Int Arch Occup Environ Health (2004) 77: 10–16
DOI 10.1007/s00420-003-0462-5

ORIGINAL ARTICLE

**Massimo Bovenzi · Fabio Barbone · Federica E. Pisa
Alberto Betta · Luciano Romeo · Alberta Tonello
Domenico Biasi · Paola Caramaschi**

A case–control study of occupational exposures and systemic sclerosis

Received: 26 March 2003 / Accepted: 28 June 2003 / Published online: 3 October 2003

Abstract ***Objectives***: A case–control study was conducted in Verona, Italy, to assess the relationship between occupation, occupational exposures and systemic sclerosis (SSc). ***Methods***: Fifty-five cases (46 female and nine male) and 171 controls were recruited. Interviews provided work histories, including job titles, industry and likelihood of occupational exposure to silica, hand–arm vibration, organic solvents, and other chemicals. Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated. ***Results***: Female teachers (OR 3.4, 95% CI 1.2–10.1) and textile workers (OR 2.1, 95% CI 1.0–4.6) were at an increased risk of SSc. Compared with those never exposed, age-adjusted and gender-adjusted ORs were 2.3 (95% CI 1.0–5.4) among subjects exposed to organic solvents, 2.5 (95% CI 0.8–8.0) for exposure to selected chemicals, 1.7 (95% CI 0.4–7.6) for exposure to silica, and 1.5 (95% CI 0.5–4.8) for usage of vibrating tools. When data analysis was stratified according to gender, only men showed a significant increase in risk for exposure to solvents and selected chemicals. ***Conclusions***: The findings of this study tend to support the role of organic solvents and certain chemicals in SSc causation. The association with teaching and working in the textile industry suggests that other exposures are involved in the aetiology of SSc among women. However, because of the small number of subjects, particularly in stratified analyses, chance cannot be ruled out as an explanation of some findings of this study.

Keywords Systemic sclerosis · Occupation · Solvents · Chemicals · Silica · Hand–arm vibration

M. Bovenzi (✉)
Clinical Unit of Occupational Medicine,
Department of Public Health Sciences,
University of Trieste, Centro Tumori,
Via della Pietà 19, 34129 Trieste, Italy
E-mail: bovenzi@units.it
Tel.: +39-040-3992313
Fax: +39-040-368199

F. Barbone · F. E. Pisa
Institute of Hygiene and Epidemiology,
DPMSC, University of Udine, Udine, Italy

A. Betta
Occupational Health Unit, National Health Service,
Trento, Autonomous Province of Trento, Italy

L. Romeo · A. Tonello
Institute of Occupational Medicine,
Department of Medicine and Public Health,
University of Verona, Verona, Italy

D. Biasi · P. Caramaschi
Department of Clinical and Experimental Medicine,
University of Verona, Verona, Italy

Introduction

Systemic sclerosis is a rare autoimmune disease of the connective tissue and microvessels, characterized by fibrosis of the skin, vascular abnormalities and alterations of the gastrointestinal system, lungs, heart and kidneys. Subsets of systemic sclerosis (SSc) include diffuse cutaneous SSc and limited cutaneous SSc (LeRoy et al. 1988). Diffuse SSc is characterized by truncal and acral skin involvement, Raynaud's phenomenon, nail-fold capillary dilatation and capillary destruction, and early and progressive visceral involvement. The limited type of SSc is associated with skin involvement limited to hands, face, feet, and forearms, Raynaud's phenomenon, dilated nail-fold capillary loops, and late occurrence of visceral involvement. Localized, non-systemic, forms of the disease include morphea and linear scleroderma that are confined to the skin and do not involve vital organs (Masi et al. 1980; LeRoy et al. 1988). The disease has an aetiology still relatively unknown. However, several environmental factors have been suggested to play a role in the causation of SSc. Cases of SSc occurring after occupational exposure to silica dust (Rodnan et al. 1967; Sluis-Cremer et al. 1985; Cowie 1987; Yanez Diaz et al. 1992; Sanchez-Roman et al. 1993), hand–arm vibration (Pelmear et al. 1992), organic

solvents (Yamakage and Ishikawa 1982; Flindt-Hansen and Isager 1987; Brasington and Thorpe-Swenson 1991; Garcia-Zamalloa et al. 1994; Altomonte et al. 1996), and other chemicals (Yamakage et al. 1980; Rush and Chaiton 1986; Owens and Medsger 1988), have been reported.

Owing to the low occurrence of the disease, only few well-designed epidemiological studies have been conducted to ascertain the association of SSc with occupation and occupational exposures. SSc has a higher incidence among women than among men, and this difference is more evident in women of childbearing age (Steen and Medsger 1990; Mayes 1996). Few studies have addressed the issue of a relationship between SSc and occupational risk factors in women. To ascertain the role of occupation and occupational exposures in the risk of SSc among both men and women, we conducted a hospital-based case–control study in Verona, in north–east Italy.

Subjects and methods

Cases

Fifty-five cases of SSc (46 female and nine male) were recruited at the Institute of Internal Medicine of the University Hospital of Verona. Cases included all subjects diagnosed with SSc [International Classification of Diseases-ninth revision (ICD-9) code 710.1] and clinically followed at the same Institute of Internal Medicine between 1 January 1997 and 30 June 1999. All of the SSc patients met the diagnostic criteria for SSc of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee (Masi et al. 1980). Fifty-one patients were affected with diffuse SSc and four with limited SSc, according to the criteria established by LeRoy et al. (1988). Patients affected with localized scleroderma (morphea, linear scleroderma) were not included in the study.

Controls

One-hundred and seventy-one controls (153 female and 18 male) were selected among patients admitted in the same study period to the Institute of Orthopaedics of the same University Hospital. Causes of hospital admission for controls included fracture, dislocation and sprain (ICD-9 codes 800–829, 830–839 and 840–848, respectively) ($n=64$, 37%), disorders of joint (ICD-9 codes 717.0–717.9, 718.0–718.9, 719.0–719.9, 726.0–726.9, 727.0-.9) ($n=40$, 23%), carpal tunnel syndrome (ICD-9 code 354.0) ($n=23$, 13%), osteoarthrosis (ICD-9 code 715) ($n=17$, 10%), acquired deformities (ICD-9 codes 736.0–736.9, 737.0–737.9) ($n=9$, 5%), osteoporosis (ICD-9 code 733.0) ($n=4$, 2%), bone infections (ICD-9 code 730.0–730.9) ($n=4$, 2%), disorders of muscle, ligament and fascia (ICD-9 codes 728.0–728.9) ($n=3$, 2%), and benign (ICD-9 codes 213.0–213.9, 214, 215.0–215.9) ($n=4$, 2%) and malignant (ICD-9 codes 170.0–170.9) ($n=3$, 2%) neoplasms. Although a control was not individually matched with the case, frequency matching by gender and age group was applied to the selection of the controls. The participation rate was 100% among cases and 98% among controls.

Questionnaire and assessment of exposure

All the subjects were interviewed in person by a trained investigator. A structured questionnaire focused on the occupational history of the subjects, including information on industrial sectors and job titles held for a minimum of 6 months. In the questionnaire, explicit reference was made to employment in occupations carrying the potential for exposure to silica, hand–arm vibration (HAV), organic solvents (chlorinated, aromatic, and aliphatic hydrocarbons), and certain chemicals (vinyl chloride, formaldehyde, epoxy resins). Exposure to solvents was evaluated separately from that to other chemicals. Hobbies involving the use of solvents, chemicals or vibratory tools were reported by a small number of subjects who were also occupationally exposed to the same agents. As a result, a separate analysis of occupational and avocational exposures was not feasible.

Interviews provided information on residence, education, smoking habit, alcohol consumption and presence of pets in the household (Silman and Jones 1990). Since some investigators reported a possible association between SSc and use of bleomycin, pentazocine, appetite suppressants, L-tryptophan, carbidopa and cocaine, past use of these selected drugs was assessed (Haustein and Herrmann 1994). In women, reproductive history (including number of children and abortions, age at first pregnancy and use of oral contraceptives), presence of silicone implants and cosmetic surgery were investigated.

With a job-exposure matrix developed in a previous investigation (Bovenzi et al. 1995), the occupational history of the subjects was reviewed by an expert in industrial hygiene and occupational health (MB), blind to the case–control condition. Generally, self-reported exposure was concordant with job-exposure based classification of exposure. However, self-reported exposure to chemicals or silica were classified as no exposure in one case and two controls. Conversely, individuals who reported themselves as unexposed were recorded as exposed in none of the cases and in one control (solvents). In data analysis, we resolved discordance for exposure allocation by using the results of job-exposure matrix classification.

Statistical methods

Nominal or categorical data were tabulated in 2×2 or $2 \times k$ contingency tables. The difference between proportions was tested by the χ^2 statistic. To estimate the relative risk for SSc according to potential predictors, we calculated the odds ratio (OR) and its 95% confidence interval (95% CI), using exact logistic regression (software LogXact, version 4, Cytel Corporation, 2000). In the analysis according to specific occupation, the reference category consisted of subjects never employed in such an occupation. In the estimation of the OR and 95% CI according to exposure to silica, HAV, organic solvents and other chemicals, the reference category included subjects not exposed to the individual occupational agent. Results are shown both pooled and gender stratified.

Results

The distribution of cases and controls according to gender, age and other personal characteristics is shown in Table 1. Cases were slightly older than controls and had a slightly higher education, but the differences were not significant ($P=0.35$ and $P=0.56$, respectively). The same proportion of cases and controls (78%) were resident in the administrative area of Verona, and 22% in other cities of north–east Italy. More controls than cases were regular drinkers of alcoholic beverages (42% vs 7%, $P<0.001$) and users of herbal drugs (46% vs 22%, $P=0.001$). Among the subjects who reported past use of selected drugs, three were cases and 33 were controls ($P<0.05$). Current smoking was more frequently reported by cases than by controls (13% vs 3%, $P<0.05$); however, when current smokers were pooled with

Table 1 Distribution of cases of SSc and controls according to selected covariates

Variable	Cases ($n=55$)		Controls ($n=171$)	
	(n)	(%)	(n)	(%)
Gender				
Female	46	84	153	89
Male	9	16	18	11
Age (years)				
< 40	8	15	29	17
40–49	10	18	44	26
50–59	17	31	56	33
60+	20	36	42	24
Residence				
Verona	43	78	133	78
Elsewhere	12	22	38	22
Education				
Primary school	26	47	75	44
Middle school	14	26	55	32
High school	11	20	35	20
College	4	7	6	4
Smoking*				
Non-smoker	38	69	131	77
Ex-smoker	10	18	35	20
Smoker	7	13	5	3
Alcohol drinking**				
Non-drinker	31	56	77	45
Seldom	20	37	22	13
Drinker	4	7	72	42
Use of selected drugs[a]**				
Yes	3	5	33	19
No	52	95	138	81
Use of herbal drugs**				
Yes	12	22	78	46
No	43	78	93	54
Pet owner				
Yes	22	25	33	24
No	67	75	104	76
Variant of SSc				
Diffuse	51	93	–	–
Limited	4	7	–	–

*$P<0.05$; **$P \leq 0.001$ (both χ^2 test) [a]Bleomycin, pentazocine, appetite suppressants, L-tryptophan, carbidopa, cocaine

ex-smokers, the difference between proportions was not significant ($P=0.29$).

Multivariate logistic models showed that education, past use of SSc-related drugs and herbal drugs, lifetime smoking and alcohol consumption did not modify the relation between SSc and the occupational variables. As a result, these terms were not retained in the final models, which were adjusted for age and gender only.

The overall and gender-stratified relative risks of SSc for having ever been employed in selected occupations are shown in Table 2. When compared with subjects never employed in these occupations, textile and tailoring workers and teachers appeared to be at increased risk, with age-adjusted and gender-adjusted ORs of 2.0 (95% CI 1.0–4.3) and 3.2 (95% CI 1.2–8.8), respectively. However, almost all of the cases and the controls included in these occupational categories were female workers. Thus, when the analysis was restricted to women, the ORs for these job titles were of the same magnitude as in the overall analysis (OR 2.1, 95% CI 1.0–4.6 and OR 3.4, 95% CI 1.2–10.1, respectively). Since the frequency of alcohol drinking was significantly greater in the controls than in the cases ($P<0.001$), data analysis was limited to non-drinking women: only small changes in the risk estimates were observed for both the textile and tailoring workers (OR 2.8, 95% CI 1.0–7.8) and the teachers (OR 4.0, 95% CI 1.0–16.6). Women who had been employed as food processors showed a slight, although not significant, increase in risk (OR 1.4, 95% CI 0.4–4.6). Addition to the model of a term for number of children did not modify the estimates of the risk for the various occupational categories.

Among men, metal-industry workers showed an increased risk for SSc, but the association was not significant (OR 7.7, 95% CI 0.6–96.4). In both genders, other occupational categories, such as health and social workers, salespersons and food service workers, other white-collar workers and farmers, were not associated with a significantly increased risk for SSc.

Table 3 shows the overall and gender-stratified relative risks of SSc according to occupational exposures. We found an age-adjusted and gender-adjusted OR of 2.3 (95% CI 1.0–5.4) among subjects exposed to organic solvents, of 2.5 (95% CI 0.8–8.0) for exposure to selected chemicals, of 1.7 (95% CI 0.4–7.6) for exposure to silica, and of 1.5 (95% CI 0.5–4.8) for usage of vibrating tools, when compared with those never exposed. However, when data analysis was stratified according to gender, only men showed a significant increase in risk for exposure to solvents (OR 17.0, 95% CI 1.3–218) and selected chemicals (OR 18.6, 95% CI 1.4–251). Men with SSc were more likely than controls to have had an exposure to HAV (OR 2.4, 95% CI 0.4–14.0). No increase in risk was apparent among men exposed to silica (one case and two controls). An increased, although not significant, risk for SSc was observed among women exposed to silica dust (OR 2.4, 95% CI 0.4–15.5) and solvents (OR 1.7, 95% CI 0.6–4.1). Addition to the model of a term for reproductive history (number of children) did not change the estimates of these ORs (results not shown).

Discussion

Occupational factors have been indicated to be involved in the aetiology of SSc, which is not the case in other autoimmune diseases. However, because of the rarity of the disease, its insidious onset and the possible overlap of its clinical and laboratory features with those of other rheumatological or autoimmune diseases, few studies have investigated the epidemiology of SSc (Schottenfeld et al. 1995). Consequently, the occupations that possibly entail increased risk and the hypothesized risk factors for SSc and SSc-like conditions have been suggested mainly by case reports and case series.

Table 2 Overall and gender-stratified OR and 95% CI for SSc according to occupation

Occupation[a]	All					Women					Men				
	Cases ($n=55$)		Controls ($n=171$)			Cases ($n=46$)		Controls ($n=153$)			Cases ($n=9$)		Controls ($n=18$)		
	(n)	(%)	(n)	(%)	OR[b] (95% CI)	(n)	(%)	(n)	(%)	OR[b] (95% CI)	(n)	(%)	(n)	(%)	OR[b] (95% CI)
Health and social workers	4	7	18	10	0.7 (0.2–2.1)	2	4	15	10	0.5 (0.1–2.4)	2	22	3	17	1.7 (0.2–13.7)
Teachers and related occupations	8	14	10	6	3.2 (1.2–8.8)	7	15	9	6	3.4 (1.2–10.1)	1	11	1	6	1.6 (0.1–32.0)
Other white-collar workers	7	13	32	19	0.7 (0.3–1.6)	6	13	29	19	0.7 (0.3–1.9)	1	11	3	17	0.8 (0.1–11.0)
Salespersons and food service workers	7	13	26	15	0.9 (0.3–2.1)	6	13	25	16	0.8 (0.3–2.1)	1	11	1	6	1.8 (0.1–35.4)
Metal-industry workers	3	5	2	1	5.1 (0.7–36.6)	0	0	1	1	–	3	33	1	6	7.7 (0.6–96.4)
Textile and tailoring workers	15	27	27	16	2.0 (1.0–4.3)	15	33	26	17	2.1 (1.0–4.6)	0	0	1	6	–
Food processors	4	7	14	8	0.9 (0.3–3.0)	4	9	11	7	1.4 (0.4–4.6)	0	0	3	17	–
Farmers	3	5	15	9	0.5 (0.1–2.0)	3	6	14	9	0.6 (0.2–2.1)	0	0	1	6	–
Other blue-collar workers	11	20	48	28	0.6 (0.3–1.4)	7	15	41	27	0.5 (0.2–1.3)	4	44	5	28	1.1 (0.2–6.0)

[a]Reference category includes subjects never employed in the occupation
[b]Adjusted for age as a continuous variable and, when appropriate, gender

Silica

Since the first observation of cases of SSc in stone masons (Bramwell 1914), there have been several case reports (Cowie 1987) and studies indicating an increased risk of the disease in miners (Rodnan et al. 1967; Sluis-Cremer et al. 1985; Erasmus 1957). Exposure to silica dust has been indicated as a possible risk factor for SSc in these working populations, who were also exposed to HAV from hand-held power tools (Rodnan et al. 1967; Pelmear et al. 1992; Erasmus 1957; Haustein et al. 1990). However, the findings of recent epidemiological studies suggest that the association between SSc and occupational exposure to silica is still uncertain. A US proportional mortality study found a slight, not significant, excess of mortality for SSc among men whose death certificates reported employment in mining, but no excess risk was found among former employees in non-mining occupations but who had had potential exposure to silica dust (Walsh 1999). In a cohort of 583 subjects with silicosis, Rosenman et al. (1999) found an increase in the risk for rheumatoid arthritis, SSc and systemic lupus erythematosus, but only the prevalence of rheumatoid arthritis was significantly greater than that estimated in the general population. A population-based case–control study in Italy found an association between SSc and exposure to silica among men but not among women (Bovenzi et al. 1995). In another population-based case–control study conducted in the USA, women occupationally exposed to silica were not at increased risk of SSc (Burns et al. 1996). In the present study, no association with exposure to silica was seen among men, while an increased, even though not significant, risk was found among women. These latter (two cases and three controls) were exposed to silica in the pottery industry and in the manufacturing of ceramic materials. This finding seems to be consistent with the results of some studies

Table 3 Overall and gender-stratified OR and 95% CI for SSc according to occupational exposure to organic solvents, selected chemicals, silica and HAV

Exposure agent	All					Women					Men				
	Cases ($n=55$)		Controls ($n=171$)			Cases ($n=46$)		Controls ($n=153$)			Cases ($n=9$)		Controls ($n=18$)		
	(n)	(%)	(n)	(%)	OR[a] (95% CI)	(n)	(%)	(n)	(%)	OR[a] (95% CI)	(n)	(%)	(n)	(%)	OR[a] (95% CI)
Solvents	11	20	18	10	2.3 (1.0–5.4)	7	15	17	11	1.7 (0.6–4.6)	4	44	1	6	17.0 (1.3–218)
Chemicals[b]	6	11	8	5	2.5 (0.8–8.0)	2	4	7	5	1.2 (0.2–6.2)	4	44	1	6	18.6 (1.4–251)
Silica	3	5	5	3	1.7 (0.4–7.6)	2	4	3	2	2.4 (0.4–15.5)	1	11	2	11	1.2 (0.1–15.8)
HAV	6	11	11	6	1.5 (0.5–4.8)	2	4	6	4	1.2 (0.2–6.5)	4	44	5	28	2.4 (0.4–14.0)

[a]Adjusted for age as a continuous variable and, when appropriate, gender
[b]Vinyl chloride, epoxy resins, formaldehyde

reporting SSc in workers employed in occupations other than mining but carrying the potential for silica exposure (Sanchez-Roman et al. 1993; Koeger et al. 1995).

Solvents

In addition to silica dust, other occupational exposures have been suggested to play a role in SSc causation. Occurrence of cases of SSc has been reported among workers exposed to organic solvents (Yamakage and Ishikawa 1982; Flindt-Hansen and Isager 1987; Brasington and Thorpe-Swenson 1991; Garcia-Zamalloa et al. 1994; Altomonte et al. 1996). Among epidemiological studies that evaluated the possible role of solvents in the aetiopathogenesis of SSc, Silman and Jones (1992) found an increased risk of SSc among men with self-reported occupational exposure to organic solvents, but the association was not confirmed when the exposure was expert-assessed on the basis of their job titles. Bovenzi et al. (1995) found occupational exposure to organic solvents to be significantly associated with the risk of SSc only in male workers. Similar findings were reported by Nietert et al. (1998), who observed a significant association between SSc and occupational exposure to solvents among men, but not among women. In the same study population, leisure-time exposure to solvents, through hobby practice, was not found to be associated overall with the risk, but exposed cases with positive Scl70 antibody showed more than a twofold increase in the risk for SSc (Nietert et al. 1999). Our results, indicating a significant increase in risk among men occupationally exposed to organic solvents, are consistent with the findings of previous studies.

Other chemical agents

A few epidemiological studies have evaluated the role of other chemical agents. In our study, we found an increased risk of SSc in men exposed to certain chemicals. Among them, one case was exposed to vinyl chloride and three cases and one control were exposed to formaldehyde. None had a work history of exposure to organic solvents. Therefore, our findings seem to be consistent with the few previous case reports of the occurrence of SSc in subjects exposed to selected chemicals (Yamakage et al. 1980; Rush and Chaiton 1986; Black et al. 1986).

Occupations and exposures in women

We found a twofold increase in risk of SSc among women who had been working in the textile and tailoring industries. To the best of our knowledge this finding has never been reported before. We also did not find any previous report of an increased risk among teachers and employees in related occupations. A Swedish cohort study, however, found an excess risk of rheumatoid arthritis among gainfully employed female teachers (Lundberg et al. 1994). Since teaching or working in textile and tailoring industries are not associated with exposure to suspected risk factors for SSc, our results of an association with these occupations could indicate the presence of other risk factors in addition to those previously suggested. Alternatively, non-occupational risk factors might explain this finding.

Since, in our study population, the great majority of subjects employed in these occupations are women and SSc is known to have a higher incidence in women than in men, hormonal or pregnancy-related factors could explain the increase of risk in these occupational groups. Reproductive status has been suggested to account, at least partially, for the excess risk seen in women, especially of childbearing age (Steen and Medsger 1990; Mayes 1996). Adjustment for the number of children, however, did not modify our findings, and the increase in risk found among female teachers and female workers in the textile and tailoring industries seems to be independent of the number of children the women had had.

Previous epidemiological studies of SSc have shown gender-related differences in the distribution of occupational exposures to silica or solvents, with women representing the higher percentage of cases but the lower percentage of exposed (Walsh 1999; Koeger et al. 1995). For instance, in the study by Walsh (1999) the majority of cases (76%) were women but they worked in only 7% of the silica-related occupations, while men represented 24% of cases and were employed in 93% of the silica-related occupations. In the study by Nietert et al. (1998), the gender distribution was not comparable between cases and controls: the majority of cases (79%) but only 31% of controls were women. Lack of an association between occupational exposure and SSc among women might arise from differences in the pattern of occupational exposures, i.e. the female population studied is not employed in occupations carrying the potential for the exposure, or have a lower level of exposure than men employed in the same job. Alternatively, the exposure assessment conducted by methods that are reliable in men, for instance a job-exposure matrix, might not correctly assess female occupational exposure (Messing et al. 1993; Cocco and Dosemeci 1999).

Methodological considerations

Since the Institute of Internal Medicine at the University Hospital of Verona is a referral centre for connective tissue diseases in the Province of Verona and the surrounding area of north–east Italy, it is unlikely that an elevated number of diagnoses of SSc in the population served by this clinic have been missed. In Italy, access to medical care is provided by the National Health Service, thus patients refer to the University Hospital independently of their social status and occupation. It seems,

therefore, unlikely that a bias in the selection of cases and controls affected the study results. Moreover, the high comparability of cases and controls according to the residence area indicates that controls arose from the same general population from which cases were enrolled.

Owing to the non-individual matching in the study design, truncation of exposure period could not be performed on the basis of the date of diagnosis of the cases. We recognize this limitation, but we suggest that, due to the low job mobility in our country, the dichotomous classification of occupational history (yes/no) would not have changed if truncation of exposure period were applied. Moreover, if such an information bias were introduced, it caused an underestimation of the OR.

In this study, occupational exposures were self-reported. Thus, cases might have recalled more precisely than controls their occupational exposures, e.g. for claiming compensation. It seems unlikely, however, that such a differential misclassification, if any, would have also affected the report of the occupational history of subjects.

Conclusions

In conclusion, the findings of our case–control study tend to support the role of some occupational risk factors in SSc causation, in particular organic solvents and certain chemicals. The possible role of silica and HAV remains uncertain. Our findings of an association with teaching and working in textile industries suggest that other unknown occupational exposures might be involved in the aetiology of SSc. However, because of the small number of subjects, particularly in stratified analyses, chance cannot be ruled out as an explanation of some significant results of this study.

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