUMULATIVE FIBRE EXPOSURE									
Ghezzi, Aresini & Vigliani 1972	?	na	ILO 1/1					Using index groups, not FY	4
Jones et al. 1989	?	na *	ILO 1/0						5
McDonald et al. 1982	?	na	Cause of death: pneumoconiosis						4
Murphy et al. 1971	?	na	ILO 1/0						5
McDonald et al. 1982	?	na	Cause of death: pneumoconiosis						4

FY: Fibre-years (f/ml-y). CEI: cumulative exposure index. CoI: conflict of interest. na: not available. ns: not statistically significant. TSFE: time since first exposure. JEM: job-exposure matrix. * observed correlation with TSFE.

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Systematic review of the association between exposure to asbestos and the development of asbestosis

Report to The Danish Working Environment Research Fund

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Appendix 1

Details on the reported associations of intensity, duration and latency with asbestosis.

Jones et al. found a significant association of radiographic abnormalities of parenchymal fibrosis with: exposure intensity of particle exposure; average exposure in million particles per cubic foot (mpcf) (p=0.038) and with duration of exposure (p=0.014) (Jones et al., 1989).

Satta et al. found an increased risk of HRCT grade II-IV fibrosis with an average exposure level of just 0.15-0.29 f/mL (OR 12.5 [95% CI 1.13-138]) and ≥0.30 f/mL (OR 18.4 [95% CI 1.75-193]) compared to ≤0.06 f/mL, but no significant difference between years of employment (≤20 yrs vs. ≥20 yrs) (Satta et al., 2020).

De Klerk et al. found a mean duration of exposure to be 1000 days and mean intensity to be 35 f/ml among employees with asbestosis, whereas controls had 394 days and 25 f/ml (statistical significance not reported) (De Klerk et al., 1991).

In a report on all hired Libby workers an increased risk of asbestosis was found for 15 months-9.9 yrs of employment (OR 6.7 [95% CI 1.8-24.9]) and for ≥10 yrs (OR 17.6 [95% CI 4.7-64.5]) compared to <15 months of employment, with no information of intensity (Sullivan, 2007).

In an earlier analysis of the data than the1984 study used in our main analysis, Finkelstein et al. found that cumulative probability of asbestosis by maximal follow-up (32 yrs from first exposure) was related to length of time spent in dust exposure. The probability was 68% for men exposed for ≥15 yrs, 37% for men exposed 6-10 yrs, 28% for men exposed ≤5 yrs, with no information on intensity (Finkelstein, 1982).

A Swedish study found an increased risk of profusion ≥1/0 for ≥30 yrs of employment (OR: 3.4 [90% CI 1.3-8.9]) compared to ≤14 yrs, and no significant association with intensity (>2 f/mL vs. ≤1 f/mL) (Jakobsson et al., 1995).

Irwig et al. found an increasing prevalence of asbestosis with more years of asbestos exposure; <1.00 yr (4%), 1.01-3.00 yrs (7.8%), 3.01-7.00 yrs (10.1%), 7.01-15.00 yrs (19.2%), >15.00 yrs (47.9%) (p<0.001) (Irwig et al., 1979).

Murphy *et al*. found no cases of asbestosis <10 yrs of exposure and 38 % with asbestosis with >20 yrs of exposure. The earliest case was found after 13 yrs of employment (Murphy et al., 1971). McDonald *et al*. found that pneumoconiosis mortality 20 yrs after first employment increased with length of service (reporting increasing no. of cases and higher SMR from <1 yr to >= 20yrs) (A. D. McDonald et al., 1982). In an earlier study, out of 42 deaths from pneumoconiosis 6 occurred in employees with <20 yrs of exposure, with no information on intensity (J. C. McDonald et al., 1980).

Larson and colleagues found duration of employment for employees with asbestosis as cause of death to be 10.4 yrs (25^{th}-75^{th} percentile: 1.2–19.5) (Larson et al., 2010).

A German study found an increased risk of asbestosis after 10 yrs of duration (OR 2.13 [95% CI 1.45-3.12]) (Eisenhawer et al., 2014).

In Paris *et al*. the mean intensity and duration among employees with fibrosis was 6.5 ± 5.6 f/mL and 23.4 ± 9.6 yrs, among healthy subjects the intensity and duration was 3.9 ± 3.4 f/mL and 22.8 ± 9.0 yrs (Paris et al., 2008).

Ehrlich et al. found that radiological abnormalities indicative of asbestosis can develop with as little as one month's exposure to high concentrations of amosite fibres, but no relation could be detected to duration alone without data om concentration (Ehrlich et al., 1992).

Terra-Filho et al. found that individuals with interstitial abnormalities had longer duration of exposure than those with only pleural plaques or normal subjects ($p<0.050$) (Terra-Filho et al., 2015).

In Feder *et al*. no correlation could be detected between duration of exposure and the actual level of asbestos exposure, for either the asbestos burden in lung tissue or for the calculated cumulative exposure (Feder et al., 2018).

Franko *et al.* also observed a significantly longer duration of exposure among cases with asbestosis than among controls (268 vs 230 months, $p=0.00$) (Franko et al., 2007).

In the heavily exposed Wittenoom cohort in which the standardised mortality ratio for pneumoconiosi was 25 the median exposure duration was only 4 months (Armstrong et al., 1988). However, the analyses were not stratified by duration, so it can't be excluded that the observed effects were driven only by those with longer exposures.

Two studies did not find a significant difference in duration between employees with and without fibrosis (Johansson et al., 1987; Paris et al., 2004). Other studies did not find a significant association either between duration or intensity and asbestosis (Cordier et al., 1984; Mastrangelo et al., 2009).

Courtice *et al*. (studying asbestosis with symptoms) found that all cases were diagnosed at least 12 yrs since first exposure with mean latencies (depending on cumulative exposure) of approximately 42 yrs (Courtice et al., 2016).

Jakobsson *et al*. found an association between time since start of employment and the presence of small opacities (profusion) ≥1/0 after 15-29 yrs (OR 4.6 [90% CI 1.2-17]) and ≥30 yrs (OR 7.3 [90% CI 1.9-29]) compared to ≤14 yrs (Jakobsson et al., 1995).

In Paris *et al*. the mean time since first exposure was 38.5 yrs in subjects with fibrosis compared to 34.3 yrs in healthy subjects (Paris et al., 2008).

Armstrong et al. observed an increased mortality already from 5 yrs after first exposure (Armstrong et al., 1988). Only Armstrong et al. reported on latency of time since first exposure until death from asbestosis, not finding a substantially different latency than the studies on incidence of the disease (Armstrong et al., 1988).

Eisenhawer *et al*. found a significant association between time since first exposure and asbestosis (OR 2.01 [95% CI 1.41-2.86]) suggesting a cut-off for latency of 28 years (Eisenhawer et al., 2014). Jones et al. found a significant association between exposure latency and radiographic abnormalities ($p=0.016$) (Jones et al., 1989).

Larson et al. found median time from date of hire to death from asbestosis to be 40.5 yrs (25^{th}-75^{th} percentile: 30.6–46.7) (Larson et al., 2010).

Details on the exposure-response functions reported in the reviewed literature and other selected papers from the same cohorts

Courtice *et al*. (2016) found that the occurrence of asbestosis increased significantly with each unit of cumulative exposure. The HR for every 100 fibre-yrs was 1.055 (95% CI 1.052–1.058) for development of asbestosis. Approx. threefold-increased risks were seen for asbestosis, for the highest exposure group (≥548 fibre-yrs) compared to the lowest exposure group (<89 fibre-yrs)) (Courtice et al., 2016). An Italian study of a subsample of that reported in (Magnani et al., 2020) found an increased mortality risk for asbestosis with increasing cum. fibre-type-corrected exposure, 103-456 fibre-yrs (RR 5.34 [95% CI 1.50-26.7]), 456-981 fibre-yrs (RR 13.6 [95% CI 3.88-66.5]), >981 fibre-yrs (RR 19.9 [95% CI 5.66–98.3]) compared to <12.9 fibre-yrs (Girardi et al., 2020). The estimated risk of asbestosis mortality increased with cumulative exposure in a convex curve, which tended to be steeper at a low exposure level (<50 fibre-yrs) than a higher exposure level (>50). The log-linear model tended to produce a higher mortality risk at high exposure level (>400 fibre-yrs) than other models.

Larson et al. found an increasing risk of asbestosis as cause of death with higher cum. exposure, for 1.4<8.6 f/cc-y (RR 2.8 [95% CI 1.0-7.6]), 8.6<44.0 f/cc-y (RR 8 [95% CI 3.2-19.5]), ≥44 f/cc-y (RR 11.8 [95% CI 4.9-28.7]) compared to <1.4 f/cc-y (p<0.0001). Median f/cc-y for employees with asbestosis as cause of death: 39.0 (14.6–283.2). Parameter estimates (SD) for increasing hazard of asbestosis mortality for each f/cc-y: 0 lag: 0.00136 (0.0001959), 20-yr lag: 0.00162 (0.0002383) (Larson et al., 2010). Paris *et al*. found a significant association between cumulative exposure and fibrosis for ≥100 fibre-yrs (OR 6.1 [95% CI 1.5-25.9]) compared to <25 fibre-yrs (p=0.002). A significant exposure–effect relationship was found between the cum. exposure and asbestosis when cumulative exposure was coded as a continuous variable (OR: 1.004 per fibre-yr [95% CI 1.002– 1.005]) (p<0.001), after adjustment for all other significant variables (Paris et al., 2004).

In studies with only particle measurements, McDonald *et al*. found an increasing risk of dying from pneumoconiosis in relation to dust exposure accumulated up to nine yrs before death of case for 30<300 mpcf-yrs (RR 1.65), 300<1000 mpcf-yrs (RR 5.57), and ≥1000 mpcf-yrs (RR 30.6) compared to <30 mpcf-yrs (J. C. McDonald et al., 1980) and Murphy *et al.* found that no asbestosis occurred in men exposed to less than 60 mpcf-yrs, and 20% of men exposed to 75-100 mpcf-yrs had asbestosis, and 38% of those exposed to >100 mpcf-yrs (Murphy et al., 1971). Jones *et al*. found a significant regression coefficient for small opacities related to cumulative exposure (mpcf-yrs): 0.038 (Jones et al., 1989). McDonald et al. (1982) found increasing risk (RR) of pneumoconiosis as cause of death with higher dust exposure (mpcf-yrs) accumulated up to 10 yrs before death: 10-<20: 4.04, 20-<40: 13.72, 40-<80: 14.93, ≥80: 37.9 compared to <10 mpcf-yrs (A. D. McDonald et al., 1982).

Paris et al. found a mean cumulative exposure of 88.9 fibre-yrs (±92.4) among healthy employees and 143.3 fibre-yrs (±135.4) in cases with asbestosis. OR for cumulative exposure (10 fibre-yrs): 1.03 (95% CI: 1.01-1.04) (Paris et al., 2008). In what appears to be the most complete investigation of the Wittenoom cohort, de Klerk *et al*. found that the median cum. exposure to onset of asbestosis was 71 fibre-yrs (De Klerk et al., 1991) . In the same cohort, the RR for onset of asbestosis related to cum.

exposure (from grade 0 to1) for 55-148 fibre-yrs was: 1 (95% CI 0.8-1.2), for >148 fibre-yrs: 0.9 (95% CI 0.6-1.4) compared to ≤54 fibre-yrs. The RR for moving from grade 1 to grade 2 asbestosis for 55-148 fibre-yrs was: 1.6 (95% CI 1.1-2.3), >148 fibre-yrs: 2.5 (95% CI 1.2-5.4) compared to <54 fibre-yrs. The RR for moving from grade 2 to grade3 for 55-148 fibre-yrs was: 2.7 (95% CI 0.9-8.2), >148 fibre-yrs: 7.1 (95% CI 0.8-66.5) compared to ≤54 fibre-yrs (Cookson et al., 1986). Finally, in a separate analysis, a mean cumulative exposure of 84 fibre-yrs was found in employees with asbestosis as the cause of death, and 6 fibre-yrs among controls and graphically increased mortality rate of appr. 75/100,000 was found 17½ year after 1. exposure for <10 fibre-yrs (Armstrong et al., 1988). (De Klerk et al., 1993). In Armstrong *et al*. age-standardized death rate/100.000 person-yrs for <10 fibre-yrs, 10-100 fibre-yrs and >100 fibre-yrs 5 yrs since first exposure was approx. 0, 10 and 120, respectively (Armstrong et al., 1988).

Another group (Mastrangelo et al., 2009) found a significant increase in risk of asbestosis with higher cumulative exposure for ≥160 fibre-yrs (OR 11.6 [95% CI 1.77-infinity]) compared to ≤8.0 fibre-yrs (p=0.004). The lowest cumulative exposure in a subject with asbestosis was 23.1 fibre-yrs.

A study found a significant association between cumulative exposure and profusion ≥1/0 for >30 fibre-yrs (OR 2.8 [90% CI 1.2-6.7]) and profusion ≥1/1 for >30 fibre-yrs (OR 13 [90% CI 2.1-77]) compared to ≤10 fibre-yrs (Jakobsson et al., 1995), and Rohs *et al*. (2008) found eight (2.9%) participants with interstitial changes, seven of which were profusion 1/1 or greater after mean (SD) 11.86 (6.46) fibre-yrs exposure compared with control group (p<0.001) and all eight below 19.1 fibre-yrs (Rohs et al., 2008). The authors expected some underestimation of exposures due to over-time work not accounted for. Satta *et al*. found a significant association between cumulative exposure and grade II-VI fibrosis for ≥5.26 fibre-yrs (OR 8 [95% CI 1.18-54.5]) and ≥10 fibre-yrs (OR 10.8 [95% 1.54-75.7]), compared to ≤1.09 fibre-yr (p=0.009) (Satta et al., 2020). A microscopy study of pulmonary tissue found the proportions of workers with histological fibrosis of grade 2 or worse to be 40% with a cumulative exposure <10 fibre-yrs, 35% with 11-40 fibre-yrs, and 62% with >40 fibre-yrs (Johansson et al., 1987). Another study found an exposure-related increase in mortality from pneumoconiosis in all exposure groups, including the lowest with < 10 fibre-yrs. SMR for pneumoconiosis: 25.5 (95% CI 18.2–35.7).

Hein *et al*. (2007) found significant (p=0.0001) higher risk (RR) of pneumoconiosis and respiratory diseases with increasing cumulative exposure (fibre-yrs): 3-<16: 1.2 (95% CI 0.57-2.52), 16-<60: 2.14 (95% CI 1.00-4.58), 60-<100: 5.61 (95% CI 2.65-11.9), 100-<150: 6.89 (95% CI 3.15-15.1), ≥150: 15.6 (95% CI 7.51-32.5) compared to <3 fibre-yrs (Hein et al., 2007). Another study found increasing risk of asbestosis as cause of death with higher cum. exposure, for 1.4-<8.6 fibre-yrs (RR 2.8 [95% CI 1.0-7.6]), 8.6-<44.0 fibre-yrs (RR 8 [95% CI 3.2-19.5]), ≥44 fibre-yrs (RR 11.8 [95% CI 4.9-28.7]) compared to <1.4 fibre-yr (p<0.0001). Median fibre-yrs for employees with asbestosis as cause of death: 39.0 (14.6–283.2). Parameter estimates (SD) for increasing hazard of asbestosis mortality for each fibre-yr : 0 lag: 0.00136 (0.0001959), 20-yr lag: 0.00162 (0.0002383) (Larson et al., 2010). One study observed no cases of asbestosis ≤ 2 fibre-yrs. Slight asbestosis occurred in the group with >2-5 fibre-yrs and moderate asbestosis occurred in employees with >5-10 fibre-yrs (Sluis-Cremer et al., 1990).

In Chen *et al*. 7.6 % had cumulative exposure > 20 fibre-yrs, majority had <10 fibre-yrs and no cases of asbestosis was observed, but decline in FVC was 9.85 ± 2.87 mL per fibre-yr and decline in FEV1 was 8.46 ± 2.47 mL per fibre-yr (Chen et al., 1992) and >=10 fibre-yrs associated with a statistically significant decline in FVC.

In Irwig *et al*. the prevalence of asbestosis after 10 yrs of exposure to <10 f/mL was 5%, and for 10-20 f/mL the prevalence was 8%. The prevalence for >20 f/mL after two yrs was 5%, after five yrs 12%, and after 10 yrs 24% (Irwig et al., 1979). A small excess prevalence of 0.1% compared with same-age non-exposed subjects was observed after less than 10 fibre-yrs.

Terra-Filho *et al*. found significant decreasing risk of asbestosis with lower cum. exposure for 44.1 fibre-yrs (±49.9) (OR 0.21 [95% CI 0.10-0.44]), 7.6 fibre-yrs (±5.4) (OR 0.07 [95% CI 0.03-0.19]) compared to 110.9 (±140.3) by thin-section CT, and for 44.1 fibre-yrs (±49.9) (OR 0.49 [95% CI 0.27-0.89]), 7.6 fibre-yrs (±5.4) (OR 0.31 [95% CI 0.16-0.61]), 3.6 fibre-yrs (±4.4) (OR 0.14 [95% CI 0.05-0.41]) compared to 110.9 (±140.3), by CXR (Terra-Filho et al., 2015).

In Eisenhawer *et al*. OR for asbestosis was 1.20 (95% CI 0.53-2.70) with CXR and 1.27 (0.41-3.91) with MDCT for ≥25 fibre-yrs compared to ≤1 fibre-yr (Eisenhawer et al., 2014). In Ehrlich *et al*. (1992) OR for asbestosis (10 fibre-yrs) was 1.07 (95% CI 1.04-1.10) (Ehrlich et al., 1992). When adjusted for age and smoking, approx. 20% of those exposed to <=5 fibre-yrs had asbestosis, and progression to grade 2 profusion was observed in several subjects exposed to <=25 fibre-yrs.

Huang found a correlation coefficient between cumulative exposure and response of 0.99, and a predicted 1% prevalence of grade I asbestosis corresponding to 22 fibre-yrs, and a predicted 0.5% prevalence at 14.5 fibre-yrs (Huang, 1990).

Another study found estimated the 1% prevalence of possible and certified asbestosis (both including crepitations) at 55 and 72 fibre-yrs respectively when simply accumulating dust exposures. When using cumulative exposure weighted by time since exposure the 1% prevalence of possible and certified asbestosis corresponded to 50 yrs exposure at 0.19 and 0.37 f/mL respectively (Berry et al., 1979).

Among 100 workers, Finkelstein & Vingilis found RR for opacities (≥0/1, ≥1/1, ≥2/1) : 0-49.9 fibre-yrs (0.26, 0.29, 0); 50-99.9 fibre-yrs (0.42, 0.52, 0.31); 150-199.9 fibre-yrs (0.94, 1.09, 2.19); ≥200 fibre-yrs (2.24, 2.57, 6.01) ($p<0.001$), compared to 100-149.9 fibre-yrs (Finkelstein & Vingilis, 1984). In an earlier study on the cohort with more participants (n: 201) the number of new cases/100,000 person-yrs at risk was: 0-49 fibre-yrs (0.5), 50-99 fibre-yrs (3.4), 100-149 fibre-yrs (6.5), 150-199 fibre-yrs (7.9), 200-249 fibre-yrs (14.3) (Finkelstein, 1982). The risk of development of asbestosis was estimated to 1 % after an exposure of 10 fibre-yrs.

Another study with a short follow-up time found no association between cumulative exposure index and radiographic changes, but prevalence of small irregular opacities ≥1/0 was 2.1% with < 300 fibre-yrs (Cordier et al., 1984).

Of limited value was a study that calculated index groups rather than using fibre-yrs for exposure (Ghezzi et al., 1972a). The authors observed an exposure-response effect From tables in the paper the

fibre-yrs exposure in the lowest index group in which 16.1% were diagnosed with asbestosis could be estimated to be < 75 fibre-yrs (Ghezzi et al., 1972).

In a recent study by Harris *et al.* interstitial lung abnormalies (ILA) on LDCT consistent with asbestosis was found with a mean latency of 50+ years at very low cumulative exposures without any difference between the median cumulative exposure of those with and those without ILA (both at 0.7 fibre-yr) (Harris et al., 2021).

A large pooled analysis of cohorts from several Italian industries by Magnani *et al*. showed clear exposure-response relationships in several of these industries, though not among dockyard workers (Magnani et al., 2020). The authors, however, only provided tertiles of exposure without modelling the response. Five deaths occurred among approximately 3571 exposed at <54 fibre-yrs (in the asbestos cement industry).

An OR of OR 3.21 in cases with a mean 38 fibre-yrs vs. controls with a mean 11 fibre-yrs was found in a case-control study on asbestosis diagnosed by CT (Franko et al., 2007).

Appendix 2

Details on the observations on smoking

Courtice *et al.*found that smoking was a significant contributing factor to increased risk of asbestosis (smoking HR: 1.94 for asbestosis) (Courtice et al., 2016). Berry *et al.* found that after taking account of age, there were significantly fewer signs in non-smokers and light smokers than in heavier and ex-smokers, for men first exposed after 1950: for crepitations, $P < 0.01$; for possible and certified asbestosis, $P < 0.1$ and for small opacities $P < 0.05$ (Berry et al., 1979). By multivariate analysis of small opacity score Cordier et al. found a significant association ($p<0.001$) between small opacity score and smoking habits, (and average asbestos fibre exposure?) (Cordier et al., 1984). Also Finkelstein and Vingilis found a significant higher risk for small opacities (RR: 3.0) for smokers vs. non-smokers (Finkelstein & Vingilis, 1984). The ratio of abnormal to normal CXR was 1.3 in smokers compared with non-smokers in the study by (Ehrlich et al., 1992). In a study applying both MDCT and CXR, Eisenhawer et al. concluded that some of the changes observed on CXR, but not on CT, probably reflected smoking (Eisenhawer et al., 2014). One of the included studies that applied both CXR and CT found a higher risk of asbestosis using both methods (Terra-Filho et al., 2015).

On the other hand, some studies did not observe associations with smoking. Johansson *et al.* found no association between smoking and either ferruginous bodies or fibrosis in exposed workers (Johansson et al., 1987). In studies applying thorax CT scans no association between smoking habits and asbestosis (Mastrangelo et al., 2009) or pack years (Paris et al., 2008) were observed. This suggests that smoking may affect CXR-based diagnosis of asbestosis more than CT-based. Jakobsson et al. observed an increased risk of asbestosis with smoking only among subjects with profusion grade 0/1 but not among those graded 1/0 (Jakobsson et al., 1995). In the study by Rohs et al. 75% of asbestosis cases were smokers compared with 60% of the entire cohort and the authors concluded that "both age and smoking are potential confounding factors regarding classification of asbestosis by CXR" (tjek citat) (Rohs et al., 2008). Satta et al. did not find an effect of smoking on histological fibrosis (Satta et al., 2020).

Details on the observations on age

Ehrlich et al. observed and independent effect of age with OR predicting parenchymal changes varying between 1.18 (95% CI: 0.96-1.46) and 1.31 (95% CI: 1.05-1.62) per decade depending on the reader (Ehrlich et al., 1992). These OR were higher than for a cum. exposure of 10 fibre-yrs. Irwig et al. observed that in general parenchymal "abnormality was significantly associated with age within each duration of exposure category" (Irwig et al., 1979). However, when the adjusting for age by calculating the amount byt which the prevalence exceeded that expected from the age distribution, they found only slight attenuations of the effects of asbestos exposure.

Other studies did not observe significant effects of age. The OR for asbestosis of after 38 vs. 11 fibre-yrs observed by Franko et al. was adjusted by matching for age and smoking (Franko et al., 2007). Similarly, Jakobsson found that cumulative exposure was associated with OR of asbestosis even after adjustment for age (and smoking) (Jakobsson et al., 1995). Paris et al. did not find that age was a significant confounder of the association between asbestos exposure and prevalence of asbestosis

(Paris et al., 2008). Confounding by age was also considered unlikely in the study by (Rohs et al., 2008).

Appendix 3

Considerations regarding risk of bias (RoB) evaluation.

The Cochrane Collaboration's "Risk of Bias" tool was not used directly. Similar to other authors of systematic review on occupational exposure and outcomes, we observed a need for significantly modifying the tool for our use (as did Lam et al. before applying them in a series of 6 case studies using the Navigation Guide systematic review methodology (Lam et al., 2016).

The tool modified by Lam et al. includes domains that address recruitment strategy, blinding, confounding, exposure assessment, outcome assessment, incomplete outcome data, selective outcome reporting, and conflict of interest. Regarding the domains recruitment strategy and incomplete outcome data, we considered virtually all studies to be of high risk of bias regarding these and did not specifically want to address them for each study. The majority of studies used existing registers of workers usually compiled for administrative purposes other than research, in many cases depending on existing exposure and outcome measurement from these or other administrative sources. Thus, in general there was a high risk of selection bias (such as, e.g. healthy survivor effects, selective drop out during the decade-long observation times, or selective focus on high-exposure tasks) causing the studied populations to not represent the overall population of asbestos exposed individuals of the time and location. At the time of most studies, the idea of documenting pre-specified outcomes was uncommon and most studies relied on existing outcomes, from e.g. existing radiological examinations or death registers. On the other hand, the comprehensive use of the ILO grading system for CXRs, acted as a pre-specified outcome generally applied in most cases allowing for comparisons of similar grades of parenchymal abnormalities (i.e. grade 0/1) even in studies that appeared to selectively emphasize other grades as primary outcomes.

Therefore, rather than using the modified RoB tool from Lam et al. we considered domains from the RoB-SPEO tool developed and tested recently (Pega et al., 2020). This tool was developed for "systematic reviews of studies estimating the prevalence of exposure to selected occupational risk factors" and has more focus on RoB in exposure assessment. We thus modified existing tools (Lam et al., 2016; Pega et al., 2020), adding domains concerning accuracy of exposure assessment and of outcomes. In addition we added a quality of evidence domain by including study design in the score, putting emphasis on the lower risk of recruitment bias in cohort studies compared with cross-sectional studies.

The tool we applied was thus an unvalidated tool consisting of 9 domains. Each domain was scored as negative if the information could not be identified in the study. The domains are listed below, followed by a figure showing the scores:

Diagnosis of high quality by accepted definitions and by at least two independent evaluators separately (or side-by-side reading) reaching consensus or death records verified by reassessment.

Fibre exposure measured in a reliable, standardised, accurate way.

Blinding of assessors (readers of CXR/CT or pathologists or clinicians) in relation to exposure or previous diagnosis of the patient.

Disease outcome assessed independently of exposure

Bias from design?

Bias from self-reported job-history?

Control for confounding by age

Control for confounding by smoking

Suspected conflict of interest

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Appendix 4

Detailed grading of the evidence

Low intensities of exposure may be associated with the development of asbestosis (if duration is sufficiently long) even below 1 f/ml.

1.
2. The vast majority of studies point in the same direction and only one study opposed it. It is biologically plausible if duration is sufficiently long. Indirectly supported by studies with long follow-up times finding effects of low cumulative exposures.

Rating for Risk of Bias (Study Limitations) -1 decrease quality 1 level	Rationale Intensity measurements most often performed with short durations, possibly to determine peak exposures and may systematically be biased both upwards and downwards. High risk of it being influenced by purpose of e.g. surveillance schemes.
Rating for Indirectness 0 no change	Rationale Association is directly related to population, exposure and outcome of interest in most studies.
Rating for Inconsistency +1 increase quality 1 level	Rationale Consistent results. Heterogeneity easily explained by variations in duration
Rating for Imprecision 0 no change	Rationale Possible to measure rather precisely
Rating for Publication bias 0 no change	Rationale No signs of this and no reason to suspect pub bias on this topic
Rating for Large Magnitude of Effect 0 no change	Rationale Not observed
Rating for Dose-Response +1 increase quality 1 level	Rationale DR usually observed also in low range of exposure
Rating for Residual Confounding Increases Confidence	Rationale

+1 increase quality 1 level	Some reason to believe that this is the case (extremely low intensity cases possibly missed due to lack of suspicion of asbestos exposure)

Final decision on overall quality of evidence: HIGH i.e. Good evidence: +++

Short duration of exposure, possibly just a few months, may be associated with the development or mortality of asbestosis (if intensity of exposure is sufficiently high).

3.

4. Only a few studies observed asbestosis with durations of around 1-3 years. Majority of studies observed an effect of duration alone, but some studies graded of high quality did not observe this. Fair RoB score and biologically plausible if intensity is sufficiently high.

Rating for Risk of Bias (Study Limitations) -1 decrease quality 1 level	Rationale High risk of bias from loss of follow-up and from unspecified inclusion criteria in many studies and from lack of details on follow-up programs in early studies with heavy exposure
Rating for Indirectness -1 decrease quality 1 level	Rationale Association is directly related to population and outcome of interest in most studies. However, duration can be regarded as only a proxy of exposure, e.g. in cases with varying tasks
Rating for Inconsistency -1 decrease quality 1 level	Rationale Results were not consistent with some studies opposing the conclusion
Rating for Imprecision 0 no change	Rationale Appeared to be precisely measured in included participants, and is easy to measure. Also in large studies.
Rating for Publication bias 0 no change	Rationale No signs of this, the effect was observed in studies of good designs and of all sizes
Rating for Large Magnitude of Effect +1 increase quality 1 level	Rationale The studies showing effects after less than one year suggest large magnitude of effect, but they were sparse
Rating for Dose-Response +1 increase quality 1 level	Rationale DR clearly and almost uniformly observed

Rating for Residual Confounding Increases Confidence 0 no change	Rationale Studies varied greatly in the handling of duration from excluding short duration to efforts to include all

Final decision on overall quality of evidence: MODERATE ie. Some evidence: ++

A cumulative exposure of 25 fibre-yr increases the risk of developing asbestosis.

5.

6. Of 10 studies reporting risk of asbestosis below 25 fibre-yr with confidence intervals and five other studies without 95% CI, seven found statistically significant associations. Fair RoB score and some studies reported increased risk well below this level. Hampered by lack of unexposed controls in all studies.

Rating for Risk of Bias (Study Limitations) 0 no change	Rationale Low-exposure studies mostly evaluated as low RoB
Rating for Indirectness 0 no change	Rationale Association is directly related to population, exposure and outcome of interest in most studies.
Rating for Inconsistency 0 no change	Rationale Minor inconsistency
Rating for Imprecision 0 no change	Rationale Several estimates without wide CIs
Rating for Publication bias 0 no change	Rationale No reason or signs that this is major
Rating for Large Magnitude of Effect 0 no change	Rationale Not observed
Rating for Dose-Response 0 no change	Rationale DR described at this level but rarely tested statistically and of little value to this particular question
Rating for Residual Confounding Increases Confidence 0 no change	Rationale No reasons to think this

7.

Final decision on overall quality of evidence: MODERATE ie. Limited evidence +

There is a threshold for the cumulative exposure to asbestos and the risk of developing asbestosis.

8. Not many studies addressed this question. A couple investigating it found no evidence of a threshold. Models suggesting threshold are mostly older with more heavily exposed workers. Poor RoB score and both supported by mechanistic evidence but also considered unplausible from biological evidence and this is discussed with differing conclusion in the literature.

Rating for Risk of Bias (Study Limitations) 0 no change	Rationale Supported by studies with low RoB
Rating for Indirectness -1 decrease quality 1 level	Rationale Association is directly related to exposure and outcome of interest in most studies. Studies may not apply directly to present day populations because of models based on exposures dating from older, heavier, or less well-defined exposures
Rating for Inconsistency -1 decrease quality 1 level	Rationale Some inconsistency in the few studies
Rating for Imprecision -2 decrease quality 2 levels	Rationale High risk of lack of precision in the lower exposure range.
Rating for Publication bias 0 no change	Rationale Unresolved question so unlikely that Pub bias prevented any studies from being published
Rating for Large Magnitude of Effect 0 no change	Rationale Not relevant
Rating for Dose-Response 0 no change	Rationale Cannot be applied to this typs of question
Rating for Residual Confounding Increases Confidence 0 no change	Rationale No reason to believe this

Final decision on overall quality of evidence: INSUFFICIENT evidence: 0

Smoking is associated with radiological changes that may increase the risk of being diagnosed with asbestosis.

9. A rather similar no. of studies suggested and did not suggest association with smoking. Some studies with better data suggested that the risk was due to low exposure groups showing unspecific signs similar to those that may be caused by smoking. Poor RoB score, but it is supported by mechanistic studies outside this review documenting that smoking is associated with radiographic and histological changes similar to early-stage asbestosis.

Rating for Risk of Bias (Study Limitations) 0 no change	Rationale Majority of studies that included smoking were high qual. studies
Rating for Indirectness -2 decrease quality 2 levels	Rationale Data on smoking likely to correspond less to smoking history in populations of interest today. Smoking may be a poor proxy for "no. of inhaled pack years" which is probably the exposure of interest. Smoking rates may have been higher in the past when asbestos exposure was also higher.
Rating for Inconsistency -1 decrease quality 1 level	Rationale Inconsistent findings
Rating for Imprecision -1 decrease quality 1 level	Rationale Self-reported smoking data known to be unreliable and unprecise. Few large studies.
Rating for Publication bias 0 no change	Rationale Unlikely
Rating for Large Magnitude of Effect 0 no change	Rationale Unlikely
Rating for Dose-Response 0 no change	Rationale Not observed for the few studies using pack-years.
Rating for Residual Confounding Increases Confidence 0 no change	Rationale Direction of residual confounding difficult to estimate

Final decision on overall quality of evidence: MODERATE ie. Limited evidence +

High age is associated with radiological changes that may increase the risk of being diagnosed with asbestosis.

10. Few studies addressed this question. They support an age association but does not support important confounding by age. A direct effect of age is supported by mechanistic evidence outside this review suggesting radiographic and histological changes similar to early-stage asbestosis. RoB fair and overall there is some evidence that this is the case, possibly in part due to association with exposure history, in part with age itself.

Rating for Risk of Bias (Study Limitations) 0 no change	Rationale Mostly studies of good quality
Rating for Indirectness -1 decrease quality 1 level	Rationale Association is directly related to population and outcome of interest in most studies. Applies rather directly mechanistically but could also be due to age being related to latency, duration and intensity.
Rating for Inconsistency 0 no change	Rationale Few studies, no major inconsistency.
Rating for Imprecision -1 decrease quality 1 level	Rationale Lacking some precision regarding age and exposure in combination. Few large studies.
Rating for Publication bias -1 decrease quality 1 level	Rationale Some risk that age was omitted in studies not observing any change in association even if data were available.
Rating for Large Magnitude of Effect 0 no change	Rationale Probably small effect.
Rating for Dose-Response +1 increase quality 1 level	Rationale DR present with higher age increasing the risk
Rating for Residual Confounding Increases Confidence 0 no change	Rationale

	On the contrary, residual confounding from age being related to other factors (smoking, latency, duration, intensity) mostly decreases confidence.

Final decision on overall quality of evidence: MODERATE ie. Some evidence ++

All types of asbestos fibres are associated with a risk of developing asbestosis.

11. Effects of similar sizes and direction observed in all major industries and with all types of fibres. No evidence that some fibres in population studies showed higher risks. Difficult to elucidate because of mixed or suspected mixed exposures in most populations. Supported by mechanistic evidence.

Rating for Risk of Bias (Study Limitations) 0 no change	Rationale Evidence is based on all studies including several with low RoB
Rating for Indirectness 0 no change	Rationale Association is directly related to population and outcome of interest in most studies. Cannot be ruled out that a lot of the information is based on exposures that differ by fibre type in ways unaccounted for and rather different from exposures relevant today
Rating for Inconsistency -1 decrease quality 1 level	Rationale A few earlier studies found huge differences in risk between fibre types (but did observe risks with sufficient exposure)
Rating for Imprecision 0 no change	Rationale Fibre types appeared to be well characterized and present in large studies
Rating for Publication bias 0 no change	Rationale Studies published across all major job and industries
Rating for Large Magnitude of Effect 0 no change	Rationale

Rating for Dose-Response 0 no change	Rationale DR observed in very different studies but no studies tried to compare if DR were similar across fibre types.
Rating for Residual Confounding Increases Confidence 0 no change	Rationale Difficult to judge

Final decision on overall quality of evidence: Some evidence ++

	Diagnosis of high quality by accepted definitions and reached by at least two independent evaluators separately (or side-by-side reading) reaching consensus? Or death records verified by reassessment	Fibre exposure measured in a reliable, standardised, accurate way	Blinding of assessors (readers of CXR/CT or pathologist or clinicians) in relation to exposure or previous diagnosis of the patient	Outcome assessed independently of asbestos exposure	Bias from design	Bias from self-reported job-history	Control for confounding by age	Control for confounding by smoking	Suspected conflict of interest	
Armstrong 1988	1	0	0	1	1	1	1	0	1	6
Berry 1979	1	0	1	1	0	1	0	0	0	5
Chen 1992	1	1	1	1	0	0	0	0	1	5
Cordier 1984	1	1	1	0	1	1	1	1	0	7
Courtice 2016	1	1	0	0	1	1	1	1	1	7
de Klerk 1991	0	1	1	1	1	1	0	0	1	6
Ehrlich 1992	1	0	1	1	1	0	1	1	0	6
Eisenhawer 2014	1	0	0	1	0	0	1	0	0	3
Feder 2018	0	0	0	1	0	0	0	0	1	2
Finkelstein 1984	0	1	1	1	1	1	0	1	1	7
Fischer 2002	0	0	0	1	0	0	0	0	1	2
Franko 2007	0	0	0	0	1	1	1	1	1	5
Ghezzi 1972	0	1	0	1	0	1	0	0	1	4
Harris 2021	0	1	1	1	0	0	0	1	1	5
Hein 2007	1	1	1	1	1	1	1	0	1	8
Huang 1990	1	0	0	1	1	0	0	0	0	3
Irwig 1979	1	0	0	1	1	1	1	0	1	6
Jakobsson 1995	1	0	1	1	0	0	1	1	0	5
Johansson 1987	0	1	1	1	0	1	0	1	1	6
Jones 1989	1	0	1	1	0	0	1	1	0	5
Larson 2010	0	0	0	1	1	1	0	0	0	3
Magnani 2020	1	0	0	1	1	1	0	0	1	5
Mastrangelo 2009	0	1	0	1	1	1	0	0	1	5
McDonald 1982	1	1	1	0	0	0	1	0	0	4
McDonald JC 1980	0	0	0	0	1	1	1	1	0	4
Murphy 1971	0	0	1	1	0	0	1	1	1	5
Paris 2008	1	0	1	1	0	1	0	0	1	5
Rohs 2008	1	1	1	1	1	0	1	1	1	8
Satta 2020	0	0	0	1	1	0	1	1	1	5
Sluis-Cremer 1990	0	1	1	1	1	0	1	0	1	6
Terra-Filho 2015	1	0	0	1	0	1	1	1	0	5

Figure. Detailed grading of RoB of the selected studies

Appendix 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	No abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1, 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5,6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5,6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6, 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	tables
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Tables and p 10-12
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	No conversions or

Section and Topic	Item #	Checklist item	Location where item is reported
			similar
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	No tabulation or display
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods 10-12. Rationale not provided
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not explored
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	No sensitivity analyses
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not assessed
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7 + figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not systematically cited. explained p 6
Study characteristics	17	Cite each included study and present its characteristics.	Tables and p 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	To the extent that this was done: tables
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	10-14
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	No statistics

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	10-14
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	No sensitivity analyses
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	10-14
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Mostly in appendix 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	We believe to have included all relevant studies and there is little context to add
	23b	Discuss any limitations of the evidence included in the review.	15-18
	23c	Discuss any limitations of the review processes used.	18-19
	23d	Discuss implications of the results for practice, policy, and future research.	Not done
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	No protocol available
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No amendsments made
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	20
Competing interests	26	Declare any competing interests of review authors.	Lacking
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Will be done if published

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 6

AES (DASAM) CRITERIA FOR CAUSAL INFERENCE

Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome.

The following categories are used:
+++ strong evidence of a causal association
++ moderate evidence of a causal association
+ limited evidence of a causal association
0 insufficient evidence of a causal association
- evidence suggesting lack of a causal association

Description of categories: Strong evidence of a causal association (+++): A causal relationship is very likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++): A causal relationship is likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association (+): A causal relationship is possible. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0): The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-): Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments: The classification does not include a category for which a causal relation is considered as established beyond any doubt. The key criterion is the epidemiological evidence. The likelihood that chance, bias and confounding may explain observed associations are criteria

that encompass criteria such as consistency, number of ‘high quality’ studies, types of design etc. Biological plausibility and contributory information may add to the evidence of a causal association.

Fyldigt dansk resumé

Baggrund.

Det har i mere end 100 år været beskrevet, at lungesygdommen asbestose kan fremkaldes ved indånding af asbestfibre i en lang række erhverv. Det er stadig omdiskuteret, hvor stor en dosis af asbest, der skal til for at fremkalde sygdommen og der er flere forskellige bud på, hvordan dosis-respons sammenhængen er. Diagnosen blev tidligere som regel stillet hos arbejdere, der fik nedsat lungefunktion og udviklede åndenød og hvor fibrose i lungevævet kunne ses på røntgenbilleder. Der har i en årrække været konsensus om, at diagnosen bedst stilles ved fund af typiske forandringer på CT-skanninger eller alternativt røntgen af thorax, som dog er mindre følsomt, samt dokumentation for tilstrækkelig tidligere udsættelse for asbest uafhængigt af om der også er symptomer på sygdom. Symptomer og forandringer i lungefunktion afgør sværhedsgraden af sygdom. Diagnosen kan også stilles patologisk eller histologisk i kombination med tilstrækkelig udsættelse. Tidlige og lette forandringer i lungevævet kan både radiologisk og histologisk være meget vanskelige at skelne fra andre interstitielle lungesygdomme. Der er ikke international konsensus om f.eks. tilstedeværelse af pleurale plaques eller erhvervsmæssig udsættelse for asbest er tilstrækkeligt til at konkludere at sådanne forandringer er asbestose – eller om der kræves dokumentation for et bestemt antal fiberår. Sådanne lette forandringer er, selv om der ikke diagnosticeres asbestose med alvorlige symptomer, i undersøgelser vist at være forbundet med øget mortalitet.

Arbejdsmiljøforskningsfonden finansierede et systematisk review af de radiologiske og kliniske kriterier for asbestose og af hvilken eksponering, der er nødvendig for at fremkalde sygdommen. Der blev bedt om fokus på intensitet, varighed, fibertyper, jobtyper, latenstid, eksponerings-respons sammenhæng, nøjagtighed af målemetoder, starttidspunkt og prognose og evt. konkurrerende arbejdsmæssige og ikke arbejdsmæssige årsager og tilstande.

Metoder.

En større gruppe arbejdsmedicinske eksperter gennemførte et systematisk review af den videnskabelige litteratur om årsagssammenhængen mellem udsættelse for asbest og risikoen for udvikling af sygdommen asbestose.

En omfattende systematisk søgning i Pubmed og Embase fandt 7824 titler af mulig relevans. Alle titler blev gennemgået og 843 abstracts læst af de samme to forfattere. 206 artikler blev udvalgt og læst af 2 forskellige forfattere fra gruppen. Ved tvivl om inklusion eller fortolkning af data blev en tredje forfatter inddraget i vurderingen. I alt indgik 31 artikler i det endelige review. Artikler blev inkluderet uanset design, hvis de var originalstudier og omhandlede asbestose eller det overordnede sygdomsbegreb pneumokoniose, (som også inkluderer andre støvlungesygdomme) vurderet ud fra røntgenbilleder, skanninger, patologiske eller histologiske undersøgelser eller dødsattester. Der skulle desuden være opgjort kumuleret udsættelse for asbest (typisk i fiberår, men i nogle ældre undersøgelser på anden vis) og være estimater for prævalens, incidens eller mortalitet i fht. udsættelsen. Endelig skulle der indgå beregninger eller grafik, der illustrerede risiko.

De 31 artikler repræsenterede så vidt det kunne vurderes 30 forskellige undersøgelser, idet en enkelt artikel, som bidrog med væsentlig anderledes undersøgelsesmetode af tidligere undersøgt population, blev inkluderet. Ellers blev altid valgt den seneste artikel med længst opfølgning af tidligere undersøgte populationer, selvom dette kunne betyde, at tidligere resultater ikke blev inddraget i reviewet.

Der kunne ikke findes et velegnet eksisterende redskab til vurdering af risiko for bias i litteraturen om asbestose, som på flere punkter adskiller sig fra anden epidemiologisk litteratur, f.eks. hvad angår brugen af undersøgelser udført som led i lovpåbudte virksomhedsundersøgelser eller obduktioner. Vi modificerede derfor eksisterende redskaber og inddrog 9 parametre i vurdering af risiko for bias: sygdom vurderet uden kendskab til eksponering; design af undersøgelsen; justering for effekt af alder; justering for effekt af rygning; mulig interessekonflikt; kvalitet af diagnosen (herunder anvendelse af mindst 2 uafhængige vurderinger af røntgen/patologi); pålidelighed af fibereksponeringsmålinger; eksponering vurderet uden kendskab til sygdom. Der blev opnået pointscore mellem 2 og 8.

Evidensen blev vurderet ud fra Navigation Guidelines med inddragelse af følgende 8 domæner: risiko for bias, indirekte/direkte evidens, konsistens af evidens, nøjagtighed af evidens, publikationsbias, størrelse af effekt, eksponering-respons gradient og hvorvidt residuel confounding bidrog til resultaters troværdighed.

Resultater.

Der blev fundet et tværsnitsstudie, 3 case-kontrol studier, 11 tværsnitsstudier med longitudinelle data for eksponering indsamlet retrospektivt og 16 kohortestudier. 11 artikler blev vurderet til en høj kvalitet med en score på mindst 6 (af maksimalt 9).

Ni studier undersøgte effekten af eksponeringsintensitet. Kun 3 viste statistisk signifikant øget risiko med øget intensitet startende ved 0,15-0,3 fibre/ml og en faktor 10 i forskel mellem de 3 studier. Der var også et meget stort spænd i hvilken intensitet der ikke viste effekter i de enkelte studier med et studie uden påvist effekt af 13,5 fibre/ml.

Sytten studier undersøgte latenstid. Der fandtes evidens for, at asbestose kan udvikles med en latenstid på helt ned til omkring et år ved ekstremt høj eksponering og op til 66 år ved meget lav eksponering.

Atten studier undersøgte effekten af varighed af eksponering og 9 af disse fandt signifikant øget risiko for asbestose med øget varighed, 8 viste samme tendens og 1 studie viste ingen sammenhæng. Sammenholdt med den øvrige litteratur blev disse resultater vurderet som:

1. Asbesteksponering med lav intensitet kan være forbundet med udvikling af asbestose (hvis varigheden er tilstrækkeligt lang) sandsynligvis selv under 1 f/ml. God evidens +++
2. Kort varighed af eksponering, muligvis kun i få måneder, kan være associeret med udvikling af asbestose (hvis intensiteten er tilstrækkelig høj). Moderat evidens ++

To studier af høj kvalitet viste med konfidensintervaller signifikant øget prævalens af asbestose ved udsættelse for mindre end 25 fiberår. En eksponerings-respons model uden nedre tærskel passede bedst til data i de ganske få studier, hvor dette blev undersøgt.

I alternative analyser uden fokus på studier med højeste kvalitetsscore fandtes, at yderligere 4 studier med lav vurderet kvalitet viste en øget prævalens efter mindre end 25 fiberår, som var statistisk signifikant i to af disse. I alt fandt fem studier med data om asbestose med større sværhedsgrad (grade 2 eller højere) statistisk øget risiko for asbestose under 25 fiberår. Af de 7 studier som havde observeringstider længere end 25 år, fandt de 3 en statistisk øget risiko for asbestose under 25 fiberår.

Seks studier med lav kvalitet observerede asbestose efter mindre end 10 fiberår og i to af disse var der tale om statistisk signifikante fund. Den laveste eksponering med statistisk signifikant øget risiko sammenlignet med lavere eksponering var på 5,3 fiberår.

Den samlede vurdering blev, da der var tale om meget forskellige studier og metoder og få studier med høj kvalitet:

3. En kumuleret eksponering på 25 fiberår eller mindre øger risikoen for at udvikle asbestose. Begrænset evidens +
4. Der findes en nedre tærskel for den kumulerede eksponering for asbest og risikoen for at udvikle asbestose. Utilstrækkelig evidens 0

Et begrænset antal studier havde oplysninger derom, men rygning og høj alder fandtes i flere studier associeret med begyndende radiologiske forandringer forenelige med asbestose mest sandsynligt som udtryk for, at det billeddiagnostisk især på røntgen kan være vanskeligt at skelne mellem disse forandringer og de letteste grader af asbestose. En mulig sammenhæng med rygning kunne også skyldes, at rygning var positivt korreleret med stor asbestudsættelse. Antallet af gode studier, der ikke fandt sammenhæng med rygning, var dog lige så stort som antallet, der fandt en sammenhæng.

Vurdering

5. Rygning er associeret med radiologiske forandringer som kan øge risikoen for at blive diagnosticeret med asbestose. Begrænset evidens +
6. Høj alder er associeret med radiologiske forandringer som kan øge risikoen for at blive diagnosticeret med asbestose. Moderat evidens ++

Risikoen for asbestose sås tydeligt for alle typer af asbestfibre og på tværs af alle større erhvervsgrupper undersøgt. Det var ikke muligt at afgøre, om der kunne være forskelle i eksponerings-respons sammenhænge mellem fibertyper.

7. Alle typer af asbestfibre er associeret med en risiko for at udvikle asbestose. God evidens +++

Lægmandsresumé

Asbestose er en lungesygdom, som man kan risikere at udvikle efter indånding af asbest. Sygdommen er sjælden i Danmark, men pga. fortsat udbredt brug af asbest i en række lande, er den stadig et stort problem globalt. Den kan opdages på røntgenbilleder eller skanninger af lungerne hos nogle tidligere asbestudsatte, men det er uklart hvor meget asbest, der skal til for at fremkalde sygdommen. Arbejdsmiljøforskningsfonden finansierede en systematisk gennemgang af den videnskabelige litteratur, der findes om sammenhængen mellem ansattes udsættelse for asbest på arbejde og risikoen for senere at få asbestose og måske dø af sygdommen. Forskerne fandt 31 studier, som havde gode oplysninger om asbestkoncentrationer i luften, om jobfunktioner, om varighed af ansættelse og om forekomsten af asbestose. De kunne derved belyse den samlede asbestudsættelses betydning for sygdommens forekomst. Der var god evidens for at konkludere, at asbestose kan optræde efter beskeden udsættelse, hvis den har varet i mange år. Der var nogen evidens for at blot få måneders udsættelse ved høj intensitet kan være tilstrækkelig, men der sås også at sygdommen kan optræde mere end 60 år efter start på arbejde med asbest. Der var flere eksempler i litteraturen på, at sygdommen kan optræde efter mindre end 25 såkaldte fiberår, men studierne var af svingende kvalitet og den samlede evidens for dette var begrænset. Der var god evidens for, at alle typer af asbestfibre kan medføre risiko for sygdommen, hvis udsættelsen har været tilstrækkelig. Rygning og høj alder giver muligvis anledning til forandringer på røntgenbilleder og måske på CT-skanninger, som i tidlige stadier kan forveksles med asbestose. Evidensen for dette var dog kun begrænset til moderat. Mere fremskreden asbestose så ikke ud til at kunne forveksles med effekter af rygning. Det var svært at afgøre om effekten af høj alder skyldtes, at man tidligere kunne være udsat for meget høje asbestkoncentrationer, som var vanskelige at dokumentere mange år senere.