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Review Article

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Relationship between occupational exposure to respirable crystalline silica and serum CC16 level as a potential biomarker for preventing silicosis: A systematic review and meta-analysis study

Hoda Arabzadeh[1], Ali Poormohammadi[2], Salman Khazaei[1], Marzieh Fattahi-Darghlou[1,*]

[1] Department of Epidemiology, Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran
[2] Center of Excellence for Occupational Health, Occupational Health and Safety Research Center, School of Public Health, Hamadan University of Medical Sciences Hamadan, Iran

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CORRESPONDING AUTHOR:

marziehfattahid@gmail.com
Tel: (+98 813) 8381643
Fax: (+98 813) 8380509

ABSTRACT

In this present study, the association between occupational exposure to Respirable Crystalline Silica (RCS) and serum level of Clara Cell Protein (CC16) was investigated in the form of a systematic review and meta-analysis. Various databases including PubMed, Scopus, and Web of Sciences were searched until August 2022 based on Medical subject headings (MeSH) such as "CC10 protein, human" OR "Clara-cell specific 10-kD protein "OR "Clara cell phospholipid-binding protein human" AND Silicosis. Standardized Mean Difference (SMD) was used to compare the mean difference in CC16 serum levels between the silicotic and non-silicotic groups.

During the initial database search until August 2022, 18 articles were found. By excluding duplicates and final screening in terms of compliance with the title and objectives, eight articles were included in our analysis. The overall effect estimate demonstrated that silicosis patients had lower serum level of CC16 (SMD:-3.58; 95% CI, from -5.14 to-2.3; I2 = 94.4% P-value<0.001) than that of the control group. Moreover, silicosis patients and exposed individuals had lower serum level of CC16 (SMD:-3.32; 95% CI, from -4.19 to -2.45; I2 = 88.6% P-value<0.001) compared to the control group. The silica exposure had a lower CC16 level (SMD:-1.92; 95% CI, from -4.22 to 0.39; I2 = 97.5% P-value<0.001) than the non-silicosis groups.

The results demonstrated that occupational exposure to RCS is associated with the reduction of serum CC16 level. Therefore, the reduced serum level of CC16 protein can be used to monitor the maximum exposure level of workers to RCS in related workplaces.

Review

Silicosis is one of the fibrotic lung diseases that is progressive, irreversible, and incurable, it is commonly caused by inhaling Respirable Crystalline Silica (RCS), exposure to RCS can occur in all environments, as they are exists in the earth's crust, but it mostly happens in the workplace. Crystalline silica is a mineral that is common in stone, concrete, and mortar and is a part of the Earth's crust. Moreover, a vast variety of processes

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and vocations, including construction sites, stone quarries, agate and production units of non-metallic products, (e.g. refractories, ceramics, glass, mica, and structural clay), can lead to exposure to silica. The free crystalline silica dusts that are trapped in the lower respiratory system are prone to fibrosis and nodular lesions due to collagen covering them, which leads to silicosis [1-3]. In previous studies, silica has been considered as a known risk factor for silicosis, and few studies have conducted this relationship in a dose-response manner and discussed the level of this exposure [4-6].

Silicosis, an interstitial lung disease and a type of pneumoconiosis is distinguished by its Pathological changes, which include diffuse fibrosis and the formation of silicosis nodules in the lungs. The clinical manifestations of this disease vary from asymptomatic forms to chronic respiratory failure [7-9]. In this disease, the upper lobes of the lung experience Chronic inflammation and scarring. Silicosis is classified according to the quantity inhaled, the period, and the term of exposure [3, 10, 11]. According to the report of the China Respiratory Diseases Meeting, pneumoconiosis was responsible for 80% of all occupational diseases in 2003, and this disease can directly and indirectly cause many economic losses in the world [12]. Various organizations have recommended strict standards Due to the adverse effects of inhaling RCS dust. For example, 0.05 mg/m^3 Time-weighted average (TWA) has been recommended as the Permissible Exposure Limit (PEL) for RCS by the National Institute for Occupational Safety and Health (NIOSH) [13]. The NIOSH has considered RCS to be a potential occupational carcinogen.

Silicosis can be diagnosed through medical history and radiological findings such as X-ray imaging and Computed Tomography (CT) scans. However, these tests are generally conducted in their advanced stages. It is noteworthy that no effective and specific treatment for this lung disease has been found so far. Hence predicting and early diagnosing the disease with biological markers may be considered a very useful screening method for monitoring the health status of exposed and high-risk workers before the occurrence of silicosis and using conventional diagnosis methods. Previously, biomarkers such as serum copper, Neopterin serum, Selenium, angiotensin-converting enzyme, heme oxygenase-1 (HO-1), and Clara Cell Protein (CC16) have been introduced as useful tools for evaluating silicosis and other respiratory diseases [8, 14-17]. CC16 secreted by Clara cells is the most plentiful protein in bronchial alveolar secretions. This anti-inflammatory and anti-fibrosis protein plays an important role in suppressing the immune system [15, 18, 19]. Although the precise physiological mechanism of CC16 is unknown, some studies suggested a significant reduction of this protein in subjects exposed to RCS without changes in respiratory symptoms, chest X-rays, and lung function tests. Recently, it has been reported in several studies that early detection of silicosis and those at-risk populations can be achieved with the use of serum CC16 level [2, 20, 21]. Moreover, some recent studies have reported a relationship between the level of CC16 and silicosis [2, 15, 18, 22]. For example, Naha's study revealed a connection between the serum CC16 level and silicosis, and the level of CC16 was significantly reduced in people with silicosis [2]. However, contradictory results have been also reported in this regard. For instance, in the previous study, no significant difference was reported between exposed and non-exposed workers [12].

CC16 is a significant player in the regulation of inflammation in the lung, and in inflammatory conditions, its decrease may indicate chronic lung inflammation and ultimately lung fibrosis. On the other hand, the basic pathological changes in silicosis include diffuse lung fibrosis, which may be associated with serum CC16 levels and silicosis [12, 18, 23]. By knowing the biomarkers of silicosis, we can diagnose this disease in the early and treatable stages, and also the contradictory results of previous individual studies and the lack of a meta-analysis in this regard, Hence, in this present study, the relationship between occupational exposure to Respirable Crystalline Silica (RCS) and serum CC16 level was investigated in the form of a systematic review and meta-analysis. Another

goal of this study was to compare the serum level of CC16 protein silicosis patients or silica exposure versus healthy individuals.

Search strategy

The criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used to conduct the meta-analysis [24].

An electronic search for finding relevant records was performed until November 2023 in various databases including PubMed, Web of Science, and Scopus using Medical subject headings (MeSH) such as CC16 protein, human, Clara-cell specific 10-kD protein, Clara cell phospholipid-binding protein human and silicosis. In addition, reference lists of reviews were screened, and manual searches were also used for finding relevant literature.

Study selection and data extraction

To organize studies, document management software (Endnote, version X8, Thomson Scientific, Stamford, Connecticut, USA) was used, and then duplicates of the included studies were removed. Then, two researchers (HA and MF), independently screened the titles and abstracts of imported articles. Finally, the full text of all studies was evaluated based on the selection criteria. The eligible papers were selected and others that did not meet the criteria in terms of aim and objectives were excluded. Disagreements between the researchers were resolved by a third reviewer. The extracted information includes the following terms: country of study, duration of exposure, sample size, age (years), occupation type, RCS measurement method, silicosis status, and serum CC16 level. All mentioned studies were reviewed regardless of the publication date and language, age, gender, and race.

Inclusion and exclusion criteria

Inclusion criteria: 1) Population: exposed workers; 2) Exposure to RCS; 3) Outcome: silicosis; 4) Study design: types of observational studies, including cohort, ecological, and cross-sectional.

Exclusion Criteria: Case series, case reports, review articles, letters to editors, animal studies, articles whose full text was not available, and irrelevant records were excluded.

Quality assessment

To reduce the bias, the quality assessment of the selected studies was done based on the Newcastle-Ottawa Scale (NOS) [25]. The NOS provides a checklist of important items for judging bias in studies. According to this protocol, the quality of studies was graded from 0 to 9, with a score of ≥7 points classified as high-quality and otherwise as low-quality.

Statistical methods

The mean difference between silicosis and non-silicosis groups was compared using the Standardized Mean Difference (SMD). A 95% Confidence Interval (CI) was used to obtain the overall estimates. The I2 statistic and the I2 statistic were used to identify and quantify statistical heterogeneity. According to Higgins cut points judgment about heterogeneity was as follows; 25% (low), 50% (moderate), and 75% (high). The summary's proportions were estimated by utilizing random effects meta-analysis. STATA/SE 11.0 (Stata-Corp, College Station, TX, USA) was used for the statistical analysis.

Search results

The PRISMA flowchart for literature search and identification can be seen in Fig. 1. During the initial database search until August 2022, 18 articles were found (8, 4, and 6 related articles were found from PubMed, Web of Science, and Scopus). After removing duplicates in the Endnote software, three articles were removed. Therefore, the analysis included eight articles that met the inclusion criteria after reviewing 15 articles [2, 8, 9, 12, 15, 18, 22, 26]. The reference list of the eligible articles was

also reviewed to find any probable relevant article, and no relevant study was found.

Study characteristics

The features of the articles that were included in the systematic review are depicted in Table 1. Of them, seven articles were from Asia and one article was from Europe. The total sample size in the two exposed or silicotic and control groups was 712 and 371, respectively. The articles included were published from 1994 to 2021. The duration of exposure in all studies was long and almost close to each other. For example, in LIU Jing's study, the average length of exposure was 27.47 years [15] and in another study, the average duration of exposure was 23.1±9.88 years [2], Except for one the duration of exposure was 15.2±2.4 months. The study population's average age ranged from 31 to 68 years. Also in only one study the mean age of people was over 60 years [15]. The method of measuring the serum level of CC16 in all studies was Elisa.

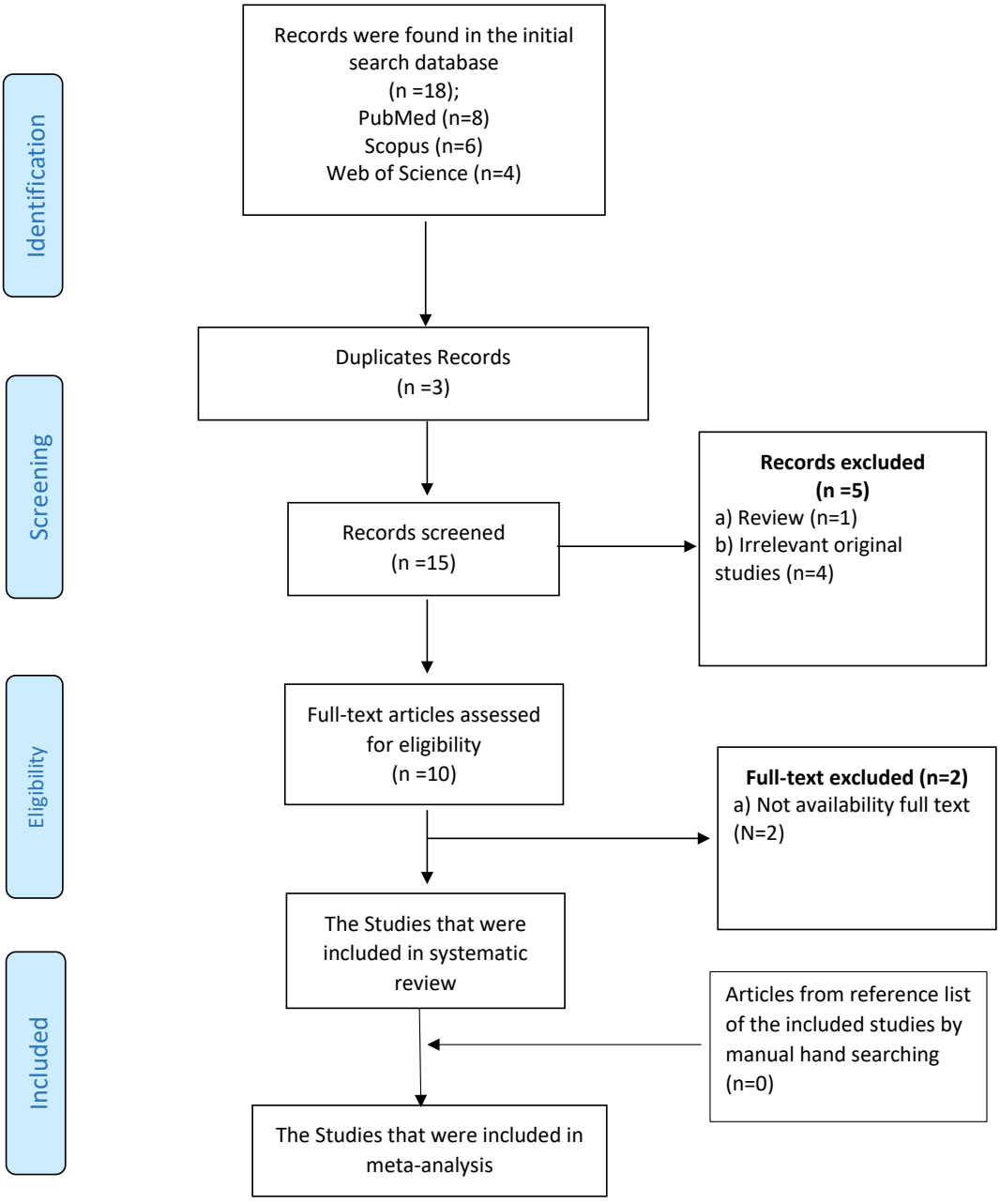

Fig. 1. The flowchart regarding the study selection process

Table 1. The features of the articles that were included in the systematic review

First author	Year of publication	Country	Study size	Duration of exposure	Age (years)	Job type	Silicosis Mean (SD)	Exposed workers	Non-silicosis Mean (SD)	Unit of cc16	Method
Bernard	1994	Belgium	Exposure: n=86 Control: n=86	15.2±2.4	exposure: 34±8 Control:36±9	quartzite rock	-	16 ± 2	22±2 (16.7±12)	ng/mL	ELISA
LIU	2019	China	Silicosis:75 Control:89	27.47	Silicosis: 68.08 Control: 66.97	workers with an occupational history of silica exposure	-2.41 (-2.83, -1.99)		non -smoker 17.87±0.95 smoker 18.23±1.06	ng/mL	ELISA
Naha	2020	India	advanced silicosis:40 dust-exposed workers:25 controls:56	23.1±9.88	silicosis 52.0±8.67 control: 338.9±12.55	ceramic factory	4.7±3.07	10.2±1.77	16.7±3.81	ng/mL	ELISA
Nandi	2021	India	Exposure:68 control:38			occupational health clinic in Delhi	3.5±1.25	7.55±0.75	12.5±1.75	ng/mL	ELISA
Sarkar	2021	India	Case:117 Control:32	28.6± 11.26	case: 47.5±3.91 control: 37.5±11.41	stone mines and stone quarries		8.4 ± 0.87	16.3±3.8	ng/mL	ELISA
Thongtip	2020	Thailand	exposed worker: 57 unexposed workers: 20	21.7±16.9	Exposure: 46.9±12.6 control: 47.2 ±11.2	stone-carving	0.112±0.100		0.003±0.006	ng/mL	ELISA
Wang	2007	China	Silica-exposed: 30 Silicosis: 60 control: 30	Silica-exposed: 21.45±5.70 Silicosis: 27.00±9.69	case: 48.47±4.15 control: 49.00±4.29	pyrite mine	-2.61 (-3.57, -1.65)	4.62±2.29	9.45 ±2.99	ng/mL	ELISA
Zhang	2021	China	Silicosis: 79 Control: 20	(12.7±6.5)	exposure: (48.6±3.9) Control: (47.4±6.3)	-	319.45±77.4		473.21±68.1	ng/mL	ELISA

Meta-analysis

As depicted in Fig. 2, the overall effect estimate suggested that those with silicosis had a lower serum CC16 level (SMD: -3.58; 95% CI, from -5.14 to-2.3; I2 = 94.4% P-value<0.001) than the control group. As depicted in Fig.3, the overall effect estimate that those who were exposed to silicosis had lower serum CC16 levels (SMD: -3.32; 95% CI, from -4.19 to -2.45; I2 = 88.6% P-value<0.001) than the control group. Moreover, the overall effect estimate showed that silica exposure caused a decrease in serum CC16 levels (SMD: -1.92; 95% CI, from -4.22 to 0.39; I2 = 97.5% P-value<0.001) compared to the control group (Fig. 4).

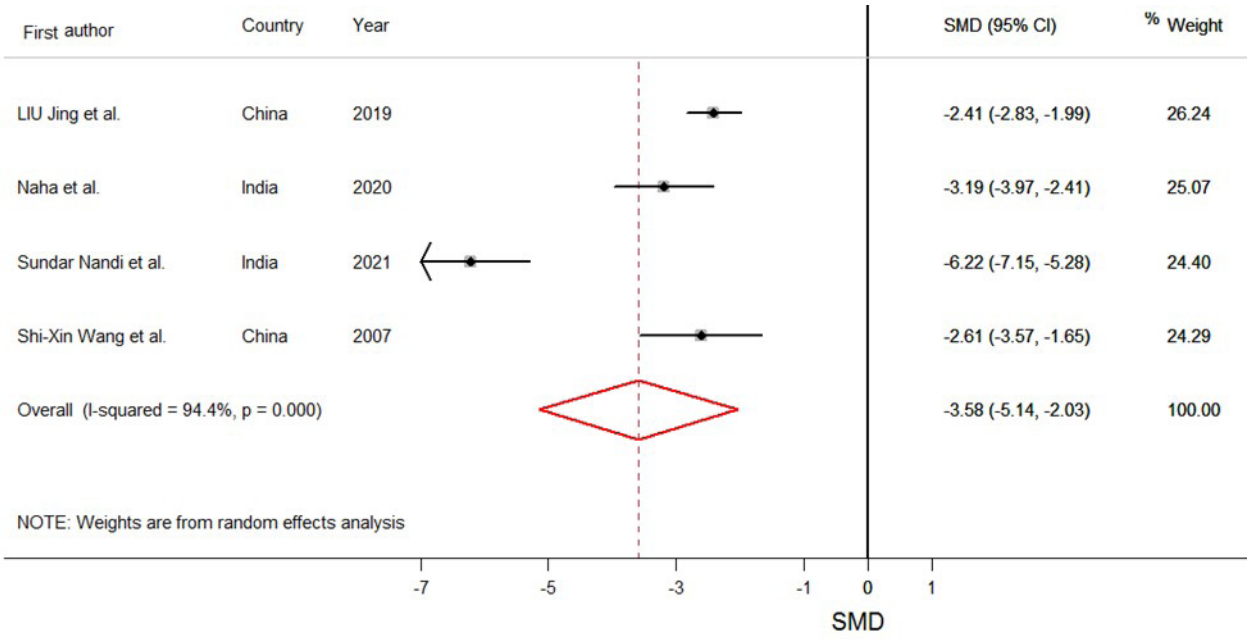

Fig. 2. Mean comparison of CC16 level in silicosis patients vs. healthy individuals

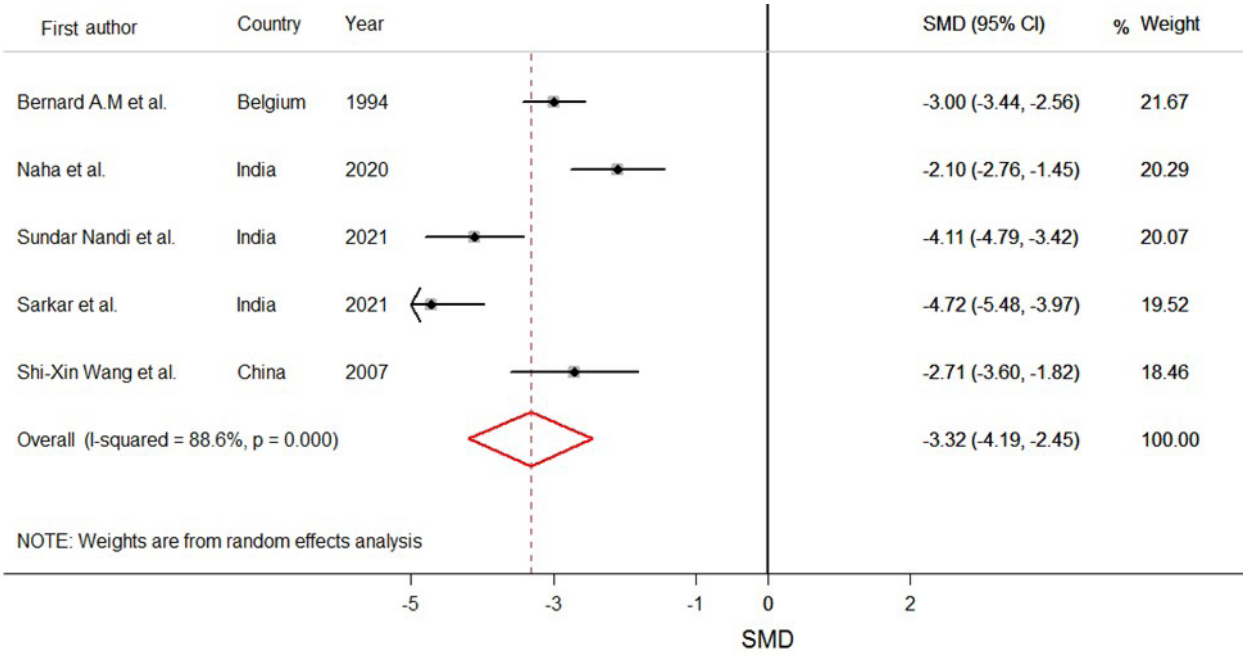

Fig. 3. Mean comparison of CC16 level in silicosis-exposed individuals vs. healthy individuals

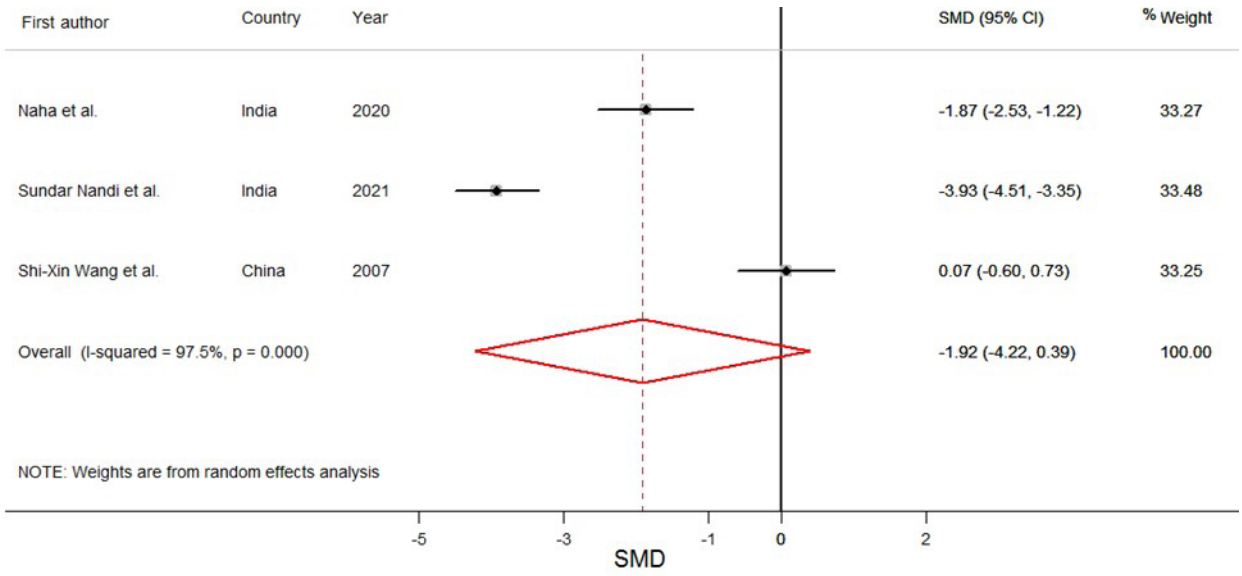

Fig. 4. Mean comparison of CC16 level in silica exposure vs. healthy individuals.

Discussion

Due to the uncertainties around the association between serum CC16 levels and silicosis. The purpose of this study was to evaluate this association, and no review study was found on the investigation of the relationship between RCS exposure and serum level of CC16. In this regard, the present meta-analysis of eight articles investigated the relationship between CC16 protein and the disease in silicosis and RSC-exposed workers. The study's findings indicated that the serum CC16 level in silicosis and RCS-exposed workers was lower compared to the control group. Statistically, there was a significant difference in CC16 mean between silicotic and non-silicotic subjects, and Compared to non-silicotic subjects, those who were cured of silicosis had a mean serum level of CC16 of 3.58 units lower [2, 12, 15, 18]. Also, the mean of serum CC16 of silica exposure was 1.92 units less than the control group [2, 12, 18]. The results of human studies conducted to confirm the biomarkers identified in the early response of cell injury have indicated that workers who were exposed to RCS had a lower serum concentration of CC16 protein than those who were not [21]. In agreement with our results, another research on animals revealed that exposure to RCS and coal mine dusts causes Clara cell hyperplasia in rat lungs [27]. However, this study did not confirm or reject this mechanism well. The review study's findings revealed that the reduction of serum CC16 levels in workers who inhale RCS dust could serve as a biomarker for early toxicity associated with RCS exposure [28].

In a study that investigated the potential applications of CC16 in the prognosis and treatment of pulmonary diseases, CC16 was introduced as a potential biomarker in the diagnosis of several pulmonary diseases. According to the results of this study in diseases such as asthma, Allergic rhinitis, Chronic Obstructive Pulmonary Disease (COPD), and Bronchopulmonary dysplasia (BPD), there is a significant reduction in CC16 level [29]. Also, the results of various other studies demonstrated that the reduction of CC16 levels can help in the diagnosis of some respiratory diseases [30]. The results of another study reported that CC16 levels decreased significantly (on average 15% per 10 pack-years of smoking history) in the serum of smokers without any symptoms. Also, in some occupational groups that have been chronically exposed to diverse air pollutants along with silica dust, the level of this protein has decreased [31].

CC16 is a protein with immunosuppressive and

anti-inflammatory properties that helps to keep the airways safe from the immune system overreacting and causing damage to the tissues. a reduction in the serum level of CC16 in silicosis has been reported in several studies, however, the exact physiological function of this protein and its reduction in exposure to crystalline silica remain unknown [20, 28, 32].

Since this protein is a regulator of inflammation in the lung, and in inflammatory conditions, its level gradually decreases, leading to chronic lung inflammation, and ultimately lung fibrosis. On the other hand, the basic pathological changes in silicosis include diffuse lung fibrosis, the reduction of CC16 serum level can be due to the fibrotic involvement of the lung tissue [23]. Silicosis is diagnosed based on radiological abnormalities which are late and irreversible manifestations of the disease. Due to the lack of effective therapy for silicosis, the response of biomarkers predicting the disease can be used as a very useful screening and monitoring method to assess the health status of the exposed workers before using the conventional diagnosis approaches [15, 28].

Limitations and challenges

Limitations of the study included: 1) Considering that most of the studies were conducted in Asian countries, it may not be representative of the whole world, so the results of this study may not be generalizable to the whole world. 2) The heterogeneity among the included studies was more than 90%, which can lead to uncertainty in the results, and 3) the lack of subgroup analysis due to a limited number of included studies.

Conclusion

Our results showed that silicosis patients, silicosis-exposed individuals, and silica-exposure individuals had significantly lower serum levels of CC16 protein compared to the control group. This analysis emphasized that early diagnosis of silicosis can be achieved by examining serum levels of CC16. This finding is very important in the early diagnosis of silicosis and in identifying high-risk workers in RCS-related workplaces. Identifying the relationship between serum CC16 levels and silicosis requires conducting prospective studies on a larger scale. Also, other research studies on animal models are suggested to determine the association between RCS exposure and serum CC16 level as a dose-response effect.

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Competing interests

The authors declared no conflict of interest regarding this research.

Authors' contributions

H.A. participated in data collection, drafting, and final approval of the manuscript.

A.P Participated in conception, study design, drafting, and final approval of the manuscript.

S.K. participated in the conception, analysis, drafting, and final approval of the manuscript.

M.F. participated in data collection, drafting, and final approval of the manuscript.

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Ethical considerations

“Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors."

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