

# Epidemiology of cleft lip and palate

## An attempt to rule out chance correlations

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**Saxén, Irma (1975).** *British Journal of Preventive and Social Medicine*, **29**, 103-110. **Epidemiology of cleft lip and palate: An attempt to rule out chance correlations.** The findings of a previous epidemiological study on oral clefts (599 children) were tested in an independent sample of 194 children, using the same source as for the previous study (Finnish Register of Congenital Malformations). Several of the earlier results—such as seasonal variation and associations between clefts and parental age, social factors, and emotional stress—were not reproduced. It is concluded that chance correlations introduce a marked problem to epidemiological studies.

The findings of both studies show that there is an exceptionally high incidence of cleft palate in Finland. Significant geographical variations and associations between clefts and prematurity, threatened abortion during the first and second trimesters, maternal drug consumption during the first trimester, and influenza and fever during the first trimester were found. The possible role of these findings in the aetiology of oral clefts is discussed, and particular attention is paid to the possible teratogenicity of salicylates.

The epidemiology of cleft lip and palate was recently studied in a series of 599 Finnish children with oral clefts (Saxén and Lahti, 1974; Saxén, 1974a, b, 1975a). In this study numerous significant associations were observed between clefts and various factors concerning the families of the children, the course of pregnancy, and different environmental influences. However, as in all epidemiological studies that are based on a single set of data which are fractionated, the problem of chance correlations or the so-called 'multiple comparison problem' remained (Mantel and Haenszel, 1959). Since the aetiological significance of a large number of factors had been studied, it could be expected that some of the apparently significant differences had occurred by chance. In order to confirm the true associations and to detect the chance correlations, the study was repeated in an independent sample.

### MATERIAL AND METHODS

The sample studied comprised all the oral clefts that had been reported to the Finnish Register of Congenital Malformations during the years 1972 and 1973, and their matched controls. Altogether there were 194 affected children, of whom 105 had

cleft palate (CP) and 85 cleft lip with or without cleft palate (CL(P)). For 4 of the children who had died soon after delivery the type of cleft was not recorded. The data were collected similarly as for the previous sample, which consisted of 599 clefts reported during the years 1967-71. The organization and mode of data collection have been described in earlier reports (Saxén, 1974b; 1975a) and more detailed information is available in a recent study by Saxén, Klemetti, and Härö (1974). The information in the Register is compiled from initial notification cards, death certificates, maternity welfare centre records (kept of all Finnish mothers during pregnancy), and an interview with the mothers after delivery.

For the purpose of this study the data in the Register were recoded by the author, so that only the information necessary for the testing of previous findings was noted. As earlier, the drugs were recoded so that each active compound of the drugs was coded separately. The type of cleft was again obtained from the records of the Finnish Red Cross Hospital for Plastic Surgery, where the treatment of such children has been centralized. The material was then prepared for computer analysis and was grouped according to the type of cleft. In the statistical

analysis each group was compared with its corresponding control group formed of the matched control pairs (matched for time of pregnancy and place of residence). The  $\chi^2$  test was used for determinations of significance. Because the sample was much smaller (194) than in the previous study (599) the statistical significance of the present associations was not of importance when comparing the results, and the associations were regarded as reproduced if the percentages in the study and control group were of the same order in both studies.

### RESULTS

#### EARLIER RESULTS CONFIRMED BY THE PRESENT STUDY

**INCIDENCE.** The incidence of different types of clefts in Finland was essentially the same during the two-year period of the present study when compared with the previous five-year period (Table I). Thus the exceptionally high incidence of cleft palate (CP) was confirmed.

TABLE I  
INCIDENCE OF CLEFT LIP AND PALATE IN FINLAND  
(PER 1000 BIRTHS)

Year	Total No. of Births	Cleft Lip With or Without Cleft Palate (CL(P))			Cleft Palate	Total Oral Cleft Incidence
		Cleft Lip	Cleft Lip and Palate	CL(P) Total		
1972	59 107	0.22	0.51	0.73	0.81	1.54 (91)*
1973	57 300	0.24	0.49	0.73	0.98	1.80 (103)
Total	116 407	0.23	0.50	0.73	0.90	1.66 (194)
1967-1971	347 316	0.22	0.45	0.83	0.86	1.72 (599)
Total	463 723	0.22	0.46	0.81	0.87	1.71 (793)

\*Number of cases in parentheses

The geographical variation of the CP incidence was similar to that of previous studies (Table II). The incidence was high in the eastern parts of the country, being highest in the most eastern province where it was twice the average incidence (1.97 per thousand, previously 1.47 per thousand)

TABLE II  
GEOGRAPHICAL VARIATION OF CLEFT PALATE  
INCIDENCE IN FINLAND IN 1972-73 AS COMPARED WITH  
THE PREVIOUS RESULTS (PER 1000 BIRTHS)

Years	Eastern Provinces	Other Parts of the Country
1972-73	1.14 (25)*	0.85 (80)
1967-71	1.17 (82)	0.79 (216)

\* Number of cases in parentheses

**FAMILY HISTORY.** The percentage of mothers reporting other cleft-affected relatives was 19.5% and thus of the same order as in the previous study (17.5%). The earlier finding was confirmed that in the Finnish series, unlike others reported, a positive family history is not more often associated with cleft lip with or without cleft palate (CL(P)) (19%, previously 16.6%) than with CP (19%, previously 18.5%).

**ADDITIONAL MALFORMATIONS.** There were 55 children with multiple malformations. In the CP group the percentage was 30% (previously 22%) and in the CL(P) group 25% (previously 20%). This result is similar to the previous one in that no excess of other defects is present in the CP group when compared with CL(P) although this has been the case in most earlier studies.

**SEX DISTRIBUTION.** An excess of females in the CP group and an excess of males in the CL(P) group were again confirmed, and the sex distributions according to family history, and additional defects were similar to those of the previous study. Thus the dominance of one sex was somewhat lessened among the cases with multiple malformations.

**EARLIER DEFECTIVE CHILDREN.** As in the earlier study, the mothers of children with clefts more often reported that they had other malformed children (3.7%, previously 4.5%) than did the control mothers (1.0%, previously 1.4%). These were, as previously, predominantly mothers of children with CP.

**PREMATURITY.** The high frequency of premature births (birth weight  $\leq$  2500 g, placental weight  $\leq$  400 g, or length of gestation  $\leq$  37 weeks), particularly among children with multiple malformations, was also confirmed (Table III). There was also a slight increase of premature births in the other groups, as in the previous study.

TABLE III  
PREMATURITY OF CHILDREN WITH CLEFTS WITH  
ADDITIONAL MALFORMATIONS:  
RESULTS OF THE 1972-73 STUDY (55 CHILDREN) COM-  
PARED WITH THE 1967-71 RESULTS (134 CHILDREN)\*

Years	Birth Weight $\leq$ 2 500 g Per cent	Placental Weight $\leq$ 400 g Per cent	Length of Gestation $\leq$ 37 Weeks Per cent
1972-73	38*** (4)	24** (4)	33*** (5)
1967-71	43*** (6)	18*** (2)	32*** (5)

$\chi^2$  test

\*  $P < 0.05$  \*\*  $P < 0.01$  \*\*\*  $P < 0.001$

Values for the control groups are given in parentheses

**THREATENED ABORTION.** The previously found association between threatened abortion during the first and second trimesters and the birth of children with clefts was confirmed (Table IV). The frequencies were again highest in the CL(P) group and in the group of multiple malformations.

TABLE IV

THREATENED ABORTION REPORTED BY MOTHERS OF CHILDREN WITH CLEFTS AND OF MATCHED CONTROLS IN 1972-73 AND 1967-71 (PER CENT)

Years	Entire Study Group	Clefts with No Additional Malformations		Clefts with Additional Malformations
		CP	CL(P)	
First trimester				
1972-73	12.5 (7.3)	8 (4)	11 (10)	20 (9)
1967-71	9.5* (5.6)	6 (4)	13* (6)	11 (8)
Second trimester				
1972-73	9.4 (6.3)	5 (7)	8 (5)	15 (7)
1967-71	7.7** (3.7)	4 (3)	10** (4)	11 (6)

CP=cleft palate

CL(P)=cleft lip with/without cleft palate

\* P<0.05

\*\* P<0.01

Values for the control groups are given in parentheses

**NAUSEA.** Cleft and nausea during pregnancy appeared to be unrelated in both studies. The frequency of reporting moderate nausea was 15.6% (previously 18.8%) in the study group and 17.7% (previously 16.1%) in the control group.

**DRUG CONSUMPTION.** A slight increase in the overall consumption of drugs (iron and vitamins excluded) was noted when compared with the earlier results (Table V). The highly significant association

TABLE V

OVERALL INTAKE OF MEDICINES (OTHER THAN VITAMINS) BY MOTHERS OF CHILDREN WITH CLEFTS AND OF MATCHED CONTROLS IN 1972-73 AND 1967-71 RESULTS\* (PER CENT)

Years	Entire Study Group	Clefts with No Additional Malformations		Clefts with Additional Malformations
		CP	CL(P)	
1972-73	48.4*** (28.1)	55*** (28)	53* (34)	35 (22)
1967-71	44.4*** (26.9)	40*** (23)	50*** (30)	45* (33)

CP=cleft palate

CL(P)=cleft lip with/without cleft palate

\* P<0.05

\*\*\* P<0.001

between clefts and an increased intake of drugs during the first trimester was confirmed. During the second trimester no difference between the study and control groups was observed (31.8%, control 33.3%) nor during the third trimester (52.6% and 46.4%).

The frequency of reporting an intake of the individual drugs was of the same order as before (Table VI). All the drugs that had been significantly associated with clefts in the earlier study (salicylates, other antipyretic analgetics, opiates, penicillins, tetracyclines, antihistaminics, and antineurotics)

TABLE VI

INTAKE OF DIFFERENT DRUGS DURING FIRST TRIMESTER BY MOTHERS OF CHILDREN WITH CLEFTS AND OF MATCHED CONTROLS: 1972-73 AND 1967-71 (PER CENT)

Years	Salicylates	Other Antipyretic Analgetics	Opiates	Antihistaminics
1972-73	11.5 (6.3)	6.8 (4.2)	5.2 (3.1)	4.7 (2.1)
1967-71	14.9*** (5.6)	7.0* (3.9)	6.7*** (2.2)	5.3** (2.3)
Years	Sulphonamides	Penicillins	Tetracyclines and/or Chloramphenicol	Antineurotics
1972-73	5.7 (5.7)	8.3 (4.2)	2.1 (0.5)	3.7 (2.1)
1967-71	6.5 (4.1)	8.5** (4.4)	2.8 (1.5)	6.2** (2.9)

\* P<0.05

\*\* P<0.01

\*\*\* P<0.001

Values for the control groups are given in parentheses

had again been consumed more frequently by the study mothers than by the control group. Because of the smaller numbers the differences did not reach statistical significance.

Sulphonamides were not associated with clefts, and this had also been noted in the previous series. Anticonvulsants had been taken by two of the mothers in the previous series, each of whom had a child with cleft lip and cleft palate. In the present series one mother reported taking anticonvulsants; she also had a child with CL(P).

The results of the previous study on the intake of different antihistaminics could not be reproduced. The association between antihistaminics and clefts was previously due to an increased intake of diphenhydramine, whereas no difference between the study and control groups was noted in the intake of cyclizines. In the present study both cyclizines (taken by two control and seven study mothers) and diphenhydramine (two control, five study mothers) accounted for the association. As in other instances, the small size of the series should be borne in mind.

**FEVER AND INFLUENZA.** The definite association between clefts and fever and influenza was also confirmed (Table VII). The association with fever was now even more pronounced.

TABLE VII

FEVER AND INFLUENZA DURING FIRST TRIMESTER REPORTED BY MOTHERS OF CHILDREN WITH CLEFTS AND OF MATCHED CONTROLS: 1972-73 AND 1967-71 (PER CENT)

Years	Fever	Influenza
1972-73	10.4* (4.2)	13.0 (7.3)
1967-71	7.5 (4.9)	10.7** (5.8)

\* P<0.05  
\*\* P<0.01

Values for the control groups are given in parentheses

TABLE VIII

FAMILIES OF CHILDREN WITH CLEFTS AND OF MATCHED CONTROLS: 1972-73 AND 1967-71 (PER CENT)

Years	Maternal Age ≥ 30	Paternal Age ≥ 30	Lowest Social Class	Mother Unmarried	Child Not Planned
1972-73	23.4 (23.9)	30.2 (34.9)	11.0 (12.0)	4.7 (6.3)	21.4 (19.8)
1967-71	30.7* (24.2)	46.1*** (34.9)	16.0** (10.9)	4.5** (1.7)	32.6* (26.3)

\* P<0.05  
\*\* P<0.01  
\*\*\* P<0.001

Values for the control groups are given in parentheses

**EARLIER RESULTS NOT REPRODUCED IN THE PRESENT STUDY**

**SEASONAL VARIATION.** In the earlier series a significant variation was noted in the incidence of CP and CL(P) during the four seasons of the year, and the trends of the two types of clefts (without other defects) were shown to differ. Such trends could not be found in the present series (Figure).

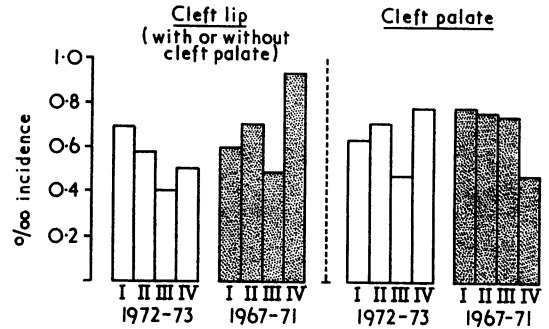


FIGURE Incidence of clefts with no additional malformations by season of birth in the present and previous studies. I-IV=quarters

**PATERNAL AGE.** No association between advanced parental age and clefts was found (Table VIII), although this association had been highly significant in the former series. There had earlier been a particularly strong association between CP and advanced paternal age, but now the percentage of fathers over 30 years of age was only 20% in the CP group, whereas in the controls it was 31% (previously 52% and 31% respectively).

**SOCIAL FACTORS.** The previous associations between clefts and low social class, unmarried mother, and unwanted children could not be confirmed (Table VIII).

## PELVIC X-RAY EXAMINATIONS BEFORE PREGNANCY.

In the study group the frequency of reporting pelvic x-ray examinations before pregnancy was of the same order as previously (18.8%, previously 17.0%). The earlier significant association could not be reproduced, however, since the percentage for the control group in the present series was higher than that for the study group (21.4%, previously 9.8%).

**SMOKING AND ALCOHOL CONSUMPTION.** In the previous study there had been a slight increase in the study group's frequency of reported smoking (more than five cigarettes per day) and consumption of alcohol during pregnancy (smoking in the study group 10.4%, control 6.4%; alcohol consumption 36.2%, control 31.5%). These differences were even smaller in the present series (9.4% v. 8.3%, and 47.4% v. 44.8%).

**EMOTIONAL STRESS.** The highly significant association between clefts and emotional stress in the earlier series could not be reproduced (Table IX). In the control groups of the present and previous series the reporting of stress was of the same order, but in the present series the frequency was not higher in the study group than in the controls.

TABLE IX

EMOTIONAL STRESS DURING PREGNANCY REPORTED BY MOTHERS OF CHILDREN WITH CLEFTS AND OF MATCHED CONTROLS: 1972-73 AND 1967-71 (PER CENT)

Years	First Trimester	Second Trimester	Third Trimester
1972-73	13.0 (12.6)	5.2 (4.2)	9.4 (8.3)
1967-71	24.4*** (15.3)	9.7* (6.4)	10.4 (7.6)

\* P&lt;0.05

\*\*\* P&lt;0.001

Values for the control groups are given in parentheses

CP—CL(P). An additional finding which could not be confirmed was the difference between the two aetiologically different types of clefts, CP and CL(P), concerning association with drug consumption. In the previous series the overall consumption of drugs was significantly higher in the CL(P) than in the CP group. In the present series, it was slightly higher in the CP group.

## SUMMARY OF SIGNIFICANT FINDINGS SUPPORTED BY BOTH STUDIES

- 1 High incidence of cleft palate in Finland (Table I)
- 2 Geographical variation of cleft palate incidence—high incidence in the eastern provinces

TABLE X

SUMMARY OF ASSOCIATIONS FOUND IN BOTH STUDIES: STATISTICAL SIGNIFICANCE OF THE ASSOCIATIONS IN THE COMBINED STUDY\*

Details	Entire Study Group	Clefts with No Additional Malformations		Clefts with Additional Malformations
		CP	CL(P)	
No.	791	306	294	189
Birth weight ≤2 500 g ..	***	**		***
Placental weight ≤400 g ..	***		**	***
Gestation ≤37 weeks ..	***	**	**	***
Threatened abortion				
First trimester ..	**		*	
Second trimester ..	**			
During first trimester:				
Overall intake of medicines ..	***	***	***	***
Salicylates ..	***	*	***	*
Other antipyretic analgetics ..	**	**		
Opiates ..	***	*	**	
Penicillins ..	***			**
Tetracyclines and/or chloramphenicol ..	*		*	
Antihistaminics ..	**			**
Antineurotics ..	**	*	*	
Fever ..	**			
Influenza ..	***		*	*

\* P&lt;0.05

\*\* P&lt;0.01

\*\*\* P&lt;0.001

CP=cleft palate

CL(P)=cleft lip with/without cleft palate

- 3 Prematurity of children with clefts (Table X)—this association was by far the strongest in the group of children with multiple malformations. The frequency of children born pre-term was increased also in other groups.
- 4 Threatened abortion during first and second trimesters (Table X)—this association was stronger in the CL(P) group and in the group of multiple malformations than in the CP group.
- 5 Increased maternal drug consumption during the first trimester (Table X)—of individual drugs, salicylates, opiates, and penicillin were particularly strongly associated with clefts.
- 6 Increased frequency of fever and influenza during the first trimester (Table X).

## DISCUSSION

In the present study several of the associations of the previous study were not reproduced, which indicates that chance correlations introduce a noteworthy problem to epidemiological studies. The danger of drawing conclusions from one single epidemiological study based on chance has often been pointed out (Mantel and Haenszel, 1959; Murphy, 1971; Saxén, 1974). The differences between the results of the two independent studies are probably explained by chance; other explanations, for example, differences in methods of data collection or in the composition of the sample are unlikely because the same source of the data was used, and the period during which both studies were performed was relatively short.

The discrepancy between results from different studies related to seasonal variations of incidences, can probably be explained by coincidence. The present study is a typical example, the seasonal trends of clefts being totally different in the two studies. Changes in the environment could be a possible explanation, but this is unlikely.

The results relating advanced parental age to oral clefts have also varied greatly in the literature (Greene *et al.*, 1964; Drillien, Ingram, and Wilkinson, 1966; Emanuel *et al.*, 1973). The result of the present study, in which the previous highly significant association between advanced paternal age and CP had almost been reversed, was quite unexpected; but this emphasizes again how careful one should be in drawing conclusions from the results of a single study. Another 'highly significant' association which could not be reproduced was the one between emotional stress and clefts. In the previous study (Saxén, 1974b) the role of maternal memory bias, known to affect results of this kind (Fraser and Warburton, 1964), was discussed, but the present results indicate that this association might instead have arisen by chance.

Other associations in the previous study such as those between clefts and social factors, were probably also chance findings. Several of the associations were, however, distinct in both studies, and their possible value in determining the causes of oral clefts will be discussed briefly. Other possible shortcomings that influenced the results of the present study, which was partly retrospective, were discussed in the previous reports (Saxén, 1974b, 1975a). The various points that should be considered when evaluating whether an association is causal were also discussed (Saxén, 1975a), and the effect of confounding in the previous series was studied (Saxén, 1975b).

The high incidence of cleft palate in Finland compared with other populations (Leck, 1972) and

its distinct geographical distribution may reflect differences in a variety of factors. Genetic and environmental factors may be involved, for example, differences in socio-economic status, parental age, or some environmental influences (Fraser, 1971). In the previous study we suggested that the exceptionally high incidence of clefts in eastern Finland might have been caused by differences in the morphological features between the eastern and western Finns (wider head of eastern Finns) (Saxén and Lahti, 1974). This needs further investigation, but the hypothesis is tempting, since it would fit well with the idea of cleft palate being a threshold phenomenon (Fraser, 1969), and would be one explanation of the nature of genetic predisposition to cleft palate. In a wide head only a small delay in the elevation of the palatal shelves could result in failure of contact between the shelves and consequently in cleft palate.

Threatened abortion seems to be associated with clefts, particularly with CL(P) and with clefts with other defects. Maternal memory bias has not affected this factor since the information was collected during pregnancy at the maternity welfare centres. The association is reinforced by similar earlier findings (Drillien *et al.* 1966; Gilmore and Hofman, 1966; Fraser, 1970) as well as by the study of Nishimura (1969) indicating a high frequency of CL(P) among aborted fetuses. This association may, however, not be causal. There was a significant association also during the second trimester; thus threatened abortion might be a symptom of an already malformed embryo rather than a cause of the defect. This has also been suggested by Rumeau-Rouquette, Goujard, and Etienne (1971), who found in a prospective study that maternal bleeding was significantly associated with anomalies of purely genetic origin.

An association between maternal drug consumption during the first trimester and oral clefts was found to be significant in both studies, and it is noteworthy that none of the previously found associations between individual drugs and clefts was disproved in the repeated study. The possible teratogenicity of the different compounds was discussed previously in the light of earlier epidemiological and experimental data (Saxén, 1975a). Salicylates were by far the most used drugs and their association with clefts was strongest. Similar associations have been reported earlier in epidemiological studies on congenital malformations in general (Richards, 1969; Nelson and Forfar, 1971; Karkinen-Jääskeläinen and Saxén, 1974). Furthermore, the study of linkage between drugs and illnesses in the previous series (Saxén, 1975b) indicated that the association between clefts and salicylate intake could not be explained by the

simultaneous intake of other drugs or by influenza. In experimental studies high doses of salicylates have caused malformations (Warkany and Takacs, 1959; Larsson and Eriksson, 1966) including cleft lip (Trasler, 1965), and a therapeutic concentration of salicylates also caused a prolongation of the *in vitro* palatal development in the mouse (Saxén, 1975c). There is thus increasing evidence indicating that salicylates might have teratogenic properties. Because of their widespread use, the teratogenic potential of salicylates must usually be very low, but it is possible that this potential is increased in certain genetic milieus or by simultaneous interference of other environmental factors. An enhancement of the teratogenicity of salicylates has in fact been demonstrated in experimental animals by stressful conditions (Goldman and Yakovac, 1963) and by simultaneous treatment with benzoic acid (Kimmel, Wilson, and Schumacher, 1971), and the genotype has also been shown to influence the susceptibility to salicylate-induced malformations (Larsson and Eriksson, 1966). Thus, as stated by Wilson in a review: 'Salicylates should not at this time be dismissed as involving no embryotoxic risk for man' (Wilson, 1973).

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