Systematic Review Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2024 (23 Nov);38.135. https://doi.org/10.47176/mjiri.38.135

Silicosis Incidence and Mortality after Occupational Exposure with Silica Dust: A Systematic Review and Dose-Response Meta-Analysis

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Received: 17 May 2024 Published: 23 Nov 2024

Abstract

Background: We conducted a systematic review of all published epidemiological research related to the relationship between occupational silica exposure and the rates of silicosis incidence and mortality.

Methods: We searched Scopus, PubMed, and Web of Sciences up to 11/07/2023, for original in any language. The search start date was not limited Observational studies, including cohort, case-control, and cross-sectional that have reported risk estimates for the association between silica exposure and silicosis mortality and incidence rates were considered. The methodological quality of the included articles was assessed using the Newcastle-Ottawa scale. Pooled estimates were calculated using the random effects model. Dose-response relations were explored through a two-stage random-effects model with "drmeta" command in Stata software version 14.

Results: Nineteen observational studies were included in the present systematic review and meta-analysis. Based on the linear dose-response analysis, with each mg/m3 increase in daily occupational exposure to silica, the mortality risk of silicosis, the odds and risk of silicosis occurrence significantly increased by 10.19%, 360.02%, and 4.43 × 108%, respectively.

Conclusion: This review revealed that there is a linear dose-response relationship between occupational exposure to silica and incidence and mortality from silicosis. Our findings could have practical applications for occupational and public health. Considering the direct relationship between occupational silica exposure and high incidence and mortality rates of silicosis, the level of silica dust should be decreased in different industries.

Keywords: Silicon Dioxide, Silica; Silicosis, Systematic-Review, Meta-Analysis, Dose-Response Relationship.

Conflicts of Interest: None declared
Funding: *This review was supported financially by the Research Vice-Chancellor of Hamedan University of Medical Sciences (Research ID: 140306275259).*

Cite this article as: Shahbazi F, Assari MJ, Shadi Y, Fattahi-Darghlou M. Silicosis Incidence and Mortality after Occupational Exposure with Silica Dust: A Systematic Review and Dose-Response Meta-Analysis. *Med J Islam Repub Iran.* 2024 (23 Nov);38:135. https://doi.org/10.47176/mjiri.38.135

Introduction

Silicosis is a potentially fatal, irreversible, fibrotic pulmonary disease that may develop subsequent to the inhalation of large amounts of silica dust over time (1). This health outcome is an occupational disease (2) mainly that occurs in almost all countries and in many industries and occupations, including sandblasting, mining, rock drilling, quarrying, brick cutting, glass manufacturing, tunneling, foundry work, stone working, ceramic manufacturing and construction activities (3, 4). Globally, silicosis accounts for 90% of all pneumoconiosis cases (5). The prevalence of silicosis in 1990 and 2019 was 33.13 and 31.60 per 100,000 people, respectively (5). According to the global burden of

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↑***What is "already known" in this topic:***
Although the relationship between Silicosis incidence and mortality after occupational exposure to silica been established in previous literature, its quantity is still not well defined. The purpose of this meta-analysis is to explore potential links between exposure to silica in the workplace and the occurrence and death rates related to silicosis.

→***What this article adds:***
The current study highlights there is a linear dose-response relationship between occupational exposure to silica and incidence and mortality from silicosis. With more details, each mg/m3 increase in daily occupational exposure to silica, the mortality risk of silicosis, and the odds and risk of silicosis occurrence significantly increased by 10.19%, 360.02% and 4.43 × 108%, respectively.

diseases study, the death number of silicosis between 1990 and 2019 has decreased from 9973 to 10043 cases, and the disability-adjusted life years (DALYs) rates have decreased from 5.05 cases per 100,000 people to 3.33 cases in 2019 (6). The highest disease burden is carried by the middle and high-middle socio-demographic index regions and elderly people (7). According to previous studies, occupational exposure to silica has an excessive mortality rate due to silicosis, although the quantity of this relationship is different in various research (8-10).

Although the relationship between exposure to silica and the risk of silicosis has been well established in previous literature (4, 11-14), its quantity is still not well defined. The purpose of this meta-analysis is to explore potential links between occupational silica exposure and the incidence and mortality rates of silicosis. While recent literature has examined this association through epidemiological studies, we believe this is the first systematic review and dose-response meta-analysis conducted so far.

Methods

Eligibility criteria (PICOS)

Population: The study population comprised people who were exposed to silica due to their jobs.

Exposure: The exposure group included people who had different levels of exposure to silica.

Control: The control group consisted of people who were not exposed to silica or were exposed to it at the lowest level.

Outcome: The primary outcome of interest was the occurrence of silicosis, as confirmed through radiological examination, or death from silicosis.

Studies: Observational studies, including cross-sectional, retrospective cohort, prospective cohort, and case-control studies, were included in the analysis regardless of their publication time, publication status or language.

Information sources and search

A systematic search was conducted in Scopus, PubMed, and Web of Science databases until 11/07/2023. The search start date was not limited. Additionally, the references of the included studies were reviewed to identify any additional studies that met the inclusion criteria. The search strategy was as follows: (((silica [Title/Abstract]) OR (Silicon Dioxide [MeSH Terms])) AND ((Silicosis [MeSH Terms]) OR (Silicosis [Title/Abstract]))) AND (((Case-Control Studies [MeSH Terms]) OR (Cohort Studies [MeSH Terms])) OR (Observational Study [Publication Type])).

Study selection

The search results from the three mentioned databases were combined using EndNote software, and duplicate records were removed. Two authors (Y.S. and M.FD.) independently reviewed the titles and abstracts of the preliminary articles to exclude those that did not meet the inclusion criteria. Then the full text of the articles whose title and abstract were in accordance with the purpose of the study was examined to determine their eligibility for inclusion in the analysis. Disagreements between authors were resolved by negotiation. Also, the Kappa statistic was calculated to measure the agreement between the two authors.

Data extraction

The data from the included studies were extracted by two authors (F.SH. and M.FD.) and recorded in Stata software. The extracted data included the first author's name, publication year, country, language, age mean/ range, study design, the number of cases at each level of exposure to silica, type of effect size with confidence interval or standard error of the outcome at each exposure level, comorbidity with tuberculosis, and daily exposure to silica (mg/m^3).

Methodological quality

We used the Newcastle-Ottawa scale (NOS) to evaluate the methodological quality of the studies included in this systematic review and meta-analysis (15). This scale was developed to assess the quality of nonrandomized studies such as case-control, cohort, and cross-sectional studies. In the NOS, a set of items about the selection of study participants, comparability of groups, and evaluation of exposure/ outcome were assessed. This scale assigns a maximum of nine stars to each study (4 stars for selection, 2 stars for comparability, and 3 stars for outcome or exposure). Studies that obtained seven or more stars were classified as high-quality, while those with fewer than seven stars were classified as low-quality.

Assessment of heterogeneity and publication bias

We used I^2 statistic and chi-square test to investigate the existence of heterogeneity between studies (16). We also performed meta-regression to identify any potential factors that could explain the observed heterogeneity in the results. We used the Begg test (17) and funnel plot (18) to check the possibility of publication bias.

Statistical analysis

The "metan" command was performed to summarize data from studies (19) using Stata software version 14 (StataCorp, College Station, TX, USA) and the random effects model. In order to investigate the dose-response relationship between silica exposure and the incidence and mortality rates from silicosis, the two-stage random-effects dose-response model using linear, quadratic, and cubic splines was used (20). Different models were fitted to the data and the best model was chosen according to Bayesian information criterion.

Results

Study selection & Characteristics

The primary search found 513 articles. Following excluding 128 duplicates, 385 articles were entered for the title and abstract reviewing. Next, 51 articles were included for the full-text screening. Finally, the data from 19 studies (6 studies for mortality and 13 studies for incidence) were included in the systematic review and dose-response meta-analysis (Figure 1). These studies included 288336 participants from six different countries (Australia, Brazil, China, Finland, Germany, and the USA). The mean of exposure to silica in incidence studies was 0.54 mg/m^3 per day and in

[DOI: 10.47176/mjiri.38.135]

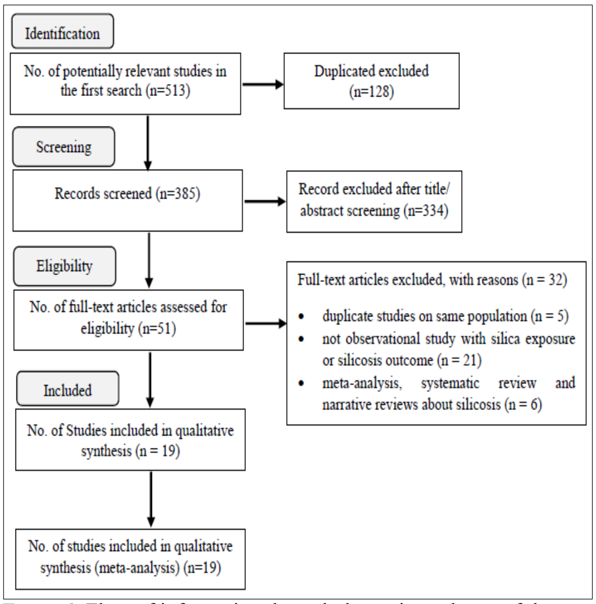

Figure 1. Flow of information through the various phases of the systematic review

the mortality studies, it was 9.50 mg/m^3 per day. The studies were published between 1994 and 2021. All studies were published in English. The percentage of agreement between data extractors was 81.5%.

Overall systematic review and meta-analysis results

We found a significant positive association between occupational silica exposure and mortality rate from silicosis (RR = 4.54, 95% CI: 2.41, 6.67) (Figure 2). We performed a subgroup analysis by measuring the association in the relationship between occupational silica exposure and silicosis incidence. The pooled OR, RR, and HR for silicosis incidence were 1.13 (95% CI: 1.03, 1.22), 2.22 (95% CI: 1.32, 3.12), and 2.41 (95% CI: -0.15, 4.97), respectively (Figure 3). The meta-regression showed no significant association between country, years of publication, study quality and risk of silicosis mortality and incidence ($P = 0.530$).

Publication bias and quality assessment

The Begg test indicates no significant publication bias in the association between occupational silica exposure and mortality from silicosis ($P = 0.535$) and silicosis incidence ($P = 0.617$). Also, the symmetry distribution of studies around the null line in all funnel plots indicates the absence of publication bias (Figure 4). In terms of quality assessment based on the NOS eight of the studies had low quality and eleven had high quality (Table 1).

Dose-response meta-analysis

We included 11 studies in a dose-response meta-analysis between occupational inhalation of silica dust and silicosis mortality and incidence. In this analysis, the studies that had not reported the number of silicosis patients or the number of deaths due to silicosis in each level of exposure to silica were excluded. According to linear dose-response analysis, the risk of mortality from silicosis increased by 10.19% for every mg/m^3 increase in daily occupational silica inhalation ($P < 0.001$). Also, the odds and risk of silicosis occurrence increased by 360.02% and 4.43 × 10^8% with an increase in mg/m^3 per day of silica exposure, respectively (P for both effect sizes were less than 0.001) (Figure 5). Given that more than one study is needed for the two-stage dose-response meta-analysis and only Mundt's study remained for HR, we could not perform a dose-response meta-analysis for this effect size.

Discussion

Although the relationship between exposure to silica and silicosis is straightforward, its magnitude has not been quantitatively investigated using a systematic review and meta-analysis. This study is the first attempt to quantify this association by a dose-response meta-analysis. According to this systematic review, there is a positive relationship between occupational silica exposure and silicosis mortality and incidence. Based on the dose-response analysis, with each mg/m^3 increase in daily exposure to silica, the mortality and incidence rates of silicosis increase linearly.

The mechanism for the risk of silicosis among various occupational industries and factories is unknown. Experimental studies have suggested that the respirable form of silica is small enough to reach the terminal bronchioles and alveoli of the respiratory system. Standard immune responses are unable to remove these particles from the lungs,

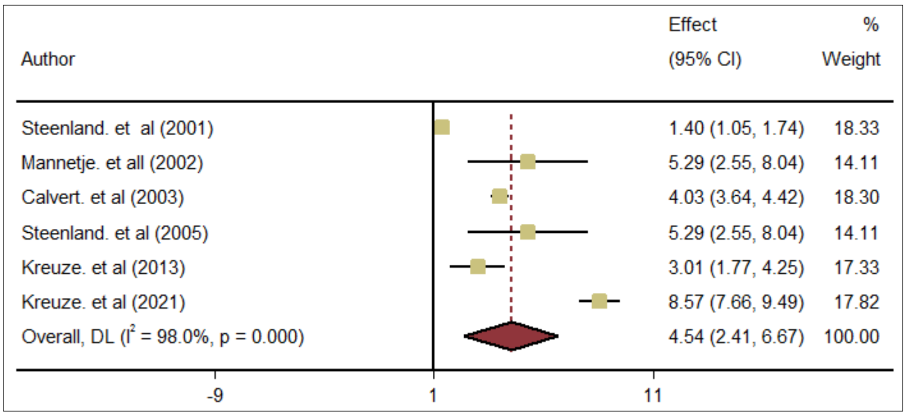

Figure 2. Forrest plot of the association between occupational silica exposure and mortality from silicosis (a measure of association is Rate Ratio)

[DOI: 10.47176/mjiri.38.135]

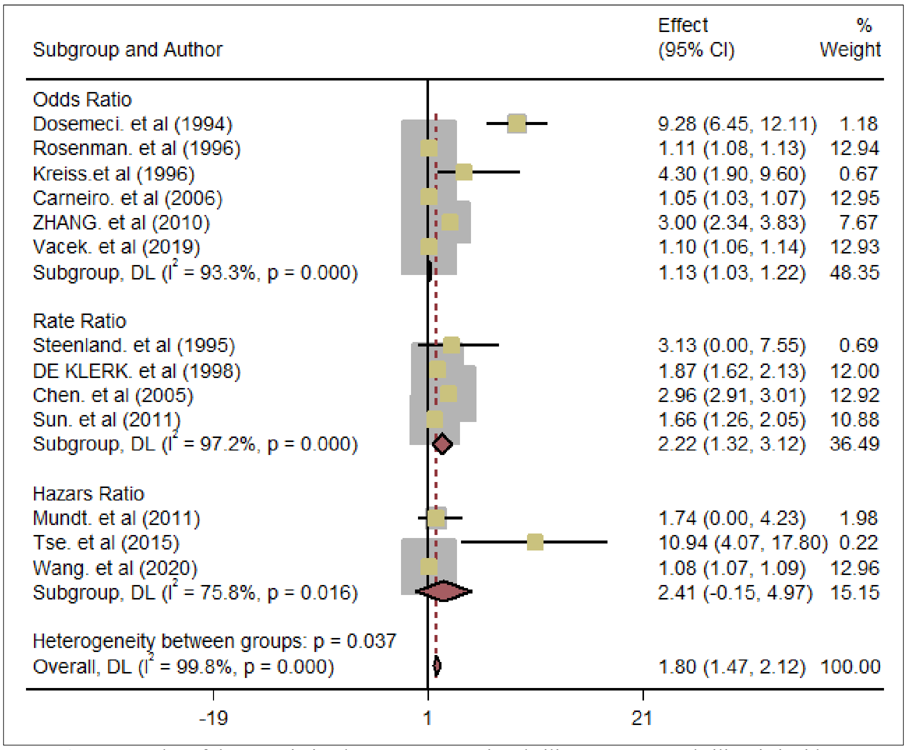

Figure 3. Forrest plot of the association between occupational silica exposure and silicosis incidence

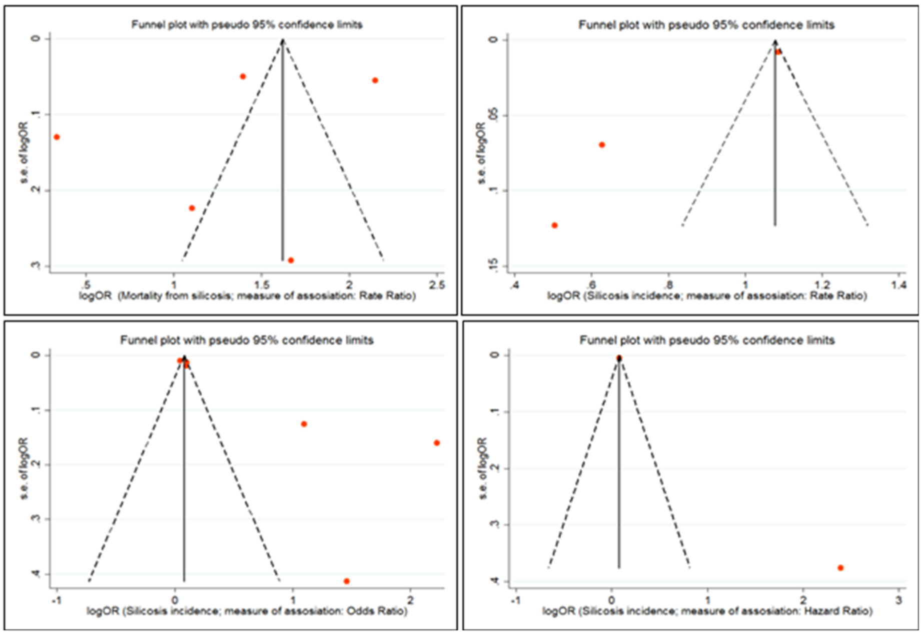

Figure 4. Funnel plots of included studies by incidence and mortality studies

setting off a harmful cycle of inflammation and tissue damage that eventually results in silicosis (8, 21). On the other hand, increasing exposure to silica increases the silicosis mortality with high intensity and steep slope. According to the Centers for Disease Control and Prevention report, despite the significant progress and global efforts, silicosis death still occurs and is a public and occupational health problem. These deaths reflect exposure to silica particles that cause silicosis-related deaths (22). So, in order to reduce the terrible deaths attributed to silicosis in workplaces, efforts should be made in cases where silicosis cannot be prevented, and the silicosis death risk factors should be identified to prevent deaths in patients with silicosis (23).

The findings of this study have important applications for occupational and public health because occupational silica exposure has long been a main universal occupational health problem. The findings of this study can be a basis to help direct public policies related to protective measures to keep workers in good health and safe working environments and away from other work activities responsible for

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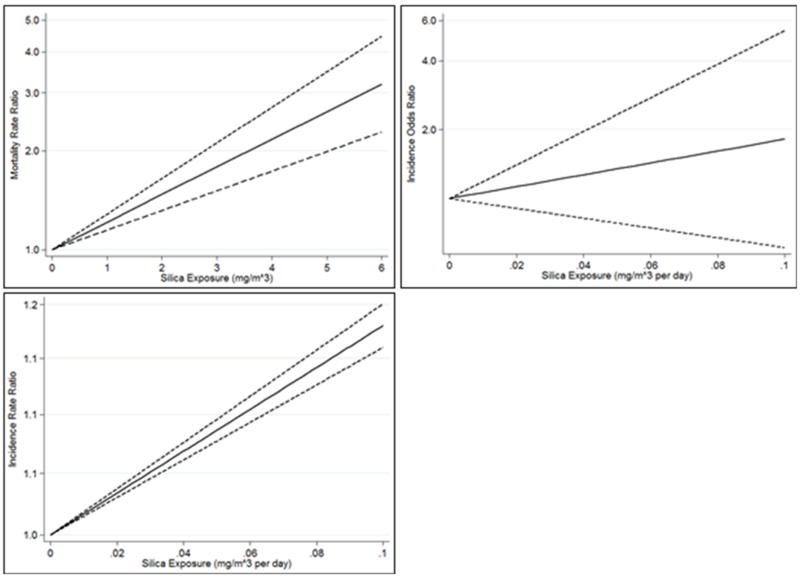

Figure 5. Dose-response analysis for the association between occupational silica exposure and silicosis mortality and incidence rates.

Table 1. Characteristic of the included studies

ID	First author	Year	Country	Study design	Sample size	Age mean/ range	Silica mean exposure	NOS Score	Quality
1	Carneiro, A. P (27)	2006	Brazil	Case-Control	82	39.57	N.R©	★★★★★★	Low Quality
2	W. Chen (28)	2005	China	Cohort	23002	42.18	0.395	★★★★★	Low Quality
3	De Klerk (29)	1998	Australia	Cohort	2297	N.R	N.R	★★★★★★★★	High Quality
4	M Dosemeci (30)	1994	USA	Case-Control	1638	N.R	0.191	★★★★★★★★	High Quality
5	Kathleen Kreiss (31)	1996	USA	Cross-Sectional	149	59.03	N.R	★★★★★	Low Quality
6	Kenneth Mundt (32)	2011	Germany	Cohort	17644	N.R	0 .115	★★★★★★★	High Quality
7	Kenneth Rosenman (25)	1996	USA	Cohort	1072	58.90	0.171	★★★★★★★	High Quality
8	Kyle Steenland (24)	1995	USA	Cohort	3330	N.R	1.800	★★★★★★★★	High Quality
9	Yi Sun (33)	2011	China	Cohort	3250	60.30	0.196	★★★★★	Low Quality
10	Lap Ah Tse (34)	2015	China	Cohort	3499	63.13	0.087	★★★★★★	Low Quality
11	Vacek PM (26)	2019	USA	Case-Control	234	43.50	1.143	★★★★★★★★	High Quality
12	Dongming Wang (10)	2020	China	Cohort	39808	45.30	2.734	★★★★★★★★	High Quality
13	Min Zhang (35)	2010	China	Cohort	1300	N.R	N.R	★★★★★★★★	High Quality
14	G M Calvert (36)	2003	USA	Cross-Sectional	7422	N.R	1.858	★★★★★★★	High Quality
15	Michaela Kreuzer (37)	2013	Germany	Cohort	58982	N.R	16.200	★★★★★★	Low Quality
16	Michaela Kreuzer (38)	2021	Germany	Cohort	35204	N.R	22.625	★★★★★★	Low Quality
17	A 't Mannetje (39)	2002	USA, Finland, Australia	Cohort	18364	68.70	10.632	★★★★★★★	High Quality
18	Kyle Steenland (40)	2001	USA	Cohort	5086	N.R	0.827	★★★★★	Low Quality
19	Kyle Steenland (41)	2005	USA	Cohort	65980	N.R	10.632	★★★★★★★	High Quality

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lung disease (4).

The dose-response association between silica and silicosis mortality and incidence has been confirmed in several previous studies (10, 24-26); however, most previous studies focus on a single industry and evidence on different work settings and industries is limited. In this systematic review, various job environments from the metal mines, iron ore, and gold industry to ceramics and pottery workers, were examined and pooled.

Our study has some limitations. First, we did not calculate a dose-response analysis of silicosis incidence for the hazard ratio effect size because some studies did not report silicosis cases at each level of exposure to silica dust. Finally, only one study remained for HR so we could not perform a dose-response meta-analysis for this measure. Second, high heterogeneity between studies is another limitation of this study, which can be attributed to the difference in study design, small number of included articles, different working environments, or differences in the mechanism of measuring exposure to silica dust in different studies. Although we performed meta-regression analysis to find the potential sources of heterogeneity, due to the small sample number of included studies, the heterogeneities remained high. The most important strength of this study was measuring the dose-response relationship of exposure to silica on the incidence and mortality rates of silicosis with a systematic review study for the first time.

Conclusion

The results of this systematic review and meta-analysis propose that the risk of silicosis mortality and incidence increases as the level of silica exposure increases. This result confirms the linear association between occupational silica exposure and incidence and mortality rates from silicosis. The existence of this dose-response relationship is one of Hill's causal criteria and can strengthen the scientific background for strenuous occupational and industrial health interventions for the control of exposure to this dust.

Authors' Contributions

FSH and MJA conceived and designed the study. MFD and YS conducted the literature search and screening. FSH and MFD gathered the data. FSH conducted the statistical analysis. FSH and YS contributed to data interpretation. MFD and MJA drafted the manuscript, which FSH critically reviewed. All authors reviewed the final version before publication. FSH assumes full accountability for the accuracy and reliability of the data analysis and has unrestricted access to the study's data.

Ethical Considerations

This study has been approved by the Research Ethics Committee of Hamadan University of Medical Sciences with ethical ID: IR.UMSHA.REC.1403.401and research ID: 140306275259.

Acknowledgment

We would like to appreciate the Vice-Chancellor for Research and Technology of the Hamadan University of Medical Sciences for supporting this work.

Conflict of Interests

The authors declare that they have no competing interests.

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