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Psychotropic Drug Use in Adolescents Born with an Orofacial Cleft: A Population Based Study

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ABSTRACT

Objectives: Being born with an orofacial cleft (OFC) can, due to an incomplete closure of the lip and/or palate, convey a deviant speech and/or deviant facial aesthetics, which may in turn increase the risk for poor psychological health later in life. Previous investigations concerning this have been based on small samples and self-reports, not distinguishing between the three different types of OFC: Cleft Lip (CL), Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO). Here, we present a large, population-based study, considering psychotropic drug use as proxy for poor psychological health and distinguishing between three different types of OFC.

Design and Methods: Using the Swedish Medical Birth Registry, and linking to it other national registries, we identified all singletons born to native mothers in Sweden 1987–1993, alive and residing in Sweden at the end of an 18-year follow-up period (N = 626 109). We compared psychotropic drug use among individuals with and without OFC during the individuals' adolescence (2005–2008) by multiple logistic regressions, adjusting for confounders (OR) and using 95% confidence intervals (CI).

Results: Suffering from CL (OR = 1.50, 95%CI: 1.00–2.26) and CPO (OR = 1.51, 95%CI: 1.16–1.98) increased the risk of psychotropic drug use during adolescence. Results were not conclusive regarding adolescents who had suffered from CLP (OR = 1.19, 95%CI: 0.80–1.77).

Conclusions: Being born with a CL or a CPO increases the risk psychotropic drugs use in adolescence, but this is not evident for adolescents born with a CLP. Our findings suggest that, since the three OFC types are associated with different long term risks of poor psychological health, the three groups ought to be studied separately concerning long-term consequences.

Strengths and Limitations of this Study

- Previous studies regarding the psychological health among adolescents being born with an OFC have been heterogeneous in their findings and limited in their generalizability as they have been mainly based on small samples and self-reported data.
- The present study was based on epidemiological data from a large Medical Birth registry and assessment of risks for poor mental health associated with OFC is based on data on prescribed medication, rather than self-reports.
- Our results suggest that being born with a CL or a CPO increases the risk for use of psychotropic drugs. Paradoxically, this risk does not seem to be present for children born with a CLP.
- There is clear clinical significance in our findings: Children with a CL and their parents may need to receive more attention than in current praxis as usual, in order to assist a prevention of long term adverse consequences of the initial condition.
- Our findings also have a clear theoretical impact: if adolescents born with a CL react differently to their condition than those with a CLP, treating CL and CLP as one and the same group is likely to lead to misunderstandings concerning the needs of these patients and their families.

In Sweden, around two of 1,000 children are born with an orofacial cleft (OFC) (1), a condition characterized by an incomplete closure of the lip, upper jaw and/or palate (2). As suffering from an OFC can be traumatic for a child and its parents (3), possibly negatively influencing his/her psychosocial development, several studies addressing psychological health in children and adolescents born with OFCs have been conducted (4-8). However, findings are diverse: While one study showed that maternal mental health affects the child's coping with her/his OFC (4), in another study the child seemed unaffected by the mother (9). Also, while it has been observed that children suffering from OFC suffer from psychosocial problems (10-12), evidence has also been presented contradicting this notion (13) and some authors have even reported evidence of a *higher* self-concept among children with OFC, compared to controls (14, 15). This heterogeneity may partly be due to methodological differences or limitations in the conducted studies. Most previous investigations are based on small samples, selected patient populations and self-reported information. These limitations threaten generalizability and the need for larger, population-based studies has been explicitly expressed (16).

Another possible explanation for this heterogeneity is that the three types of OFC, Cleft Lip (CL), Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO), are often considered together; particularly CL and CLP are treated as one group (CL/P). Nonetheless, what distinguishes these three conditions from each other has been shown to be of importance. In CL mainly facial aesthetics are affected, particularly the upper jaw and the nose, and there may be some impact on speech development (17). Yet, speech development is more strongly affected in children born with a CLP, as they also suffer from an incomplete closure of their palate (18), creating a characteristic, deviant speech, often classified as "the cleft palate speech" (19). CLP can also lead to a hearing impairment and a troublesome breast feeding. These problems also affect children born with a CPO (20), but the aesthetic concerns are not equally strong as children in this group have a complete lip closure (21).

Indeed, physical facial abnormalities and severity of speech impairment seem to be related to challenged psychosocial health in affected children (18, 22, 23), perhaps partly by influences on how the affected children are perceived by others (24, 25). Furthermore, the ways different types of OFC are related to psychological well-being may vary across development (15, 23). When the child is approaching adolescence, an emotionally turbulent period when peers and their acceptance become increasingly significant, both the speech impairment and the aesthetic concerns associated with the OFC become increasingly important for the child's quality of life (13, 23).

To our knowledge, there are no large population-based studies investigating the impact of OFC on the psychological health in adolescence, and there are no studies examining the different types of OFC separately. Therefore, the main aim of the present investigation is to improve our knowledge on the psychological health of adolescents affected by an OFC, trying to disentangle the effect of specific OFC malformations. Using the Swedish nation-wide healthcare registers, we conducted a large epidemiological study including all adolescents being born to native Swedish mothers between 1987 and 1993, who were alive and residing in Sweden at the end of our follow-up period (2005 – 2008). We investigated the use of psychotropic drugs in adolescence in relation to congenital OFC malformations, considering *use of psychotropic medication* as a surrogate of *impaired psychological health*. This approximation has been previously used (26, 27) and seems appropriate in a homogenous and accessible healthcare system as is the case in Sweden.

METHODS

Participants and Procedures

We obtained a database derived from the *Swedish Medical Birth Register* linked to other national databases such as the *Swedish Drug Prescription Register*, the *National Mortality Register*, the *Emigration Register* and the *National Inpatient Register*. These registers,

administered by Statistics Sweden and by the National Board of Health and Welfare, are linked using personal identification numbers given to each person residing in Sweden. In the data we received, the identification numbers were replaced with arbitrary numbers, thereby securing anonymity. We identified all children born to mothers in Sweden during the period 1987 to 1993 (N = 811 599). As there is evidence of an underuse of psychotropic drugs in relation to the needs of adolescent descendants of migrant women (27), potentially confounding the outcomes' analysis in the current study, we excluded children of parents born outside Sweden. We also excluded children who were not singletons, died or emigrated from Sweden before the 31st of December 2008 (end of follow-up period). The final cohort consisted of 626 109 adolescents (Figure 1). The database used for the study was approved by a Regional Ethical Review Board.

<Insert Figure 1 about here>

Measures

Outcome variables

Orofacial cleft: We identified all children registered with an OFC in the Patient Registry and/or in the Medical Birth Registry, by their ICD-9 and/or ICD-10 diagnoses (WHO, 2011b), and categorized them into four subgroups: CL, CLP, CPO and Unspecified OFC. The ICD-codes for CL were 749B (ICD-9) and Q36 (ICD-10), for CLP the codes were 749C (ICD-9) and Q37 (ICD-10) and, finally, for CPO the codes were 749A and Q35 for ICD-9 and ICD-10 respectively. The "Unspecified OFC" group consisted of those cases where the type of OFC was not clear (for instance if more than one of the different types of OFC was registered for the same child or registered only with the ICD-9 code 749). In the analyses, we set children without any OFC as reference in the comparisons.

Psychotropic drugs: From the Swedish Drug Prescription Register we obtained information about prescribed and dispensed psychotropic drugs. We distinguished six categories of

psychotropic drugs according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2011a): antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and psycho-stimulants (N06B). The register contains individual information on medication starting1st July 2005, which conditions the period of analysis for this study. We defined the outcome variable as at least one dispensed prescription of any of these drugs during 1st July 2005 to 31st December 2008 (yes/no).

Other child characteristics

Birth year: We included birth years 1987 to 1993. We used children born in 1993 as reference group in the comparisons.

Sex: Girls are more at risk for CPO while boys are overrepresented among children born with a CL or a CLP (28). Also, girls are in general consuming more psychotropic drugs than boys (29). Therefore, we set boys as reference.

Small for Gestational Age (SGA): Babies born with a CLP or a CPO are more likely to be Small for Gestational Age (SGA) than children without any OFC (30), and being SGA is also suggested to be related to later impaired psychological health (31). Therefore, we identified children registered in the Medical Birth Registry as SGA (32). We dichotomized the variable into 'child being SGA' or 'child not being SGA'. There was a certain number of missing values (N= 1,417) that we recoded into a group of its own, 'missing'. We set 'Not SGA' as reference group in the analyses.

Other significant malformation: OFCs are often associated with other disorders (33-36). As these accompanying pathologies may increase the risk of impaired psychological health, we adjusted in the analyses for the presence of "Other significant malformation" according to the definition provided by the Swedish National Board of Health and Welfare (37). Children that did not present any of these diagnoses in our registries were considered as the reference group in the comparisons.

Mother characteristics

Age at delivery: We classified maternal age at delivery into six groups (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, >39 years). Mother's age at delivery has been found to be a risk factor for giving birth to a child with an OFC (38); however this risk seems to differ with cleft type (39). Mother's age may also affect the risk for the offspring developing poor psychological health (40). We considered mothers younger than 20 years at the time for delivery as reference in the comparisons.

Smoking: Information regarding mother's self-reported smoking status was collected when she was first assigned to Antenatal Care (between 8th and 12th gestational week). Maternal smoking during pregnancy has been associated with giving birth to a child with an OFC (41, 42) and with behavioral difficulties in the child (43). We categorized smoking habits into four categories: 'no smoking', 'light smokers (1-9 cigarettes per day)', 'heavy smokers (>9 cigarettes per day)' and 'no information' where there were missing values (N = 37 477). The non-smoking group was considered as reference.

Congenital malformation: Orofacial clefts are to some extent genetic (44). Therefore, we identified mothers being admitted to hospital with any of the following diagnoses used to register congenital malformations: ICD 10-codes Q00-99 respectively ICD 9-codes 740-758. Mothers who were never admitted to hospital with one of those diagnoses were set as reference.

Statistical analysis

In a first step, we hypothesized and probed variables (confounders) that may be associated both with being born with an OFC (subgroups analyzed separately) and with prescription of psychotropic drugs. In cases where two variables showed multicollinearity, we selected the variable that provided a better goodness of fit by means of a chi-square test (e.g., Mother's age at delivery compared with Parity, where the latter one was excluded). Next, we applied

logistic regression analyses in two consecutive models to investigate the association between the different types of OFC and the use of psychotropic drugs in adolescence. In the first model we investigated the bare association between being born with an OFC and the use of psychotropic drugs in adolescence. In the second model (Table 1) we adjusted for potential confounders (i.e., Sex, Birth year, Other significant malformations, SGA, Maternal smoking, Mother's age at delivery and Mother congenital malformation) and obtained odds ratios (OR) and 95% confidence intervals (CI). Since the prevalence of congenital OFC anomalies is very low, the ORs are an appropriate approximation of the relative risk (RR) (45). We used IBM SPSS Statistics for Windows, Version 20.0 for the analyses.

RESULTS

Overall, 2.2 per thousand (1 334 out of 626 109) children suffered from an OFC. Of those, 264 children were born with a CL, 317 with a CLP, 542 with a CPO, and 211 were born with an unspecified OFC. Table 1 summarises the characteristics of the population affected by an OFC and the population not affected. The distribution of children born with different types of OFCs was roughly the same as the distribution of children without OFC for all years (1988 – 1993). Children affected by a CLP, CPO and unspecified OFC, who were also SGA, were more likely to in addition have suffered other congenital malformations, but this did not apply for children with a CL. Girls were underrepresented in the CL, CLP and unspecified OFC groups but overrepresented in the CPO group.

<Insert Table 1 about here>

Concerning maternal characteristics, a higher percentage of mothers to children born with a CL or a CPO smoked heavily (over 9 cigarettes per day) during pregnancy, and more mothers of children born with CLP and CPO had been hospitalized with a congenital malformation. Also, there were fewer mothers older than 35 years of age among children born

with a CL, for the CLP group there were fewer mothers in the age group 30-34 while the opposite pattern was observed for mothers to children born with a CPO (Table 1).

Table 2 informs about the OR for using psychotropic drugs in relation to the presence of an OFC and in relation to possible confounders. In the initial analysis it appeared that being born with a CPO increased the risk of using psychotropic drugs in adolescence, compared with individuals without an OFC. However closer analysis revealed that the diagnostic subgroups behaved differently. Individuals with a CLP or with an unspecified OFC presented a similar use of psychotropic medication as individuals without an OFC, but there were significantly more adolescents with psychotropic drug prescriptions among those with a CL or a CPO, compared to unaffected controls. Also after adjusting for confounders, being born with a CLP did not increase the risk of psychotropic drugs use in adolescence. Nevertheless, CL was associated with higher risk for need of psychotropic drugs as indicated by recorded prescriptions, and this result persisted after adjusting for confounders.

<Insert Table 2 about here>

DISCUSSION

Our analyses, based on a large population database covering the whole of Sweden, indicate that children born with a CPO or CL type of OFC are at a higher risk of using psychotropic medication than unaffected children. Since use of psychotropic medication is a clear indicator of psychological health impairment, these findings suggest that those adolescents are indeed in higher risk for impaired mental health. Our analyses confirm previous findings that children suffering from an OFC have more difficulties in psychosocial adjustment, compared to their peers without such malformations (10-12). Interestingly, our results also indicate that this association is present only in adolescents suffering from a CL or a CPO, but not in adolescents suffering from a CLP. Previous studies investigating facial disfigurement suggested that minor facial disfigurement can be more difficult to bear than more severe

disfigurement (46). It is important to note that, particularly the CL group (minor disfigurement) has been often overlooked or mixed with the CLP group (more severe disfigurement) (21, 22, 47, 48). Our study suggests that, using prescriptions of psychotropic drugs as proxy for poor psychological health, CL increases the risk of poor psychological health during adolescence while CLP does not.

There are important clinical implications of these findings. Children born with a CL may need more attention from better informed health care staff, and closer monitoring over a long period of time, compared to current praxis. Also, parents to children born with a CL might need to receive more support in the direction of promoting secure attachments and their concerns concerning their children's wellbeing may need to be addressed with equal gravity as parents' concerns when a child suffers a more severe type of OFC. Specifically for children born with a CL, these issues have been insufficiently addressed in clinical praxis.

It may appear paradoxical that children born with a CLP do not seem to be more at risk of impaired psychological health during adolescence, considering that this type of OFC is most severe. However, the fact that children with a CLP receive more attention initially, both from healthcare services and from their parents, who tend to spend considerable time with them at the hospital (49), may act as buffer against potential negative consequences of the CLP condition itself on children's psychological health. Indeed, children with a visible cleft (in Havstam's study a CL or a CLP) have been found to be more emotionally resilient, possibly due to the increased efforts made by parents and other adults in the children's growing environment (healthcare professionals, teachers) to protect them from psychological threats (50). These children may also have long standing contacts with treating Psychologists. Finally, as it has been suggested that stronger posttraumatic stress disorder symptoms in mothers who gave birth to a child with a cleft may be associated with stronger attachment bonds to the child later on (51), it is possible that mothers who gave birth to children with a CLP perhaps suffered a more profound chock initially, but also developed stronger bonds to

their children later on. While it is clear that the origins of this apparently paradoxical resilience needs to be further investigated, our findings suggest clearly that children born with different OFC types experience different degrees of psychosocial difficulties during their development, and therefore, treating them as one clinical group will likely lead to erroneous conclusions, possibly overestimating the impact of one type of OFC (for example, CLP, as a more severe condition) and underestimating the impact of another type (for example, CL as a less severe condition).

Our study has limitations. To begin with, while use of psychotropic medication is a clear indicator of poor psychological health, other possible treatments of poor mental health commonly used with children and adolescents, such as psychotherapeutic intervention, were not considered here as no information on such treatments was available in the databases. This may have resulted in an underestimation of poor mental health in all populations considered here. If, in addition, more OFC children have ongoing contacts with psychologists to which they can turn when experiencing psychosocial problems, there is a risk that our analysis suffers differential information bias towards the 1, particularly for the CLP group. Moreover, children with OFC malformations, particularly those born with a CLP or a CPO, suffer from a number of other pathologies (34) which are related both to OFCs and to an impaired psychological health in adolescence. To avoid this potential confounding, we adjusted for the presence of other significant malformations recorded by the Swedish National Board of Health and Welfare, including syndromes known to be associated with OFCs. However, we cannot exclude that some confounding disorder was missed. Finally, our data included a small group of children for whom it was unclear what type of OFC they were suffering from (the "unspecified OFC" group). This group did not appear to suffer adverse consequences in the psychosocial sphere (OR=1.00, 95%CI: 0.61 – 1.64). It is possible that the OFC in those cases was of minor importance and therefore, difficult to diagnose and not equally affecting the child. But it may also be the case that some of these children were actually born with both a

cleft lip and a cleft palate, really belonging to the CLP group, further strengthening the idea that CLP does not constitute a risk for poor psychological health. Sensitivity analysis (i.e., assigning all these children to one subgroup at a time) in order to explore how our findings would have been affected if all children in the unspecified group were located into the CL, CLP or CPO group, respectively, revealed that the risk for consumption of psychotropic drugs in adolescence decreased for all three redefined groups, becoming (OR=1.31, 95%CI: 0.95 – 1.79) for the CL group, (OR=1.12, 95%CI: 0.82 – 1.53) for the CLP group and (OR=1.38, 95%CI: 1.09 – 1.75) for the CPO group. These results support the hypothesis that the OFC in the unspecified group was minor.

CONCLUSION

Suffering from an OFC malformation can increase the risk of impaired psychological health in adolescence, expressed by a higher use of psychotropic medication than the rest of the population. However, this association seems to be present only in adolescents suffering from a CL or a CPO and appears to be of less importance, if any, in adolescents who were born with a CLP. Hence, children with a CL and their parents may need to receive more attention than in current praxis, in order to assist a prevention of long term adverse consequences of the initial condition. Our findings have a clear theoretical impact for further research; if adolescents born with a CL react differently to their condition than those with a CLP, treating them as one group is likely to lead to misunderstandings concerning the needs of these patients and their families.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

Nilsson: Study conception and design, Analysis and interpretation of data, Drafting of manuscript

Merlo: Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript

Lyberg-Åhlander: Study conception and design, Analysis and interpretation of data

Psouni: Study conception and design, Analysis and interpretation of data, Drafting of manuscript, Critical revision of manuscript

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Table 1 Characteristics of the population by presence of congenital orofacial cleft (OFC) distinguishing between Cleft Lip (CL), Cleft Lip and Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC. All numbers are percentage unless otherwise indicated.

	No OFC	CL	CLP	CPO	Unspec. OFC
Child's characteristics					
Psychotropic drug use	7.2	10.5	8.5	11.6	7.5
Girls	48.6	34.0	28.0	55.4	41.2
Other Significant malformation	2.1	3.2	11.6	13.1	12.7
SGA	2.5	2.4	6.6	4.6	4.8
· Missing	0.2	0.0	0.0	0.6	0.9
Born in year					
· 1987	13.0	12.1	12.3	14.9	11.4
· 1988	13.9	10.1	11.9	11.1	15.4
· 1989	14.4	11.3	15.4	13.8	14.5
· 1990	15.1	15.8	15.1	14.4	15.4
· 1991	15.1	20.2	14.8	16.2	14.9
· 1992	14.7	16.2	15.1	15.3	18.4
· 1993	13.8	14.2	15.4	14.2	10.1
Maternal characteristics					
Smoking during pregnancy (cig/day)					
· No	70.9	67.2	67.6	68.1	69.7
· 1-9	14.4	13.4	14.8	12.5	14.9
· >9	8.7	13.8	10.7	13.1	8.3
· Missing	6.0	5.7	6.9	6.3	7.0

Age at delivery (years)					
· <20	2.5	2.8	3.1	2.2	3.5
· 20-24	22.6	21.1	25.2	22.5	21.1
· 25-29	38.3	42.1	39.3	36.0	40.4
· 30-34	25.5	25.1	19.2	24.5	25.4
· 35-39	9.4	7.7	10.1	13.5	8.3
· >39	1.7	1.2	3.1	1.3	1.3
Hospitalized with a congenital malformation	1.9	2.0	4.1	3.3	3.1

Table 2 Psychotropic drug use in childhood and adolescence by being born with a congenital Orofacial Cleft Malformation (OFC), distinguishing between Cleft Lip (CL), Cleft Lip And Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC.

	OR	95 % CI		OR	95 % CI	
Child's characteristics						
OFC						
· No OFC	1	(Reference)		1	(Reference)	
· CL	1.51	1.00	2.27	1.63	1.08	2.46
· CLP	1.19	0.80	1.77	1.21	0.81	1.80
· CPO	1.69	1.30	2.19	1.54	1.18	2.01
· Unspec. OFC	1.03	0.63	1.69	1.00	0.61	1.64
Girls vs. Boys				1.52	1.49	1.55
Other significant malformation (yes vs no)				1.48	1.40	1.57
SGA						
· No				1	(Reference)	
· Yes				1.22	1.15	1.29
· Missing				1.26	1.06	1.51
Born in year						
· 1987				2.52	2.43	2.63
· 1988				2.19	2.11	2.28
· 1989				2.00	1.92	2.09
· 1990				1.69	1.62	1.76
· 1991				1.40	1.34	1.46

· 1992	1.20	1.15	1.25
· 1993	1	(Reference)	
Maternal characteristics			
Smoking during pregnancy (cig/day)			
· No	1	(Reference)	
· 1-9	1.37	1.34	1.41
· >9	1.65	1.60	1.70
· Missing	1.23	1.19	1.28
Age at delivery (years)			
· <20	1	(Reference)	
· 20-24	0.68	0.65	0.72
· 25-29	0.58	0.55	0.61
· 30-34	0.57	0.54	0.60
· 35-39	0.63	0.60	0.67
· >=40	0.73	0.67	0.79
Hospitalized with a congenital malformation (yes vs no)	1.29	1.21	1.38

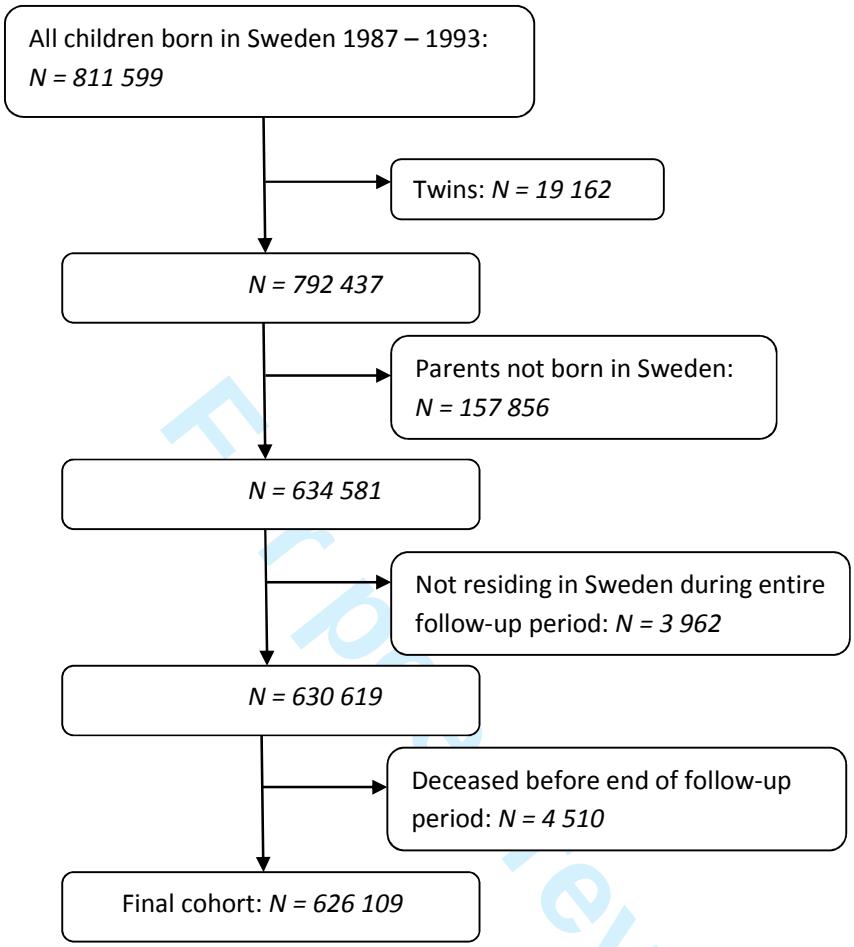

Figure 1 Study Population

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Psychotropic Drug Use in Adolescents Born with an Orofacial Cleft: A Population Based Study

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ABSTRACT

Objectives: Being born with an orofacial cleft (OFC) can, due to an incomplete closure of the lip and/or palate, convey a deviant speech and/or deviant facial aesthetics, which may in turn increase the risk for poor psychological health later in life. Previous investigations concerning this issue have been based on small samples and self-reports, not distinguishing between the three different types of OFC: Cleft Lip (CL), Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO). Here, we present a large, population-based study, considering psychotropic drug use as proxy for poor psychological health and distinguishing between three different types of OFC.

Design and Methods: Using the Swedish Medical Birth Registry, and linking to it other national registries, we identified all singletons born to native mothers in Sweden 1987–1993, alive and residing in Sweden at the end of an 18-year follow-up period (N = 626 109). We compared psychotropic drug use among individuals with and without OFC during the individuals' adolescence (2005–2008) by multiple logistic regressions, using odds ratios (OR) with 95% confidence intervals (CI).

Results: Suffering from CL (OR = 1.50, 95%CI: 1.00–2.26) and CPO (OR = 1.51, 95%CI: 1.16–1.98) increased the risk of psychotropic drug use during adolescence. Results were not conclusive regarding adolescents who had suffered from CLP (OR = 1.19, 95%CI: 0.80–1.77).

Conclusions: Being born with a CL or a CPO increases the risk psychotropic drugs use in adolescence, but this is not evident for adolescents born with a CLP. Our findings suggest that, since the three OFC types are associated with different long term risks of poor psychological health, the three groups ought to be studied separately concerning long-term consequences.

Strengths and Limitations of this Study

- Previous studies regarding the psychological health of adolescents born with an OFC have been based mainly on small samples and self-reported data and therefore heterogeneous in their findings and limited in their generalizability. By contrast, the present study was based on epidemiological data from a large Medical Birth registry and assessment of risks for poor mental health associated with OFC was based on data on prescribed medication, rather than self-reports.
- While most research regards two subgroups of patients with facial clefts, Cleft Lip with or without Cleft Palate (CL/P) and Cleft Palate Only (CPO), the present study regards Cleft Lip (CL) and Cleft Lip and Palate (CLP) as two distinct subgroups. Importantly, results suggest that being born with a CPO, as well as with a CL, increases the risk for use of psychotropic drugs, but this risk does not seem to be present for children born with a CLP.
- There is clinical significance in our findings: Children with a CL and their parents may need to receive more attention than in current praxis as usual, in order to assist a prevention of long term adverse consequences of the initial condition. In addition, if adolescents born with a CL react differently to their condition than those with a CLP, treating CL and CLP as one group is likely to lead to misconceptions concerning the needs of these patients and their families.
- The present study regarded psychotropic drug use as proxy for poor mental health. This may have resulted in an underestimation of poor mental health among adolescents, as other, non-medical treatments were not considered.
- Children with OFC malformations may suffer from other pathologies that may also be associated with increased poor mental health. Despite statistical adjustment to avoid this confounding, it cannot be excluded that some confounding disorder was missed.

In Sweden, around two of 1,000 children are born with an orofacial cleft (OFC) (1), a condition characterized by an incomplete closure of the lip, upper jaw and/or palate (2). As suffering from an OFC can be traumatic for a child and its parents (3-5), possibly negatively influencing his/her psychosocial development, several studies addressing psychological health in children and adolescents born with OFCs have been conducted (6-10). However, findings are diverse: While one study showed that maternal mental health affects the child's coping with her/his OFC (6), in another study the child seemed unaffected by the mother (11). Also, while it has been observed that children with OFC suffer from psychosocial problems (12-14), evidence has also been presented contradicting this notion (6, 15) and some authors have even reported evidence of a *more positive* self-concept among children with OFC, compared to controls (16, 17). This heterogeneity may partly be due to methodological differences or limitations in the conducted studies. Most previous investigations are based on small samples, selected patient populations and self-reported information. These limitations threaten generalizability and the need for larger, population-based studies has been explicitly expressed (18, 19).

Another possible explanation for this heterogeneity is that the three types of OFC, Cleft Lip (CL), Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO), are often considered together; particularly CL and CLP are treated as one group (CL/P). Nonetheless, what distinguishes these three conditions from each other has been shown to be of importance. In CL mainly facial aesthetics are affected, particularly the upper jaw and the nose, and there may be some impact on speech development (20). Yet, speech development is more strongly affected in children born with a CLP, as they also suffer from an incomplete closure of their palate (21), creating a characteristic, deviant speech, often classified as "the cleft palate speech" (1, 7, 19). CLP can also lead to a hearing impairment and difficulties with breast feeding during infancy (22). These problems also affect children born with a CPO (23), but

the aesthetic concerns are not equally strong as children in this group have a complete lip closure (24, 25).

Indeed, physical facial abnormalities and severity of speech impairment seem to be related to challenged psychosocial health in affected children (21, 26, 27), perhaps partly by influences on how the affected children are perceived by others (28, 29). Furthermore, the ways different types of OFC are related to psychological well-being may vary across development (17, 27). When the child is approaching adolescence, an emotionally turbulent period when peers and their acceptance become increasingly significant, both the speech impairment and the aesthetic concerns associated with the OFC become increasingly important for the child's quality of life (4, 15, 27, 30).

Large population-based analysis produced little evidence that individuals with OFC are in increased risk for psychopathology of such nature and severity that it required hospitalization (31). However, poor mental health can be suffered during long periods, with detrimental effects on wellbeing and quality of life, without any hospitalization being involved. In addition, to our knowledge, there are no large population-based studies investigating the impact of OFC on the psychological health in adolescence, and there are no studies examining the different types of OFC separately. Therefore, the main aim of the present investigation was to improve our knowledge on the psychological health of adolescents affected by an OFC, trying to disentangle the effect of specific OFC malformations. Using the Swedish nation-wide healthcare registers, we conducted a large epidemiological study including all adolescents being born to native Swedish mothers between 1987 and 1993, who were alive and residing in Sweden at the end of our follow-up period (2005 – 2008). We investigated the use of psychotropic drugs in adolescence in relation to congenital OFC malformations, considering *use of psychotropic medication* as a surrogate of *impaired psychological health*. This approximation has been previously used (32, 33) and seems appropriate in a homogenous and accessible healthcare system as is the case in Sweden, and adequate for

capturing a broad spectrum of poor mental health conditions that cannot be ignored but that may not require hospitalization.

METHODS

Participants and Procedures

We obtained a database derived from the *Swedish Medical Birth Register* linked to other national databases such as the *Swedish Drug Prescription Register*, the *National Mortality Register*, the *Emigration Register* and the *National Inpatient Register*. These registers, administered by Statistics Sweden and by the National Board of Health and Welfare, are linked using personal identification numbers given to each person residing in Sweden. In the data we received, the identification numbers were replaced with arbitrary numbers, thereby securing anonymity. We identified all children born to mothers in Sweden during the period 1987 to 1993 (N = 811 599). As there is evidence of an underuse of psychotropic drugs in relation to the needs of adolescent descendants of migrant women (33), potentially confounding the outcomes' analysis in the current study, we excluded children of parents born outside Sweden. We also excluded children who were not singletons, died or emigrated from Sweden before the 31st of December 2008 (end of follow-up period). The final cohort consisted of 626 109 adolescents (Figure 1). The database used for the study was approved by a Regional Ethical Review Board.

<Insert Figure 1 about here>

Measures

Outcome variables

Orofacial cleft: We identified all children registered with an OFC in the Patient Registry and/or in the Medical Birth Registry, by their ICD-9 and/or ICD-10 diagnoses (WHO, 2011b), and categorized them into four subgroups: CL, CLP, CPO and Unspecified OFC. The ICD-codes for CL were 749B (ICD-9) and Q36 (ICD-10), for CLP the codes were 749C (ICD-9)

and Q37 (ICD-10) and, finally, for CPO the codes were 749A and Q35 for ICD-9 and ICD-10 respectively. The "Unspecified OFC" group consisted of those cases where the type of OFC was not clear (for instance if more than one of the different types of OFC was registered for the same child or registered only with the ICD-9 code 749). In the analyses, we set children without any OFC as reference in the comparisons.

Psychotropic drugs: From the Swedish Drug Prescription Register we obtained information about prescribed and dispensed psychotropic drugs. We distinguished six categories of psychotropic drugs according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2011a): antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and psycho-stimulants (N06B). The register contains individual information on medication starting1st July 2005, which conditions the period of analysis for this study. We defined the outcome variable as at least one dispensed prescription of any of these drugs during 1st July 2005 to 31st December 2008 (yes/no).

Other child characteristics

Birth year: We included birth years 1987 to 1993. We used children born in 1993 as reference group in the comparisons.

Sex: Girls are more at risk for CPO while boys are overrepresented among children born with a CL or a CLP (34). Also, girls are in general consuming more psychotropic drugs than boys (35). Therefore, we set boys as reference.

Small for Gestational Age (SGA): Babies born with a CLP or a CPO are more likely to be Small for Gestational Age (SGA) than children without any OFC (36), and being SGA is also suggested to be related to later impaired psychological health (37). Therefore, we identified children registered in the Medical Birth Registry as SGA (38). We dichotomized the variable into 'child being SGA' or 'child not being SGA'. There was a certain number of missing

values (N= 1,417) that we recoded into a group of its own, 'missing'. We set 'Not SGA' as reference group in the analyses.

Other significant malformation (OSM): OFCs are often associated with other disorders (39-43). As these accompanying pathologies may increase the risk of impaired psychological health, we adjusted in the analyses for the presence of "Other significant malformation (OSM)" according to the definition provided by the Swedish National Board of Health and Welfare (44). The variable OSMs is computed by this authority following standardized criteria (44). Children that did not present any of these diagnoses in our registries were considered as the reference group in the comparisons.

Mother characteristics

Age at delivery: We classified maternal age at delivery into six groups (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, >39 years). Mother's age at delivery has been found to be a risk factor for giving birth to a child with an OFC (45); however this risk seems to differ with cleft type (46). Mother's age may also affect the risk for the offspring developing poor psychological health (47). We considered mothers younger than 20 years at the time for delivery as reference in the comparisons.

Smoking: Information regarding mother's self-reported smoking status was collected when she was first assigned to Antenatal Care (between 8th and 12th gestational week). Maternal smoking during pregnancy has been associated with giving birth to a child with an OFC (48, 49) and with behavioral difficulties in the child (50). We categorized smoking habits into four categories: 'no smoking', 'light smokers (1-9 cigarettes per day)', 'heavy smokers (>9 cigarettes per day)' and 'no information' where there were missing values (N = 37 477). The non-smoking group was considered as reference.

Congenital malformation: OFCs are to some extent genetic (51-53). Therefore, we identified mothers being admitted to hospital with any of the following diagnoses used to register

congenital malformations: ICD 10-codes Q00-99 respectively ICD 9-codes 740-758. Mothers who were never admitted to hospital with one of those diagnoses were set as reference.

Statistical analysis

In a first step, we hypothesized and probed variables (confounders) that may be associated both with being born with an OFC (subgroups analyzed separately) and with prescription of psychotropic drugs. In cases where two variables showed multi-co-linearity, we selected the variable that provided a better goodness of fit by means of a chi-square test (e.g., Mother's age at delivery compared with Parity, where the latter one was excluded). Next, we applied logistic regression analyses in two consecutive models to investigate the association between the different types of OFC and the use of psychotropic drugs in adolescence. In the first model we investigated the bare association between being born with an OFC and the use of psychotropic drugs in adolescence. In the second model (Table 1) we adjusted for potential confounders (i.e., Sex, Birth year, Other significant malformations, SGA, Maternal smoking, Mother's age at delivery and Mother congenital malformation) and obtained odds ratios (OR) and 95% confidence intervals (CI). Since the prevalence of congenital OFC anomalies is very low, the ORs are an appropriate approximation of the relative risk (RR) (54). We used IBM SPSS Statistics for Windows, Version 20.0 for the analyses.

RESULTS

Overall, 2.2 per thousand (1 334 out of 626 109) children suffered from an OFC. Of those, 264 children were born with a CL, 317 with a CLP, 542 with a CPO, and 211 were born with an unspecified OFC. Table 1 summarises the characteristics of the population affected by an OFC and the population not affected. The distribution of children born with different types of OFCs was roughly the same as the distribution of children without OFC for all years (1988 – 1993). Children affected by a CLP, CPO and unspecified OFC, who were also SGA, were more likely to in addition have suffered other congenital malformations, but this did not apply

for children with a CL. Girls were underrepresented in the CL, CLP and unspecified OFC groups but overrepresented in the CPO group.

<Insert Table 1 about here>

Concerning maternal characteristics, a higher percentage of mothers to children born with a CL or a CPO smoked heavily (over 9 cigarettes per day) during pregnancy, and more mothers of children born with CLP and CPO had been hospitalized with a congenital malformation. Also, there were fewer mothers older than 35 years of age among children born with a CL, for the CLP group there were fewer mothers in the age group 30-34 while the opposite pattern was observed for mothers to children born with a CPO (Table 1).

Table 2 informs about the OR for using psychotropic drugs in relation to the presence of an OFC and in relation to possible confounders. In the initial analysis it appeared that being born with a CPO increased the risk of using psychotropic drugs in adolescence, compared with individuals without an OFC. However closer analysis revealed that the diagnostic subgroups behaved differently. Individuals with a CLP or with an unspecified OFC presented a similar use of psychotropic medication as individuals without an OFC, but there were significantly more adolescents with psychotropic drug prescriptions among those with a CL or a CPO, compared to unaffected controls. Also after adjusting for confounders, being born with a CLP did not increase the risk of psychotropic drugs use in adolescence. Nevertheless, CL was associated with higher risk for need of psychotropic drugs as indicated by recorded prescriptions, and this result persisted after adjusting for confounders.

<Insert Table 2 about here>

DISCUSSION

Our analyses, based on a large population database covering the whole of Sweden, indicate that children born with a CPO or CL type of OFC are at a higher risk of using psychotropic medication than unaffected children. Since use of psychotropic medication is a clear indicator

of psychological health impairment, these findings suggest that those adolescents are indeed in higher risk for impaired mental health. Our analyses confirm previous findings that children suffering from an OFC have more difficulties in psychosocial adjustment, compared to their peers without such malformations (12-14). Interestingly, our results also indicate that this association is present only in adolescents suffering from a CPO, consistently with other findings (31) or a CL, but not in adolescents suffering from a CLP. Previous studies investigating facial disfigurement suggested that minor facial disfigurement can be more difficult to bear than more severe disfigurement (55), highlighting the fact that, in essence, the perceived gravity of facial disfigurement is a subjective matter (31, 56). It is important to note that, particularly the CL group has been often overlooked or mixed with the CLP group (24, 26, 31, 57, 58). Our findings that, using prescriptions of psychotropic drugs as proxy for poor psychological health, CL increases the risk of poor psychological health during adolescence while CLP does not, may be regarded as further support to other findings pointing to the subjective nature of experiencing and coping with facial cleft disfigurement of different kinds.

There are important clinical implications of these findings. Children born with a CL may need more attention from better informed health care staff, and closer monitoring over a long period of time, compared to current praxis. Also, parents to children born with a CL might need to receive more support in the direction of promoting secure attachments and their concerns concerning their children's wellbeing may need to be addressed with equal gravity as parents' concerns when a child suffers other types of OFC. Specifically for children born with a CL, these issues have been insufficiently addressed in clinical praxis.

It may appear paradoxical that children born with a CLP do not seem to be more at risk of impaired psychological health during adolescence, considering that this type of OFC affects more parameters (i.e. both speech and facial aesthetics). However, the fact that children with a CLP receive more attention initially, both from healthcare services and from their parents, who tend to spend considerable time with them at the hospital (59), may act as buffer against

potential negative consequences of the CLP condition itself on children's psychological health. Indeed, children with a visible cleft (in Havstam's study a CL or a CLP) have been found to be more emotionally resilient, compared to children with a non-visible cleft (CPO), possibly due to the increased efforts made by parents and other adults in the children's growing environment (healthcare professionals, teachers) to protect them from psychological threats (60). These children may also have long standing contacts with treating Psychologists. Finally, stronger posttraumatic stress disorder symptoms in mothers who gave birth to a child with a cleft may be associated with stronger attachment bonds to the child later on (61), so it is possible that mothers who gave birth to children with a CLP perhaps suffered a more profound chock initially, but also developed stronger bonds to their children later on. While it is clear that the origins of this apparently paradoxical resilience needs to be further investigated, our findings suggest that children born with different OFC types experience different degrees of psychosocial difficulties during their development, and therefore, treating them as one clinical group will likely lead to erroneous conclusions, possibly overestimating the impact of one type of OFC (for example, viewing CLP as a more severe condition as it involves problems in more parameters) and underestimating the impact of another type (for example, CL on the basis that it involves problems in fewer parameters). The importance of such systematic sub-group differences as the ones demonstrated in the present study increases further as a result of the difficulties posed by the general subjective nature of experiencing and coping with a facial cleft, and the wide range of psychosocial consequences associated with these experiences (10). Both aesthetical concerns and speech impairments may lead to severe psychosocial challenges such as peer rejection, social isolation or bullying (62), but as treatment, training and psychosocial support during development must specifically address each of these two parameters separately, information that differentiates these parameters with respect to consequences is important. Also, the neuropsychological implications of the

different OFC types may be different, which may also be reflected on psychological well-being (63).

Our study has limitations. To begin with, while use of psychotropic medication is a clear indicator of poor psychological health, other possible treatments of poor mental health commonly used with children and adolescents, such as psychotherapeutic intervention, were not considered here as no information on such treatments was available in the databases. This may have resulted in an underestimation of poor mental health in all populations considered here. If, in addition, more OFC children have ongoing contacts with psychologists to whom they can turn when experiencing psychosocial problems, there is a risk that our analysis suffers differential information bias towards the 1, particularly for the CLP group.

Moreover, it is known that children with OFC malformations, particularly those born with a CLP or a CPO, suffer from a number of other pathologies (40) which are related both to OFCs and to an impaired psychological health in adolescence and might thus confound the association with use of Psychotropic drugs. To avoid this potential confounding, we adjusted for the presence of other significant malformations (OSMs) as defined and recorded by the Swedish National Board of Health and Welfare through standardized criteria, including most syndromes known to be associated with OFCs (44). Still, the OSM definition may be less exhaustive than more detailed follow-up studies (64). While most associated congenital defects can be detected by a physical examination at delivery and are therefore included in our definition of OSMs, some malformations, such as congenital heart malformations, might only present clinical symptoms later after delivery. Therefore, we cannot exclude that some confounding disorder was missed; particularly since the prevalence of OSMs found in our databases somewhat low, although not lower than reported elsewhere (31, 43).

Finally, our data included a small group of children for whom it was unclear what type of OFC they were suffering from (the "unspecified OFC" group). This group did not appear to suffer adverse consequences in the psychosocial sphere (OR=1.00, 95%CI: 0.61 – 1.64). It is

possible that the OFC in those cases was of minor importance and therefore, difficult to diagnose and not equally affecting the child. But it may also be the case that some of these children were actually born with both a cleft lip and a cleft palate, really belonging to the CLP group, further strengthening the idea that CLP does not constitute a risk for poor psychological health. Sensitivity analysis (i.e., assigning all these children to one subgroup at a time) in order to explore how our findings would have been affected if all children in the unspecified group were located into the CL, CLP or CPO group, respectively, revealed that the risk for consumption of psychotropic drugs in adolescence decreased for all three redefined groups, becoming (OR=1.31, 95%CI: 0.95 – 1.79) for the CL group, (OR=1.12, 95%CI: 0.82 – 1.53) for the CLP group and (OR=1.38, 95%CI: 1.09 – 1.75) for the CPO group. These results support the hypothesis that the OFC in the unspecified group was minor.

CONCLUSION

Suffering from an OFC malformation can increase the risk of impaired psychological health in adolescence, expressed by a higher use of psychotropic medication than the rest of the population. However, this association seems to be present only in adolescents suffering from a CL or a CPO and appears to be of less importance, if any, in adolescents who were born with a CLP. Hence, children with a CL and their parents may need to receive more attention than in current praxis, in order to assist a prevention of long term adverse consequences of the initial condition. Our findings have a clear theoretical impact for further research; if adolescents born with a CL react differently to their condition than those with a CLP, treating them as one group is likely to lead to misunderstandings concerning the needs of these patients and their families.

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AUTHOR CONTRIBUTIONS

Nilsson: Study conception and design, Analysis and interpretation of data, Drafting of manuscript

Merlo: Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript

Lyberg-Åhlander: Study conception and design, Analysis and interpretation of data

Psouni: Study conception and design, Analysis and interpretation of data, Drafting of manuscript, Critical revision of manuscript

COMPETING INTERESTS

None declared

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No additional data is available.

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Table 1 Characteristics of the population by presence of congenital OFC distinguishing between Cleft Lip (CL), Cleft Lip and Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC. All numbers are percentage unless otherwise indicated.

	No OFC	CL	CLP	CPO	Unspec. OFC
Child's characteristics					
Psychotropic drug use	7.2	10.5	8.5	11.6	7.5
Girls	48.6	34.0	28.0	55.4	41.2
Other Significant malformation	2.1	3.2	11.6	13.1	12.7
SGA	2.5	2.4	6.6	4.6	4.8
· Missing	0.2	0.0	0.0	0.6	0.9
Born in year					
· 1987	13.0	12.1	12.3	14.9	11.4
· 1988	13.9	10.1	11.9	11.1	15.4
· 1989	14.4	11.3	15.4	13.8	14.5
· 1990	15.1	15.8	15.1	14.4	15.4
· 1991	15.1	20.2	14.8	16.2	14.9
· 1992	14.7	16.2	15.1	15.3	18.4
· 1993	13.8	14.2	15.4	14.2	10.1
Maternal characteristics					
Smoking during pregnancy (cig/day)					
· No	70.9	67.2	67.6	68.1	69.7
· 1-9	14.4	13.4	14.8	12.5	14.9
· >9	8.7	13.8	10.7	13.1	8.3
· Missing	6.0	5.7	6.9	6.3	7.0

Age at delivery (years)					
· <20	2.5	2.8	3.1	2.2	3.5
· 20-24	22.6	21.1	25.2	22.5	21.1
· 25-29	38.3	42.1	39.3	36.0	40.4
· 30-34	25.5	25.1	19.2	24.5	25.4
· 35-39	9.4	7.7	10.1	13.5	8.3
· >39	1.7	1.2	3.1	1.3	1.3
Hospitalized with a congenital malformation	1.9	2.0	4.1	3.3	3.1

Table 2 Psychotropic drug use in childhood and adolescence by being born with a congenital OFC, distinguishing between Cleft Lip (CL), Cleft Lip And Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC.

	OR	95 % CI		OR	95 % CI	
Child's characteristics						
OFC						
· No OFC	1	(Reference)		1	(Reference)	
· CL	1.51	1.00	2.27	1.63	1.08	2.46
· CLP	1.19	0.80	1.77	1.21	0.81	1.80
· CPO	1.69	1.30	2.19	1.54	1.18	2.01
· Unspec. OFC	1.03	0.63	1.69	1.00	0.61	1.64
Girls vs. Boys				1.52	1.49	1.55
Other significant malformation (yes vs no)				1.48	1.40	1.57
SGA						
· No				1	(Reference)	
· Yes				1.22	1.15	1.29
· Missing				1.26	1.06	1.51
Born in year						
· 1987				2.52	2.43	2.63
· 1988				2.19	2.11	2.28
· 1989				2.00	1.92	2.09
· 1990				1.69	1.62	1.76
· 1991				1.40	1.34	1.46
· 1992				1.20	1.15	1.25

· 1993	1	(Reference)	
Maternal characteristics			
Smoking during pregnancy (cig/day)			
· No	1	(Reference)	
· 1-9	1.37	1.34	1.41
· >9	1.65	1.60	1.70
· Missing	1.23	1.19	1.28
Age at delivery (years)			
· <20	1	(Reference)	
· 20-24	0.68	0.65	0.72
· 25-29	0.58	0.55	0.61
· 30-34	0.57	0.54	0.60
· 35-39	0.63	0.60	0.67
· >=40	0.73	0.67	0.79
Hospitalized with a congenital malformation (yes vs no)	1.29	1.21	1.38

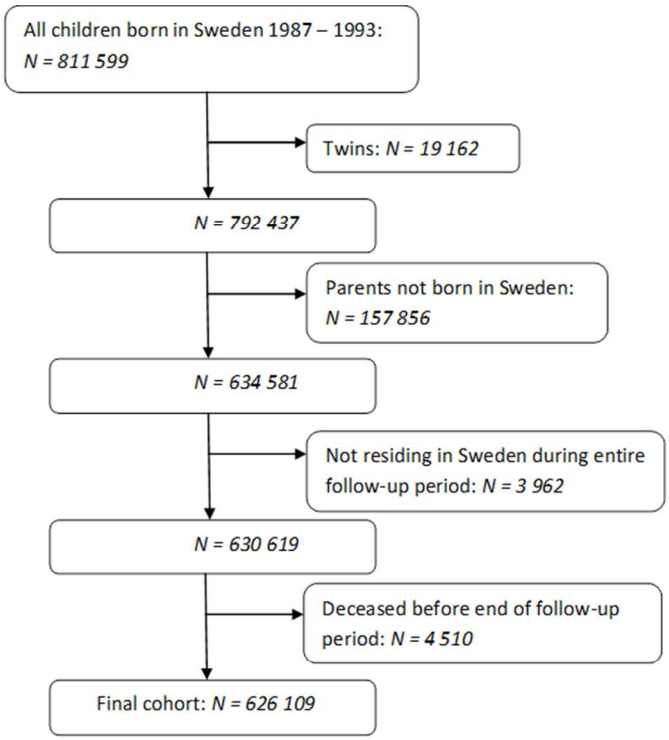

Figure 1 Study Population

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Psychotropic Drug Use in Adolescents Born with an Orofacial Cleft: A Population Based Study

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ABSTRACT

Objectives: Being born with an orofacial cleft (OFC) can, due to an incomplete closure of the lip and/or palate, convey a deviant speech and/or deviant facial aesthetics, which may in turn increase the risk for poor psychological health later in life. Previous investigations have been based on small samples and self-reports, not distinguishing between the three different types of OFC: Cleft Lip (CL), Cleft Lip and Palate (CLP), and Cleft Palate Only (CPO). Here, we present a large, population-based study, considering psychotropic drug use as proxy for poor psychological health and distinguishing between three different types of OFC.

Design and Methods: Using the *Swedish Medical Birth Register*, and linking to it the *Swedish Drug Prescription Register*, the *National Mortality Register*, the *Emigration Register* and the *National Inpatient Register*, we identified all singletons born to native mothers in Sweden 1987–1993, alive and residing in Sweden at the end of an 18-year follow-up period (N = 626 109). We compared psychotropic drug use among individuals with and without OFC during the individuals' adolescence (2005–2008) by multiple logistic regressions, using odds ratios (OR) with 95% confidence intervals (CI).

Results: When adjusted for potential confounders, having a CL (OR = 1.63, 95%CI: 1.08–2.46) or a CPO (OR = 1.54, 95%CI: 1.18–2.01) increased the risk of psychotropic drug use. Results were not conclusive regarding adolescents who had a CLP (OR = 1.21, 95%CI: 0.81–1.80).

Conclusions: Being born with a CL or a CPO increases the risk for psychotropic drug use in adolescence, but not for adolescents born with a CLP. Our findings suggest that, since the three OFC types are associated with different long term risks of poor psychological health, the three groups should be studied separately concerning long-term psychosocial consequences.

Strengths and Limitations of this Study

- Previous studies regarding the psychological health of adolescents born with an OFC have been based mainly on small samples and self-reported data and are therefore heterogeneous in their findings and limited in their generalizability. By contrast, the present study was based on epidemiological data from a large Medical Birth registry and assessment of risks for poor mental health associated with OFC was based on data on dispensed prescribed medication, rather than self-reports.
- While most research regards two subgroups of patients with facial clefts, Cleft Lip with or without Cleft Palate (CL/P) and Cleft Palate Only (CPO), the present study regards Cleft Lip (CL) and Cleft Lip and Palate (CLP) as two distinct subgroups. Importantly, results suggest that being born with a CPO, as well as with a CL, increases the risk for use of psychotropic drugs, compared to unaffected controls, but not for children born with a CLP.
- There is clinical significance in our findings: Children with a CL and their parents may need to receive more attention than in current praxis as usual, in order to assist a prevention of long term adverse consequences of the initial condition. In addition, if adolescents born with a CL react differently to their condition than those born with a CLP, treating CL and CLP as one group is likely to lead to misconceptions concerning the needs of these patients and their families.
- The present study regarded psychotropic drug use as proxy for poor mental health. This may have resulted in an underestimation of poor mental health among adolescents, as other, non-medical treatments were not considered.
- Children with OFC malformations may suffer from other pathologies that may also be associated with increased poor mental health. Despite statistical adjustment to avoid this confounding, it cannot be excluded that some confounding disorder was missed.

In Sweden, around two of 1,000 children are born with an orofacial cleft (OFC) (1), a condition characterized by an incomplete closure of the lip, upper jaw and/or palate (2). As being born with an OFC can be traumatic for a child and its parents (3-5), possibly negatively influencing his/her psychosocial development, several studies addressing psychological health in children and adolescents born with OFCs have been conducted (6-10). However, findings are diverse: While one study showed that maternal mental health affects the child's coping with her/his OFC (6), in another study the child seemed unaffected by the mother (11). Also, there is evidence that children with OFC suffer from psychosocial problems (12-14), but also evidence contradicting this notion (6, 15) and even a *more positive* self-concept among children with OFC, compared to controls, has been reported (16, 17). This heterogeneity may partly be due to methodological differences or limitations in the conducted studies. Most previous investigations are based on small samples, selected patient populations and self-reported information. As these limitations threaten generalizability, a need for larger, population-based studies has been expressed (18, 19).

Another possible explanation for this heterogeneity is that the three types of OFC, Cleft Lip (CL), Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO), are often considered together; particularly CL and CLP are treated as one group (CL/P). Nonetheless, what distinguishes these three conditions from each other has been shown to be of importance. In CL, facial aesthetics are affected, particularly the upper jaw and the nose, and there may be some impact on speech development (20). Yet, speech development is more strongly affected in children born with a CLP, as they also suffer from an incomplete closure of their palate (21), creating a characteristic, deviant speech termed "the cleft palate speech" (1, 7, 19). CLP can also lead to a hearing impairment and difficulties with breast feeding during infancy (22). These problems also affect children born with a CPO (23), but the aesthetic concerns are not equally strong as children in this group have a complete lip closure (24, 25).

Indeed, physical facial abnormalities and severity of speech impairment have been related to challenged psychosocial health in affected children (21, 26, 27), perhaps mediated by how the affected child is perceived by others (28, 29). Furthermore, how different types of OFC are related to psychological wellbeing may vary across development (17, 27). When the child is approaching adolescence, an emotionally turbulent period when peer acceptance becomes increasingly significant, both the speech impairment and the aesthetic concerns associated with OFC become increasingly important for the child's quality of life (4, 15, 27, 30).

Large population-based analysis produced little evidence that individuals with OFC are at increased risk for psychopathology of such nature and severity that it requires hospitalization (31). However, poor mental health can be suffered, with detrimental effects on wellbeing and quality of life, without any hospitalization being involved. In addition, to our knowledge, there are no large population-based studies investigating the impact of OFC on psychological health during adolescence, and there are no studies examining the different types of OFC separately. Therefore, the main aim of the present study was to improve our knowledge on the psychological health of adolescents affected by an OFC, trying to disentangle the effect of specific OFC malformations. Using the Swedish nation-wide healthcare registers, we conducted a large epidemiological study including all adolescents being born to native Swedish mothers between 1987 and 1993, who were alive and residing in Sweden at the end of a follow-up period (2005 – 2008). We investigated the use of psychotropic drugs in adolescence in relation to congenital OFC malformations, considering *use of psychotropic medication* as a surrogate of *impaired psychological health*. This approximation has been used previously (32, 33) and seems appropriate in a homogenous and accessible healthcare system as is the case in Sweden, and adequate for capturing a broad spectrum of poor mental health conditions that cannot be ignored but that may not require hospitalization.

METHODS

Participants and Procedures

We obtained a database derived from the *Swedish Medical Birth Register* linked to other national databases such as the *Swedish Drug Prescription Register*, the *National Mortality Register*, the *Emigration Register* and the *National Inpatient Register*. These registers, administered by Statistics Sweden and by the National Board of Health and Welfare, are linked using personal identification numbers assigned to each person residing in Sweden. In the data we received, identification numbers were replaced with arbitrary numbers, thereby securing anonymity. We identified all children born in Sweden during the period 1987 to 1993 (N = 811 599). As there is evidence of an underuse of psychotropic drugs in relation to the needs of adolescent descendants of migrant women (33), potentially confounding the outcomes' analysis in the current study, we excluded children of parents born outside Sweden. We also excluded children who were not singletons, died or emigrated from Sweden before the 31st of December 2008 (end of follow-up period). The final cohort consisted of 626 109 adolescents (Figure 1). The database used for the study was approved by a Regional Ethical Review Board.

<Insert Figure 1 about here>

Measures

Outcome variables

Orofacial cleft: We identified all children registered with an OFC in the Patient Register and/or in the Medical Birth Register, by their ICD-9 and/or ICD-10 diagnoses (WHO, 2011b), and categorized them into four subgroups: CL, CLP, CPO and Unspecified OFC. The ICD-codes for CL were 749B (ICD-9) and Q36 (ICD-10), for CLP the codes were 749C (ICD-9) and Q37 (ICD-10) and, finally, for CPO the codes were 749A and Q35 for ICD-9 and ICD-10 respectively. The "Unspecified OFC" group consisted of those cases where the type of OFC was not clear (for instance if more than one of the different types of OFC was registered for the same child or registered only with the ICD-9 code 749). In the analyses, we set children without any OFC as reference in the comparisons.

Psychotropic drugs: We obtained information about prescribed and dispensed psychotropic drugs from the Swedish Drug Prescription Register, which records standardized information on all prescribed drugs in open healthcare that are dispensed at pharmacies in Sweden. However, information on medication use within hospitals and nurse homes is not recorded in the PDR. We distinguished five categories of psychotropic drugs according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2011a): antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and psycho-stimulants (N06B). The register contains individual information on medication starting1st July 2005, which conditions the period of analysis for this study. We defined the outcome variable as at least one dispensed prescription (33) of any of these drugs during 1st July 2005 to 31st December 2008 (yes/no).

Other child characteristics

Birth year: We included birth years 1987 to 1993. Children born in 1993 were set as reference group for comparisons.

Sex: Girls are more at risk for CPO while boys are overrepresented among children born with a CL or a CLP (34). Also, girls are in general consuming more psychotropic drugs than boys (35). Therefore, we set boys as reference group for comparisons.

Small for Gestational Age (SGA): Babies born with a CLP or a CPO are more likely to be Small for Gestational Age (SGA) than children without any OFC (36), while being SGA is suggested to be related to impaired psychological health (37) later on. Thus, we identified children registered in the Medical Birth Registry as SGA (38) and dichotomized the variable into 'child being SGA' or 'child not being SGA'. Data were missing for a few cases (N= 1,417), which we recoded into a separate group 'missing'. We set 'Not SGA' as reference group for comparisons.

Other significant malformation (OSM): OFCs are often associated with other disorders (39-43). As these accompanying pathologies may increase the risk of impaired psychological health, we adjusted in our analyses for the presence of "Other significant malformation (OSM)" according to the definition provided by the Swedish National Board of Health and Welfare (44). The variable OSMs is computed by this authority following standardized criteria (44). Children that did not present any of these diagnoses in our registries were considered as the reference group in the comparisons.

Mother characteristics

Age at delivery: We classified maternal age at delivery into six groups (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, >39 years). Mother's age at delivery has been found to be a risk factor for giving birth to a child with an OFC (45); however this risk seems to differ with cleft type (46). Mother's age may also affect the risk for the offspring developing poor psychological health (47). We considered mothers younger than 20 years at the time for delivery as reference in the comparisons.

Smoking: Information regarding mother's self-reported smoking status was collected when she was first assigned to Antenatal Care (between 8th and 12th gestational week). Maternal smoking during pregnancy has been associated with giving birth to a child with an OFC (48, 49) and with behavioral difficulties in the child (50). We categorized smoking habits into four categories: 'no smoking', 'light smokers (1-9 cigarettes per day)', 'heavy smokers (>9 cigarettes per day)' and 'no information' where there were missing values (N = 37 477). The non-smoking group was considered as reference.

Congenital malformation: OFCs are to some extent genetic (51-53). Therefore, we identified mothers being admitted to hospital with any of the following diagnoses used to register congenital malformations: ICD 10-codes Q00-99 respectively ICD 9-codes 740-758. Mothers who were never admitted to hospital with one of those diagnoses were set as reference.

Statistical analysis

In a first step, we hypothesized and probed variables (confounders) that may be associated both with being born with an OFC (subgroups analyzed separately) and with prescription of psychotropic drugs. In cases where two variables showed multi-co-linearity, we selected the variable that provided a better goodness of fit by means of a chi-square test (e.g., Mother's age at delivery compared with Parity, where the latter one was excluded). Next, we applied logistic regression analysis in two consecutive models to investigate the association between the different types of OFC and the use of psychotropic drugs in adolescence. In the first model we investigated the bare association, i.e. before adjusting for potential confounders, between being born with an OFC and the use of psychotropic drugs in adolescence. In the second model (Table 1) we adjusted for potential confounders (i.e., Sex, Birth year, Other significant malformations, SGA, Maternal smoking, Mother's age at delivery and Mother congenital malformation) and obtained odds ratios (OR) and 95% confidence intervals (CI). Since the prevalence of congenital OFC anomalies is very low, the ORs are an appropriate approximation of the relative risk (RR) (54). We used IBM SPSS Statistics for Windows, Version 20.0, for the analyses.

RESULTS

Overall, 2.2 per thousand (1 334 out of 626 109) children were born with an OFC. Of those, 247 children were born with a CL, 318 with a CLP, 542 with a CPO, and 228 were born with an unspecified OFC. Table 1 summarises the characteristics of the population affected by an OFC and the population not affected. The proportion of children born with some type of OFC, compared to children born without an OFC, was roughly the same for all years (1987 – 1993). Children affected by a CLP, CPO and unspecified OFC, who were also SGA, were more likely to in addition have had other congenital malformations, but this was not the case for children with a CL. Girls were underrepresented in the CL, CLP and unspecified OFC groups but overrepresented in the CPO group.

<Insert Table 1 about here>

Concerning maternal characteristics, a higher percentage of mothers to children born with a CL or a CPO smoked heavily (over 9 cigarettes per day) during pregnancy, and more mothers of children born with CLP and CPO had been hospitalized with a congenital malformation. Also, there were fewer mothers older than 35 years of age among children born with a CL, for the CLP group there were fewer mothers in the age group 30-34 while the opposite pattern was observed for mothers to children born with a CPO (Table 1).

Table 2 presents the OR for using psychotropic drugs in relation to the presence of an OFC and in relation to possible confounders. In the unadjusted model it appeared that being born with a CPO increased the risk of using psychotropic drugs in adolescence, compared with individuals without an OFC. Furthermore, closer analysis revealed that the diagnostic subgroups behaved differently: Adolescents born with a CLP or with an unspecified OFC did not seem at a greater risk of being prescribed psychotropic medication, compared to unaffected controls, but the risk of being prescribed psychotropic medication was higher for adolescents born with a CL or a CPO. These results persisted after adjusting for confounders.

<Insert Table 2 about here>

When the analysis was repeated using the variables "malformations" and "other significant malformations" to exclude cases with other congenital abnormalities and syndromes, results persisted and were only slightly altered regarding the odds ratios: after adjusting for potential confounders, having a CL (OR = 1.60, 95%CI: 1.05–2.45) or a CPO (OR = 1.38, 95%CI: 1.02–1.87) still increased the risk of psychotropic drug use, while results were still not conclusive regarding adolescents with a CLP (OR = 1.13, 95%CI: 0.72–1.76).

DISCUSSION

Our analyses, based on a large population database covering the whole of Sweden, indicate that children born with a CPO or CL type of OFC are at a higher risk of using psychotropic

medication compared to unaffected children. Since use of psychotropic medication is a clear indicator of psychological health impairment, these findings suggest that those adolescents may be in higher risk for impaired mental health. Therefore, our analyses confirm previous findings that children born with an OFC have more difficulties in psychosocial adjustment, compared to their peers without such malformations (12-14). However, the closer follow-up of those children by medical providers may result in a higher rate of detection and medication treatment for psychiatric concerns, compared to detection rates in the general population.

Interestingly, our results indicate that this association is present in adolescents born with a CPO, consistently with other findings (31), and in adolescents born with a CL, but not in adolescents born with a CLP. Previous studies investigating facial disfigurement suggested that minor facial disfigurement can be more difficult to bear than more severe disfigurement (55), highlighting the fact that, in essence, the perceived gravity of facial disfigurement is a subjective matter (31, 56). It is important to note that, particularly the CL group has been often overlooked or mixed with the CLP group (24, 26, 31, 57, 58). Our findings that, using prescriptions of psychotropic drugs as proxy for poor psychological health, CL increases the risk of poor psychological health during adolescence while CLP does not, may be regarded as further support to other findings pointing to the subjective nature of experiencing and coping with facial cleft disfigurement of different kinds.

There are important clinical implications of these findings. Children born with a CL may need more attention from better informed health care staff, and closer monitoring over a long period of time, compared to current praxis. Also, parents to children born with a CL might need to receive more support and their concerns about their children's wellbeing may need to be addressed with equal gravity as parents' concerns when a child is born with other types of OFC. Specifically for children born with a CL, these issues have been insufficiently addressed in clinical praxis.

It may appear paradoxical that children born with a CLP do not seem to be more at risk of impaired psychological health during adolescence, considering that this type of OFC affects more parameters (i.e. both speech and facial aesthetics). However, the fact that children with a CLP receive more attention initially, both from healthcare services and from their parents, who tend to spend considerable time with them at the hospital (59), may act as buffer against potential negative consequences of the CLP condition itself on children's psychological health. Indeed, children with a visible cleft (in Havstam's study a CL or a CLP) have been found to be more emotionally resilient, compared to children with a non-visible cleft (CPO), possibly due to the increased efforts made by parents and other adults in the children's growing environment (healthcare professionals, teachers) to protect them from psychological threats (60). These children may also have long standing contacts with treating Psychologists. Finally, stronger posttraumatic stress disorder symptoms in mothers who gave birth to a child with a cleft may be associated with stronger attachment bonds to the child later on (61), so it is possible that mothers who gave birth to children with a CLP perhaps suffered a profound shock initially, but also developed strong bonds to their children later on. While it is clear that the origins of this apparently paradoxical resilience needs to be further investigated, our findings suggest that children born with different OFC types experience different degrees of psychosocial difficulties during their development, and therefore, treating them as one clinical group when the focus is on psychosocial outcomes may lead to erroneous conclusions, possibly overestimating the impact of one type of OFC (for example, viewing CLP as a more severe condition as it involves problems in more parameters) and underestimating the impact of another type (for example, CL on the basis that it involves problems in fewer parameters). The importance of such systematic sub-group differences as the ones demonstrated in the present study increases further because of the general subjective nature of experiencing and coping with a facial cleft, and the wide range of psychosocial consequences associated with these experiences (10). Both aesthetical concerns and speech impairments may lead to severe

psychosocial challenges such as peer rejection, social isolation or bullying (62), but as treatment, training and psychosocial support during development must specifically address each of these two parameters separately, information that differentiates these parameters with respect to consequences is important. Also, the neuropsychological implications of the different OFC types may be different, which may also be reflected on psychological well-being (63).

Our study has limitations. To begin with, while use of psychotropic medication is a clear indicator of poor psychological health, other possible treatments of poor mental health commonly used with children and adolescents, such as psychotherapeutic intervention, were not considered here as no information on such treatments was available in the databases. This may have resulted in an underestimation of poor mental health in all populations considered here. If, in addition, more OFC children have ongoing contacts with psychologists to whom they can turn when experiencing psychosocial problems, there is a risk that our analyses suffer differential information bias towards the 1, particularly for the CLP group.

Moreover, it is known that children with OFC malformations, particularly those born with a CLP or a CPO, suffer from a number of other pathologies (40) which are related both to OFCs and to an impaired psychological health in adolescence and might thus confound the association with use of Psychotropic drugs. To avoid this potential confounding, we adjusted for the presence of other significant malformations (OSMs) as defined and recorded by the Swedish National Board of Health and Welfare through standardized criteria, including most syndromes known to be associated with OFCs (44). Still, the OSM definition may be less exhaustive than more detailed follow-up studies (64). While most associated congenital defects can be detected by a physical examination at delivery and are therefore included in our definition of OSMs, some malformations, such as congenital heart malformations, might only present clinical symptoms later after delivery. Therefore, we cannot exclude that some confounding disorder was missed; particularly given the low prevalence of OSMs found in

our databases, although comparable to what has been reported elsewhere (31, 43). At the same time, although the percentage of children with birth defects is small at a population level, the fact that the population of children not born with an OFC wasn't restricted to children without other known birth defects may have resulted in residual confounding. Also, as all information used in this study was collected from registries using only the ICD-9 and the ICD-10 codes, and thus not confirmed by a geneticist in order to check the origin of the malformation as was done in other studies (65), it cannot be excluded that some cases were misclassified.

Finally, our data included a small group of children for whom it was unclear what type of OFC they were born with (the "unspecified OFC" group). This group did not appear to suffer adverse consequences in the psychosocial sphere (OR=1.00, 95%CI: 0.61 – 1.64). It is possible that the OFC in those cases was of minor importance and therefore, difficult to diagnose and not equally affecting the child.

CONCLUSION

Being born with an OFC malformation can increase the risk of impaired psychological health in adolescence. However, this increased risk seems to be present only in adolescents being born with a CL or a CPO and appears to be non-significant in adolescents born with a CLP. Hence, children with a CL and their parents may need to receive more attention than in current praxis, in order to assist a prevention of long term adverse consequences of the initial condition. Our findings have a clear theoretical impact for further research; if adolescents born with a CL react differently to their condition, in terms of psychosocial adjustment, than those with a CLP, treating them as one group is likely to lead to misunderstandings concerning the needs of these patients and their families.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

Nilsson: Study conception and design, Analysis and interpretation of data, Drafting of manuscript

Merlo: Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript

Lyberg-Åhlander: Study conception and design, Analysis and interpretation of data

Psouni: Study conception and design, Analysis and interpretation of data, Drafting of manuscript, Critical revision of manuscript

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Table 1 Characteristics of the population (N = 626 109) by presence of congenital OFC distinguishing between Cleft Lip (CL), Cleft Lip and Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC. All numbers are percentage unless otherwise indicated.

	No OFC	CL	CLP	CPO	Unspec. OFC
	N= 624 774	*N = 247*	*N = 318*	*N = 542*	*N = 228*
Child characteristics					
Psychotropic drug use in adolescence	7.2	10.5	8.5	11.6	7.5
Girls	48.6	34.0	28.0	55.4	41.2
Other Significant malformation	2.1	3.2	11.6	13.1	12.7
SGA	2.5	2.4	6.6	4.6	4.8
· Missing	0.2	0.0	0.0	0.6	0.9
Born in year					
· 1987	13.0	12.1	12.3	14.9	11.4
· 1988	13.9	10.1	11.9	11.1	15.4
· 1989	14.4	11.3	15.4	13.8	14.5
· 1990	15.1	15.8	15.1	14.4	15.4
· 1991	15.1	20.2	14.8	16.2	14.9
· 1992	14.7	16.2	15.1	15.3	18.4
· 1993	13.8	14.2	15.4	14.2	10.1
Maternal characteristics					
Smoking during pregnancy (cig/day)					
· No	70.9	67.2	67.6	68.1	69.7
· 1-9	14.4	13.4	14.8	12.5	14.9

· >9	8.7	13.8	10.7	13.1	8.3
· Missing	6.0	5.7	6.9	6.3	7.0
Age at delivery (years)					
· <20	2.5	2.8	3.1	2.2	3.5
· 20-24	22.6	21.1	25.2	22.5	21.1
· 25-29	38.3	42.1	39.3	36.0	40.4
· 30-34	25.5	25.1	19.2	24.5	25.4
· 35-39	9.4	7.7	10.1	13.5	8.3
· >39	1.7	1.2	3.1	1.3	1.3
Hospitalized with a congenital malformation	1.9	2.0	4.1	3.3	3.1

Table 2 Psychotropic drug use in adolescence by being born with an OFC, distinguishing between Cleft Lip (CL), Cleft Lip And Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC. Odds Ratios (OR) and 95 % Confidence Intervals (CI) of psychotropic drug use are presented. Adjusted model includes all variables.

Adolescent characteristics	*Unadjusted model*			*Adjusted model*		
	OR	95 % CI		OR	95 % CI	
OFC						
· No OFC	1	(Reference)		1	(Reference)	
· CL	1.51	1.00	2.27	1.63	1.08	2.46
· CLP	1.19	0.80	1.77	1.21	0.81	1.80
· CPO	1.69	1.30	2.19	1.54	1.18	2.01
· Unspec. OFC	1.03	0.63	1.69	1.00	0.61	1.64
Girls vs. Boys				1.52	1.49	1.55
Other significant malformation (yes vs no)				1.48	1.40	1.57
SGA						
· No				1	(Reference)	
· Yes				1.22	1.15	1.29
· Missing				1.26	1.06	1.51
Born in year						
· 1987				2.52	2.43	2.63
· 1988				2.19	2.11	2.28
· 1989				2.00	1.92	2.09
· 1990				1.69	1.62	1.76
· 1991				1.40	1.34	1.46

· 1992	1.20	1.15	1.25
· 1993	1	(Reference)	
Maternal characteristics			
Smoking during pregnancy(cig/day)			
· No	1	(Reference)	
· 1-9	1.37	1.34	1.41
· >9	1.65	1.60	1.70
· Missing	1.23	1.19	1.28
Age at delivery (years)			
· <20	1	(Reference)	
· 20-24	0.68	0.65	0.72
· 25-29	0.58	0.55	0.61
· 30-34	0.57	0.54	0.60
· 35-39	0.63	0.60	0.67
· >=40	0.73	0.67	0.79
Hospitalized with a congenital malformation (yes vs no)	1.29	1.21	1.38

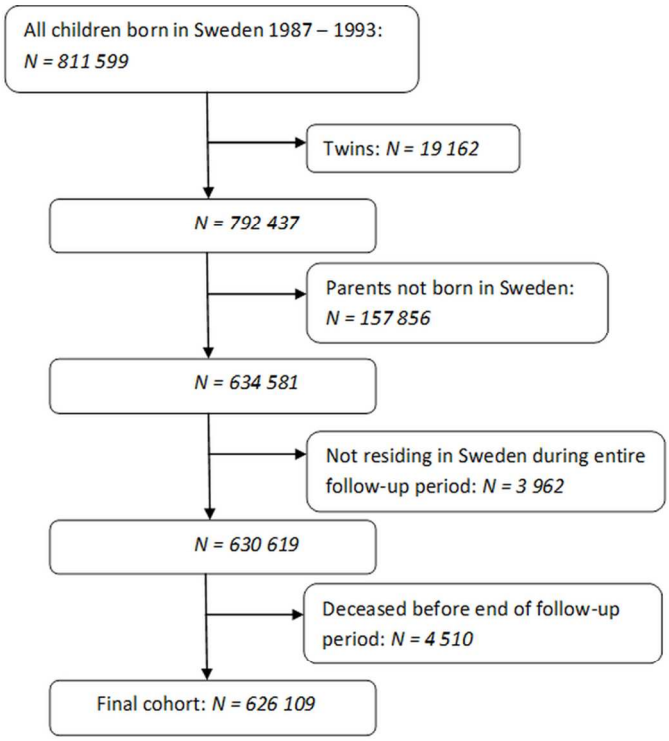

Figure 1 Study Population

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Psychotropic Drug Use in Adolescents Born With an Orofacial Cleft: A Population Based Study

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Psychotropic Drug Use in Adolescents Born with an Orofacial Cleft: A Population Based Study

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ABSTRACT

Objectives: Being born with an orofacial cleft (OFC) can, due to an incomplete closure of the lip and/or palate, convey a deviant speech and/or deviant facial aesthetics, which may in turn increase the risk for poor psychological health later in life. Previous investigations have been based on small samples and self-reports, not distinguishing between the three different types of OFC: Cleft Lip (CL), Cleft Lip and Palate (CLP), and Cleft Palate Only (CPO). Here, we present a large, population-based study, considering psychotropic drug use as proxy for poor psychological health and distinguishing between three different types of OFC.

Design and Methods: Using the *Swedish Medical Birth Register*, and linking to it the *Swedish Drug Prescription Register*, the *National Mortality Register*, the *Emigration Register* and the *National Inpatient Register*, we identified all singletons born to native mothers in Sweden 1987–1993, alive and residing in Sweden at the end of an 18-year follow-up period (N = 626 109). We compared psychotropic drug use among individuals with and without OFC during the individuals' adolescence (2005–2008) by multiple logistic regressions, using odds ratios (OR) with 95% confidence intervals (CI).

Results: When adjusted for potential confounders, having a CL (OR = 1.63, 95%CI: 1.08–2.46) or a CPO (OR = 1.54, 95%CI: 1.18–2.01) increased the risk of psychotropic drug use. Results were not significant regarding adolescents who had a CLP (OR = 1.21, 95%CI: 0.81–1.80).

Conclusions: Being born with a CL or a CPO increases the risk for psychotropic drug use in adolescence, but not for adolescents born with a CLP. Our findings suggest that, since the three OFC types are associated with different long term risks of poor psychological health, the three groups should be studied separately concerning long-term psychosocial consequences.

Strengths and Limitations of this Study

- Previous studies regarding the psychological health of adolescents born with an OFC have been based mainly on small samples and self-reported data and are therefore heterogeneous in their findings and limited in their generalizability. By contrast, the present study was based on epidemiological data from a large Medical Birth registry and assessment of risks for poor mental health associated with OFC was based on data on dispensed prescribed medication, rather than self-reports.
- While most research regards two subgroups of patients with facial clefts, Cleft Lip with or without Cleft Palate (CL/P) and Cleft Palate Only (CPO), the present study regards Cleft Lip (CL) and Cleft Lip and Palate (CLP) as two distinct subgroups. Importantly, results suggest that being born with a CPO, as well as with a CL, increases the risk for use of psychotropic drugs, compared to unaffected controls, but not for children born with a CLP.
- There is clinical significance in our findings: Children with a CL and their parents may need to receive more attention than in current praxis as usual, in order to assist a prevention of long term adverse consequences of the initial condition. In addition, if adolescents born with a CL react differently to their condition than those born with a CLP, treating CL and CLP as one group is likely to lead to misconceptions concerning the needs of these patients and their families.
- The present study regarded psychotropic drug use as proxy for poor mental health. This may have resulted in an underestimation of poor mental health among adolescents, as other, non-medical treatments were not considered.
- Children with OFC malformations may suffer from other pathologies that may also be associated with increased poor mental health. Despite statistical adjustment to avoid this confounding, it cannot be excluded that some confounding disorder was missed.

In Sweden, around two of 1,000 children are born with an orofacial cleft (OFC) (1), a condition characterized by an incomplete closure of the lip, upper jaw and/or palate (2). As being born with an OFC can be traumatic for a child and its parents (3-5), possibly negatively influencing his/her psychosocial development, several studies addressing psychological health in children and adolescents born with OFCs have been conducted (6-10). However, findings are diverse: While one study showed that maternal mental health affects the child's coping with her/his OFC (6), in another study the child seemed unaffected by the mother (11). Also, there is evidence that children with OFC suffer from psychosocial problems (12-14), but also evidence contradicting this notion (6, 15) and even a *more positive* self-concept among children with OFC, compared to controls, has been reported (16, 17). This heterogeneity may partly be due to methodological differences or limitations in the conducted studies. Most previous investigations are based on small samples, selected patient populations and self-reported information. As these limitations threaten generalizability, a need for larger, population-based studies has been expressed (18, 19).

Another possible explanation for this heterogeneity is that the three types of OFC, Cleft Lip (CL), Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO), are often considered together; particularly CL and CLP are treated as one group (CL/P). Nonetheless, what distinguishes these three conditions from each other has been shown to be of importance. In CL, facial aesthetics are affected, particularly the upper jaw and the nose, and there may be some impact on speech development (20). Yet, speech development is more strongly affected in children born with a CLP, as they also suffer from an incomplete closure of their palate (21), creating a characteristic, deviant speech termed "the cleft palate speech" (1, 7, 19). CLP can also lead to a hearing impairment and difficulties with breast feeding during infancy (22). These problems also affect children born with a CPO (23), but the aesthetic concerns are not equally strong as children in this group have a complete lip closure (24, 25).

Indeed, physical facial abnormalities and severity of speech impairment have been related to challenged psychosocial health in affected children (21, 26, 27), perhaps mediated by how the affected child is perceived by others (28, 29). Furthermore, how different types of OFC are related to psychological wellbeing may vary across development (17, 27). When the child is approaching adolescence, an emotionally turbulent period when peer acceptance becomes increasingly significant, both the speech impairment and the aesthetic concerns associated with OFC become increasingly important for the child's quality of life (4, 15, 27, 30).

Large population-based analysis produced little evidence that individuals with OFC are at increased risk for psychopathology of such nature and severity that it requires hospitalization (31). However, poor mental health can be suffered, with detrimental effects on wellbeing and quality of life, without any hospitalization being involved. In addition, to our knowledge, there are no large population-based studies investigating the impact of OFC on psychological health during adolescence, and there are no studies examining the different types of OFC separately. Therefore, the main aim of the present study was to improve our knowledge on the psychological health of adolescents affected by an OFC, trying to disentangle the effect of specific OFC malformations. Using the Swedish nation-wide healthcare registers, we conducted a large epidemiological study including all adolescents being born to native Swedish mothers between 1987 and 1993, who were alive and residing in Sweden at the end of a follow-up period (2005 – 2008). We investigated the use of psychotropic drugs in adolescence in relation to congenital OFC malformations, considering *use of psychotropic medication* as a surrogate of *impaired psychological health*. This approximation has been used previously (32, 33) and seems appropriate in a homogenous and accessible healthcare system as is the case in Sweden, and adequate for capturing a broad spectrum of poor mental health conditions that cannot be ignored but that may not require hospitalization.

METHODS

Participants and Procedures

We obtained a database derived from the *Swedish Medical Birth Register* linked to other national databases such as the *Swedish Drug Prescription Register*, the *National Mortality Register*, the *Emigration Register* and the *National Inpatient Register*. These registers, administered by Statistics Sweden and by the National Board of Health and Welfare, are linked using personal identification numbers assigned to each person residing in Sweden. In the data we received, identification numbers were replaced with arbitrary numbers, thereby securing anonymity. We identified all children born in Sweden during the period 1987 to 1993 (N = 811 599). As there is evidence of an underuse of psychotropic drugs in relation to the needs of adolescent descendants of migrant women (33), potentially confounding the outcomes' analysis in the current study, we excluded children of parents born outside Sweden. We also excluded children who were not singletons, died or emigrated from Sweden before the 31st of December 2008 (end of follow-up period). The final cohort consisted of 626 109 adolescents (Figure 1). The database used for the study was approved by a Regional Ethical Review Board.

<Insert Figure 1 about here>

Measures

Outcome variables

Orofacial cleft: We identified all children registered with an OFC in the Patient Register and/or in the Medical Birth Register, by their ICD-9 and/or ICD-10 diagnoses (WHO, 2011b), and categorized them into four subgroups: CL, CLP, CPO and Unspecified OFC. The ICD-codes for CL were 749B (ICD-9) and Q36 (ICD-10), for CLP the codes were 749C (ICD-9) and Q37 (ICD-10) and, finally, for CPO the codes were 749A and Q35 for ICD-9 and ICD-10 respectively. The "Unspecified OFC" group consisted of those cases where the type of OFC was not clear (for instance if more than one of the different types of OFC was registered for the same child or registered only with the ICD-9 code 749). In the analyses, we set children without any OFC as reference in the comparisons.

Psychotropic drugs: We obtained information about prescribed and dispensed psychotropic drugs from the Swedish Drug Prescription Register, which records standardized information on all prescribed drugs in open healthcare that are dispensed at pharmacies in Sweden. However, information on medication use within hospitals and nurse homes is not recorded in the PDR. We distinguished five categories of psychotropic drugs according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2011a): antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and psycho-stimulants (N06B). The register contains individual information on medication starting1st July 2005, which conditions the period of analysis for this study. We defined the outcome variable as at least one dispensed prescription (33) of any of these drugs during 1st July 2005 to 31st December 2008 (yes/no).

Other child characteristics

Birth year: We included birth years 1987 to 1993. Children born in 1993 were set as reference group for comparisons.

Sex: Girls are more at risk for CPO while boys are overrepresented among children born with a CL or a CLP (34). Also, girls are in general consuming more psychotropic drugs than boys (35). Therefore, we set boys as reference group for comparisons.

Small for Gestational Age (SGA): Babies born with a CLP or a CPO are more likely to be Small for Gestational Age (SGA) than children without any OFC (36), while being SGA is suggested to be related to impaired psychological health (37) later on. Thus, we identified children registered in the Medical Birth Registry as SGA (38) and dichotomized the variable into 'child being SGA' or 'child not being SGA'. Data were missing for a few cases (N= 1,417), which we recoded into a separate group 'missing'. We set 'Not SGA' as reference group for comparisons.

Other significant malformation (OSM): OFCs are often associated with other disorders (39-43). As these accompanying pathologies may increase the risk of impaired psychological health, we adjusted in our analyses for the presence of "Other significant malformation (OSM)" according to the definition provided by the Swedish National Board of Health and Welfare (44). The variable OSMs is computed by this authority following standardized criteria (44). Children that did not present any of these diagnoses in our registries were considered as the reference group in the comparisons.

Mother characteristics

Age at delivery: We classified maternal age at delivery into six groups (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, >39 years). Mother's age at delivery has been found to be a risk factor for giving birth to a child with an OFC (45); however this risk seems to differ with cleft type (46). Mother's age may also affect the risk for the offspring developing poor psychological health (47). We considered mothers younger than 20 years at the time for delivery as reference in the comparisons.

Smoking: Information regarding mother's self-reported smoking status was collected when she was first assigned to Antenatal Care (between 8th and 12th gestational week). Maternal smoking during pregnancy has been associated with giving birth to a child with an OFC (48, 49) and with behavioral difficulties in the child (50). We categorized smoking habits into four categories: 'no smoking', 'light smokers (1-9 cigarettes per day)', 'heavy smokers (>9 cigarettes per day)' and 'no information' where there were missing values (N = 37 477). The non-smoking group was considered as reference.

Congenital malformation: OFCs are to some extent genetic (51-53). Therefore, we identified mothers being admitted to hospital with any of the following diagnoses used to register congenital malformations: ICD 10-codes Q00-99 respectively ICD 9-codes 740-758. Mothers who were never admitted to hospital with one of those diagnoses were set as reference.

Statistical analysis

In a first step, we hypothesized and probed variables (confounders) that may be associated both with being born with an OFC (subgroups analyzed separately) and with prescription of psychotropic drugs. In cases where two variables showed multi-co-linearity, we selected the variable that provided a better goodness of fit by means of a chi-square test (e.g., Mother's age at delivery compared with Parity, where the latter one was excluded). Next, we applied logistic regression analysis in two consecutive models to investigate the association between the different types of OFC and the use of psychotropic drugs in adolescence. In the first model we investigated the bare association, i.e. before adjusting for potential confounders, between being born with an OFC and the use of psychotropic drugs in adolescence. In the second model (Table 1) we adjusted for potential confounders (i.e., Sex, Birth year, Other significant malformations, SGA, Maternal smoking, Mother's age at delivery and Mother congenital malformation) and obtained odds ratios (OR) and 95% confidence intervals (CI). Since the prevalence of congenital OFC anomalies is very low, the ORs are an appropriate approximation of the relative risk (RR) (54). We used IBM SPSS Statistics for Windows, Version 20.0, for the analyses.

RESULTS

Overall, 2.2 per thousand (1 334 out of 626 109) children were born with an OFC. Of those, 247 children were born with a CL, 318 with a CLP, 542 with a CPO, and 228 were born with an unspecified OFC. Table 1 summarises the characteristics of the population affected by an OFC and the population not affected. The proportion of children born with some type of OFC, compared to children born without an OFC, was roughly the same for all years (1987 – 1993). Children affected by a CLP, CPO and unspecified OFC, who were also SGA, were more likely to in addition have had other congenital malformations, but this was not the case for children with a CL. Girls were underrepresented in the CL, CLP and unspecified OFC groups but overrepresented in the CPO group.

<Insert Table 1 about here>

Concerning maternal characteristics, a higher percentage of mothers to children born with a CL or a CPO smoked heavily (over 9 cigarettes per day) during pregnancy, and more mothers of children born with CLP and CPO had been hospitalized with a congenital malformation. Also, there were fewer mothers older than 35 years of age among children born with a CL, for the CLP group there were fewer mothers in the age group 30-34 while the opposite pattern was observed for mothers to children born with a CPO (Table 1).

Table 2 presents the OR for using psychotropic drugs in relation to the presence of an OFC and in relation to possible confounders. In the unadjusted model it appeared that being born with a CPO increased the risk of using psychotropic drugs in adolescence, compared with individuals without an OFC. Furthermore, closer analysis revealed that the diagnostic subgroups behaved differently: Adolescents born with a CLP or with an unspecified OFC did not seem at a greater risk of being prescribed psychotropic medication, compared to unaffected controls, but the risk of being prescribed psychotropic medication was higher for adolescents born with a CL or a CPO. These results persisted after adjusting for confounders.

<Insert Table 2 about here>

When the analysis was repeated using the variables "malformations" and "other significant malformations" to exclude cases with other congenital abnormalities and syndromes, results persisted and were only slightly altered regarding the odds ratios: after adjusting for potential confounders, having a CL (OR = 1.60, 95%CI: 1.05–2.45) or a CPO (OR = 1.38, 95%CI: 1.02–1.87) still increased the risk of psychotropic drug use, while results were still not conclusive regarding adolescents with a CLP (OR = 1.13, 95%CI: 0.72–1.76).

DISCUSSION

Our analyses, based on a large population database covering the whole of Sweden, indicate that children born with a CPO or CL type of OFC are at a higher risk of using psychotropic

medication compared to unaffected children. Since use of psychotropic medication is a clear indicator of psychological health impairment, these findings suggest that those adolescents may be in higher risk for impaired mental health. Therefore, our analyses confirm previous findings that children born with an OFC have more difficulties in psychosocial adjustment, compared to their peers without such malformations (12-14). However, the closer follow-up of those children by medical providers may result in a higher rate of detection and medication treatment for psychiatric concerns, compared to detection rates in the general population.

Interestingly, our results indicate that this association is present in adolescents born with a CPO, consistently with other findings (31), and in adolescents born with a CL, but not in adolescents born with a CLP. Previous studies investigating facial disfigurement suggested that minor facial disfigurement can be more difficult to bear than more severe disfigurement (55), highlighting the fact that, in essence, the perceived gravity of facial disfigurement is a subjective matter (31, 56). It is important to note that, particularly the CL group has been often overlooked or mixed with the CLP group (24, 26, 31, 57, 58). Our findings that, using prescriptions of psychotropic drugs as proxy for poor psychological health, CL increases the risk of poor psychological health during adolescence while CLP does not, may be regarded as further support to other findings pointing to the subjective nature of experiencing and coping with facial cleft disfigurement of different kinds.

There are important clinical implications of these findings. Children born with a CL may need more attention from better informed health care staff, and closer monitoring over a long period of time, compared to current praxis. Also, parents to children born with a CL might need to receive more support and their concerns about their children's wellbeing may need to be addressed with equal gravity as parents' concerns when a child is born with other types of OFC. Specifically for children born with a CL, these issues have been insufficiently addressed in clinical praxis.

It may appear paradoxical that children born with a CLP do not seem to be more at risk of impaired psychological health during adolescence, considering that this type of OFC affects more parameters (i.e. both speech and facial aesthetics). However, the fact that children with a CLP receive more attention initially, both from healthcare services and from their parents, who tend to spend considerable time with them at the hospital (59), may act as buffer against potential negative consequences of the CLP condition itself on children's psychological health. Indeed, children with a visible cleft (in Havstam's study a CL or a CLP) have been found to be more emotionally resilient, compared to children with a non-visible cleft (CPO), possibly due to the increased efforts made by parents and other adults in the children's growing environment (healthcare professionals, teachers) to protect them from psychological threats (60). These children may also have long standing contacts with treating Psychologists. Finally, stronger posttraumatic stress disorder symptoms in mothers who gave birth to a child with a cleft may be associated with stronger attachment bonds to the child later on (61), so it is possible that mothers who gave birth to children with a CLP perhaps suffered a profound shock initially, but also developed strong bonds to their children later on. While it is clear that the origins of this apparently paradoxical resilience needs to be further investigated, our findings suggest that children born with different OFC types experience different degrees of psychosocial difficulties during their development, and therefore, treating them as one clinical group when the focus is on psychosocial outcomes may lead to erroneous conclusions, possibly overestimating the impact of one type of OFC (for example, viewing CLP as a more severe condition as it involves problems in more parameters) and underestimating the impact of another type (for example, CL on the basis that it involves problems in fewer parameters). The importance of such systematic sub-group differences as the ones demonstrated in the present study increases further because of the general subjective nature of experiencing and coping with a facial cleft, and the wide range of psychosocial consequences associated with these experiences (10). Both aesthetical concerns and speech impairments may lead to severe

psychosocial challenges such as peer rejection, social isolation or bullying (62), but as treatment, training and psychosocial support during development must specifically address each of these two parameters separately, information that differentiates these parameters with respect to consequences is important. Also, the neuropsychological implications of the different OFC types may be different, which may also be reflected on psychological well-being (63).

Our study has limitations. To begin with, while use of psychotropic medication is a clear indicator of poor psychological health, other possible treatments of poor mental health commonly used with children and adolescents, such as psychotherapeutic intervention, were not considered here as no information on such treatments was available in the databases. This may have resulted in an underestimation of poor mental health in all populations considered here. If, in addition, more OFC children have ongoing contacts with psychologists to whom they can turn when experiencing psychosocial problems, there is a risk that our analyses suffer differential information bias towards the 1, particularly for the CLP group.

Moreover, it is known that children with OFC malformations, particularly those born with a CLP or a CPO, suffer from a number of other pathologies (40) which are related both to OFCs and to an impaired psychological health in adolescence and might thus confound the association with use of Psychotropic drugs. To avoid this potential confounding, we adjusted for the presence of other significant malformations (OSMs) as defined and recorded by the Swedish National Board of Health and Welfare through standardized criteria, including most syndromes known to be associated with OFCs (44). Still, the OSM definition may be less exhaustive than more detailed follow-up studies (64). While most associated congenital defects can be detected by a physical examination at delivery and are therefore included in our definition of OSMs, some malformations, such as congenital heart malformations, might only present clinical symptoms later after delivery. Therefore, we cannot exclude that some confounding disorder was missed; particularly given the low prevalence of OSMs found in

our databases, although comparable to what has been reported elsewhere (31, 43). At the same time, although the percentage of children with birth defects is small at a population level, the fact that the population of children not born with an OFC wasn't restricted to children without other known birth defects may have resulted in residual confounding. Also, as all information used in this study was collected from registries using only the ICD-9 and the ICD-10 codes, and thus not confirmed by a geneticist in order to check the origin of the malformation as was done in other studies (65), it cannot be excluded that some cases were misclassified.

Finally, our data included a small group of children for whom it was unclear what type of OFC they were born with (the "unspecified OFC" group). This group did not appear to suffer adverse consequences in the psychosocial sphere (OR=1.00, 95%CI: 0.61 – 1.64). It is possible that the OFC in those cases was of minor importance and therefore, difficult to diagnose and not equally affecting the child.

CONCLUSION

Being born with an OFC malformation can increase the risk of impaired psychological health in adolescence. However, this increased risk seems to be present only in adolescents being born with a CL or a CPO and appears to be non-significant in adolescents born with a CLP. Hence, children with a CL and their parents may need to receive more attention than in current praxis, in order to assist a prevention of long term adverse consequences of the initial condition. Our findings have a clear theoretical impact for further research; if adolescents born with a CL react differently to their condition, in terms of psychosocial adjustment, than those with a CLP, treating them as one group is likely to lead to misunderstandings concerning the needs of these patients and their families.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

Nilsson: Study conception and design, Analysis and interpretation of data, Drafting of manuscript

Merlo: Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript

Lyberg-Åhlander: Study conception and design, Analysis and interpretation of data

Psouni: Study conception and design, Analysis and interpretation of data, Drafting of manuscript, Critical revision of manuscript

DATA SHARING

No additional data is available.

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Table 1 Characteristics of the population (N = 626 109) by presence of congenital OFC distinguishing between Cleft Lip (CL), Cleft Lip and Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC. All numbers are percentage unless otherwise indicated.

	No OFC	CL	CLP	CPO	Unspec. OFC
	N= 624 774	*N = 247*	*N = 318*	*N = 542*	*N = 228*
Child characteristics					
Psychotropic drug use in adolescence	7.2	10.5	8.5	11.6	7.5
Girls	48.6	34.0	28.0	55.4	41.2
Other Significant malformation	2.1	3.2	11.6	13.1	12.7
SGA	2.5	2.4	6.6	4.6	4.8
· Missing	0.2	0.0	0.0	0.6	0.9
Born in year					
· 1987	13.0	12.1	12.3	14.9	11.4
· 1988	13.9	10.1	11.9	11.1	15.4
· 1989	14.4	11.3	15.4	13.8	14.5
· 1990	15.1	15.8	15.1	14.4	15.4
· 1991	15.1	20.2	14.8	16.2	14.9
· 1992	14.7	16.2	15.1	15.3	18.4
· 1993	13.8	14.2	15.4	14.2	10.1
Maternal characteristics					
Smoking during pregnancy (cig/day)					
· No	70.9	67.2	67.6	68.1	69.7
· 1-9	14.4	13.4	14.8	12.5	14.9

· >9	8.7	13.8	10.7	13.1	8.3
· Missing	6.0	5.7	6.9	6.3	7.0
Age at delivery (years)					
· <20	2.5	2.8	3.1	2.2	3.5
· 20-24	22.6	21.1	25.2	22.5	21.1
· 25-29	38.3	42.1	39.3	36.0	40.4
· 30-34	25.5	25.1	19.2	24.5	25.4
· 35-39	9.4	7.7	10.1	13.5	8.3
· >39	1.7	1.2	3.1	1.3	1.3
Hospitalized with a congenital malformation	1.9	2.0	4.1	3.3	3.1

Table 2 Psychotropic drug use in adolescence by being born with an OFC, distinguishing between Cleft Lip (CL), Cleft Lip And Palate (CLP), Cleft Palate Only (CPO) and Unspecified OFC. Odds Ratios (OR) and 95 % Confidence Intervals (CI) of psychotropic drug use are presented. Adjusted model[1] includes all variables.

Adolescent characteristics	*Unadjusted model*			*Adjusted model*		
	OR	95 % CI		OR	95 % CI	
OFC						
· No OFC	1	(Reference)		1	(Reference)	
· CL	1.51	1.00	2.27	1.63	1.08	2.46
· CLP	1.19	0.80	1.77	1.21	0.81	1.80
· CPO	1.69	1.30	2.19	1.54	1.18	2.01
· Unspec. OFC	1.03	0.63	1.69	1.00	0.61	1.64
Girls vs. Boys				1.52	1.49	1.55
Other significant malformation (yes vs no)				1.48	1.40	1.57
SGA						
· No				1	(Reference)	
· Yes				1.22	1.15	1.29
· Missing				1.26	1.06	1.51
Born in year						
· 1987				2.52	2.43	2.63
· 1988				2.19	2.11	2.28
· 1989				2.00	1.92	2.09
· 1990				1.69	1.62	1.76
· 1991				1.40	1.34	1.46

· 1992	1.20	1.15	1.25
· 1993	1	(Reference)	
Maternal characteristics			
Smoking during pregnancy (cig/day)			
· No	1	(Reference)	
· 1-9	1.37	1.34	1.41
· >9	1.65	1.60	1.70
· Missing	1.23	1.19	1.28
Age at delivery (years)			
· <20	1	(Reference)	
· 20-24	0.68	0.65	0.72
· 25-29	0.58	0.55	0.61
· 30-34	0.57	0.54	0.60
· 35-39	0.63	0.60	0.67
· >=40	0.73	0.67	0.79
Hospitalized with a congenital malformation (yes vs no)	1.29	1.21	1.38

[1] In the adjusted model we adjusted for Sex, Birth year, Other significant malformations, SGA, Maternal smoking, Mother's age at delivery and Mother congenital malformation.

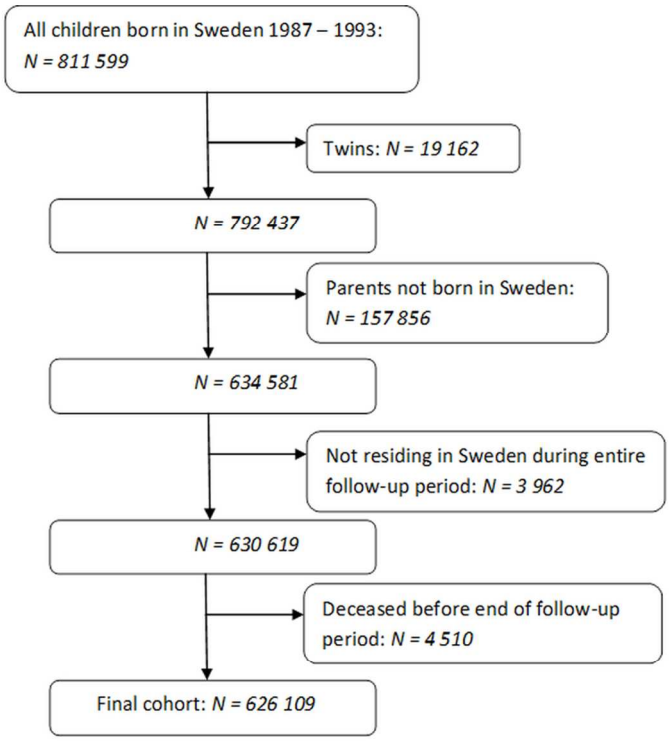

Figure 1 Study Population

90x119mm (300 x 300 DPI)