



Bilateral orofacial clefts are associated with increased risk of psychiatric morbidity relative to unilateral clefts

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Summary *Background:* Orofacial clefts are associated with neurodevelopmental conditions. However, whether or not this risk is different among children with unilateral compared with bilateral clefts is not known. The aim of this study was to compare children with bilateral clefts to those with unilateral clefts regarding psychiatric disorders, suicide, and self-harm.

Methods: We utilized data on all children born in Sweden between 1973 and 2012 with unilateral cleft lip (UCL), bilateral cleft lip (BCL), unilateral cleft lip and palate (UCLP), and bilateral cleft lip and palate (BCLP). We performed Cox regression analyses with direct comparisons between bilateral and unilateral clefts and comparisons to matched community cohorts, adjusting for confounders.

Results: Children with BCL compared with UCL showed risk increases for any psychiatric disorder (adjusted Cox-derived hazard ratios [aHRs], 2.13; 95% confidence interval [CI], 1.04-4.36), including intellectual disability (aHR, 5.31; 95% CI, 1.29-21.78). Children with BCLP compared with UCLP demonstrated risk increases for any psychiatric disorder (aHR, 1.55; 95% CI, 1.20-2.01), including speech and language disorders (aHR, 1.99; 95% CI, 1.00-3.97), neurodevelopmental disorders (aHR, 1.66; 95% CI, 1.11-2.47), and other psychiatric disorders (aHR, 1.54; 95% CI, 1.11-2.15), including personality disorders (aHR, 5.76; 95% CI, 2.13-15.55). No significant associations were observed for suicide or self-harm.

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Conclusions: This large nationwide register study showed, for the first time, that individuals with bilateral clefts demonstrated elevated risks of psychiatric disorders compared with unilateral clefts. This is of clinical relevance to professionals as well as information that needs to be conveyed to families of children with orofacial clefts.

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Orofacial clefts (OFC) are the most common craniofacial anomalies and affect approximately 2 in 1000 live births in Sweden.^{1,2} The etiology of OFC reflects a complex, multifactorial interplay between genetic vulnerability and environmental risk factors. Approximately 30% of OFC cases are associated with a known genetic syndrome (syndromic OFC), but the remaining 70% of clefts occur without a known syndrome identified (nonsyndromic OFC).^{3,4} OFC can be anatomically divided into cleft lip (CL), CL and palate (CLP), and cleft palate only (CPO), and the location of CL and CLP can be either unilateral or bilateral.² Unilateral clefts with or without palatal engagement (UCL/UCLP) are the most common (76%), and bilateral clefts (bilateral CL [BCL]/bilateral CL and palate [BCLP]) are less common (24%).²

Our previous study revealed increased risks for psychiatric disorders in a large population-based register study of all individuals born with nonsyndromic OFC in Sweden between 1973 and 2012.⁵ CPO showed the highest risk increases, and CL the lowest, and girls demonstrated generally higher risk increases than boys, and previous studies on the same population across a more narrow timespan have reached similar conclusions.⁵ Some other previous studies have reported less favorable academic and cognitive outcomes in children born with CLP compared with non-OFC peers in US, Australian, and Hungarian populations.⁶⁻⁸ However, little is known about the differential risk of psychiatric morbidity in unilateral versus bilateral OFC, and there are previous studies on Swedish registries that suggest this risk does not manifest, at least during the preschool years.⁹

Studies on differences between children born with nonsyndromic unilateral and bilateral OFC and their post-surgical outcomes have reached mixed conclusions. One study found more comorbidities (e.g., asthma, cardiac comorbidity, developmental delay, and nutritional support) at baseline pre-surgery among BCL compared with UCL.¹⁰ A more recent study found partially contradictory results with a higher occurrence of baseline comorbidities, including developmental delay, in UCL, compared with BCL.¹¹ Yet another recent study described a higher risk of poor academic achievement among children with bilateral than unilateral clefts.¹²

The primary aim of this study was to evaluate the risk of psychiatric disorders, suicide, and self-harm among children with bilateral clefts compared with unilateral clefts in a large population-based Swedish cohort. Suicide and self-harm were added as psychiatric outcomes based on their close relation to psychiatric conditions and their importance as real-world outcomes.¹³⁻¹⁵ As a secondary aim, we wanted to assess possible sex-related differences in psychiatric outcomes.

Methods

Data sources

Data were obtained from the National Board of Health and Welfare as well as Statistics Sweden. All registers use the 10-digit National Registration Number, assigned to all Swedish residents, which allows the linkage of studies. These numbers were replaced with arbitrary ones in the data we received to secure pseudonymity. The following registers were used: the Swedish Medical Birth Register (MBR), the National Patient Register (NPR), the Swedish Cause-of-Death Register (SCDR), the Multi-Generation Register (MGR), the Register of Total Population (RTP), the Census of the population and housing, and the longitudinal integration database for health insurance and labor market studies (LISA). These databases are described in more detail in [Supplementary Materials 1](#).

Ethical considerations

The Uppsala Ethics Committee approved the study (Reg. No. 2012/363).

Participants

Through MBR and NPR, we identified 2454 children born in Sweden between January 1, 1973, and December 31, 2012, who received the diagnosis of UCL, BCL, UCLP, or BCLP at birth or before 5 years of age.

A comparison group from the population was used with 10 individuals without OFC diagnosis for each participant with OFC diagnosis identified ($n = 24,535$), matched by month and year of birth, sex, and county of birth.

Any diagnoses of congenital malformations, deformations, and chromosomal abnormalities (International Classification of Diseases [ICD]-8 and 9 codes 740-759 and ICD-10 codes Q00-Q99, except for the facial cleft codes 749 in ICD-8 and 9 and Q35-Q37 in ICD-10) were identified as possible syndromic indicators in order to adjust the analyses for nonidentified syndromic cases of OFC.

All participants were observed from their date of birth until their outcome, emigration, death, or the end of the study on December 31, 2012.

Exposure

The exposure was a diagnosis of UCL, BCL, UCLP, or BCLP, as indicated in the MBR or NPR by their ICD-8, ICD-9, or ICD-10

diagnoses. The respective ICD codes were UCL: 749.10, 749BA, and Q36.9A; BCL: 749.11, 749BB, and Q36.0A; UCLP: 749.20, 749CC, and Q37.5; and BCLP: 749.24, 749CD, and Q37.4.

Outcome measures

Information on psychiatric diagnoses and self-harm incidents was extracted from the NPR, and suicides were extracted from the Swedish Cause of Death Register. We studied the following psychiatric diagnoses (see Table 1 for ICD codes): any psychiatric disorder (aggregated variable for all the studied disorders in the study); intellectual disability (including mental retardation in ICD-8); speech and language disorders; neurodevelopmental disorders (including autism spectrum disorder (ASD); attention-deficit/hyperactivity disorder (ADHD); and behavioral or emotional disorders with onset in childhood; and other psychiatric disorders, including psychotic disorders, bipolar disorder, depression, neurotic, stress related, or somatoform disorder, eating disorders, alcohol and substance use disorder, personality disorder, and incidents of self-harm and suicide.

As the ICD-8 and ICD-9 codes for eating disorders were not specific, and we would rather not include early events of feeding difficulties, we only analyzed those receiving a diagnosis of eating disorder from 10 years of age. Specific diagnostic codes for ADHD and ASD are lacking in the ICD-8, so we decided to exclude the individuals who died before ICD-9 in the analyses for ASD and ADHD.

Covariates

We used the same strategy in choosing the covariates for the multivariate analyses as in our previous research on psychiatric morbidity in OFC.⁵ We controlled the multivariate analyses for several confounders: gestational complications and somatic indicators, year and season of birth, sex, congenital malformations or known genetic syndromes, parental psychiatric morbidity, and sociodemographic factors.

The following perinatal variables were collected from the MBR: Gestational age at birth, dichotomized into term birth or preterm birth (≥ 37 or < 37 gestational weeks). Small for gestational age, defined as < -2 standard deviations below age-matched weight norms. Birth weight was defined as low if < 2500 g. Low Apgar score, defined as < 7 at 5 min after birth. A binary variable for gestational complications was used in the models (preterm, SGA, low birth weight, and low Apgar).

Sociodemographic variables and parental mental health were assessed by linkage of all participants through MGR to their biological parents. Parental age at the time of birth was identified, and we used the mean age of the parents or the age of one parent if one was missing for the multivariate analyses.

Maternal country of birth was accessed from the MBR and aggregated across regions: Sweden, other Nordic countries, and outside of the Nordic countries. The parental educational level was retrieved from the LISA database and entered into the model as a categorical five-level variable

Table 1 ICD-8, 9, and 10 codes for specific psychiatric disorders, as well as attempted and completed suicide.

Psychiatric disorder	ICD-8	ICD-9	ICD-10
Any psychiatric disorder	290-315	290-319	F00-F99
Intellectual disability	310-315	317-319	F70- F79
Speech and language disorders	306,00 781,59	315D	F80 R47
Neurodevelopmental disorders (ASD, ADHD, other behavioral)	306,20-308,99	299 312-314	F84 F90 F91-F98
ASD	-	299	F84
ADHD	-	314	F90
Other behavioral and emotional disorders with onset in childhood	306,20-308,99	312-313	F91-F98
Specific learning disorder	306,10 781,5 781,6	315A 315B 7846	F81, 0-F81,3 F81,8-F81,9 R48,0
Other psychiatric disorders (including all below)	See all diagnostic codes below	See all diagnostic codes below	See all diagnostic codes below
Psychotic disorders	295 297-299 (except 298,00)	295 297 298 (except 298A)	F20-F29
Bipolar disorder	296 (except 296,00)	296 (except 296B, 296X)	F30-F31
Depression	298,00 300,40 790,20	298A 300E 311	F32-F33
Eating disorders	306,50	307B 307F	F50
Neurotic, stress-related, or somatoform disorder	300 (except 300,40); 305 306,80 306,98 307,99	300 (except 300E) 306 307W 308 309	F40-F48
Alcohol and substance use disorder	291 303 294,30 304 971	291 303 305A 292 304 305X	F10-F16 F18 F19
Personality disorder	301	301	F60
Self-harm	E950-E959	E950-E959	X60-X84
Suicide	E950-E959	E950-E959	X60-X84

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, autism spectrum disorder; ICD, International Classification of Diseases.

according to the Swedish Education Terminology: ≤ 9 years, 10-11 years, 12-14 years, and > 14 years (university). The highest level of education obtained by either of the parents was used in the analysis.

Psychiatric morbidity among parents was defined as at least one psychiatric diagnostic code or a code for self-harm in the NPR (290-315 in ICD-8, 290-319 in ICD-9, and F00-F98 in ICD-10 or E950-E959 in ICD-8 and ICD-9 and X60-X84 in ICD-10), or a death by suicide in the SCDR. This ordinal variable would take the value of 0, 1, or 2 (number of parents with psychiatric morbidity). We treated the variable as time-varying in the analyses.

Statistical analysis

The statistical software Stata v.15 was used for the data analyses.¹⁶ Crude and adjusted Cox proportional hazard regression models were used to investigate hazard ratios (HRs) and 95% confidence intervals (CIs) for the outcomes, and age was the underlying time scale. Since the controls cannot be considered as independent from the corresponding case (matched for birth month, sex, and county), cluster robust variance-covariance estimation was used.¹⁷ We compared the individuals with BCL with the individuals with UCL and the individuals with BCLP with the individuals with UCLP. We also performed additional analyses with these different cleft types and the matched comparison cohort.

For the continuous covariates concerning parental age and year of birth, we used a restricted cubic spline to avoid forcing the relationship to the outcomes to be linear.

To examine a possible moderating effect of sex, we estimated separate Cox models where an interaction term of sex and the exposure was included. The *p*-value of the interaction term was calculated, except for some of the models that were not possible to estimate because of too rare outcomes.

Results

Descriptives of the study population are demonstrated in Table 2. A total of 2454 children were identified and followed during the study period from 1973 to 2012. Among them, 1878 children (76.5%) had a diagnosis of unilateral cleft and 576 children (23.5%) had bilateral clefts. The incidence of bilateral CL and CLP in the sample is representative of previously reported incidence rates of these types of clefts.^{18,19} Among the study participants, 1640 (67%) were boys and 814 (33%) were girls (Table 2).

Children born with BCL were more likely than children born with UCL to receive any psychiatric disorder (adjusted Cox-derived HR [aHR] 2.13; 95% CI, 1.04-4.36) and intellectual disability (aHR 5.31; 95% CI, 1.29-21.78). Children born with BCLP compared with children born with UCLP demonstrated higher risks of any psychiatric disorder (aHR, 1.55; 95% CI, 1.20-2.01), speech and language disorders (aHR, 1.99; 95% CI, 1.00-3.97), neurodevelopmental disorders (aHR, 1.66; 95% CI, 1.11-2.47), other psychiatric disorders (aHR, 1.54; 95% CI, 1.11-2.15), and personality disorders (aHR, 5.76; 95% CI, 2.13-15.55) (Figures 1 and 2, Table S1).

In the analyses comparing the cohort of exposed children with the non-OFC individuals in the population, children born with UCL showed increased risks for intellectual disability (aHR 2.45; 95% CI, 1.22-4.91), psychotic disorders (aHR, 2.82; 95% CI, 1.29-6.14), and personality disorders (aHR, 2.57; 95% CI, 1.19-5.55). Children born with BCL only demonstrated risk increases for any psychiatric disorder (aHR, 2.50; 95% CI, 1.23-5.06) and intellectual disability (aHR 29.30, 95% CI 1.02-841.60) compared with non-OFC individuals (Table S2).

Children born with UCLP showed risk increases for any psychiatric disorder (aHR, 1.35; 95% CI, 1.14-1.58), intellectual disability (aHR, 3.32; 95% CI, 2.28-4.84), and speech and language disorders (aHR, 3.08; 95% CI, 1.90-4.99) compared with the comparison cohort with non-OFC individuals in the population (Table S3).

Children born with BCLP showed risk increases for any psychiatric disorder (aHR, 2.22; 95% CI, 1.77-2.79), intellectual disability (aHR, 7.48; 95% CI, 4.16-13.44), speech and language disorders (aHR, 5.97; 95% CI, 3.06-11.63), neurodevelopmental disorders (aHR, 1.98; 95% CI, 1.40-2.80), ASD (aHR, 2.23; 95% CI, 1.03-4.83), other psychiatric disorders (aHR, 1.72; 95% CI, 1.29-2.29), and personality disorders (aHR, 3.13; 95% CI, 1.14-8.58) (Tables S2 and S3).

The analyses of sex interaction revealed higher risks for males than females born with BCL for any psychiatric disorder (aHR male [aHRm], 3.66; 95% CI, 1.58-8.48; aHR female [aHRf], 0.53; 95% CI, 0.12-2.25; interaction *p*-value=0.04). For children born with BCLP compared with UCLP, the opposite pattern was revealed regarding sex interaction. Girls born with BCLP showed risk increases for intellectual disability (aHRf, 3.58; 95% CI, 1.69-7.59; aHRm, 0.86; 95% CI, 0.39-1.86; interaction *p* = 0.03) and neurodevelopmental disorders (aHRf, 3.53; 95% CI, 1.62-7.66; aHRm, 1.25; 95% CI, 0.73-2.12; interaction *p* = 0.02). There were also borderline significant sex differences (interaction *p*-values, 0.05-0.07), pointing to higher risks for girls than boys born with BCLP for a diagnosis of any psychiatric disorder, ADHD, other behavioral and emotional disorders with onset in childhood, and anxiety disorders (Tables S4 and S5).

Discussion

In this large nationwide cohort study, we compared the outcome of psychiatric disorders and associated outcomes among children with unilateral and bilateral OFCs and showed that children born with bilateral clefts demonstrate higher risks for psychiatric disorders than children with unilateral clefts. Similar associations were not seen for self-harm and suicide, but these results should also be interpreted cautiously, given their rarity in our sample as a whole and the consequently small sample sizes involved. We presented important new findings that contributed to the growing evidence indicating a need for psychiatric screening in individuals born with OFC overall, and especially so for individuals with bilateral OFC.

We have previously shown that children born with clefts demonstrate increased risk for psychiatric disorders and especially neurodevelopmental disorders compared with non-OFC children from the general population and

Table 2 Descriptive characteristics of individuals with unilateral and bilateral cleft lip and palate.

Characteristic	Individuals with unilateral CL n (%)	Individuals with bilateral CL n (%)	Individuals with unilateral CLP n (%)	Individuals with bilateral CLP n (%)
Total sample	527	47	1351	529
Male	344 (65.3%)	33 (70.2%)	907 (67.1%)	356 (67.3%)
Female	183 (34.7%)	14 (29.8%)	444 (32.9%)	173 (32.7%)
Sociodemographic indicators				
Maternal age, y				
≤24	175 (33.2%)	12 (25.5%)	333 (24.6%)	121 (22.9%)
25-34	287 (54.5%)	32 (68.1%)	810 (60.0%)	326 (61.6%)
≥35	61 (11.6%)	3 (6.4%)	189 (14.0%)	78 (14.7%)
Unknown	4 (0.8%)	0 (0.0%)	19 (1.4%)	4 (0.8%)
Paternal age, y				
≤24	71 (13.5%)	7 (14.9%)	164 (12.1%)	60 (11.3%)
25-34	345 (65.5%)	30 (63.8%)	804 (59.5%)	298 (56.3%)
≥35	107 (20.3%)	10 (21.3%)	351 (26.0%)	163 (30.8%)
Unknown	4 (0.8%)	0 (0.0%)	32 (2.4%)	8 (1.5%)
Maternal psychiatric history				
Yes	79 (15.0%)	8 (17.0%)	214 (15.8%)	85 (16.1%)
No	444 (84.3%)	39 (83.0%)	1118 (82.8%)	440 (83.2%)
Unknown	4 (0.8%)	0 (0.0%)	19 (1.4%)	4 (0.8%)
Paternal psychiatric history				
Yes	70 (13.3%)	8 (17.0%)	200 (14.8%)	65 (12.3%)
No	453 (86.0%)	39 (83.0%)	1119 (82.8%)	456 (86.2%)
Unknown	4 (0.8%)	0 (0.0%)	32 (2.4%)	8 (1.5%)
Maternal region of birth				
Sweden	454 (86.1%)	41 (87.2%)	1105 (81.8%)	431 (81.5%)
Other Nordic	15 (2.8%)	1 (2.1%)	48 (3.6%)	15 (2.8%)
Outside Nordic	31 (5.9%)	1 (2.1%)	93 (6.9%)	34 (6.4%)
Unknown	27 (5.1%)	4 (8.5%)	105 (7.8%)	49 (9.3%)
Parental education, y				
0-9	43 (8.2%)	6 (12.8%)	67 (5.0%)	41 (7.8%)
10-11	161 (30.6%)	8 (17.0%)	328 (24.3%)	131 (24.8%)
12-14	163 (30.9%)	15 (31.9%)	509 (37.7%)	204 (38.6%)
> 14	154 (29.2%)	17 (36.2%)	421 (31.2%)	148 (28.0%)
Unknown	6 (1.1%)	1 (2.1%)	26 (1.9%)	5 (0.9%)
Perinatal and somatic indicators				
Preterm birth	31 (5.9%)	4 (8.5%)	96 (7.1%)	50 (9.5%)
Term birth	470 (89.2%)	39 (83.0%)	1149 (85.0%)	429 (81.1%)
Unknown	26 (4.9%)	4 (8.5%)	96 (7.1%)	50 (9.5%)
The child is small for gestational age				
Yes	28 (5.3%)	3 (6.4%)	70 (5.2%)	28 (5.3%)
No	470 (89.2%)	39 (83.0%)	1172 (86.8%)	450 (85.1%)
Unknown	29 (5.5%)	5 (10.6%)	109 (8.1%)	51 (9.6%)
Birthweight				
< 1500 g	4 (0.8%)	1 (2.1%)	9 (0.7%)	5 (0.9%)
1500-2499 g	20 (3.8%)	3 (6.4%)	71 (5.3%)	39 (7.4%)
2500-3499 g	243 (46.1%)	21 (44.7%)	541 (40.0%)	231 (43.7%)
≥3500 g	231 (43.8%)	17 (36.2%)	622 (46.0%)	204 (38.6%)
Unknown	29 (5.5%)	5 (10.6%)	108 (8.0%)	50 (9.5%)
Apgar				
< 7 at 5 min	8 (1.5%)	0 (0.0%)	23 (1.7%)	4 (0.8%)
≥7 at 5 min	438 (83.1%)	35 (74.5%)	1136 (84.1%)	443 (83.7%)
Unknown	81 (15.4%)	12 (25.5%)	192 (14.2%)	82 (15.5%)
Gestational Complications				
Yes	60 (11.4%)	7 (14.9%)	176 (13.0%)	75 (14.2%)
No	391 (74.2%)	29 (61.7%)	994 (73.6%)	375 (70.9%)
Unknown	76 (14.4%)	11 (23.4%)	181 (13.4%)	79 (14.9%)

(continued on next page)

Table 2 (continued)

Characteristic	Individuals with unilateral CL n (%)	Individuals with bilateral CL n (%)	Individuals with unilateral CLP n (%)	Individuals with bilateral CLP n (%)
Any congenital malformations, deformations, and chromosomal abnormalities				
Yes	67 (12.7%)	8 (17.0%)	284 (21.0%)	163 (30.8%)
No	460 (87.3%)	39 (83.0%)	1067 (79.0%)	366 (69.2%)
Year of birth				
1965-1974	62 (11.8%)	6 (12.8%)	118 (8.7%)	57 (10.8%)
1975-1984	268 (50.9%)	28 (59.6%)	403 (29.8%)	137 (25.9%)
1985-1994	113 (21.4%)	9 (19.1%)	166 (12.3%)	76 (14.4%)
1995-2004	23 (4.4%)	1 (2.1%)	356 (26.4%)	137 (25.9%)
2005-2012	61 (11.6%)	3 (6.4%)	308 (22.8%)	122 (23.1%)
Birth month				
Winter December-February	139 (26.4%)	15 (31.9%)	362 (26.8%)	146 (27.6%)
Spring March-May	156 (29.6%)	11 (23.4%)	358 (26.5%)	138 (26.1%)
Summer June-August	108 (20.5%)	10 (21.3%)	325 (24.1%)	125 (23.6%)
Autumn September-November	124 (23.5%)	11 (23.4%)	306 (22.6%)	120 (22.7%)

CL, cleft lip; CLP, cleft lip and palate.

compared with their full siblings. The risk increases were highest for CPO and lowest for CL, while the risk in CLP was in the intermediate range. We believe that these results, coupled with those of the present study, imply that cerebral anomalies concurrent with malformation of the cleft and palate may be present in OFC.

In the BCL group, some of our results imply very dramatic effects, especially on intellectual disability, compared with UCL. Caution must be urged regarding these results regarding discrete disorders due to the small sample sizes

present in the CL groups for all psychiatric outcomes. However, we do believe that the results for psychiatric disorders in general do hold up for CL and point to a greater overall risk in BCL compared with UCL for less favorable psychiatric outcomes. The fact that diagnoses such as personality disorders were so strongly associated with BCLP compared with the unilateral subtype (UCLP) also shows that this association holds over the lifespan, given that these disorders are not usually diagnosed before adulthood. In addition, it may also indicate that associations between

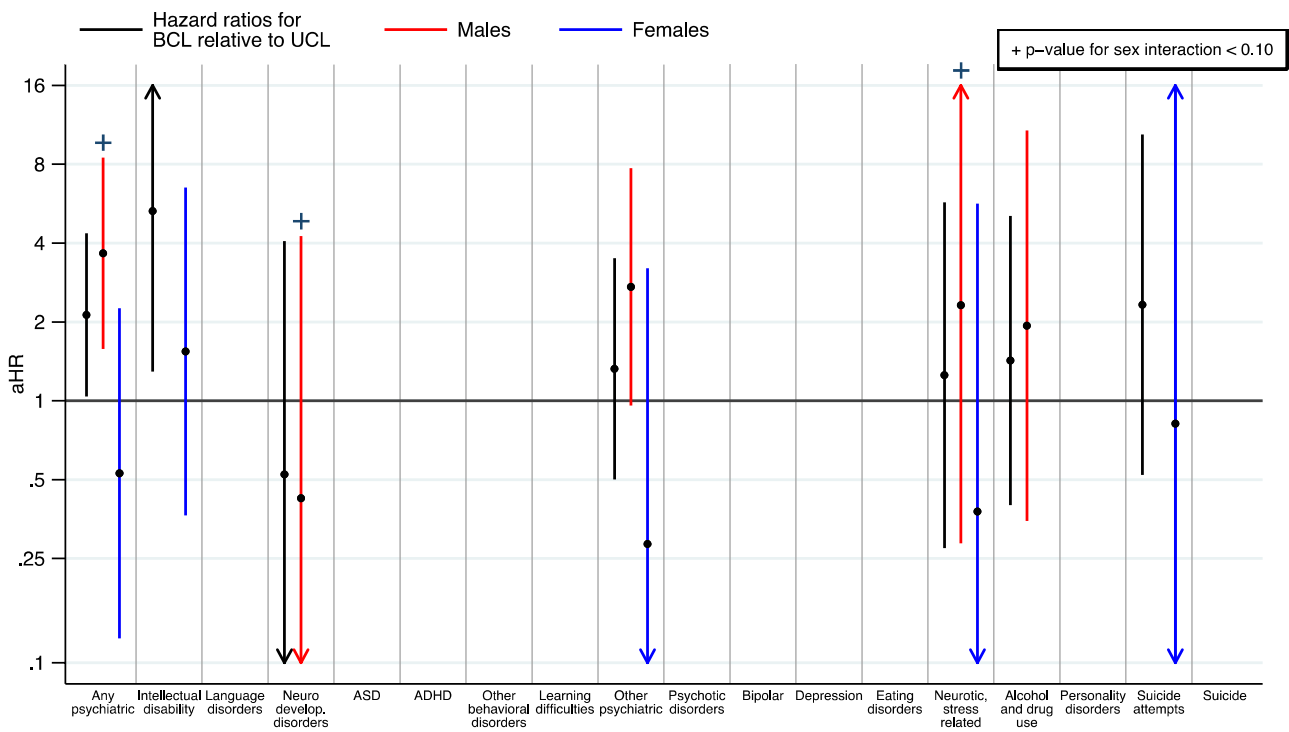


Figure 1 Adjusted Cox-derived hazard ratios (aHRs) with 95% confidence intervals (95% CIs) for psychiatric diagnoses, self-harm, and suicide among 47 children with bilateral cleft lip (BCL) compared with 527 children with unilateral cleft lip (UCL). aHRs are presented separately for males and females.

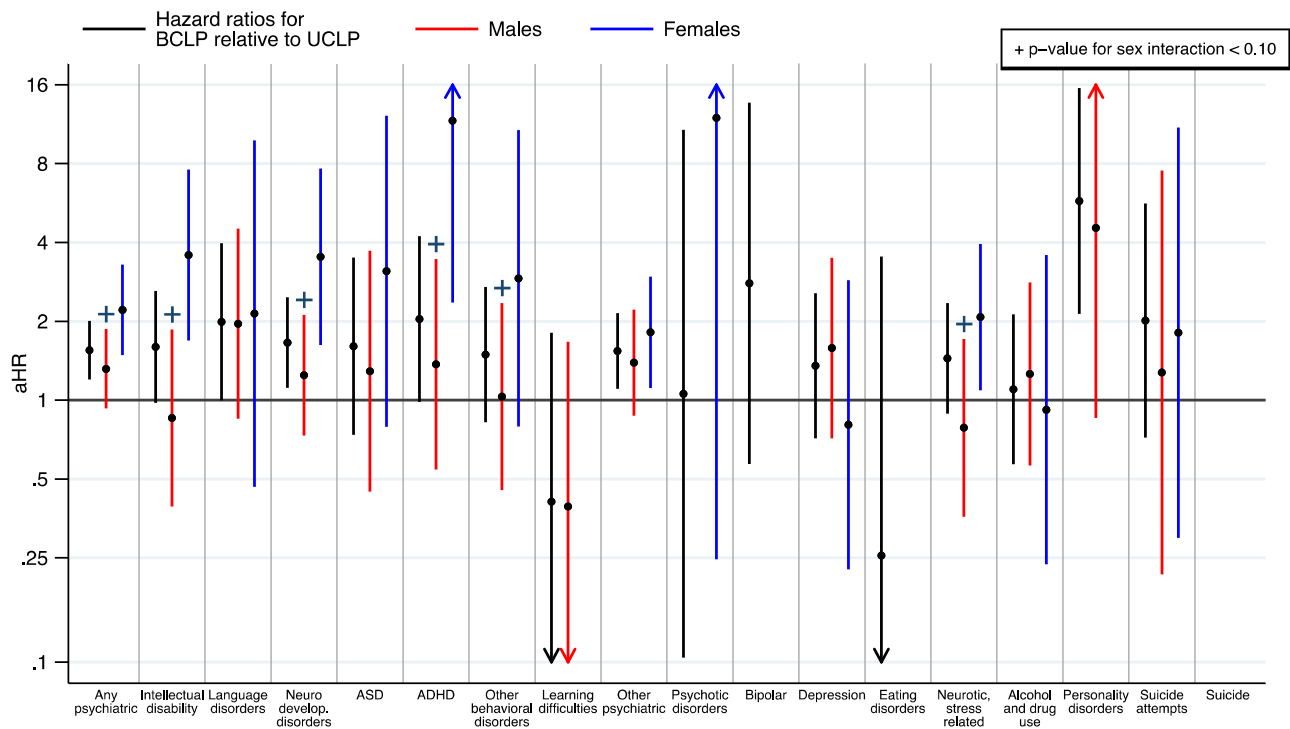


Figure 2 Adjusted Cox-derived hazard ratios (aHRs) with 95% confidence intervals (95% CIs) for psychiatric diagnoses, self-harm and suicide among 529 children with bilateral cleft lip and palate (BCLP) compared with 1351 children with Unilateral cleft lip and palate (UCLP). aHRs are presented separately for males and females.

OFCs and psychiatric outcomes are not necessarily being affected by differences in neurodevelopment only, but also through social mechanisms that might involve factors such as bullying in school, issues with identity formation during late adolescence, or absences from social interactions due to lengthy hospitalizations during childhoods.²⁰

Girls born with BCLP showed more than threefold risk increases for neurodevelopmental disorders compared with girls born with UCLP. Interestingly, the opposite pattern was seen in the BCL group, where boys had more than threefold risk increases of being diagnosed with any psychiatric disorder compared with boys born with UCL, with no risk increase for girls born with BCL compared with UCL. This could reflect a power problem in the much smaller female BCL sample compared with the other examined subgroups (Tables S4 and S5). Overall, the significant interactions with female sex found across both these groups in terms of intellectual disability and other neurodevelopmental disorders, especially ADHD, point to less favorable adaptive outcomes in girls compared with boys. This association seems to be carried, at least in part, by bilaterality versus unilaterality of the cleft.

Compared with non-OFC individuals in the population, we found two- to three-fold risk increases for intellectual disability, psychotic disorders, and personality disorders among children born with UCL. In previous studies, risk increases were found among CL (unilateral and bilateral combined) for any psychiatric disorder and intellectual disability, but no increased risks for psychotic disorders and personality disorders.^{5,21} Thus, unilaterality versus bilaterality of the cleft might be of greater importance than previously known, in line with the notion that orofacial clefts

are a group of highly heterogeneous malformations with complex embryopathogenesis.

There are several theories about neurodevelopmental disturbances in nonsyndromic OFC, including abnormal neurodevelopment in utero and secondary postnatal environmental effects on neurodevelopment.^{22,23} The observed differences in psychiatric outcome may therefore indicate a link between brain development and abnormal facial development early in morphogenesis. Facial malformations have been associated with structural midline abnormalities among children with nonsyndromic OFC.²⁴⁻²⁶ Midline brain anomalies have, in turn, been associated with intellectual disability, developmental delay, and schizophrenia in previous studies outside OFC samples.^{27,28} A few studies have also found more midline abnormalities among children with nonsyndromic bilateral clefts than unilateral clefts,²⁹ which could explain the association with higher risk increases for psychiatric disorders among children with bilateral clefts. Furthermore, a few studies have found that right-sided clefts are associated with more structural brain abnormalities than left-sided clefts and higher risks of other malformations and adverse academic outcomes, which might be of relevance to our results.^{12,30}

Strengths and limitations

The major strength of the present study is the design of a nationwide, register-based cohort with long follow-up time, eliminating the risk of recall and selection bias and enabling us to study a large sample over time, which is important when assessing relatively rare disorders. Another important

strength is the availability of data to adjust for confounders in the multivariate analyses.

Our study also has some limitations. Mild psychiatric symptoms treated within the primary health care system and ICD diagnoses from outpatient specialist visits before 2001 are not included in the NPR and are therefore missing. We also may not have captured all unilateral or bilateral clefts in Sweden, due to clinical misclassification and due to the fact that unspecific OFC codes were not included. Furthermore, clinicians sometimes have difficulties identifying diagnostic codes for a genetic condition. We have adjusted for all congenital malformations and chromosomal abnormalities in the ICD-8, -9, and -10 and adjusted for calendar year in the multivariate analyses to eliminate this risk to the greatest extent possible. Also, the fact that our study uses data collected across a long time period means we cannot rule out that societal trends towards more inclusiveness in school and health care, as well as better cleft management over time, might be influencing our results.

Unfortunately, we were also unable to analyze if left- or right-sided clefts had different psychiatric outcomes, due to ICD codes being the same for both lateralities in the data we received. Therefore, we cannot rule out that the addition of the right-sided clefts per se explains the differences in psychiatric outcomes reported in this study, given that right-sided clefts are primarily linked to worse outcomes, possibly in turn caused by different genetic etiologies in cleft lateralities.^{31,32} In addition, children with bilateral clefts are exposed to more surgeries than unilateral ones, which we cannot rule out as an alternative explanation for our findings, given that a widely discussed topic is the potential detrimental effect of early anesthesia on brain development.^{33,34} However, comparisons within a cohort of individuals with OFC offer an opportunity to address psychiatric morbidity among individuals that we argue are more comparable in terms of anesthesia exposure than the healthy cohorts usually used for comparisons in previous studies of psychiatric outcomes in OFC.

Conclusions

The present large nationwide register study elucidates knowledge that has not previously been captured regarding psychiatric comorbidity among children with nonsyndromic OFC.^{5,21} Children with bilateral clefts show a more prominent risk increase for psychiatric disorders and specifically neurodevelopmental disorders and personality disorders than children with unilateral clefts.

These findings indicate a link between aberrant facial and cerebral development occurring early in morphogenesis. The clinical relevance of these findings supports the need for mental health professionals within the cleft teams and is an important message to be conveyed to families and patients alike. Further research is needed to better understand the observed sex differences in psychiatric outcomes among individuals born with OFC.

Ethical approval

The Uppsala Ethics Committee (Reg. No. 2012/363).

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Declaration of Competing Interest

None declared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.bjps.2025.12.038](https://doi.org/10.1016/j.bjps.2025.12.038).

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