Occupational Exposure to Solvents and Gender-Related Risk of Systemic Sclerosis: a Metaanalysis of Case-Control Studies

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ABSTRACT. ***Objective.*** In 2001 a metaanalysis reported an excess risk of systemic sclerosis (SSc) related to solvents exposure. The magnitude of risk varied among studies and sources of heterogeneity have not been investigated due to a lack of statistical power. We conducted a new metaanalysis to identify features associated with the magnitude of SSc risk in patients exposed to solvents.

Methods. We searched 4 databases (Medline, Pascal, Pascal Biomed, Francis). Inclusion criteria were: case-control study, occupational exposure to solvents (OES) assessed by questionnaire and summarized to "any solvent" or "any organic solvent," SSc defined by the American College of Rheumatology or the consultant's criteria. The quality of studies within this metaanalysis was scored according to the Newcastle-Ottawa scale. Odds ratios (OR) were adjusted for the "publication bias" and validated by a sensitivity analysis. Subgroup analyses investigated the effect of gender, quality of studies, and the type of controls.

Results. Among 11 studies (1291 patients and 3435 controls), 9 involved a majority of women (76.2 to 100%), while 2 involved men only. The risk of SSc associated with OES was variable among studies (p for heterogeneity = 0.01) and overrepresentation of higher OR values in smaller studies (p = 0.003) suggested "publication bias." SSc was associated with OES (OR 2.4; 95% CI 1.7–3.4; p < 0.0001), including after adjusting for bias (OR 1.8; 95% CI 1.2–2.5; p = 0.002). The relative risk was higher (p = 0.03) in men (OR 3.0; 95% CI 1.9–4.6; p < 0.0001) than in women (OR 1.8; 95% CI 1.5–2.1; p < 0.0001).

Conclusion. Whereas SSc affects women predominantly, among subjects with occupational exposure to solvents, men are at higher risk than women for the disease. (First Release Nov 15 2006; J Rheumatol 2007;34:97–103)

Key Indexing Terms:
METAANALYSIS SCLERODERMA EPIDEMIOLOGY
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Systemic sclerosis (SSc) is a rare autoimmune disease with a prevalence estimate varying from 3 to 250 per million[1]. Mortality rate varies with the extent of the disease, up to 35% within 5 years in cases of multiple organ involvement[2]. Among connective tissue diseases, SSc may be particularly related to environmental exposure. Incidence rate increased in the USA from 0.6 per million annually in 1947 to 19 in 1991[1]. However, early incidence rates are questionable, as the definition of scleroderma was not uniform in these studies and classification of the disease published in 1982. Clusters of cases have been reported in heavily industrialized areas near London[3] and in a rural area near Rome[4]. SSc occurs rarely in twin pairs suggesting that while inherited genetic factors may play a role, environmental exposure may be the main factor in disease development[5].

A high relative risk for SSc, suggestive of causal relationship, exists in men submitted to occupational exposure to silica dust[6]. In France SSc is recognized as an occupational disease, in patients with former or present exposure to crystalline silica[7]. Occupational exposure to silica involves mainly male workers, while SSc affects especially women, with an approximate sex ratio of 4:1[2]. Therefore several other occupational or environmental exposures were investigated for the risk of SSc. A possible relationship between silicone gel-filled breast implants and SSc was suggested by case reports and series but not confirmed by a metaanalysis[8].

The role of organic solvents and other chemicals has also been invoked, from case reports, as possibly contributing to the disease[9]. In 1981, a toxic oil syndrome involving more than 20,000 subjects who had ingested colza oil contaminated with aniline shared several common clinical and pathological characteristics with SSc[10]. Several epidemiological studies investigated the relationship between SSc

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and occupational exposure to solvents assessed by questionnaires for substances or substance categories, or specific jobs at risk. In 2001, 7 case-control studies[11-17] and a cohort study[18] were combined in a metaanalysis[19] that calculated a significantly increased relative risk for the disease (RR = 2.9, 95% CI 1.6–5.3) in subjects exposed to solvents. This metaanalysis also revealed a significant heterogeneity among the magnitude of relative risks reported by individual studies. However, due to a lack of statistical power, it was not possible to identify those features associated with the magnitude of relative risks that may explain heterogeneity among studies. Since then, additional relevant studies have been published, including a case-control study with additional subjects[20], and at least 4 others[7,21-23] are now available. The aim of this review was to measure the association between SSc and occupational exposure to solvents by a metaanalysis of case-control studies investigating that relationship, and identify population or study-specific characteristics that may influence the magnitude of risk.

MATERIALS AND METHODS

Search strategy. In February 2005, we performed a systematic search of 4 databases (Medline®, Pascal®, Pascal Biomed®, Francis®) through the INIST ERL server, with the assistance of a professional librarian. Our search was not restricted for period or language and used the text terms [(*systemic sclerosis* or *scleroderma)* and *solvent*]. Authors were not contacted but references provided in these studies were hand-searched to identify other potential data sources. The process from selection of studies to data coding was performed independently by 2 investigators (AK and OA). At the end of each step of the process, the results were reviewed and validated by consensus among investigators.

Inclusion criteria. We included any case-control study that summarized occupational exposure to any solvent and/or to organic solvents, assessed by questionnaire in patients with SSc defined in cases by the American College of Rheumatology (ACR) or the consultant's criteria and controls chosen from among apparently healthy subjects or patients with diseases other than SSc.

Quality control. We assessed the quality of included studies in the context of this metaanalysis with a modified version of the Newcastle-Ottawa scale (NOS) for case-control studies (available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). This scale rates high quality choices by stars for selection, comparability, and exposure items. The selection item is rated over a maximal number of 4 stars, one for adequacy of case definition, one for representativeness of the cases, one for selection of controls, and one for definition of controls. The comparability item is rated over a maximal number of 2 stars, one for the most important factor for comparability and one for another important factor. We selected matching by age and sex as the most important factor and matching by residency area as the other important factor. The exposure item is rated over a maximal number of 3 stars, one for ascertainment of exposure, one if the same method of ascertainment of exposure was used in cases and controls, and one for nonresponse rate.

Statistical analysis. We coded data about country, year, and language of publication, age, and sex for cases and controls. Frequencies of exposure of the subjects to any solvent or any organic solvent were determined in cases and controls. As a measure of association between exposure to solvents and SSc, we combined odds ratios (OR) with 95% confidence intervals (CI) stratified by study. First, heterogeneity among samples was tested at the level of significance of 5%, by the statistic for Mantel-Haenszel method. Then, OR were combined by the Mantel-Haenszel fixed effect model if the heterogeneity statistic did not reach significance level and by the DerSimonian and Laird random effect model otherwise[24]. Influence analysis investigated the effect of each individual sample on overall estimation by calculating OR and CI values after omitting each study in turn (jackknife method)[25]. Publication bias was assessed by funnel plots and Begg and Mazumdar's adjusted rank correlation test[26].

To assess the publication bias effect of missing studies on the estimated association between exposure to solvents and SSc, we used the Duvall and Tweedie "trim and fill" method[27]. Briefly, that method estimates the outcome and number of missing studies that would be necessary to correct the publication bias, and provides an adjusted estimation of OR by incorporating these theoretical missing studies in the metaanalysis. To investigate potential heterogeneity sources and identify features associated with the magnitude of risk we conducted subgroup analyses, when results were available for at least 4 studies, for sex, types of exposure (any solvent and organic solvents), and quality scores (below and above average). The relative risks were compared between independent subgroups by p values for z scores of the difference between logarithms of OR. All analyses were performed with Stata Statistical Software: Release 8.2 (Stata Corporation, College Station, TX, USA).

RESULTS

Study selection. Our search identified 24 references, which we retrieved for in-depth screening. We did not include case reports or series, reviews, or a case-control study[28] that assessed exposure to solvent in hobbies rather than occupational exposure. Among the 16 remaining references, we excluded 4 preliminary reports[14,29-31] for which a further report was redundant, extended sample size or provided additional data. We also excluded the cohort study of Lundberg, *et al*[18] included in the previous metaanalysis[19], which involved only 6 men with SSc and assessed exposure only for a specific solvent. Thus, we finally included 11 distinct case-control studies[7,11-13,15-17,20-23] that compared the frequencies of occupational exposure to any or organic solvents between patients with SSc and controls.

Study description. The 11 eligible reports[7,11-13,15-17,20-23] included 1291 cases and 3335 controls (Table 1). A majority of reports (8/11) came from European countries. Mean or median age of cases was not stated in 2/11 but was similar among other studies (range 50–57.3). Sex ratio was extremely variable among studies, but was similar in each study between cases and controls. Diagnosis of SSc was based on ACR criteria in a majority of studies (8/11). Only 4 studies involved community controls while the 7 others referred to hospital controls, including patients with other connective diseases. According to the NOS, 4 studies were scored below the virtual average value of 4.5 stars.

Exposure to solvents and the risk for SSc. Exposure was assessed for any solvent in 8 and organic solvents in 3 studies. Nietert, *et al*[17] used 3 exposure scores (maximal intensity, cumulative intensity, and maximal probability) to summarize a subject's lifetime exposure status. In our study, we selected the maximal probability score as the measure of exposure to any solvent, to ensure comparability with studies in which intensity of exposure was not quantified. In the whole sample, where exposure was assessed either for any

Table 1. Characteristics of the studies examined in the metaanalysis.

Study	Controls	N	Patients Age/%men	ACR Criteria	Quality Score S	C	E
Czirjak, Hungary 1989[11]	CC	61	50/1.7	No	***	*	
Silman*, UK 1992[12]	CC	56	57.3/100	No	***	**	*
Bovenzi, Italy 1995[13]	HC	21	NR/23.8	Yes	**	*	**
Goldman*, USA 1996[15]	CD	33	NR/9.0	Yes	**		*
Zachariae*, Denmark 1997[16]	HC	28	56.7/100	Yes	***	*	
Nietert, USA 1998[17]	HC	178	51.8/20.7	No	*		**
Diot, France 2002[21]	HC	80	55.8/13.8	Yes	**	**	**
Czirjak, Hungary 2002[22]	HC	63	52/0	Yes	**	**	**
Garabrant, USA 2003[20]	CC	623	56.3/0	Yes	****	**	**
Bovenzi, Italy 2004[23]	HC	55	50/16.4	Yes	***	**	*
Maître, France 2004[7]	CC	93	54.8/10.7	Yes	****	**	***

S: Selection; C: Comparability; E: Exposure; ACR: American College of Rheumatology; CC: Community controls; HC: Hospital controls; CD: Patients with other connective tissue diseases. NR: Not reported. * Exposure assessed for organic solvents only.

solvent or only for organic solvents, the risk of SSc was significantly higher in exposed subjects (OR 2.41, 95% CI 1.73–3.37; p < 0.0001; Table 2, Figure 1). The funnel plot of the logarithm of estimated OR against the standard error (Figure 2) showed significant asymmetry (p = 0.003) and suggested publication bias as higher relative risk values were reported by smaller studies. After adjusting for publication bias, the risk of SSc was still higher in exposed subjects (OR 1.76, 95% CI 1.24–2.50; p = 0.002; Table 3). In the influence analysis (Table 3), removing any one study resulted in little change for the estimation of OR and 95% CI. Significant heterogeneity was measured among studies for the risk of SSc associated with solvents exposure (OR range: 1.28 to 23.18; p = 0.01). Subgroup analyses identified sex and the quality of studies rated by the NOS, but not the type of control subjects, as potential sources for heterogeneity in the magnitude of relative risks among studies (Table 2). The relative risk of SSc in subjects exposed to solvents was significantly higher (p = 0.03) in men (OR 2.96, 95% CI 1.89–4.64) than in women (OR 1.75, 95% CI 1.48–2.09). Tendency was similar thus not reaching significance level (p = 0.29) after adjusting OR for publication bias (Figure 3).

DISCUSSION

As reported by a previous metaanalysis[19], our results confirm a higher risk of SSc in subjects with past occupational exposure to solvents. Unlike the previous metaanalysis, our results took selection bias into account, and included subgroup analyses showing a higher relative risk of SSc related with occupational exposure to solvents in men than in women.

Adding to the results of funnel plots and statistical tests for bias, a trend toward higher OR in studies with low quality scores than in others also suggests a potential bias in the selection of studies, the so-called "publication bias." The NOS rating is intended for metaanalysis purposes rather than for the absolute rating of the papers. The quality score does not represent the quality of the individual study per se. It represents a measure of the study's usefulness towards developing a more precise measurement of association in

Table 2. Exposure to solvents and the risk of systemic sclerosis in the whole sample and subgroups.

(Sub) sample	Studies N	Cases N (%*)	Controls N (%*)	OR (95% CI)	Pooled risk p for OR	p for Heterogeneity	p for Bias
Overall	11	1291 (24.6)	3435 (15.5)	2.41 (1.73–3.37)	< 0.0001	0.01	0.003
Any solvent	8	1174 (23.4)	3064 (15.9)	2.09 (1.48–2.95)	< 0.0001	0.06	0.01
Men	7	156 (42.3)	277 (22.7)	2.96 (1.89–4.64)	< 0.0001	0.18	0.001
Women	8	1102 (21.7)	2912 (15.5)	1.75 (1.48–2.09)	< 0.0001	0.17	0.09
Community controls	4	833 (26.4)	2493 (17.5)	2.14 (1.27–3.62)	0.005	0.04	0.05
Hospital controls	8	458 (21.4)	942 (10.2)	2.46 (1.78–3.39)	< 0.0001	0.15	0.11
NOS score ≥ 5 stars	7	991 (25.8)	2900 (16.8)	1.76 (1.48–2.10)	< 0.0001	0.32	< 0.0001
NOS score < 5 stars	4	300 (20.7)	535 (8.8)	3.86 (1.34–11.09)	0.01	0.006	0.26

* Proportion of subjects exposed to solvents. NOS: Newcastle-Ottawa Scale.

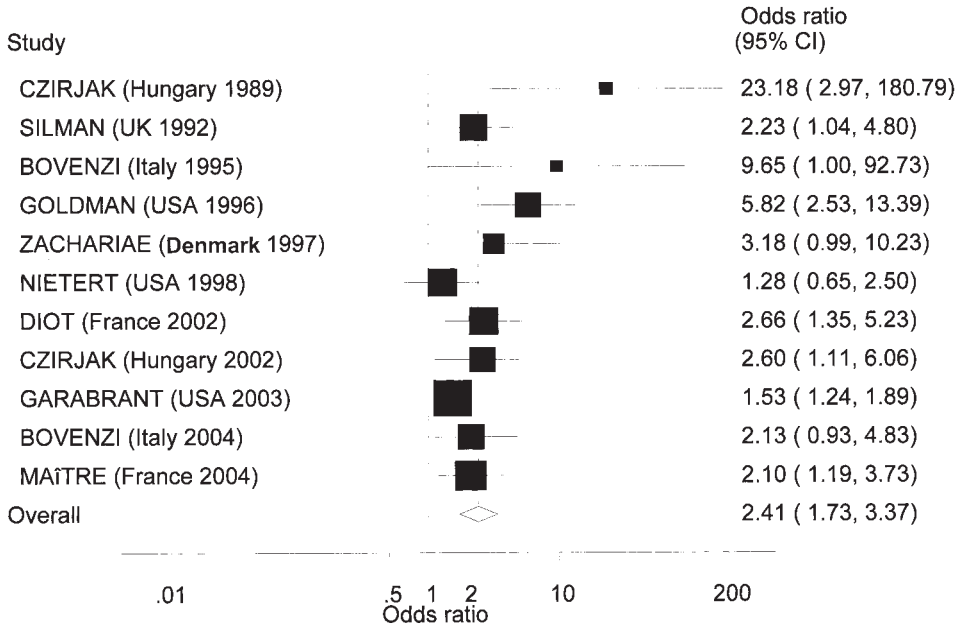

Figure 1. Exposure to any or any organic solvent and the risk of systemic sclerosis (SSc) in the whole sample. Points and overall (diamond) estimates are given as odds ratios (OR) with 95% CI. The size of each box is roughly proportional to the weight of the corresponding study in the metaanalysis.

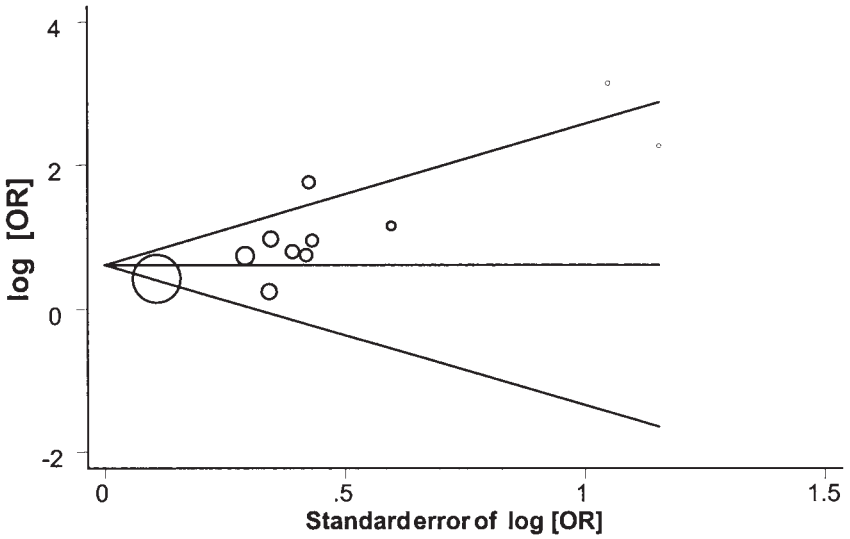

Figure 2. Assessment of publication bias by a funnel plot of the logarithm of individual study OR against corresponding standard error. Each study OR is represented by a circle. The size of each circle is roughly proportional to the weight of the corresponding study in the metaanalysis. Each individual study weight is inversely related to the value of the standard error of the logarithm of the corresponding OR represented on the horizontal axis.

the context of the metaanalyses. For example, while the Nietert study did not employ matching on selected covariates between cases and controls (which would be helpful for metaanalysis purposes), Nietert, *et al*[17] certainly considered these factors in their analyses. Further, population-based controls given a higher quality rating in the NOS scoring may not be optimal given the bias they may introduce. Among published sources, studies reporting negative results tend to be underrepresented, while low power studies reporting large effect size tend to be overrepresented[32]. A lack of statistical power may have impaired the ability to detect a publication bias in the previous metaanalysis, which still included 3 studies with remarkably high values for the relative risks: 5.8 (95% CI 2.5–13.4)[15], 9.3 (95% CI 1.08–244)[13], and 23.2 (95% CI 3.0–181)[11].

In our study as well as in the previous metaanalysis, there

Table 3. Influence analysis and adjustment for publication bias in the whole sample and subgroups.

(Sub) sample	Pooled Risk OR (95% CI)	Influence Analysis OR range (95% CI)	Risk Adjusted for Bias* OR (95% CI)	p for OR
Overall	2.41 (1.73–3.37)	2.11 to 2.65 (1.57 to 1.86–2.83 to 3.81)	1.76 (1.24–2.50)	0.002
Any solvent	2.09 (1.48–2.95)	1.82 to 2.38 (1.38 to 1.56–2.31 to 3.62)	1.64 (1.15–2.35)	0.007
Men	2.96 (1.89–4.64)	2.68 to 3.73 (1.71 to 2.11–4.27 to 6.60)	2.27 (1.45–3.55)	0.01
Women	1.75 (1.48–2.09)	1.65 to 2.51 (1.38 to 1.76–1.99 to 3.60)	No significant bias	
Community controls	2.14 (1.27–3.62)	1.62 to 2.99 (1.03 to 1.34–1.97 to 7.14)	1.68 (0.99–2.84)	0.05
Hospital controls	2.46 (1.78–3.39)	2.20 to 3.05 (1.55 to 2.11–3.10 to 4.40)	No significant bias	
NOS score ≥ 5 stars	1.76 (1.48–2.10)	1.71 to 2.40 (1.43 to 1.75–2.05 to 3.28)	1.62 (1.37–1.90)	< 0.0001
NOS score < 5 stars	3.86 (1.34–11.09)	2.78 to 5.77 (0.84 to 2.48–7.62 to 18.95)	No significant bias	

NOS: Newcastle-Ottawa Scale. * According to a "trim and fill" analysis.

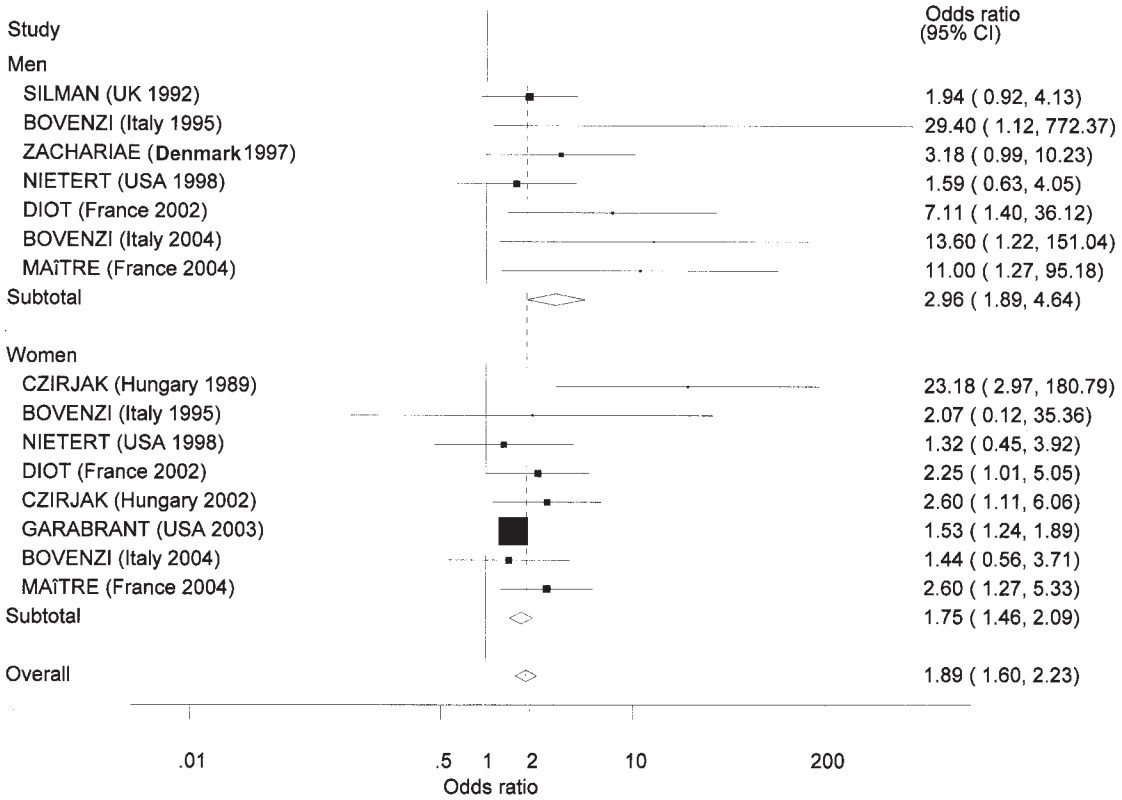

Figure 3. Exposure to any or any organic solvent and the risk of SSc in men and women. Points and overall (diamond) estimates are given as OR with 95% CI. The size of each box is roughly proportional to the weight of the corresponding study in the meta-analysis.

was evidence of heterogeneity, revealing high differences between the relative risks reported in studies. The previous analysis mixed studies with extremely variable sex ratios (0 to 100% women) and with various levels of exposure (a specific solvent, a solvents group, or any solvent). However, because of a lack of statistical power, the previous report did not include subgroup analyses to identify features associated with the magnitude of relative risks.

Heterogeneity may arise from distinct risks for sexes or various types of exposure. It may also result from mixing studies with diverse quality scores and type of controls involved. Heterogeneity may also be related to differences in the underlying exposure levels in the populations represented by the controls, of which the cases are members. A high level of exposure in a population may result in an underestimation of the relative risk of SSc.

Selection of appropriate controls is an essential point in case-control studies. Hospital controls may have distinct features of exposure related to disease-specific socioeconomic characteristics and risk factors. On the other hand,

cases having a disease of unknown etiology may tend to excessively attribute their illness to some type of exposure, introducing a possible recall bias. Hospital controls with a disease of unknown etiology may then be more appropriate than community controls and contribute to limit the effect of the recall bias on the estimation of OR. In our sample the 4 studies referring to community controls accounted for 67% of the total number of cases and 80% of the total number of controls. Nevertheless the relative risks were quite similar between studies referring to community controls and others. Therefore we do not believe that the profile of controls substantially biased our results.

We were not able to conduct separate analyses for specific solvent subtypes, due to a limited number of studies for each solvent category. However, we obtained similar OR from the whole sample, mixing exposures either for any or for organic solvents only, and from the subsample of studies in which exposure was assessed for any solvent.

The mechanisms by which solvents might increase the risk of SSc are poorly understood. They could modify self-antigens. It has been hypothesized that solvents could penetrate through the skin and/or airways[13,15], initiate the autoimmune humoral and cell mediated responses, and stimulate the production of fibrogenic proteins and growth factors that are generated in SSc[33]. Vinyl chloride (CH2=CHCl), a volatile compound with a molecular structure related to trichloroethylene ($CHCl=CCl_2$), may increase immunogenicity of cell molecules, activation of CD8 cells[34], and skin thickening related to collagen deposition[35]. In Goodpasture's syndrome solvents have been involved in the formation of antibodies to alveolar basement membrane[36]. Solvents may also induce the production of several autoantibodies commonly found in SSc. Trichloroethylene and a related metabolite induce antinuclear, anti-DNA, and anticardiolipin antibodies in female autoimmune prone mice (MRL +/+)[37]. In 2 case-control studies of Nietert, *et al*[17,28], occupational or hobby-oriented exposure to solvent was associated with SSc and, among these patients, with positive tests for topoisomerase I (Scl70) antibodies. However, these results were not confirmed in a large sample study[20].

To our knowledge, this is the first report of a sex difference in the magnitude of SSc risk associated with solvents exposure. However, this finding needs to be confirmed, as the difference between sexes was reduced and not significant after adjustment for publication bias. The strength of the relationship between occupational exposure to solvents and SSc in women may have been underestimated because of a higher level of nonoccupational exposure in women, who are usually more involved in household activities than men. In a case-control study[28], odds of high cumulative exposure in solvents-oriented hobbies were higher in patients with SSc than in controls. Little is known about the extent of household exposure to solvents in patients with scleroderma. Solvents include a variety of chemicals hidden in adhesives, carpet glue, cleaning fluids and deodorizers, paints and varnishes, plastics, textiles, polishes and waxes, and vinyl lining of water distribution pipes. Traffic, heating, being in the neighborhood of a dry cleaning shop, and cigarette smoke are also potential sources of exposure to volatile organic compounds[38-43]. Current level of personal exposure to chemicals is measurable, but only indirect methods are appropriate to evaluate past exposure for volatile compounds such as solvents. Specific solvents are well assessed by questionnaires for past occupational exposure and by expert coding of individuals' jobs for specific contaminants, but questionnaires are less reliable for the assessment of nonoccupational exposure to hidden solvents.

Scleroderma shares similarities, in skin lesions particularly, with the graft-versus-host disease[44,45]. H-Y minor histocompatibility antigens encoded by male-specific genes of the Y chromosome are involved in the chronic graft-versus-host disease. In male patients who receive stem cell transplant from HLA-matched female donors, the receiver H-Y antigens may be recognized by the donor's T and B cells as "non-self," which may then elicit a strong immune response directed at recipient cells[46]. However, whether these sex-specific histocompatibility genes are involved in sex-specific immune responses to some environmental antigens has not been established yet.

Our results confirm the hypothesis of a link between SSc and occupational exposure to solvents. A difference in the relative risks in men and women suggests that further studies are needed to assess the role of nonoccupational exposure, screen specific solvents, and investigate involvement of sex-specific histocompatibility genes in the immune response to environmental exposure.

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