Systematic Review of the Association and Dose-Response Relationship Between Silica Dust Exposure, Silicosis, Risk of TB Disease and TB Mortality

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DECLARATION

MPH Mini-Dissertation

I Paula Akugizibwe Student No. AKGPAU001

declare that the work that I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowledged.

Signed by candidate

Signature: Signature Removed

Date: 19 May 2014

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SUMMARY

Silicosis is a fibrotic lung disease caused by prolonged inhalation of silica dust, which is produced in many industries that work with sand and stone products, such as mining. An association between tuberculosis (TB) and silicosis is well recognised in the literature, but the underlying dose-response relationship is not clear, especially with respect to the effect of silica dust in the absence of silicosis.

This systematic review synthesised the findings of studies that quantify the association – and where available, the dose-response relationship – between silicosis or silica dust, and both risk of TB disease and TB mortality. Epidemiologic studies that addressed the review's questions, were published in peer-reviewed journals between 1970 and the present – and met pre-defined inclusion, exclusion and quality criteria – were included in the review, the findings of which are presented in this mini-dissertation.

The protocol for the review is presented in part A – outlining the background, justification, structure and process for the review. In part B, a general literature review is presented. This is different from the systematic review in that it only covers studies published prior to 1970, biological studies published at any time, prevalence studies, and studies of any design that measure the association between silica or silicosis and other outcomes included in the systematic review (e.g. treatment relapse). A full list of references is included at the end of each chapter.

Part C presents the findings of the systematic review in the form of a journal article. 27 studies were included in the review, most of them retrospective cohort studies. They showed that the risk of TB disease and TB mortality were increased by the presence of silicosis, and also by exposure to silica dust whether or not silicosis was present. The associations displayed significant dose-response relationships, gradients of which varied across studies. However, extensive heterogeneity between studies precluded meta-analysis. Given that low levels of silica dust increase TB risks, even in the absence of silicosis, the review concludes that there is an urgent need to invest in strengthening silica dust control both for the occupational health of workers, and for the health of their communities given the transmissibility of TB.

GLOSSARY OF ACRONYMS AND ABBREVIATIONS

BCG	Bacillus Calmette-Guérin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD	International Classification of Diseases
ILO	International Labour Organisation
OEL	Occupational Exposure Limit
OR	Odds Ratio
OSHA	Occupational Safety and Health Authority
PEL	Permissible Exposure Limit
RR	Relative Risk (Risk Ratio or Rate Ratio – specified in the text)
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
TB	Tuberculosis

PART A: PROTOCOL

CONTENTS

1. Background

1.1. Context

Throughout the 20th century and into the 21st, epidemiological and biological studies have examined the association between silicosis and tuberculosis (TB). Epidemiological studies were mostly conducted on miners, including South African miners. Mining, especially for gold, generates dust that contains high levels of respirable crystalline silica – prolonged inhalation of which can lead to the irreversible inflammatory lung disease known as silicosis. Currently, it is known that the South African mining sector, particularly gold mining, has one of the highest rates of tuberculosis (TB) in the world (Republic of South Africa, Department of Health 2007), which is partly driven by the exposure of miners to silica dust and the accompanying silicosis.

Departing from an early misconception that silicosis and TB were one disease (known as 'phthisis'), 20th century scientific literature began to shed light on the ways in which silicosis influences the risk, clinical features, treatment and prognosis of TB. More specifically, these studies were able to quantify the relationship using modern epidemiologic techniques.

1.2. Silicosis and TB

Silicosis greatly increases the risk of TB disease, between 2 and 6 fold (Cowie 1994, Kleinschmidt 1997, Corbett 2000, Li 2011). This risk persists even after the exposure has ended (Hnizdo 1998). As such TB has long been considered a compensable occupational disease in miners and ex-miners in South Africa, and in silica-exposed workers in other countries including Australia, Germany and India (Boyko 2014).

The association between silicosis and TB strengthens as silicosis becomes more advanced, but even a slight degree of silicosis which cannot be detected through radiology is associated with a significantly increased risk of TB (Sluis-Cremer 1980).

1.3. Silica dust and TB

There has been less study of the effect of exposure to respirable silica on the risk of TB in the absence of radiological silicosis. However, there is both laboratory and epidemiological evidence that even in the absence of silicosis, exposure to silica dust is likely to increase the risk of TB due to the toxic effect of silica on macrophages (Snider 1978, Rajamouli 2010), which are central to the body's immune defense against tuberculosis.

However, although the independent effect of silica dust on TB risk is acknowledged in the literature, compensation systems in countries where TB is compensable often do not take this effect into account, limiting their coverage to silicotuberculosis. In South African miners, an exception is made only if non-silicotic TB disease occurs within 12 months of leaving mine work, but this does not account for the lifelong risk (Boyko 2014).

In addition to increasing the risk of TB, silicosis also affects its clinical presentation (Snider 1978) and can complicate diagnosis, treatment and outcomes – including increasing the risk of relapse and death (Russell 1941, Meiklejohn 1957, Cowie 1994, Churchyard 2003). Again, even in the absence of radiological silicosis, silica retention in the lung may affect the natural history of tuberculosis – for example by increasing the likelihood of profuse nodular TB, which is otherwise rare (Solomon 2000).

1.4. Silica, silicosis and TB in South Africa

In South Africa, the relationship between silica dust or silicosis and TB is of particular interest due to the large gold mining industry in the country, as well as the fact that a high HIV prevalence in miners also increases the risk of TB in this population (Kleinschmidt 1997, Mallory 2000, Girdler-Brown 2008). When the increased relative risk of TB conferred by silicosis is combined with the increased relative risk conferred by HIV, the impact is not an addition, but a multiplication of these relative risks for TB (Corbett 2000).

HIV, silica and silicosis thus combine to create exceedingly high rates of TB among miners and ex-miners, as revealed in epidemiological and autopsy studies (Cowie 1989, Murray 1996, Steen 1997, Trapido 1998, teWaterNaude 2005, Corbett 2004, Girdler-Brown 2008). A recent cross-country modelling study found that a one standard deviation increase in mining production is associated with 760,000 new cases of TB in sub-Saharan Africa every year. (Stuckler 2010). Control of the epidemic of TB, HIV and silicosis in miners and ex-miners is therefore both an occupational health and a public health priority in Southern Africa

2. Study Justification

2.1. Need for a global systematic review

While the literature has been clear in demonstrating associations between silica, silicosis and TB, and several reviews on silicosis and TB have been written by prominent researchers in the field over the past decade (Davies 2001, Rees 2007, Barboza 2008), to the author's knowledge no systematic review has been conducted to date. In addition, most of the reviews have been limited to specific areas or countries of interest such as the South African mining sector, although there is a wide variety of published literature on silicosis and TB from multiple countries and industries.

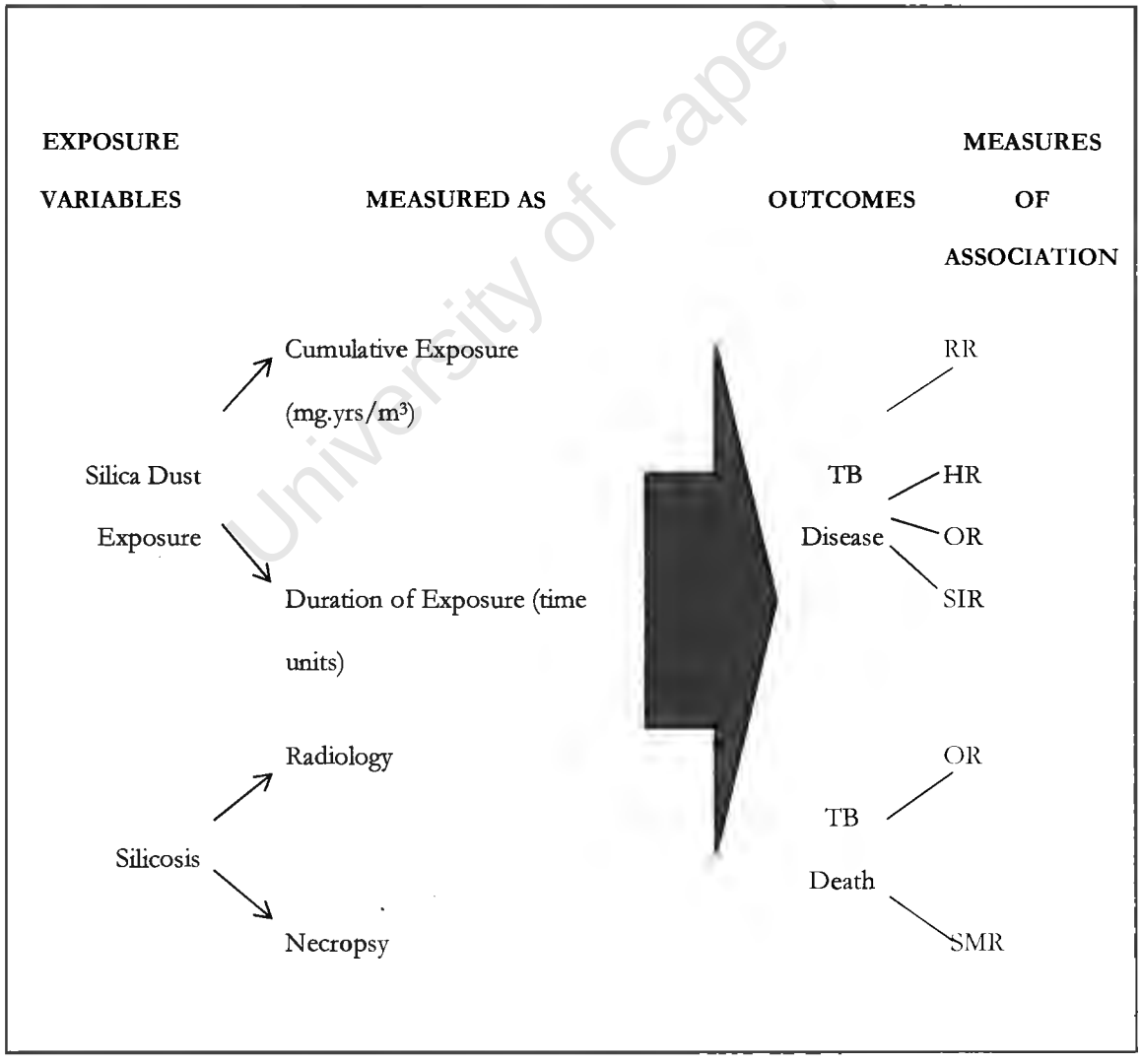
2.2. Understanding dose-response relationships

Most important, there have been no efforts to systematically review the dose-response relationships characterising these associations, which is a focus of this systematic review. This is particularly of interest with regards to the association between silica dust exposure and TB, as the threshold of silica exposure for TB risk is not known. Although, in South Africa and the USA, the occupational/permissible exposure limit used for silica is 0.1 mg/m^3, it is not clear whether or not this limit is protective against TB. Additionally, in the South African mining system compensation for TB that occurs over a year after work ends is limited to silicotuberculosis, not taking into consideration the effect of silica dust on TB risk even in the absence of silicosis.

2.3. Considering multiple pathways of association

There are several ways in which the association between silica dust exposure and TB outcomes could be quantified, and effective occupational health policies need to take into account all of these pathways, as outlined in Figure 1. Various confounders, which will be discussed in more detail in the background review (Part B) could also influence the strength of the associations observed along any of these pathways. Potential confounders include previous TB, age, and living and working conditions (crowded spaces). Good quality studies should therefore seek to measure and control for these variables where appropriate

Figure 1: Lines of association between silica / silicosis and TB



Abbreviations: RR: Relative Risk (Rate Ratio, Risk Ratio). OR: Odds Ratio. SIR: Standardised Incidence Ratio. SMR: Standardised Mortality Ratio.

This systematic review will use these lines of association as a framework to lay out the findings from epidemiological studies, which could help to inform future research as well as the development of appropriate occupational and public health and compensation interventions.

3. Purpose and Objectives

The purpose of this review is to summarise epidemiological evidence on the association between silica dust exposure, silicosis and TB, as systematically retrieved from published scientific research on TB incidence and mortality in silica-containing dust-exposed populations. Its specific objectives are to address the following questions:

Primary Question: What magnitude of increased risk of TB disease (and dose-response relationship, where available) is associated with:

- Exposure to silica dust;
- Silicosis and different grades of silicosis?

Secondary Question: What magnitude of increased risk of TB death (and dose-response relationship, where available) is associated with:

- Exposure to silica dust;
- Silicosis and different grades of silicosis?

4. Methods

4.1. Approaching Systematic Reviews

Systematic reviews use clearly defined search strategies, selection criteria and data extraction methods to retrieve and compile information on specific research question(s). Central to a systematic review is its reproducibility. Its advantage over a traditional review is that it minimises arbitrariness by clearly pre-defining questions, methodology, selection criteria and data extraction formats; so that in principle, another person with access to the same protocol and information resources could replicate the systematic review with identical or similar results (Abalos 2001).

The Cochrane Collaboration, which is widely regarded as the gold standard in systematic reviews, publishes methodology standards that are required for a review to be considered systematic. Although these standards are largely applicable to reviews of experimental and clinical interventions, they provide a guide for developing a rigorous approach to systematic reviews of observational studies.

This includes, for example, designing appropriate vocabulary for the search strategy; using two independent reviewers to apply selection criteria so as to determine which abstracts retrieved during the initial search should be included; and developing a standard data collection form to extract information from included studies (Chandler, 2012).

The standards also stipulate that quantitative meta-analyses should only be conducted when there is enough similarity in the study populations and outcomes for the meta-analysis to be meaningful. It is anticipated that in this review, however, there is likely to be wide heterogeneity in study design, population and outcomes measured, precluding meta-analysis.

The first standard stipulated by the Cochrane Collaboration is the need to formulate a review question that is not driven purely by scientific curiosity, but is relevant to current public health concerns (Chandler 2012). Given that the mining sector is a major driver of the TB epidemic in Southern Africa (Basu 2009) and that recent years have seen an intensification of the South African government's response to this epidemic (DOH 2007), this systematic review is both relevant and timely, and will support evidence-based decision making in this field.

4.2. Scope of Review

The systematic review will focus on English-language studies published in peer-reviewed journals after 1970 which quantified the association between silica or silicosis, and risk of TB disease or TB death. However, the data used in these studies may have been collected during any calendar period. The background review (Part B) will cover data findings published prior to 1970 and from government commissions of inquiry, prevalence studies and other literature not included in the systematic review.

The year 1970 was chosen because prior to this, most epidemiologic studies on the association between silicosis and TB were prevalence studies that did not measure relative risk or mortality, which are the two main outcomes of this review. In addition, the association between silica dust exposure and TB, in the absence of silicosis, was only investigated by biological studies, which will not be included in the systematic review – and it was generally believed that no dose-response relationship could be established between silica dust inhalation and risk of disease (Burke 1978).

In more recent decades, advances in epidemiological techniques have resulted in the re-exploration of data that were collected and analysed in pre-1970 studies, such as the cohort study on Vermont granite miners, allowing for the estimation of standardised mortality ratios and dose-response relationships (Graham 2004). The questions of interest to this review are therefore likely to be answered most adequately in post-1970 studies.

Studies on all silica-exposed populations will be included, regardless of their industry of work. A combination of electronic and manual search strategies will be used as follows.

4.3. Search Strategy

PubMed, CINAHL, Academic Search Premier and Health Source: Academic/Nursing Edition will be searched using combinations of the following keywords: 'silicosis' 'silica' 'tuberculosis' 'mining' 'miners' 'association' 'dose' 'response' 'risk' 'diagnosis' 'outcome' 'outcomes' 'mortality' 'case study'. As the

searches are conducted, all of the specific search terms used will be recorded, as well as the titles and abstracts of relevant corresponding results.

The reference lists of studies selected for inclusion, as well as reviews, will be manually searched to identify additional studies that were not captured during the electronic search.

4.4. Study Selection

A set of inclusion and exclusion criteria, outlined below, will be used to select studies for inclusion in the systematic review. Selection will be conducted by two independent reviewers, and any discordance resolved by discussion until consensus. Pre-defined quality criteria will also be applied to further refine the selection of studies, and studies that fail to achieve a minimum quality score will be excluded.

4.4.1. Inclusion Criteria

- All epidemiological study designs, prospective or retrospective;
- Studies include the population of interest – humans of any age who have been exposed to silica;
- Exposures measured by the study include either silica dust exposure, or silicosis;
- Outcomes measured by the study include either the incidence of TB disease or TB mortality;
- Studies published in academic peer-reviewed journals.
- Studies in English.

4.4.2. Exclusion Criteria

- Studies that address only one of these diseases, i.e. silicosis or tuberculosis, with no reference to the association between the two nor to an association between tuberculosis and silica dust exposure.
- Studies without non-silicotic controls, or exposed groups without a low or non-exposed stratum.
- Studies in which only prevalence of TB is the outcome.
- Biological studies on animals or humans, and modelling studies; these will be reviewed as part of the background (Part B) but will not be included in the systematic review.

- Routine surveillance data published by government institutions or employers will be reviewed as part of the background but will not be included in the systematic review.

4.4.3. Quality Appraisal Criteria

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement recommended by the Cochrane Collaboration, the global authority on systematic reviews, contains guidelines for quality reporting of observational studies, which include: detailed descriptions of participants and settings; clearly defined variables, data sources and statistical methods; wellexplained efforts to address bias and adjusting for confounders (von Elm 2008). These guidelines will inform the criteria used to assess the quality of studies for inclusion in this systematic review.

Annex E lays out the quality assessment criteria.

5. Summary of Process and Logistics

5.1. A **background review** will be conducted (Part B), the scope of which will be pre-1970 articles on the relationship between silica or silicosis and TB; as well as studies from any calendar period that fall outside the study questions examined here (such as prevalence studies and studies on treatment outcome).

5.2. An **electronic search** will be conducted using the keywords listed above in the search strategy, leading to list of potential titles and abstracts.

5.3. **Inclusion and exclusion criteria** will be applied to select studies from this pool.

5.4. A **manual search** of the reference lists of selected studies will be conducted and subjected to inclusion and exclusion criteria.

5.5. The **quality of the selected studies will be assessed**, and any studies that fail to meet the minimum score will be excluded.

5.6. **Data will be extracted** from the final pool of selected studies, using a standard data collection form.

5.7. Findings will be **synthesised**. It is anticipated that there will be a great degree of heterogeneity in the studies retrieved, precluding a meta-analysis. Synthesis is therefore likely to be in the form of a narrative supplemented by tables, diagrams and graphs. The findings of the selected studies and data will be summarised under each of the specific questions outlined in the research objectives. The final review will be circulated to the network of researchers active in this field, and submitted to a peer-reviewed journal for publication.

It will take six months to complete the review. The dissertation supervisor will also serve as co-reviewer, so no additional budget is required.

6. Ethics

As this is a desktop review of published literature without direct involvement of human subjects, no ethical clearance is required. Any ethical issues that arise in the studies included in this review will be reported in the discussion.

7. Summary of structure of mini-dissertation

Part A: Protocol containing background, study justification, objectives, methodology, selection criteria, logistical details and references.

Part B: General review of studies published prior to 1970, biological studies published at any time, prevalence studies, studies of any design that measure the association between silica or silicosis and other outcomes included in the systematic review (e.g. treatment relapse) and references.

Part C: Article presenting the background, methods and findings of the systematic review through a narrative supplemented with summary tables, arranged according to the review's questions:

- Association and dose-response relationship between silica dust exposure and risk of TB disease
- Association and dose-response relationship between silicosis and risk of TB disease
- Association and dose-response relationship between silica dust exposure and risk of TB mortality
- Association and dose-response relationship between silicosis and risk of TB mortality

The narrative of findings will be followed by a discussion of the value, limitations and implications of the review's findings; and references.

Annexes: A-D present a detailed summary of studies found under each of the above questions. Annex E presents the detailed quality scores for all studies selected for inclusion and those excluded. F sets out the Instructions for Authors from the journal PLOS/One, on which the article format is based.

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PART B: BACKGROUND REVIEW

CONTENTS

1. Introduction

Over the past century, epidemiological and biological studies have advanced scientific understanding of the association between silicosis and tuberculosis (TB) disease at the cellular, clinical and population levels. Although much of the literature focuses on the association between radiologically detected silicosis and TB, studies have found that even in the absence of detectable silicosis, exposure to silica dust has a potent effect on TB in exposed populations (Sluis-Cremer 1980).

The risk of TB disease is increased by silica dust exposure and silicosis. Clinical features and outcomes are also affected. As such, TB is regarded as an occupational disease in industries which generate high levels of crystalline silica. The gold mining industry is a prominent source of silica dust exposure along with other mining and non-mining industries, such as stonework, sand-blasting and ceramics (Rees 2007).

An effective programmatic response to preventing, managing and compensating occupational TB in silica-exposed populations requires an understanding of the degree to which the risk and outcomes of TB are influenced by silica exposure or silicosis, and what dose-response relationships exist here.

These questions will form the focus of the systematic review in Part C, which is limited to epidemiological studies published since 1970, while this general background review covers pre-1970s literature on silica and TB. It also presents an overview of methods of measuring silica exposure and silicosis, research findings on the biology of the association between these and TB, prevalence studies on this association and the clinical features that characterise it. Studies for inclusion in the general literature were identified through a combination of input from experts in the field, and searching the reference lists of articles, reviews and reports from all calendar periods.

2. Measuring silica dust exposure and silicosis

2.1. Measuring silica dust exposure

In the context of occupational health, the term 'silica' is generally used in reference to free crystalline silica, which is most often found in a polymorph known as quartz (Rees 2007). Quartz is one of the most common compounds on the earth's surface, and as such is released in the process of drilling for minerals – a process that enhances its effect on the human lung, as the use of drilling and abrasive mechanisms leads to finer particle sizes which have greater potency (Meldrum 2002). Silica exposure occurs also in a wide variety of other industries that make use of materials derived from sands, stones and rocks – such as construction, ceramics, masonry and agriculture (Rees 2007).

Dusts produced in different workplace settings contain different levels of respirable silica. In many countries, air samples from workplaces are regularly drawn to measure dust concentration. Gravimetric dust exposure measurement, which is now the universally accepted standard, further quantifies, for example through x-ray diffraction analysis, the specific respirable silica content within the dust sample. It is respirable free silica that is the toxicologically relevant metric for silicosis and tuberculosis.

Gravimetric measurements, both for dust and respirable silica, are expressed in units of milligrams per cubic metre (mg/m^3). However, not all studies isolate the respirable silica content within their dust measurements. The systematic review will specify the definitions of silica exposure used by different studies, as failure to measure fractions of respirable silica within the respirable dust poses a limitation to the quantification of associations, and can also result in misclassification of exposure. In the absence of dust measurements, categories of work (surface versus underground) can also serve as a proxy for silica exposure, as can duration of service – although the use of the latter has been shown to dilute the silica effect when assessed against gravimetric measurements of cumulative silica exposure for the same population (teWaterNaude 2006).

2.2. Silica exposure limits

Countries adopt gravimetric standards, e.g. occupational exposure limits (OEL) or permissible exposure limits (PEL), to regulate the levels of respirable silica produced in the workplace. The exposure limit in South Africa and the US is currently set at 0.1 mg/m^3, although the literature strongly suggests that this may not be protective against silicosis.

A study of the silica-silicosis exposure-response relationship in South African gold miners estimated that 18.3 – 19.9% of participants exposed on average within the protective exposure range (<0.1 mg/m^3) had developed silicosis (Churchyard 2004). However, this was based on the arguable assumption that dust exposure concentrations had remained static for two or more decades. Another study on South African gold miners estimated that after 28 years of working in mines with a level of 0.1 mg/m^3 of respirable quartz), 25% of miners developed radiological signs of silicosis (Hnizdo and Sluis-Cremer 1993).

Similarly, a study which analysed data from cohort studies in the US, Finland and Australia had found that even an exposure limit of 0.05 mg/m^3 was associated with a cumulative risk of death for silica-related diseases that was six times higher than the acceptable limit set by the US Occupational Health and Safety Administration (tMannetje 2002). The findings of this study led to calls for the US permissible exposure limit to be lowered to at least 0.05 mg/m^3 in order to protect workers from silicosis (Sherson 2002) but to date it remains, as in South Africa, at 0.1 mg/m^3.

2.3. Measuring silicosis

Inhalation of silica dust can lead to the inflammatory and fibrotic disease of the lungs known as silicosis. Silicosis is most often diagnosed using radiology, although necropsy is sometimes used and is a more accurate method of diagnosis as it is able to detect sub-radiological silicosis. In a study comparing radiology to pathology as the gold standard for diagnosis of silicosis, sensitivity of radiological diagnosis for autopsy confirmation did not exceed 0.4 for any of the three readers (Hnizdo 1993). Sensitivity was improved by lowering the threshold at which radiographic opacities (the characteristic feature of silicosis) could be interpreted as a positive diagnosis for silicosis.

Radiographic opacities are the basis of silicosis grading, and radiographic readings have been largely standardised since the introduction of the International Labour Organisation (ILO) international classification system in 1970. The ILO classification of silicosis is based on 4 major grades (0, 1, 2, 3), each divided into minor grades (e.g. 1/0, 1/1 and 1/2) – with severity of silicosis increasing as the numerical grades and sub-grades increase.

The ILO classification system is the most widely used method for grading silicosis, although there is variation in how different studies group ILO grades to define the presence or absence of silicosis, and categories of severity. Some studies that lacked direct access to the population relied on occupational, hospital or compensation registers, which make the findings vulnerable to recall and selection bias. The systematic review will specify the definitions of silicosis applied by each study, and address any associated limitations.

3. Measuring TB

TB disease also has different diagnostic methods. In relation to silica or silicosis, it is specifically pulmonary TB which is relevant, although extra-pulmonary TB can also occur as a complication of pulmonary TB, especially in HIV-positive individuals. The main methods for diagnosing pulmonary TB are radiological, bacteriological (sputum microscopy or sputum culture) and clinical (symptomatic) diagnosis. Sputum culture is considered the gold standard, and can be used to diagnose extra-pulmonary TB as well, but due to the cost as well as the time lag, is not used as often as the other three in combination. More recently, rapid molecular diagnosis has become available through GeneXpert, but although GeneXpert is used as first-line investigation in some settings, in most settings the older three methods are still the mainstay of TB diagnosis.

These methods have their limitations – a 1978 editorial on the relationship between TB and silicosis stated that "regardless of the skill of the investigator, the recognition of TB accompanying silicosis can be

extremely difficult....Even the routine use of sputum cultures in making diagnosis leaves something to be desired, because some authors believe that incidence of false negative cultures is higher among patients with silico-TB [as] TB foci are walled in by the silicotic fibrosis" (Snider 1978).

Solomon et al. later suggested that ILO guidelines on the classification of radiography for pneumoconiosis be accompanied by a guideline specifically addressing tuberculosis, since silicosis, and even silica dust exposure in the absence of silicosis, have been shown to alter the radiographic presentation of TB, most notably through an increased likelihood and rapidity of nodular profusion (Solomon 2000). As with silicosis, TB is more accurately diagnosed by necropsy, but this method is rarely used. As for silicosis, the systematic review will specify the definitions of tuberculosis used by different studies.

4. Early studies on silicosis and TB

In the early 20th century, advanced silicosis – which came to be known as progressive massive fibrosis in its most destructive form – was more common due to extremely poor dust control, and hence was often conflated with TB under the umbrella of "phthisis". But with a decline in the prevalence of advanced silicosis, it became clear that the two diseases were distinct although intertwined, leading to more specific investigation of the association between silicosis and TB.

Irvine and Watt were among the first to explicitly address the predisposition of silicotics to TB (Irvine 1912), which in black South African gold miners was "very commonly associated with a commencing or early degree of silicosis". Post-mortem studies conducted on this population in 1928 found that 81% had tuberculosis and/or silicosis, a rate that remained relatively stable over the decades: 84% in 1944, and 83% in 1949 (McCulloch 2012). Britain's TB Research Committee (TRC) found, from routine surveillance data, that mortality from TB was 8 times higher in silica dust-producing industries than in the general population (TRC, 1932).

The TRC also observed that TB incidence rates in cohorts of miners rose steeply after five years of service, which was attributed to the "silicotic element", as longer-serving miners would have had greater exposure to silica dust (TRC, 1932). The relationship between length of service, silica dust exposure and TB was further confirmed by a two-year cohort study on granite workers, which found that the incidence rate of TB in a sub-group of workers, after ten years of service, was 160 per 1,000 years of observation. After thirty years of service, the rate in the same sub-group increased to 380 per 1,000 years of observation (Russell 1941).

In the early 1950s, the South African government established a committee of enquiry into the links between silicosis and TB. The committee reviewed data collected by the industry over the two preceding decades, which showed that close to one third of silicotic miners also had TB (Oosthuizen 1954) –of whom the vast majority, 88%, had first stage silicosis. A study in Zambian copper mines found that incidence rates of TB were 30 times greater among miners with silicosis than those without it (Paul 1961). In Sardinia, rates of TB were 40 times greater in silicotic miners than in the general population (Monaco 1964).

Although throughout the 20th century, the use of BCG vaccination to prevent the spread of TB disease was increasingly widespread among the general population, there was a suggestion in one study that it may aggravate the silica-TB association in miners. A cohort study of Bulgarian miners found that BCG vaccination, administered in adulthood, accelerated the progression of silicosis and led to a ten-fold increase in silicotuberculosis morbidity, although the sample was not large enough for the findings to be statistically significant (Pramatarov 1965).

5. Biology of the silica-TB interaction

From early on, it was believed that silica dust exerted its effect on TB risk through a reaction with the human lung, rather than with the TB bacilli (Meiklejohn 1957)). It was later demonstrated that exposure

to silica in some cases led to death of alveolar macrophages (Ebina 1960), which are central to the body's defence against mycobacterial infection.

In the silica dust-exposed lung, research has identified several different reactions that can occur between alveolar macrophages and silica, due to surface qualities of the silica particle itself – for example, the production of free oxygen radicals – or mechanisms by which silica triggers self-destruction of the alveolar macrophage (Hamilton 2008). One such mechanism is the rupture of lysosome membranes resulting in the release of hydrolytic enzymes into the macrophage, leading to programmed cell death (Allison 1968). When lysosomes rupture, silica is also released, causing a repetition of the destructive cycle (Snider 1978).

A unique animal study in 2009 also revealed impairment of macrophage anti-mycobacterial capacity as another important mechanism through which silica increases risk of TB. In this study, silica was administered to mice, followed by mycobacterium tuberculosis at various time intervals. The mice were sacrificed at defined time points, and the numbers of mycobacteria in their alveolar macrophages (AMs) were counted. The investigators found that silica-exposed mice had significantly higher numbers of mycobacteria, leading the authors to conclude that silica exposure increases risk of TB through a process that likely involves a new population of AMs that are more susceptible to mycobacterial infection (Pasula 2009).

Additionally, this study measured mycobacteria levels at different time points in relation to administration of silica and mycobacteria, and showed that silica dust causes immediate damage to AMs, but that 30 days was the critical time point for increased mycobacterial susceptibility (Pasula 2009). It also revealed that AMs themselves act as reservoirs of mycobacteria in silica-exposed lungs, echoing earlier autopsy studies on humans which found that high levels of silica dust persist in the lungs until death, meaning that its effect on macrophages – and hence, on increased risk of TB disease – is life-long (Morgan 1979).

6. Prevalence of TB in silica-exposed populations with specific reference to gold mining in South Africa

The elevated prevalence of TB in silicotics and silica-exposed individuals has been confirmed by several studies, some of which have also demonstrated an increasing prevalence as the degree of silica exposure, or grade of silicosis, increases.

Between 1974 and 1978, Sluis-Cremer et al. conducted an autopsy study on deceased black miners in South African gold and coal mines, and found an 11.1% prevalence of TB in silicotic miners, more than double the prevalence of 4.4% found in non-silicotic miners (Sluis-Cremer 1980). A cross-sectional, x-ray based study of former South African miners found an 83.7% prevalence of TB in silicotic ex-miners, compared to 50.28% in non-silicotics with an associated OR of 5.08, and concluded that silicosis was the most important risk factor for TB disease (Meel 2002).

A cross-sectional study of South African gold miners found a prevalence OR of 1.45 (95% confidence interval 1.14 to 1.85) for TB, defined as a history of TB or TB-related changes on the chest x-ray, associated with an increment of a one quartile of cumulative respirable quartz exposure (teWaterNaude 2006). This was so whether silicosis was adjusted for in the regression model, or the analysis was limited to non-silicotics. This study was unique in that it specifically commissioned research dust measurements to supplement measurements from routine surveillance, which provide the sole source of exposure data for most studies. X- ray diffraction was used to estimate the content of respirable quartz (the most common form of crystalline silica) within the respirable dust.

7. Effect of continued exposure to silica post-silicosis diagnosis

In Brazilian gold miners, continued exposure to silica after being diagnosed with silicosis (relative to cessation of further exposure) was associated with a TB OR of 4.06 per unit increase in the cumulative silica exposure index, and 4.61 in severe cases of silicosis (Carneiro 2006). Carneiro's study has potentially

important implications for labour regulations on continued employment of miners who have been diagnosed with silicosis. However, it was a retrospective analysis of compensation claimants who by definition survived and were able to access the compensation system, which makes selection bias highly likely. Carneiro's findings are also distinct from those covered in the systematic review, which focuses on TB incidence or mortality in silicotic or silica-exposed populations irrespective of whether exposure continued after diagnosis.

8. Silica, silicosis and TB in the clinical setting

8.1. Effect of silica on TB treatment outcomes

Silica does not only affect TB risk, but also its clinical presentation. Britain's TRC pointed out that "tuberculosilicosis furnishes the only cases of 'chronic' tuberculosis which we have seen" (TRC, 1932). Miners with chronic TB often appeared to be in good working health for a long period of time, with the disease localised in the lung, and often harder to detect and treat.

Following intake of silica, macrophages release a factor that accelerates the development of fibrosis around silicotic nodules in the lung (Heppleston 1967, Snider 1978). Where TB disease subsequently develops, this fibrosis has multiple effects on the clinical presentation, diagnosis and treatment of disease. Fibrosis can wall off infection, preventing the spread of bacilli to other parts of the body and resulting in a lower prevalence of extra-pulmonary TB in silicotics – but in the process, could prevent tubercle bacilli in the nodule from entering bronchial sputum, thus decreasing the sensitivity of diagnostic techniques that are based on bacilli detection in sputum samples (Oosthuizen 1954, Snider 1978). Diagnosis is further complicated by the atypical x-ray patterns of silicotuberculosis (Russell 1941, Evers 1957, Bailey 1974, Solomon 2001).

In addition, the TB treatment that became available from the 1950s was less successful in silicotics than non-silicotics (Evers 1957, Allison 1968). This was thought to be due to macrophage damage as well as difficulty with TB chemotherapy penetrating into silicotic nodules (Snider 1978).

Cohort studies investigating TB relapse rates after treatment in South African gold miners in the 1980s and 90s concluded that short-course chemotherapy was effective for this population. One study suggested that there was no significant difference in TB relapse rates between silicotic and non-silicotic miners followed up for 36 months after short-course chemotherapy (Escreet 1984), while another found a modestly increased risk of relapse in silicotic miners followed up for 5 years after treatment, although the study was somewhat underpowered statistically (Cowie 1995).

Higher TB mortality rates have also been noted among TB patients with silicosis or high levels of exposure to silica dust (Meiklejohn 1957, Russell 1941), in comparison to those without – even when they underwent post-treatment sputum conversion (Bailey 1974). In Pasula's study on the effect of silica on alveolar macrophages, silica-exposed mice also exhibited higher mortality rates (Pasula 2009).

8.2. Reverse causation

More recent research has suggested that TB relapse or mortality are not the only outcomes of interest in silicotics undergoing TB treatment. A case series study on South African gold miners showed that in silica-exposed miliary TB patients undergoing treatment, profusion of silicosis-like nodules appeared or increased in the lung even after bacteriological cure and clinical improvement, and was especially marked among miners who had the least lung damage prior to treatment. In a few cases, miners who had no nodules before treatment developed them afterwards (Charalambous 2001).

This study – which was the first, and to date the only, one of its kind – is intriguing in the light of the hypothesis of reverse causation: namely, that TB infection in the presence of silica dust can promote and exacerbate fibrosis in the lung. This notion had been put forward decades before, when it was suggested by Vigliani that TB bacilli is a "very powerful adjuvant of the antigen-antibody response...when an antigen is injected together with dead TB bacilli, the antibody response to this antigen is increased up to 50 times" – which would intensify the immunological response to silica dust and thus promote fibrosis

(Meiklejohn 1959). The Charalambous (2001) study mentioned above appears to document this phenomenon.

9. Confounders

There are a few variables that could potentially confound the relationship between silica exposure or silicosis, and TB disease. To act as confounder such variables need to be correlated with silica exposure or silicosis prevalence, be a risk factor for tuberculosis and not lie on the causal pathway. Controlling for relevant confounders will thus be a criterion in assessing the quality of studies.

Some confounders are specific to the ecology associated with populations who are occupationally exposed to silica dust. For example, overcrowded housing conditions in South African miners which exacerbate the spread of TB (Dharmadhikari 2013), or malnutrition in labour-sending communities and at the mines themselves (McCulloch 2012). These variables would serve as confounders when a mining population is compared to a general population as in standardised mortality ratio (SMR) studies.

Age is another potential confounder. In silica-exposed populations, older age is associated with a higher risk of TB, particularly TB mortality (Meiklejohn 1957). Confounding might arise as older individuals are also likely to have higher cumulative silica exposure. For example, the TRC cited earlier found that "the incidence of TB in relation to age shows a striking similarity to the incidence in relation to length of service" (TRC 1912).

10. Effect modifiers: HIV status

HIV infection is a major risk factor for active tuberculosis, of the order of two to six in gold mining populations (Corbett 2000). Studies on ex-miner populations in South Africa and Lesotho have found HIV prevalence of 27% and 23% respectively (Corbett 2004, Girdler-Brown 2008), which have undoubtedly had an effect on rates of TB disease over the past two decades. When miners have both HIV and silicosis, Corbett (2000) demonstrated that the resulting effect on TB risk is multiplicative: in the

sample of miners included in this study, prevention of silicosis would reduce the relative risk of developing active tuberculosis from sixteen to three among dust-exposed HIV positive miners.

11. Conclusion

Silica dust exposure and silicosis increase the risk of TB disease through an interaction at the cellular level, and also affect the clinical features and outcomes of TB. This association is a major public health concern not only due to its implications for populations exposed to silica, but also because TB is considered a public health emergency in Southern Africa. This is the first systematic review to the author's knowledge that specifically investigates the effect of silica on TB risk and outcomes, including a focus on the dose-response relationship that characterises this association.

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PART C: ARTICLE

CONTENTS

Note: The article was prepared according to the instructions for authors of PLOS | One (Annex F). The key exceptions are that tables are included in the text (in PLOS One's online format, they would be placed at the bottom with a hyperlink from the main text). The author has also used a different referencing style, which would be adapted to the final journal of choice.

ABSTRACT

Introduction

Silicosis is a fibrotic lung disease caused by prolonged inhalation of silica dust, which is generated in many industries that work with sand and stone products, such as mining. An association between tuberculosis (TB) and silicosis is well recognised in the literature, but the underlying dose-response relationship is not clear, especially with respect to the effect of silica dust in the absence of silicosis. This systematic review will synthesise the findings of studies that quantify the association – and where available, the dose-response relationship – between silicosis or silica dust and both risk of TB disease and TB mortality

Methods

A systematic search was conducted for relevant studies published in peer-reviewed journals between 1970 and the present. Pre-defined inclusion, exclusion and quality criteria were applied to select a smaller group of studies for review.

Results

27 studies were included in the review, most of them retrospective cohort studies. They showed that risk of TB disease and TB mortality were increased by the presence of silicosis, and by exposure to silica dust whether or not there was clinical evidence of silicosis. The magnitude of increased risk was up to 3.3-fold and 30-fold for TB disease and mortality respectively in silica-exposed individuals. The associations displayed significant dose-response relationships, gradients of which varied across studies. However, extensive heterogeneity between studies precluded meta-analysis. Studies were also limited by the risk of exposure misclassification due to lack of measurement of the specific silica content within respirable dust.

Conclusion

A dose-response relationship exists between both silicosis and silica dust exposure in the absence of radiological silicosis, and the risk of TB disease or TB mortality. There is an urgent need to invest in strengthening silica dust control so as to reduce TB risk both for the occupational health of workers and for the health of their communities, given the transmissibility of TB.

Key words: tuberculosis, silicosis, silica, dust, mining, South Africa, dose-response

1. INTRODUCTION

1.1 Background

Epidemiological and biological studies have long established an association between silicosis and tuberculosis disease (TB) at the cellular, clinical and population levels. The risk of TB disease is increased by silicosis, an inflammatory and fibrotic lung disease, itself the result of inhalation of respirable crystalline silica ("silica"). Clinical features and outcomes of the TB are also affected. As such, TB is regarded as an occupational disease in industries which produce high levels of crystalline silica.

The gold mining industry exposes workers to high levels of silica dust, along with other mining and non-mining industries such as stonework, sand-blasting and ceramics. (Rees 2007). Although much of the relevant literature focuses on the association between radiologically detected silicosis and TB, studies have found that even in the absence of detectable silicosis, silica exposed populations have a significantly increased risk of TB (Sluis-Cremer 1980, Sherson 1990, Hnizdo 1998).

The South African mining sector, particularly gold mining, has one of the highest rates of TB in the world (Republic of South Africa, Department of Health 2007). Several reviews on silicosis and TB have been written over the past decade (Davies 2001, Rees 2007, Barboza 2008), but no systematic review has been conducted to date. Additionally, the reviews have focused on specific areas of interest such as the South African mining sector, although there is a wide variety of published literature on silicosis and TB from a number of countries and industries.

1.2 Purpose

This review aims to distill epidemiological evidence on the association between silica dust exposure, silicosis and the incidence of and mortality from tuberculosis, as systematically retrieved from peer-reviewed scientific research on TB in silica-exposed populations. It will address the following questions:

Primary Question: What is the magnitude of the increased risk of TB disease (and the dose-response relationship, where available) associated with:

- exposure to silica dust;
- silicosis and different grades of silicosis?

Secondary Question: What is the magnitude of the increased risk of TB death (and the dose-response relationship, where available) associated with:

- exposure to silica dust;
- silicosis and different grades of silicosis?

2. METHODS

2.1 Study Design

A systematic review of published, peer-reviewed epidemiological studies was conducted to determine the population-level association, and dose-response relationship where available, between silica dust exposure, silicosis and the risk of TB disease and TB mortality.

2.2 Literature Search Strategy

A search was conducted via EBSCO host on Academic Search Premier, Health Source: Nursing/Academic Edition and CINAHL, and on PubMed. The following search string was used: Silica OR Silicosis AND Tuberculosis OR Miners OR Mining OR Risk OR Outcome OR Outcomes OR Mortality OR Dose OR Response. The search was limited to articles published in peer reviewed journals between 1970 and the present. However, the data used in these studies may have been collected during any calendar period. Additionally, a manual search of the reference list of included studies, as well as all previously published reviews, was conducted.

2.3 Selection of studies

A set of inclusion and exclusion criteria was established to determine which of the retrieved studies would be included in the review. Two reviewers independently screened all the abstracts using the defined criteria. Any discordance on selected studies was resolved through discussion.

The inclusion criteria were as follows:

- All epidemiological study designs, prospective or retrospective;
- Studies from anywhere in the world;
- Studies limited to or including the population of interest – humans of any age who have been exposed to silica;
- Exposures measured by the study include either silica dust exposure or silicosis;
- Outcomes measured by the study include either TB incidence or TB mortality;
- Studies published in academic peer-reviewed journals;
- Studies in English.

Studies that did not meet these requirements were excluded from the systematic review. The following additional exclusion criteria were applied:

- Studies in which only prevalence of tuberculosis was the outcome;
- Studies of silicosis without non-silicotic controls, or of silica-exposed groups without a low or non-exposed stratum;
- Studies limited to the biology of the silica-TB association, with no epidemiological measurements;
- Case studies or case series;
- Routine surveillance data published by government institutions or employers, or in legal/inquiry processes; and
- Studies that address only one of these diseases, i.e. silicosis or tuberculosis, with no reference to the association between the two.

2.4 Quality assessment

A quality assessment form was designed, using 8 quality criteria based on the STROBE guidelines for quality reporting of observational studies (von Elm 2008). Studies were scored according to their adherence to this set of pre-defined quality criteria – receiving a score of 1 if the criterion was fully met, 0.5 if it was partially met, or 0 if it was not met at all. Studies that received below 4 out of 8 were excluded.

Quality Criteria Used in Assessing Selected Studies

1) Is the setting clearly defined? This refers to the geographical as well as workplace context in which the study is set.
2) Is the population clearly described? Does the study report basic demographic and occupational data on participants, which may be relevant to the analysis – such as age, industry and duration of service?
3) Are all data sources clearly explained?
4) Are the methods that were used for measuring the exposure and outcome variables (silica dust exposure, silicosis, and TB incidence or mortality) clearly explained?
5) Does the study directly measure the exposure variables (silica dust exposure or silicosis), or are these measurements retrieved from other sources?
6) Are statistical methods and calculations clearly explained?
7) Are confounders/covariates adjusted for when calculating measures of association – does the study include multivariate analysis?
8) Are the study's findings statistically significant?

Once the final group of studies had been selected, data were extracted using standard forms tailored to the study's questions (Annexes A-D).

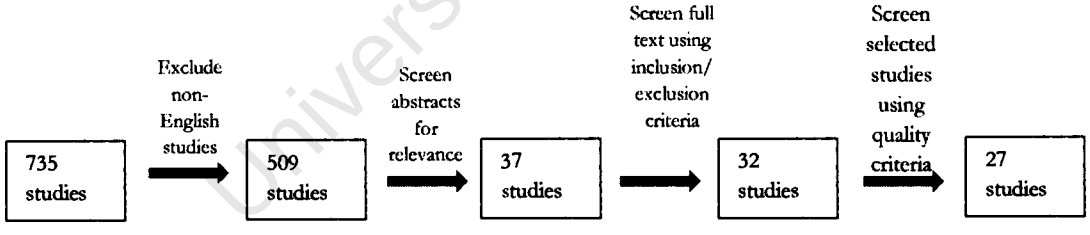
3. RESULTS

3.1 Literature search and study selection

The literature search yielded a total of 735 studies for possible inclusion. After excluding non-English studies, 509 studies remained, whose abstracts were then screened for relevance. 36 abstracts were deemed relevant, and their full text was retrieved and assessed in line with the inclusion and exclusion criteria, as well as the quality criteria. The manual search yielded one additional article.

From these 37 studies, after scrutinising the full text, 32 studies were selected for inclusion – however, a further five were excluded for not meeting the minimum quality score. A final total of 27 studies were therefore included in the systematic review. There was 93% agreement between the two reviewers, with discordance on only two studies, which was resolved by discussion until consensus. The process is summarised in Figure 1 below.

Figure 1: Steps from literature search to systematic review



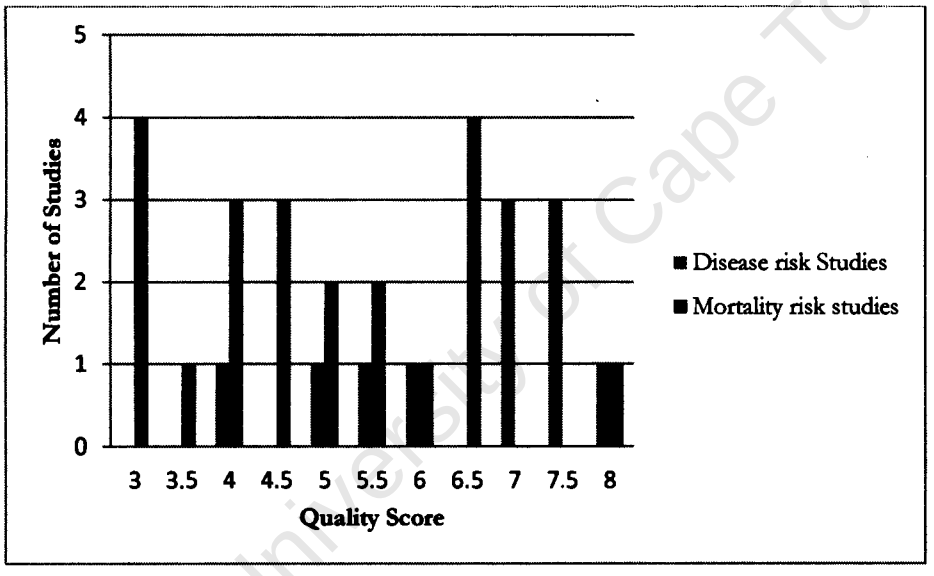
3.2 Quality assessment

On average, studies on disease risk were of a better quality than those on mortality risk, with an average score of 6.55. For mortality studies however, the average score was 4.86. The areas in most studies which scored poorly were related to absent or inadequate measurement of exposure, or failure to adjust for covariates/potential confounders.

In many such cases, the poor score was due to the use of a retrospective cohort design, meaning that investigators relied on historical records and hence were not able to determine how exposure or covariates were measured, or even to include the latter. This diminished the quality of the ensuing analysis. The data used in retrospective mortality studies were often sourced from official death registers, which also limited the authors' ability to describe the study setting and population based on the information available in historical registers.

The overall scores of the studies are summarised below, with a full breakdown of scores in Annex E.

Figure 2: Quality score of studies included in the review



3.3 Findings

The data were largely from cohort studies, most of them retrospective – relying on data from mortality, occupational and compensation databases. The studies were organised into two main groups: those that investigated the association between silica exposure/silicosis and incidence of TB, and those that investigated the association between silica exposure/silicosis and mortality from TB. Table 1 provides a summary of the study types – more details on study designs, populations and measured outcomes are contained in Annexes A-D.

Table 1: Summary of study types included in systematic review

	MEASURES OF ASSOCIATION						
EXPOSURE VARIABLES	**TB incidence Studies**				**TB mortality Studies**		
	RR*	**OR**	**SIR**	**HR**	**SMR**	**RR**	**OR**
Silica exposure	4	0	0	0	5	1	2
Silicosis	3(2)	1	2	1	6	0	1(2)
TOTAL				11			16

*RR: Rate Ratio. OR: Odds Ratio. SIR: Standardised Incidence Ratio. HR: Hazard Ratio. SMR: Standardised Mortality Ratio.

The total number of studies in Table 1 may appear to be less than those that are listed in the results section. This is because some of the studies provided multiple measures of association – namely, Hnizdo 1998 and Corbett 2003, which measured risks of TB in relation to both silica exposure and silicosis; and Chen 1997 and Calvert 2003, which measured odds ratios for TB in relation to both silica exposure and silicosis. Numbers in brackets indicate studies that reported measures of association in that category but are not counted in the total to avoid duplication.

The findings were as follows.

3.3.1 Studies measuring the association between silica exposure and TB disease risk

Three studies, all conducted on gold miners in South Africa, measured the association between TB disease risk and silica dust exposure (Table 1). Two of these calculated incidence rate ratios (IRR) for TB in underground workers compared to surface workers who are assumed to be exposed to little or no dust (Kleinschmidt 1997, Corbett 2003). The IRRs for TB were over two in most underground occupations.

The third study examined the dose-response relationship between silica exposure and TB risk by stratifying individuals' silica exposure into quartiles and calculating the relative risk of TB for each in

comparison to the lowest quartile (Hnizdo 1998). There was clearly an association between level of dust exposure and risk of TB – with the rate ratio of TB in the highest quartile of exposure being 3.22 times that in the lowest quartile; after adjusting for silicosis detected by radiology or necropsy (Hnizdo 1998). For subjects who did not have silicosis detected through either radiology or necropsy, the rate ratio from lowest to highest quartile of exposure increased by a factor of 3.78 (see Annex A).The Hnizdo (1998) study was the only one to adjust for silicosis as a potential confounder of the silica dust-TB association.

Table 2: Rate Ratio of TB disease in relation to different categories of respirable silica-containing dust exposure

	Kleinschmidt 1997 **RR (95% CI)[1]**	**Hnizdo 1998** **RR (95% CI)[2]**	**Corbett 2003** **RR (95% CI)**
Low/Surface exposure	1	1	1
Underground exposure	Mining team: 2.15 (1.47 – 3.47)** Driller: 2.25 (1.49 – 3.38)** Stope team: 2.42 (1.52 – 3.86)** Mining helper: 2.56 (1.57 – 4.18)**	Quartile 2: 1.51 (0.78 – 2.91)* Quartile 3: 2.35 (1.28 – 4.32) Quartile 4: 3.22 (1.75 – 5.90)	3.33 (6.66 – 1.15)

*Unless otherwise stated, $p < 0.05$ for all measurements

** $p < 0.01$

[1] The order of underground occupations listed here is not an indication of increasing levels of silica exposure, as the study did not specify this.

[2] Cumulative Dust Exposure for: Quartile 1: $\leq$9 mg/m^3.yr | Quartile 2: 10-13 mg/m^3.yr | Quartile 3: 14 – 17 mg/m^3.yr | Quartile 4: $\geq$18 mg/m^3.yr. RR excluded subjects with radiological or necropsy silicosis.

Sherson (1990) also measured the SIR of TB in relation to silica exposure, but classified this by duration of exposure rather than gravimetric measurements. This study found that in non-silicotic workers, the SIR of TB increased as length of employment increased: from 133 in workers with $\leq$ 14.5 years of employment, to 353 in workers with $\geq$ 25 years of employment.

3.3.2 Studies measuring the association between silicosis and TB risk

Six studies measured the effect of silicosis on risk of TB disease (Table 3), without specifying the degree of silicosis involved, all using different measures of association. In South African gold miners, studies found relative risks between 1.54 and 4.18 (Cowie 1994, Kleinschmidt 1997, Hnizdo 1998). Of the studies that measured rate ratios, the highest was found in the only one that used necropsy in addition to radiology for diagnosis of silicosis, and is therefore a more accurate estimate of association as a lot of silicosis is sub-radiological (Hnizdo 1998). This study also controlled for the effect of cumulative dust exposure in silicotics. Li (2011) found a hazard ratio of 5.82 in end-stage renal patients with silicosis in Taiwan, compared to non-silicotics. The highest relative risk, an OR of 30.25 for TB, was measured in Westerholm's 1986 cohort study of silica-exposed workers.

Table 3: Risk of TB disease in relation to presence of silicosis

Study	Study Design	Study Population	N	Measure of Association	Estimate (95% CI)
Westerholm 1986	Cohort	Mining, tunnelling and quarry workers	1522	Odds ratio	30.25 (no CI)
Sherson 1990	Cohort	Foundry workers	5579	Standardised incidence ratio	1000 (272 - 2561)
Cowie 1994	Cohort	Gold miners	1153	Rate ratio	2.8 (1.9 – 4.1)
Kleinschmidt 1997	Retrospective Cohort	Gold miners	4976	Rate ratio	1.54 (1.00 - 2.37)
Hnizdo 1998	Cohort	Gold miners	2255	Rate ratio	4.18 (2.75 - 6.36)
Li 2011	Cohort	End-stage renal patients, some with silicosis	49 983	Hazard ratio	5.82 (2.17 – 15.6)

Westerholm (1980) also estimated TB risk in relation to silicosis, stratified according to years since diagnosis of silicosis (Table 4). Standardised Incidence Ratios (SIR) relative to the general population rates were then calculated for each of these categories, with the highest SIR being recorded 18 years after diagnosis of silicosis. While it may be reasonably assumed that the severity of silicosis increased with time, these strata cannot be taken to indicate a dose-response relationship as participants entered the study with different grades of silicosis, and this was not controlled for when calculating the risk associated with time since exposure.

Table 4: Risk of TB disease in relation to presence, and years since diagnosis, of silicosis*

Years**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
SIR	0	7.68	4.97	4.23	5.45	6.8	7.57	7.86	7.64	7.48
Years	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
SIR	7.85	9.24	8.4	7.44	3.82	5.32	7.65	17.38	13.65	0

*General population TB rates as reference

**Years since diagnosis of silicosis

3.3.3 Studies measuring the dose-response relationship between silicosis and TB risk

Six studies investigated the association between different grades of silicosis and risk of TB measured using risk ratios (Table 5). Silicosis grade was determined by radiology in five of the studies, (Corbett 1999, Corbett 2000, Chang 2001, Corbett 2003) and necropsy in the sixth (Hnizdo 1998). With the exception of Chang, whose study population was all silicotic patients in Hong Kong, these studies were conducted on South African gold miners.

Cowie (1994) measured incidence rates of TB disease in relation to grade of silicosis, but did not calculate relative risks – although the crude rate ratios have been indicated here without confidence intervals. This study also used the major ILO categories as the grades, while the others classified silicosis slightly differently using the ILO system.

All showed the risk of TB rising as degree of silicosis increased. The only exception was Hnizdo's autopsy study, which found that the RR of TB in moderate/marked silicosis was lower than in slight silicosis after adjusting for cumulative dust exposure, although the confidence intervals overlapped considerably – 2.30 (1.16 – 4.58) and 2.69 (1.35 – 5.37), respectively (Hnizdo 1998).

Table 5: Risk of TB disease in relation to different grades of silicosis

Grade of Silicosis	Cowie 1994[5] (RR)	Hnizdo 1998 (RR)[1]	Corbett 1999[6] (OR)	Corbett 2000 IRR)[2]	Chang 2001 (RR)[3]	Corbett 2003 (RR)[4]
0	1	1	1	1	1	1
1	2.2	1.88 (0.97 - 3.64)	1.6 (0.86 – 2.90)	1.4 (1.0 - 2.2)**	1.80 (1.26 – 2.56)	1.6 (0.91 - 3.0)
2	2.9	2.69 (1.35 - 5.37)	2.8 (1.24 – 6.46)	1.8 (1.0 - 3.0)**		1.9 (0.91 - 3.0)
3	6.3		4.9 (2.32 – 10.58)	2.2 (1.3 - 3.7)**	3.37 (2.19 – 5.17)	2.5 (1.1 - 5.4)
4		2.30 (1.16 - 4.58)		2.5 (1.6 - 4.0)**		4.7 (2.7 - 8.2)

[1]Grading system (autopsy findings): 1 = Negligible (<5 nodules); 2-3 = Slight (6 - 14 nodules); 4 = Moderate/marked (15- 30 nodules)

[2]Grading system: 1 = ILO 0/1; 2 = ILO 1/0; 3 = ILO 1/1; 4 = All higher ILO grades

[3]Grading system: 1-2 = Small opacities exceeding 1.5 mm 3-4 = Progressive Massive Fibrosis; RR (risk ratio) was calculated relative to general population TB risk

[4]Grading system: 1 = ILO 0/1; 2= ILO 1/0; 3 = ILO 1/1 and 1/2; 4 = All higher ILO grades.

[5]Grades based on standard ILO categories 0, 1, 2, 3

[6]Modified ILO grading system (details not specified)

3.3.4 Studies measuring the effect of silica exposure on TB mortality

Six retrospective cohort studies measured the association between exposure to silica (or working in exposed settings) and TB mortality, without specifically investigating a dose-response relationship

between the two (Table 6). In these studies, which were conducted on miners and people working with ceramic and stone industries, mortality was measured for a whole population of silica-exposed individuals. For most of the studies, this was then compared to the expected number of TB deaths based on general population mortality rates in the countries in which the study was set; using this reference, standardized mortality ratios (SMRs) were calculated.

Only three studies provided estimates of respiratory silica-containing dust exposure (Ogawa 2003, Zhang 2008, Chen 2012). There was a wide range in these study populations' average cumulative exposure to dust – ranging from 3.9 mg/m^3.yr to 184.9 mg/m^3.yr. Regardless, in all the studies SMRs were significantly elevated – ranging from 3.29 in lead and zinc miners (Cocco 1994) to 21.75 in granite miners (Vacek 2011). The one study that measured relative risk found that the risk of TB mortality among silica-exposed ceramic factory workers was almost twice that of non-exposed workers in the same factory (Zhang 2008).

Table 6: TB mortality ratios in relation to silica exposure

Study	Study Population	N	Measure of Association	SMR/RR (95% CI)
Cocco 1994	Lead and zinc miners	4740	SMR	329 (233 – 452)
Ogawa 2003	Whetstone cutters[1]	200	SMR	347 (161 - 2236)
Graham 2004	Granite and quarry miners	5408	SMR	1177 (982 - 1399)
Zhang 2008	Ceramic factory workers[2]	4851	RR[4]	1.81 (1.34 - 2.45)
Vacek 2011	Granite miners	7052	SMR	2175 (1837 - 2556)
Chen 2012	Metal miners, pottery workers[3]	74040	SMR	488 (467 - 509)

[1] Average dust concentration > 0.24 mg/m^3.

[2]Average cumulative dust exposure: 184.9 $\pm$ 116.1 mg/m^3.yr.

[3]Average cumulative dust exposure: 3.9 $\pm$ 4.2 mg/m^3.yr.

[4]Risk of mortality in silica-exposed relative to non-exposed in the same cohort.

3.3.5 Studies measuring the dose-response relationship between silica exposure and TB mortality

Six studies stratified silica exposure and measured the association between different degrees of exposure and TB mortality (Table 7). Again, although there was wide inter-study variation in the silica exposure levels and how these were categorised, SMRs for TB consistently increased as silica exposure increased, across different studies and industries (Cocco 1994, Graham 2004, Chen 2012), as did the relative risk of TB mortality in a retrospective cohort of Chinese ceramic workers (Zhang 2008).

Steenland (1995) measured exposure in dust days – each representing one day exposed to 1mppcf of dust (not silica specific) and found that SMRs for TB increased with duration of dust exposure in retrospective cohorts of gold miners. However, the SMRs were below 1, and not statistically significant, except for miners with over 48000 dust days, the highest category of exposure –(SMR = 6.95, $p<0.05$) (Steenland 1995). Case-control studies of mortality registers also revealed that TB deaths had higher odds of having worked in industries with high levels of silica exposure (Chen 1997, Calvert 2003).

Table 7: TB mortality ratios in relation to different categories of silica exposure

Exposure Category	Cocco 1994 (SMR) [1]	Chen 1997 (OR) [2]	Calvert 2003 (OR) [3]	Graham 2004 (SMR) [4]	Zhang 2008 (RR) [5]	Chen 2012 (SMR) [6]
Low			1.47 (1.37- 1.57)		1.50 (1.0 - 2.2)	130 (106 - 160)
Medium	128 (35- 329)	1.07 (0.77 - 1.47)	1.34 (1.23- 1.47)	52 (6 - 108)	1.70 (1.2 - 2.5)	314 (271 - 364)
High		1.3 (1.14 - 1.48)	1.60 (1.45- 1.76)		2.20 (1.60- 3.10)	453 (394 - 520)
Very high	706 (473-1014)		2.48 (1.68- 3.65)	1789 (1503-2131)		

[1] The study compared TB mortality between two mines, one of which had a dust concentration approximately 10 times greater than the other.

[2] Exposure categories assigned by a panel of industrial hygienists based on occupational history – no specific measurements involved.

[3] Exposure was categorised as follows – Low: Little or no silica exposure. Medium: Exposure below permissible limit (0.1 mg/m3). High: Exposure between 1 and 5 times permissible limit. Very-high: exposure over 5 times the permissible limit.

[4] TB mortality rates were compared between miners recruited pre-1940 and post-1940 when mines instituted an 80-90% reduction in dust levels – indicated here as "Very High" and "Medium" respectively.

[5] Cumulative exposure was categorised as follows – Low: 0.1 - 119.99 mg/m^3.yr. Medium: 120 - 219.99 mg/m^3.yr. High: $\geq$220 mg/m^3.yr

[6] Cumulative exposure was categorised as follows: Low: 0.6 $\pm$ 0.3 mg/m^3.yr. Medium: 2.5 $\pm$ 0.9 mg/m^3.yr. High: 8.5 $\pm$ 4.1 mg/m^3.yr

3.3.6 Studies measuring the effect of silicosis on TB mortality

The largest sub-group of studies was of those that measured the effect of silicosis on TB mortality (Table 6). This association was measured largely through cohort studies calculating standard mortality ratios for TB in silicotics, which ranged from 2.17 among silicotic miners, tunnel and quarry workers in Switzerland (Zambon 1987) to 56.35 among all compensated silicotics in California (Goldsmith 1995).

Table 8: Cohort studies measuring standardised mortality ratios for TB in silicotics

Study	Study Population	n	SMR (95% CI)
Zambon 1987	Compensated silicotics working in mines and quarries	1 313	2.17 (2.01 – 2.23)
Carta 1991	Diagnosed silicotics employed in lead, zinc and coal mines	724	11.92 (9.05 - 15.71)
Goldsmith 1995	Compensated silicotics across all industries	590	56.35 (41.10 - 75.40)
Starzynski 1996	Diagnosed silicotics with >20 years	1 796	2.86 (1.77 – 4.37)

	exposure to silica		
Carta 2001	Diagnosed silicotics employed in lead, zinc and coal mines	724	22.0 (17.38 - 27.84)
Scarselli 2011	Retrospective cohort	2 034	5.85 (3.03 - 11.30)

Three studies also measured odds ratios for TB mortality in silicotics, which ranged from 3.0 in a cohort of South African gold miners (Churchyard 2000) to 39.5 in a case-control study of all reported TB deaths in 27 American states between 1982 and 1995 (Calvert 2003). Another case-control study conducted in the US during an overlapping calendar period (1983 – 2002), but which was limited *a priori* to deaths associated with occupational disease or injury, found an odds ratio of 31.8 for silicosis in occupational TB deaths (Chen 1997).

Table 9: Studies measuring odds ratios for TB mortality in silicotics

Study	Study Population	N	OR (95% CI)
Chen 1997	All reported deaths associated with occupational hazards in the US (case-control study)	92078	31.8 (17.4 – 57.9)
Churchyard 2000	South African gold miners (retrospective cohort study)	2 236	3.0 (1.4 - 6.3)
Calvert 2003	All reported deaths in 27 US states (case-control study)	4 309 315	39.5 (16.9 - 92.4)

3.4 Causality

From these findings, it can be concluded that both silica exposure and silicosis meet the criteria for causality laid out by Bradford-Hill (Bradford-Hill 1965), which are widely regarded as a gold standard for assessing causality in epidemiologic studies. These criteria include:

- **Strength and consistency of association**: Despite wide variation in the measures of association, all of the studies reviewed – drawn from over 20 different workplace settings – found increased relative risks of TB disease and TB death associated with both silica exposure and silicosis. Most of the studies reported an association over the order of two, with a rate ratio for TB disease that was up to 3.78 in individuals in the highest quartile of cumulative silica exposure, who did not have silicosis detectable through either radiology or necropsy (Hnizdo 1998), and 4.7 in individuals with advanced silicosis (Corbett 2003). Mortality studies found SMRs of up to 1789 in silica-exposed workers (Graham 2004) and 5635 in silicotics (Goldsmith 1995).

  It is possible that other factors affecting silica-exposed populations could contribute to the increased risk of TB disease, such as malnutrition and living conditions in miners. These and other confounders will be addressed in the discussion. However, even in studies that drew comparison groups from the same setting (Corbett 1999), that matched cases with controls (Westerholm 1986) and/or that adjusted for possible confounders (see discussion), strong associations were still observed.

- **Temporality**: Many of the studies identified cohort participants who were diagnosed with silicosis or exposed to silica dust, and then followed them over time to measure TB incidence and/or TB mortality, so that cause preceded effect.

- **Dose response**: An important aspect of this review has been its demonstration of a dose-response relationship between silica exposure or silicosis grade and risk of TB disease or TB mortality. Once again, despite variation in the specific measures of association, a biological gradient has been firmly established.

- **Plausibility and Coherence**: The general review (Part B) presents several mechanisms through which the effect of silica or silicosis on TB has been explained in biological studies, offering an argument for plausibility as well as establishing coherence between epidemiology and laboratory findings.

4. DISCUSSION

4.1 Heterogeneity in studies

A limitation of this systematic review was the heterogeneity of the studies being reviewed, which precluded meta-analysis. Heterogeneity was particularly marked in the methods used to estimate and classify silica exposure or silicosis, the denominators of standardised mortality ratios, and the different measures of association used especially among the disease risk studies.

4.1.1 Heterogeneity in measurement of respirable dust and respirable silica

In studies measuring a dose-response relationship between TB and silica exposure, conducting accurate measurement of the quantity of respirable silica or respirable dust to which individuals were exposed or validation of such measurements would require a substantial amount of time and resources. Most cohort studies rely on routine measurement of respirable dust or silica. Thus historical records of dust concentration samples in workplaces were the sole data source for the majority of studies (Cocco 1994, Steenland 1995, Chen 2012, Graham 2004, Vacek 2011).

Measurement of the respirable silica content of respirable dust occurred only in two studies (Cocco 1994, Vacek 2011). Others used occupation as a proxy to categorise miners into different levels of dust exposure, based either on expert opinion (Kleinschmidt 1997, Calvert 2003) or estimates based on previous studies which may have taken place long before (Hnizdo 1998). There was thus a great degree of heterogeneity in exposure measurements.

4.1.2 Heterogeneity in classification of silicosis

There was also heterogeneity in the methods used to classify grade of silicosis, as radiology-based silicosis studies used different adaptations of the ILO system (Cowie 1994, Corbett 2000, Corbett 2003, Chang

2001). One study made use of necropsy to diagnose and grade silicosis (Hnizdo 1998), and did not perform detailed ILO grading.

4.1.3 Heterogeneity in underlying TB population incidence or prevalence

Among the mortality studies, only one compared mortality in silica-exposed workers to that in non-exposed workers from the same cohort (Zhang 2008). Most of the other studies used Standardised Mortality Ratios (SMR) to measure associations between silica/silicosis and mortality, adding another layer of heterogeneity, as the studies were conducted in over ten different settings. Since the denominator for calculating SMRs ("expected deaths") is based on general population mortality rates in the setting where the study takes place, inter-study similarity or variation in the SMRs reported in this review would reflect not only the effect of silica/silicosis on TB mortality, but also the variation in TB mortality rates across different populations.

The underlying population rates of TB would be high in studies conducted on South African gold miners, as South Africa has a high burden of TB disease, particularly from the 1990s onwards when this burden was exacerbated by the growth of the HIV epidemic. Participants in the South African studies would therefore be exposed to a large infectious pool and one could expect to see high rates of TB disease and TB mortality in this context.

However, even in settings where you would not expect a high underlying TB incidence or prevalence – for example, studies in the US, the measured silica-TB associations are still very strong. It is likely that these associations may be even stronger, as mathematical analysis of SMR estimates alongside calculations of relative risk of mortality in the same population have shown that SMRs significantly under-estimate risk of mortality, particularly in contexts where the disease of interest is rare (Jones 1998).

4.2 Dose-response relationship between silica dust exposure and TB

Despite the heterogeneity among them, the studies were unanimous in their depiction of an association between silica exposure or silicosis and TB risk or TB mortality. While such an association has long been

recognised, this review is the first, to the author's knowledge, to include a specific focus on the dose-response relationship between silica/silicosis and TB risk or mortality.

A dose-response relationship was clearly demonstrated in both mortality and risk studies, including studies of exposure reduction. For example, in retrospective cohort studies of lead and zinc miners, and granite workers, an approximately 90% reduction in dust concentration corresponded with respective decreases in SMR from 7.06 to 1.28 (Cocco 1994) and 17.89 to 0.52 (Graham 2004) respectively.

In gold miners, the incidence rate ratio of TB in underground workers who are exposed to silica dust, in comparison to surface workers, was increased by a factor of at least 2 (Kleinschmidt 1997, Corbett 2003). Hnizdo (1998) found that relative risk of TB was increased from 1.0 to 3.78 between the lowest and highest quartiles of silica dust exposure, among miners in whom silicosis was not detectable either through radiology or necropsy.

This result demonstrates that despite fewer studies of this relationship, silica dust exposure increases TB risk even when silicosis is not radiologically detectable, as suggested by an earlier autopsy prevalence study (Sluis-Cremer 1980) and cross-sectional study (teWater Naude 2006). When silicosis was controlled for in Hnizdo's study, the effect of cumulative silica dust exposure was still significant, with relative risk of TB increasing from 1.0 to 3.22 in the lowest and highest quartiles respectively – or, up to 13.4 if the miner had silicosis and was also in the highest quartile of silica dust exposure (Hnizdo 1998) – a multiplicative interaction between cumulative dust exposure and silicosis.

4.3 Dose-response relationship between silicosis and TB

Hnizdo's landmark autopsy study showed that silicosis even of negligible or slight pathological grade, after controlling for different quartiles of cumulative dust exposure, was associated with an increased relative risk for TB (Hnizdo 1998).

Although Kleinschmidt (1997) also adjusted for silicosis as a confounder, Hnizdo's was the only study that clearly partitioned the total silica effect into that due to silicosis and that due to silica dust in the

absence of silicosis, by formally controlling for silicosis when measuring the effect of cumulative silica dust exposure and vice versa.

Studies further showed that the strength of the silicosis-TB association is related to the severity of radiological silicosis. Again, even a mild grade of silicosis was associated with a relative risk for TB - 1.80 in Hong Kong clinic attendees and 1.86 in South African gold miners. In the same cohorts, RRs of 3.37 (Chang 2001) and 2.71 (Hnizdo 1998) were associated with advanced silicosis.

There were no mortality studies that measured a dose-response relationship with silicosis grade, but an association between silicosis and TB mortality was clearly shown, with the lowest TB SMR in silicotics standing at 2.17 in a retrospective cohort of Italian miners and quarry workers (Zambon 1987), and reaching as high as 56.35 in a retrospective cohort of Californian silicotics (Goldsmith 1995). Both of these studies were based on cases of silicosis as recorded in compensation registers several decades before the study was conducted, with mortality follow-up stretching into the decade in which the study took place.

4.4 Effect of previous TB on future risk of TB

One study on silicotics in Hong Kong found that those with a history of TB treatment had a lower relative risk of TB after silicosis diagnosis than those without such a history, which the authors believed to be due to anti-TB treatment offering protection against the subsequent endogenous reactivation of TB (Chang 2001).

Similarly, Corbett (2000) found that a history of previous tuberculosis in South African miners was slightly protective if it had happened in the past five years (RR = 0.9, $p<0.001$). However, if the TB had occurred more than five years before, the RR for recurrence increased to 5.9 – possibly demonstrating the time-bound benefit of previous TB treatment as a chemoprophylactic measure against TB disease. In a later paper also published by Corbett (2003) which combined data from her 2000 paper and two other cohort studies, previous TB was associated with an increased risk ratio of 2.2 in South African gold

miners ($p<0.001$). These estimates of relative risk did not specifically examine silicotics, where effect modification would be observed.

The problem of distinguishing between reactivation and reinfection makes it difficult to interpret the findings of studies of TB relapse in silicotics (Escreet 1984). Any persistent risk of TB disease in silicotic or silica-exposed individuals could be a result of either reactivation or reinfection in the context of impaired immunological defences. Distinct from the risk reactivation is the thus the fact that silica exposure leads to macrophage death (Hamilton 2008) and/or impairs the function of macrophage populations (Pasula 2009), making the individual more susceptible to disease if newly infected with TB.

4.5 **Limitations of study designs**

4.5.1 Adjusting for confounders

Most of the studies used a retrospective cohort design. This design has the major advantage of convenience, as the cohort is drawn from pre-existing data in which exposure, and sometimes outcome, has already been recorded. However, it also has limitations, since researchers rely on variables that were captured in historical records, multivariate analysis is limited because covariates of interest may not have been measured at the time. Smoking, for example, increases the risk of TB (Yen 2014), but historical registers – particularly if they are not medical records – are not likely to record individual smoking habits. However, the studies that were able to adjust for smoking (Hnizdo 1998, Chang 2001) still found strong dose-response associations between silica/silicosis and TB.

Living conditions could also affect the silica/silicosis-TB association, particularly the risk of TB disease, as cramped conditions are conducive to the rapid spread of TB. In studies where all participants were drawn from one workplace, this confounder is less of a concern as both groups are likely to have similar living conditions. However, as many of the studies drew from multiple workplaces, variations in living conditions (which in most of the studies were not described) could confound the measured silica/silicosis – TB association. Additionally, in studies where the general population is used as the reference group,

crowded living and working conditions would also increase the background TB risk of the exposed population.

This failure to adjust for confounders remains a limitation of the findings presented here. Among the mortality studies, this was to be expected as the majority of them measured SMRs, which do not generally include adjustment for confounders. One case-control study which estimated the OR for TB mortality in silicotics, as registered in a US occupational mortality surveillance database (Chen 1997), adjusted for the presence of other pneumoconiosis, age, gender, race, socio-economic status and potential exposure to active TB. A cohort study of South African gold miners, which also measured the OR for TB mortality in silicotics, adjusted for HIV status, method of TB detection, sputum status, age, treatment category and extent of disease (Churchyard 2000).

Among studies measuring the risk of TB disease, there was a greater degree of adjustment for confounders. Chang (2001) adjusted for age, sex, smoking, cigarette pack-years, co-morbidities with TB effect, duration of dust exposure, radiographic features, and history of TB treatment in a retrospective cohort of silicotic patients in Hong Kong. In a case-control study of South African gold miners, which estimated the odds ratio for TB disease in miners with silicosis, Corbett (1999) was able to adjust for HIV status, premorbid radiological scarring, age group, employment duration, dust level of occupation at diagnosis, and calendar month of presentation. In a later study, Corbett (2003) also measured the rate ratio for TB in silica-exposed and silicotic gold miners, adjusting for age, employment duration and calendar period.

4.5.1.1 Silicosis as a confounder of silica-TB associations

Two of the three studies measuring the dose-response relationship between silica-containing dust exposure and risk of TB disease adjusted for silicosis. Kleinschmidt (1997), when estimating the rate ratio of TB disease in South African gold miners exposed to silica-containing dust, adjusted for age, period, cumulative service, occupation and silicosis status.

However, this study was limited to radiologically detectable silicosis, which another autopsy study found would miss over half the cases of silicosis (Hnizdo 1998). Hnizdo's is a particularly important study in that it controlled for silicosis diagnosed at necropsy, as well as age and smoking, and the results showed a significant confounding effect of silicosis on the silica-TB relationship, and vice versa. Other studies on the relationship between silica-containing dust and TB risk that do not control for silicosis would therefore remain confounded.

4.5.2 Bias

4.5.2.1 Misclassification of silicosis

Misclassification of silicosis could be non-differential or differential with respect to TB. The effect of non-differential misclassification would be to weaken the observed association between silicosis and TB where the misclassified silicotics were included in the non-silicotic comparison group, as in cohort studies.

The most common source of such misclassification would be sub-radiological silicosis. This is a limitation of almost all the studies. In the one autopsy study, only 34% of the subjects found to have silicosis at necropsy had been diagnosed radiologically during their lifetime (Hnizdo 1998).

Differential misclassification could occur in interpreting the radiological signs of silicosis in populations with high incidence of pulmonary TB. For example, silicosis could be under-detected in the presence of TB, leading to a weakening of the observed silicosis-TB association.

The frequency of silicosis is also likely to have been under-estimated in studies whose cohorts were drawn from compensation registers (Zambon 1987, Goldsmith 1995, Chen 1997, Scarselli 2011). Various factors such as access to bureaucratic channels, availability of resources to pursue the necessary legal processes, and death in the sickest individuals, could prevent silicotics from receiving compensation and thus being recorded in the register. If any of these factors were related to TB risk, differential misclassification might arise.

4.5.2.2 Misclassification of silica dust exposure

The estimation of silica exposure was also open to misclassification, as most of the studies – with the exception of two retrospective cohort studies on TB mortality (Cocco 1994, Vacek 2011) did not measure the levels of respirable silica within the respirable dust. Given that the silica fraction in respirable dust changes over time within the same mine, one would therefore be measuring associations in populations with varying levels of silica exposure even within the same cohort, and classification of dust exposure may not necessarily align with classification of silica exposure. Such misclassification is likely to be non-differential with respect to TB. In addition to posing a limitation to the findings of individual studies, this bias also limits comparison between studies..

4.5.2.3 Selection bias and age effects

Some of the studies were also vulnerable to selection bias. It is likely that sicker workers would have left service or died before the study was conducted, so cohort selection would be biased towards healthier individuals (Kleinschmidt 1997), which could result in under-estimation of TB. For incidence studies, the silica-TB association could be under-estimated in workers who were still alive when the follow-up period ended, as the increased risk of TB in silicotics is life-long, possibly due to encapsulation of TB bacilli in silicotuberculotic nodules, posing an enduring risk of future activation (Hnizdo 1998).

In a case-control study of deceased silica-exposed workers across the US, odds ratios for TB mortality showed similar age curves in silicotic and non-silicotic workers, although the age range in which maximum TB mortality was observed was lower in the workers who had the highest potential silica exposures (Chen 1997). This suggests that, as Kleinschmidt (1997) noted, selection bias in favour of survivors may act against detection of a silica/silicosis-TB association of TB in old age. TB incidence is also higher at older ages (Corbett 2003), which could be due to older individuals having a greater exposure to TB over time (Kleinschmidt 1997).

This could in turn be the result of latent TB acquired in the period before chemotherapy became widely available and thus reduced the size of the infectious pool in the general population. This modifying effect

of age is likely to be observed in retrospective cohort studies whose populations include people born in the first half of the 20th century. In Steenland's cohort study of American gold miners, when the population was stratified by year of hire (pre-1930, 1930-1950 and post 1950), the SMR for TB fell from 11 to 1 to 0, respectively (Steenland 1995).

Steenland also stratified this population by cumulative days of dust exposure, and found an SMR of 6.95 ($p<0.05$) in those with 48,000 dust-days, compared to 0.52 in those with less than 8,000 dust-days. When measuring the silicosis-TB association in the absence of dust measurements, interpreting the confounding effect of age is made difficult by the fact that older age may be associated with greater cumulative dust exposure (Cowie 1994), greater latency (Finkelstein 2000), and possibly a greater prevalence of sub-radiological silicosis (Kleinschmidt 1997).

4.6 Implications for future health programming

While such limitations may have weakened the findings of the studies included in this systematic review, the most likely effect would have been to underestimate the strength of the association between silica exposure or silicosis, and TB risk or mortality.

4.6.1 Public health implications

This association between silica/silicosis and TB has implications not only for the health of silica-exposed workers, but also their close occupational and domestic contacts, as TB is an airborne disease. One cohort study of Chinese miners and pottery workers showed that non silica-exposed workers also had elevated SMRs for TB, although less so than silica-exposed workers in the same cohort (Chen 2012). Although the elevated SMR in non-exposed workers could also be due to other environmental workplace factors that are conducive to TB, such as crowded working and living conditions, the increased risk of TB infection by virtue of proximity to the infectious pool in the silica-exposed sub-population is a plausible route of effect.

The review provides evidence against the view, in the Southern African context, that gold mining only appears to have an increased risk of TB because of more intensive surveillance of a population with very high background risk from rural areas in which TB was poorly ascertained (Martiny 1978). It is clear from this review that regardless of background TB risk, exposure to silica dust increases the risk of TB disease and TB death. It also indirectly increases background risk by contributing to the infectious pool in labour-sending areas, where occupational disease is indeed very poorly monitored. In sub-Saharan Africa where TB is considered a public health emergency, silica dust control should therefore be regarded not only as an occupational health imperative, but as a public health priority.

4.6.2 Silica dust reduction

The author believes that this review is timeous in that it focuses attention on silica dust exposure not only as the cause of silicosis but also as a risk factor for TB. Given the historical uncertainty about whether silica dust in and of itself, in the absence of radiological silicosis, has an effect on TB risk (Balmes 1990), the balance of evidence presented in this review supports such an association.

The findings thus reiterate the need for evidence-based dust reduction targets. An occupational exposure limit (OEL) of 0.1 mg/m^3, as currently applied in South Africa, is widely believed not to be protective against silicosis (Hnizdo 1993, tMannetje 2002, Churchyard 2004, TeWaterNaude 2006, Chen 2012).

Even if an OEL of 0.1 mg/m^3 were protective against silicosis, it is not likely to be protective against TB. Since the literature shows that TB risk is elevated by silica dust exposure even in the absence of radiological silicosis, and that the impairment of macrophage function begins immediately upon exposure to silica dust (Pasula 2009), a more ambitious dust reduction target would be appropriate.

The US Occupational Health and Safety Administration (OSHA) is considering lowering its permissible exposure limit (PEL) for silica from 0.1mg/m^3 to 0.05 mg/m^3, due to its recognition that the current regulation does not adequately protect workers' health, while other expert bodies such as the US National Institute for Occupational Safety and Health (NIOSH) recommend an even lower exposure limit of 0.025 mg/m3 (OSHA 2013). While this proposed PEL revision is based largely on protection against cancer,

for which silicosis is also a risk factor, OSHA has recognised and called for comments on "the magnitude of non-quantified health benefits arising from the proposed rule and methods for better measuring these" – citing TB prevention as a specific example (OSHA 2013). The studies presented in this review shed some light on the quantifiable benefits for TB prevention associated with reductions in silica exposure, which may be of use to such policy formulation processes.

4.6.3 Improving exposure measurements

Alongside dust control programmes, research in this area would be strengthened by ensuring regular quality controlled measurements of both respirable dust and silica levels in workplaces and recording of these in a publicly accessible database,

Besides the value for regulatory purposes, dust measurements needs to be combined with the recording of occupational histories, (as currently done by TEBA for South Africa's mining sector), to enable an integrated metric of individual exposure

Cohort studies are also urgently needed of black miners and particularly ex-miners, drawing on such exposures and combined with enhanced surveillance, both radiological and autopsy-based.

The availability of such data would enable more studies like that of Hnizdo (1998), which can measure the effect of both silicosis and silica dust exposure in the same population, controlling for each so as to understand the combined and independent effects of these covariates on risk of TB disease and TB death.

4.6.4 Silica, TB and HIV

These relationships especially need clear exposition in the context of the triple epidemic of HIV, TB and silicosis in Southern Africa, which has a long history of migrant labour in the mining sector fuelling the spread of disease across the region (Stuckler 2010). In discussions about TB and TB control in mining in Southern Africa, there is a tendency for the dust or silicosis factor to be overshadowed by the TB-HIV association, which is the focal point of the broader public health response. This review illustrates that

efforts to address TB control in mining populations will be significantly sub-optimal if they do not address the relationships between TB and silica dust exposure or silicosis as a strategic priority.

4.6.5 Chemoprophylaxis of TB in silica-exposed populations

Chemoprophylaxis against TB in the form of Isoniazid Preventive Therapy (IPT) is recommended for HIV positive populations – in which its efficacy has been demonstrated by multiple studies (Churchyard 2007). It is also recommended, by Work and Health Southern Africa (WAHSA) for silicotic populations (WAHSA 2007), but limited evidence suggests that it may not be as effective in this context as in HIV infected cohorts. IPT therapy in silicotics has been associated with poor uptake (Leung 2003) and with mixed results regarding effectiveness (HK Chest Service 1992, Cowie 1996). The largest clinical study on IPT to date, which was conducted in South African gold miners without reference to silicosis, found that although a lower incidence of TB was observed during an IPT treatment course, this protective effect did not persist 12 months after IPT ended. The authors concluded that an IPT programme does not effectively reduce TB disease or TB death in gold miners (Churchyard 2014) – which once again highlights the need for a focus on dust reduction as a key underlying factor driving the high rates of TB in miners.

4.6.6 Strengthening follow-up systems in labour-sending areas

Strengthening follow-up systems for silica-exposed workers when they have left the workforce would improve monitoring of silicosis, TB and the silica-TB association, as the majority of such workers are probably diagnosed with TB after the end of silica exposure (Hnizdo 1998). This would be beneficial for the development of evidence-based policies and programmes, and would also increase workers' likelihood of accessing compensation where indicated, which in turn could constitute a financial incentive for accelerating dust reduction efforts.

5. CONCLUSION

This systematic review confirms the powerful association, and dose-response relationship, between silicosis and the risk of TB disease or TB mortality. The studies further show that although silicosis acts as a confounder in the effect of silica dust on TB, even in the absence of or adjustment for radiological silicosis, silica-containing dust is in itself an independent risk factor for TB. .

Lack of adjustment for confounders is a common limitation of these studies, most of which are based on historical records of retrospective cohorts and therefore not able to control for covariates. However, given that studies which were able to adjust for a wide variety of covariates including age, HIV status and occupational and medical history (Corbett 1999) also found a strong association and dose-response relationship between silicosis and TB; the limitation posed by inadequate adjustment in other studies cannot be seen to negate the findings of this review.

Another common limitation in the studies was the risk of misclassification – both of silicosis, as almost all of the studies relied on radiology instead of necropsy and are therefore likely to have missed over half of the cases; and of silica exposure, as most of the studies measured respirable dust but did not calculate the specific fraction of respirable silica within this dust. Selection bias via the healthy worker effect is also likely. However, these limitations are likely to have under-estimated the strength of the association.

It is clear from this review that silica-producing occupations such as gold mining confer major TB risks. It is also clear that improved dust control is a critical measure needed to address the epidemic of TB in silica-exposed populations, particularly in countries like South Africa where the effect of silicosis combines multiplicatively with HIV to increase risk of TB disease, and broader methods of TB prevention such as IPT chemoprophylaxis have limited effectiveness in silicotic populations.

This review further emphasises the need for silica dust reduction efforts to be evidence-based. The literature suggests that current exposure limits for silica are not protective against silicosis; and furthermore that even low levels of exposure to silica, in the absence of silicosis, might confer an increased risk of TB disease. Reduction of respirable silica dust exposure to less than 0.05 mg/m^3 would thus both prevent silicosis and reduce the burden of TB in exposed populations.

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ANNEXES

CONTENTS

ANNEX A: SILICA DUST EXPOSURE AND RISK OF TB DISEASE

Study	Design	Calendar Period	Study Population	n	Exposure measurement	TB measurement	Measure of Association	Exposure Category	Estimate (95% CI)
Chen 1997	Case-control study	1983 – 1992	All deaths reported to the National Occupational Mortality Surveillance database during study period	8 740 cases, 83 338 controls	Occupations classified by potential for silica exposure as determined by panel of expert industrial hygienists	ICD codes from death certificates (pulmonary TB)	OR for TB mortality	None	1
								Intermediate	1.07 (0.77 – 1.47)
								High	1.30 (1.14 – 4.18)
Kleinschmidt 1997	Retrospective cohort analysis	1975 - 1996 (55 822 person-years)	Gold miners active during the study period (SA)	4 976	Occupation used as proxy to group into categories of exposure; only respirable dust estimated	Radiology; sputum microscopy and/or cultures; clinical; all TB	Incidence rate ratio for TB; adjusted for age, period, cumulative service, occupation and silicosis	Low (not underground)	1
								Driller	2.25 (1.49 -3.38)
								Mining helper	2.56 (1.57 -4.18)
								Mining team	2.15 (1.47 -3.14)
								Stop team	2.42 (1.52 -3.86)
								Winch operator	1.54 (1.00 -2.35)

Hnizdo 1998	Prospective cohort analysis	1968 - 1995 (39 319 person-years)	Gold miners aged 45 - 55 years, without radiological or necropsy silicosis (SA)	1 388	Occupation-specific estimates derived from a previous study (Beadle 1970); only respirable dust estimated	Radiology and necropsy; only pulmonary TB	Relative risk of TB; adjusted for age and smoking	Quartile 1 (Lowest quartile) of respirable dust exposure	1
								Quartile 2	1.59 (0.62 – 4.08)
								Quartile 3	2.39 (0.97 – 5.89)
								Quartile 4	3.78 (1.57 – 9.42)
			Gold miners aged 45 - 55 years, adjusted for radiology or necropsy silicosis (SA)	2 255			Relative risk of TB controlled for age, smoking and necropsy silicosis	Quartile 1	1
								Quartile 2	1.51 (0.78 – 2.91)
								Quartile 3	2.35 (1.28 – 4.32)
								Quartile 4	3.22 (1.75 – 5.90)
Corbett 2003	Cohort study	1991 – 1999	Gold miners (SA)	6 454	No gravimetric measurement – exposure grouped into work type (surface vs underground)	Radiology and bacteriology (sputum microscopy and/or cultures); all TB	Rate ratio for TB (adjusted for age, employment duration, calendar period)	Underground worker (compared to surface)	3.33 (6.66 – 1.15)

ANNEX B: SILICOSIS AND RISK OF TB DISEASE

Table 1: Studies measuring association between silicosis and risk of TB disease

Study	Study Design	Calendar Period	Study Population	N	Silicosis measurement	TB measurement	Measure of Association	95% CI
Westerholm 1980	Cohort study	1951 – 1969	Mining, quarrying, tunnelling, steel, iron, ceramics	4 584	Records from Swedish Pneumoconiosis register	Sputum culture for pulmonary TB	Standardised incidence ratio (age-standardised and matched for occupation and latency)	6 -7 (crude estimate reported by authors, no CI)
Westerholm 1986	Cohort study	1959 – 1977	Mining, tunnelling, quarrying, iron and steel workers	1 522	Records from Swedish silicosis register	Records from Swedish tuberculosis register; only pulmonary TB	Odds ratio (unadjusted)	30.25
Sherson 1990	Cohort study	1967 - 1986	Foundry workers (silicotic and non-silicotic) (Denmark)	5 579	Records from Foundry Worker Registry of the Danish Labor	Records from Danish Tuberculosis Registry; only pulmonary	Standardised incidence ratio (age-standardised)	100 (272 - 2561)

					Inspectorate	TB		
Cowie 1994	Cohort study	1984 – 1991	Gold miners without prior history of TB (SA)	1 153	Radiographic silicosis using ILO guidelines (positive if ≥1/0)	Positive culture, TST and/or chest radiography; only pulmonary TB	Incidence rate ratio; unadjusted	2.8 (1.9 – 4.1)
Kleinschmidt 1997	Retrospective Cohort Analysis	1975 - 1996 (55 822 person-years)	Gold miners active during the study period (SA)	4 976	Radiology based on ILO grading (positive if ≥ 1/1)	Radiology, Bacteriology (sputum microscopy and/or cultures) and clinical; all TB	Incidence rate ratio for TB; adjusted for age, period, cumulative service, occupation and silicosis	1.54 (1.00 - 2.37)^
Hnizdo 1998	Cohort study	1968 - 1995 (39 319 person-years)	Gold miners aged 45 - 55 (SA)	2 255	Radiology based on ILO grading (positive if ≥ 1/1), necropsy	Radiology and necropsy; only pulmonary TB	Rate ratio for TB; adjusted for age and smoking	4.18 (2.75 - 6.36)
Li 2011	Cohort study	1998 – 2004 (186 793	End-stage renal patients (Taiwan)	49 983	Hospital records	At least 3 hospital visits	Hazard ratio for TB	5.82

		person-years)				for TB and insurance claims for anti-TB drugs; all TB	(unadjusted)	(2.17 – 15.6)

ILO: International Labour Organisation. TST: Tuberculin skin test (tests for an antibody reaction to TB antigen in order to confirm prior TB infection).

Table 2: Studies measuring the association and dose-response relationship between silicosis and risk of TB disease

Study	Study Design	Calendar Period	Study Population	n	Silicosis measurement	TB measurement	Silicosis Grade	Measure of Association	(Estimate) 95% CI
Cowie 1994	Cohort Study	1984 – 1991	Gold miners without prior history of TB (SA)	1 153	Radiography silicosis using ILO* guidelines (positive if ≥1)	Positive sputum culture, TST^ and chest radiography; only pulmonary TB	ILO Grade 1	Incidence rate of TB (% per annum); unadjusted	2.2 (0.8 – 3.6)
							Grade 2		2.9 (1.1 – 4.6)
							Grade 3		6.3 (0.0 – 13.4)
Hnizdo 1998	Cohort study	1968 - 1995 (39 319 person-years)	Sub-population: Gold miners aged 45 - 55 years who died and had necropsy to detect and grade silicosis (SA)	1 296	Necropsy	Radiology and necropsy; only pulmonary TB	None	Relative risk (RR) of TB; adjusted for age, smoking and cumulative dust exposure	1
							Negligible (≤5 nodules)		1.88 (0.97 - 3.64)
							Slight (6 - 14 nodules)		2.69 (1.35 - 5.37)
							Moderate/marked (15- 30 nodules)		2.3 (1.16 - 4.58)
Corbett 1999	Case-control study	1993 – 1996	Gold miners (SA)	561	Radiography based on modified ILO classification	Sputum microscopy and sputum culture (pulmonary TB)	None	Odds ratio for TB; adjusted for HIV status, premorbid radiological scarring, age	1
							Possible		1.6 (0.86 – 2.90)
							Probable		2.8 (1.24 – 6.46)
							Early/high-grade		4.9 (2.32 –

								group, employment duration, dust level of occupation at diagnosis, and calendar month of presentation)	10.58)
Corbett 2000	Retrospective cohort study	1991 - 1996	Gold miners testing for HIV during study period (SA)	4 022	Radiography based on ILO classification (positive if ≥ 0/1)	Sputum microscopy and sputum culture; all TB	None	Incidence rate ratio for TB; unadjusted	1
							Possible (ILO 0/1)~		1.4 (1.0 - 2.2)
							Probable (ILO 1/0)		1.8 (1.0 - 3.0)
							Early (ILO 1/1)		2.2 (1.3 - 3.7)
							Advanced (all higher ILO grades)		2.5 (1.6 - 4.0)
Chang 2001	Retrospective cohort analysis	1988 - 1993	Silicotic patients (Hong Kong)	702	Radiography based on ILO classification	Sputum microscopy and/or culture, with compatible clinical history and radiology;	Small opacity exceeding 1. 5mm	Risk ratio compared to general population; adjusted for age, sex,	1.80 (1.26 - 2.56)
							Progressive massive fibrosis		3.37 (2.19 - 5.17)

						all TB		smoking, cigarette pack-years, co-morbidities with TB effect, duration of dust exposure, radiographic features, and history of TB treatment)	
Corbett 2003	Cohort study	1991 - 1999	Gold miners (SA)	6 454	Radiography based on ILO classifications	Clinical, radiology and either: positive sputum smear, positive sputum culture or positive response to TB treatment; all TB	None	Incidence rate ratio for TB; unadjusted – silicosis was not included in the multivariate analysis as some grades were not available)	1
							Possible (ILO 0/1)		1.6 (0.91 - 3.0)
							Probable (ILO 1/0)		1.9 (0.91 - 3.0)
							Early (ILO 1/1 and 1/2)		2.5 (1.1 - 5.4)
							Moderate-Advanced (ILO 2/1 - 3/3)		4.7 (2.7 - 8.2)

ILO: International Labour Organisation. TST: Tuberculin Skin Test.

ANNEX C: SILICA EXPOSURE AND TB MORTALITY

Table 1: Studies measuring the association between silica exposure and TB mortality

Study	Study Design	Calendar Period	Study Population	n	Exposure measurement	TB measurement	Measure of Association	Exposure Category	(Estimate) 95% CI
Cocco 1994	Retrospective cohort study	1960 - 1988 (119 390.5 person-years)	Workers employed in lead and zinc mines between 1932- 1971 minimum 12 months (Italy)	4 740	Routine gravimetric measurements of respirable silica concentration	ICD codes from death certificates	SMR	All workers	329 (233 - 452)
Steenland 1995	Retrospective cohort study	1940 – 1990 (106 000 person-years)	Gold miners working underground between 1940 and 1965	3 328	Gravimetric measurements of total dust concentration (not silica-specific) – estimated at 0.1mg/m^3	Records from Social Security and National Death Index	SMR	All workers exposed to dust for at least 12 months	352 (247 – 487)
Ogawa 2003	Retrospective cohort study	1955 - 1995	Whetsone cutters (Kyoto, Japan)	200	No gravimetric measurements : calculating backwards	WHO codes from death certificate	SMR	All exposed (concentrations in excess of 0.24 mg/m3)	347 (161 - 2236)

					based on silicosis prevalence and dose-response relationship				
Graham 2004	Retrospective cohort study	1950 – 1996	Workers employed in granite sheds and quarries between 1950 and 1982, but hired at any point (Vermont, USA)	5 408	Assumption that quarries complied with with the PEL (0.1mg/m^3 of respirable silica)	ICD codes from death certificates	SMR	All periods of exposure	11.77 (9.82 - 13.99)
Zhang 2008	Retrospective cohort study	1972 - 2003 (128 970 person-years)	Workers employed in ceramic factories between 1972 and 1974 (Jingdezhen, China)	4 851	Routine gravimetric measurements of respirable silica	China Ministry of Health cause-of-death codes from employment registers, and personal and medical records	Risk ratio (compared to controls in cohort)	All silica-exposed (Average cumulative respirable dust exposure was 184.9 $\pm$ 116.1 mg/m3.yr, with a 28-30% respirable silica content	1.81 (1.34 - 2.45)

Vacek 2011	Retrospective cohort study	1947 - 2004 (269 253 person-years)	Workers employed in granite mines 1947- 1998 (Vermont, USA)	7 052	Gravimetric measurements of respirable silica in different occupations used to develop job-exposure matrix	ICD codes from the US National Death Index, Social Security Administration and State Records	SMR	All silica-exposed	21.75 (18.37 - 25.56)
Chen 2012	Retrospective cohort study	1960 - 2003 (2 306 428 person-years)	Workers employed in metal mines or pottery factories for at least 1 year 1960-1974 (Central and Southern China)	74 040	Routine gravimetric measurements of respirable dust in different occupations	Medical records, employment registers, death certificates Sand oral reports from family.	SMR	All silica-exposed between 1970 and 2003 (average cumulative dust exposure - 3.9 $\pm$ 4.2 mg/m3.yr)	4.88 (4.67 - 5.09)

ICD: International Classification of Diseases. SMR: Standardised Mortality Ratio. PEL: Permissible Exposure Limit.

Table 2: Studies measuring the dose-response relationship between silica exposure and TB mortality

Study	Study Design	Calendar Period of Study	Study Population	n	Exposure measurement	Outcome measurement	Measure of Association	Exposure Category	(Estimate) 95% CI
Cocco 1994	Retrospective cohort study	1960 - 1988 (119 390.5 person-years)	Workers employed in lead and zinc mines between 1932 and 1971 for a minimum of 12 months (Sardinia, Italy)	4 740	Routine gravimetric measurements of respirable silica	ICD death codes from death certificates	SMR	Surface workers	98 (27 - 252)
								Underground workers	460 (317 - 646)
								Mine A Underground workers	128 (35 - 329)
								Mine B underground workers (approx. 10-fold higher dust concentration)	706 (473 - 1014)
Steenland 1995	Retrospective cohort study	1940 – 1990 (106000 person-years)	Gold miners working underground between 1940 and 1965 for a minimum of 12 months (South Dakota, US)	3 328	Gravimetric measurements of total dust concentration (not silica-specific) estimated at 0.1mg/m^3;	Records from Social Security and National Death Index	SMR	<8000 dust days	0.52
								8000 – 32000 dust days	0.78
								32000 – 48000 dust days	0.89
								>48000 days	6.95
								High	1.3 (1.14 - 1.48)

					dust days calculated per worker, each indicating one day of exposure at this concentration				
Calvert 2003	Case-control study	1982 - 1995	All deaths from twenty-seven states during study period (US)	4 309 315	Occupations grouped into respirable silica categories by a panel of industrial hygienists with experience assessing silica exposure	ICD codes from death certificates	Odds ratio for TB mortality	Low/No (occupations involving tasks with little or no potential for silica exposure)	1.47 (1.37 - 1.57)
								Medium (occupations involving tasks with exposures below the OSHA PEL	1.34 (1.23 - 1.47)
								High (occupations involving tasks with exposure between 1 and 5	1.60 (1.45 - 1.76)

								times the OSHA PEL)	
								Super-high (occupations involving tasks with exposure > 5x the OSHA PEL)	2.48 (1.68 - 3.65)
Graham 2004	Retrospective cohort study	1950 – 1996	Workers employed in granite sheds and quarries between 1950 and 1982, but hired at any point (Vermont, USA)	5408	Assumption that quarries complied with pre- and post-1940 PELs	ICD codes from death certificates	SMR	Workers hired pre-1940	1789 (1503 - 2131)
								Workers hired post-1940 (approx 80-90% reduction in dust levels)	52 (6 - 108)
Zhang 2008	Retrospective cohort study	1972 - 2003 (128 970 person-years)	Workers employed in ceramic factories 1972-1974 (Jingdezhen, China)	4851	Routine gravimetric measurements of respirable dust in different occupations	Ministry of Health cause-of-death codes from employment registers, personal and medical records	RR of mortality (comparison to non silica-exposed in cohort)	Low (0.1 - 119.99 mg/m3.yr)	1.5 (1.0 - 2.2)
								Medium (120 - 219.99 mg/m^3.yr	1.7 (1.2 - 2.5)
								High (≥220 mg/m3.yr)	2.2 (1.6 - 3.1)

Chen 2012	Retrospective cohort study	1960 - 2003 (2 306 428 person-years)	Workers employed in metal mines or pottery factories for at least 1 year between 1960 and 1974 (Central and Southern China)	74 040	Gravimetric measurements of respirable silica in different occupations	Medical records, employment registers, death certificates and oral reports from family	SMR	Low (0.6 ± 0.3 mg/m3.yr)	1.30 (1.06 - 1.60)
								Medium (2.5 ± 0.9 mg/m3.yr)	3.14 (2.71 - 3.64)
								High (8.5 ± 4.1 mg/m3.yr)	4.53 (3.94 - 5.20)

ICD: International Classification of Disease. OSHA: Occupational Safety and Health Authority. PEL: Permissible Exposure Limit. SMR: Standardised Mortality Ratio. RR: Risk Ratio.

ANNEX D: STUDIES MEASURING THE ASSOCIATION BETWEEN SILICOSIS AND TB MORTALITY

Study	Study Design	Period of study - or follow up for cohort studies	Study Population	n	Silicosis measurement	Outcome measurement	Measure of Association	95% CI
Zambon 1987	Retrospective cohort study	1959 - 1984 (23 494 person years)	Workers in mines, tunnels and quarries who were compensated for silicosis between 1959 and 1963 (Italy)	1 313	Compensation register, confirmed by autopsy in 66% of participants	ICD codes from death certificates	SMR	217 (201 - 223)
Carta 1991	Cohort study	1964 - 1987 (10 956.5 person-years)	Silicotics, mainly employed in lead, zinc and coal mines, and granite quarries, who were first diagnosed between 1964 and 1970 and admitted to hospital for this (Italy)	724	Radiology using ILO classification	ICD codes from death certificates, verified by insurance company records	SMR	1 192 (905 – 1 571)
Goldsmith 1995	Retrospective cohort study	1946 - 1991	Silicotics who received compensation between 1945 and 1975 (USA)	590	Records from California Workers Claims Registry	Records from California Workers Claims Registry	SMR	5 635 (4 110 – 7 540)

Starzynski 1996	Retrospective cohort study	1970 - 1985 (person-years not specified)	Pneumoconiosis patients with 20+ years exposure to silica dust (Poland)	1 796	Radiology using ILO classification	ICD codes from death certificates	SMR	286 (177 - 437)
Chen 1997	Case-control study	1983 – 1992	All deaths reported to the National Occupational Mortality Surveillance database during study period	8 740 cases, 83 338 controls	Records from Occupational Mortality Surveillance database	ICD codes from death certificates (pulmonary TB)	OR for TB mortality	1.30 (1.14 – 1.48)
Carta 2001	Cohort study	1964 - 1997 (13 202 person-years)	Silicotics, mainly employed in lead, zinc and coal mines, and granite quarries, who were first diagnosed between 1964 and 1970 (Italy)	724	Radiology using ILO classification	ICD codes from death certificates	SMR	22.0 (17.38 - 27.84)
Churchyard 2000	Retrospective cohort study	1993 - 1997 (person-years not specified)	Workers employed in gold mines between 1993 and 1997 who were diagnosed with TB (South Africa)	2 236	Radiology using ILO classification	Bacteriology (sputum microscopy and cultures), radiology	OR for TB death in silicotics adjusted for HIV status, method of detection,	3.0 (1.4 - 6.3)

							sputum status, age, treatment category and extent of disease	
Calvert 2003	Matched case-control study	1982 - 1995	All deaths from twenty-seven states during study period (US)	4 309 315	Occupations grouped into exposure categories by a panel of industrial hygienists with experience assessing silica exposure	ICD codes from death certificates	OR for TB death in silicotics	39.5 (16.9 - 92.4)
Scarselli 2011	Retrospective cohort study	1987 - 2006 (26 976 person years)	Workers in construction, ceramics and mining industries who were compensated for silicosis between 1943 and 1986 (Italy)	2 034	Records from compensation register (which require radiology, verified history of occupational exposure to silica dust and 35% decline in respiratory function)	Causes of death as recorded in the regional mortality registry and the Italian Agency for New Technologies, Energy and the Environment.	SMR	5.85 (3.03 - 11.30)

SMR: Standardised mortality ratio. ILO: International Labour Organisation. OR: Odds ratio. ICD: International Classification of Diseases.

ANNEX E: QUALITY SCORES OF ALL SELECTED STUDIES

Key:

Symbol	Interpretation	Score
Y	Criterion fully met	1
N	Criterion not met	0
YN	Criterion partially met	0.5
H	Historical measurements (for silica/silicosis measurements)	0.5

Studies scoring less than 4/8 (highlighted) were excluded from the review.

QUALITY ASSESSMENT OF ALL SELECTED STUDIES

Reference	Setting clearly described	Population clearly described	Data sources explained	Silica/silicosis/TB measurement methods explained	Does the study conduct direct measurements of silica exposure/silicosis	Statistical calculations explained	Are covariates adjusted for	Are the findings statistically significant	Score
Westerholm 1980	Y	YN	Y	YN	N	Y	N	N	4
Westerholm 1986	Y	Y	Y	N	N	Y	YN	N	5.5
Sherson 1990	Y	Y	Y	N	N	Y	N	Y	5
Cowie 1994	Y	Y	Y	Y	Y	Y	YN	Y	7.5
Kleinschmidt 1997	Y	Y	Y	Y	N	Y	Y	Y	7
Hnizdo 1998	Y	Y	Y	Y	YN	Y	Y	Y	7.5
Corbett 1999	Y	Y	Y	YN	Y	Y	Y	Y	7.5
Corbett 2000	Y	Y	Y	Y	Y	Y	Y	Y	8

Chang 2001	Y	Y	Y	Y	N	Y	Y	Y	7
Corbett 2003	Y	Y	Y	YN	Y	Y	YN	Y	7
Li 2011	Y	Y	Y	N	N	Y	Y	Y	6
[redacted]									
Zambon 1987	N	Y	Y	N	N	Y	N	Y	4
[redacted]									
Carta 1991	Y	Y	Y	Y	H	Y	N	Y	6.5
Cocco 1994	Y	Y	Y	Y	H	Y	N	Y	6.5
[redacted]									
Goldsmith 1995	Y	N	Y	N	H	Y	N	Y	4.5
Steenland 1995	N	Y	Y	Y	H	Y	N	Y	5.5
Starzynski 1996	N	YN	Y	Y	N	Y	N	Y	4.5
[redacted]ng 1996	N	N	Y	N	N	Y	N	Y	3
[redacted]wn 1997	Y	N	Y	N	N	Y	N	N	3
Chen 1997	YN	N	Y	N	N	Y	Y	Y	4.5
Churchyard 2000	Y	Y	Y	Y	Y	Y	Y	Y	8
Carta 2001	Y	Y	Y	Y	H	Y	N	Y	6.5
Calvert 2003	YN	YN	Y	N	N	Y	N	Y	4
Ogawa 2003	N	Y	Y	N	N	Y	N	Y	4
Graham 2004	Y	Y	Y	N	N	Y	N	Y	5
[redacted]									
Zhang 2008	Y	Y	Y	N	Y	Y	N	Y	6
Scarselli 2011	Y	Y	Y	N	N	Y	N	Y	5
Vacek 2011	Y	Y	Y	N	H	Y	N	Y	5.5
Chen 2012	Y	Y	Y	Y	H	Y	N	Y	6.5

ANNEX F: INSTRUCTIONS FOR AUTHORS

PLOS | One

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All manuscripts should be double-spaced and include line numbers and page numbers.

Manuscripts should begin with the ordered sections:

- Title
- Authors
- Affiliations
- Abstract
- Introduction

and end with the sections of:

- Acknowledgments
- References
- Figure Legends
- Tables

Figures should not be included in the main manuscript file. Each figure must be prepared and submitted as an individual file. Find more information about preparing figures here.

The title, authors, and affiliations should all be included on a title page as the first page of the manuscript file.

There are no explicit requirements for section organization between these beginning and ending sections. Articles may be organized in different ways and with different section titles, according to the authors' preference. In most cases, internal sections include:

- Materials and Methods
- Results
- Discussion
- Conclusions (optional)

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Abbreviations should be kept to a minimum and defined upon first use in the text. Non-standard abbreviations should not be used unless they appear at least three times in the text.

Standardized nomenclature should be used as appropriate, including appropriate usage of species names and SI units.

Title

Manuscripts must be submitted with both a full title and a short title, which will appear at the top of the PDF upon publication if accepted. Only the full title should be included in the manuscript file; the short title will be entered during the online submission process.

The full title must be 250 characters or fewer. It should be specific, descriptive, concise, and comprehensible to readers outside the subject field. Avoid abbreviations if possible. Where appropriate, authors should include the species or model system used (for biological papers) or type of study design (for clinical papers).

Examples:

- Impact of Cigarette Smoke Exposure on Innate Immunity: A *Caenorhabditis elegans* Model
- Solar Drinking Water Disinfection (SODIS) to Reduce Childhood Diarrhoea in Rural Bolivia: A Cluster-Randomized, Controlled Trial

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The introduction should:

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- Note any relevant controversies or disagreements in the field
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Results, Discussion, and Conclusions
These sections may all be separate, or may be combined to create a mixed Results/Discussion section (commonly labeled "Results and Discussion") or a mixed Discussion/Conclusions section (commonly labeled "Discussion"). These sections may be further divided into subsections, each with a concise subheading, as appropriate. These sections have no word limit, but the language should be clear and concise.
Together, these sections should describe the results of the experiments, the interpretation of these results, and the conclusions that can be drawn. Authors should explain how the results relate to the hypothesis presented as the basis of the study and provide a succinct explanation of the implications of the findings, particularly in relation to previous related studies and potential future directions for research.
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- **Books**. Bates B (1992) Bargaining for life: A social history of tuberculosis. Philadelphia: University of Pennsylvania Press. 435 p.

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Figure legends should describe the key messages of a figure. Legends should have a short title of 15 words or less. The full legend should have a description of the figure and allow readers to understand the figure without referring to the text. The legend itself should be succinct, avoid lengthy descriptions of methods, and define all non-standard symbols and abbreviations.