

Exposure to quartz dust/sand (crystalline silica) and the risk of development of connective tissue diseases (for instance scleroderma) and kidney diseases (for instance glomerulonephritis)

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Foreword

The authors received a research grant from the Danish Work Environment Fund in December 2013 following an open call of the funding agency. The title of the call was “Exposure to quartz dust/sand (crystalline silica) and the risk of development of connective tissue diseases (for instance scleroderma) and kidney diseases (for instance glomerulonephritis)”

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

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

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

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

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

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

Aarhus, April 2, 2015

The authors

Dansk resumé

Siden midten af 1950'erne har der været en række anekdotiske og senere systematiske beskrivelser af ophobning af systemisk sklerodermi og leddegigt blandt arbejdere, som indåndede kvartsstøv på arbejdet. Gennem de senere år er der tilkommet studier som også beskriver sammenhæng mellem kvartseksposering og andre bindevævssygdomme, primært systemisk lupus erythematosus og småkarsvaskulitis, som ofte rammer nyrene og medfører glomerulonefritis.

Bindevævssygdomme er autoimmune sygdomme, hvor kroppen danner antistoffer mod eget væv og sygdommene er ofte forbundet med svær invaliditet. Én procent af den voksne befolkning rammes af disse sygdomme. Der er eksperimentel dokumentation for at indånding af kvartsstøv kan sætte den immunologiske destruktive proces i gang, en proces som er relevant for alle fire sygdommes patologi.

Kvarts udgør en væsentlig bestanddel af jordskorpen og er allestedsnærværende i miljøet. Høje niveauer af respirabelt kvarts finder man i arbejdsmiljøet, bl.a. indenfor industri, bygge og anlæg, og det grønne område. I Danmark er omkring 60.000 personer på et givet tidspunkt udsat for betydelige kvartsniveauer på arbejdet. Et langt større antal har i kortere eller længere perioder været eksponeret i løbet af deres erhvervskarriere. I de senere år er der i Danmark anerkendt flere tilfælde af systemisk sklerodermi som erhvervs sygdomme.

Vi udførte et systematisk review baseret på PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) kriterierne. Vi udførte en litteratursøgning i PubMed og flere andre databaser foråret 2014, hvor vi identificerede artikler som afrapporterede analyser af sammenhængen mellem udsættelse for kvarts og sklerodermi, leddegigt, systemisk lupus erythematosus eller småkarsvaskulitis med et relevant design (kohorte eller case control undersøgelse) og som var forfattet på engelsk eller et skandinavisk sprog. Centrale karakteristika blev ekstraheret og systematiseret i tabeller. Kvaliteten af hver undersøgelse blev klassificeret efter 8 punkter vedrørende design (3), eksponering (2), sygdom (2) og confounding (1). Ud fra disse beregnede vi et samlet kvalitetsscore. Studier med tilstrækkelige oplysninger om effekt (odds ratio eller relativ risiko) blev inkluderet i en meta-analyse og vi beregnede vægtede gennemsnit for hver sygdom og alle fire bindevævssygdomme under ét. Vi vurderede publikationsbias med funnel plot og statistiske tests.

Vi identificerede i alt 22 artikler, som rapporterede 24 uafhængige analyser af sklerodermi (n=8), systemisk lupus erythematosus (n=4), leddegigt (n=5), eller småkarsvaskulitis (n=7). Ingen undersøgelser blev klassificeret med det højeste opnåelige kvalitetsniveau (et kvalitetsscore på 8), fire studier opnåede et score på 6 eller 7. Alle undersøgelser havde metodologiske svagheder i form af mangelfuld kontrol gruppe, lav deltagelse, selvrapporterede eksponeringsoplysninger, ikke-kvantitative eksponeringsmål, lav diagnostisk specificitet eller begrænset confounder kontrol. Mange studier havde få deltagere og der var stærke holdepunkter for publikationsbias og dermed oppustede risiko estimater.

Kvatseksponering var associeret med systemisk sklerodermi (meta-odds ratio [meta-OR] 2,94, 95% sikkerheds interval [SI] 1,93-4,49), systemisk lupus erythematosus (meta-OR 2,80, SI 1,30-6,02) og småkarsvaskulitis (meta-OR 2,45, 95% SI 1,55-3,88). Der var også indikationer for sammenhæng med leddegigt (OR 1,78, 95% SI 0,91-3,50). For alle fire bindevævslidelser samlet var der en meta-odds ratio på 2,45 (95% CI 1,77-3,40). Der var moderat eller stor heterogenitet for alle lidelser bortset fra leddegigt. Studier klassificeret med lav kvalitet rapporterede generelt højere risiko estimater end studier klassificeret med høj kvalitet. De fire studier, som blev klassificeret med den højeste kvalitet (ét studie for hver sygdom), viste dog effekter svarende til meta-odds ratioerne. Der var ikke gode holdepunkter for eksponeringsrespons, men der var kun få undersøgelser som vurderede dette. Effekterne var uafhængige af køn.

Alt i alt er det forfatterens vurdering at der er begrænset til nogen evidens (+/++) for en årsagssammenhæng mellem kvartseksponering og systemisk sklerodermi, systemisk lupus erythematosus, småkarsvaskulitis og leddegigt i henhold til de kriterier som er defineret af Arbejdsskadestyrelsen og Erhvervssygdomsudvalget.

Med henblik på at afklare denne sammenhæng nærmere og afdække sikre eksponeringsniveauer (tærskelniveauer, som grundlag for tilstrækkelige grænseværdier) bør fremtidige studier baseres på kvantitative arbejdspladsmålinger, specifikke diagnostiske oplysninger baseret på de nyeste internationale kriterier, store studiepopulationer, da dette ikke er hyppige sygdomme, og datakilder, hvor der ikke er nævneværdigt frafald. Danske og nordiske nationale registre over beskæftigelse, hospitalsdata og lægemiddelordinationer kombineret med veludviklede kvantitative job eksponerings matricer (JEM) giver det bedste udgangspunkt for dette. Denne viden vil ikke kun

være af betydning for et sikkert arbejdsmiljø, men vil også kunne bidrage med væsentlig ny viden om de sygdomsmekanismer som ligger bag autoimmune lidelser.

Abstract

Objectives: Exposure to quartz has been associated with the occurrence of connective tissue diseases. The aim of our study was to systematically review the risk of connective tissue diseases following quartz exposure.

Methods: In a systematic review based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria and involving searches in 4 databases 1162 articles were primarily identified. Our eligibility criteria led to an inclusion of 22 studies covering 24 analyses on the relation between quartz exposure and the risk of systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and small vessel vasculitis. Meta-analyses for each disease and for all 4 diseases together were performed together with funnel plots.

Results: The disease-specific meta-analyses showed that quartz exposure was associated with systemic sclerosis [meta-odds ratio (OR) 2.94, 95% confidence interval (CI) 1.93-4.49, $I^2 = 24.3\%$], systemic lupus erythematosus (OR 2.80, 95% CI 1.30-6.02, $I^2 = 57.0\%$), and small vessel vasculitis (OR 2.45, 95% CI 1.55-3.88, $I^2 = 48.5\%$). Increased risks were also indicated for rheumatoid arthritis (OR 1.53, 95% CI 0.80-2.25, $I^2 = 88.1\%$). The overall odds ratio for all four connective tissue diseases was 2.45 (95% CI 1.77-3.40, $I^2 = 82.9\%$). Heterogeneity was small for systemic sclerosis, moderate for systemic lupus erythematosus, and small vessel vasculitis, and high for rheumatoid arthritis as indicated by the I^2 values.

Funnel plots strongly indicated publication bias and the reviewed studies had several limitations like inappropriate control groups, low response rates, qualitative exposure information, lack of exposure response data, low diagnostic specificity, and limited confounder adjustment.

Conclusion: This review provides some evidence to the hypothesis that quartz exposure is associated with the occurrence of connective tissue diseases: systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and small vessel vasculitis. More high quality studies are needed in order to confirm or refute a causal relation between quartz exposure and the risk of connective tissue diseases.

Introduction

Quartz is the most abundant form of crystalline silica (1). Since quartz is the type of silica mainly involved in occupational exposures, quartz is in this paper used as a synonym for silica.

Quartz is used in a wide variety of industrial applications and products and numerous different job groups are exposed to quartz including workers in mines, quarries, foundries, roadway and other construction sites, masonry, sandblasting, production of pottery, glass, and tile (2). Quartz is used in different materials like absorbents, catalysts, fillers, lubricants, and paint (3).

Exposure to quartz particles can induce autoimmunity experimentally in cell cultures (4) and there has been reports of an increased risk of several systemic autoimmune diseases including systemic sclerosis (SSc) (5, 6), rheumatoid arthritis (RA) (7), systemic lupus erythematosus (SLE) (8), and small vessel vasculitis (SVV), including kidney diseases such as glomerulonephritis (9-11). High-level quartz exposure has also been reported in cases of hemolytic anemia, dermatomyositis, Sjögren syndrome, and Graves disease (2).

Connective tissue diseases

SSc is a rare generalized autoimmune connective tissue disorder characterized by small vessel vasculopathy and skin fibrosis, often with involvement of internal organs such as lungs, heart, kidneys and the gastrointestinal tract. SSc often leads to considerable morbidity and has the highest disease related mortality among the connective tissue diseases. Epidemiologic evidence suggest that there may be geographical clustering of the disease and the reported prevalence rates vary widely between 31 and 658 per million (12). The aetiology of SSc is largely unknown. Autoimmune and environmental factors could play important roles, but genes seem to play a minor role in the onset of disease (13, 14)). Racial disparities are poorly described, but some information exists on North Americans in which the susceptibility and severity of SSc are higher in blacks compared to whites. Disparities in socioeconomic status and access to health care do not seem to explain the differences in prevalence and mortality (15). The age of onset is most often between 30 and 60 years. There is a high 75-90 % female preponderance. There is some evidence that exposure to organic solvents, epoxy resins, and welding fumes may play a role (16). SSc has also been linked to bleomycin therapy

(17). Silicon breast implants have been under suspicion of causing SSc, but a meta-analysis failed to show an association between silicone breast implants and SSc (18). Smoking appears only to have impact on SSc disease severity but not the risk of the disease (19).

SLE is a diverse autoimmune disease that may affect any organ of the body. Female preponderance is high with female:male ratio of 8:1. The prevalence is 37.9 and 4.7 per 100.000 women and men, respectively in Denmark (20). Internationally the overall prevalence is between 20 and 60 per 100.000 (21). The mortality is increased four to five times in SLE patients (22). Cigarette smoking may confer a short-term increased risk while moderate alcohol consumption may protect against SLE (23). It has also been suggested that infections may play a role in SLE development (22). A high concordance rate for SLE among monozygotic twins (24%) has been reported. Geographic clusters of SLE have been described and it has been proposed that trichloroethylene and pesticides could play a role.

RA affects about 1 % of the Danish adult population and is 2-3 times more frequent in women than men (24). The prevalence is much lower in some areas of China and higher in Native American Indians (25). RA often has considerable morbidity and after 10 years about half of the patients are incapacitated for work. The mortality rate of RA is approximately twice the general population. Monozygotic twins have concordance rates of 15-30% but environmental factors are also important. Tobacco is a strong risk factor for RA, especially in genetically predisposed (the HLA-DRB1 shared epitope) and anti-CCP antibody positive persons. Moderate alcohol consumption, fasting followed by vegetarian diet, and long-term breast-feeding seems to protect against the development of RA. Socioeconomic status measured by education and occupational class has an inverse association with the risk of RA. Furthermore, a birth weight >4 kg has been associated with 2-3 times higher risk of RA. Conflicting results have been reported on vitamin D deficiency and coffee consumption (26, 27).

SVV are rare diseases that can lead to serious organ damage and before the newer treatment principles were developed mean survival for granulomatosis with polyangiitis (Wegeners granulomatosis) was 5 months (28).

Quartz

The term silica covers a range of chemical combinations of silicon dioxide (SiO₂) and oxygen.

Crystalline silica is tetrahedras of silicon and oxygen lined up in order thereby creating a repeatable pattern, whereas amorphous silica has randomly oriented bonds. Quartz, the most abundant form of crystalline silica makes up to 12% of the minerals of the earth's crust as it is found in rock, sand (90-95% quartz), and soil (1).

All forms of crystalline silica are fibrogenic and biologically toxic whereas amorphous silica is less toxic (29). Mechanical processing of silica results in the formation of fractured silica crystals with Si and Si-O radicals on their surface and an altered surface reactivity (3). In addition, the negative surface charge of these crystals could lead to increased cellular absorption and interaction with cellular components (3).

Quartz is, depending on the country, listed as number three to five of the carcinogenic components workers were most exposed to in Europe (30). In Denmark, around 59,000 workers were exposed to quartz in 1990-1993 (30). The main pathway for uptake is inhalation. In 1974, highest quartz levels were found when manufacturing scouring powder (3.6 mg/m³) and during blasting (2.1 mg/m³) whereas low concentrations were measured in mining industry (0.087 mg/m³) (31). In 1990, the average level of respirable quartz had been reduced by approximately a factor 10 in Sweden and was at a similar level in 2005 (31). Interestingly, it is reported that 7 to 34% of personal measurements exceeded or equaled the exposure limit of 0.1 mg/m³ in Sweden and Norway in 2005 and 2007-2009, respectively (31). In addition, Peters *et al.* described an empirical model for exposure to respirable crystalline silica exposure that was based on measurements, performed during a time period from 1976 to 2009 (32). They found that exposure levels were higher in the UK and Canada, and lower in Northern Europe and Germany. Based on their model they predicted that in 1998 chimney bricklayers, monument carvers and other stonecutters and carvers have the highest exposure levels with a geometric mean of 0.11 mg/m³ and 0.10 mg/m³, respectively.

The objective of this study is systematically to present and evaluate the scientific evidence corroborating or refuting a causal relation between occupational exposure to quartz and the development of connective tissue diseases (systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and small vessel vasculitis).

Material and methods

Literature search

The systematic review is based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria (33) that are a revision of the QUOROM (quality of reporting of meta-analysis) (34).

The following international databases were used for the literature search: the National Library of Medicine (PubMed), Embase, and the Cochrane Library. In addition, searches were performed in the Scandinavian databases bibliotek.dk and SveMed+. The literature search was performed by CB based on the search terms shown in supplementary I. Depending on the database, we included papers published in English, Danish, Swedish, and Norwegian (see supplementary I). However, only articles in English passed the pre-selection by the core group (VS, HK, KS, DS, and CB). The search results were imported into a database (RefWorks). Duplicates were subsequently removed. All articles were reviewed independently by two members of the core group. Both reviewers had to agree on an article before it was included for data extraction. In addition to language, the pre-selection of articles were based on the following eligibility criteria: Epidemiologic peer-reviewed studies on relevant exposure and outcome including case-control, cross-sectional and follow-up studies with an external control group or exposure contrast in the exposed group. In addition, the outcome had to be clearly defined. Studies with mixed outcomes that did not allow disentangling the four diseases of this review, or studies relying on a diagnosis of silicosis as a proxy measure of quartz exposure were not included. Case reports, meta-analysis, and reviews were excluded as well. After pre-selection of the articles, the remaining articles were divided between all members of the project group. The relevant data were transferred into a data table that was the basis for the following data analysis. All articles were searched for relevant literature citations (snowball search) not included in the original search.

The literature search resulted in a total of 1169 articles. Sixty articles originated from the biblioteket.dk, 12 from the SveMed+, 86 from the Cochrane library, 335 from EMBASE, and 676 from PubMed. After removing 7 duplicates, 1162 articles were included in the evaluation procedure (Fig. 1). Based on the title only, 843 articles were excluded (Fig. 2). The remaining 319 articles were then evaluated based on the abstract and 225 articles were excluded. 94 articles were evaluated based on the complete text and 16 articles were regarded as suitable for data extraction.

We performed a systematic search for relevant systematic reviews or meta-analysis on quartz exposure and connective tissue disorders,

Six snowball articles were found suitable and a total of 22 studies reporting 24 analyses were included with eight SSc, four SLE, five RA, and seven small SVV studies.

Data extraction

From each study, we extracted core information relevant for subsequent quality assessment as well as overall confounder-adjusted measures of association between quartz exposure and the four disease entities under study. This was done separately as well as combined for the two sexes dependent on which information was available. Two reviewers extracted the data independently and disagreements were solved by discussion.

Quality assessment

We systematically assessed all studies for the eight quality factors that related to study design (3 parameters), exposure assessment (2 parameters), outcome (2 parameters) and confounding (1 parameter). For each study, we dichotomized each factor as high or low quality according to specified criteria: i) study design: cohort study or case control study with population or hospital controls vs. case control study with convenience controls. ii) Number of participants: ≥ 75 cases vs. < 75 cases, iii) response rate: $> 60\%$ vs. $\leq 60\%$, iv) source of exposure information: non-self-reports vs. self-reports, v) exposure measure: quantitative or semi-quantitative vs. qualitative, vi) source of diagnosis: hospital vs. surveillance schemes, death certificates or not well defined sources), vii) diagnosis: well defined diagnostic criteria vs. other criteria, viii) possible confounding: accounted for age and sex in adjusted analyses or by matching vs. no account for age and sex. In case no information was provided the item was classified to the "low" category. Each item was assigned a score of "1" if classified as "high" and "0" if classified as "low" and a total sum score was generated for each study with 8 as the maximum.

Meta-analysis

We included 19 studies (21 analyses) with appropriate measures of association (odds ratios or rate ratios) in the meta-analysis. Rodnan *et al.* did not report confidence interval for their odds ratio estimate, which we estimated from the p-value (35). The mortality study by Gold *et al.* differed significantly from the other studies with respect to setting and design (a study of death certificates), outcome source and criteria (ICD-9 diagnoses coded from death certificates), and dimension (several thousand study subjects), and was not included in the meta-analysis (36). This was also the case for two studies presenting no measures of association (37, 38). We used the combined risk estimates provided for both sexes if available, if only available for men or women, these sex specific estimates were used. If more estimates were presented, we selected the overall estimate, otherwise the estimate provided for the highest exposure category (8, 39-41).

We combined estimates across studies for each of the four diseases as well as for all diseases combined by random models. We assessed heterogeneity by I^2 statistics and publication bias by funnel plot of the total dataset. We explored a possible gender effect based on all 12 male study results and all 6 female study results without specification on diseases due to the small numbers. We tested asymmetry of the funnel plots by the Egger' test based on all 19 study results.

We also computed meta-estimates for each of the eight dichotomized quality items to illustrate how these affected study results. All analyses were performed by STATA version 13.0 (StataCorp, College Station, Texas, USA).

Results

Overall study characteristics

Tables 1 to 4 summarize the characteristics and main results of 22 epidemiologic studies presenting 24 analyses of quartz exposure and the risk of SSc (n=8 (35-37, 39, 40, 42-44)), SLE (n=4 (8, 36, 41, 45)), RA (n=5 (36, 46-49)), and SVV (n=7 (38, 50-55)). The study by Gold *et al.*, reported results for SSc, SLE, and RA (36). Studies were conducted in South Africa (37), Europe (Finland, Sweden, UK, Belgium, Czech Republic, Italy and France) (38-40, 43, 44, 46, 47, 49-51, 53, 55), USA (8, 35, 36, 41, 52, 54), Canada (45), Malaysia (48) and Australia (42) and were published between 1967 and 2014. Seven studies exclusively analyzed men (35, 37, 42, 46-48, 50) and one study exclusively women (8) whereas both genders were included in the other studies from which five reported results for men and women separately (39-41, 43, 49). The age distribution was between 15 and 81 years with a mean age between 34 and 62 years (tables 1-4). However, not all studies provided detailed information on the age distribution (36, 43, 46, 47, 51, 55).

Design

A total of 20 case control studies (22 analyses) were included and were either hospital-based (35, 38-40, 43, 48, 50-55), population-based (8, 41, 42, 44, 45, 47), nested within an industry (37, 49), or based on mortality register data (36). Three of these studies used convenience controls sampled through media, patient organizations, or among hospital employees (8, 40, 48). Two follow-up studies were included (46, 49). The studies, except the study by Gold *et al.*, included between 16 and 577 cases (median 114.5), 10 studies included less than 75 cases (tables 1-4). The median number of controls was 206. The study by Gold *et al.* included several thousand cases (up to 36,178) and controls (264,569) (36). Seven studies reported a participation rate >60% for both, cases and controls (41, 43, 44, 46-48, 53), four a response rate <60% for either cases or controls, or both (51, 52, 54, 55) and 11 studies (13 analyses) did not provide complete information on response rate (i.e. for both cases and controls) (8, 35-40, 42, 45, 49, 50).

Exposure

Exposure information relied on participant's own retrospective reports of quartz exposure or quartz related work tasks alone (38, 45, 47, 48, 52, 55) or in combination with expert assessments (8, 39-41, 43, 44). Exposure information that was obtained independently of participants was based on ad hoc expert assessments that were blinded to case status (41, 42, 50, 51), job exposure matrices (36, 53), or from work history or work place measurements of airborne quartz levels or personnel file information (37, 46, 49). One study did not report how exposure information was obtained (35). Exposure was provided as semi-quantitative (8, 39-41) or quantitative measures of airborne quartz (37, 49) or qualitative information, typically any versus no quartz exposure (35, 36, 38, 42-48, 50-55).

Outcome

All seven studies of SVV enrolled cases diagnosed at hospitals (38, 50-55) as it was the case for four studies of SSc (35, 39, 40, 43), two studies of RA (47, 48) and one study of SLE (45). Other studies relied on medical surveillance schemes (37, 49), death certificates (36), a registry of disability pensions (46) or multiple sources (8, 41, 42). No studies relied on self-reported case information.

American College of Rheumatology (ACR) criteria were used for the classification of SSc (n=4), SLE (n=3), and RA (n=3). In two studies of SSc most patients fulfilled the ACR 1980 criteria (42, 44). The mortality study by Gold *et al.* classified SSc, SLE and RA according to the international classification of diseases, 9th edition (ICD-9). In one study most (56 of 60) patients met the later ACR 1980 SSc criteria (35, 49). One study did not report diagnostic criteria for RA (35, 49). Clinical cases of SVV were classified according to Chapel Hill Consensus Conference (CHCC) definitions and biopsy verified glomerulonephritis (50, 52, 54, 55) according to ACR criteria (51, 53), or by kidney biopsies in nearly all (46/48) cases (38).

Confounding

All but three studies accounted for age and sex (37, 50, 51). Some studies included additional potential confounders in the multivariable models that are not well-established risk factors for connective tissue diseases such as exposure to pesticides and gasoline (52), parity (49), and hair

dye use (39). Most studies applied state of the art multivariable methods such as logistic regression, but not all (35, 37, 38, 46, 50, 55).

Overall quality assessment

No studies were classified with a sum score of 8, the maximum obtainable (table 5). The study by Lane *et al.* had a sum score of 7 (53) while the studies of Parks *et al.*, Stolt *et al.* and Diot *et al.* had sum scores of 6 (39, 41, 47). The remaining studies had sum scores of 3, 4, or 5. One study of each of the four connective diseases was included among these four studies assessed with the highest quality.

Results of the meta-analysis

Quartz exposure was associated with SSc [meta-odds ratio (OR) 2.94, 95% confidence interval (CI) 1.93-4.49, $I^2 = 24.3\%$], SLE (OR 2.80, 95% CI 1.30-6.02, $I^2 = 57.0\%$) and SVV (OR 2.45, 95% CI 1.55-3.88, $I^2 = 48.5\%$) (Figure 3). Increased risks were also indicated for RA (OR 1.78, 95% CI 0.91-3.50, $I^2 = 88.1\%$). The overall odds ratio for all four connective tissue diseases was 2.45 (95% CI 1.77-3.40, $I^2 = 82.9\%$). Heterogeneity was small for SSc, moderate for SLE and SVV, and high for RA as indicated by the I^2 values.

Figures 4 and 5 present separate male and female results for the four connective tissue diseases combined, and show comparable meta-odds ratios between 2 and 3 for men and women. Significant heterogeneity was observed for both meta-analyses.

Figure 6 depicts risk estimates by the eight dichotomized quality parameters to be commented on in the discussion. Gold *et al.*'s results that were not included in this analysis and were close to unity for SSc, RA, and SLE (36), Sluis-Cremer *et al.* and Rihova *et al.* that were not included in the meta analysis indicated that quartz exposure was associated with SSc and SVV (37, 38).

Publication bias

The funnel plot of the 19 studies used for analysis was not symmetrical (figure 3) and the p-value of the Egger's test was highly statistically significant ($p=0.004$) strongly indicating biased publication of positive associations between quartz exposure and connective diseases.

Sensitivity analysis

When we restricted the analysis to the 4 studies with the maximum quality score of 6 (Rodnan, Finckh, Gregorini, Nuyts, Hogan 2001, Hogan 2007), the overall meta-odds ratio was 2.14 (95% CI 1.32-2.24, $I^2=0.0\%$).

Exposure response

Diot *et al.* and Marie *et al.* reported separate risk estimates for high-level quartz exposure and SSc that were not higher than for overall analyses (39, 40). Parks *et al.* and Finckh *et al.* indicated higher risks for SLE for higher and longer quartz exposure, but no formal statistical test for this was performed (8, 41). Turner *et al.* found a statistically significant negative association between duration and risk of RA, but no association between exposure level and RA (49).

Discussion

We identified 22 epidemiological studies presenting 24 analyses of the risk of connective tissue diseases following occupational, airborne quartz exposure. Quartz exposure showed associations with SSc, SLE, and SVV and such effects were also indicated for RA with meta-OR values between 1.8 and 2.9. Study results showed moderate to large heterogeneity for all diseases, except for SSc. Four studies obtained a quality sum score of 6 on an 8-level scale reflecting study design, exposure, outcome, and account for confounding and showed a doubled risk for connective diseases. However, this category included only one study for each of the four diseases, which limit the conclusions to be drawn from this sub-sample. There were only weak indication of exposure response relations, but this was only examined superficially in a small number of studies. We observed no consistent gender effects.

The studies were generally conducted as state of the art case control or cohort studies. A limited number of studies (8, 40, 48) relied on convenient control samples, which may not provide estimates of the exposure prevalence of the source population from which the cases originated. An obvious example of this is the study by Yahya *et al.* where controls were recruited among employees of the same hospitals that are not expected to be quartz exposed (48). As expected, these studies presented higher risk estimates than those who recruited controls *lege artis* (figure 7).

A relatively high fraction of studies (n=10) included less than 75 cases and the small studies on average presented higher risk estimates than the large studies (figure 7) which was in accordance with the Egger's test and funnel plot that strongly indicated publication bias.

Selection bias may significantly distort risk estimates because of differential participation related to disease and exposure. When participation rate is low, as was the case of several studies, the risk of such bias is increased. Incomplete reporting of participation rate disallows a qualified evaluation of selection bias, and this was the case for 11 studies. Figure 7 shows that studies with low participation or not reporting participation rate reported higher risk estimates supporting that their findings were inflated by bias.

Unbiased exposure information is crucial for valid identification of occupational risk factors. Exposure information that is retrospectively reported by the participants is more likely to be affected by reporting bias than independent and blinded exposure information from experts or job

exposure matrices. Some of the reviewed studies classified exposure by a combination of self-reports and independent sources and this approach is also expected to be vulnerable to reporting bias. Figure 7 does, however, not show higher risk estimates for studies relying on self-reports and does not indicate strong reporting bias.

Quantitative exposure information is to be preferred to qualitative information (any vs. no exposure) since the risk is expected to be dose dependent and less likely to include irrelevant exposure leading to risk estimates biased towards no effect. Six studies relied on quantitative or semi-quantitative exposure data (8, 37, 39-41, 49) and reported higher risks compared with studies relying on qualitative data, which is in favor of a real effect (figure 7). A positive exposure response relation is a crucial characteristic of a causal association. Only Turner *et al.* conducted a formal test of this and showed no trend (49).

Case definitions with low specificity are expected to dilute any real associations with exposure towards the null. This was probably not a major problem for the several hospital based case control studies with access to clinical data that allowed classification according to well established and internationally acknowledged criteria. These studies showed higher risk estimates than studies relying on less specific case definitions as expected for a specific causal relation between exposure and disease (figure 7).

Age and sex are well known risk factors for the reviewed connective tissue diseases and this review indicated that not accounting for this may confound results towards too high risk estimates (figure 7). Few other extraneous risk factors are known that could be accounted for, thus confounding may at least partly have affected the overall results.

When scrutinizing the study quality items for the individual diseases, there were no indications that some of the outlined limitations were disease specific but represented a general tendency.

Comparisons with other systematic reviews

A systematic search revealed only few relevant systematic reviews or meta-analysis on quartz exposure and connective tissue disorders, essentially one per investigated disease, McCormic *et al.* (SSc) (6), Parks and Cooper (SLE) (56), Khuder *et al.* (RA) (7), and Gómez-Puerta *et al.* (SVV) (9).

We included all studies included by Gómez-Puerta *et al.* (9) and one additional study (38).

McCormic *et al.* included 16 articles of SSc, and only 6 of these studies fulfilled our inclusion criteria (6). We did not include two German articles who did not meet our criteria for study design (57, 58). Other reasons for exclusion were: case series (59); a mixed outcome of morphea and SSc (60); possible misclassification of exposure and not adequately described confounders (61); reply to a comment, not an epidemiological study (62); silicosis used as proxy for quartz exposure (63); and an ecological study with inappropriate comparison of cases and control (64). The studies by Gold *et al.* and Marie *et al.* that we included were not included by McCormic *et al.*.

Parks and Cooper included seven studies of SLE (56). Only one study was also included in our review (41). One study could not be identified using available databases (ref. 7 in (56)), but as authors and study population were identical with (8) included by us, we have probably included the same study population. One study was a case series (65); tree studies were ecologic with inappropriate control group or inappropriate comparison of cases and controls (64, 66); and in one study silicosis was used as proxy for quartz exposure (63). We included the study of Gold (36) that was not included by Parks and Cooper.

Khuder *et al.* included 9 studies of RA (7). Two of these fulfilled our eligibility criteria (46, 49) whereas the other seven were excluded as silicosis was used as proxy for quartz exposure (63, 67); imprecise outcome definition (any joint disease) (68, 69); ecologic studies with inappropriate comparison of cases and controls (64); multiple causes for mortality (70); and insufficient exposure description (71). We included the studies by Gold *et al.* (36), Stolt *et al.* (47), and Yahya *et al.* (48) that were not included by Khuder *et al.* (7).

Mechanisms linking autoimmune diseases and quartz exposure

Autoimmunity is the reaction of the immune system to self-structures and is evidenced by the presence of autoantibodies and T cells that are reactive with host antigens (72). Interestingly, autoimmune diseases disproportionately affect women and are among the leading causes of death for women under the age of 65 (72, 73). In addition, a role for genetic factors in the etiology of autoimmune diseases has been suggested (72). It is widely accepted that the development of these diseases is triggered in genetically susceptible individuals upon exposure to one or more external exposures, e.g., silica (74). The identification of involved genes is challenging, as most autoimmune diseases are classical examples of multigene diseases (74). A number of genes have been identified.

The encoded proteins are involved in apoptosis and clearance of apoptotic material or immune complexes, innate and adaptive immunity, production of cytokines, chemokines, and adhesion molecules (74-77). Because of the complexity of the diseases, the immunological events that lead to the appearance of autoantibodies are still not completely understood (74).

There are a number of hypothesis and evidences of how silica can induce autoimmune diseases; mainly based on in vitro studies or animal models (72). Inhalation of silica particles leads to their deposition in the alveolar spaces of the lung. Studies in rats have shown that silica particles at sub-pathogenic doses are phagocytised by alveolar macrophages, which are subsequently removed by the mucociliary movement or drained to the lymphatics (78). This process is quite efficient without residual damage by the respired particles (3). At pathogenic doses this clearance is impaired leading to an accumulation of silica-loaded alveolar macrophages in the lymphatics and interstitial spaces of the lung (78) followed by cellular activation and the subsequent release of chemokines, pro-inflammatory cytokines, lysosomal enzymes and reactive oxygen species (ROS). Several of these cytokines and chemokines can activate fibroblasts. The mentioned intra cellular release of lysosomal enzymes leads to the death of the silica-loaded macrophages, most likely by apoptotic processes. The intracellular silica particles are released again and re-phagocytised by other macrophages, which ultimately leads to a cyclical process of inflammation and cell death (72). The silica-loaded macrophages of the lung have been shown to migrate to the lymph nodes leading to an increased systemic immunoglobulin production (79). In vitro, incubating T cells with silica dust causes polyclonal lymphocyte activation (80). The activation of lymphocytes potentially increases antibody production (72).

Chronic exposure to silica particles have been shown to activate both responder T-cells and regulatory T-cells. The activated responder T-cells enter the peripheral CD4+25+ fraction and the regulatory T-cells are lost earlier from this fraction, leading to reduced inhibitory function (4). The stimulated responder T-cells express Fas-mediated apoptosis inhibitory molecules such as soluble Fas and therefore survive longer (81). These fractions potentially contain auto-reactive clones and cause progression from sub-clinical manifestation of autoimmune diseases (82).

Conclusion

This review provides evidence that quartz exposure is associated with the development of connective tissue diseases: systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and small vessel vasculitis.

However, there were few high quality studies and limitations that affected a varying fraction of all studies were inappropriate control groups, low response rates, non-quantitative exposure information, lack of exposure response data, low diagnostic specificity, and limited confounder adjustment. Several studies included only few cases and there were strong indications of publication bias and inflated risk estimates. Many studies relied on self-reported exposure, often recognized as a major limitation of epidemiological studies of occupational exposures, but this did not seem to have major effect of the here reviewed studies.

Taken all together, we find that the degree of evidence of a causal association between quartz exposure and systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and small vessel vasculitis is limited (+) to moderate (++) according to the criteria of the National Board of Industrial Injuries and the Occupational Diseases Committee.

Future studies should rely on quantitative exposure assessment based on work site measurements, specific diagnostic information according to up-to-date criteria, and large study populations due to the relative rarity of these diseases, and secure limited drop out. Danish and Scandinavian registers on employment, hospitalization, and prescribed medications in combination with job exposure matrices may provide a unique opportunity to clarify the relation between quartz exposure and connective tissue.

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Figures 1-7 and tables 1-5

Figure 1. Description of the literature search

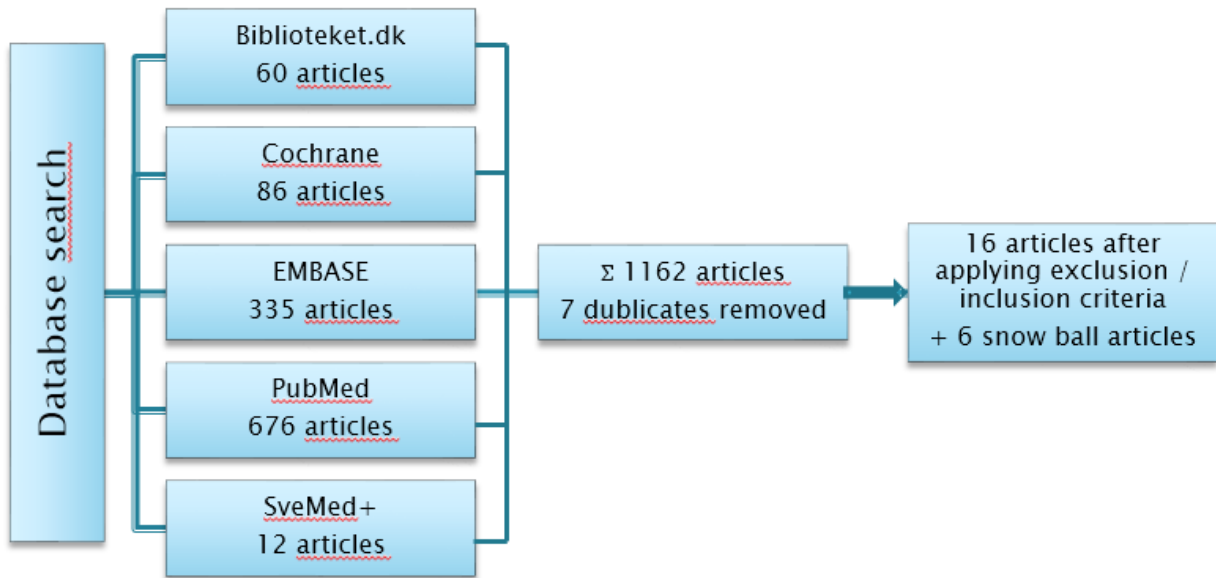


Figure 2. Description of exclusion of papers received from database search

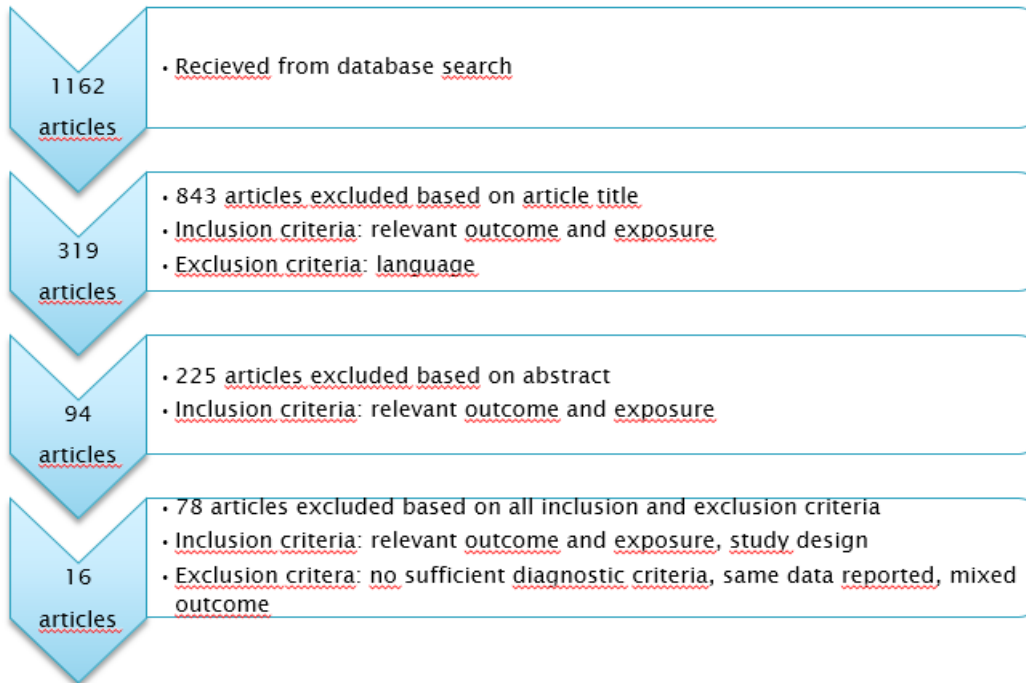


Figure 3. A random-effects meta-analysis on the association between quartz exposure and systemic sclerosis, systemic lupus erytmematosus, rheumatoid arthritis, and small vessel vasculitis, men and women, 19 studies

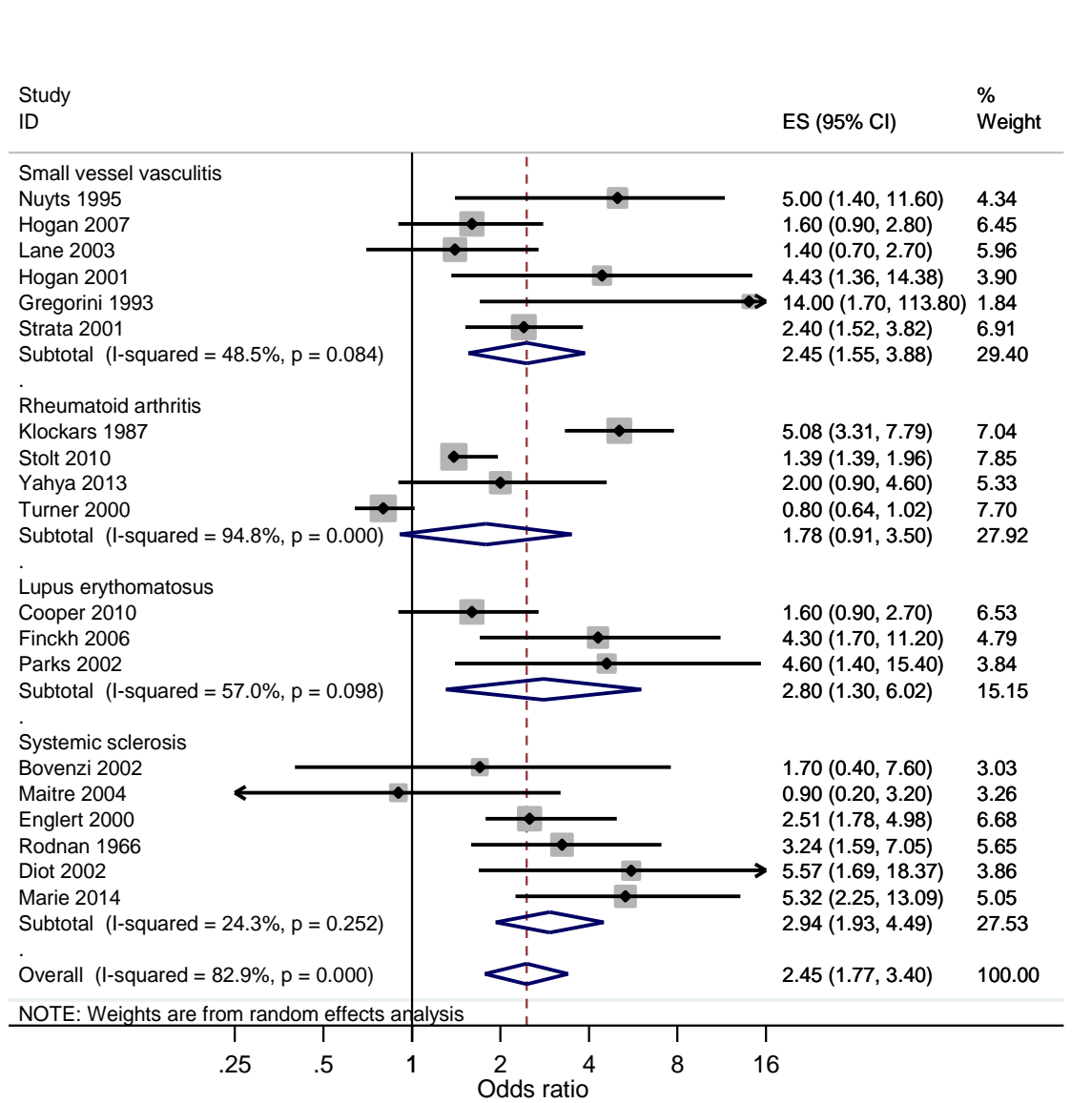


Figure 4. A random-effects meta-analysis on the association between quartz exposure and connective tissue disease (systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and small vessel vasculitis), men only, 12 studies

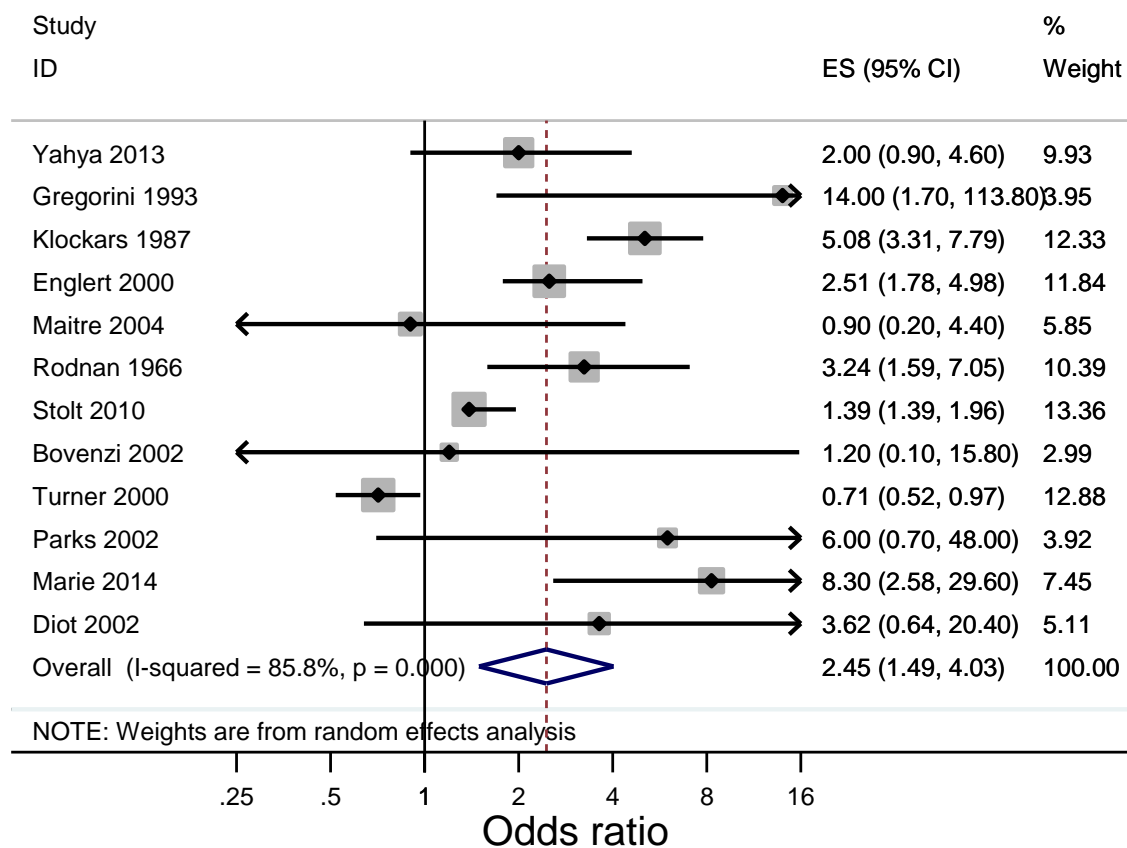


Figure 5. A random-effects meta-analysis on the association between quarts exposure and connective tissue disease (systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and small vessel vasculitis), women only, 6 studies

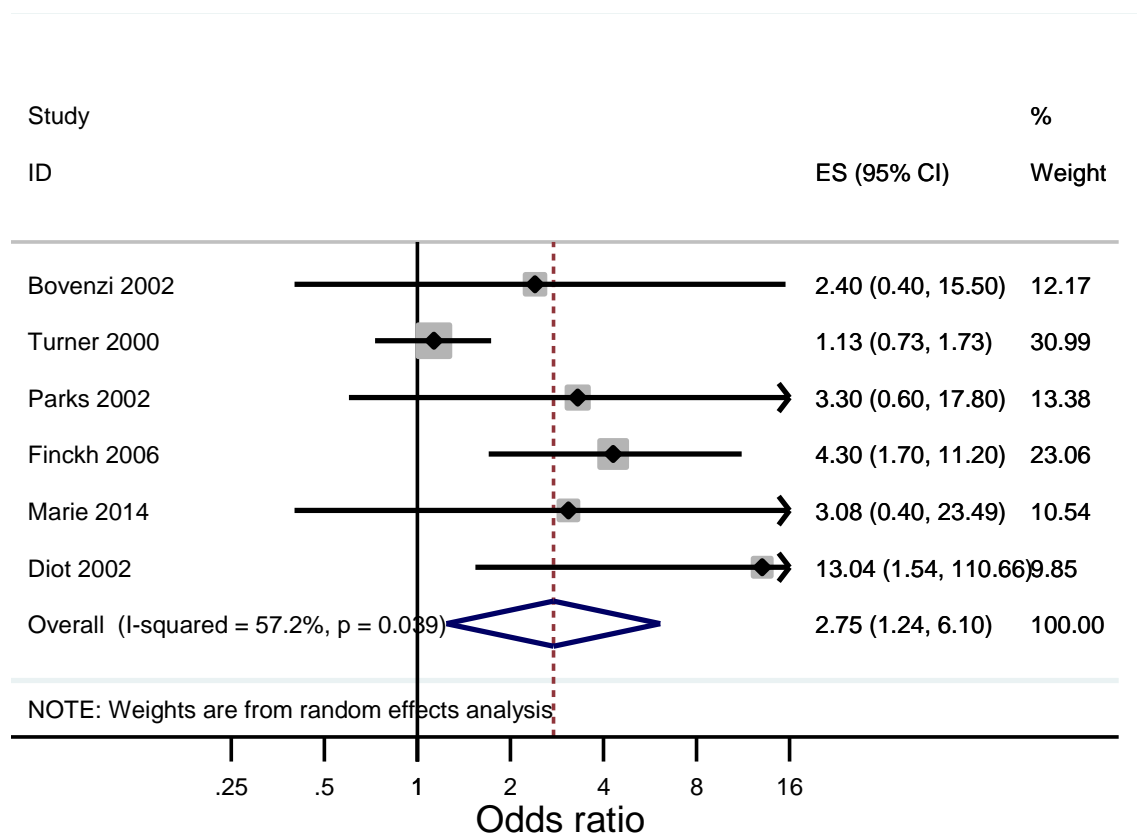


Figure 6. A funnel plot on the associations of exposure to quartz and connective tissue diseases (systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and small vessel vasculitis), men and women, 19 studies

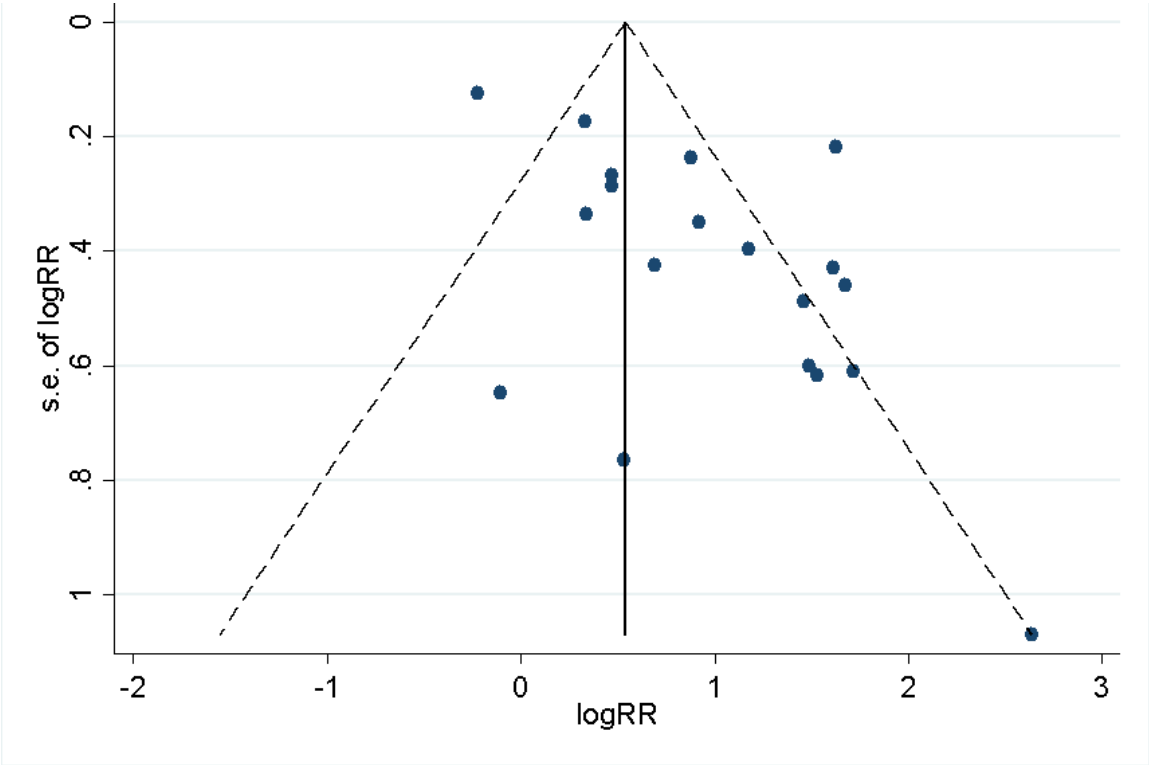


Figure 7. Eight quality parameters assessed by pooled relative risk estimates for high vs. low quality classification as specified in table 5. Results from 19 studies on the associations of exposure to quartz and connective tissue disorders (systemic sclerosis, systemic lupus erytmematosus, rheumatoid arthritis, and small vessel vasculitis)

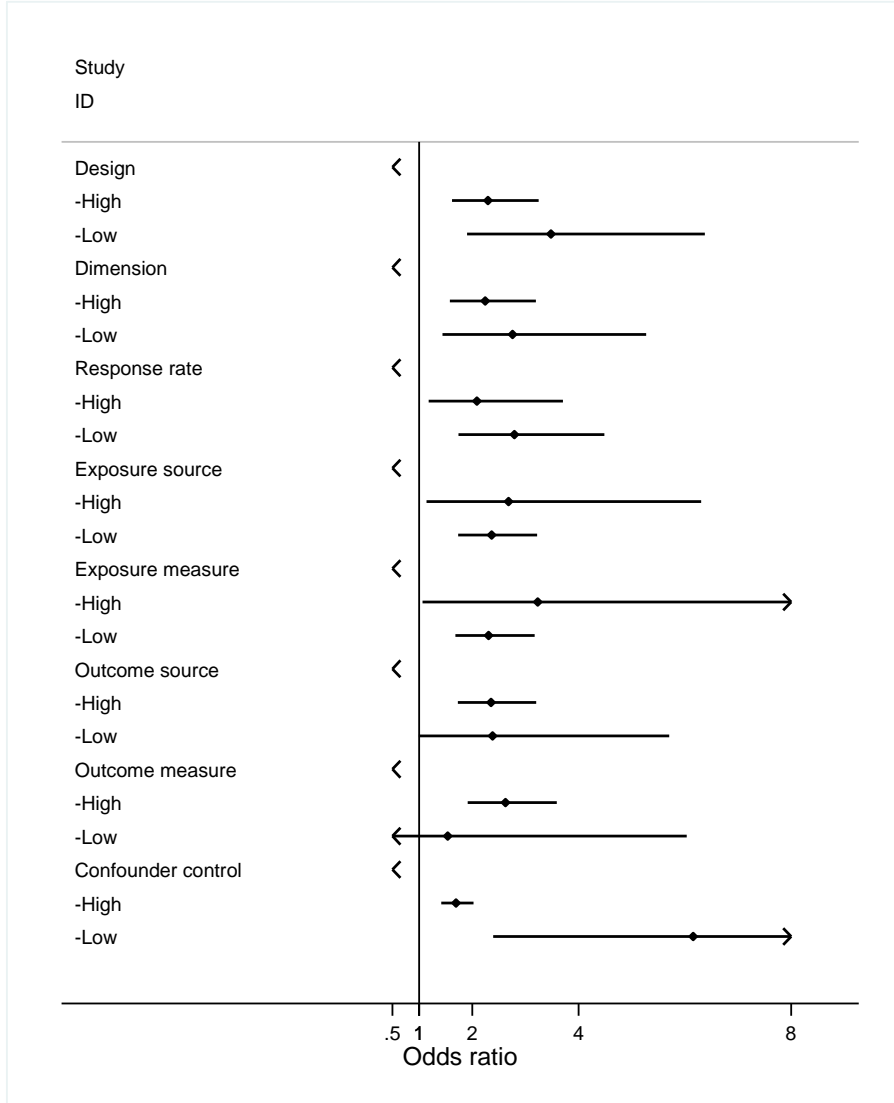


Table 1: Characteristics and main results of eight epidemiologic studies of quartz exposure and risk of systemic sclerosis (SSc)

Author Year Country (ref.)	Study Design and Population	Cases/controls (participation rate); Mean age and range	Exposure assessment	Outcome	Covariates accounted for	Result		
						Men OR/RR (95% CI)	Women OR/RR (95% CI)	Total OR/RR (95% CI)
Rodnan 1967 USA (35)	Hospital based case control study of 146 men	60 / 86 50% of cases >50 years of age, n.r. for controls	Occupation as coal miner or other occupation with silica exposure	Clinical diagnosis of systemic sclerosis 56/60 SSc patients meet the later ACR 1980 criteria since they had diffuse cutaneous SSc	Age, race	3.24 (1.59-7.05)		
Sluis-Cremer 1985 South Africa (37)	Nested case control study of 158 male gold miners who underwent medical surveillance Controls were non-cases participating in same health examinations as cases	79 (n.r.) /79 (n.r.); 45.3 years (27-71)	Cumulative exp. assessed by expert from number of shifts and measured quartz levels	Definite and probable SSc patients according to the ACR 1980 criteria based on periodical and benefit health examinations	None reported	Higher intensity and cumulative exp. in cases than controls ($p<0.05$)		
Englert 2000 Australia (42)	Population based case control study of 243 living and deceased men. Controls ascertained from general medical practices	160 (n.r.) /83 (n.r.); 59.0/59.7 years	Any quartz exp. assessed blindly by expert from occupation (self-reported or reported in medical records)	Patients with diffuse and limited SSc ascertained from death certificates, hospitals, and other sources. The most meeting ACR 1980 criteria. The rest had sclerodactyly as major criterion and at least two of the following minor criteria: Raynaud's phenomenon, oesophageal dysmotility, calcinosis, telangiectasia, or an elevated antinuclear antibody titre	Age, sex, SES	2.51 (1.78 - 4.98)		
Diot 2002 France (39)	Hospital based case control study of 33 men and 207 women. Controls were other patient categories from the same hospital.	80 (n.r.) /160 (n.r.); 55.8/56.4 years	Semi-quantitative quartz cumulative exp. score assessed by experts blinded to case status from occupational history and self-reported exp.	SSc patients according to the ACR 1980 criteria (26 diffuse, 54 limited)	Age, sex, smoking habits, alcohol, medication, lifestyle, silicone implants, cosmetic surgery, hair dyeing	3.62 (0.64 - 20.40)	13.04 (1.54 - 110.66)	5.57 (1.69 - 18.37)
Bovenzi 2004 Italy (43)	Hospital based case control study of 27 men and 199 women. Controls were other categories of patients from the same hospital	55 (100%) /171 (98%); <40-60+ years	Any occupational exp. to quartz assessed by experts blinded to case status from occupational history and self-reported exp.	SSc patients according to the ACR 1980 criteria (51 diffuse, 4 limited)	Age, sex	1.2 (0.1 - 15.8)	2.4 (0.4 - 15.5)	1.7 (0.4 - 7.6)

Author Year Country (ref.)	Study Design and Population	Cases/controls (participation rate); Mean age and range	Exposure assessment	Outcome	Covariates accounted for	Result		
						Men OR/RR (95% CI)	Women OR/RR (95% CI)	Total OR/RR (95% CI)
Maitre 2004 France (44)	Population based case control study of 50 men and 249 women. Controls randomly ascertained from regional telephone lists	93 (98%) /206 (96%); 53.1-55.4 years	Any occupational exp. to quartz assessed blindly by experts from occupational history and self-reported exp.	Clinical cases meeting most of the ACR 1980 criteria including 28 cases with signs of early disease reported to SSc registry.	Sex, age, education	0.9 (0.2-4.4)		0.9 (0.2-3.2)
Gold 2007 USA (36)	Death certificate based case control study, 27% men, 73% women. Controls randomly selected amongst all other causes of death	5578 (n.r.) /264,569 (n.r.); 25 – 65+ years	Occupational exp. to quartz assessed from longest held job reported on death certificate by JEM	SSc patients (ICD-9 code 710.1) reported on death certificate as underlying or contributing cause of death	Age, sex, race, year of death, geographical region, SES			1.02 (0.92-1.13)
Marie 2014 France (40)	Hospital based case control study of 88 men and 312 women. Controls recruited through media and among other patient categories.	100 (98%) /300 (n.r.); 52 years (45-61)	Semi quantitative cumulative quartz exp. scores based on self-reported exposures and expert assessment	SSc patients according to the ACR 1980 criteria (33 diffuse, 67 limited)	Age, sex, smoking	8.30 (2.58-29.60)	3.08 (0.40-23.49)	5.32 (2.25 - 13.09)

Ctrl – controls; ACR – American College of Rheumatology; Exp. – exposure; JEM – job-exposure matrix; SSc – systemic sclerosis; RR – Relative risk; OR – Odds ratio; n.r. – not reported; SES – socioeconomic status

Table 2: Characteristics and main results of four epidemiologic studies of quartz exposure and risk of systemic lupus erythematosus (SLE)

Author Year Country (ref.)	Study Design and Population	Cases/controls (participation rate); Mean age and range	Exposure assessment	Outcome	Covariates accounted for	Result		
						Men OR/RR (95% CI)	Women OR/RR (95% CI)	Total OR/RR (95% CI)
Parks 2002 USA (41)	Population-based case control study of 561 women and 59 men. Cases ascertained from rheumatologists and other sources and controls through driver license records	265 (93%)/ 355 (75%); 39 years (15 – 81)	Intensity of quartz exp. assessed by experts blinded to disease status from occupational history and self-reported exposures	SLE patients according to the ACR 1997 criteria	Age, sex, state, race, education	6.0 (0.7–48.0)	3.3 (0.6–17.8)	4.6 (1.4–15.4)
Finckh 2006 USA (8)	Population-based case control study of 286 women of Afro-American ethnicity (89%). Cases and controls were ascertained from department of public health, patient advocacy groups and other sources	95 (44%)/ 191 (n.r.); 44/47 years (SD 13/15)	Duration of quartz exp. assessed by experts blinded to disease status from occupational history and self-reported exposures	SLE patients according to the ACR 1982 criteria	Age, ethnicity, education, smoking, parity		4.3 (1.7-11.2)	
Gold 2007 USA (36)	Death certificate based case control study, 27% men, 73% women. Controls randomly selected amongst all other causes of death	7153 (n.r.) / 264,569 (n.r.); 25 – 65+ years	Any quartz exp. assessed by JEM from longest held job recorded on death certificate	SLE underlying or contributing cause of death as reported on death certificate (ICD-9 code 710.0)	Age, sex, race, year of death, residence, SES			1.02 (0.92-1.12)
Cooper 2010 Canada (45)	Population based case control study of 45 men and 476 women. Cases with 2 live parents agreeing to participate were ascertained from 11 rheumatology centers and controls from phone number listings	258 (n.r.)/ 263 (26%); 34.0/35.6 (SD 9.4-9.7)	Any self-reported quartz related jobs and tasks	SLE patients according to the ACR 1997 criteria	Age, sex, residential area			1.6 (0.90-2.7)

* Diagnosis based on American College of Rheumatology (ACR) criteria for systemic lupus erythematosus; Ctrl – controls; Exp. – exposure; SD – standard deviation; RR – Relative risk; OR – Odds ratio; n.r. – not reported; SES – socioeconomic status

Table 3: Characteristics and main results of five epidemiologic studies of quartz exposure and risk of rheumatoid arthritis (RA)

Author Year Country (ref.)	Study Design and Population	Cases/controls (participation rate); Mean age and range	Exposure assessment	Outcome	Covariates accounted for	Result		
						Men OR/RR (95% CI)	Women OR/RR (95% CI)	Total OR/RR (95% CI)
Klockars 1987 Finland (46)	Follow-up study of 1026 male granite workers identified from personnel records compared to the general population	17 cases (1.69/1000 pyrs); 100%. 27 years at entry (15-27)	Occupation as granite worker	Disability pension for RA according to ACR 1959 criteria	Age	5.08 (3.31-7.79)		
Turner 2000 UK (49)	Nested case control study of 215 men and 75 women from the pottery, sandstone, and refractory material industry, who underwent medical surveillance	58 (n.r.) / 232 (n.r.) Age at start of employment in the industry 23.7 8SD 10.0) / 23.4 (SD 10.1) years	Quantitative measures of quartz exposure based on work history and air samples	Physician diagnosed RA, no diagnostic criteria	Age, sex, year of first exposure, smoking, employment in coal mining industry, parity,	Cumulative exp. 0.71 (0.52-0.97)	Cumulative exp. 1.13 (0.73-1.73)	Cumulative exp. 0.80 (0.64-1.02)
Gold 2007 USA (36)	Death certificate based case control study, 27% men, 73% women. Controls randomly selected amongst all other causes of death	36,178 (n.r.) / 264,569 (n.r.); 25 – 65+ years	Any exp. to quartz assessed by JEM from job recorded on death certificate	RA (ICD-9 code 714.0-714.2) cause of death as reported on death certificate	Age, sex, race, year of death, geographical region			0.99 (0.94-1.03)
Stolt 2010 Sweden (47)	Population based case control study of 1236 men. Cases reported from 21 rheumatology units. Controls ascertained from population register	577 (95%) / 659 (81%); 18-70 years	Any self-reported quartz exposure or quartz related job tasks	RA patients according to ACR 1987 criteria	Age, residence	1.39 (0.98 to 1.96)		
Yahya 2013 Malaysia (48)	Hospital based case control study of 362 men. Cases reported from 7 rheumatology centres, controls recruited from hospital staff and other patient categories	149 (92%) / 213 (76%); 50.1/49.8 years	Any self-reported quartz exposure or job tasks	RA patients according to ACR 1987 criteria	Age, residence	2.0 (0.9–4.6)		

Ctrl – controls; Exp. – exposure; JEM – job-exposure matrix; RR – Relative risk; OR – Odds ratio; PY – Person year; RF – rheumatoid factor; αCCP – anti cyclic citrullinated peptides; n.r. – not reported; pyrs – person years

Table 4: Characteristics and main results of seven epidemiologic studies of quartz exposure and risk of small vessel vasculitis (SVV)

Author Year Country (ref.)	Study Design and Population	Cases/controls (participation rate); Mean age and range	Exposure Assessment	Outcome	Covariates accounted for	Result		
						Men OR/RR (95% CI)	Women OR/RR (95% CI)	Total OR/RR (95% CI)
Gregorini 1993 Italy (50)	Hospital based case control study of 48 men. Controls were other nephropathy patient categories	16 (n.r.)/32 (n.r.); 53.8 years (20-70)	Any exp. to quartz assessed blindly by experts from occupational history	Clinical cases of ANCA-positive rapidly progressive glomerulonephritis determined by kidney biopsies in 46 of 48 patients	None	14.0 (1.7-113.8)		
Nuyts 1995 Belgium (51)	Hospital based case control study of 48 predominantly men. Controls were recruited from voters' lists	16 (100%)/32 (33%); 27-77 years	Any exp. to quartz assessed blindly by experts from occupational history	Clinical cases of GPA (Wegener's granulomatosis) according to ACR 1990 classification criteria	None			5.0 (1.4-11.6)
Hogan 2001 USA (52)	Hospital based case control study of 66 men and 64 women. Controls were patients with other renal diseases	65 (24%)/65 (32%); 54/55 years	Self-reported regular quartz related work tasks	Clinical cases of ANCA-positive SVV according to CHCC 1994 definition and determined by kidney biopsy exhibiting pauci-immune necrotizing glomerulonephritis	Age, sex, race smoking, pesticides, gasoline/fuels, cleaning agents, glues/adhesives, paint products			4.43 (1.36-14.38)
Lane 2003 UK (53)	Hospital based case control study of 348 participants (sex distribution n.r.). Controls were patients diagnosed with other diseases	75 (73%)/ 273 (94%); 60.2/58.9 years (17-89)	Ever exposed to quartz assessed by JEM from occupational history	SVV: GPA (Wegener's granulomatosis) MPA (Microscopic polyangiitis) and EGPA (Churg-Strauss) according to GPA: ACR 1990 criteria and CHCC 1994 definition, MPA: CHCC 1994 definition, EGPA: ACR 1990 criteria and Hammerschmidt criteria	Age, smoking, residence, social class			PSV: 1.4 (0.7-2.7)
Rihova 2005 Czech Republic (38)	Hospital based case control study of 19 men and 12 women. Controls were healthy ANCA-negative office employees.	31 (n.r.) / n.r. (n.r.); 51 years (18-75)	Self-reported exposure to quartz-containing chemicals	ANCA Associated Vasculitis according to CHCC definition and determined by kidney biopsy and ANCA positivity	Age, sex, residence			12.9% of patients and 0% of controls exposed to quartz
Hogan 2007 USA (54)	Hospital based case control study of 128 men and 110 women. Controls were identified by random digit dialling	129 (60%)/ 109 (12%); 62/55 years (SD 14/17)	Ever exp. to quartz assessed by experts from occupational history and self-reports	Clinical cases of ANCA-positive SVV according to CHCC 1994 definition and kidney biopsy (all had pauci-immune crescent glomerulonephritis)	Age, sex, residence			1.6 (0.9-2.8)

Stratta 2001 Italy (55)	Hospital based case control study of 48 men and 41 women. Controls were patients diagnosed with other kidney diseases	31 (51%) / 58 (50%); Age distribution n.r.	Self-reported quartz exposure	Clinical cases of Extracapillary glomerulonephritis (n=16), MPA (n=9) and GPA (Wegener's granulomatosis (n=6) according to CHCC 1994 definition and kidney biopsy	Age, sex, residence			2.4 (p=0.04)
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Ctrl – controls; Exp. – exposure; JEM – job-exposure matrix; RR – Relative risk; OR – Odds ratio; ANCA – Anti-neutrophil cytoplasmic antibodies; ACR - American College of Rheumatology; CHCC - Chapel Hill Consensus Conference; SVV - Small vessel vasculitis, GPA - Granulomatosis with polyangiitis (Wegener's granulomatosis); MPA - Microscopic polyangiitis; EGPA - Eosinophilic Granulomatosis with polyangiitis

Table 5. Quality assessment of 22 studies presenting 24 analyses on the association of quartz exposure and connective tissue disorders (systemic sclerosis, systemic lupus erytmematosus, rheumatoid arthritis, and small vessel vasculitis)

Author	Study design	Dimension	Response rate	Exposure source	Exposure measure	Outcome source	Outcome measure	Confounder control	Total score
Rodnan 1967	1	0	0	0	0	1	0	1	3
Sluis-Cremer 1985	1	1	0	1	1	0	1	0	5
Englert 2000	1	1	0	1	0	0	1	1	5
Bovenzi 2004	1	0	1	0	0	1	1	1	5
Diot 2002	1	1	0	0	1	1	1	1	6
Maitre 2004	1	1	1	0	0	0	1	1	5
Gold 2007	1	1	0	1	0	0	0	1	4
Marie 2014	0	1	0	0	1	1	1	1	5
Parks 2002	1	1	1	0	1	0	1	1	6
Finckh 2006	0	1	0	0	1	0	1	1	4
Gold 2007	1	1	0	1	0	0	0	1	4
Cooper 2010	1	1	0	0	0	1	1	1	5
Klockars 1987	1	0	1	1	0	0	1	1	5
Turner 2000	1	0	0	1	1	0	0	1	4
Gold 2007	1	1	0	1	0	0	0	1	4
Stolt 2010	1	1	1	0	0	1	1	1	6
Yahya 2013	0	1	1	0	0	1	1	1	5
Gregorini 1993	1	0	0	1	0	1	1	0	4
Nuyts 1995	1	0	0	1	0	1	1	0	4
Hogan 2001	1	0	0	0	0	1	1	1	4
Stratta 2001	1	0	0	0	0	1	1	1	4
Lane 2003	1	1	1	1	0	1	1	1	7
Rihova 2005	1	0	0	0	0	1	1	1	4
Hogan 2007	1	0	0	0	0	1	1	1	4

Supplementary I

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Search Embase

Languages: English

Search terms: quartz, silicon dioxide, scleroderma, rheumatoid arthritis, lupus erythematosus, glomerulonephritis, immunoglobulin a nephropathy, small vessel vasculitis, vasculitis

(MeSH term search)

Search date: 27.02.2014

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Languages: English

Search terms: *Exposure:* silicon dioxide, Diatomaceous earth, Tridymite, Cristobalite, silica

Outcome: glomerulonephritis, bright disease, glomerulosclerosis, anti-glomerular basement membrane disease, small vessel vasculitis, granulomatosis, Churg Strauss, vasculitis, Lupus Erythematosus, Libman-Sacks, Lupus Nephritis, Lupus Vasculitis, Rheumatoid Arthritis, Caplan, Kaplan, Felty*, Splenomegaly, Neutropenia, Rheumatoid Nodule, Rheumatoid Nodulosis, Theumatoid Noduloses, Nodular rheumatoid, Rheumatoid Vasculitis, Sjogren, Sicca Syndrome, Still's, rheumatoid pneumoconiosis, scleroderma, Frontal Linear Scleroderma en Coup de Sabre, Morphea*, Dermatosclerosis, Sclerodactyly, Raynard*, Telangiectasia, CRST, CREST, Linear sclerosis, Circumscribed sclerosis, Localized sclerosis, Sudden Onset sclerosis, Progressive systemic sclerosis, Progressive sclerosis, Limited systemic sclerosis, Limited sclerosis, Diffuse cutaneous systemic sclerosis, Diffuse systemic sclerosis, diffuse sclerosis, systemic sclerosis, Eosinofil fasciitis, Atrophoderma parini et pasini, Atrophoderma

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