The Cleft Palate-Craniofacial Journal 50(5) pp. 591–596 September 2013

ORIGINAL ARTICLE

Is Gravidity 4+ a Risk Factor for Oral Clefts? A Case-Control Study in Eight South American Countries Using Structural Equation Modeling

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Background: **There is disagreement about the association between cleft lip with or without cleft palate and multigravidity, which could be explained by differences of adjusting for maternal age, Amerindian ancestry, and socioeconomic status.**

Objective: **The aim was to evaluate gravidity 4+ (four or more gestations) as a risk factor for cleft lip with or without cleft palate in South America.**

Design: **We used a matched (1:1) case-control study with structural equation modeling for related causes. Data were obtained from 1,371,575 consecutive newborn infants weighing ≥500 g who were born in the hospitals of the Estudio Colaborativo Latinoamericano de Malformaciones Congénitas (ECLAMC) network between 1982 and 1999. There were a total of 1,271 cases with cleft lip with or without cleft palate (excluding midline and atypical cleft lip with or without cleft palate). A total of 1,227 case-control pairs were obtained, matched by maternal age, newborn gender, and year and place of birth. Potential confounders and intermediary variables were analyzed with structural equation modeling.**

Results: **The crude risk of gravidity 4+ was 1.41 and the 95% confidence interval was 1.14 to 1.61. When applying structural equation modeling, the effect of multigravidity on the risk of cleft lip with or without cleft palate was 1.22 and the 95% confidence interval was 0.91 to 1.39.**

Conclusions: **Multigravid mothers (more than four gestations) showed no greater risk of bearing children who had cleft lip with or without cleft palate than mothers with two or three births. Therefore, the often observed and reported association between multigravidity and oral clefts likely reflects the effect of other risk factors related to low socioeconomic status in South American populations.**

KEY WORDS: *cleft lip with or without cleft palate, ECLAMC, gravidity 4+, matched case-control, South America, structural equation modeling*

Oral clefts are common structural birth defects, with the global prevalence ranging from 1 in 500 to 1 in 2500 (Tolarová and Cervenka, 1998). In Latin America, the observed prevalence of cleft lip with or without cleft palate (CL±P) is 12 per 10,000 births (Castilla and Orioli, 2004; Poletta et al., 2007), varying by ethnicity, geographical origin (Croen et al., 1998; Bender, 2000), altitude above sea level (Menegotto and Salzano, 1991; Poletta et al., 2007), and socioeconomic status (SES) (Clark et al., 2003; Poletta et al., 2007). Some birth defects such as heart anomalies (Tay et al., 1982; Vieira and Orioli, 2002) and neural tube defects (Bianca et al., 2002; Vieira and Orioli, 2002) have been associated with gravidity 4+ (more than four gestations). However, there is disagreement about the association of multigravidity with oral clefts. Some authors have found no higher rates of infants with CL±P born to mothers who have had more than three pregnancies (Shaw et al., 1991; Stoll et al., 1991; Mitchell, 1997; Rajabian and Sherkat, 2000); whereas, other researchers have observed a higher rate of such births among women with more than three pregnancies (Menegotto and Salzano, 1991; Lopez-Camelo and Orioli, 1996; Vieira and Orioli, 2002). These inconsistencies may be explained in part by adjusting for three major confounding factors: maternal age (Menegotto and Salzano, 1991; Vieira and Orioli, 2002), SES (Lopez-

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This study was supported by Agencia Nacional de Promoción Científica y Tecnológica, Argentina; Grant sponsor: Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina.

Submitted January 2012; Revised September 2012; Accepted October 2012.

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DOI: 10.1597/11-320

Camelo and Orioli, 1996), and Amerindian ancestry (Mitchell, 1997).

Structural equation modeling (SEM) is a statistical framework useful for analyzing data in which an outcome is determined by direct or indirect influences of the predictor variables in addition to their unobserved common cause. In recent years, SEM has been increasingly used in medical statistical studies (Kupek, 2006). To our knowledge, the association between gravidity 4+ and CL±P has not been previously analyzed using SEM. This approach quantifies the direct and indirect effects, which provides a better estimation of the true risk.

The aim of this study was to estimate the direct risk of gravidity 4+ (multiparity as well as previous fetal loss) on CL±P in a series of newborns in South America by using a case-control study design with a SEM approach.

Materials and Methods

Sample

Data were obtained from 75 maternity hospitals participating in the Estudio Colaborativo Latinoamericano de Malformaciones Congénitas (ECLAMC) network in eight South American countries: 32 in Argentina, 2 in Bolivia, 16 in Brazil, 9 in Chile, 3 in Colombia, 1 in Peru, 6 in Uruguay, and 6 in Venezuela. Between 1982 and 1999, 1,378,392 consecutive liveborn infants with birth weights ≥500 g were examined for congenital anomalies. Of 43,981 malformed babies, 1,271 had CL±P as a single defect and were included in the study. Demographic data and informed consent were obtained through interviews with the mothers before discharge in accordance with ECLAMC procedures (Castilla and Orioli, 2004). This project has been approved by the Centro de Educación Médica e Investigaciones Clínica (CEMIC) Institutional Review Board (Office for Human Research Protection, U.S. Department of Health and Human Services, IRB00001745-IORG 0001315).

Study Design

A matched (1:1) case-control study was performed. For each newborn with CL±P, a healthy newborn from the same hospital and year, matched by gender, maternal age (stratified by 1-year intervals), and Amerindian ancestry (yes/no, Amerindian ancestry versus other [Castilla and Orioli, 2004; Poletta et al., 2007]), was selected as control. A total of 1,227 matched case-control pairs were obtained. The matching scheme was proposed because the relationship between gravidity 4+ and oral clefts could be due to a maternal or paternal age effect, both closely related to gravidity (Aliyu et al., 2005).

Multigravidity Definition

The mothers were classified according to the number of pregnancies, regardless of their result, in three categories: Gravidity 1 means the current pregnancy is the first gestation. Gravidity 2–3 indicates women who carried out two or three gestations (reference group), and Gravidity 4+ refers to four or more gestations. Each gravidity category comprises the number of previous fetal losses (consider yes/no, including stillbirths and miscarriages) plus the number of live births (parity 1: the current is the first newborn; parity 2–3: women delivered out two or three newborns; and parity 4+: women with four or more live births), including the current pregnancy.

Confounding Factors

The following variables were obtained from each subject, not with intention to evaluate teratogenicity but so they could be indirectly associated with CL±P (more detail about ECLAMC procedures can be found in Castilla and Orioli, 2004): paternal age ≥40 years (yes/no); parental consanguinity (yes/no, regardless of the degree of relationship); maternal pregnancy antecedents including acute maternal illnesses during the first trimester of pregnancy, like flu or urinary tract infections (yes/no); chronic maternal illnesses, like diabetes or hypertension (yes/no); any medicine use during the first trimester of pregnancy (yes/no); and low socioeconomic status (yes/no), which was established throughout a confirmatory factorial analysis with low maternal education (<12 years education), low paternal education (<12 years education), and low paternal occupation (yes = *levels 1 to 3* versus no [non–low paternal occupation] = *levels 4 to 8*); and paternal occupation levels, which indicate sociocultural status: 1 = *unemployed*; 2 = *househusband*; 3 = *odd job/unskilled labor*; 4 = *skilled labor*; 5 = *independent labor*; 6 = *manager*; 7 = *clerk* ("white collar"); 8 = *professional, university*; 0 = *unspecified*. One factor was extracted from a 3 × 3 tetrachoric matrix, and scores were estimated for the family of each newborn using the regression method suggested by Bartlett (1937). The score distribution (mean, 0.0 ± 0.9) was classified into two groups: low socioeconomic status (score ≥ 0.57, mean, 1.20 ± 0.19) and non–low socioeconomic status (score < 0.57, mean, 0.14 ± 0.18). The loading factors were 0.867 for low maternal education, 0.898 for low paternal education, and 0.721 for low paternal occupation. The explained variance for one factor was 0.912. Cases and controls were classified upon this score as low SES using a yes or no inquiry upon the score's first tercile distribution.

Structural Equation Modeling

The proposed model included two variable groups: exogenous variables, indicators of maternal profile previous to the actual pregnancy, and endogenous variables, which belong to the current pregnancy. Previous fetal loss, low SES, and consanguinity describe the maternal profile (exogenous variables). Paternal age $\geq$40 and maternal pregnancy antecedents (exogenous) and Parity 4+ (endogenous) belong to the actual pregnancy. Gravidity 4+ effect on CL±P was estimated through previous fetal loss and parity. We performed SEM for the binary variables using the Yule transformation to approximate the matrix of Pearson correlation coefficients from the bivariate odds ratio (OR) by a well-known formula ((OR − 1) / (OR + 1)) (Kupek, 2006). The bivariate ORs were estimated using a conditional logistic regression. The correlation matrix and the paths between variables were analyzed with the LISREL 8 software (Jöreskog and Sörbom, 1993). The coefficient for each causal path was estimated by the maximum likelihood method. The following were the reference values of goodness of fit (how well the model reproduces the observed covariance matrix) used for each statistic: Minimum fit function chi-square $<$ 3.84; root mean square error of approximation (RMSEA) $\leq$ 0.05; goodness-of-fit index (GFI) and adjusted goodness-of-fit index (AGFI) are both $>$0.90; and for both parsimony normed fit index (PNFI) and Akaike information criterion (AIC), smaller is better (Jöreskog and Sörbom, 1993). The power study was estimated based on noncentral chi-square distribution (Faul et al., 2007), which provided the number of observations required to achieve 80% power (beta or type II error of 0.20) and alpha (type I error $<$ 0.05). In our model, for seven variables, a total of 28 free parameters could be estimated. Within these parameters, the minimum sample size required was 900 case-control pairs. The population attributable fraction was obtained with the formula ((IT –IE) / IT), where IT is the incidence of CL±P in the total population and IE the incidence of CL±P in the gravidity 2–3 group.

Results

A significant increase in the rate of CL±P was observed for gravidity 4+ (Fig. 1). The incidence of CL±P was 9.2 per 10,000 (1,271 per 1,378,392). The incidence for gravidity 1 to 3 and gravidity 4+ were 8.3 per 10,000 (824 per 992,381) and 11.6 per 10,000 (447 per 386,011), respectively. The distribution of variables between gravidity 4+, gravidity 2–3, and gravidity 1 were similar in cases and controls. Low paternal occupation, previous fetal loss, parental consanguinity, and maternal antecedents (medicament use, acute, and chronic maternal illness) showed higher values among gravidity 4+ cases than gravidity 4+ controls (Table 1).

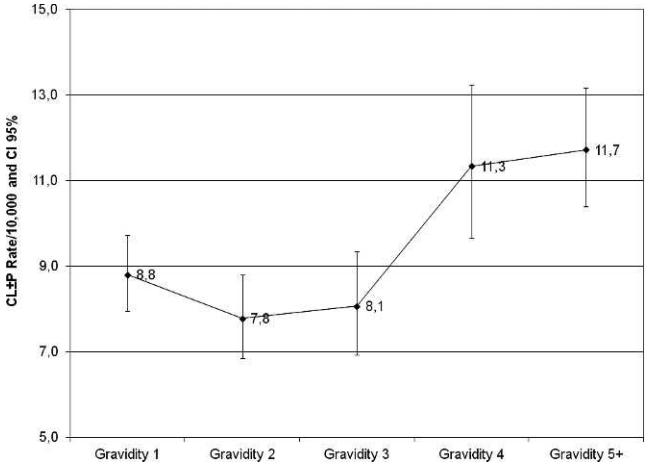

FIGURE 1 Rates of CL±P by order of gravidity.

Figure 2 shows the best fitting model from the SEM analysis. The Yule coefficients, ORs, and 95% confidence intervals (CIs) for the SEM model are shown in Table 2. Association of CL±P with previous fetal loss, maternal antecedents, and consanguinity were statistically significant.

The SEM showed seven variables, four covariance errors, 16 estimated parameters, and six structural equations for 28 possible free parameters (independence model) to be estimated. The absolute-adjusted indices show the minimum fit function $\chi^2_{12} = 2.16$ ($P = .14$) and RMSEA = 0.040 (95% CI, 0.001 to 0.116; $P = .454$). The comparative fit index was 1.0, and the AGFI was 0.98. The parsimony index was PNFI = 0.048, the $AIC_{model} = 56.15$, and the $AIC_{saturated} = 56.00$. All indices showed a good fit between the observed and expected model upon the correlation matrix. The sample size in this study was 2454 cases and controls, greater than the critical number of 2233 and adequate to obtain a minimal power $(1 - \beta)$ of 80%.

Discussion

In the present work, the crude risk of CL±P for gravidity 4+ was 1.41 and was statistically significant ($P = .002$). However, when the gravidity 4+ risk was assessed with SEM, a nonsignificant OR (1.22; $P = .237$) was observed. Thus, the risk of gravidity 4+ was not independent of other variables that were proposed to be associated with clefts. Gravidity 4+ seemed to be an indirect mediator of other risk factors, with consanguinity being the most important. The proposed model showed an increased risk of CL±P in mothers with previous fetal loss and mothers who had some antecedent during the first trimester of pregnancy (medication use or illnesses) and some consanguinity grade within their couple, with these variables affecting cleft chance independently of each other. This was supported by the good fit of the model indices.

TABLE 1 Parental Demographic and Clinical Characteristics in Gravidity 4+ and Reference Mothers of Cases and Controls

	Controls, n = 1227					*CL±P Cases, n = 1227*				
	Gravidity 1 n = 418 (34.1%) Mean ± SD	*Gravidity 2–3 n = 457 (37.3%) Mean ± SD*	*Gravidity 4+ n = 352 (28.7%) Mean ± SD*	*F*	*P**	*Gravidity 1 n = 382 (31.1%) Mean ± SD*	*Gravidity 2–3 n = 412 (33.6%) Mean ± SD*	*Gravidity 4+ n = 433 (35.3%) Mean ± SD*	*F*	*P**
Paternal age	25.6 ± 6.1	29.7 ± 7.4	35.1 ± 8.7	153.4	<.001	24.8 ± 5.6	29.0 ± 6.7	34.1 ± 7.8	180.5	.001
Maternal age	21.9 ± 5.5	25.8 ± 5.8	30.4 ± 5.6	217.1	<.001	21.0 ± 4.7	25.4 ± 5.7	30.3 ± 5.6	307.5	<.001
	n *(%)*	n *(%)*	n *(%)*	χ^2	*P***	n *(%)*	n *(%)*	n *(%)*	χ^2	*P***
Low paternal education	72 (18.4)	112 (25.2)	142 (41.9)	52.5	<.001	64 (18.5)	107 (27.5)	166 (40.1)	43.4	<.001
Low maternal education	113 (27.2)	145 (31.9)	173 (50.0)	46.9	<.001	92 (24.5)	124 (30.3)	186 (43.6)	35.1	<.001
Low paternal occupation	139 (35.1)	167 (37.5)	147 (43.0)	5.0	.082	141 (40.4)	158 (40.3)	199 (47.5)	5.6	.062
Low socioeconomic status†	79 (20.4)	115 (26.1)	145 (43.3)	48.7	<.001	70 (20.8)	104 (27.4)	167 (40.6)	36.5	<.001
Amerindian ethnicity	301 (72.0)	346 (75.7)	287 (81.5)	9.6	.008	283 (74.1)	295 (71.6)	356 (82.2)	14.4	.001
Previous fetal loss	–	59 (12.9)	86 (24.4)	17.9	<.001	–	62 (15.1)	144 (33.3)	37.9	<.001
Parity 1	418	28	1			382	32	0		
Parity 2–3	–	429	25			–	380	60		
Parity 4+	–	–	326			–	–	373		
Parental consanguinity	2 (0.5)	7 (1.6)	4 (1.2)		.296***	5 (1.3)	8 (2.0)	11 (2.6)		.466***
Maternal pregnancy antecedents‡	122 (29.4)	129 (28.2)	102 (29.1)	0.2	.923	209 (55.6)	200 (49.0)	220 (51.5)	3.4	.180

† Low socioeconomic status estimated from scores obtained by confirmatory factorial analysis (factor loading: maternal education <12 years: 0.867, paternal education <12 years: 0.898, and low paternal occupation (odd job/unskilled labor or less): 0.721, explained variance one factor = 91%).

‡ Maternal pregnancy antecedents: antecedents during the first trimester of pregnancy and included acute maternal illness (like flu or urinary tract infections), chronic maternal illnesses (like diabetes or hypertension), and any medicine use. CL±P: cleft lip with or without cleft palate.

* *P* value for analysis of variance *F* test, ** *P* value for Pearson chi-square test, *** *P* value for Fisher exact test.

Matched Study Design

The reasons to develop such an elaborate matched case-control design arise from the review of literature regarding the variables involved in CL±P epidemiologic studies. Some authors have observed an increased risk for CL±P (Womersley and Stone, 1987) and for CL±P and CP (Shaw et al., 1991; Robert et al., 1996; Poletta et al., 2007); whereas, others authors found no association with maternal age (Baird et al., 1994). Bille et al. (2005) reported both older maternal and paternal ages as risk factors for nonsyndromic CL±P with an interaction between them, which the authors considered to be due to social confounders. Other studies demonstrated a positive association between oral clefts and multigravidity but a negative association between oral clefts

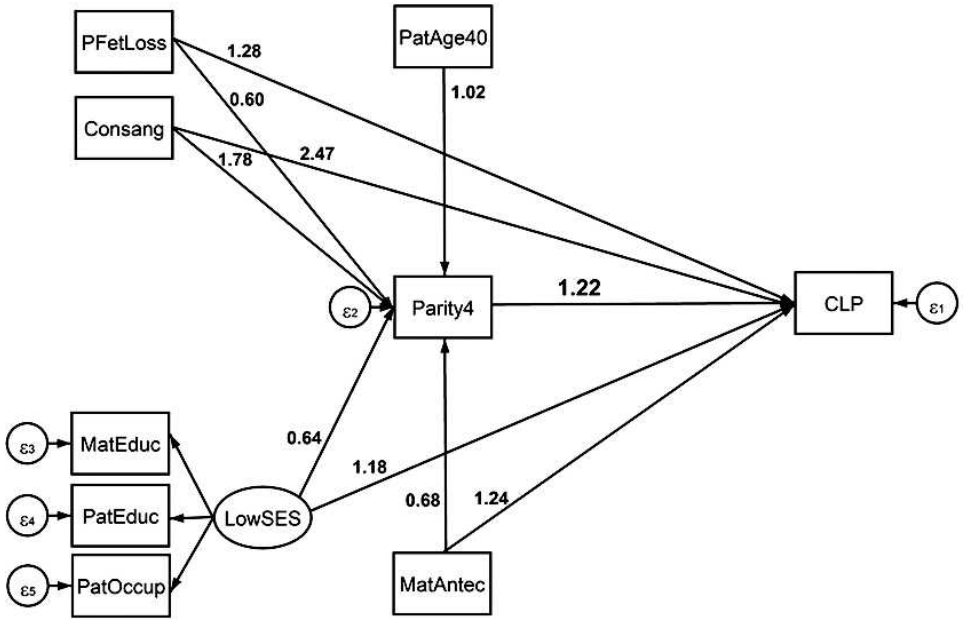

FIGURE 2 The model of related causes using the structural modeling equation. Numbers indicate the odds ratio obtained with SEM analysis. Observed variables: Parity4 = parity ≥4 live births; PatAge40 = paternal age ≥40 years; PFetLoss = previous fetal losses; Consang = parental consanguinity; MatAntec = maternal antecedents of medicine use and maternal illnesses (chronic or acute) during the first trimester of pregnancy; CLP = cleft lip with or without cleft palate (CL±P); MatEduc = low maternal education; PatEduc = low paternal education; PatOccup = low paternal occupation. Latent variables: LowSES = low socioeconomic status.

TABLE 2 Gravidity 4+ (Parity 4+ Plus Previous Fetal Loss) and CL±P SEM Yule Coefficient and OR and 95% CI; ECLAMC 1982–1999*

Path From→	*To*	*Structural Equation Model*			
		*B**	*SE*	*OR*	*95% CI*
Gravidity 4+ to cleft lip	Cleft lip				
Parity 4+		0.100	0.03	1.22	0.91–1.39
Previous fetal loss		0.123	0.04	1.28	1.12–1.48
Low socioeconomic status†		0.081	0.05	1.18	0.95–1.46
Maternal pregnancy antecedents‡		0.108	0.05	1.24	1.03–1.51
Consanguinity		0.424	0.05	2.47	1.93–3.26
Paternal age ≥40	Parity 4+	0.012	0.04	1.02	0.87–1.21
Previous fetal loss		−0.252	0.04	0.60	0.50–0.71
Low socioeconomic status		−0.220	0.07	0.64	0.48–0.83
Maternal pregnancy antecedents		−0.192	0.06	0.68	0.53–0.85
Consanguinity		0.279	0.07	1.78	1.33–2.43

* CL±P = cleft lip with or without cleft palate; SEM = structural equation modeling; OR = odds ratio; 95% CI = 95% confidence interval; ECLAMC = Estudio Colaborativo Latinoamericano de Malformaciones Congénitas; B = SEM coefficient; SE = standard error.

† Low socioeconomic status: Estimated from scores obtained by confirmatory factorial analysis with maternal education <12 years, paternal education <12 years, and low paternal occupation (odd job/unskilled labor or less).

‡ Maternal pregnancy antecedents: Antecedents during the first trimester of pregnancy, including acute maternal illness (like flu or urinary tract infections), chronic maternal illnesses (like diabetes or hypertension), and any medicine use.

and maternal age (Padron Caceres and Prytkov, 1982; Menegotto and Salzano, 1991). Finally, some authors reported an independent effect of multigravidity and maternal age on oral clefts (Hay and Barbano, 1972; Robert et al., 1996). All these discordances could be due to the complex relationship among the involved variables, as well as to methodological differences, including the selection of confounding factors, sample size, study design, or controlling for maternal and/or paternal ages (Menegotto and Salzano, 1991). The relationship between ethnicity and clefts has been clearly established. The prevalence of CL±P is high among people of Asian ancestry, intermediate among people of Caucasian ancestry, and low among people of African ancestry (Tolarová and Cervenka, 1998; Mitchell, 1997). Accordingly, in South America a predominantly Amerindian background has been observed in high prevalence regions of CL±P; whereas, a high proportion of African ancestry was identified in regions of low CL±P prevalence (Menegotto and Salzano, 1991; Poletta et al., 2007). Furthermore, native populations of South America show higher rates of multigravidity and high frequencies of CL±P. This inverse relationship between both ethnic groups and clefts, despite having similarly high rates of multigravidity (Mor-Yosef et al., 1990) and the lowest SES in South American populations (Poletta et al., 2007), could be indicative of a stronger genetic component than an environmental component in the etiology of clefts.

CL±P Risks Obtained From SEM

In South American populations, multigravidity is one of the main indicators of low SES (Gadow et al., 1998) and has been considered as a major determinant of reproductive risks and obstetric complications (Mor-Yosef et al., 1990). Its association with CL±P may reflect the effect of one or more lifestyle- and poor-income–related factors, such as cigarette smoking (Lieff et al., 1999), alcohol use (Munger et al., 1996), poor prenatal care, and inadequate nutrition (Warkany, 1957; Gadow et al., 1998), none of which were assessed in the present study. However, other sociodemographic characteristics that were assessed are similar indicators of low income, such as low parental educational levels and parental occupation, considered the most stable indicators of SES because they reflect a person's ability to access and interpret health-related information. All three indicators used as a proxy for low SES (low maternal education, low paternal education, and low paternal occupation) were more frequent among gravidity 4+ than among reference mothers, with a direct and significant correlation between SES and gravidity 4+.

The hypothesis was that the effect of gravidity 4+ on CL±P is causally indirect and that it mediates the effect of low SES, consanguinity, maternal antecedents, and previous fetal loss on CL±P. Thus, further research exploring factors that may explain the associations among gravidity, other related factors, and CL±P is needed and may uncover important clues regarding the complex etiology of CL±P.

Strengths and Limitations

The ECLAMC is an epidemiological and clinical research program dedicated to birth defects carried out by qualified pediatricians who work with specific diagnostic criteria, thereby providing reliable clinical data. Furthermore, South American populations often consist of large families with broad ethnic and socioeconomic ranges, allowing for an adequate approach. Limitations included the lack of information on exposures, such as smoking and alcohol use, lack of specification of maternal illnesses, and the recognized memory bias for retrospectively obtained data. In this

study, to control for confounders, cases and controls were matched by maternal age at 1-year intervals, native ancestry, gender, and location and year of birth. However, a possible residual effect of matching cannot be ruled out.

Conclusion

To our knowledge, the effect of gravidity 4+ on cleft lip has not been studied using SEM. The advantage over the classical approaches in epidemiology, for example logistic regression models, is that SEM can assess the indirect effect of gravidity 4+ in a framework of causal relationships. After matching maternal age at 1-year intervals, native ancestry, gender, and location and year of birth of the newborn, multigravid mothers ($\geq$4) showed no greater risk of having a newborn with oral cleft than mothers with two or three births. Therefore, the often observed and reported association between gravidity 4+ and oral clefts likely reflects the effect of other risk factors related with a low SES in South American populations, such as native ethnicity, parental consanguinity, and a poor reproductive history. As have already been pointed out by McKeown and Record (1956), research on multigravidity should be done not as an end in itself but rather as a means to identify conditions that are more common in certain gravidity orders than in others, which in turn could disclose other associations.

Acknowledgments. The authors wish to thank all people working in collaboration in ECLAMC, a network that has been active for more than 40 years.

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