

# Congenital malformations and maternal occupation in Finland: multivariate analysis

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**SUMMARY** The Finnish Register of Congenital Malformations was used in a multivariate analysis to explore the associations between maternal occupation in industry and children born with central nervous system (CNS) or musculoskeletal or oral cleft malformations. Possible confounding factors were selected in preliminary screening of risk indicators for malformations. These factors included characteristics of the mother, the child, and the family; maternal illnesses; and maternal medication at the time of pregnancy. Tobacco smoking was a confounding factor for all types of malformations; number of children born to the mother, maternal age, malformations in the family, number of rooms occupied by the family, sex of the child, threatened abortion, and continuous medication of the mother during the first trimester confounded the association for certain types of malformations. After adjusting for confounding factors, maternal occupation in industrial trades significantly correlated with CNS, oral cleft, and musculoskeletal malformations in the offspring. Maternal occupation in industry and construction only was significantly associated with CNS malformations in the offspring but the associations with oral cleft and musculoskeletal malformations were not significant.

Environmental factors are thought to contribute to the aetiology of congenital malformations because the incidence of these malformations shows a large geographical variation and some seasonal variations.<sup>1</sup> Furthermore, in migrant families the incidence appears to be adjusted towards the level of the new population which the migrants are joining.<sup>2-4</sup> Other evidence on the role of environmental factors is the socioeconomic variation in the incidence of congenital malformations observed in many countries.<sup>1</sup>

The environmental factors that cause human malformations appear to be largely unknown.<sup>5</sup> Yet several chemical factors, such as medicines, have been implicated as being teratogenic to man.<sup>6-8</sup> Certain kinds of work may lead to exposure to harmful chemicals and some apparently at-risk occupations have been described in the literature. An increased incidence of congenital malformations has been reported in the offspring of operating theatre personnel,<sup>9-11</sup> vinyl chloride polymerisation workers,<sup>12</sup> copper smelters,<sup>13</sup> laboratory technicians,<sup>14</sup> and people exposed to solvents.<sup>15</sup> In addition, studies on the relationship of parental occupation to malformations in the offspring have suggested increased risks for certain industrial occupations.<sup>16-19</sup>

We have reported previously that industrial occupations are more often found among mothers of

cases than among mothers of controls in the Finnish Register of Congenital Malformations.<sup>20</sup> The parental occupations were recorded prospectively, thus avoiding the effects of a selective memory bias. However, as the controls were matched only for time and place of birth, the observed associations between industrial occupations and malformations could have been confounded by many factors. In the present study we attempt to control for the effects of these factors using multivariate analysis.

## Material and methods

The Finnish Register of Congenital Malformations has been maintained since 1963 at the National Board of Medicine. It is a case-control register including three types of malformations: central nervous system (CNS), oral cleft, and musculoskeletal. The cases are identified from compulsory notifications filled in at the maternity hospitals. The controls are the previous birth in the maternity welfare district. The cases and the referents are interviewed at the maternity welfare centres by the midwives. The standardised interview forms and the copies of the maternity welfare centre records are sent to the National Board of Medicine for inclusion in the register. The organisation of the register has been described previously in more detail.<sup>21</sup>

We coded the maternal occupations based on the records of the maternity welfare centres according to the three-digit classification of the Central Statistical Office of Finland.<sup>22</sup> As the occupations were collected from the records of the maternity welfare centre, filled in during pregnancy, no selective memory bias could affect the results. All the cases and their referents from 1967 to 1977 were collected, covering a total of about 3300 pairs. A case with multiple malformations was entered separately in each of the appropriate groups of malformations. Other information on the case and the referent mothers, such as age, number of children, smoking habits, and illnesses and medication during the actual pregnancy, was coded by the National Board of Medicine. Most of this information was recorded by interviewing the mothers after the birth of the child and it may thus be subject to memory bias. The effect of maternal occupations on the risk of defects in the offspring was evaluated by calculating odds ratios according to the formula for a matched series (ratio of discordant pairs).<sup>23</sup> The crude odds ratios obtained were referred to as 'original odds ratios'. McNemar's test was used for the evaluation of statistical significance.

In this study the influence of the possible confounding factors on the association between maternal occupation and malformations in the offspring was estimated using the linear logistic regression model.<sup>24-27</sup> The parameters of the model were tested as described.<sup>26</sup>

In this model a dichotomous exposure variable, F, and a disease indicator variable, D, are considered, and data of affected (case) and healthy (control) individuals are analysed to ascertain exposure. The model is set for these conditional exposure probabilities:

$$\text{logit } P(F | D, Z_i) = \ln \frac{P(F = 1 | D, Z_i)}{P(F = 0 | D, Z_i)} = \delta_i + \alpha \cdot D + Z_i \beta$$

where D = 1 for cases and D = 0 for controls; F = 1 if exposure is present and F = 0 if it is not present; Z<sub>i</sub> is a vector of confounding factors for the i:th pair (that is, the influence of Z on exposure probabilities is common to both cases and controls). From the above formula the exposure odds ratio (EOR) can be derived:

$$\begin{aligned} \ln(\text{EOR}) &= \text{logit } P(F | D = 1, Z_i) - \text{logit } P(F | D = 0, Z_i) \\ &= \alpha + (Z_i - Z_i') \cdot \beta \end{aligned}$$

and

$$\begin{aligned} \text{EOR} &= e^\alpha, \text{ if } Z_i = Z_i' \end{aligned}$$

Thus the linear logistic model for matched data assumes the relationship is linear for the log odds ratio.  $\alpha$  and  $\beta$  are regression parameters. The odds ratio after the elimination of the confounding factors (referred to as 'revised odds ratio') is  $e^\alpha$ . The parameters ( $\alpha$  and  $\beta$ ) of the model were estimated by the Walker-Duncan method<sup>28</sup> and tested by the asymptotically normally distributed statistic  $t_j = \hat{\beta}_j / \text{Se}(\hat{\beta}_j)$

The confounding factors were chosen for the multivariate analysis on the basis that they associated with the three types of malformations in a preliminary screening of the factors and that they were conceivably related to occupation. Table 1 shows all the variables which were taken into the multivariate analysis. Some apparent confounding factors were omitted from the analysis for two reasons, either because they were considered a product of maternal memory bias (for example, reported depressive state during pregnancy), or because they were considered to be caused by the malformation (for example, low birthweight of the child). The factors are considered as binary variables in Table 1 and in the calculation of the original odds ratios for occupation in Tables 2, 3, and 4. In multivariate analysis each confounding factor was described quantitatively in 2 to 10 different categories, increasing or decreasing in magnitude. Only the first trimester of pregnancy was considered and the maternal illnesses and medication were listed in three categories according to the month (1 = first, 2 = second, 3 = third) of pregnancy in which an illness was first contracted or a medication used.

## Results

The risk indicators of malformations considered as possible confounding factors in the association of maternal occupation with malformations in the offspring (see Table 1) were taken into the multivariate analysis. The selection of the possible confounding factors was not stringent in terms of biological or causal considerations, because it turned out that most variables tested did not associate with the occupation. All the 22 different variables were controlled in groups with each of the three main types of malformations. The groups of variables controlled at one time included maternal factors (three variables), social factors (five variables), factors relating to obstetric history (four), maternal diseases (six), and medication ingested (four). The variables showing a significant ( $p < 0.10$ ) association with maternal occupation in industry were considered technically as true confounders, and they were included in the final analysis described in Tables 2 to 4.

*Congenital malformations and maternal occupation in Finland*

**Table 1 Odds ratios of the risk indicators considered as possible confounders of the association of maternal occupation with malformations in the offspring**

Risk indicator	ODDS RATIOS		
	CNS malformation	Oral cleft	Musculoskeletal malformation
Maternal age >35	1.39*	1.27	1.14
No. of children born alive ≥5	1.54*	1.23	1.37
Previous stillbirths: yes	3.09***	27.00***	1.56
Previous premature births: yes	2.24**	1.41	1.24
Previous abortions ≥2	1.56	1.41	1.00
Malformations in family: yes	2.24***	3.76***	3.65***
Weight of placenta ≤400 g	3.26***	3.02***	5.48***
Multiparous pregnancy: yes	4.38***	3.10**	2.08*
Sex of child: boy	0.82*	1.10	1.19*
Number of rooms occupied by family ≤1.2 person	4.09***	1.54**	1.52**
Tobacco smoking >5 cigarettes a day	1.61***	1.49	1.35
<i>Diseases and conditions during pregnancy</i>			
Threatening abortion: yes	1.65***	1.52***	1.77***
Influenza 1st trimester	2.56***	1.82***	2.04***
High fever 1st trimester	2.50***	2.38***	2.22***
Other disease 1st trimester	2.70***	2.38***	2.78***
Chronic illness: yes	1.64**	1.56**	1.67***
No. of diseases ≥1	1.61***	1.72***	2.78***
<i>Medication and treatment during 1st trimester</i>			
Analgesics	2.86***	2.22***	2.63***
Antineurotics	1.92*	2.33**	1.64
Continuous medication	2.22**	1.67*	2.50***
Temporary medication	1.69***	1.61***	1.92***
X rays	1.83***	1.12	1.65**

\*p <0.05; \*\*p <0.01; \*\*\*p <0.0001; McNemar's test.

**Table 2 Influence of the confounding factors on the association of maternal occupation with CNS malformations in the offspring in the linear logistic regression model**

Original odds ratio	no. of discordant pairs analysed	After analysis with the following confounding factors	Test statistics <sup>1</sup>	Revised odds ratio
Mother in industry, construction, transport, communications 1.49**	164	No. children born	-2.50*	1.98***
		Malformations in family	-1.73 <sup>a</sup>	
		No. rooms occupied by family	-2.70**	
		Smoking	1.18	
		Continuous medication	-2.15*	
Mother in industry, construction 1.62**	160	No. children born	-3.11**	1.81**
		No. rooms occupied by family	-1.74 <sup>a</sup>	
		Smoking	1.91 <sup>a</sup>	

<sup>1</sup>Test statistics indicate the significance of the individual confounding factors.

<sup>a</sup>p <0.10; \*p <0.05; \*\*p <0.01; \*\*\*p <0.001

**Table 3 Influence of the confounding factors on the association of maternal occupation with oral clefts in the offspring in the linear logistic regression model**

Original odds ratio	No. of discordant pairs analysed	After analysis with the following confounding factors	Test statistics	Revised odds ratio
Mother in industry, construction, transport, communication 1.26	248	Maternal age	-2.22*	1.38*
		Smoking	3.25***	
		Threatening abortion	-1.87 <sup>a</sup>	
Mother in industry, construction 1.13	241	Maternal age	-3.42***	1.23
		Smoking	3.43***	

<sup>a</sup>p <0.10; \*p <0.05; \*\*p <0.01; \*\*\*p <0.001.

Table 4 Influence of the confounding factors on the association of maternal occupation with musculoskeletal malformations in the offspring in the linear logistic regression model

Original odds ratio	No. of discordant pairs analysed	After analysis with the following confounding factors	Test statistics	Revised odds ratio
<i>Mother in industry, construction, transport, communications</i>				
1.35*	253	Malformations in family	-2.13*	1.33*
		Sex of child	2.48*	
		Smoking	2.71**	
<i>Mother in industry, construction</i>				
1.30*	225	Malformations in family	-2.08*	1.22
		Sex of child	1.74 <sup>a</sup>	
		Smoking	2.75**	

<sup>a</sup>p <0.10; \*p <0.05; \*\*p <0.01.

The variables that appeared to confound the association of maternal occupation in industry with CNS malformations in the offspring were the number of children born to the mother, malformations in other family members, number of rooms occupied by the family (probably a social class factor), maternal tobacco smoking habits, and continuous medication of the mother during the first trimester. The controlling of these factors increased the odds ratio from the original 1.49 to 1.98 ( $p < 0.001$ ) for the offspring of the mothers employed in industry, construction, transport and communications (Table 2). Consideration of the offspring of only industrial and construction workers resulted in a revised odds ratio of 1.81 compared with the original odds ratio of 1.62.

A similar analysis was carried out of the association of maternal occupation in the industrial trades with oral clefts in the offspring (Table 3). After adjustment for maternal age, tobacco smoking, and threatened abortion during the relevant pregnancy, the odds ratio increased from the original 1.26 to 1.38 ( $p < 0.05$ ). Consideration of only industrial and construction workers increased the odds ratio to 1.23 (non-significant).

Adjustment for the confounding factors (malformations in the family, sex of the child, and smoking habits of the mother) in the analysis of the relationship between industrial occupations and musculoskeletal malformations in the offspring only slightly affected the odds ratio (1.33; Table 4). The odds ratio for the offspring of industrial and construction workers only was smaller, 1.22, after the multivariate analysis.

## Discussion

The original analysis of parental occupation in relation to congenital malformations in the offspring showed increased odds ratios for certain maternal but not paternal occupational groups.<sup>29</sup> Central nervous system and musculoskeletal malformations were more common in the offspring of industrial and

construction workers; oral clefts were more common in the offspring of transport and communication workers. However, as the series was matched only for the time and place of birth, confounding factors related to occupation could affect the observed relationship. In respect of industrial workers, the most likely sources of confounding are the determinants of employment or of social class. These may include age, family size, social habits such as tobacco smoking, dietary and hygienic factors, and illnesses.

In the present multivariate analysis attempts were made to control the confounding factors. Three different types of variables were controlled. The first included characteristics of the mother and the child, and of their family, found to be associated with the three types of malformations in our primary screening. Several variables of this group appeared to confound the association of maternal occupation in industry with malformations in the offspring. The only confounding factor for all types of malformations was tobacco smoking, which has been reported as being associated with malformations in some previous studies,<sup>30 31</sup> whereas no association has been found in other studies.<sup>32</sup>

Another group of variables controlled included maternal illnesses during the first trimester of pregnancy. Of these, maternal influenza and threatened abortion have previously been associated with CNS defects and oral clefts in the offspring.<sup>26 33</sup> Maternal illness could conceivably be a confounder, as certain illnesses appear to be more common among workers compared with managers and office personnel according to a Finnish study.<sup>34</sup> However, in the present analysis, only threatened abortion turned out to be a confounding variable associated with oral clefts.

The third group of variables controlled included the medication ingested and the x ray treatment given. Medicines associated with malformations in our preliminary screening (Table 1) are in agreement with other reports.<sup>26 33</sup> The only type of treatment found to be a confounding factor was the reported

continuous, regular medication of the mother during the first trimester, associating with CNS malformations.

In the present study, based on information accumulated in the Finnish Register of Congenital Malformations, we could control a number of factors confounding the relationship between maternal occupation in industry and malformation in the offspring. Many of the factors controlled were related to social class (for example, smoking habits, number of rooms occupied, family size, etc.) and yet the association of maternal occupation in industrial trades with malformations in the offspring remained. Thus the results do not suggest a mere social class effect. In agreement, analysis of the register according to parental social class revealed no clear gradient.<sup>29</sup> Yet the possibility remains that the variables available fail to describe social class adequately and that social class would indeed be one of the underlying factors.

One possible source of spurious associations is the design of the register, as the time interval between the delivery and the interview is from two to six months. A deficit of an occupation in the controls may develop if those in that occupation move frequently, or if the number of persons employed decreases rapidly. Such bias should, however, affect all the types of malformations equally; thus the findings of the present study cannot be explained by the bias.

The controlling of the confounding factors either increased or decreased the association of maternal employment in industrial trades with malformation in the offspring. After the multivariate analysis, maternal occupation in industry (industry, construction, transport, and communications) was significantly associated with CNS, oral cleft, and musculoskeletal malformations in the offspring. Central nervous system malformations appeared to be particularly common among the children of industrial and construction workers, while oral cleft and musculoskeletal malformations were common among the children of transport and communications workers, although this group was so small that it could not be analysed separately. Thus some occupational factors may constitute a true risk for the embryo. The identification of the specific agents and factors which constitute the occupational exposures is a challenge to be met in further studies.

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