

# Long term follow up study of survival associated with cleft lip and palate at birth

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## Abstract

**Objective** To assess the overall and cause specific mortality of people from birth to 55 years with cleft lip and palate.

**Design** Long term follow up study.

**Setting** Danish register of deaths.

**Participants** People born with cleft lip and palate between 1943 and 1987, followed to 1998.

**Main outcome measures** Observed and expected numbers of deaths, summarised as overall and cause specific standardised mortality ratios.

**Results** 5331 people with cleft lip and palate were followed for 170 421 person years. The expected number of deaths was 259, but 402 occurred, corresponding to a standardised mortality ratio of 1.4 (95% confidence interval 1.3 to 1.6) for males and 1.8 (1.5 to 2.1) for females. The increased risk of mortality was nearly constant for the three intervals at follow up: first year of life, 1-17 years, and 18-55 years. The participants had an increased risk of all major causes of death.

**Conclusions** People with cleft lip and palate have increased mortality up to age 55. Children born with cleft lip and palate and possibly other congenital malformations may benefit from specific preventive health measures into and throughout adulthood.

## Introduction

Children with repairable anomalies such as cleft lip and palate are often presumed to have normal health and survival in adulthood. Some evidence, however, suggests an increased incidence of cancer early in life among children with some congenital malformations, including cleft lip and palate, and it is unknown whether this susceptibility continues into adulthood.<sup>1-3</sup> Evidence indicates that parents of children with cleft lip and palate have an increased risk of cancer, which suggests a role for genetic factors.<sup>4</sup> Population based studies from Scandinavia have found a higher risk of psychiatric diseases and behavioural problems in adults with cleft lip and palate that are associated with increased morbidity.<sup>5,6</sup> We used data from Danish registers to assess the long term prognosis associated with cleft lip and palate, particularly overall mortality and cause specific mortality.

## Materials and methods

The Danish cleft lip and palate register is described elsewhere.<sup>7-9</sup> We excluded infants with malformations other than cleft lip and palate to eliminate the effect of multiple anomalies on increased mortality. Overall, 6627 people were born with cleft lip and palate in Denmark between 1943 and 1987; 6394 (96%) could be identified through the Danish civil registration system and Danish register of causes of death (see

bmj.com for details of these registers). We excluded 1063 (17%) as they had associated anomalies, leaving 5331 people for analysis.

We calculated the expected number of deaths by multiplying the observed person years with mortality stratified by sex, one year age groups, and five year calendar period.

## Results

We followed 5331 people with cleft lip and palate for a total of 170 421 person years. The expected number of deaths was 259, but 402 occurred: standardised mortality ratio 1.4 (95% confidence interval 1.3 to 1.6) for males and 1.8 (1.5 to 2.1) for females. The increased risk was almost constant for the three intervals of follow up (table).

Deaths from cancer (36 *v* 28 expected) and cardiovascular events (15 *v* 13 expected) were only marginally increased in people with cleft lip and palate. The risk of suicide, however, was significantly increased and of similar magnitude in both sexes (standardised mortality ratio 1.6). We found no increased risk for deaths due to accidents. Around half of overall deaths were attributed to "other causes." This category comprised mostly "cleft lip and palate" as the cause of death and mainly deaths within the first year of life. We traced 79 of these death certificates. In 39% of cases cause of death was prematurity, whereas pneumonia and bronchopneumonia accounted for 28% of deaths and postoperative complications for 10%. The remaining cases included asphyxia, aspiration, sepsis, and unknown cause. Other causes of death were mainly attributed to respiratory diseases, infectious diseases, and diseases of the central nervous system. Unlike the other categories which showed increased but non-significant standardised mortality ratios (range 1.2-1.6), mortality due to diseases of the central nervous system showed a significant increased risk for females (9 observed *v* 2.6 expected). Of the nine cases, six were due to epilepsy (1.2 expected; standardised mortality ratio 8.3, 1.7 to 14.2).

We stratified the analysis for type of anomaly (cleft lip only, cleft lip and palate, cleft palate only). The cleft lip only group had only a slight and non-significant increased risk of mortality, whereas it was significant for those with cleft lip and palate (standardised mortality ratio 1.6, 1.3 to 1.8 for males and 2.2, 1.7 to 3.0 for females) and cleft palate only (1.9, 1.5 to 2.5 for males and 1.9, 1.4 to 2.5 for females).

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Overall mortality from 1943 to 1998 for 5331 Danish people born with cleft lip and palate between 1943 and 1987

Period	Age at follow up (years)							
	0 to <1		1 to <18		18 to 55		0 to 55	
	Observed/ expected No of deaths	SMR	Observed/ expected No of deaths	SMR	Observed/ expected No of deaths	SMR	Observed/ expected No of deaths	SMR (95% CI)
<b>Males:</b>								
1943-64	86/53.6	1.60	27/17.8	1.52	105/72.4	1.45	218/143.9	1.51 (1.32 to 1.73)
1965-87	21/20.8	1.01	10/9.2	1.09	15/9.9	1.51	46/39.9	1.15 (0.84 to 1.54)
Total	107/74.5	1.44	37/27.0	1.37	120/82.4	1.46	264/183.8	1.44 (1.27 to 1.62)
<b>Females:</b>								
1943-64	55/25.8	2.13	14/7.92	1.77	42/26.4	1.59	111/60.1	1.85 (1.52 to 2.22)
1965-87	13/9.1	1.42	7/3.9	1.80	7/2.2	3.14	27/15.3	1.77 (1.17 to 2.57)
Total	68/35.0	1.94	21/11.8	1.78	49/28.6	1.71	138/75.4	1.83 (1.54 to 2.16)

SMR=standardised mortality ratio.

## Discussion

Children born with cleft lip and palate and no other known malformations seem to have an increased risk of mortality not only in the first year of life but throughout childhood and adulthood. One explanation could be that we included people with discrete malformations associated with cleft lip and palate. This is unlikely since more than 80% of our cases were described by a surgeon who was a leading expert throughout the period of ascertainment.<sup>9 10</sup>

Adults with cleft lip and palate have an increased incidence of structural brain anomalies, including major differences in the sizes of the cerebrum and cerebellum associated with mild cognitive impairments.<sup>11</sup> Such malformations may predispose to seizures, which were observed as an increased cause of death in this study. These anomalies of the midline are more commonly associated with cleft palate than with cleft lip. This is consistent with the higher risk of early mortality in patients with cleft palate than cleft lip only, as seen in this study. We also observed an increased risk of suicide in both sexes, and recognition of potential risk factors affords opportunities for prevention.

The increased risk associated with all major causes of death suggests that the cause of excess mortality is multifactorial. We did not have information on birth weight and gestational age, and it is possible that such

factors could have attenuated the excess mortality for people with cleft lip and palate. We found only a marginally increased mortality due to cancer, which does not support previous observations.<sup>4 12</sup>

Considerable attention is paid to the health of children born with congenital malformations during the first years of life. As more infants are surviving serious birth defects into adult life, it will be important to understand their clinical course to provide optimal preventive health care and anticipate treatable causes of morbidity and mortality.

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- 1 Windham GC, Bjerkedal T, Langmark F. A population-based study of cancer incidence in twins and in children with congenital malformations or low birth weight, Norway, 1967-1980. *Am J Epidemiol* 1985; 121:49-56.
- 2 Mili F, Khoury MJ, Flanders WD, Greenberg RS. Risk of childhood cancer for infants with birth defects. I. A record-linkage study, Atlanta, Georgia, 1968-1988. *Am J Epidemiol* 1993;137:629-38.
- 3 Mili F, Lynch CE, Khoury MJ, Flanders WD, Edmonds LD. Risk of childhood cancer for infants with birth defects. II. A record-linkage study, Iowa, 1983-1989. *Am J Epidemiol* 1993;137:639-44.
- 4 Zhu JL, Basso O, Hasle H, Winther JF, Olsen JH, Olsen J. Do parents of children with congenital malformations have a higher cancer risk? A nationwide study in Denmark. *Br J Cancer* 2002;87:524-8.
- 5 Ramstad T, Ottem E, Shaw WC. Psychosocial adjustment in Norwegian adults who had undergone standardised treatment of complete cleft lip and palate. II. Self-reported problems and concerns with appearance. *Scand J Plast Reconstr Surg Hand Surg* 1995;29:329-36.
- 6 Christensen K, Mortensen PB. Facial clefting and psychiatric diseases: a follow-up of the Danish 1936-1987 facial cleft cohort. *Cleft Palate Craniofac J* 2002;39:392-6.
- 7 Christensen K, Schmidt MM, Vaeth M, Olsen J. Absence of an environmental effect on the recurrence of facial-cleft defects. *N Engl J Med* 1995;333:161-4.
- 8 Christensen K. The 20th century Danish facial cleft population—epidemiological and genetic-epidemiological studies. *Cleft Palate Craniofac J* 1999;36:96-104.
- 9 Christensen K, Fogh-Andersen P. Etiologic subgroups in non-syndromic isolated cleft-palate—a genetic-epidemiologic study of 52 Danish birth cohorts. *Clin Genetics* 1994;46:329-35.
- 10 Fogh-Andersen P. *Inheritance of harelip and cleft palate*. Copenhagen: Arnold Busck, 1942.
- 11 Nopoulos P. Structural brain anomalies in adult males with clefts of the lip and/or palate. *Genet Med* 2002;4:1-9.
- 12 Zack M, Adami HO, Ericson A. Maternal and perinatal risk factors for childhood leukemia. *Cancer Res* 1991;51:3696-701.

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### What is already known on this topic

Infants with cleft lip and palate have an increased risk of mortality in the first years of life

Cleft lip and palate may be associated with an increased risk of cancer

### What this study adds

Cleft lip and palate is associated with an increased risk of mortality in infancy and up to age 55

The risk of mortality due to cancer is not substantially increased

The increased risk of mortality in people with cleft lip and palate was attributable to all major causes of death