

# Case-control study of leatherwork and male infertility

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## Abstract

**Objectives**—To test the hypothesis that leatherwork is associated with male infertility mediated through the development of oligozoospermia. The basis of any association was postulated, at the outset, to be with exposure to the solvents used in leatherwork.

**Methods**—All new referrals with infertility presenting in Leicestershire hospital clinics between November 1988 and September 1992 and Kettering District General Hospital from August 1990 were eligible to participate; 88.5% agreed to be interviewed. Exposure to leatherwork and work with solvents was defined by job title. Comparisons were made with fertile controls and in an analysis within men from infertile couples with oligozoospermia as the primary outcome. Effects on sperm motility and deformity were investigated secondarily. Analyses used logistic regression for binary outcomes and multi-level modelling for continuous outcomes.

**Results**—1906 men were interviewed. Compared with the fertile controls the men from infertile couples were 1.10 times (95% confidence interval (95% CI) 0.46 to 2.63;  $p=0.99$ ) more likely to be leatherworkers and 1.73 times (95% CI 1.26 to 2.38;  $p<0.001$ ) more likely to work with solvents. Compared with other men, leatherworkers were 1.20 times (95% CI 0.43 to 3.33;  $p=0.73$ ) more likely to present with oligozoospermia and 1.65 times (95% CI 0.37 to 7.30;  $p=0.51$ ) more likely to present with teratozoospermia. Being a leatherworker was associated with only a 6% reduction in sperm concentration; motility and deformity were similarly unaffected by this exposure. Work with solvents did not statistically, nor clinically, increase the risk of oligozoospermia, teratozoospermia, or asthenozoospermia.

**Conclusions**—There was little evidence to support the hypothesis that leatherwork is associated with an increased risk of presenting with infertility or oligozoospermia. There was limited evidence that leatherwork is a risk factor for teratozoospermia. Workers with solvents were at an increased risk of presenting with infertility, although this was not mediated through effects on standard measures of semen quality; this finding merits further investigation.

(*Occup Environ Med* 2001;58:217-224)

Keywords: leatherwork; solvents; male infertility

Leatherwork has been implicated as a risk factor for several diseases. These include nasal, paranasal, bladder, lung, and testicular cancers.<sup>1-6</sup> There is also some evidence of an association between leatherwork and haematopoietic malignancies, although this is thought to be related to exposure to solvents rather than leather itself.<sup>7-9</sup> Several adverse reproductive outcomes associated with maternal exposure to leatherwork have been described and include an increased risk of perinatal death, reduced female fertility, spontaneous abortion, preterm delivery, low birth weight, and cleft palate.<sup>10-18</sup> These reports include two that describe the relation between leatherwork and reproductive outcome in Leicestershire.<sup>10,15</sup> However, the effects of exposure to leatherwork on male reproductive function, other than testicular cancer, have not been described.

In 1988 a Leicestershire gynaecologist reported a cluster of five men who worked in the Leicestershire boot and shoe industry who had attended his clinic with their wives complaining of difficulty conceiving; subsequent semen analysis showed them to have oligozoospermia (R Graham, personal communication). The aim of this study was to test the hypothesis that leatherwork is associated with male infertility mediated through the development of oligozoospermia. The basis of any association was thought, at the outset, to be exposure to the solvents used in leatherwork, rather than exposure to the leather itself or to leather substitutes.

## Methods

Leicestershire is a county in central England with a population in excess of 860 000. All couples complaining of infertility and presenting as new referrals to any general gynaecological or specialist infertility clinic in Leicestershire between November 1988 and September 1992 inclusive were eligible and were invited to participate. A few Leicestershire residents who had been referred to hospitals outside Leicestershire were also identified and approached. Despite a high response to the study, recruitment did not meet the required target and therefore new patients referred with infertility to Kettering District General Hospital, Northamptonshire, were also included from August 1990 to September 1992. Northamptonshire is a county adjacent to Leicestershire and, like Leicestershire, it had an active boot and shoe industry. The only infertility specialist at the Kettering Hospital sees all referrals with infertility.

The study had the approval of the Leicestershire District Health Authority Ethics Com-

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Accepted 14 November 2000

mittees. All participants gave verbal informed consent.

#### DATA COLLECTION

The data were collected with a structured questionnaire administered by an interviewer. Both members of each couple were interviewed separately at the clinic. However, for the purposes of the results reported here only data from the interviews with male partners were used. Home interviews were conducted when patients were missed at the clinic. The questionnaire was designed to collect demographic and personal details, detailed occupational history, general medical and lifestyle information, and reproductive history. The results of routine semen analyses performed for clinical indications were obtained from the microbiology laboratories of the Leicester Royal Infirmary (the only testing laboratory in Leicestershire at that time) and Kettering District General Hospital. Semen analysis was carried out in both laboratories in accordance with the World Health Organisation guidelines.<sup>19</sup>

#### EXPOSURE DEFINITION

The two exposures of interest were leatherwork defined as a binary term (yes or no) and any occupations which involved work with solvents, similarly defined (yes or no). These were derived from the reported occupations that were coded with the 1970 and 1980 Office of Population Censuses and Surveys classification of occupation.<sup>20 21</sup> Leatherwork has a series of exclusive codes within each classification and was therefore straightforward to define. Jobs involving work with solvents were defined at the outset by reference to the occupational literature. The jobs and their codes included in both groups are given as an appendix, this list includes only those occupations experienced by the study participants.

#### CASE-CONTROL COMPARISONS

Two sets of case-control comparisons were carried out. The first comparisons used men from couples presenting with infertility resident in Leicestershire who were defined as the cases (Kettering patients and other couples living outside Leicestershire were excluded). The controls for this set of comparisons were the fathers of the control birth population from the Leicestershire perinatal mortality case-control study born 1985–92 inclusive.<sup>22 23</sup> The perinatal mortality study, which started in 1976, is an ongoing population based case-control study of all perinatal deaths to Leicestershire residents. The controls are a robust representative sample of all Leicestershire births.<sup>22</sup> The control exposure information used in the comparison for the study reported here was derived from the parental details recorded in the perinatal study. The details collected about the father in the perinatal study were limited to current occupational details only and were collected from the mother. Thus, confounder data were not available and could not be adjusted for in this part of the analysis.

The second set of comparisons was based on an analysis within the men of couples presenting with infertility. That is, all the men from infertile couples with semen results were divided, on the basis of the results of the semen analysis, into cases who had oligozoospermia and controls who did not. Oligozoospermia was defined as a sperm concentration of 20 million/ml or less.<sup>19</sup> Cases were defined as those men who had oligozoospermia in both samples when two semen samples were tested and in the single sample when only one sample was available. Men without a semen result were not included in this part of the study analysis. The effects of exposure on sperm motility and morphology were also examined. Asthenozoospermia was defined as having 50% or less motile sperm in all samples tested.<sup>19</sup> A high percentage of deformed sperm, teratozoospermia, was defined as having 70% or greater deformed sperm in all samples tested.<sup>19</sup>

The calculation of sample size for the study was based on the second arm of the analysis. The prevalence of leatherwork in the general population of men of reproductive age was estimated as 13/1000 men. The calculation of sample size indicated that for the analysis based on oligozoospermia to have 90% power to detect a relative risk of 3.0 at the 5% level of significance, the comparison would need to be based on 1000 cases and 1000 controls.<sup>24</sup> As pilot work had indicated that the split of oligozoospermia to a normal sperm concentration was 50:50, the target sample size for interview was 2 000 men.

#### ANALYSIS

##### Binary outcome analysis

Unadjusted odds ratios (ORs) were estimated with 95% confidence intervals (95% CIs) and adjusted ORs were estimated with unconditional logistic regression.<sup>25</sup> All potential confounding variables were included as categorical or binary terms in the regression model containing the outcome (case or control) and explanatory variable of interest (occupational exposure). The conventional likelihood ratio test was used to assess whether terms could be removed from the model—that is, twice the change in log likelihood was compared with the  $\chi^2$  distribution on the change in degrees of freedom commensurate with the term removed on each occasion. The terms were removed in ascending order of the likelihood ratio test and all terms that did not represent a significant ( $p < 0.05$ ) component of the model were removed. The need for interaction terms was then assessed. The confounders considered were: illnesses possibly causing infertility; operations potentially affecting fertility; medicines or drugs potentially affecting fertility; exposure to  $x$  radiation; alcohol consumption; caffeine intake; smoking; whether they were currently working or not; social class; age; marital status; working pattern; fixed (or not) place of work; use of cleaning agents; use of solvents; use of paints; use of colour mixing solutions; and use of welding equipment. The operations we considered as potentially affecting fertility were: operations for testicular

Table 1 Demographic characteristics of the participants of the male infertility study (n=1906)

| Characteristics                                    | n     | %    |
|--|-------|------|
| Age (y):   |       |      |
| Range  | 18–65 |      |
| Mean   | 31.4  |      |
| SD   | 5.96  |      |
| % Aged 20–44                                       |       | 96.7 |
| Marital status:                                    |       |      |
| Married  | 1590  | 83.4 |
| Living together                                    | 300   | 15.7 |
| Not living together                                | 16    | 0.9  |
| Place of birth:                                    |       |      |
| United Kingdom                                     | 1520  | 79.7 |
| Africa   | 193   | 10.1 |
| India, Pakistan, and Bangladesh                    | 118   | 6.2  |
| Elsewhere  | 75    | 4.0  |
| Current employment:                                |       |      |
| Working  | 1747  | 91.7 |
| Unemployed   | 143   | 7.5  |
| Student  | 12    | 0.6  |
| Retired  | 4     | 0.2  |
| Area of residence*:                                |       |      |
| Leicestershire                                     | 1606  | 83.4 |
| Northamptonshire                                   | 259   | 13.6 |
| Elsewhere  | 41    | 2.2  |
| Social class (1980 classification) <sup>21</sup> : |       |      |
| I  | 135   | 7.1  |
| II   | 435   | 22.8 |
| IIIN   | 193   | 10.1 |
| IIIM   | 758   | 39.8 |
| IV   | 322   | 16.9 |
| V  | 48    | 2.5  |
| Armed forces and students                          | 12    | 0.6  |
| Never worked                                       | 3     | 0.2  |

\*Residence defined on the basis of postcode and address.

adenoma and testicular torsion; prostatectomy; bladder lesion excision; bowel excision or resection; colectomy; inguinal hernia repair; hydrocoele excision; orchidopexy (unilateral or bilateral); unilateral orchidectomy; renal transplant; and varicocele excision.

#### Continuous outcome analysis

The values of the results from the semen analysis were compared by occupational exposure group. Because individual men had multiple semen samples multilevel modelling was used to estimate the change in sperm concentration, motility, and deformity associated with exposure, having adjusted for the effects of other factors of interest.<sup>26</sup> For the analysis of the skewed sperm concentration data a log<sub>e</sub> (+1) transformation was used to normalise the data. The motility and morphology data were near normal and did not require transformation. The level 1 residuals were checked and found to be approximately normally distributed for all three parameters.

#### Statistical inference

Like most epidemiological investigations, our study was not large enough to estimate small effects with high precision. Thus, 95% CIs

Table 2 Comparison of the men from couples presenting with infertility (cases, n=1606) with the perinatal controls (n=1013) for exposure to leatherwork and work with solvents in the current (or most recent) job; Leicestershire residents only

| Exposure            | Cases |      | Controls |      | OR   | 95% CI       | p Value |
|---------------------|-------|------|----------|------|------|--------------|---------|
|                     | n     | %    | n        | %    |      |              |         |
| Leatherwork:        |       |      |          |      |      |              |         |
| No                  | 1592  | 99.1 | 1005     | 99.2 | 1*   |              |         |
| Yes                 | 14    | 0.87 | 8        | 0.79 | 1.10 | 0.46 to 2.63 | 0.99    |
| Work with solvents: |       |      |          |      |      |              |         |
| No                  | 1458  | 90.8 | 957      | 94.5 | 1*   |              |         |
| Yes                 | 148   | 9.2  | 56       | 5.5  | 1.73 | 1.26 to 2.38 | <0.001  |

\*Baseline comparison group.

were often relatively wide and included regions of clinically relevant increased and decreased risk or no effect. This presents an interpretational difficulty. To assist interpretation we used a simple Bayesian method described by Burton *et al.*<sup>27, 28</sup> In effect we estimated the posterior probability that the true OR was 2.0 or greater. This particular threshold value (2.0) was chosen as it was thought to be an OR that would reflect an effect of clinically important magnitude worth observing. If the calculated probability is small it suggests that there is unlikely to be an aetiological effect of clinically relevant magnitude. These results are quoted as percentages to avoid confusion with p values derived from significance testing.

#### Results

Of the 2154 men from couples presenting with infertility eligible for inclusion during the study period 1906 were interviewed; a response of 88.5%. The demographic characteristics of the study participants are given in table 1.

As the Leicestershire resident participants (n=1606) were derived from a geographically defined population their characteristics could be compared with 1991 Leicestershire census data.<sup>29</sup> The main differences were that a greater proportion of the study participants were married compared with the general population of men aged 20–44 (84.7% *v* 56.7%). Fewer of the study participants were born in the United Kingdom than the general population (77.1% *v* 90.9%) and more were born in Africa or the Indian subcontinent (18.8% *v* 5.9%).

In total there were 26 men who were current leatherworkers or were recently unemployed leatherworkers. One worked in a tannery; one worked in coat and jacket fabrication; two worked in handbag manufacture; and the remaining 22 worked in shoe manufacture. At the time of interview 22 were currently employed, one had been unemployed for 1 month, one for 4 months, one for 6 and one for 12 months. That is, they had all had relatively recent exposure to leatherwork. Four of the leatherworkers did not have a semen analysis result available. In total 71 men currently worked or had worked at some stage in the past as leatherworkers (ever leatherworker) and had at least one semen analysis result available.

Overall 153 men with semen results had a current (or most recent) occupation which fell into the category of work involving possible exposure to solvents (solvent work) and 285 men worked in these occupations either currently or at some stage in the past (ever solvent work).

#### COMPARISONS WITH CONTROLS FROM THE PERINATAL MORTALITY SURVEY

The cases for comparisons with the controls from the perinatal mortality survey were defined as all 1606 Leicestershire male residents in the infertility study population. The controls comprised the 1013 Leicestershire resident fathers of the perinatal mortality study controls born 1985–92 who did not have a history of infertility (table 2)

Table 3 Adjusted ORs for oligozoospermia, asthenozoospermia, and teratozoospermia and leatherwork (current or most recent job) (n=1580)

| Exposure (yes v no)                  | Adjusted†<br>OR | 95% CI       | p Value |
|--------------------------------------|-----------------|--------------|---------|
| <b>Oligozoospermia:</b>              |                 |              |         |
| Leatherwork (current or most recent) | 1.20            | 0.43 to 3.33 | 0.73    |
| Surgical operations*                 | 2.43            | 1.64 to 3.62 | <0.001  |
| Social class III: rest               | 1.35            | 1.07 to 1.71 | 0.013   |
| Leicestershire resident              | 2.02            | 1.37 to 2.96 | <0.001  |
| <b>Asthenozoospermia:</b>            |                 |              |         |
| Leatherwork (current or most recent) | 0.46            | 0.17 to 1.28 | 0.14    |
| Surgical operations*                 | 2.02            | 1.37 to 2.99 | <0.001  |
| Leicestershire resident              | 2.15            | 1.59 to 2.91 | <0.001  |
| <b>Teratozoospermia:</b>             |                 |              |         |
| Leatherwork (current or most recent) | 1.65            | 0.37 to 7.30 | 0.51    |
| Surgical operations*                 | 2.20            | 1.23 to 3.93 | 0.008   |
| Social class III: rest               | 0.89            | 0.60 to 1.31 | 0.55    |
| Leicestershire resident              | 1.13            | 0.64 to 1.99 | 0.67    |

\*Surgical operations which may potentially impair fertility.

†Each OR listed for each subheading was adjusted for the effects of all other factors listed under that subheading.

The OR for the comparison between cases and controls for exposure to current (most recent) leatherwork was 1.10 (95% CI 0.46 to 2.63;  $p=0.99$ ); this was not significant. The OR for current (most recent) work with solvents was 1.73 (95% CI 1.26 to 2.38;  $p<0.001$ ). This suggests that there was a significant 70% excess risk of presenting for the investigation of infertility associated with work with solvents.

#### CASE-CONTROL COMPARISONS WITHIN MEN FROM COUPLES PRESENTING WITH INFERTILITY

##### Leatherwork

These analyses were based on the 1580 male infertility study participants, regardless of place of residence, who had at least one semen sample tested. Of these, 367 were defined as cases with oligozoospermia and 1213 as controls without. Five (1.35%) of the cases were leatherworkers in their current (or most recent) job, as were 17 (1.4%) of the controls (unadjusted OR 0.97; 95% CI 0.36 to 2.65;  $p=0.84$ ). The adjusted ORs are given in table 3.

Having adjusted for the factors listed compared with non-leatherworkers, leatherworkers were 20% (OR 1.20; 95% CI 0.43 to 3.33;  $p=0.73$ ) more likely to present with oligozoospermia. This result was not significant. The probability that the true relative risk was 2.0 or greater was 17%. This indicates that there was less than a one in five chance that leatherwork leads to a twofold increase, or greater, in the risk of oligozoospermia.

Of the 1580 men included in the analysis 704 (44.6%) had asthenozoospermia. Five of the 704 (0.71%) with asthenozoospermia were leatherworkers as were 17 of the 876 (1.94%) who had normal sperm motility (unadjusted OR 0.36; 95% CI 0.14 to 0.96;  $p=0.046$ ). The adjusted OR was 0.46 (95% CI 0.17 to 1.28;  $p=0.14$ ) and was not significant (table 3). There was only a 0.2% chance that the true relative risk of asthenozoospermia associated with leatherwork was 2.0 or greater.

Teratozoospermia was present in 108 (6.8%) of the 1580 men with results and two (1.85%) of these were leatherworkers. By comparison 20 (1.36%) of those with normal levels of sperm deformity were leatherworkers (unadjusted OR 1.37; 95% CI 0.32 to 5.91;  $p=0.99$ ). Table 3 shows that the adjusted OR was 1.65

Table 4 Semen characteristics for leatherworkers and non-leatherworkers (current or most recent job) (n=1580)

| Characteristics   | Leatherworkers | Non-leatherworkers |
|---|----------------|--------------------|
| <b>Sperm concentration (<math>\times 10^6</math> per ml):</b> |                |                    |
| Men (n)   | 22             | 1558               |
| Mean  | 62.0           | 62.7               |
| SD  | 59.7           | 63.7               |
| Median  | 50.0           | 47.5               |
| Range   | 0-239          | 0-565              |
| <b>Sperm motility:</b>  |                |                    |
| Men (n)   | 22             | 1558               |
| Mean (%)  | 51             | 48                 |
| SD (%)  | 23.5           | 22.2               |
| Median (%)  | 56             | 40                 |
| Range (%)   | 0-92.5         | 0-95               |
| <b>Sperm deformity:</b>                                       |                |                    |
| Men (n)   | 20             | 1560               |
| Mean (%)  | 35             | 39                 |
| SD (%)  | 19.1           | 20.6               |
| Median (%)  | 37.5           | 38                 |
| Range (%)   | 0-78.0         | 0-98               |

(95% CI 0.37 to 7.30;  $p=0.51$ ), which suggests that leatherwork was associated with a 65% excess risk of teratozoospermia, although this result was not significant. There was a 43% chance that the true relative risk was 2.0 or greater and a 23% chance that it was 3.0 or greater.

Table 4 gives the results of the semen analysis comparing leatherworkers and non-leatherworkers. On the basis of these univariate results there was little evidence of a difference in sperm concentration, motility or deformity between the two groups.

The results of multilevel modelling indicated that having adjusted for the effects of surgical operations which may potentially impair fertility, social class, and place of residence, being a leatherworker was associated with only a 6% reduction (95% CI -44% to +59%) in sperm concentration compared with not being a leatherworker. Having adjusted for the same factors, comparing leatherworkers with non-leatherworkers, there was an estimated increase in sperm motility of 0.78% (95% CI -8.3% to +9.9%). Similarly, after adjustment there was a 0.84% reduction in sperm deformity (95% CI -9.4% to +7.7%).

Exposure to leatherwork at any stage in their career (ever leatherwork) was also investigated (table 5). Having adjusted for confounders, ever having been a leatherworker was associated with a non-significant 12% reduction (OR 0.88; 95% CI 0.48 to 1.60;  $p=0.67$ ) in the risk of oligozoospermia. There was only a 0.14% chance that ever being a leatherworker was associated with a true relative risk of 2.0 or greater. The results relating to the risk of asthenozoospermia and teratozoospermia were similar to those for oligozoospermia. Multilevel modelling results indicated that ever being a leatherworker was associated with a 7% increase in sperm concentration (95% CI -21% to +45%); a reduction in sperm motility of 1.3% (95% CI -6.6% to +3.9%); and an estimated increase in sperm deformity of 2.2% (95% CI -2.7% to +7.0%).

##### Work with solvents

As can be seen from table 6 a current (or most recent) occupation involving work with solvents was associated with a 30% increase in the

Table 5 Adjusted ORs for oligozoospermia, asthenozoospermia, and teratozoospermia and ever leatherwork with the probability of the true relative risk being  $\geq 2.0$

| Exposure (yes v no) | Adjusted OR | 95% CI       | p Value | Probability that the true RR is $\geq 2.0$ |
|---------------------|-------------|--------------|---------|--|
| Oligozoospermia†:   |             |              |         |  |
| Ever leatherwork*   | 0.88        | 0.48 to 1.60 | 0.67    | 0.14%                                      |
| Asthenozoospermia‡: |             |              |         |  |
| Ever leatherwork*   | 1.00        | 0.61 to 1.64 | 0.99    | 0.3%                                       |
| Teratozoospermia§:  |             |              |         |  |
| Ever leatherwork*   | 0.88        | 0.32 to 2.45 | 0.81    | 7%   |

\*Adjusted for surgical operations which may potentially impair fertility, social class, and Leicestershire residence.

†Cases=oligozoospermia, n=367; controls=not oligozoospermia, n=1213.

‡Cases=asthenozoospermia, n=704; controls=not asthenozoospermia, n=876.

§Cases=teratozoospermia, n=108; controls=not teratozoospermia, n=1472.

Table 6 Adjusted ORs for oligozoospermia, asthenozoospermia, and teratozoospermia and current (most recent) work with solvents and ever work with solvents; with the probability of the true relative risk (RR) being  $\geq 2.0$

| Exposure (yes v no) | OR   | 95% CI       | p Value | Probability that the true RR is $\geq 2.0$ (n) |
|---------------------|------|--------------|---------|--|
| Oligozoospermia†:   |      |              |         |  |
| Solvent work*       | 1.33 | 0.91 to 1.95 | 0.14    | 1.5%   |
| Ever solvent work*  | 1.20 | 0.91 to 1.78 | 0.23    | 0.03%  |
| Asthenozoospermia‡: |      |              |         |  |
| Solvent work*       | 1.14 | 0.81 to 1.61 | 0.44    | 0.1%   |
| Ever solvent work*  | 1.22 | 0.94 to 1.58 | 0.14    | 0.0%   |
| Teratozoospermia§:  |      |              |         |  |
| Solvent work*       | 1.14 | 0.60 to 2.17 | 0.71    | 5.1%   |
| Ever solvent work*  | 1.17 | 0.71 to 1.92 | 0.51    | 2.3%   |

\*Adjusted for surgical operations which may potentially impair fertility, social class, and Leicestershire residence.

†Cases=oligozoospermia, n=367; controls=not oligozoospermia, n=1213.

‡Cases=asthenozoospermia, n=704; controls=not asthenozoospermia, n=872.

§Cases=teratozoospermia, n=108; controls=not teratozoospermia, n=1451.

risk of oligozoospermia; a 14% increase in the risk of asthenozoospermia; and a 14% increase in the risk of teratozoospermia. None of these results were significant and it was highly improbable that the true relative risk associated with any of these outcomes was 2.0 or greater. By definition the solvent worker group included leatherworkers; excluding these men had no material effect on the results. The adjusted multilevel modelling results showed that compared with non-solvent workers, solvent workers experienced an 8.0% reduction (95% CI -25% to +15%) in sperm concentration; a 1.4% reduction (95% CI -5.0% to +2.3%) in sperm motility; and a 0.4% increase (95% CI -3.1% to +3.8%) in sperm deformity. Table 6 shows that the results relating to ever having worked with solvents were similar to the results for current (or most recent) work.

The adjusted results from the multilevel modelling showed that compared with never solvent workers, ever solvent workers experienced a 1.0% reduction (95% CI -16% to +17%) in sperm concentration; a 1.6% reduction (95% CI -4.5% to +1.3%) in sperm motility; and a 1.2% increase (95% CI -1.5% to +3.9%) in sperm deformity.

## Discussion

### LEATHERWORK

The results of this large case-control comparison with fertile controls suggest that men employed as leatherworkers are not at an increased risk of presenting, with their partner, for the investigation of infertility. We have two caveats to this conclusion. Firstly, the effects of

confounders were not adjusted for. However, given the minimal effect of confounding found in those analyses in which we were able to make adjustments it seems likely that such an adjustment would have made little material difference to our inferences. Our second caveat is that as factors related to the decision to seek medical care may be associated with occupation the use of only men from infertile couples as cases, without including those who did not present for medical care, may have led to case selection bias. The effects of this potential bias would be to shrink the OR estimate towards the null.

Although there is a possibility that leatherwork was associated with an increase in the risk of oligozoospermia, this possibility was very small indeed. The results of this study clearly show the difficulty of concluding, with certainty, that there is no increase in the risk of a disease associated with an exposure. However, the Bayesian method described by Burton *et al*<sup>27,28</sup> is helpful in that it allows the estimation of the chance that the true value of an OR exceeds a certain threshold value which is chosen as one being of clinical importance. In the case of the result associated with oligozoospermia there was only a 17% chance that the true OR was 2.0 or greater. In other words, although this possibility cannot be formally excluded, the odds in favour of a lesser effect are greater than 4:1.

The findings relating to the risk of teratozoospermia was the only one of concern in relation to leatherwork. Although not significant the result suggests that leatherworkers may be at a 65% increased risk of teratozoospermia compared with other men. Furthermore, the Bayesian analysis indicated that there was a 43% chance that the true OR was 2.0 or greater. By contrast, the analysis based on the actual values from the semen analysis did not indicate a difference between leatherworkers and other men in the mean or median values for the proportion of deformed sperm. Interestingly, by contrast, Bigelow *et al*<sup>30</sup> detected differences in semen parameters analysed as continuous variables associated with particular workplace exposures which were not identified in a binary outcome analysis; leatherwork was not one of these exposures. However, in the absence of an important increase in the risk of presenting with infertility the evidence relating to teratozoospermia is not compelling, although it probably merits further investigation. Furthermore, if leatherwork is a risk factor for teratozoospermia, exposure to solvents does not seem to be the explanation for this. Overall, our findings should provide reassurance to the leatherworkers who use leather in manufacturing. Nothing can be concluded from these data about any potential risks related to tanning.

### WORK WITH SOLVENTS

Work in the boot and shoe and leather goods industry is associated with exposure to a wide range of organic solvents.<sup>31</sup> Animal work has shown adverse effects of glycol ethers on the reproductive function of many species.<sup>32</sup> These effects include "microscopic testicular lesions,

testicular atrophy, reduced numbers of late maturation-stage cells, and infertility.<sup>32</sup> In particular testicular histology was found to correlate with abnormal sperm morphology.

We investigated the effects of work with solvents on male reproductive function, as we postulated at the outset that if there was an increased risk of oligospermia associated with leatherwork this would be mediated through exposure to solvents. Our results indicate that men currently working in occupations associated with exposure to solvents had a modest (73%), but clinically relevant and significant increased risk of presenting for investigation of infertility. We were, however, unable to adjust this result for the effects of potential confounders and differential reporting between the cases and controls may have led to an overestimate of the OR. By contrast, our other results strongly suggest that work involving exposure to solvents is not a risk factor for oligozoospermia, asthenozoospermia, or teratozoospermia.

The evidence in the scientific literature of the possible effects of organic solvents on male fertility is inconsistent. Sallmén *et al*<sup>33</sup> and Eskenazi *et al*<sup>34</sup> found a small but non-significant decrease in fecundability associated with use of tetrachloroethylene. In the same study Eskenazi *et al*<sup>34</sup> found some effects on sperm morphology for dry cleaners but no effect on other sperm parameters. Compared with agricultural and cement workers, Danish painters were found to have an increased risk of infertility.<sup>35</sup> By contrast Sallmén *et al* found little evidence of an effect on time to pregnancy for painters.<sup>33</sup>

Our finding of an increase in the risk of male infertility associated with occupations involving solvents taken as a group is in keeping with the overall findings of Sallmén *et al*.<sup>33</sup> They found some evidence, although the role of chance was not excluded, that paternal exposure to organic solvents is associated with decreased fertility as assessed in a retrospective time to pregnancy study in which all couples conceived at least once.

The effects of solvents on sperm quality have also been investigated, again with some inconsistent and inconclusive findings. Welch *et al*<sup>36</sup> found that compared with controls, painters were nearly three times more likely to have oligospermia and Ratcliffe *et al*<sup>37</sup> found that metal cast workers were at nearly a twofold increased risk of oligospermia. Neither of these results was significant and cigarette smoking was the only confounder adjusted for. Veulemans *et al*<sup>38</sup> described similar findings. Chia *et al*<sup>39</sup> reported that sperm density was lower in employees in the electronics industry who were exposed to high concentrations of trichloroethylene; whereas in a smaller study, Rasmussen *et al*<sup>40</sup> found no effect on semen parameters for metal degreasers exposed to trichloroethylene. Plastics workers exposed to styrene were found to have an increase in the number of abnormal sperm.<sup>41</sup>

In our study a wide range of occupations with possible exposure to solvents was investigated. Exposure misclassification is likely to have occurred and there was a combination of occu-

pations with high and low levels of exposure. Indeed, job title as used in this study has been criticised as an imprecise measure of exposure to specific agents in the workplace,<sup>42</sup> although other investigators advocate this approach.<sup>43 44</sup> Thus, although a relation was not found between those occupations defined in this study as work with solvents and abnormal semen findings, the possibility remains that this was a false negative finding resulting from misclassification. Indeed, the finding that work with solvents may increase the risk of presenting with infertility supports the view that we simply failed to detect the mechanism by which exposure to solvents operates to adverse effect and further investigation is recommended to clarify this issue.

## Conclusions

There was little evidence to support the hypotheses that leatherwork is associated either with an increased risk of presenting with infertility or oligospermia. Overall, these findings are reassuring for workers who use leather in manufacturing. There is some, although far from compelling, evidence that leatherwork may be a risk factor for teratozoospermia. Although workers with solvents seemed to be at an increased risk of presenting with infertility, this did not seem to be mediated through direct effects on semen quality as measured in standard semen analysis tests.

We thank the Health and Safety Executive who funded this study and the Wellcome Trust who provided the research training fellowship for JJK. The analysis was finally completed while JJK was funded by the Australian National Health and Medical Research Council (grant 96/3209). We also thank the study interviewers Lesley Parr, Sue Pittam, Linda Jones, Anne Peel, Mark Peel, Mary Mustin, and Elaine Metcalf. Our thanks also go to the study subjects, who generously agreed to participate; the clinic and consultant staff who facilitated our access to patients; and Elizabeth Draper who provided access to the perinatal mortality study control data.

## Appendix: Office of Populations, Censuses and Surveys (OPCS) codes

- (1) Codes defining leatherwork using the 1970 OPCS classification of occupation<sup>20</sup>
  - 061 Shoemakers and shoe repairers
  - 062 Cutters, lasters, sewers, footwear and related workers
  - 063 Leather products makers nec\*
- (2) Codes defining work with solvents using the 1970 OPCS classification of occupation<sup>20</sup>
  - 012 Chemical production process workers nec\*
  - 061 Shoemakers and shoe repairers
  - 062 Cutters, lasters, sewers, footwear and related workers
  - 063 Leather products makers nec\*
  - 070 Dyers of textiles
  - 071 Textile fabrics and related products makers and examiners nec\*
  - 087 Printers (so described)
  - 088 Printing workers nec\*
  - 089 Workers in rubber
  - 090 Workers in plastics
  - 099 Aerographers, paint sprayers
  - 100 Painters, decorators nec\*
  - 101 Coach painters (so described)
  - 204 Chemists†
  - 219 Laboratory assistants, technicians
- (3) Codes defining leatherwork using the 1980 OPCS classification of occupation<sup>21</sup>
  - 08401 Foremen: Tannery production workers
  - 08402 Foremen: Shoe repairers
  - 08403 Foremen: Leather cutters and sewers, footwear lasters, makers, finishers
  - 08404 Foremen: Other making and repairing, leather

08501 Workers: Tannery production workers  
 08502 Workers: Shoe repairers  
 08503 Workers: Leather cutters and sewers, footwear lasters, makers, finishers  
 10707 All others in making and repairing leather  
 (4) Codes defining work with solvents using the 1980 OPCS classification of occupation<sup>21</sup>  
 08401 Foremen: Tannery production workers  
 08402 Foremen: Shoe repairers  
 08403 Foremen: Leather cutters and sewers, footwear lasters, makers, finishers  
 08404 Foremen: Other making and repairing, leather  
 08501 Workers: Tannery production workers  
 08502 Workers: Shoe repairers  
 08503 Workers: Leather cutters and sewers, footwear lasters, makers, finishers  
 10707 All others in making and repairing leather  
 16002 General labourers: Chemical and allied trades  
 15902 Foremen: Chemical and allied trades  
 13801 Laboratory assistants  
 13804 Inspectors, viewers, examiners: Rubber goods  
 13805 Inspectors, viewers, examiners: Plastic goods  
 13807 Inspectors, sorters in paper production, processing and printing  
 13808 Assemblers in paper production, processing and printing  
 13809 Assemblers (plastic goods)  
 13604 Foremen: Rubber goods  
 13605 Foremen: Plastic goods  
 13405 Foremen: Assemblers - plastic goods  
 13404 Foremen: Assemblers - paper production, processing and printing  
 13301 Painters, decorators, french polishers - pottery decorators  
 13302 Painters, decorators, french polishers - coach painters (so described)  
 13303 Painters, decorators, french polishers - other paint sprayers  
 13304 Painters, decorators, french polishers - painters and decorators nec\*, french polishers  
 13201 Foremen: Pottery decorators  
 13202 Foremen: Coach painters (so described)  
 13203 Foremen: Other paint sprayers  
 13204 Foremen: Painters and decorators nec\*, french polishers  
 10709 All others in making and repairing - paper goods and printing  
 10710 All others in making and repairing - rubber  
 10711 All others in making and repairing - plastic  
 10001 Painting workers, screen and block printers - compositors  
 10002 Painting workers, screen and block printers - electrotypers, stereotypers, printing plate and cylinder preparers  
 10003 Painting workers, screen and block printers - printing machine minders and assistants  
 10004 Painting workers, screen and block printers - screen and block printers  
 10005 Painting workers, screen and block printers - printers (so described)  
 09901 Foremen - printing - compositors  
 09902 Foremen - printing - electrotypers, stereotypers, printing plate and cylinder preparers  
 09903 Foremen - printing - printing machine minders and assistants  
 09904 Foremen - printing - screen and block printers  
 09905 Foremen - printing - printers (so described)  
 09701 Rubber process workers, moulding machine operators, tyre builders  
 09702 Calender and extruding machine operators, moulders (plastics)  
 09509 Foremen - rubber  
 09510 Foremen - plastics  
 09504 Foremen - rubber process workers, moulding machine operators, tyre builders  
 09305 Foremen - other making and repairing, paper goods and printing  
 08900 Chemical, gas and petroleum process plant operators  
 08800 Foremen - chemical processing  
 08707 Textile workers - bleachers, dyers, finishers

08607 Foremen - bleachers, dyers, finishers  
 07503 Launderers, dry cleaners, pressers  
 05503 Sales assistants - petrol pump, forecourt attendants  
 05402 Sales supervisor - petrol pump, forecourt attendants  
 02801 Chemical engineers  
 02402 Chemical scientists  
 \*nec: not elsewhere classified  
 †Chemists not pharmacists

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- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- 3 Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology, mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.