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Maternal underweight and obesity and risk of orofacial clefts in a large international consortium of population-based studies

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Abstract

Background: Evidence on association of maternal pre-pregnancy weight with risk of orofacial clefts is inconsistent.

Methods: Six large case-control studies of orofacial clefts from Northern Europe and the USA were included in analyses pooling individual-level data. Cases included 4943 mothers of children with orofacial clefts (cleft lip only: 1135, cleft palate with cleft lip: 2081, cleft palate only: 1727) and controls included 10 592 mothers of unaffected children. Association of orofacial cleft risk with pre-pregnancy maternal weight classified by level of body mass index (BMI, kg/m^2) was evaluated using logistic regression adjusting for multiple covariates.

Results: Cleft palate, both alone and with cleft lip (CP+/-CL), was associated with maternal class II+ pre-pregnancy obesity ($\geq$ 35)compared with normal weight [adjusted odds ratio (aOR) = 1.36; 95% confidence interval (CI) = 1.16, 1.58]. CP+/-CL was marginally associated with maternal underweight (aOR = 1.16; 95% CI = 0.98, 1.36). Cleft lip alone was not associated with BMI.

Conclusions: In this largest population-based study to date, we found an increased risk of cleft palate, with or without cleft lip, in class II+ obese mothers compared with normal-weight mothers; underweight mothers may also have an increased risk, but this

requires further study. These results also suggest that extremes of weight may have a specific effect on palatal development.

Key words: Cleft lip, cleft palate, maternal weight, underweight, obesity, case-control study

Key messages

- Maternal pre-pregnancy body mass index has been associated with risk of orofacial clefts in some studies, although the findings have been inconsistent.
- In the largest international population-based study to date, class II+ obesity was associated with an increased risk of cleft palate alone and cleft palate with cleft lip.
- Maternal underweight may possibly increase the risk of cleft palate, with or without cleft lip; however, further studies are needed to determine if this is likely to be a causal association.
- Cleft lip alone was not associated with maternal weight, suggesting that factors related to maternal weight may have a specific influence on palatal development.

Introduction

Cleft lip and cleft palate are among the most common and burdensome birth defects.[1–3] There is considerable variation in the occurrence of orofacial clefts by ethnicity, socioeconomic status and geographical location. However, there are no consistent global data on time trends in birth prevalence. Further, examining population trends in birth prevalence of orofacial clefts is fraught with difficulties in inferring causation, because potential protective factors and potential risk factors may have changed in frequency over time. Although several genetic factors have been associated with orofacial clefts, they explain little of the variation within and between populations in occurrence.[4] Several behavioural and environmental risk factors may increase orofacial cleft risk, including maternal exposure to tobacco smoke, medications, workplace teratogens, alcohol, insufficient folate intake, poor nutrition and unplanned pregnancy.[1,5]

Maternal obesity is a serious public health problem in both developed and developing countries,[6] and has been associated with a wide variety of birth defects.[7] Several obesity-related mechanisms may cause birth defects, including insulin resistance, hyperinsulinaemia, hyperglycaemia, systemic inflammation, oxidative stress, advanced glycation end-products and genomic damage.[8] Maternal obesity may also be associated with poor nutrient intake and low blood levels of nutrients critical for fetal development.[9] Maternal underweight is also linked to poor nutrition, metabolic abnormalities and poor reproductive outcomes.[10,11] Therefore, both extremes of maternal body weight range may influence the risk of orofacial clefts.

Some studies have shown positive associations between maternal obesity and risk of orofacial clefts,[7,12–16] whereas others have not.[17–21] Fewer studies have examined the association between maternal underweight and orofacial cleft risk, and only two studies found associations;[15,19] five other studies were inconclusive.[12,13,18,21,22] We investigated the association between maternal pre-pregnancy body mass index (BMI) and risk of orofacial clefts in a pooled analysis of individual-level data from six population-based studies in Denmark, Norway and the USA.

Methods

Study design

The present study reports on pooled case-control analyses of data from six population-based studies conducted in Denmark, Norway and the USA between 1987 and 2008. Each study included data obtained directly from mailed questionnaires or interviews completed by mothers of children affected with orofacial clefts (cases) and mothers of unaffected children (controls) after the index pregnancy. Controls in each study included randomly selected children with no birth defects born in the same years and geographical areas as cases. All procedures were approved by local institutional review boards. The total sample before any exclusion was 5280 cases and 11 461 controls. The only exclusion criterion was having incomplete data on one or more of the study variables (including BMI and covariates). The final analytical sample included 4943 cases and 10 592 controls.

Denmark

The Danish study included 187 mothers of children with an orofacial cleft, and a random sample of 828 mothers of

unaffected children born between 1997 and 2003, from the Danish National Birth Cohort study for a nested case-control analysis.[23,24] All children born with orofacial clefts in this cohort were identified through their registration in the Danish National Facial Register, since all cleft repair surgeries are centralized in two hospitals in Denmark. The analytical sample with complete data, collected before delivery, included 131 cases and 627 controls.

Norway

Two studies were included from Norway. The Norway Facial Clefts Study (NCL) is a population-based case-control study of children born with orofacial clefts throughout Norway during 1996–2001.[25] Mothers of 570 cases were recruited from records of infants who received treatment for orofacial clefts at surgical centres when surgeries are centralized. Control mothers ($n = 763$) were selected randomly from all Norway births in the Medical Birth Registry of Norway. The analytical sample with complete data included 559 cases and 754 controls.

The Norway National Mother and Child Cohort Study (MoBa) involved a population-level sample of about 100 000 pregnancies between 1999 and 2009.[26] The MoBa cohort contributed 184 children with orofacial clefts and 551 unaffected children randomly selected as controls for a nested case-control analysis. The analytical sample with complete data, collected before delivery, included 139 cases and 426 controls.

Utah

The Utah case-control study included 561 cases with orofacial cleft born between 1 January 1995 and 30 June 2004 and ascertained via the state-wide birth defect registry, and 660 unaffected births randomly selected from all Utah birth certificates as controls.[27] Utah cases and controls born after 30 June 2004 were eligible for the U.S. National Birth Defects Prevention Study (NBDPS) with similar protocols, as described below. The analytical sample with complete data included 557 cases and 658 controls.

Iowa

The Iowa case-control study was conducted in 1987–91 with an overall sample of 287 cases identified via the state-wide Iowa Registry of Congenital and Inherited Disorders and 302 controls randomly selected from all Iowa birth certificates.[28] Iowa cases and controls born f1997–2007 were included in the NBDPS, described below with similar protocols. The analytical sample with complete data included 280 cases and 293 controls.

U.S. National Birth Defects Prevention Study

The NBDPS included orofacial cleft cases and controls from 10 participating states, including Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah.[29] Orofacial cleft cases were ascertained from birth defect registries in each state, and controls were unaffected live births with a date of delivery during the same time frames as case pregnancies and randomly selected from either hospital delivery logs (AR and GA 1997–2000; CA, NY, TX 1997–2007) or birth certificate files (AR 2000–07; GA 2001–07; IA, MA, NC, NJ, UT 1997–2007).[30] The overall sample from the NBDPS included 3491 cases and 8357 controls born between 1997 and 2007. The analytical sample with complete data included 3277 cases and 7834 controls.

Covariates and classification of orofacial clefts

Pre-pregnancy weight and height data were self-reported by mothers in each study. Standard definitions were used for BMI categories,[31] including underweight (BMI $<$ 18.5), normal weight (18.5 $\leq$BMI $<$ 25), over-weight (25 $\leq$BMI $<$ 30), obese class I (BMI $\geq$ 30, $<$ 35) and obese classes II and III (BMI $\geq$ 35). Covariates of interest as potential confounding factors that were available from all studies were: maternal age in years at time of delivery; maternal smoking and alcohol use during the first trimester (categorized as user vs non-user); use of folic acid supplements or multivitamins in the first trimester (user vs non-user); and maternal education as an indicator of socioeconomic status (less than high school vs high school graduate or higher).

Orofacial clefts were classified as isolated or non-isolated (occurring with other major birth defects) and into types including cleft lip only ($n = 1135$), cleft lip with cleft palate ($n = 2081$) or cleft palate only ($n = 1727$). The non-isolated orofacial clefts included children with other major birth defects, and in most sites these included known syndromes as well as children with multiple birth defects with no known syndrome. It is known that some syndromic forms of orofacial clefts (for example Van der Woude syndrome) share common aetiological factors with isolated orofacial clefts; thus we judged it useful to consider orofacial clefts in both groups, as this likely represents a spectrum of related disorders. However, the NBDPS excluded cases resulting from known single gene or chromosomal abnormalities. The sample of isolated orofacial clefts included 4048 cases (1030 cleft lip only; 1743 cleft lip with cleft palate; 1275 cleft palate only).

Statistical analyses

Logistic regression was used to evaluate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) as an estimate of risk of having a child with an orofacial cleft in underweight, overweight, class I obese and class II + obese mothers compared with the reference group of normal-weight mothers. In addition to the potential maternal confounders described above, we also included indicator variables (fixed effects) for study sites to control for differences in case-control ratios and unobservable confounders across studies. We estimated another model with an ordinal BMI variable instead of the three dummy variables for BMI and compared the two models using a likelihood ratio test. In additional logistic regression models, we included interaction terms between the study fixed effects and BMI-level dummy variables to test for heterogeneity between studies. As another check for study influence on the pooled sample estimate, we estimated the main fully adjusted models separately for the NBDPS, the largest study, and for the other studies combined. In addition to the fully adjusted models, we estimated for comparison a partially adjusted model that only included the study fixed effects as covariates and omitted the maternal covariates described above. Separate models were evaluated for cleft lip only, cleft lip with cleft palate, cleft palate only and all cleft palates combined. Additional models were estimated excluding non-isolated cases.

Results

Population characteristics

The numbers of controls and cases by orofacial cleft type in the analytical sample are listed by study site in Table 1. The rate of missing data overall was 9.4% for cases and 9.2% for controls; this varied between studies, but was close between cases and controls within studies as follows: Utah: 0.7% vs 0.3%, Norway NCL: 1.9% vs 1.2%, Iowa: 2.4% vs 3.0%, U.S. NBDPS: 6.1% vs 6.3%, Norway MoBa cohort: 24.5% vs 22.7%, Danish cohort: 30.0% vs 24.3%. The missing data in the Moba and Danish cohorts were mainly driven by missing data on covariates including smoking, alcohol and education. The distribution of BMI categories and maternal characteristics by case-control status is shown in Table 2. Class II+ obesity (BMI $\geq$ 35) showed the widest range in prevalence, from a low in the Norway case-control study (2.5% in cases, 0.9% in controls) to a high in the NBDPS (8.7% in cases, 7.0% in controls). Mean maternal age at the child's birth was similar between cases and controls. First-trimester smoking rates ranged from a low in Utah (13.5% in cases, 8.1% in controls) to a high in the Norway case-control study (41.3% in cases, 31.8% in controls).

Maternal BMI associations

Risk of cleft palate, both alone and with cleft lip, was associated with maternal underweight in the partially adjusted model (Table 3; aOR for all cleft palates = 1.22; 95% CI = 1.04, 1.43); this association was attenuated in the fully adjusted model (aOR = 1.16; 95% CI = 0.98, 1.36). Risk of cleft palate, alone or with cleft lip, was increased by about 38% in the partially adjusted model (aOR for all cleft palate = 1.38; 95% CI = 1.18, 1.61) with maternal class II+ obesity (BMI $\geq$ 35) vs normal weight; the estimate was similar in the fully adjusted model (aOR = 1.36; 1.16, 1.58). Class I obesity and overweight were not associated with changes in cleft palate risk. However, a test for trend using an ordinal BMI variable excluding the underweight group and using the normal weight group as the reference, found an increasing trend in risk with increasing BMI levels ($P < 0.001$). In contrast, there was no evidence that cleft lip alone was associated with any of the underweight, overweight or obesity groups, and the aORs were noticeably smaller than those for cleft palate and close to 1.0.

Table 1. Number of controls and orofacial cleft cases by cleft type and study site[a]

Site and birth years	Number of study participants by type				
	Controls	Cleft lip only	Cleft palate with cleft lip	Cleft palate only	All orofacial clefts
Utah, USA (1995–2004)	658	141	230	186	557
Danish National Birth Cohort (1998–2001)	627	39	51	41	131
Norway Facial Cleft (NCL) Study (1996–2001)	754	135	230	194	559
Norway Mother-Baby (MoBa) Study (2000–09)	426	18	71	50	139
Iowa, USA (1987–91)	293	56	108	116	280
U.S. National Birth Defects Prevention Study (1997–2008)	7834	746	1391	1140	3277
Total sample	10592	1135	2081	1727	4943

[a]Includes isolated orofacial clefts and non-isolated orofacial clefts.

Table 2. Distribution of body weight measures and maternal characteristics by study site and orofacial cleft status[a]

Characteristic	Mean (SD) or % by study site											
	Utah		Danish National Birth Cohort		Norway: NCL		Norway: MoBa		Iowa		U.S. NBDPS	
	Case $n = 557$	Control $n = 658$	Case $n = 131$	Control $n = 628$	Case $n = 559$	Control $n = 754$	Case $n = 139$	Control $n = 426$	Case $n = 280$	Control $n = 293$	Case $n = 3277$	Control $n = 10168$
Body-mass index (BMI; kg/m^2)	24.32 (5.02)	24.24 (5.34)	23.99 (4.61)	23.41 (3.98)	23.69 (4.39)	23.44 (3.71)	24.04 (4.28)	24.15 (4.28)	23.54 (5.19)	23.00 (4.24)	25.33 (6.15)	25.05 (5.77)
Underweight %, < 18.5 BMI	5.9	6.8	3.8	3.4	4.3	3.7	2.9	4.9	9.3	8.2	6.6	5.5
Normal weight %, 18.5, < 25 BMI	57.6	59.6	66.4	71.3	67.1	70.4	68.4	62.0	60.4	65.2	48.9	51.4
Overweight %, ≥ 25, < 30 BMI	22.8	21.4	19.9	19.1	20.2	18.8	17.3	22.1	22.1	17.8	24.0	25.0
Obese Class I %, ≥ 30,< 35 BMI	9.3	6.7	5.3	4.3	5.9	6.1	9.4	8.2	3.6	7.9	11.9	11.2
Obese II & III %, ≥ 35 BMI	4.3	5.5	4.6	1.9	2.5	0.9	2.2	2.8	4.6	1.0	8.7	7.0
Maternal age in years	27.0 (5.7)	26.8 (5.2)	29.3 (4.5)	30.2 (4.0)	29.0 (4.9)	29.3 (4.8)	29.9 (4.8)	30.4 (4.5)	26.7 (5.4)	27.1 (4.9)	27.0 (6.2)	27.0 (6.1)
Smoker	13.5	8.1	32.1	25.8	41.3	31.8	30.9	21.4	25.4	22.2	22.0	16.7
Alcohol use in 1st trimester	7.5	6.4	45.8	42.4	37.9	30.6	12.2	14.8	35.0	35.2	23.5	23.1
Multivitamin or folic acid use	75.9	75.7	56.5	60.3	36.7	40.5	76.3	81.2	63.6	71.0	83.7	85.8
Education ≤ high school[b]	7.9	6.5	5.3	4.8	15.6	11.1	5.8	1.9	10.0	7.9	17.4	15.0

[a]Includes isolated and non-isolated clefts.

[b]Coded as a highest maternal education of less than 10th class for Denmark.

Table 3. Risk of isolated and non-isolated orofacial cleftsby maternal body mass index (BMI) group[a]

Maternal body mass index (BMI) group	Cleft lip only	Cleft palate with cleft lip	Cleft palate only	All cleft palates
	Partially adjusted odds ratios[b] (95% confidence intervals)			
Underweight BMI < 18.5	1.11 (0.85, 1.45)	1.22 (1.00, 1.50)	1.21 (0.97, 1.50)	1.22 (1.04, 1.43)
Normal weight BMI ≥ 18.5, < 25	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Overweight BMI ≥ 25, < 30	1.00 (0.86, 1.17)	1.02 (0.90, 1.14)	1.08 (0.95, 1.22)	1.04 (0.95, 1.14)
Obese Class I ≥ 30, < 35 BMI	1.06 (0.85, 1.31)	1.16 (0.99, 1.36)	1.10 (0.92, 1.31)	1.13 (1.00, 1.29)
Obese II & III > 35 BMI	1.10 (0.84, 1.44)	1.37 (1.13, 1.66)	1.40 (1.14, 1.72)	1.38 (1.18, 1.61)
	Fully adjusted odds ratios[c] (95% confidence intervals)			
Underweight BMI < 18.5	1.07 (0.82, 1.40)	1.12 (0.91, 1.37)	1.21 (0.97, 1.51)	1.16 (0.98, 1.36)
Normal weight BMI ≥ 18.5, < 25	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Overweight BMI ≥ 25, < 30	1.00 (0.86, 1.17)	1.01 (0.90, 1.14)	1.06 (0.94, 1.21)	1.03 (0.94, 1.13)[d]
Obese Class I ≥ 30, < 35 BMI	1.04 (0.84, 1.29)	1.12 (0.95, 1.32)	1.08 (0.90, 1.29)	1.10 (0.97, 1.25)[d]
Obese II & III ≥ 35 BMI	1.09 (0.83, 1.42)	1.35 (1.12, 1.64)	1.37 (1.11, 1.69)	1.36 (1.16, 1.58)[d]

[a]Body mass index calculated as weight in kg/height in m^2; sample includes 1135 cleft lip, ,081 cleft palate with cleft lip, 1727 cleft palate only, 3808 all cleft palates and 10 592 controls.

[b]Covariates in multiple logistic regression models include only study site indicators.

[c]Covariates in multiple logistic regression models include study site indicators, maternal age, indicators for maternal smoking and alcohol use during first three months of pregnancy, multivitamin or folic acid use and education (less than high school vs high school graduate or greater).

[d]Test for trend excluding underweight group with normal weight group as reference: P <.0.001.

A similar pattern of results was generally observed when limiting the analysis to isolated orofacial clefts (Table 4). The association between underweight and cleft palate was attenuated in the fully adjusted model, likely driven by the smaller number of cases than the full sample. The association with class II+ obesity was also slightly attenuated in both partially and fully adjusted models in the isolated vs the combined isolated and non-isolated orofacial cleft groups.

Heterogeneity between studies

The logistic regressions including interaction terms between the BMI levels and study fixed effects in the total analytical sample found little evidence of heterogeneity in the association between BMI and orofacial clefts between studies (results of interaction tests reported in Supplementary Table S1, available as Supplementary data at *IJE* online). No interactions with underweight, overweight or class I obesity were found. For cleft lip with palate and for all cleft palates combined, a stronger association with class II+ obesity in the Norway (NCL) and Iowa studies (relative to the NBDPS as the omitted/reference study) was observed ($P < 0.05$). If anything, these results suggest that some studies could have stronger associations with class II+ obesity than the average estimate based on the pooled analysis.

Also, we overall find a consistent pattern of results when examining the NBDPS alone (the largest study) compared with the other studies combined in a separate analysis, focusing on the fully adjusted model (Supplementary Table S2 for isolated and non-isolated clefts combined, and S3 for isolated clefts only, available as Supplementary data at *IJE* online). The associations between class II+ obesity and cases with cleft palate (with or without cleft lip) are observed in both study groups. In the case of underweight however, some differences emerge. Underweight was associated with increased risk of all cleft types, especially in isolated cases in the NBDPS alone but not in the other studies. These results indicate that the estimates for underweight and cleft palate are mainly driven by the NBDPS in the pooled estimate, but that the association with cleft lip may be attenuated when combining all studies.

Sensitivity checks

We estimated additional sensitivity checks for the results. The first of these analyses added family history of orofacial clefts among first-degree relatives, which is captured only in the NBDPS and the Utah study. We estimated the fully adjusted models combining the NBDPS and the Utah study, first without adjustment for family history and then adjusting for an indicator for history of clefts in first-degree relatives. We find overall the same pattern of results as in the total pooled sample without adjustment for family history (Supplementary Tables S4 for isolated and non-isolated clefts combined and S5 for isolated clefts only, available as Supplementary data at *IJE* online). Furthermore, the association of class II+ obesity with cleft

Table 4. Risk of isolated orofacial clefts by maternal body mass index (BMI) group[a]

Maternal body mass index (BMI) group	Cleft lip only	Cleft lip with cleft palate	Cleft palate only	All cleft palate
	Partially adjusted odds ratios[b] (95% confidence intervals)			
Underweight BMI < 18.5	1.07 (0.81, 1.42)	1.24 (1.00, 1.54)	1.15 (0.90, 1.48)	1.21 (1.02, 1.44)
Normal weight BMI ≥ 18.5, < 25	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Overweight BMI ≥ 25, < 30	1.01 (0.86, 1.18)	1.02 (0.90, 1.16)	1.02 (0.88, 1.17)	1.02 (0.92, 1.13)
Obese Class I ≥ 30, < 35 BMI	1.07 (0.86, 1.33)	1.12 (0.94, 1.33)	1.11 (0.91, 1.35)	1.11 (0.97, 1.28)
Obese II & III ≥ 35 BMI	1.04 (0.78, 1.37)	1.34 (1.09, 1.64)	1.32 (1.05, 1.67)	1.33 (1.13, 1.57)
	Fully adjusted odds ratios[c] (95% confidence intervals)			
Underweight BMI < 18.5	1.04 (0.78, 1.39)	1.12 (0.91, 1.40)	1.14 (0.89, 1.48)	1.14 (0.95, 1.36)
Normal weight BMI ≥ 18.5, < 25	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Overweight BMI ≥ 25, < 30	1.00 (0.85, 1.17)	1.01 (0.89, 1.15)	1.02 (0.88, 1.18)	1.02 (0.92, 1.13)[d]
Obese Class I ≥ 30, < 35 BMI	1.05 (0.84, 1.31)	1.09 (0.91, 1.30)	1.09 (0.89, 1.33)	1.09 (0.95, 1.25) [d]
Obese II & III ≥ 35 BMI	1.03 (0.78, 1.37)	1.30 (1.05, 1.60)	1.29 (1.02, 1.64)	1.29 (1.10, 1.53)[d]

[a]Body mass index, weight calculated as weight in kg/height in m^2; sample includes 1030 cleft lip, 1743 cleft palate with cleft lip, 1275 cleft palate only, 3018 all cleft palate and 10 592 controls.

[b]Covariates in multiple logistic regression models include study site indicators.

[c]Covariates in multiple logistic regression models include study site indicators, maternal age, indicators for maternal smoking and alcohol use during first three months of pregnancy, multivitamin or folic acid use and education (less than high school vs high school graduate or greater).

[d]Test for trend excluding underweight group with normal weight group as reference: $P = 0.004$.

palates is slightly more pronounced when adjusting for family history. The association between underweight and all cleft palate combined also remains suggestive. We also examined the associations of body weight with non-isolated clefts alone by cleft type (Supplementary Table S6, available as Supplementary data at *IJE* online). Focusing on the fully adjusted models, we found that class II+ obesity is associated with increased risk for all non-isolated cleft types and that the associations are also more pronounced (larger odds ratios) than those for isolated clefts(Supplementary Table S6). Risk also appears to increase with underweight.

In order to examine the possibility of residual confounding in smoking from differences in smoking intensity, we re-estimated the fully adjusted model replacing any smoking with the number of cigarettes per day (including 0 for non-smokers). We found similar results to those adjusting for any smoking (Supplementary Table S7, available as Supplementary data at *IJE* online).

We also re-estimated a multinomial logistic regression for the three cleft types vs the controls and found virtually the same results as those based on the separate regressions for each cleft type (Supplementary Table S8, available as Supplementary data at *IJE* online). Finally, we tested the difference in association of class II+ obesity with cleft lip only and all cleft palates combined, by re-estimating the multinomial logit model combining all cleft palates into one category and using a Wald-type test for the difference in odds ratios between cleft lip only and cleft palates (Supplementary Table S9, available as Supplementary data at *IJE* online). The *P*-value for the difference in odds ratios was 0.11 (0.14 for isolated cases only).

Discussion

We found an increased risk of having a child with cleft palate, with or without cleft lip, for women with grade II+ obesity (BMI ≥ 35) in the pre-pregnancy period compared with normal-weight women. Cleft palate, with or without cleft lip, was associated with maternal underweight; however, this was attenuated in the fully adjusted model. This finding suggests that underweight mothers may also have an increased risk, but further study is needed to examine if this is a causal association. Cleft lip alone was overall not associated with BMI.

This pooled analysis represents the largest international study to date of environmental risk factors including maternal weight, based on a consortium of studies with population-based ascertainment of orofacial clefts and controls. All studies collected similar data on pre-pregnancy weight and covariates. Study limitations included the potentialof recall bias inherent to case-control studies, though this would not apply to the Norwegian and Danish cohort studies since data were collected close to the end of the first trimester. Maternal pre-pregnancy height and weight were self-reported; thus some error in reporting is possible, as weight tends to be overestimated by underweight persons and underestimated by obese persons.[32] Such errors would be expected to bias BMI effects on orofacial cleft risk toward the null, and thus the observed associations for cleft

palate in the present study may be slightly underestimated. Despite inclusion of data on several potential confounders, including smoking, alcohol use, folic acid and multivitamin intake and education in multivariate models, residual confounding is a possibility; however, whereas there were observable differences between cases and controls in potential confounding factors, adjusting for them did not have a major impact on the results related to maternal weight. It is also uncertain whether these results can be generalized to populations in low-resource settings.

Our findings are consistent with several previous studies.[7,12–14,16] Queisser-Luft *et al.* were among the first to report an elevated risk of orofacial clefts with maternal obesity (OR = 1.7; 95% CI: 1.1, 2.8; orofacial cleft type was unspecified).[14] Cedergren *et al.*, using Swedish Medical Birth Registry data, found associations between BMI > 29 and cleft lip and palate (aOR = 1.42; 95% CI: 1.00, 1.84).[13] A later paper from the Swedish registry found that women with a > 3-unit increase in pre-pregnancy BMI at the beginning of their second pregnancy compared with the beginning of their first pregnancy, had a 2.3-fold higher risk of cleft palate in their infant, but the risk of cleft lip was not increased.[16] In a meta-analysis, Stothard *et al.* found that obese mothers had an increased risk of isolated cleft palate and cleft palate with cleft lip, but no increase in risk of cleft lip only.[7] In an analysis of birth certificate data from Florida, Block *et al.* found obesity was associated with an increase in risk of cleft lip with or without cleft palate and with cleft palate only, but did not evaluate cleft lip only.[12] Furthermore, the accuracy of body weight and height and covariate data in birth certificates may be less than in data collected in interviews.[33]

Several other studies were less conclusive due to one or more of the following issues: limitations in study design including small sample sizes, limited data on potential confounding or modifying factors, birth certificate data with excessive missing data or inconsistent definitions of BMI groups and orofacial cleft types.[15,17–21] Few studies have examined the association between maternal pre-pregnancy underweight, only two studies found associations with orofacial cleft risk[15,19] and five other studies were inconclusive.[12,13,18,21,22] Our study is the largest population-based sample to date that simultaneously evaluated five body weight categories—underweight, normal weight, overweight, class I obese and class II+ obese—for the three orofacial cleft types separately.

Our study strengthens and extends the findings of the previously published NBDPS study[15] based on a much smaller sample size that found an elevated risk for cleft lip with or without cleft palate among underweight mothers; no other birth defects of any type were associated with maternal underweight. An association was also reported between maternal obesity (BMI ≥ 30) and increased risk of cleft lip with or without cleft palate in infants with multiple (non-isolated) birth defects, but not in the children with isolated clefts; the group with cleft lip only was not analysed separately, and combining this group with cleft palates may be one reason why no association was found between obesity and isolated clefts in the combined lip and palate groups.

Cleft lip alone and cleft lip with cleft palate are often viewed as aetiologically similar, differing only in severity; a severe cleft in the lip can lead to a cleft in the hard palate which may be viewed as a secondary effect of disturbance in the primary palate.[34] Cleft lip can however occur with a cleft of the soft but not hard palate, evidence of two separate defects.[35] In a study of Norwegian cases, Harville *et al.* found that cleft lip alone, compared with cleft lip and palate, was less likely to occur with other birth defects, less common among boys and more likely among twins and parents who were closely related.[36] These authors suggested that cleft lip only and cleft lip with cleft palate should be analysed separately, to explore the possibility that some risk factors may affect one but not the other. Our study supports the theory of different aetiological mechanisms between cleft lip alone and cleft lip with palate, and suggests that they should be considered separately; furthermore, our studies suggest that cleft lip with cleft palate and cleft palate alone may share certain risk factors or causal pathways.

The underlying mechanisms for the increased risk of cleft palate in both underweight and obese mothers are unclear and could be very different. In additional models, we added two indicators for maternal diabetes and hypertension (Supplementary Table S10, available as Supplementary data at *IJE* online), first combining isolated and non-isolated orofacial clefts and then for isolated orofacial clefts only. We found generally similar patterns for BMI results especially for the models combining isolated and non-isolated cases; the class II+ obesity associations slightly decreased but remained strong for cleft palate. We did not control for diabetes and hypertension in the main model, as these may be causally influenced by body weight in which case they would be mediators rather than confounders. Nonetheless, these additional results suggest that the observed associations with body weight are not explained by these two risk factors.

Our results suggest that the substantial rise in the prevalence of obesity[37] may result in an increased occurrence of cleft palate, with or without cleft lip, in the years ahead. Much less discussed is the possible excess risk among underweight mothers. Our findings from a large and diverse international study of increased risk of cleft palate, with or without cleft lip, in mothers with extremes in

pre-pregnancy weight, underscores the need for mechanistic studies to understand the underlying causes and for public health campaigns with periconceptional care that promote the maintenance of normal, healthy weight.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest: None

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