

# Familial risk of oral clefts by morphological type and severity: population based cohort study of first degree relatives

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## ABSTRACT

**Objective** To estimate the relative risk of recurrence of oral cleft in first degree relatives in relation to cleft morphology.

**Design** Population based cohort study.

**Setting** Data from the medical birth registry of Norway linked with clinical data on virtually all cleft patients treated in Norway over a 35 year period.

**Participants** 2.1 million children born in Norway between 1967 and 2001, 4138 of whom were treated for an oral cleft.

**Main outcome measure** Relative risk of recurrence of isolated clefts from parent to child and between full siblings, for anatomic subgroups of clefts.

**Results** Among first degree relatives, the relative risk of recurrence of cleft was 32 (95% confidence interval 24.6 to 40.3) for any cleft lip and 56 (37.2 to 84.8) for cleft palate only (P difference=0.02). The risk of clefts among children of affected mothers and affected fathers was similar. Risks of recurrence were also similar for parent-offspring and sibling-sibling pairs. The "crossover" risk between any cleft lip and cleft palate only was 3.0 (1.3 to 6.7). The severity of the primary case was unrelated to the risk of recurrence.

**Conclusions** The stronger family recurrence of cleft palate only suggests a larger genetic component for cleft palate only than for any cleft lip. The weaker risk of crossover between the two types of cleft indicates relatively distinct causes. The similarity of mother-offspring, father-offspring, and sibling-sibling risks is consistent with genetic risk that works chiefly through fetal genes. Anatomical severity does not affect the recurrence risk in first degree relatives, which argues against a multifactorial threshold model of causation.

## INTRODUCTION

The birth prevalence of oral clefts in Norway is 2.2 per 1000 live births,<sup>1</sup> among the highest rates of clefts in the Western world. The defects range from mild forms to complete clefts affecting both the lip and the palate. The genetic and environmental causes of non-syndromic oral clefts are largely unknown. Given the uncertainty about the causes of clefts, the tendency for clefts to recur in families is striking. Estimates of the risk of recurrence for first degree relatives range from 24-fold to 82-fold.<sup>2,3</sup> Such estimates provide evidence for inferences on causation. Fogh-Andersen showed that cleft palate is causally different from cleft lip with and without cleft palate by showing that families at high risk for one are not at increased risk for the other.<sup>4</sup>

We used a population based study of clinically verified cases to estimate familial risks of recurrence of clefting in first degree relatives and to describe the risk of recurrence by severity of the cleft. We also considered whether having a cleft of a certain type affects subsequent reproduction.

## METHODS

The population based medical birth registry of Norway includes all children born in Norway since 1967 (about 2.1 million). Babies born with oral clefts in Norway are treated in one of two national centres. From 1967 to 2001, 4138 patients with oral clefts were treated in these hospitals. Two clinicians classified the clefts morphologically. We linked these clinical data to the population registry, which allowed us to combine high quality clinical information on cleft morphology with virtually complete ascertainment of biological family members for the whole country over a 35 year period.

Between 1967 and 1983, 944 908 babies were born in Norway. We excluded plural births from these analyses.<sup>5</sup> We were able to follow this cohort of children to 2001, at which time the cohort was 18-34 years of age. During this time, 367 301 of the babies reported in the registry had become parents of babies also reported in the registry. We expressed the risk of recurrence of clefts from parent to child as relative risk. We estimated relative risks by odds ratios in logistic regression models. We used estimation of variances to account for correlation between repeated observations within nuclear families.

We also linked full siblings in order to estimate the recurrence risk of clefts in sibships. By 2001, 572 772 babies had at least one subsequent full sibling in the registry. Again, we estimated the risk of recurrence as the relative risk of recurrence.

We estimated the risk of recurrence of the same or dissimilar cleft types among these first degree relatives (offspring or siblings) by using three categories of clefts: cleft lip only, cleft lip and palate, and cleft palate only. We graded the severity of the cleft on the basis of the morphological details of the cleft in the clinical records.<sup>1</sup>

We excluded cleft index cases with any other birth defect (10% of cleft lip, 29% of cleft palate only). We also restricted the index cleft cases to those who had been referred for surgical treatment, as these cases had a morphological description of their cleft.

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## RESULTS

### Follow-up from parent to child

We followed children born between 1967 and 1983, allowing follow-up to at least age 18 by 2001. Of the female babies born with a cleft, 45% had become mothers by 2001 compared with 48% of those without a recorded birth defect ( $P=0.16$ ). Among male babies, 24% of those with a cleft and 30% of those without birth defects had become fathers by 2001 ( $P<0.001$ ). Overall, the prevalence of clefts in offspring was 3.6% for mothers with oral clefts and 4.7% for fathers with oral clefts ( $P$  difference=0.39), whereas the prevalence for parents without clefts was 0.2%.

### Follow-up in siblings

We found 1554 women whose first registered child had an oral cleft. Of these women, 879 (57%) had a subsequent child with the same father, the same proportion as for mothers whose first registered child had no defect. Among the subsequent siblings of the cleft cases, 4.6% had an oral cleft compared with 0.2% of the siblings of unaffected babies.

### Specificity in recurrence of cleft types

The estimates of recurrence did not differ for parent-offspring recurrence and sibling-sibling recurrence for any of the cleft types (cleft lip only,  $P$  difference=0.32; cleft lip and palate,  $P$  difference=0.21; cleft palate only,  $P$  difference=0.86). We therefore pooled the generational data with the full sibling data to estimate joint recurrence risks of subgroups of clefts for first degree relatives.

When we compared the relative risk of recurrence of cleft lip only (relative risk=30.0, 95% confidence interval 16.6 to 54.2) with that of cleft lip and palate (41.1, 27.8 to 60.7), we found no statistical evidence of difference ( $P=0.38$ ). The risk of cleft lip only was similar after cleft lip only and after cleft lip and palate ( $P$  difference=0.50), and the risk of cleft lip and palate was similar after cleft lip only and after cleft lip and palate ( $P$  difference=0.36). These numbers support the assumption that cleft lip only and cleft lip and palate are different expressions of the same underlying

condition. We therefore pooled these two types into a general category of cleft lip, containing all isolated cleft lip cases with or without cleft palate.

### Recurrence for first degree relatives combined

We estimated the overall risk of recurrence of cleft lip as 32-fold (95% confidence interval 24.6 to 40.3) (table 1). We found no difference in recurrence of cleft lip from mother to offspring or from father to offspring (relative risks 27.1 and 26.6;  $P$  difference=0.97). Recurrence of cleft lip in siblings was slightly higher than recurrence from parents to offspring (relative risks 35.1 and 26.7), but these estimates were also not significantly different ( $P$  difference=0.31).

The overall recurrence risk of cleft palate only was 56-fold (37.2 to 84.8) (table 2) and significantly different from recurrence of cleft lip ( $P$  difference=0.02). Although cleft lip and cleft palate only have long been considered to be distinct defects, we found a threefold elevated risk of the other after the occurrence of either one (95% confidence interval 1.3 to 6.7;  $P=0.007$ ). We found no apparent differences between mother-offspring and father-offspring recurrence or between parent-offspring and sibling-sibling recurrence for cleft palate only (table 2).

### Recurrence by severity

We found little evidence that the risk of recurrence was related to the severity of the defect. Relative risk of recurrence of cleft lip was 26 after a mild cleft lip (severity 1), 43 after a moderate cleft lip (severity 2), and 31 after a severe cleft lip (severity 3) ( $P$  difference=0.53). The mean severity of cleft lip in the recurrent case (on the scale of 1-3) was 2.4 after a mild cleft lip, 2.3 after a moderate cleft lip, and 2.3 after a severe cleft lip. Relative risk of recurrence was 30 with unilateral cleft lip in the index case and 39 with bilateral cleft lip ( $P$  difference=0.35).

We did the same analysis for cleft palate. Relative risk of recurrence was 44 after mild (submucous) cleft palate only, 41 after moderate (soft palate) cleft palate only, and 82 after severe (hard palate) cleft palate only ( $P$  difference=0.34). The mean severity of cleft palate was 1.5 after mild cleft palate only, 2.1 after moderate cleft palate only, and 2.5 after severe cleft palate only (not significantly different,  $P=0.20$ ).

**Table 1** Relative risk\* of recurrence for cleft lip (with or without cleft palate) for first degree relatives of an index case with isolated cleft lip†

Familial relationship	Recurrence of cleft lip (with or without cleft palate)			
	At risk	Recurrences of cleft lip	Relative risk* (95% confidence interval)	P difference
Mother-offspring	295	11	27 (14.9 to 49.2)	0.97
Father-offspring	338	12	27 (15.0 to 47.2)	
Parent-offspring total	633	23	27 (17.7 to 40.3)	0.31
Subsequent full sibling	879	40	35 (25.5 to 48.4)	
All first degree relatives	1512	63	32 (24.6 to 40.3)	

\*Relative risks (estimated as odds ratios in logistic regression models) are ratios of risk of recurrence and risk in reference group without index cleft cases.

†Index cases are clinically verified cleft cases without non-cleft birth defects. Recurrent cases include all recorded cases among stillborn or live born babies, cases with or without other defects, and cases that were registered either in clinical data or in medical birth registry.

## DISCUSSION

We found almost complete specificity of risk of recurrence for the two major types of clefts—any cleft lip and cleft palate only—showing their nearly distinct causes. Within cleft lip cases, we found no evidence for specificity of risk between cleft lip only and cleft lip and palate; risks for both were high after either. This supports the assumption that these two types of cleft lip comprise a single genetic risk group.

This study combined a large sample size and population coverage with a high level of clinical detail and verification from surgical examinations.<sup>1</sup> The use of the compulsory national registration of births in the medical birth registry, together with low

**Table 2** | Relative risk\* of recurrence for cleft palate only (without cleft lip) for first degree relatives of an index case with isolated cleft palate only†

Familial relationship	Recurrence of cleft palate only			P difference
	At risk	Recurrences of cleft palate only	Relative risk* (95% confidence interval)	
Mother-offspring	204	7	48 (22.7 to 103.1)	0.60
Father-offspring	84	4	68 (25.3 to 181.7)	
Parent-offspring total	288	11	54 (29.7 to 98.0)	0.98
Subsequent full sibling	342	14	58 (32.8 to 102.8)	
All first degree relatives	630	25	56 (37.2 to 84.8)	

\*Relative risks (estimated as odds ratios in logistic regression models) are ratios of risk of recurrence and risk in reference group without index cleft cases.

†Index cases are clinically verified cleft cases without non-cleft birth defects. Recurrent cases include all recorded cases among stillborn or live born babies, cases with or without other defects, and cases that were registered either in clinical data or in medical birth registry.

rates of emigration, has made the data virtually complete.

As in the classic study of Fogh-Andersen,<sup>4</sup> risk of recurrence in our data was quite specific for cleft lip to cleft lip and for cleft palate only to cleft palate only, although we did find a threefold elevation in the risk of either cleft type after the occurrence of the other. This crossover risk may be caused by genes such as *MSX1* or rare syndromes that can produce both cleft lip and cleft palate only.<sup>6,7</sup>

The lack of difference between mother-offspring and father-offspring recurrence for cleft lip and cleft palate only has implications for the genetic model.<sup>8</sup> If maternal genes operating during pregnancy had a major impact, mother-offspring recurrence should have been higher than father-offspring recurrence. The lack of such a difference also indicates that genes subject to genomic imprinting or operating through maternal mitochondrial mechanisms are not major contributors to the risk of oral clefts. Thus, fetal genes are likely to explain the great majority of genetic risk in oral clefts. Furthermore, as we did not find sibling recurrence to be detectably higher than parent-offspring recurrence, persistent environmental factors carried by the mother apparently have much weaker effects than genes.

#### WHAT IS ALREADY KNOWN ON THIS TOPIC

The causes of oral clefts are thought to be multifactorial in nature and include several genes, environmental factors, and their interaction effects

Cleft lip and cleft palate have strong tendencies to recur in families

#### WHAT THIS STUDY ADDS

The anatomical severity of an isolated cleft does not seem to affect the risk of recurrence in first degree relatives

This has implications for clinical counselling, as families with mildly affected members have recurrence risks similar to families with more severely affected members, with equivalent severity among recurrent cases

The absence of an effect of severity of cleft on risk of recurrence was unexpected. Previous studies of first degree relatives have reported that risk of recurrence may increase from 2.5% to 5.7%, depending on the severity of the index case. However, these estimates were based on smaller numbers and coarser definitions of the severity of clefts.<sup>9,10</sup> With much more statistical power and careful clinical criteria for severity, we found no evidence of an effect of severity on risk of recurrence. Furthermore, the severity of the recurring defect in our data was unrelated to the severity of the index case.

Our data are consistent with a few other studies suggesting that cleft lip and cleft palate do not fit the multifactorial threshold model of inheritance.<sup>7,11-14</sup> Other genetic models seem to be needed to explain why severity is nearly independent of heritability.

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**Competing interests:** None declared.

**Ethical approval:** Norwegian Data Inspectorate. Studies of anonymous data from health registries do not require review by a regional committee for medical research ethics in Norway.

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