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Oral clefts and academic performance in adolescence: the impact of anesthesia-related neurotoxicity, timing of surgery and type of oral clefts

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Abstract

Objective—Early life exposure to anesthesia and surgery is suspected to associate with cognitive impairment later in life. We compared academic achievement among adolescents with cleft lip only (CL), cleft palate only (CP) and cleft lip and cleft palate (CLP) with a non-cleft control group

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to investigate, whether outcome depends on timing and number of operations during childhood and/or type of oral cleft.

Design—Nation-wide, register-based follow-up study.

Setting—Danish birth cohort 1986–1990

Participants—558 children with isolated CL (n=171), CLP (n=222) or CP (n=195), of which 509 children had been exposed to anesthesia and one or more cleft operation(s), and a 5% sample of the birth cohort (n=14,677).

Main Outcome Measures(s)—Test-score in the Danish standardized 9th grade exam and proportion of non-attainment, defined as 'results for 9th grade exam unavailable'. Data adjusted for sex, birth weight, parental age and parental level of education.

Results—Compared to controls, children with CL achieved higher scores (mean difference 0.12, 95% CI −0.05; 0.29) and children with CLP presented with lower scores (mean difference −0.06, 95% CI −0.21; 0.09), albeit both statistically insignificant. Children with CP achieved significantly lower scores, mean difference −0.20 (95% CI −0.38; −0.03). Odds ratios for non-attainment at final exam were: CL 0.79 (95% CI 0.46; 1.35), CLP 1.07 (95% CI 0.71; 1.61), CP 2.59 (95% CI 1.78; 3.76).

Conclusions—Oral cleft type rather than number and timing of anesthesia and operations associate to poorer academic performance. Although a potential neurotoxic effect due to anesthetic agents is not reflected in the data it cannot be completely excluded.

Keywords

oral clefts; craniofacial surgery; general anesthesia; neurotoxicity; anesthesia-related neurotoxicity; outcome; neurodevelopment; age; infants; neonates

INTRODUCTION

Numerous studies have shown that most anesthetic agents used in clinical practice are neurotoxic to the developing animal brain, causing deficits in learning later in life (Jevtovic-Todorovic and Olney, 2008, Nemergut et al., 2014, Jevtovic-Todorovic et al., 2003, Mellon et al., 2007, Ikonomidou et al., 1999). Initially, these studies involved rodents but similar results have been documented in non-human primates. Accelerated neurotoxic damage is seen when neurons are exposed to anesthetics at the time of peak synaptogenesis (Kolb and Gibb, 2011), suggesting an age-related vulnerability. Whether these findings have a human corollary is unknown. Human cohort studies have shown conflicting results (Beers et al., 2014). Some studies have indicated an association between exposure to anesthesia and surgery in early ages and neurocognitive impairment later in life (Wilder et al., 2009, DiMaggio et al., 2009, Flick et al., 2011, Ing et al., 2012). Other studies have been unable to find any such association (Hansen et al., 2011, Bartels et al., 2009, Hansen et al., 2013, Kalkman et al., 2009). However, most studies have focused on older children undergoing all types of surgeries rather than neonates and infants undergoing a single and well-defined surgery. None of the existing studies have convinced surgeons or anesthesiologists to change clinical practice or advice parents differently, although a potential neurotoxic effect of anesthetics cannot be excluded.

Recently, Laub and Williams reviewed the literature on the topic in this journal with a focus on craniofacial/cleft operations stating: “Recent research has suggested that administration of an apparently uncomplicated general anesthetic in an otherwise healthy child may lead to later permanent cognitive or behavioral deficits.” Their conclusion is, that: “The evidence is unclear”. Further they question whether: “There could be a reduced risk of neurotoxicity by changing a surgical protocol to one of later cleft repair or with fewer surgical stages?” (Laub and Williams, 2014).

In order to shed more light on these issues we compared academic achievements in adolescence between children exposed to anesthesia and surgery for correction of isolated oral clefts (OC) and a 5% randomly selected control group. We hypothesized, that any potential neurotoxic effect due to anesthetic agents would be reflected in poor test scores and higher rates of non-attainment at 9^{th} grade final exams. The most vulnerable period in human neurodevelopment is believed to be from 3^{rd} trimester to age 2 years (Dobbing and Sands, 1979, Poulopoulos, 2010). Hence we expected exposure at an early age and/or multiple exposures to associate with worse outcome than no or few exposures or exposure at an older age.

METHOD

A Danish nationwide cohort study was conducted based on data obtained through several civil registers using the unique personal civil registration (CPR) numbers. These individual numbers are assigned at birth, collected in a national database (www.cpr.dk) and enable researchers to follow an individual through all civil registers (Pedersen et al., 2006).

The cohort comprised all 293,540 children born in Denmark from 1986 to 1990, found in the Central Person Register (CPR). Only by death and migration, the latter registered in the *Danish Demographic Database* (Petersen, 2000), an individual was lost to follow up. Within the cohort, 588 children with isolated cleft lip- (CL), cleft palate- (CP) or cleft lip and cleft palate (CLP) malformations, were identified in *the Danish Facial Cleft Register,* containing information on individuals with oral clefts (OC) born in Denmark since 1936 (Christensen, 1999). Overall, 689 children with OC were identified, but 101 children with associated anomalies or syndromes were excluded (13 with CL, 26 with CLP and 62 with CP) (supplementary table I). A 5% random sample of the birth cohort served as the control group. The *Danish National Patient Registry* (DNPR) contains both administrative and clinical information on each admission since 1977, including surgical procedures (Lynge et al., 2011, Andersen et al., 1999). For each individual in the exposure and the control group, the DNPR was searched for the total number of operations before the age of 16. Among these individuals, procedures categorized as ‘cleft operations’ were identified (Appendix 1). Any other type of operation was categorized as ‘non-cleft operation’. Age at first exposure was registered in months.

Previous studies have used academic performance as an estimate of long-term impairments of cognition caused by anesthetics (Wilder et al., 2009, Bartels et al., 2009, Hansen et al., 2011). In this study, test scores in the standardized Danish 9th grade exam served as primary outcome measures and were obtained through the *Register of Compulsory School Completion Assessments and Test Scores* compiled by the Danish Ministry of Education (Education, 2004). The test scores combine average results in all major school subjects. The teacher's ratings served as an additional outcome measure. Since most children in Denmark enter school at the age of six or seven years, average scores were identified for the period of 2002 to 2006, corresponding to the birth cohorts 1986–1990. Generally, students are 15 to 16 yrs old when they sit the tests. Although the potential for anesthetic neurotoxicity is assumed to be most significant in the newborn and/or infant, the exact timing of a deleterious effect is unknown(Hansen, 2015). Hence, all exposures until detection of outcome are included in the analysis. Children with physical and/or mental deficits unable to pass public school exams and attending special schools as well as children, who attended private schools that do not use standardized testing, were registered as the 'non-attainment group'.

Birth weight, paternal age and level of education are confounders knowingly associated with learning impairment (Christensen et al., 2006) and oral clefts (Wehby et al., 2014a, (Wehby et al., 2014b) and were hence adjusted for: birth weight in gram (g) differentiated into 6 intervals: up to 1,499g, 1,500–1,999g, 2,000–2,499g, 2,500–2,999g, 3,000–3,999g, 4,000g and more; maternal age in years (yrs) at child birth: up to 19 yrs, 20–27 yrs, 28–35 yrs, 36 yrs or older, paternal age at child birth: up to 21 yrs, 22–29 yrs, 30–39 yrs, and 40 yrs or older; maternal and paternal education ranked from 0 to 6 with 6 being the highest score achievable. The ranking corresponds as follows: 0 equals 'basic school' up to 8th-10th grade; 1 equals vocational main course ('vocational'); 2 equals upper secondary education; 3 equals short cycle higher education; 4 equals medium cycle higher education; 5 equals bachelor's degree; 6 equals master's degree and PhD ('long higher education'). Ranks 2–5 are referred to as 'short higher education'. Data on parental level of education were obtained through the *Integrated Database for Labour Market research*.

This study was approved by the Danish Data Protection Agency (j.no: 2007–41-1317).

Statistical analyses

Demographic data stratified for sex are presented for the OC-group overall and CL-, CLP-, CP- and 5% control group respectively (Table 1). Age at first cleft operation, number of cleft- and non-cleft operations are presented for each cleft type (Table 2). Table 3 presents average test scores stratified on cleft type, *number* of cleft operations and sex. Stratified on number of all operations before age 16 and sex, proportion of non-attainment and average test scores are shown for the control group in Table 4. Average test scores were analyzed using a linear regression model. Confounders were statistically adjusted for (Table 5a). Rates of non-attainment were analyzed by logistic regression after adjustment for the same covariates as the average test score (Table 5b). Model assumptions were checked by residual plots and quantile plots of residuals. Statistical significance was determined at a 5% significance level, 95% CIs were used.

We repeated the analyses for four different subpopulations: 1) including individuals with syndromic OC (supplementary table II/i+ii); 2) excluding individuals with OC who did not have a cleft operation (supplementary table III/i+ii); 3) excluding controls that have had a surgical procedure (supplementary table IV/i+ii) and 4) restricted to the birth cohorts 1987–1989 (data not shown). Furthermore, the analysis was repeated with 'teacher's ratings in addition to 'test scores' (data not shown).

RESULTS

Characteristics of the oral cleft population and the 5% random control group

Basic characteristics are shown in Table 1. During the study period, 588 children were born with isolated OC; the majority of malformations were CLP (n=222), besides CP (n=195) and CL (n=171). As noted above, individuals, who had either died or migrated prior to June 1st, 2006 are not part of our data. Consequently, the total analytical sample included 558 children in the OC group (94.9% of initial sample comprising 588 individuals) and 13,735 controls (93.6% of initial sample). Overall, 61.6% of children with OC (CP=49.2%, CL=64.6%, CLP=70.1%) and 51.4% of the controls were males. Average birth weight for children with OC was slightly lower compared to the control group (3,315g vs. 3,433g). Parental age was comparable in the two study groups: 28.3 versus 28.1 years for maternal- and 31.2 vs. 30.7 years for paternal mean age. Within the OC subgroups, parental ages were similar. Mean level of maternal-/paternal education was similar in the OC-group and among controls.

Average test-scores and teachers' scores were comparable in both sexes. After stratification according to sex and cleft type, males in both the exposure and control group scored lower average test-/teachers' scores than females (test score – OC group: 7.82(male)/8.08(female); - 5% controls: 7.83(male)/8.14(female); teacher's score – OC group: 7.80(male)/ 8.26(female) – 5% controls 7.80(male)/8.25(female)). With 81.5% of test scores available for children with OC, and 86.8% available for controls, the proportion of non-attainments was more frequent in the OC group. Children with CP presented the highest non-attainment among children with CL, CLP and the controls.

Timing of first cleft operation, numbers of cleft- and non-cleft operations

Age at first cleft operation is reported for each cleft type in Table 2. Median age at first exposure to a cleft operation was 2.8 months for children with CL and CLP and 22.1 months for children with CP.

The majority of children with CL and CP only had one cleft operation. In comparison, 25.1% of children with CLP had two cleft operations and 68.2% had three or more. Among children with CP, 24.6% did not undergo any cleft operation, most likely due to conservative treatment of a sub-mucous CP type. Among controls, 4 patients are registered as having one cleft operation, which may be a registration error.

With respect to non-cleft operations, more than half (54.8%) of controls never had surgery and 25.8% only had one operation. In comparison, 70.7% of children with CL, 28.9% with CLP and 50.8% with CP underwent none or only one non-cleft operation. The proportion undergoing two or more non-cleft operations was 29.3% in children with CL, 71.1% in children with CLP, 49.1% in children with CP and 19.4% among controls (Table 2).

For each cleft type, table 3 shows average test scores stratified according to number of cleft operations and gender. The average test score does not correlate with the number of cleft operations. Due to small sample sizes and wide confidence intervals in the groups of children with multiple operations, these results must be interpreted with caution. Contrarily, among controls there is a tendency towards lower average test scores and higher rates of non-attainment with increasing number of operations for both males and females (Table 4). Once again, the sample sizes of children with multiple operations are rather small.

For each cleft type, logistic regression revealed no association between number of cleft operations and risk of non-attainment controlling for sex (results not shown).

Regression of test score and unavailability of scores on covariates

Unadjusted and adjusted linear regressions of test scores on type of OC, controlling for gender, birth weight, paternal and maternal age and education are presented in table 5a. None of the differences in test score for each of the three cleft types were statistically significant in the unadjusted regression analysis. In the adjusted regression analysis, differences in test score between children with CL (0.12, 95% CI −0.05; 0.29) and CLP (−0.06, 95% CI −0.21; 0.09) and the controls remained insignificant. However, children with CP scored one fifth of a SD lower than the control group (mean difference −0.20, 95% CI −0.38; −0.03).

On average, girls scored 0.35 (95%CI 0.31–0.38) higher than boys. Children of parents belonging to the youngest age group had lower test scores, even after adjustment for confounders. Test scores increased with parental education, as shown by the significantly increasing score with parental education above ‘basic school level’. Test scores tended to decline with lower birth weight but the associations were generally insignificant (except for 2500–2999 versus 3,000–3,999g). Interestingly, scores of extremely low birth weight children (<1499g) did not differ from children with a birth weight of 3000–3999g although low birth weight has previously been associated with impaired neurocognitive development. In the present data, low birth weight children have a high rate of non-attainment (OR 2.93; 95% CI 1.74; 4.94). After stratification according to birth weight the sample sizes are small and hence associated with statistical uncertainty.

Table 5b shows the results from unadjusted and logistic regression of non-attainment of grades adjusted for the same variables as the average test- score. In the adjusted analysis, children with CP had a higher risk of non-attainment, the odds ratio (OR) being 2.59 (95% CI 1.78; 3.76). Children with CL had lower risk of non-attainment (OR 0.79; 95% CI 0.46; 1.35) whereas there was little difference in non-attainment between children with CLP and controls (OR 1.07; 95% CI 0.71; 1.61). Non-attainment was significantly lower among girls than boys (OR 0.55, 95% CI 0.50; 0.62). Young maternal age (19 yrs) related to higher risk of non-attainment (OR 1.34, 95% CI 1.01; 1.79) compared to maternal age of 20 to 27 yrs at child’s birth. The same pattern was seen for paternal age. Risk of non-attainment declined with increasing parental education. Lower birth weight was associated with higher rates of non-attainment with the strongest difference between birth weight below 1,500g and 3,000–3,999g (OR 2.93, 95% CI 1.74; 4,94).

Analysis of subgroups

The control group is a random sample of all children not previously having cleft operations, including individuals with anomalies and syndromes. Hence, comparison of outcome between controls and children with *isolated* OC could lead to an underestimation of a true difference. Consequently, analysis was repeated between controls and children with OC *including* children with syndromes in both groups. Results do not vary substantially (supplementary table II/i+ii).

As shown in table 2, a total of 49 individuals (n= 4 CL, n=45 CP) did not undergo any cleft operation. Regression analysis was repeated excluding these individuals yielding virtually unchanged results (supplementary table III/i+ii).

Among controls, 45.2% of the individuals had one or more non-cleft operations before the age of 15–16 years. Although our data do not specify the types of non-cleft operations, it is well known that ear-nose-throat operations comprise the majority of exposures (Ing et al., 2012, Glatz P, 2015)

In order to compare the outcome in children with OC with truly unexposed controls, analysis was repeated after exclusion of these individuals, which did not influence our results (supplementary table IV/i+ii).

To control for potential bias from students graduating later than expected (e.g. pupils from the 1990 cohort graduating in 2007 instead of 2006) a sub-analysis restricted to the birth cohorts 1987–1989 was made. However, this did not affect the overall results (data not shown).

In order to detect whether ‘test score’ and ‘teacher’s score’ interrelate with regard to outcome, analysis was repeated with ‘teacher’s ratings’. Results were virtually unchanged, suggesting a strong relation between ‘test score’ and ‘teacher’s score’ (data not shown).

DISCUSSION

Cognitive dysfunction and academic underachievement in children with OC are well described phenomena in the literature (Richman et al., 2012). The type of OC is important since children with CP tend to perform poorest, followed by children with CLP and CL, the latter two performing comparably better academically. Overall, children with OC score lower on several measures of academic achievement compared with their controls (Wehby et al., 2014a, Knight et al., 2015). This was confirmed in a Swedish population-based study. The authors compared grades achieved at the compulsory school graduation at age 16 and the proportion of children not receiving a leaving certificate between children with different kinds of OC and their classmates(Persson et al., 2012). Results indicate deficits in educational achievement among children with oral clefts. Moreover, children with CP present the most negative outcome and children with CP and CLP were more likely to leave school without a leaving certificate compared to the general school population.

Multiple etiologies have been suggested as an explanation for cognitive deficiencies among children with OC, ranging from abnormal brain development (Nopoulos et al., 2007) to poor socioeconomic background (Clark et al., 2003, Collett et al., 2014). Since anesthetic exposure may impair neuronal development as previously mentioned, exposure to anesthetic agents could be suspected as yet another factor influencing neuro-cognition of children with OC. Importantly, the current study does not support this contention:

In the present study, children with CP have the highest rates of non-attainment and lowest test- and teachers' scores, similar to the Persson study. In contrast to both Perssons study and a population in the United States, (Wehby et al., 2014) children with CL have lower rates of non-attainment and higher test scores compared to children with CLP- and CP and the control group, although the difference in test score is not statistically significant.

Further, children with CLP, who are exposed to anesthesia and surgery both numerous times and at an early age, do not underperform significantly compared to controls. Children with CL, who are exposed at the youngest age, have test- and teacher's scores that tend to be even higher as well as lower non-attainment rates than the control group, albeit the differences are not statistically significant. In contrast, children with CP present with the lowest test- and teacher's scores and highest rates of non-attainment, although these individuals are not exposed until a later age and with a proportion not operated at all but presumably treated conservatively instead. These findings strongly indicate that type of cleft is more important for subsequent academic achievements later in life, rather than timing of and number of exposures to surgery and anesthesia.

When interpreting the current data, the following should be considered:

Among children with CP, 10.5% (n=27) suffer from various neurodevelopmental impairments (supplementary table I) and there are likely additional underlying issues in the CP population that may not have been formally diagnosed or documented. This could potentially negatively impact both academic outcome and rate of non-attainment at 9th grade exams.

The adjusted difference in 9th grade test score between children with CP and controls is significant. Importantly, the influence of parental age and education, gender and birth weight is statistically stronger. This pattern suggests, that many factors influence neurocognitive outcome in children with OC.

Although widely debated, the definite age of peak vulnerability to general anesthetics is unknown. Therefore, we included all operations and anesthetics which children had been subjected to from the neonatal period to young adolescence.

In the control group there is a tendency towards higher rates of non-attainment and lower test scores with increasing number of exposures to surgery/anesthesia. Contrarily, number of cleft operations and test results do not seem to be associated in children with CL, CLP and CP. These tendencies are difficult to interpret, since we cannot separate the effect of underlying conditions and surgery from the effect of general anesthesia. Further, we cannot account for specific reasons for non-attainment at 9th grade exam, of which several could potentially influence results. Reasons for non-attainment can be: lack of ability due to physical or mental conditions or parental preference of a non-governmental school (e.g. Rudolph Steiner schools).

We assume, that children, who lacked the ability to sit the 9th grade exam, are overrepresented among children with associated anomalies. Instead of adjusting the control group for associated anomalies, we chose to repeat the analysis while *including* children with anomalies in both the OC- and control group. Since neither mean test score difference, nor odds ratio for non-attainment at final exam varied substantially from the initial analyses, the influence of anomalies must be minor.

Academic performance has been questioned as an outcome measure in these types of studies (Ing et al., 2014). Previous large-scale cohort studies by our group did not detect any underperformance following exposure to GA (Hansen et al., 2013, Hansen et al., 2011). Consistent with these findings, a recent 2-year interim analysis of the General Anaesthesia and Awake-Regional Anaesthesia in infancy (GAS) study reports that sevoflurane exposure of up to one hour in infancy undergoing inguinal hernia repair does not increase the risk of adverse neurodevelopmental outcome compared to regional anesthesia (caudal and/or spinal block) (Davidson et al., 2015). Davidson et al evaluated outcome using the Bayley Scales of Infants and Toddler Development III; a tool, which briefly assesses cognitive, language and motor functioning of the child. (Johnson and Marlow, 2006) Still, it remains unknown which neuropsychological assessments are most useful in this context, and how results obtained in a 2-year old infant compare to academic achievements in adolescence. Academic performance is of major interest and concern to parents (Nemergut et al., 2014, Hill and Tyson, 2009) and corresponds well to cognitive skills. Specific competences (i.e. languages, mathematics) as well as the ability to communicate, interact and interrelate with teachers and fellow students are also reflected in school test scores

The strengths of this study are the unique collections of data, on which it is based. Since the Danish civil registers are independent of geographical and organizational relations, there is little risk of selection bias. Further, our data include number and timing of surgical exposures/anesthesia for conditions other than OC and results are augmented by analysis of relevant subgroups, as outlined in the ‘Method’ section.

The animal-based data mentioned above on neurotoxicity from anesthesia exposure lack verification in humans (Lei et al., 2014, Vutskits et al., 2012, Jevtovic-Todorovic, 2011). Fortunately, human studies performed so far have been unable to confirm any long term neurodevelopmental impairment following anesthetic and surgical exposure in early life (Hansen, 2015). As outlined in this study, several other factors are more prominent contributors to academic performance in adolescence, e.g. parental age and level of education, birth weight and sex. Specific surgical conditions have recently been shown to associate with impaired academic achievements in adolescence. These findings emphasize the impact of surgery and the underlying condition on neurocognitive outcome (Hansen et al., 2015).

Although our data are reassuring from a neurotoxicity point of view, they cannot exclude that anesthesia/surgical exposure at an early age may impair later neurocognitive functions.

CONCLUSION

This Danish nationwide, follow-up study of the birth cohort 1986–1990 finds an association between academic achievements at 9th grade exams and cleft type: children with CP produce lower test scores and higher non-attainment rates than children with CLP, CL and controls. Although children with CL are exposed early in life and often several times, their academic performance equals that of the general population. Children with CLP undergo most surgeries related to both cleft- and non-cleft procedures; however, they only score slightly lower than controls. Finally, children with CP, exposed to surgery at an age comparably older than children with CL or CLP, perform notably poorer than controls and the other cleft subgroups.

Although a potentially neurotoxic effect due to the use of anesthetic agents cannot be excluded, this study does not indicate any such association. Currently, there is no evidence to suggest a change in clinical anesthetic practice nor to postpone or cancel truly urgent surgeries in young children. Hence, oral cleft- and craniofacial surgeons are reassured not to change clinical practice regarding treatment and timing of surgical procedures for children with OC. The decision to delay surgery or diagnostic procedures should only be made with a clear understanding that any potentially added risk of delay is being balanced against a still ambiguous and unknown risk of neurotoxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Characteristics of children with Oral Clefts and a random 5% sample, identified in the Danish birth cohort during 1986–90.

	Oral cleft		CL		CLP		CP		5% population	
	n	**percent**	**n**	**percent**	**n**	**percent**	**n**	**percent**	**n**	**percent**
No of live births	588		171		222		195		14,677	
Deaths *	9	1.5%	2	1.2%	5	2.3%	2	1.0%	184	1.3%
Migrations *	21	3.6%	5	2.9%	6	2.7%	10	5.1%	758	5.2%
Study base **	558	94.9%	164	95.9%	211	95.0%	183	93.8%	13,735	93.6%
Males	344	61.6%	106	64.6%	148	70.1%	90	49.2%	7,054	51.4%
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Birth weight (g)	3,315	635	3,367	663	3,350	621	3,229	618	3,433	560
Maternal age	28.3	5.1	28.4	5.3	28.3	5.2	28.4	4.7	28.1	4.8
Paternal age	31.2	5.7	31.4	5.8	30.8	5.5	31.5	5.8	30.7	5.4
Maternal education ***	1.88	1.81	1.97	1.85	1.73	1.79	1.96	1.79	1.77	1.74
Paternal education ***	1.70	1.80	1.73	1.93	1.64	1.69	1.75	1.82	1.67	1.78
Average test score	7.93	1.09	8.10	1.04	7.83	1.12	7.85	1.10	7.99	1.08
Males	7.82	1.09	8.03	1.06	7.75	1.10	7.66	1.11	7.83	1.08
Females	8.08	1.08	8.22	1.02	8.02	1.16	8.02	1.08	8.14	1.06
Average teachers' score	7.98	1.09	8.14	1.07	7.87	1.09	7.96	1.11	8.03	1.10
Males	7.80	1.10	7.98	1.08	7.75	1.10	7.63	1.11	7.80	1.10
Females	8.26	1.02	8.41	0.99	8.15	1.02	8.24	1.05	8.25	1.04
	n	**percent**	**n**	**percent**	**N**	**percent**	**n**	**percent**	**n**	**percent**
Available test score	455	81.5%	145	88.4%	178	84.4%	132	72.1%	11,921	86.8%
Males	274	79.7%	90	84.9%	124	83.8%	60	66.7%	5,916	83.9%
Females	181	84.6%	55	94.8%	54	85.7%	72	77.4%	6,005	89.9%
Available teachers' score	456	81.7%	146	89.0%	178	84.4%	132	72.1%	11,966	87.1%
Males	277	80.5%	92	86.8%	124	83.8%	61	67.8%	5,951	84.4%
Females	179	83.6%	54	93.1%	54	85.7%	71	76.3%	6,015	90.0%

Denominators may vary owing to missing values

* Prior to June 1st, 2006

** Rest of table gives percentages of study base

*** 0=basic school 8th-10th form; 1=vocational main course; 2=upper secondary education; 3=short cycle higher education; 4=medium cycle higher education; 5=bachelor's degree; 6=master's degree and PhD.

Table 2:

Timing of first cleft operation, numbers of cleft- and non-cleft operations.

	CL	CLP	CP	5% population
Study base, n	164	211	183	13,735
Age at first cleft operation in months				
25-percentile	2.4	2.5	21.8	-
50-percentile	2.8	2.8	22.1	-
75-percentile	3.3	3.1	23.5	-
Number of cleft operations, n (%)				
0	4 (2.4)	0 (0.0)	45 (24.6)	13,731 (100.0)
1	126 (76.8)	14 (6.6)	96 (52.5)	4 (0.0)
2	29 (17.7)	53 (25.1)	35 (19.1)	0 (0.0)
≥3	5 (3.0)	144 (68.2)	7 (3.8)	0 (0.0)
Number of non-cleft operations, n (%)				
0	63 (38.4)	15 (7.1)	54 (29.5)	7,529 (54.8)
1	53 (32.3)	46 (21.8)	39 (21.3)	3,537 (25.8)
2	17 (10.4)	50 (23.7)	31 (16.9)	1,471 (10.7)
3	19 (11.6)	39 (18.5)	22 (12.0)	615 (4.5)
≥4	12 (7.3)	61 (28.9)	37 (20.2)	583 (4.2)

Table 3:

Average test scores stratified on cleft type, number of cleft operations, and sex.

	CL							
	Males				Females			
Number of cleft operations	n	Mean	95% CI		n	Mean	95% CI	
1	71	8.13	7.87	8.39	38	8.30	7.97	8.63
≥2	18	7.75	7.37	8.13	14	8.15	7.52	8.79
	CLP							
	Males				Females			
Number of cleft operations	n	Mean	95% CI		n	Mean	95% CI	
1	10	7.57	6.80	8.35	4	7.72	6.06	9.38
2	31	8.04	7.62	8.45	12	8.10	7.33	8.87
3	48	7.60	7.27	7.92	16	8.09	7.50	8.69
≥4	35	7.75	7.39	8.11	22	7.99	7.44	8.54
	CP							
	Males				Females			
Number of cleft operations	n	Mean	95% CI		n	Mean	95% CI	
0	16	7.48	6.99	7.96	16	8.34	7.74	8.94
1	32	7.76	7.34	8.19	38	7.88	7.55	8.21
≥2	12	7.63	6.85	8.40	18	8.02	7.43	8.61

Table 4:

Unavailability of scores (= non-attainment) and average test scores among the randomly selected 5% of the cohort (=controls), stratified on number of all operations before age 16 and sex.

Number of all operations	5% population - Males								
		Non-attainment				Average test score			
	n	n	%	95% CI		n	Mean	95% CI	
0	3557	503	14.1	13.0	15.3	3054	7.89	7.86	7.93
1	1929	292	15.1	13.6	16.8	1637	7.81	7.76	7.86
2	835	154	18.4	15.9	21.2	681	7.72	7.64	7.80
3–4	548	136	24.8	21.3	28.7	412	7.72	7.62	7.82
≥5	185	53	28.6	22.3	35.7	132	7.55	7.36	7.74

Number of all operations	5% population - Females								
		Non-attainment				Average test score			
	n	n	%	95% CI		n	Mean	95% CI	
0	3971	367	9.2	8.4	10.2	3604	8.19	8.15	8.22
1	1609	157	9.8	8.4	11.3	1452	8.09	8.04	8.15
2	635	78	12.3	9.8	15.1	557	8.07	7.98	8.16
3–4	353	53	15.0	11.5	19.2	300	7.96	7.84	8.08
≥5	113	21	18.6	11.9	27.0	92	7.88	7.66	8.09

Table 5:

a) Linear regression of 9th grade exam composite score; presented as differences in test score
b) Results from logistic regression of unavailability of scores (= non-attainment) presented as Odds Ratios and 95% confidence intervals.
Both a) and b) analysis are conducted unadjusted for each variable and adjusted controlling for all the variables on cleft type, sex, birth weight, maternal/paternal age and education.

	a) Mean test score difference (95% CI)		**b) Odds Ratio for non-attainment at final exam (95% CI)**	
	Unadjusted (n=12,375*)	**Adjusted (n=11,249)**	**Unadjusted (n=14,293*)**	**Adjusted (n=12,875)**
Oral Cleft vs. 5%-population (ref. 5%)				
CL	0.12 (−0.06;0.29)	0.12 (−0.05;0.29)	0.86 (0.53; 1.39)	0.79 (0.46; 1.35)
CLP	−0.15 (−0.31;0.01)	−0.06 (−0.21;0.09)	1.22 (0.84;1.77)	1.07 (0.71; 1.61)
CP	−0.13 (−0.32;0.06)	**−0.20 (−0.38;−0.03)**	**2.54 (1.83; 3.52)**	**2.59 (1.78; 3.76)**
Sex (ref. Boys)				
Girls	**0.31 (0.27;0.34)**	**0.35 (0.31;0.38)**	**0.59 (0.53; 0.65)**	**0.55 (0.50; 0.62)**
Maternal age (referred to age 20–27)				
−19	**−0.56 (−0.68;−0.44)**	**−0.28 (−0.41;−0.15)**	**1.90 (1.50; 2.41)**	**1.34 (1.01; 1.79)**
28 – 35	**0.30 (0.26;0.34)**	**0.08 (0.04;0.13)**	**0.75 (0.67; 0.83)**	**0.90 (0.79; 1.03)**
36+	**0.45 (0.37;0.53)**	**0.14 (0.05;0.23)**	0.81 (0.66; 1.00)	**0.88 (0.66; 1.17)**
Paternal age (referred to age 22–29)				
−21	**−0.52 (−0.63;−0.41)**	**−0.19 (−0.31;−0.08)**	**1.66 (1.32; 2.09)**	1.21 (0.93; 1.58)
30 – 39	**0.22 (0.18;0.26)**	0.03 (−0.02;0.07)	**0.76 (0.68; 0.84)**	0.89 (0.78; 1.01)
40+	**0.27 (0.19;0.36)**	0.06 (−0.03;0.15)	0.98 (0.80; 1.20)	1.10 (0.84; 1.42)
Paternal education (referred to level: basic school)				
Vocational	**0.33 (0.28;0.38)**	**0.23 (0.18;0.27)**	**0.56 (0.50; 0.63)**	**0.66 (0.59; 0.75)**
Short**	**0.77 (0.71;0.82)**	**0.50 (0.45;0.56)**	**0.37 (0.32; 0.43)**	**0.51 (0.43; 0.60)**
Long***	**1.28 (1.21;1.35)**	**0.81 (0.73;0.89)**	**0.25 (0.19; 0.33)**	**0.40 (0.30; 0.55)**
Maternal education (referred to level: basic school)				
Vocational	**0.31 (0.26;0.36)**	**0.24 (0.19;0.29)**	**0.54 (0.48; 0.60)**	**0.59 (0.52; 0.67)**
Short**	**0.84 (0.79;0.88)**	**0.58 (0.52;0.63)**	**0.38 (0.33; 0.43)**	**0.50 (0.43; 0.59)**
Long***	**1.37 (1.28;1.46)**	**0.83 (0.73;0.93)**	**0.26 (0.18; 0.36)**	**0.47 (0.32; 0.69)**
Birth weight in gram (referred to 3000–3999g)				
−1499	0.09 (−0.18;0.36)	0.05 (−0.21;0.31)	**2.84 (1.78; 4.54)**	**2.93 (1.74; 4.94)**
1500 – 1999	−0.15 (−0.36;0.06)	−0.10 (−0.30;0.10)	**2.33 (1.58; 3.44)**	**1.95 (1.23; 3.09)**
2000 – 2499	**−0.15 (−0.27;−0.04)**	−0.04 (−0.15;0.07)	**1.58 (1.23; 2.02)**	**1.33 (1.00; 1.76)**
2500 – 2999	**−0.20 (−0.25;−0.14)**	**−0.11 (−0.17;−0.06)**	**1.35 (1.18; 1.54)**	**1.25 (1.07; 1.45)**
4000+	**0.06 (0.00;0.11)**	0.05 (0.00;0.10)	0.91 (0.79; 1.05)	0.94 (0.80; 1.09)

*Number of observations in unadjusted analyses may vary owing to missing value in the variable concerned.

**short=upper secondary education, short or medium cycle higher education or bachelor's degree.

*** long=master's degree or PhD.