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Use of Psychotropic Medications and Visits to Psychiatrists and Psychologists among Individuals with Non-Syndromic Oral Clefts: A Population-Based Cohort Study

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Abstract

Background—Oral clefts (OC) are among the most common congenital malformations and can have a large impact on the life of the affected individual. Research findings regarding the psychological and psychosocial consequences of OC are inconclusive.

Methods—Using Danish nationwide registers we investigated redeemed prescriptions of psychotropic medication 1996–2012 and visits to psychiatrists and psychologists 1996–2011 among individuals born with non-syndromic OC in Denmark 1936–2009 and a comparison cohort of individuals without OC. This includes 8,244 individuals with OC and 82,665 individuals without OC.

Results—Cox-regression analysis revealed 12% (95%CI: 7%–16%) increased risk of using any psychotropic medication for individuals with OC. When examining by cleft type, higher risks for medication use were observed in individuals with cleft lip and palate (CLP) or cleft palate only (CP). The largest increased relative risk was found for use of antipsychotics and stimulants for individuals with CP followed by use of antipsychotics for individuals with CLP. We found increased risk of visits to psychiatrists for individuals with CP and no increased risk for visits to psychologists for either group.

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Conclusions—This study indicates that a small group of individuals with non-syndromic OC, in particular those with palatal involvement, have greater risk of using psychotropic medications. Elevated use was however also observed among younger individuals with cleft lip only. There seems to be only a modest increase in visits to health professionals for psychological reasons. Undiagnosed syndromes, e.g. 22q11 deletion syndrome, may however contribute to an overestimation of the associations.

Introduction

Non-syndromic oral clefts (OC) include cleft lip only (CL), cleft lip and cleft palate (CLP) and cleft palate only (CP) with no other major physical or developmental anomalies or syndrome and are among the most common congenital malformations. Depending on the type and severity of the cleft, children with oral clefts may have feeding problems, experience stress related to surgical treatment, and often have long term orthodontic care and speech therapy throughout childhood and into adolescence. Studies have reported increased dissatisfaction with speech and appearance and increased rates of peers' teasing among individuals with non-syndromic OC (Marcusson et al., 2002; Hunt et al., 2006; Hunt et al., 2007). Some studies have also reported that children with non-syndromic OC have lower academic performance on average (Persson et al., 2012; Knight et al., 2014; Wehby et al., 2014; Wehby et al., 2015), although such deficits have only been observed for children with CP in Denmark (Clausen et al., 2016). Since physical appearance, communication skills, and academic achievement play a major role in the social life and interaction with others, individuals with OC might be at risk of developing social problems which might result in mental health problems. Studies have shown associations between teasing, dissatisfaction with appearance and depressive symptoms in individuals with OC (Marcusson et al., 2002; Feragen and Stock, 2016). Individuals with both cleft lip and cleft palate may be at greater risk of depression from these effects, especially those with bilateral clefts of the lip. Higher levels of depression have been reported among children with bilateral CLP than those with unilateral CLP (Millard and Richman, 2001). Lower marriage rates have been reported among individuals with CLP, especially if the CLP is bilateral (Ramstad et al., 1995).

We have previously studied psychiatric diagnoses at Danish psychiatric hospitals and found an elevated risk of psychiatric disorders for individuals with CLP and CP, but not for individuals with CL (Pedersen et al., 2016). The increased risks were found for schizophrenia-like disorders, mental retardation and pervasive developmental disorders for individuals with CLP and CP and for behavioral and emotional disorders (including hyperkinetic disorder) for individuals with CP. These findings are consistent with neuroimaging studies that have reported increased rates of midline brain anomalies among males with non-syndromic OC (Nopoulos et al., 2001; Weinberg et al., 2013) which in other studies have been associated with schizophrenia, developmental delay and mental retardation (Nopoulos et al., 1997; Bodensteiner et al., 1998; Landin-Romero et al., 2016). They are also consistent with reports of increased frequency of CP among patients with schizophrenia (Gourion et al., 2004) and increased rates of hyperactivity, impulsivity and inattention in boys with OC (Nopoulos et al., 2010; Wehby et al., 2012). However, there was no evidence from this recent work for any increased risk of mood disorders and anxiety-related disorders (Pedersen et al, 2016), which is in line with studies finding no or minimal

differences in overall psychological functioning of individuals with non-syndromic OC (Collett et al., 2012; Lima et al., 2015) but inconsistent with studies reporting individuals with OC to have reduced quality of life (Wehby and Cassell, 2010; Ward et al., 2013), increased rates of depression and anxiety in children (Hunt et al., 2006; Hunt et al., 2007; Murray et al., 2010; Demir et al., 2011) and increased risk of separation anxiety in children (Tyler et al., 2013).

One weakness of work focusing on diagnoses at psychiatric hospitals is overrepresentation of severe psychiatric disorders requiring hospitalizations and underrepresentation of less severe mental health problems like milder anxiety disorders and mild to moderate depression which are disorders that would generally be treated in the primary health care system. A recent study that investigated psychotropic drug use in adolescence using Swedish national registers and captured non-hospitalized cases found increased medication use for adolescents with CL and CP but not for individuals with CLP (Nilsson et al., 2015). That study, however, only included adolescents, and did not investigate specific types of psychotropic medications to further understand medication use patterns and underlying illnesses. They also did not examine visits to psychiatrists and psychologists. To our knowledge, only one other population-based study investigated medication use among individuals with oral clefts (Pedersen et al., 2015). In this study we compared use of health services and medication use of individuals with oral clefts to their siblings using register data from Denmark and found an increase in the likelihood of taking medications especially for children and adults with CLP. When examining general drug groups, the study showed an increase in taking drugs associated with the nervous system particularly among adults with CLP or CP; that analysis however did not examine specific types of psychotropic medications. Pedersen et al (2015) also reported increased likelihood of visiting specialist physician visits for children and adults with CLP or CP, but did not separate into type of health professional. Furthermore, data were limited to 2005.

The aim of this study was to investigate use of psychotropic medications and visits to psychiatrists and psychologists among individuals with non-syndromic OC compared to a cohort of the general population of individuals without OC, matched by birth year and sex. We used four Danish nationwide registers providing data on psychotropic medications between 1996 and 2012 and visits to psychiatrists and psychologists between 1996 and 2011. Our datasets include data from multiple settings including the primary national healthcare system in Denmark, where the out-of-pocket cost is minimal, and capture both mild mental health problems as well as severe ones. Our study provides one of the largest samples and longest follow-up periods to date for studying mental health and use of mental treatments among individuals with OC in a population-based setting. These strengths, combined with a detailed analysis of specific types of psychotropic medications and clefts not only across the three types of CL, CLP, and CP but also by cleft severity, make our study unique in its capacity and in its contribution to the literature.

Materials and Methods

Data sources

This population-based cohort study was based on a linkage of the following four Danish nationwide registers:

The Danish Facial Cleft Register (DFCR) encompasses individuals born with OC in Denmark in the period 1936 to 2009. Throughout the period there is high ascertainment for the complete cohort and in the period 1983 to 1987 the ascertainment for CL(P) has been found to be 99% (Christensen et al., 1992). OC such as submucous CP that may be discovered after infancy are also included. The register includes information on cleft type and severity of the cleft, including separate categories for unilateral or bilateral clefts of the lip as well as cleft laterality (right or left side) for unilateral cases. For CP, it is registered whether the cleft palate is submucous, in the soft palate only, or both the soft and the hard palate. Microforms such as bifid uvula are not included in the DFCR. Information on associated anomalies are also registered and classified into major or minor depending on whether the anomaly is likely to be part of a syndrome. In the DFCR, non-syndromic OC is defined as individuals with no major associated anomalies and no more than 2 minor associated anomalies. The number of associated anomalies was likely to be underestimated in the birth cohorts 1936–1987 since only anomalies/syndromes identified at birth or in infancy are registered (Christensen et al., 1992), but in the later birth cohorts medical records have been reviewed to obtain more comprehensive information on associated anomalies. In the DFCR, 11% of the individuals with CL(P) and 32% of the individuals with CP are registered as syndromic. The register is described in further detail elsewhere (Christensen, 1999; Bille et al., 2005).

The Danish Civil Registration System (CRS) was established for administrative purposes in 1968, when all persons alive and living in Denmark were registered and assigned a unique personal identification number, which enables unambiguous linkage of all national registers in Denmark. Since then all persons with permanent residence in Denmark are registered. The CRS includes basic variables like birth registration code, sex, date of birth, date of death, and continuously updated information on date and place of residence. The accuracy of the information is generally accepted to be high (Pedersen et al., 2006; Pedersen, 2011).

The Danish National Prescription Registry (DNPR) contains information on all prescription drugs dispensed at Danish community pharmacies since 1994. Until 1996, drugs prescribed for children under age 16 were registered in the personal identification number of the mother or father, which implies that before 1996 it is not possible to distinguish if these were prescribed for the child or the parents, and therefore the present study only used prescription drugs dispensed from 1996 and onwards. Only redeemed medications that were prescribed in the primary health care system (i.e. by general practitioners and psychiatrists) are registered; over-the-counter medications and those dispensed at hospitals are not included. The DNPR registers, among other variables, the Anatomical Therapeutic Chemical (ATC) classification code and the date of redeeming the prescription. Every Danish resident redeeming a prescription at a Danish pharmacy is registered. Because the register is based on

automated bar-code data entry and reimbursement-driven record-keeping, the data is thought to be of high quality and completeness (Kildemoes et al., 2011).

The Danish National Health Service Register (NHSR) contains information on activities in the primary health care system from 1990 and onwards. Until 1996, services provided to children younger than 16 years were registered in the personal identification number of the mother or the father, thus before 1996 it is not possible to distinguish if these were provided for the child or the parents, and therefore the present study only included services from 1996 and onwards. The register contains, among other things, information on type of health care provider (e.g. general practitioners, psychiatrists and psychologists), type of service (e.g. consultation, telephone consultation and blood sample), week or month of settlement of accounts between health care provider and the Regional Health Administration, but does not include information on diagnosis codes or reasons for using the service. Consultations at psychiatrists are free of charge, but a referral from a general practitioner is required, while consultations at psychologists are self-paid, but subsidy is granted if there is a referral from a general practitioner. Only an inconsiderable number of psychiatrists provide consultations without a referral, whereas consultations with psychologists are possible without a referral but in this case the consultations are not registered in the NHSR. Only general practitioners can refer to a psychiatrist or psychologist. Every Danish resident obtaining primary healthcare is included in the NHSR and even though no validity studies exist, the coverage is assumed to be good because the health care provider needs to report services to the Regional Health Administration in order to receive reimbursement (Andersen et al., 2011).

This study was approved by the Danish Data Protection Agency (Project No. 2016-41-4534) and no informed consent was required, because the study is based on secondary, de-identified data stored on servers located at Statistics Denmark and accessed via a secure virtual private network connection.

Study population

All individuals born in Denmark, January 1, 1936 to December 31, 2009, with non-syndromic OC were identified using the DFCR and a 5% random sample of the entire population in Denmark in each year was extracted by Statistics Denmark. Individuals with OC were excluded from the random sample. The DFCR only includes individuals born in Denmark and therefore only individuals with a Danish birth registration code and a Danish code of residence from birth were included. Furthermore, only individuals who did not die or emigrate from Denmark in their first year of life were included. From the remaining 5% random sample, we randomly selected a comparison cohort of individuals without OC matched 10 to 1 to the group with OC by sex and birth year. Finally, the study sample was restricted to those alive and living in Denmark January 1, 1996, where follow up is reliable in DNPR and NHSR. The final study sample consisted of 8,244 individuals with OC and 82,665 in the comparison cohort. The ratio of number of individuals with OC to number of individuals in the comparison cohort is not precisely 1 to 10, since individuals who died or emigrated prior to 1996, which is the first year of follow-up for measuring the study outcomes, are excluded (see Figure 1).

Assessment of use of psychotropic medication

From the DNPR, we included all redeemed prescriptions in the period from January 1, 1996 to December 31, 2012 with an ATC code from the following six major subgroups of psychotropic medications: Antipsychotics (N05A), Anxiolytics (N05B), Hypnotics and sedatives (N05C), Antidepressants (N06A), Stimulants (N06BA) and Lithium (N05AN). The outcomes were binary indicators for each of these six medication subgroups, in addition to a binary indicator for using any of these psychotropic medications. A few medications in these ATC subgroups are to some degree used for other indications than treatment of psychiatric disorders and are therefore excluded (see Supplementary Table S1 for the list of all ATC codes we included in each subgroup). For instance, Diazepam (ATC code N05BA01) is often given to pediatric febrile convulsions; therefore, we excluded this prescription if age at the date of medication dispensing were less than 7 years. Furthermore, anxiolytics with long half-time (48 hours or more) are sometimes used for treatment refractory epilepsy both in children and adults, and therefore we performed additional analyses for the any psychotropic medication outcome and the anxiolytics indicator excluding prescriptions of Diazepam (N05BA01), Chlordiazepoxide (N05BA02) and Potassium clorazepate (N05BA05) if the individual has previously had a antiepileptic medication prescription (N03A).

Assessment of visits to psychiatrists and psychologists

From the NHSR, we identified all services from psychiatrists (health care provider code 24), pediatric psychiatrists (health care provider code 26) and psychologists (health care provider code 63) in the period from January 1, 1996 to December 31, 2011 with a service code for consultation (see Supplementary Table S2 for a complete list of the services included). We then coded separate binary indicators for visiting psychiatrists and psychologists. For children, we combined visits to pediatric and general psychiatrists because pediatric psychiatrists were mostly visited before age 7; after that, children also visited general psychiatrists.

Study design and statistical analysis

Descriptive analysis—To examine time trends, we calculated the prevalence of the outcomes for each follow-up year as number of individuals with at least one event of the outcome of interest divided by the total number of individuals alive and resident in Denmark by January 1st and over age 1 year during the relevant year. Furthermore, to illustrate the age-trends, the prevalence for each age 1–70 was calculated as number of individuals at each age with at least one event of the outcome of interest divided by the total number of individuals in the particular age alive and resident in Denmark on January 1st in the relevant year. The prevalence was calculated stratified by sex and OC status.

Time to event analysis—Separate analyses were performed for each outcome of interest: redeemed prescriptions of any psychotropic medication and for each of the specific ATC subgroups; visit to psychiatrist; and visit to psychologist. We employed a time-to-event or “survival” analysis, in which individuals were followed from January 1, 1996 or date of age 1 year, whichever came later. Follow-up was terminated at date of first event of the outcome

of interest, death, first emigration from Denmark or December 31, 2012, whichever came first. Emigration from Denmark was defined as residence outside Denmark for more than 2 years. When examining any psychotropic medication use, the first redeemed prescription under any of the 6 categories was the event of interest. Only the first event of each outcome was included in the time-to-event analyses. For each outcome, a Cox proportional hazard model with age as the underlying time scale was used to compute hazard ratios (HRs) of time to first event of the outcome of interest during the follow-up period for individuals with OC compared with the matched comparison cohort. The proportional hazard assumption across age was assessed graphically and formally tested on the basis of Schoenfeld residuals.

Models were stratified by cleft type and each cleft type was compared with its matched comparison cohort. Additional models were stratified by sex (because of variation in prevalence of mental health disorders and treatment use between males and females), age group (0–34 years and 34–76 years) and birth cohort (1936–1975 and 1976–2009). Furthermore since a recent Swedish register based study on use of psychotropic medications in individuals with OC focused on adolescents (Nilsson et al., 2015) and many studies focus primarily on children (Hunt et al., 2006; Murray et al., 2010; Wehby et al., 2012; Tyler et al., 2013), we also restricted analyses to the children and adolescent (aged 0–17 years). Additionally, for the outcomes that significantly varied by OC types, additional analyses were stratified by severity including separating: unilateral and bilateral status for CLP; submucous, soft palate only, or soft and hard palate for CP; and cleft laterality (left versus right sided) for unilateral CLP.

Results

The analytical sample included 8,244 individuals with non-syndromic OC observed for 125,344 person-years and 82,665 individuals without OC followed for 1,265,978 person-years. In the OC cohort, 2,569 (31%) individuals had CL, 3,148 (38%) individuals had CLP, and 2,527 (31%) individuals had CP.

Table 1 summarizes the characteristics of individuals with OC and the matched comparison cohorts. The individuals with OC had significantly fewer emigrations ($\chi^2 = 14.9$, $p < 0.001$) but higher mortality ($\chi^2 = 36.0$, $p < 0.001$) during the follow-up period. A total of 2,472 (30.0%) of the individuals with OC and 22,981 (27.8%) in the comparison group had at least one redeemed prescription for any psychotropic medication. Stratifying by cleft type indicated a crude absolute risk increase for any medications by 1.28% (95% CI: −0.56%–3.11%) for CL, 2.42% (95% CI: 0.75%–4.09%) for CLP and 2.82% (95% CI: 0.93%–4.71%) for CP. A higher proportion of individuals with OC had at least one psychiatrist visit compared to individuals without OC (5.1% vs 4.7%), but the rates of any psychologist visits were similar (6.6% vs 6.6%).

Figure 2 shows the prevalence of any psychotropic medication use as well as use by specific ATC subgroups, and any visits to psychiatrists and psychologists by follow-up year for individuals with OC and the matched comparison cohort stratified by sex. For both males and females, any psychotropic medication use was more common among individuals with OC than the comparison cohort in all years. This greater use was primarily due to an

increased use of: antipsychotics in both sexes; antidepressants in females; and stimulants in males in the later years of follow-up. There were no consistent trends in differences in psychiatric and psychologist visits between the two groups.

Figure 3 shows these trends stratified by age. Beginning in adolescence, use of any psychotropic medications and antipsychotics is more common among individuals with OC at almost all subsequent ages. Males with OC have greater rate of stimulant use in childhood and adolescence than unaffected males. Furthermore, females with OC are more likely to use antidepressants than unaffected females at any age.

Table 2 shows the Hazard Ratios (HRs) from the Cox regression for each outcome. Individuals with OC had a 12% (95% CI: 7%–16%) higher risk of using any psychotropic medication compared with individuals without OC. When stratifying by cleft type, individuals with CLP (HR=1.13, 95% CI: 1.05–1.21) and those with CP (HR=1.17, 95% CI: 1.09–1.26) had greater use compared to unaffected individuals, but there was no significant difference for individuals with CL (HR=1.05, 95% CI: 0.98–1.14). Examining specific psychotropic medication subgroups revealed significantly elevated risks of using antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants among individuals with OC. The largest relative risk increase was for use of antipsychotics and stimulants for individuals with CP (by over 40%) followed by use of antipsychotics for individuals with CLP (by over 30%). Individuals with CP had 27% (95% CI: 8%–51%) increased risk of a psychiatrist visit, but there were no significant differences for individuals with CL or CLP. Finally, there were no significant differences in visiting a psychologist when examining any OC or OC types.

Stratifying by sex, age group (0–34 years and 35–76 years) and birth cohort (1936–1975 and 1976–2009), respectively, revealed similar findings overall to the total sample (results not shown) with a few exceptions worth mentioning. The increased risk of stimulant use for individuals with CP was only significant for males (HR=1.64, 95% CI: 1.12–2.39) but not females (HR=1.25, 95% CI: 0.72–2.17). Overall, the HRs were higher in the younger age group (0–34 years) and for anxiolytics, and hypnotics and sedatives, the HRs were only significant in this group (HR=1.21, 95% CI: 1.08–1.35 for anxiolytics and HR=1.24, 95% CI: 1.11–1.39 for hypnotics and sedatives). For individuals with CL, the risk of any psychotropic medication use was significantly increased in the younger age group (HR=1.19, 95% CI: 1.06–1.34), and even though the only significant finding for CL in the subgroups of psychotropic medication was in use of hypnotics and sedatives (HR=1.24, 95% CI: 1.02–1.52), the HRs for all medication groups were above 1 and similar in magnitude to those in the CLP group. Also, the increased risk of visiting a psychiatrist for individuals with CP was only observed in the younger age group (HR=1.41, 95% CI: 1.13–1.75). Stratifying by birth cohort showed overall similar results to those by age group. Among children and adolescents (0–17 years), we found similar HRs to the age group 0–34 years for any psychotropic medication when combining all OC (HR = 1.25, 95% CI: 1.07–1.46), but the HRs were larger for use of anxiolytics (HR = 1.67, 95% CI: 1.23–2.26) and for use of hypnotics and sedatives (HR = 1.56, 95% CI: 1.01–2.18), whereas there was no increased risk of use of antipsychotics (HR=1.00, 95% CI: 0.67–1.49).

As noted above, we also evaluated models accounting for cleft severity. Among individuals with CLP, 2,112 had unilateral CLP, 891 had bilateral CLP and 145 had unknown severity. The HRs for any psychotropic medication use were 1.08 (95% CI: 1.00–1.18) for individuals with unilateral CLP and 1.23 (95% CI: 1.09–1.39) for those with bilateral CLP compared to their respective comparison cohorts. Among individuals with CP, 648 had submucous CP, 624 had a cleft of the soft palate only, 1,081 had a cleft of both soft and hard palate, and 174 had unknown severity. The HRs for any psychotropic medication use were 1.12 (95% CI: 0.96–1.31) for submucous CP, 1.12 (95% CI: 0.97–1.30) for CP in the soft palate only, and 1.22 (95% CI: 1.10–1.35) for CP in both soft and hard palate. For individuals with unilateral CLP, stratifying by whether the cleft of the lip was on the right or the left side did not reveal any significant differences.

Our sensitivity analyses for any psychotropic medication use and anxiolytics only changed the estimates marginally from HR=1.12 (95% CI: 1.07–1.16) to HR=1.11 (95% CI: 1.07–1.16) and from HR=1.09 (95% CI: 1.03–1.16) to HR=1.08 (95% CI: 1.01–1.15), respectively when excluding Diazepam, Chlordiazepoxide and Potassium clorazepate in cases of prior antiepileptic medications as mentioned above. Finally, the proportional hazard assumption was assessed and could not be rejected except for any psychotropic medications (driven by anxiolytics, and hypnotics and sedatives) for individuals with CL, for whom the HRs were significantly larger in younger age groups.

Discussion

In this large, population-based cohort study, we found a significantly increased risk of using any psychotropic medications for individuals with non-syndromic OC compared with an age- and sex-matched comparison cohort of individuals without OC, although the absolute risk difference was modest (1–3 percentage-points). For all ages combined we found an increased use for individuals with CLP and CP, but not for individuals with CL. For younger individuals with CL however, we found an increased risk of any psychotropic medication use. When dividing into the specific subgroups of psychotropic medications, we found significantly increased use of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants for individuals with OC. The largest increased risk was found for use of antipsychotics and stimulants among individuals with CP followed by use of antipsychotics for individuals with CLP. We found smaller differences in use of anxiolytics, hypnotics and sedatives, and antidepressants, and for all outcomes the absolute risk estimates were modest. We found no significant differences in visits to psychiatrists or psychologists, except for individuals with CP who were more likely to see a psychiatrist.

Our finding of increased use of psychotropic medications by individuals with CP is consistent with the recent study from Sweden focused on adolescents (Nilsson et al., 2015). That study also reported increased use among individuals with CL but not those with CLP. In contrast, when focusing on younger individuals (0–34 years), we found significant increases in any psychotropic medication use among both individuals with CL or CLP that are of similar magnitude. In particular, we found increased risk of use of anxiolytics and hypnotics and sedatives for children and adolescents (aged 0–17 years). Our results suggest that mental health problems are more similar across cleft types at younger age, but later in

life, individuals with CLP or CP become more vulnerable to mental health problems than those with CL.

The primary indication for use of antipsychotics is psychosis, and for use of stimulants it is hyperkinetic disorder (Attention Deficit Hyperactivity Disorder**).** Our finding of higher risk of using antipsychotics for individuals with CLP and CP and increased use of stimulants for males with CP are consistent with our previous study of the same population (Pedersen et al., 2016), which found increased risk of hospitalization with a diagnosis of schizophrenia-like disorders for individuals with CLP or CP and with a diagnosis of behavioral and emotional disorders (including hyperkinetic disorder) for males with CP. The increased use of antipsychotics and stimulants among individuals with OC is also in line with reports of an association between non-syndromic OC and midline brain anomalies in males (Nopoulos et al., 2001; Weinberg et al., 2013) which, in other studies, have been associated with schizophrenia, mental retardation and developmental delay (Nopoulos et al., 1997; Bodensteiner et al., 1998; Landin-Romero et al., 2016). They are also consistent with prior studies reporting increased frequency of CP among patients with schizophrenia (Gourion et al., 2004) and increased rates of hyperactivity, impulsivity and inattention among individuals with non-syndromic OC (Nopoulos et al., 2010; Wehby et al., 2012).

The primary indications for prescribing anxiolytics, and hypnotics and sedatives are anxiety and insomnia, respectively, and the primary indication for prescribing antidepressants is depression, although antidepressants are sometimes used for anxiety disorders like obsessive compulsive disorder. Psychological stress might lead to depression and anxiety in vulnerable persons and might explain the increased use of antidepressants and anxiolytics. In contrast to the prior study of diagnoses in psychiatric hospitals suggesting no increased risks of mood disorders and anxiety related disorders (Pedersen et al., 2016), we find significantly increased risk of using anxiolytics, hypnotics and sedatives, and antidepressants. Even though the risk increases are modest, our findings are consistent with studies reporting increased rates of depression and anxiety (Hunt et al., 2006; Hunt et al., 2007; Demir et al., 2011; Tyler et al., 2013) and suggest that individuals with OC may face increased risks for depression and anxiety but not necessarily in the severe range that would require hospitalization.

Although we found no significant association between severity of the OC and the use of psychotropic medications, there is a tendency to overall greater risks in use of psychotropic medication increasing cleft severity, which is found in prior work indicating lower self-reported levels of depression among individuals with unilateral CLP than bilateral CLP or CP (Millard and Richman, 2001).

Strengths and Limitations

The strengths of this study are the large, well-defined and population-based study sample, and the use of high-quality nationwide administrative population-based registers with long follow-up period. Furthermore, all outcomes: redeemed prescription of psychotropic medications and visits to psychiatrists and psychologists are objective measures that are collected independently of information on OC, which minimizes the risk of selection bias and differential misclassification. The ascertainment of individuals with OC in Denmark is

very high (Christensen et al., 1992) and the automated bar-code data entry for prescriptions and reimbursement-driven record-keeping (for both prescriptions and visits to psychiatrists and psychologists) provides high-quality data (Andersen et al., 2011; Kildemoes et al., 2011). Furthermore, it is not possible to purchase psychotropic medications without a prescription in Denmark since none of these drugs are available over-the-counter. Furthermore, use of most of the psychotropic medications is partly covered in the Danish national insurance system, which reduces out-of-pocket costs and the likelihood of a large proportion of unfilled prescriptions the social bias is a smaller issue than in most settings.

One of the limitations of this study is that some of the individuals classified as having non-syndromic OC may have unidentified associated anomalies or syndromes that can also be associated with increased risks of psychiatric disorders. This is expected to be more of a concern for early birth cohorts where there is higher underreporting of associated anomalies. However, we expect minor anomalies to be primarily undetected not major anomalies as these are most likely identified. Undetected syndromic cases could contribute to over-estimating the association between non-syndromic OC and psychiatric disorders. We do, however, observe greater increases in risks of psychotropic medication use at younger ages (later birth cohorts) than in the older age group (earlier birth cohorts) when rates of undetected syndromic cases are possibly higher, which is reassuring. However, CP, which is more often part of a syndrome than is CL(P), is associated with 22q11 deletion syndrome. This syndrome has been shown to be associated with a range of psychiatric disorders including schizophrenia, autism, mild retardation and ADHD (Swillen and McDonald-McGinn, 2015). The prevalence of 22q11 deletions among individuals with CP and no other symptoms of 22q11ds has been reported to be about 1% (Ruiter et al., 2003), and another study found 1.8% 22q11 deletions among children with CP with or without additional malformations (Sivertsen et al., 2007). So, it is possible that this syndrome as well as other undiagnosed syndromes is contributing to an overestimation of the association between non-syndromic CP and psychiatric disorders.

Furthermore, there are no diagnoses or indications for the prescriptions or for visits to psychiatrists or psychologists in these datasets. Use of psychotropic medications however is a clear indicator of psychiatric disorder, although some psychotropic medications might be used for other secondary indications. The primary indication for antipsychotics is psychosis, but it has also other clinical applications such as depression, post-traumatic stress disorder and bipolar disorders. Primary indications for anxiolytics, and hypnotics and sedatives are anxiety and insomnia. The primary indication for prescribing antidepressants is depression, but this medication is also used for anxiety disorders like panic attacks, social anxiety and obsessive compulsive disorder. Anxiolytics with long half-time [especially Diazepam (N05BA01), Chlordiazepoxide (N05BA02) and Potassium clorazepate (N05BA05)] are used for treatment of epilepsy. However, we observed similar results in sensitivity analyses excluding these medications from anxiolytics for individuals with prior antiepileptic medication use. Still we cannot totally rule out the possibility that some of the association between OC and anxiolytics might be due to epilepsy. In addition, some antiepileptic medications are used for bipolar disorder, depression and anxiety; we excluded these drugs however because their primary indication is epilepsy.

The DNPR only captures medications prescribed in primary health care settings. Psychiatric patients however may be hospitalized for longer periods and medication use during hospitalizations would not be captured for these individuals. Since individuals with OC have higher risk of hospitalization at psychiatric hospitals (Pedersen et al., 2016) this would lead to an underestimation of the risk of psychotropic drug use for individuals with OC. This would, however, mostly affect the use of antipsychotics and stimulants since prior work suggests increased hospitalization risks for schizophrenia-like disorders and behavioral and emotional disorders (including hyperkinetic disorder). Furthermore, in Denmark depression is commonly treated by general practitioners and we do not have information on such visits, although we still capture use of psychotropic medications if these are prescribed. In addition, the DNPR does not register prescribed medications unless they are redeemed. As noted above, we do not however expect these concerns to differ between individuals with OC and those without OC, and so they would probably not affect the estimates notably.

A last concern is differential loss to follow-up between individuals with OC and the comparison cohort. Individuals with OC have significantly higher mortality and fewer emigrations from Denmark, which might result in underestimation of the association since the higher mortality is partly due to increased risk of suicide (Christensen et al., 2004; Pedersen et al., 2016) and emigrating individuals are likely to be healthier on average. Since number of suicides is low (Pedersen et al., 2016) and there is only a minor difference in proportion of emigrations between the two cohorts, this is probably a negligible concern.

Conclusions

Individuals with non-syndromic OC in Denmark are more likely to use psychotropic medications than individuals without OC, although absolute risk changes are overall modest (1–3 percentage points). This increased use was mainly found in individuals with CLP or CP. For individuals with CL, an elevated risk was only observed among younger individuals. When examining psychotropic medication subgroups, the largest increased risk was for use of antipsychotics for individuals with CLP or CP and for use of stimulants in individuals with CP. Individuals with CP also had increased risk of psychiatrist visits. We only found modest increased risks for using anxiolytics, hypnotics and sedatives and antidepressants and no increased risk for psychologist visits. This suggests that most individuals with OC manage just as well as individuals without OC although there seems to be a small group especially among individuals with clefts of the palate who have more severe mental health problems requiring treatment with antipsychotics or stimulants and psychiatrist visits. The increased risk of using anxiolytics, hypnotics and sedatives and antidepressants does seem to be higher at younger ages, which might suggest that individuals at younger ages (or the later birth cohorts) have more psychological difficulties. This is particularly the case for individuals with CL who do not appear to have significant differences in medication use from unaffected individuals at older age. In contrast, the effects on individuals with CLP and CP appear to be much more long-term in life than those with CL.

In terms of clinical relevance, these findings do suggest that being born with OC increases a person’s risk of psychiatric morbidity. Clinicians should be aware of these risks, carefully ask about psychiatric symptoms (as these are often not spontaneously mentioned by the

patient) and refer to support and treatment as needed as early as possible. Furthermore, it might be relevant to screen for 22q11 deletions among individuals with CP and mental health problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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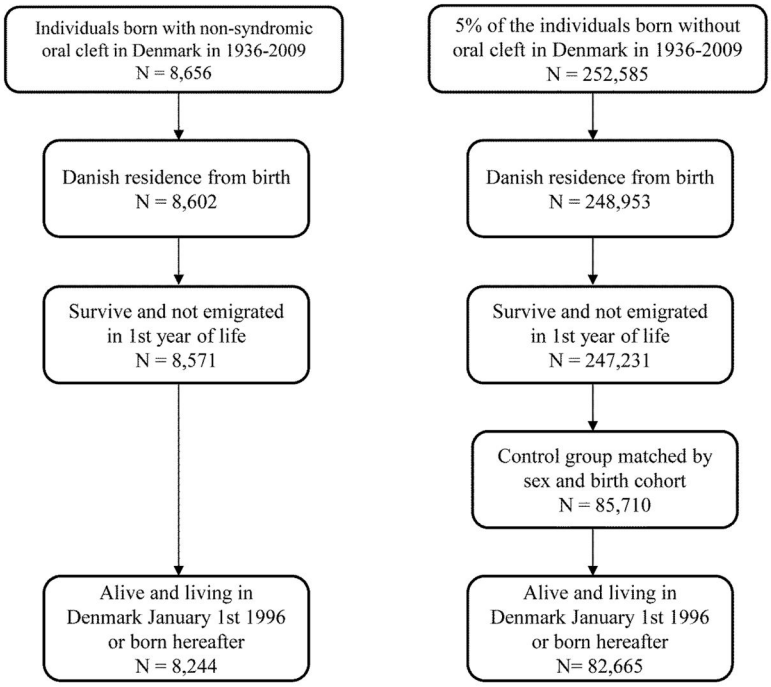

Fig. 1.

Inclusion Criteria for Individuals with Non-Syndromic Oral Cleft and Matched Comparison Cohort.

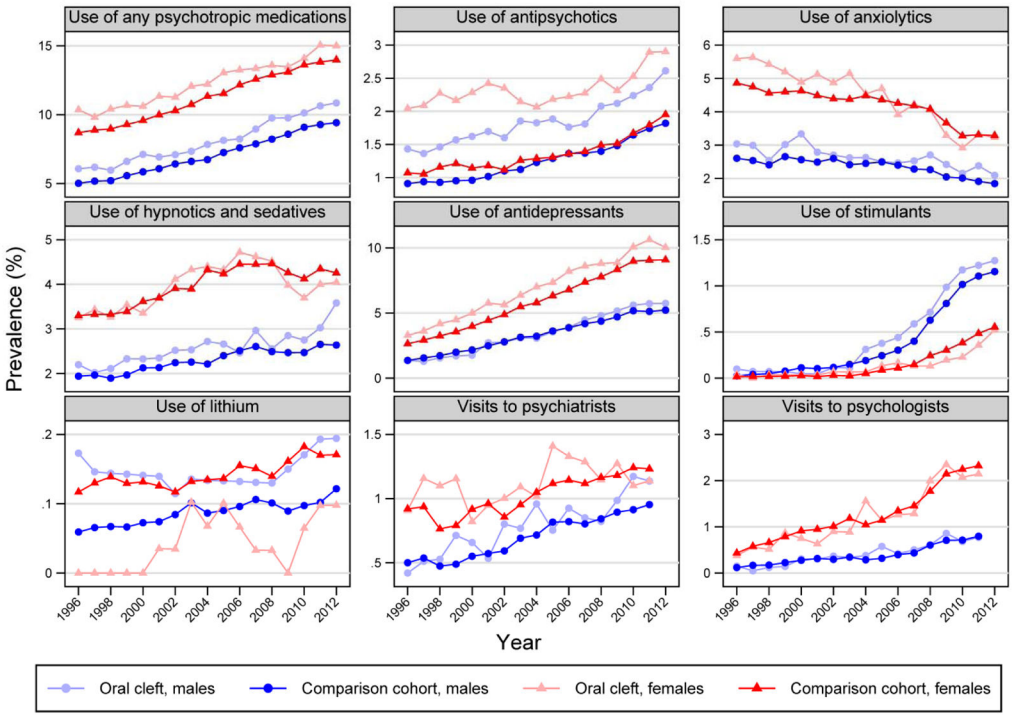

Fig. 2.

Prevalence Proportion of Redeemed Prescription of any Psychotropic Medications and for each of the Specific Subgroups of Psychotropic Medication, Visits to Psychiatrists and Psychologists by Calendar Year for Individuals with Non-Syndromic Oral Cleft and Matched Comparison Cohort Stratified by Sex.

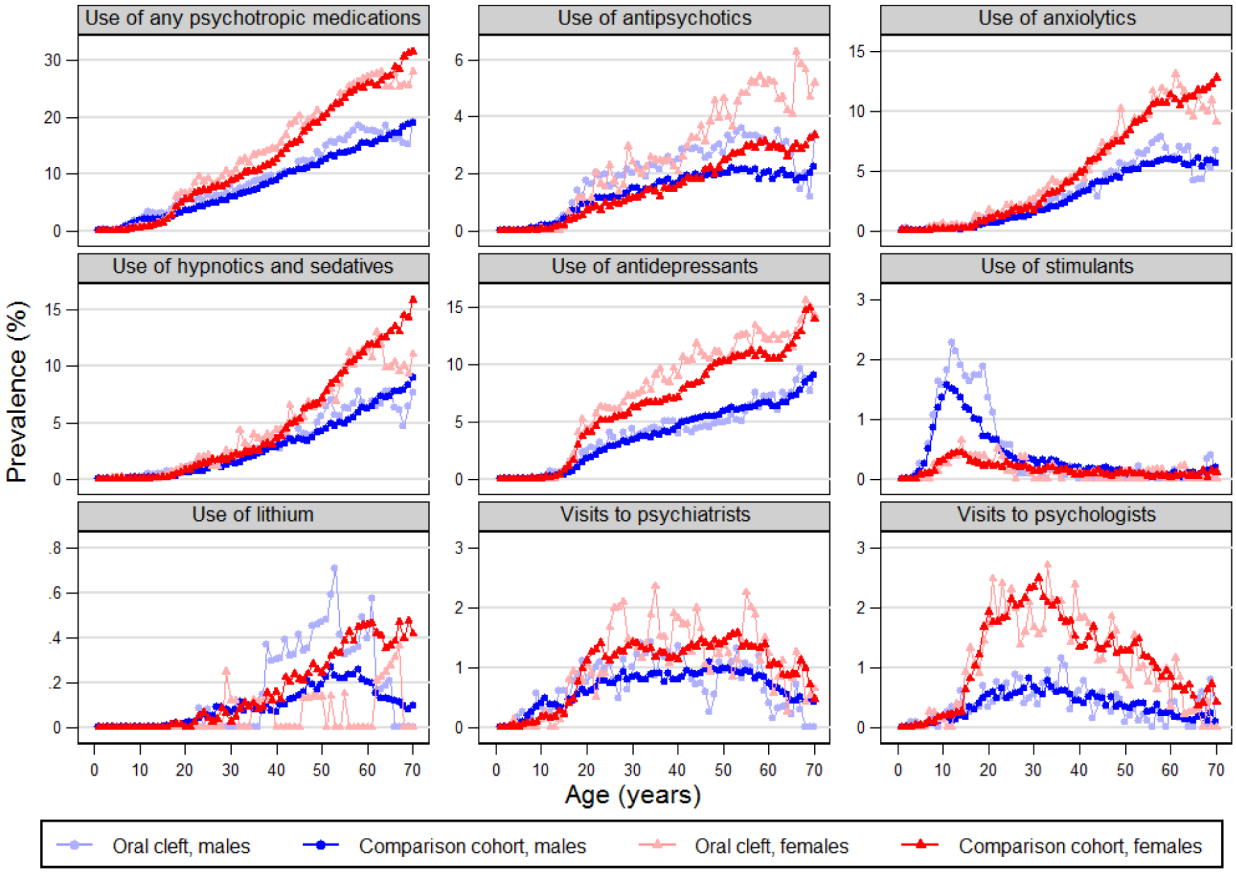

Fig. 3.

Prevalence Proportion of Redeemed Prescription of any Psychotropic Medications and for each of the Specific ATC Subgroups of Psychotropic Medication, Visits to Psychiatrists and Psychologists by Age for Individuals with Non-Syndromic Oral Cleft and Matched Comparison Cohort Stratified by Sex.

Table 1

Characteristics of Individuals with Non-Syndromic Oral Cleft and the Matched Comparison Cohort.

	Oral cleft		Cleft lip		Cleft lip and palate		Cleft palate	
	Affected individuals, n (%)	Comparison cohort, n (%)	Affected individuals, n (%)	Comparison cohort, n (%)	Affected individuals, n (%)	Comparison cohort, n (%)	Affected individuals, n (%)	Comparison cohort, n (%)
Total sample	8,244 (100.0)	82,665 (100.0)	2,569 (100.0)	25,724 (100.0)	3,148 (100.0)	31,422 (100.0)	2,527 (100.0)	25,519 (100.0)
Male	4,997 (60.6)	50,077 (60.6)	1,651 (64.3)	16,564 (64.4)	2,201 (69.9)	21,951 (69.9)	1,145 (45.3)	11,562 (45.3)
Year of birth								
1936–1955	1,771 (21.5)	17,900 (21.7)	574 (22.3)	5,840 (22.7)	707 (22.5)	7,046 (22.4)	490 (19.4)	5,014 (19.6)
1956–1975	2,616 (31.7)	26,176 (31.7)	807 (31.4)	8,020 (31.2)	1,008 (32.0)	10,063 (32.0)	801 (31.7)	8,093 (31.7)
1976–1995	2,319 (28.1)	23,209 (28.1)	692 (26.9)	6,904 (26.8)	850 (27.0)	8,483 (27.0)	777 (30.7)	7,822 (30.7)
1996–2009	1,538 (18.7)	15,380 (18.6)	496 (19.3)	4,960 (19.3)	583 (18.5)	5,830 (18.6)	459 (18.2)	4,590 (18.0)
Number of deaths[a]	436 (5.3)	3,243 (3.9)	126 (4.9)	1,033 (4.0)	193 (6.1)	1,325 (4.2)	117 (4.6)	885 (3.5)
Any emigration[a]	181 (2.2)	2,431 (2.9)	57 (2.2)	797 (3.1)	59 (1.9)	918 (2.9)	65 (2.6)	716 (2.8)
Use of any psychotropic medication[a]	2,472 (30.0)	22,981 (27.8)	742 (28.9)	7,101 (27.6)	935 (29.7)	8,571 (27.3)	795 (31.5)	7,309 (28.6)
Antipsychotics	549 (6.7)	4,369 (5.3)	142 (5.5)	1,327 (5.2)	221 (7.0)	1,690 (5.4)	186 (7.4)	1,352 (5.3)
Anxiolytics	1,154 (14.0)	10,789 (13.1)	314 (12.2)	3,265 (12.7)	445 (14.1)	3,991 (12.7)	395 (15.6)	3,533 (13.8)
Hypnotics and sedatives	1,151 (14.0)	10,920 (13.2)	351 (13.7)	3,364 (13.1)	438 (13.9)	4,105 (13.1)	362 (14.3)	3,451 (13.5)
Antidepressants	1,431 (17.4)	13,301 (16.1)	432 (16.8)	4,082 (15.9)	541 (17.2)	4,897 (15.6)	458 (18.1)	4,322 (16.9)
Stimulants	119 (1.4)	1140 (1.4)	37 (1.4)	361 (1.4)	37 (1.2)	470 (1.5)	45 (1.8)	309 (1.2)
Lithium	23 (0.3)	277 (0.3)	5 (0.2)	87 (0.3)	10 (0.3)	111 (0.4)	8 (0.3)	79 (0.3)
Visit to psychiatrist[b]	422 (5.1)	3,872 (4.7)	114 (4.4)	1,183 (4.6)	155 (4.9)	1,451 (4.6)	153 (6.1)	1,238 (4.9)
Visit to psychologist[b]	541 (6.6)	5,446 (6.6)	152 (5.9)	1,646 (6.4)	191 (6.1)	1,844 (5.9)	198 (7.8)	1,956 (7.7)

[a]Numbers are the total number in the period Januaryl 1, 1996 to December 31, 2012 independent of any other prior events

[b]Numbers are the total number in the period Januaryl 1, 1996 to December 31, 2011 independent of any other prior events

Table 2

Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Redeemed Prescription for Psychotropic Medications and Visits to Psychiatrists and Psychologists in Individuals with Non-Syndromic Oral Cleft Compared with the Matched Comparison Cohort stratified by Cleft Type.

	Oral cleft		Cleft lip		Cleft lip and palate		Cleft palate	
	Oral cleft	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Any psychotropic medication	1.12***	1.07–1.16	1.05	0.98–1.14	1.13**	1.05–1.21	1.17***	1.09–1.26
Antipsychotics	1.29***	1.18–1.41	1.09	0.91–1.29	1.34***	1.16–1.54	1.44***	1.23–1.68
Anxiolytics	1.09**	1.03–1.16	0.96	0.85–1.08	1.14**	1.04–1.26	1.16**	1.05–1.29
Hypnotics and sedatives	1.08*	1.01–1.15	1.05	0.94–1.18	1.08	0.98–1.19	1.10	0.99–1.23
Antidepressants	1.10***	1.04–1.16	1.07	0.97–1.18	1.12**	1.03–1.23	1.10	1.00–1.21
Stimulants	1.05	0.87–1.27	1.03	0.73–1.44	0.79	0.57–1.10	1.49*	1.09–2.04
Lithium	0.81	0.53–1.26	0.59	0.24–1.46	0.83	0.42–1.63	1.04	0.50–2.14
Visit to psychiatrist	1.11*	1.00–1.22	0.97	0.80–1.18	1.08	0.91–1.27	1.27**	1.08–1.51
Visit to psychologist	0.99	0.91–1.08	0.93	0.78–1.09	1.02	0.88–1.19	1.02	0.88–1.18

* $p < 0.05$,

** $p < 0.01$

*** $p < 0.001$