

# Maternal Obesity and the Risk for Orofacial Clefts in the Offspring

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**Objective:** To estimate whether obese women have an increased risk of orofacial clefts in their offspring, compared with average-weight women.

**Design and Participants:** The study was based on information on maternal body mass index (BMI) collected in early pregnancy and on the existence of orofacial clefts in the offspring, ascertained from multiple sources. The study included 1686 women who had infants with an orofacial cleft and as controls all delivered women ( $n = 988,171$ ) during the study period, 1992 through 2001. Infants with chromosome anomalies were excluded. The women were divided into underweight (BMI <19.8), average weight (reference group, BMI 19.8 to 26), overweight (BMI 26.1 to 29), and obese (BMI >29). Adjustments were made for year of birth, maternal age, parity, and maternal smoking.

**Results:** Obese (BMI >29) mothers had an overall increased risk for having an infant with orofacial clefts: odds ratio 1.30 (95% confidence interval 1.11 to 1.53). This increased risk was higher when the cleft was associated with other major malformations than when it was isolated. There was no statistically significant difference between the risk estimates for cleft lip and cleft palate.

**Conclusions:** In this large sample, a positive association appears between maternal obesity in early pregnancy and orofacial clefts in the offspring. The explanation for this association is not known, but a relationship with undetected type 2 diabetes is one possibility.

KEY WORDS: *body mass index, cleft lip, cleft palate, epidemiology*

Maternal obesity seems to be associated with the development of neural tube defects (Waller et al., 1994; Shaw et al., 1996; Källén, 1998; Watkins et al., 2003) and congenital heart malformations in the offspring (Waller et al., 1994; Queisser-Luft et al., 1998; Moore et al., 2000; Watkins et al., 2001, 2003; Cedergren and Källén, 2003). Whether the same association exists between maternal obesity and infant orofacial clefts is still unclear (Queisser-Luft et al., 1998; Moore et al., 2000; Shaw et al., 2000; Watkins et al., 2003), and most studies performed are based on a relatively small number of cases. Even a weak association is important to detect on the basis of the ongoing obesity epidemic worldwide. In Sweden the prevalence of overweight women in their fertile years doubled during the years 1980 through 1997 (Lissner et al., 2000).

Oral clefts include cleft lip, cleft palate, and cleft lip with cleft palate and collectively represent a common major birth defect. The total prevalence at birth varies between different

populations: in Sweden the total prevalence at birth (excluding cases associated with chromosome anomaly) was 1.8 per 1000 births (Källén, 2003). The etiology is suggested to be multifactorial, involving both genetic and environmental factors. Among nongenetic risk factors that have been mentioned are maternal smoking, use of certain drugs like some anticonvulsants and corticosteroids, organic solvent exposure, and folic acid deficiency (Wyszynski and Beaty, 1996; Wyszynski et al., 1997). In Sweden maternal drug use during pregnancy apparently plays a minor role (Källén, 2003). Maternal diabetes is associated with an increased risk of orofacial clefts (Moore et al., 2000; Åberg et al., 2001; Spilson et al., 2001).

The objective of this study was to assess, in a large data set from Swedish medical health registries, whether an association between maternal obesity, defined as body mass index (BMI) >29, was associated with an increased risk of infant orofacial clefts in total and for specific cleft diagnoses. To look for trends, other BMI classes also were studied.

## MATERIALS AND METHODS

### Study Population and Exposure Assessment

The study population consisted of 988,171 infants born in Sweden January 1, 1992, through December 31, 2001. In 817,697 (83%) infants, information on maternal height and maternal weight in early pregnancy had been recorded in early pregnancy.

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The women were identified using the Swedish Medical Birth Registry. Medical and other data on almost all (98% to 99%) deliveries in Sweden are listed in the register, which also includes stillbirths after 28 weeks of gestation. It is based on copies of the standardized medical record forms completed at the maternity health care centers at the start of prenatal care, usually in gestational weeks 10 to 12; records from the delivery units; and the pediatric examination of the newborn. The system is identical throughout the country. A description and validation of the register content is available (Cnattingius et al., 1990; National Board of Health and Welfare, 2003).

Midwives record maternal weight and height on a standardized form at the first visit at the maternity health care center. Ninety percent of women who will give birth present themselves to the antenatal clinic during the first trimester of their pregnancy.

BMI (kilograms per square meter) was calculated from maternal weight and height data. Women were grouped in four categories of BMI: underweight (<19.8), average weight (19.8 to 26), overweight (26.1 to 29), and obese (>29) according to the Institute of Medicine (IOM) weight-for-height categories (Institute of Medicine, 1990).

### Identification and Classification of Subjects With Orofacial Clefts

Infants with a congenital orofacial cleft were identified from three sources: the Swedish Medical Birth Registry, the Swedish Registry of Congenital Malformations (Källén and Winberg, 1968), and the Hospital Discharge Registry (National Board of Health and Welfare, 2003). The Medical Birth Register and the Register of Congenital Malformations both refer to the neonatal period. The Hospital Discharge Registry contains information on discharge diagnoses of all patients admitted to Swedish hospitals. The various sources were linked using the personal identification numbers of mothers, infants, or both. These numbers are given to each person living in Sweden and are extensively used in society, including all health care. In most instances, the diagnoses agreed among the three registers (but subjects were not always recorded in all three registers).

In this study, subjects were infants with an orofacial cleft, reported to any one of the above-described registers with data in the Medical Birth Register. Controls were all infants born and registered in the Medical Birth Register.

All infants with cleft with an unrelated major malformation or a chromosome anomaly were also identified from the above-described registers. Minor and variable conditions like preauricular tags, undescended testicle, unstable hip, and nevus were not counted as associated malformations. Infants with a diagnosis of a chromosomal aberration were excluded. Clefts were divided into the following categories: isolated cleft palate without cleft lip (CP), cleft lip without cleft palate (CL), and cleft lip with cleft palate (CLP). CL+CLP thus represents all cleft lips.

All subjects were divided into isolated (without any other

major malformation present) or nonisolated (with other major malformations).

### Confounding Factors

Maternal age (7-year classes), parity (1 to 4+), smoking (no smoking, less than 10 cigarettes/day, more than 10 cigarettes/day), and year of birth were thought to be potential confounding factors and were included as covariates in the adjusted analyses. Information on these variables was obtained from the antenatal care center documents.

Socioeconomic level was evaluated from maternal educational level, only available up to and including the year 1995.

### Statistical Analyses

Odds ratios (ORs) were determined using the Mantel-Haenszel technique for adjusted rates (Mantel and Haenszel, 1959). Estimates of 95% confidence intervals (95% CIs) were made with a test-based method, based on the Mantel-Haenszel chi-square test (Miettinen, 1974). When two stratified ORs were compared, *z* tests were performed based on the variances obtained from the stratified analyses.

## RESULTS

A total of 1686 infants with orofacial clefts were identified during the observation period, a rate of 1.7/1000 births. In this material 1408 (84%) of the orofacial clefts were isolated (i.e., the cleft was the only major congenital malformation present). CP occurred in 36%, CL in 25%, and CLP in 38%. Information that enabled the calculation of BMI was available in 1422 (84.3%) of the case mothers and in 83% of all delivered women.

The absolute majority of the women in the study population were of European Caucasian origin, 1.0% was born in South America, 1.4% was Asian, and 1.0% came from sub-Saharan Africa.

The case mothers of isolated orofacial clefts were compared with all delivered women with respect to maternal age, parity, and smoking in early pregnancy (Table 1).

Table 2 shows the distribution of orofacial clefts according to maternal BMI class and the ORs for each group are presented in Table 3.

In the maternal underweight group, no change in the risk for an infant with cleft was seen. In the overweight group, the risk was above 1 for CP, CL, CLP, and CL+CLP as well as for isolated and nonisolated defects separately, although statistical significance was reached only in the nonisolated group.

In the group of obese mothers, there was an overall increased risk for infants with cleft. The increased risk was higher when the clefts were associated with other major malformations than when they were isolated. A comparison of the two ORs gives  $z = 2.20$ ,  $p = .01$ . The association between CLP and obesity seemed to be stronger than that between CL and obesity, but this difference could be random ( $z = 1.01$ ,

**TABLE 1** Maternal Characteristics of Infants With Isolated Orofacial Clefts and Infants of All Delivered Women

Maternal Characteristics	Case Mothers (n = 1408)		All Delivered Women (n = 988,171)	
	n	%	n	%
Maternal age, y				
<20	37	2.6	20,859	2.1
20–24	254	18.0	169,017	17.1
25–29	502	35.7	359,664	36.4
30–34	421	29.9	296,578	30.0
35–39	162	11.5	119,928	12.1
≥40	32	2.3	22,125	2.2
Parity				
1	559	39.7	406,708	41.2
2	525	37.3	355,800	36.0
3	219	15.6	152,059	15.4
4	105	7.5	73,604	7.4
Maternal smoking				
Unknown	70	5.0	57,091	5.8
No smoking	1081	76.7	778,750	78.8
<10 cigarettes/d	155	11.0	98,847	10.0
≥10 cigarettes/d	102	7.2	53,483	5.4

$p = .24$ ). Even though the OR for CP was not quite statistically significant, there was no significant difference between the OR for CP or CLP ( $z = 0.55$ ,  $p = .34$ ) or between CP and total cleft lip ( $z = 0.14$ ,  $p = .40$ ).

The proportional attributable risk of orofacial clefts because of maternal obesity (BMI >29) is  $([1.30 - 1]/1.30) = 0.23$ . In the general population of delivered women in Sweden, 10.4% are obese; the population attributable fraction of orofacial clefts is therefore  $0.23 \times 10.4 = 2.4$ .

To study the possible impact of socioeconomic conditions on the association between maternal obesity and infant clefts, maternal education level was used as a proxy for socioeconomic class. This information was available only up to and including 1995, so the analysis was restricted to 718 subjects with a known BMI. The OR for infant cleft at maternal obesity was 1.01 (95% CI 0.74 to 1.36) at low maternal education (maximum 2 years after compulsory school) and 1.43 (95% CI 0.93 to 2.20) at high maternal education. These two ORs did not differ significantly ( $z = 0.98$ ,  $p = .25$ ). However, the effect seems, if anything, to be stronger at high than at low socioeconomic level.

## DISCUSSION

A positive association was found between maternal obesity in early pregnancy and orofacial clefts in the offspring. This association has been observed in a few other studies, although low numbers of cases limited their statistical power. Moore et al. (2000) found a twofold increased risk for orofacial clefts among infants of obese women, defined as BMI  $\geq 28$  and based on 35 subjects. A case-control study from Germany also reported an elevated OR, 1.7 (95% CI 1.1 to 2.8), among women with BMI >30 for infant orofacial clefts (Queisser-Luft et al., 1998). Contradictory results from the Centers for Disease Control and Prevention (Atlanta, GA) were recently presented in which a decreased risk for any type of orofacial cleft was seen among obese women (Watkins et al., 2003). This study included only 90 infants with orofacial clefts. This is in accordance with the results from a study by Shaw et al. (2000) in which no association between maternal obesity and oral clefts was found.

The present study can be looked on as a large case-control study based on 1422 mothers with known BMI and who had given birth to infants with an orofacial cleft. The completeness of ascertainment of the infants with orofacial clefts is probably high because we used multiple sources for ascertainment. Infants with chromosome anomalies were excluded from the analysis because of their known association with orofacial clefts.

An advantage of register studies is the large number of individuals, which gives high statistical power and makes it possible also to demonstrate weak effects on reproductive outcome. Another advantage is the access to information on at least some putative confounders.

Exposure information (weight and height) was recorded in early pregnancy and therefore prospective with regard to the identification of the orofacial defect. Recall bias was thus avoided. The percentage of women with a known BMI did not differ markedly between subjects and controls.

A problem concerning studies in this field is the definition of obesity. Different thresholds or cut-off values for defining obesity were used in different studies, which makes it difficult to exactly compare risk estimates. Our data are based on the IOM categorization of BMI; the World Health Organization suggests another classification.

A slightly increased risk for orofacial clefts of any type in

**TABLE 2** Distribution of Body Mass Index (BMI) Among All Delivered Women and Women With Infants With Orofacial Clefts\*

BMI	All Delivered Women	CP	CL	CLP	Unspecified	Isolated	Nonisolated	Total
<19.8	82,624	55	32	60	1	127	21	148
19.8–26	544,127	339	222	332	2	760	135	895
26.1–29	104,189	69	55	69	2	158	37	195
>29	86,757	68	41	74	1	145	39	184
Unknown	170,474	79	75	109	1	218	46	264
Total	988,171	610	425	644	7	1408	278	1686

\* The clefts are shown according to cleft defect type. Isolated and nonisolated defects are displayed separately. CP = cleft palate; CL = cleft lip; CLP = cleft lip and palate.

**TABLE 3 Adjusted Odds Ratio (OR) for Each Body Mass Index (BMI) Class to Have an Infant With an Orofacial Cleft**

BMI	CP Adjusted OR* (95% CI)	CL Adjusted OR* (95% CI)	CLP Adjusted OR* (95% CI)	CL + CLP Adjusted OR* (95% CI)	Isolated Adjusted OR* (95% CI)	Nonisolated Adjusted OR* (95% CI)	Total Adjusted OR* (95% CI)
<19.8	1.05 (0.60–0.99)	0.95 (0.66–1.37)	1.17 (0.89–1.54)	1.08 (0.87–1.35)	1.08 (0.90–1.31)	1.02 (0.64–1.63)	1.08 (0.90–1.28)
19.8–26	1.00	1.00	1.00	1.00	1.00	1.00	1.00
26.1–29	1.08 (0.84–1.40)	1.27 (0.94–1.71)	1.11 (0.86–1.44)	1.18 (0.97–1.43)	1.09 (0.92–1.30)	1.48 (1.03–2.12)	1.15 (0.98–1.34)
>29	1.28 (0.98–1.67)	1.14 (0.81–1.59)	1.42 (1.00–1.84)	1.31 (1.07–1.60)	1.20 (1.00–1.44)	1.88 (1.32–2.68)	1.30 (1.11–1.53)
Unknown	0.77 (0.60–0.99)	1.08 (0.81–1.42)	1.01 (0.81–1.27)	1.04 (0.87–1.24)	0.93 (0.79–1.08)	0.99 (0.70–1.40)	0.94 (0.81–1.08)

\* Adjustments were made for maternal age, parity, smoking in early pregnancy, and year of birth. CP = cleft palate; CL = cleft lip; CLP = cleft palate and cleft lip; CI = confidence interval.

the overweight group was observed in this study, although the finding could be random, whereas maternal obesity was statistically significantly associated with orofacial clefts in the offspring (OR 1.30). The risk estimates concerning maternal obesity and neural tube defects range from 1.35 to 2.7 (Waller et al., 1994; Shaw et al., 1996; Källén, 1998; Watkins et al., 2003) and for maternal obesity and congenital cardiovascular malformations from 1.18 to 2.1 (Waller et al., 1994; Moore et al., 2000; Watkins et al., 2001, 2003; Cedergren and Källén, 2003).

The association between maternal obesity and orofacial clefts was stronger when another major congenital defect was present than when the cleft was isolated, but an increased risk also was present for isolated clefts. Concerning the subgroups of clefts, obese women tended to be more likely to have an infant with CLP than CL or CP, but there was no significant difference between the risk estimates.

The OR assesses how much more likely a woman with obesity is to give birth to a child with an orofacial cleft than an average-weight woman, but it gives no indication of the magnitude of the excess risk in absolute terms. This could be measured by the attributable risk expressed as a proportion of the total incidence rate among the exposed. The proportional attributable risk of orofacial clefts because of maternal obesity (BMI >29) is  $(1.30 - 1)/1.30 = 0.23$ , with maternal obesity accounting for 23% of all cases of orofacial clefts among the obese mothers. The overall impact of the risk factor obesity on orofacial clefting in the population is 2.4%.

Whatever the underlying mechanism behind the observed association between maternal obesity and orofacial clefts is, it affects the closure of the lip and palate in early pregnancy. One possible explanation is undetected type 2 diabetes because obese women in the absence of overt diabetes have been found to have an impaired glucose metabolism (Scheen et al., 1995), which may be associated with an increased risk for orofacial clefts (Moore et al., 2000; Åberg et al., 2001; Spilson et al., 2001). Another possible explanation for the association between obesity and orofacial clefts could be improper nutrition. In studies based on retrospective data, it has been suggested that deficient folic acid supply could increase the risk for orofacial clefts (Shaw et al., 1995; Itikala et al., 2001), but prospective data on folic acid supplementation gave no support for such an association (Czeizel et al., 1999; Källén and Otterblad Olausson, 2002). Other suggested causes of orofacial clefts are smoking (Källén, 1997; adjustment for maternal

smoking in early pregnancy was made); exposure to organic solvents; and the use of some drugs such as anticonvulsants and corticosteroids (Källén, 2003). None of these factors is likely confounders. Other confounders that could not be taken into consideration may exist. Socioeconomic level is one. In Sweden smoking during pregnancy is closely related to socioeconomic level, and adjustment was made for maternal smoking. Our finding suggested that in a subgroup (infants born 1992 through 1995), the effect of maternal obesity was stronger at high than at low maternal education. If so, it indicated that the effect of obesity is not a direct one but may be secondary to or interacting with other factors.

The observed association between maternal obesity and orofacial clefts in the offspring could be of importance from a public health point of view. The knowledge about various negative reproductive effects of prepregnancy obesity could perhaps contribute to behavioral changes concerning nutrition and physical exercise among women of fertile age.

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