Published in final edited form as:

Am J Med Genet A. 2013 July ; 161(7): 1569–1578. doi:10.1002/ajmg.a.35955.

Descriptive Epidemiology of Idiopathic Clubfoot

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Abstract

Clubfoot is a common structural malformation, occurring in approximately 1/1000 live births. Previous studies of sociodemographic and pregnancy-related risk factors have been inconsistent, with the exception of the strong male preponderance and association with primiparity. Hypotheses for clubfoot pathogenesis include fetal constraint, Mendelian-inheritance, and vascular disruption, but its etiology remains elusive. We conducted a population-based case-control study of clubfoot in North Carolina, Massachusetts, and New York from 2007 to 2011. Mothers of 677 clubfoot cases and 2,037 non-malformed controls were interviewed within one year of delivery about socio-demographic and reproductive factors. Cases and controls were compared for child's sex, maternal age, education, cohabitation status, race/ethnicity, state, gravidity, parity, body mass index (BMI), and these pregnancy-related conditions: oligohydramnios, breech delivery, bicornuate uterus, plural birth, early amniocentesis (<16 weeks), chorionic villous sampling (CVS), and plural gestation with fetal loss. Odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted for state. Cases were more likely to be male (OR: 2.7; 2.2–3.3) and born to primiparous mothers (1.4; 1.2–1.7) and mothers with BMI ≥ 30 kg/m² (1.4; 1.1–1.8). These associations were greatest in isolated and bilateral cases. ORs for the pregnancy-related conditions ranged from 1.3 (breech delivery) to 5.6 (early amniocentesis). Positive associations with high BMI were confined to cases with a marker of fetal constraint (oligohydramnios, breech delivery, bicornuate uterus, plural birth), inheritance (family history in 1st degree relative), or vascular disruption (early amniocentesis, CVS, plural gestation with fetal loss). Pathogenetic factors associated with obesity may be in the causal pathway for clubfoot.

INTRODUCTION

Talipes equinovarus or clubfoot is a congenital structural defect of several tissues of the foot and ankle, resulting in abnormal positioning of joints. Specifically, the hindfoot is rotated inward, the foot is pointed downward, the midfoot is arched, and the forefoot is turned inward. Decades ago, clubfoot was thought to arise from mechanical or constraining forces, such as breech delivery, oligohydramnios, bicornuate uterus, and multiple gestations, which would suggest that pathogenesis occurs later in gestation. Recent evidence counters this hypothesis on the basis of known embryologic development. Specifically, the foot begins to

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develop during the 9th week of gestation when the orientation of the limb buds is in a vertical axis. Early on, the soles of the feet normally face one another, but by the 14th week they should have rotated medially and assumed the position of adult feet. Thus, the pathogenesis of the structural-type of clubfoot is thought to occur during these early weeks of gestational development. Structural clubfoot can be confused with positional-type clubfoot which has a generally similar phenotype except that it is possible postnatally to manually move the foot into normal position and is thought to arise from uterine constraint. Structural-type clubfoot is estimated to affect approximately 1 per 1000 births, making it one of the most common congenital malformations [Byron-Scott et al., 2005]. It occurs as part of known syndromes and secondary to bilateral renal agenesis and neural tube defects, but the majority of structural cases are not attributed to another primary anomaly and are labeled 'idiopathic.' Epidemiologic studies have consistently reported higher prevalences of idiopathic clubfoot in males and in first-born children, but any associations with race/ethnicity and maternal age are not clear [Cardy et al., 2007; Carey et al., 2005; Dickinson et al., 2008; Honein et al., 2000; Kancherla et al., 2010; Moorthi et al., 2005; Pavone et al., 2012; Skelly et al., 2002]. Here we describe the largest population-based series of orthopedist-confirmed, structural-type clubfoot cases as they compare to control subjects without clubfoot in terms of demographic and reproductive factors. We further extend the literature by exploring phenotypic subgroups of cases to identify whether risk factors vary according to the presence of associated major malformations, laterality and sidedness of the affected foot or feet, child's sex, family history of clubfoot, and the presence of indicators of fetal constraint or vascular disruption.

SUBJECTS AND METHODS

We conducted a population-based case-control study of births in Massachusetts (October 2006–September 2011), North Carolina (October 2006–September 2011), and parts of New York State (October 2006–May 2011). The birth defect registries employed active (NC) and a combination of active and passive (NY and MA) case ascertainment to identify cases with clubfoot and assigned ICD-9 CM codes to all malformations. These registries reported to the study all cases less than 11 months of age with a diagnosis of talipes equinovarus or clubfoot (British Pediatric Association extension of ICD-9 codes 7545x, and 7547x) without a known chromosomal anomaly, inherited syndrome, bilateral renal agenesis, Potter syndrome, or neural tube defect. In addition, control subjects were a sample of children born during the same month and years as cases but without known malformations, were selected from birth certificates (MA and NC) or birth hospitals (NY), reported to the study within 11 months of age, and represented approximately 4 controls per case. Mothers of case and control subjects were sent an introductory letter and consent form by mail and then called by telephone to invite participation in the study. Mothers who agreed were interviewed by either of two study nurses within 12 months after delivery about pregnancy events and exposures. The institutional review boards at Boston University and the state health departments in Massachusetts, North Carolina, and New York approved the study protocol.

Case Classification

Each case mother was asked about treatments for her child's right and left foot, separately; each control mother was asked if her child had any foot problems and, if so, what treatments, if any, had been administered. Mothers of all cases were asked to provide permission for orthopedic and pediatric medical record releases. Medical records were reviewed and abstracted to record all diagnoses and treatments of the foot and diagnoses of other birth defects. Cases were defined as orthopedist-confirmed talipes equinovarus or clubfoot (77%) or, in the absence of medical records, maternal report of at least 3 castings of an affected foot (23%), all without diagnoses of amniotic bands or arthrogryposis.

Questionable records or reports were reviewed by a pediatric orthopedist (STM) for final determination.

Cases were further classified as ‘isolated’ or ‘multiple’ according to the presence of additional major malformations as reported by the state birth defect registries or stated in the medical records. Isolated cases had no other major malformation. Cases with notation of heart murmur but no supporting evidence of structural heart or other cardiac abnormality were considered isolated. Because it is not clear if clubfoot occurrence might be related to CNS anomalies other than neural tube defects [Bronstein et al., 1992], multiple cases with CNS anomalies were identified for sub-group analyses. Laterality and sidedness of clubfoot was based on maternal report and confirmed with medical records.

Three non-mutually exclusive case subgroups were created according to possible pathogenesis. The ‘constraint’ group comprised cases whose mothers reported oligohydramnios, breech presentation, bicornuate uterus, or plural births. The ‘genetic’ group comprised cases with a clubfoot-affected first-degree relative (according to maternal report). The ‘vascular disruption’ group comprised cases occurring in the presence of amniocentesis before 16 weeks, CVS, or plural gestation with fetal loss, based on maternal report.

Demographic, Reproductive, and Pregnancy Descriptors

Case and control mothers were asked about demographic factors, including sex of the child and her age, years of education, cohabitation status, number of previous pregnancies and births, height, and pre-pregnancy weight. They were also asked to describe what they considered to be their race or ethnicity. Women who reported Hispanic ethnicity, regardless of race, were considered Hispanic. Each mother was also asked whether her pregnancy was affected by oligohydramnios or too little amniotic fluid, if she had been diagnosed with a bicornuate uterus, whether the baby was in breech position at the time of delivery, whether she had undergone amniocentesis or chorionic villous sampling (CVS), and, if so, the timing of the procedure. Each mother was asked whether she had carried twins or more and, if so, whether she had experienced any fetal loss of twins or triplets, and whether any of the child’s relatives were born with clubfoot and, if so, which relative(s).

Analyses

The number and percent of case and control mothers were tabulated for demographic and reproductive factors, including child’s sex and maternal age (<20, 20–24, 25–29, 30–34, 35 years), education (<12, 12, and 13 years), cohabitation status (living with baby’s father or not), race/ethnicity (White non-Hispanic, Hispanic, Black non-Hispanic, other), maternal residence (North Carolina, Massachusetts, New York), number of pregnancies (primigravid, 2), number of births (primiparous, 1), and pre-pregnancy body mass index (BMI) as kg/m² (underweight <18.5, normal 18.5–24.9, overweight 25.0–29.9, and obese 30.0). In addition, case and control mothers were compared for pregnancy-related factors, including oligohydramnios, breech presentation, bicornuate uterus, plural births, amniocentesis (yes, at gestational week <16; yes, at gestational week 16; no), CVS, and plural gestation with fetal loss. The distributions of demographic, reproductive, and pregnancy-related factors were tabulated for cases according to isolated/multiple status, sidedness (bilateral, unilateral right, unilateral left), and child’s sex. Finally, cases subgroups according to possible etiology were compared for demographic and reproductive factors. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated, after adjustment for maternal residence. A sub-analysis was conducted after exclusion of cases whose clubfoot diagnosis was based solely on maternal report of treatment pattern. Analyses were conducted using PASW Statistics v18 [PASW 2009].

RESULTS

The mothers of 1,323 cases with eligible diagnoses were approached for study participation; of them, 286 (21.6%) could not be contacted (due to incorrect or missing telephone numbers or nonresponse), 82 (6.2%) refused participation, and 955 (72.2%) were interviewed. Of cases whose mothers were interviewed, medical records were obtained on 618 (64.7%). Clubfoot diagnoses were confirmed for 520 children based on medical record review and 157 children based on mother's report of clubfoot treatment regimen, for a total of 677 cases. This group excluded 269 children due to ineligible diagnoses (30 with arthrogryposis, 11 with amniotic bands, 4 with syndromes, 3 with primary defects, 1 with severe 2nd trimester oligohydramnios, 1 with a surrogate mother, 5 with questionable clubfoot, and 214 who did not have clubfoot) and 8 with ineligible birthdays. The mothers of 3,298 controls were approached for study participation; of them 954 (28.9%) could not be contacted, 243 (7.4%) refused participation, 10 (0.3%) were ineligible due to death, incarceration, previously been interviewed for a similar study, relocation abroad, or lack of interpreter and 2,091 (63.4%) were interviewed. Of those interviewed, the mothers of 23 and 31 controls reported their child having some type of foot problem or other congenital anomaly, respectively, and were excluded, leaving 2,037 controls for the present study.

Of the 677 cases, 646 (95.4%) had no other major malformations and were considered to be isolated. Both feet were affected in 49.9% of cases and, when unilateral, the left foot was slightly more likely to be affected (27.6%) than the right foot (22.5%).

The distributions of demographic, reproductive and pregnancy-related factors for control and case groups are presented in Table I and corresponding ORs and 95% CIs in Table II. Males comprised approximately half the controls, compared to 71.8% of cases overall; the adjusted OR was 2.7 (2.2–3.3). The male preponderance was evident for isolated, bilateral, and both sides of unilateral clubfoot cases, with adjusted ORs ranging from 2.4 to 2.9. The subgroup of 31 multiple cases had a smaller excess of males (adjusted OR: 2.0; 95% CI: 1.0–4.3). Teen mothers were less common among all case groups compared to controls, but the distributions of older age categories were generally similar across all groups. Maternal education and cohabitation status did not appreciably differ for overall, isolated, male and female cases, and controls. Mothers of multiple cases were less likely than control mothers to have >12 years of education (OR: 0.4; 0.2–1.0). Maternal Black non-Hispanic race was less common among all case groups compared to controls. Case mothers were as likely to have had no previous pregnancies as control mothers, but were more likely in all but multiple cases to have had no previous births than controls. Female cases were most likely to have mothers with no previous births (adjusted OR: 1.7; 1.3–2.3). Case mothers were more likely to be obese than control mothers; this pattern was present for all case groups (with ORs ranging from 1.34 to 1.7) except those affected on the right side.

Case mothers reported having oligohydramnios, breech presentation, and bicornuate uterus more often than control mothers. Oligohydramnios was associated with clubfoot in the presence of multiple defects (adjusted OR: 3.1; 1.2–8.2); renal anomalies were not present in any of the five clubfoot cases whose mothers reported oligohydramnios. Clubfoot was also associated with breech delivery when the case was female (adjusted OR: 2.3; 1.5–3.5) and with bicornuate uterus when both feet were affected (adjusted OR: 2.3; 1.1–4.5). Plural birth was present in 5.9% of overall cases compared to 3.6% of controls (adjusted OR: 1.8; 1.3–2.7). This pattern held for all case groups, with ORs for plural births ranging from 1.5 to 2.2.

Amniocentesis at <16 weeks, CVS, and plural gestation with fetal loss were each associated with clubfoot. No multiple cases were exposed to amniocentesis at <16 weeks; for isolated cases, the adjusted OR was 5.8 (1.7–20.2). Amniocentesis at 16 weeks was also associated

with clubfoot (adjusted OR: 3.7; 2.7–5.1). Cases overall were more than twice as likely as controls to have had CVS (adjusted OR: 2.2; 1.1–4.0). Plural gestation with fetal loss was reported to have occurred among 1.2% of overall cases versus 0.3% of controls; the adjusted OR was 4.1 (1.4–11.9).

Four multiple cases also had CNS anomalies, including one with septo-optic dysplasia, two with hydrocephaly, and one with a fetal brain infarct. These CNS anomalies might be considered primary defects that caused clubfoot [Bronshtein et al., 1992]. After excluding these four cases, no material change in the distributions of descriptive factors was observed (data not shown).

The ‘constraint’ subgroup included 155 (22.9%) cases whose mothers reported oligohydramnios, breech presentation, bicornuate uterus, or plural births; the ‘genetic’ subgroup included 78 (11.5%) cases with a similarly affected first-degree relative; and the ‘vascular disruption’ subgroup included 32 (4.7%) cases with amniocentesis before 16 week’s gestation, CVS or were plural gestations with a fetal loss (Table III). ‘Constraint’ and ‘genetic’ cases were slightly less likely to be male than their counterparts; adjusted ORs were 0.8 (0.5–1.1) and 0.6 (0.4–1.0), respectively. No differences between constraint- or genetic-based case groups were apparent for maternal age, education, cohabitation status, race/ethnicity, residence, gravidity and parity. In contrast, the small ‘vascular disruption’ group was more likely than ‘non-vascular disruption’ cases to be male (adjusted OR: 1.4; 0.6–3.4) and to have mothers who were ≥ 35 years old (50.0% vs 19.1%).

Pre-pregnancy BMI differed across each of the pathogenetically-determined case groups. Specifically, BMI ≥ 30.0 was more common among ‘constraint’ than ‘non-constraint’ cases (adjusted OR: 1.7; 1.1–2.7), among ‘genetic’ than ‘non-genetic’ cases (adjusted OR: 2.0; 1.2–3.6), and among ‘vascular disruption’ than ‘non-vascular disruption’ cases (adjusted OR: 2.5; 1.0–6.4).

After exclusion of the 157 cases whose clubfoot diagnosis was not confirmed by medical record review, no material change in ORs was observed for all risk factors, with one exception. The adjusted OR for clubfoot overall and maternal Black non-Hispanic race decreased from 0.73 to 0.59, resulting from a lower proportion of Black non-Hispanic mothers providing consent for copies of the child’s medical record.

DISCUSSION

This is the largest population-based series of orthopedist-confirmed clubfoot cases and controls to assess patterns of occurrence. The male preponderance that has been observed in other studies was confirmed in this study for isolated cases, those that were accompanied with other major malformations, bilateral and unilateral cases, and those that might be attributed to fetal constraint or genetics. However, the lowest proportions of male births were observed among cases that occurred in the presence of other major malformations, those associated with fetal constraint, and those with a positive family history in first degree relatives, possibly due to etiologic heterogeneity among them. Indeed, other major malformations which have a male preponderance also appear to have a more equivocal sex ratio in non-isolated cases [Lisi et al., 2005]. In both animals and humans, there is some evidence to suggest that environmental and psychosocial stressors alter sex ratios in favor of females, possibly through activation of hypothalamic-pituitary adrenal (HPA) axis [Navara 2010]. Why more males than females are born with clubfoot remains a mystery, but environmental or psychosocial exposures that alter the sex ratio in favor of males might be worth exploring as risk factors.

Socio-demographic factors have not been consistently associated with clubfoot and we also found no strong differences between cases and controls. Maternal age and level of education have been reported to be both inversely and positively associated with clubfoot [Cardy et al., 2007; Dickinson et al., 2008; Honein et al., 2000; Kancherla et al., 2010], but other studies found no association [Byron-Scott et al., 2005; Carey et al., 2005; Moorthi et al., 2005; Pavone et al., 2012; Skelly et al., 2002], as we observed. We examined cohabitation status as another indicator of socioeconomic status and found it was also not associated with clubfoot, contrary to a higher risk in unmarried mothers in a UK study [Cardy et al., 2007]. A higher risk of clubfoot in the offspring of White mothers compared to non-White mothers was reported in two studies [Dickinson et al., 2008; Honein et al., 2000], which was not substantiated in four other studies [Alderman et al., 1991; Kancherla et al., 2010; Moorthi et al., 2005; Skelly et al., 2002]. We did observe a higher percentage of White-non-Hispanic mothers among cases. In our study, Hispanic mothers were similarly distributed between case and control groups and lower proportions of case mothers were Black non-Hispanic or in the 'other' race/ethnicity group (comprising Asian, Native American or mixed race). Of the three previous US studies that examined maternal Black non-Hispanic race as a risk factor, one found no association [Alderman et al., 1991] and two found lower ORs compared to Whites [Dickinson et al., 2008; Moorthi et al., 2005]. In the present study, gravidity was not associated with clubfoot, but primiparous women were 70% more likely to have a child with clubfoot. The latter association has been consistently reported [Alderman et al., 1991; Byron-Scott et al., 2005; Cardy et al., 2007; Carey et al., 2005; Dickinson et al., 2008; Honein et al., 2000; Kancherla et al., 2010; Moorthi et al., 2005; Pavone et al., 2012; Skelly et al., 2002]. No clear deviations from these patterns of occurrence were observed for isolated, multiple, bilateral, unilateral, male or female cases.

Clubfoot has been suspected to result from fetal constraint in at least some cases, based on clinical observations of cases occurring in the presence of oligohydramnios, bicornuate uterus, breech presentations, and multiple births. However, previous epidemiologic studies have found inconsistent results, with positive, inverse and null associations [Byron-Scott et al., 2005; Carey et al., 2005; Kancherla et al., 2010; Philip et al., 2004]. We did identify 30 to 40% increased risks of clubfoot in association with breech delivery and bicornuate uterus and 60 to 80% increased risks for oligohydramnios and multiple births, in support of a constraint mechanism for a minority of cases. When we compared socio-demographic factors between cases that occurred in the presence or absence of 'constraint' indicators, only obesity ($> 30.0 \text{ kg/m}^2$) showed a clear preponderance among the constraint group. The consistently observed association between clubfoot and primiparity [Alderman et al., 1991; Byron-Scott et al., 2005; Cardy et al., 2007; Carey et al., 2005; Honein et al., 2000; Kancherla et al., 2010; Moorthi et al., 2005; Pavone et al., 2012; Skelly et al., 2002] has been raised as evidence in support of a fetal constraint pathogenesis under the assumption that, after a first birth, the intrauterine space is expanded as a result of carrying the fetus [Cardy et al., 2007; Carey et al., 2005]. Although we did estimate a 40% increased risk of clubfoot for women with no previous births, we did not include primiparity as an indicator of constraint because nearly half of all women fell into that group and they would have diluted the sensitivity of any true constraint. For example, when primiparity was added to the 'constraint' definition, no association was observed for obesity (OR: 1.1; 0.7–1.7).

Clubfoot is known to recur in some families [Cardy et al., 2007], and studies have estimated that 7 to 21% of clubfoot cases have an affected first degree relative [Cardy et al., 2007; Cartlidge 1984; Honein et al., 2000; Skelly et al., 2002; Wynne-Davies 1972]. Among the 11.5% of cases whose mothers reported clubfoot in one of the child's first degree relatives, the patterns of socio-demographic factors were similar to those cases without such a history, with one exception: Like the group with a purported 'constraint' pathogenesis, pre-

pregnancy obesity (BMI ≥ 30.0 kg/m²) was associated with clubfoot cases whose etiology possibly includes inheritance.

Another hypothesized pathogenetic pathway for clubfoot is vascular disruption, based on increased risks of clubfoot in women undergoing amniocentesis in early gestation [Philip et al., 2004; Sundberg et al., 1997] or exposed to the abortifacient misoprostol [Pastuszek et al., 1998; Vargas et al., 2000]. In our study, we considered amniocentesis before 16 weeks' gestation, CVS, or fetal loss of a twin or triplet to be markers of vascular disruption. These factors were associated with a 5.6, 2.2, and 4.1-fold increased risk of clubfoot, respectively, in support of a possible vascular disruption pathogenesis. This case group, albeit small (n=32), stood out from others with opposite patterns of some socio-economic factors. Vascular disruption cases have an even stronger male preponderance (78%), were not more likely to be primiparous, and were born to older mothers (66% were >30 years). The positive age association and null parity associations could be explained by more common exposure to assisted reproductive technologies and earlier or more intensive prenatal testing in older mothers. The even greater preponderance of males raises the question of whether vascular disruption disproportionately affects males and contributes to the increase in males for all cases of clubfoot; although we can identify which cases had early amniocentesis, CVS, or fetal loss, these factors are not a substitute for a sensitive marker to identify any true subset of cases with a vascular disruption pathogenesis. Other congenital malformations have been proposed to result, at least in part, from vascular disruption [Van Allen 1981]; while some so-called vascular disruption defects are more common in males, as a group this pattern has not been observed [Lisi et al., 2005]. Placental disorders, such as abruption and preeclampsia, are more common in male fetuses [Murji et al., 2012], but have not been reported to accompany clubfoot. Studies of placental vascular morphology among clubfoot-affected births would be feasible and potentially informative.

Pre-pregnancy overweight and obesity have been associated with a wide range of birth defects [Waller et al., 2007], but body habitus has not previously been studied in relation to clubfoot. We found mothers whose pre-pregnancy BMI was in the overweight (25.0–29.9 kg/m²) or obese (≥ 30.0 kg/m²) categories were at least 40% more likely to have a child with clubfoot compared to normal weight women (18.5–24.9 kg/m²). Interestingly, this association was apparent for all case phenotypes except unilateral, right-sided cases. Obesity was most common in mothers of clubfoot cases that occurred in the presence of markers of fetal constraint, vascular disruption, or genetic inheritance. When these case groups were compared to their unaffected counterparts, ORs were elevated (Table III); compared to control subjects, ORs were further increased to 2.1, 2.6 and 3.4 for 'constraint,' 'genetic,' and 'vascular' cases, respectively, while ORs for their counterparts approached the null. Vascular inflammation and oxidative stress are linked to obesity [Challier et al., 2008; Farah et al., 2012], which may be exacerbated in the presence of fetal constraint or genetic-predisposing factors or may interfere with recovery from vascular damage. Studies of markers of these pathogenetic processes in amniotic fluid, the placenta, or cord blood may shed light on this potential pathway toward clubfoot development.

In this study, maternal reports of oligohydramnios, bicornuate uterus, breech presentation, fetal loss of a multiple gestation, chorionic villus sampling, or amniocentesis were not confirmed in medical records because we did not seek consent to review the mother's medical records. It is possible that mothers of cases were more accurate reporters of such conditions than mothers of controls or even over-reporters if unconfirmed diagnoses were reported. Amniocentesis after 16 weeks gestation was also associated with clubfoot in this study, even though vascular disruption is not thought to result from such testing later in gestation. While the possibility cannot be fully dismissed that amniocentesis later in pregnancy increases clubfoot risk and the observed association may represent over-reporting

or inaccurate reporting of the timing of amniocentesis by cases, we believe this observation more likely represents increased diagnostic testing after ultrasound evidence of clubfoot.

In consideration of potential selection bias as an explanation for our findings, might differential participation according to maternal race account for the observed lower proportion of cases with Black non-Hispanic mothers? Such a bias is not a likely explanation: Based on 2008 birth certificate data for our catchment areas, the proportion of births to Black non-Hispanic mothers was 9% in Massachusetts [MDPH 2010], 24% in North Carolina [NCDHHS 2010], and 11% in New York [NYSDOH 2010] compared to 8%, 22%, and 14%, respectively, among our control subjects. Could our novel finding that maternal obesity is associated with clubfoot risk be due to differential participation by mothers? If so, obese mothers of cases would have been more likely to participate relative to corresponding control mothers. Population-based proportions of births according to BMI were not available for our catchment areas, leaving open the possibility of participation bias. Inaccurate reporting of height and weight can lead to misclassification of BMI [Bodnar et al., 2010; Craig and Adams, 2009] and could bias OR estimates in either direction. If such misclassification is not associated with case/control status, the most likely bias would be toward no association. If case mothers were more accurate reporters and controls tended to under-report their weight, our results for BMI would be biased away from the null.

Clubfoot diagnoses, on the other hand, were based on medical record review for the majority of cases and orthopedic expertise for all cases. Given that this study was population-based and not clinic-based, it was not possible to administer standardized examinations of cases for classification, which would be necessary to scale severity of clubfoot. Indeed, clubfoot can range from relatively mild to severe, and distinguishing the milder end of the spectrum from positional clubfoot without direct examination can be difficult. Less severe diagnoses may also not be identified at birth or seen by an orthopedist within the first year of life, and therefore would be missed by either passive or active surveillance programs and not included in this study. If so, our results may not be generalizable to less severe clubfoot phenotypes.

Mothers were administered a standardized questionnaire by nurses within one year after delivery, a method that is known to produce better quality data than that from vital records and sometimes medical records [Srisukhumbowornchai et al., 2012]. The large number of cases and the geographically- and temporally-similar aspects of the control group are also strengths, allowing comparisons of phenotype subgroups. We did not make adjustments for multiple testing, since our analysis of phenotype subgroups was exploratory.

In conclusion, the lack of strong associations between clubfoot and socio-demographic factors such as maternal age, education, cohabitation status, and gravidity suggests that its etiology involves other independent exposures. The increased risks of clubfoot associated with obesity and male sex of the fetus provide possible clues to pathogenesis such as inflammation or oxidative stress. The stronger associations for both male sex and obesity in some case sub-groups suggests future studies may improve sensitivity of identifying associations by creating clubfoot subgroups based on phenotype or possible pathogenesis.

Acknowledgments

Support for this work was provided by Eunice Kennedy Shriver National Institute for Child Health and Human Development grant RO1-HD051804. We thank Lisa Crowell RN and Mary Beth Pender RN, Interviewers; Michelle Heinz and Eileen Mack, Research Assistants; Michael Bairos, Oleg Starobinets, and Elie Sirotta, Database Analysts; and the mothers who participated in the study.

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Table 1

Descriptive factors by case phenotype.

Descriptive Factors	Controls n=2037	Cases n=677	Isolated n=646	Multiple n=31	Bilateral n=338	Right n=148	Left n=187	Male n=486	Female n=191
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Child's sex									
Male	1006 (49.4)	486 (71.8)	466 (72.1)	20 (64.5)	246 (72.8)	103 (69.6)	134 (71.7)		
Female	1031 (50.6)	191 (28.2)	180 (27.9)	11 (35.5)	92 (27.2)	45 (30.4)	53 (28.3)		
Maternal Factor									
Age									
<20	107 (5.3)	20 (3.0)	19 (2.9)	1 (3.2)	9 (2.7)	3 (2.0)	8 (4.3)	15 (3.1)	5 (2.6)
20–24	369 (18.1)	138 (20.4)	132 (20.4)	6 (19.4)	58 (17.2)	41 (27.7)	38 (20.3)	95 (19.5)	43 (22.5)
25–29	536 (26.3)	189 (27.9)	178 (27.6)	11 (35.5)	105 (31.1)	32 (21.6)	52 (27.8)	137 (28.2)	52 (27.2)
30–34	568 (27.9)	191 (28.2)	183 (28.3)	8 (25.8)	94 (27.8)	40 (27.0)	54 (28.9)	140 (28.8)	51 (26.7)
35	452 (22.2)	139 (20.5)	134 (20.7)	5 (16.1)	72 (21.3)	32 (21.6)	35 (18.7)	99 (20.4)	40 (20.9)
Unknown	5 (0.2)	0	0	0	0	0	0	0	0
Education									
<12 years	283 (13.9)	87 (12.9)	80 (12.4)	7 (22.6)	36 (10.7)	16 (10.8)	34 (18.2)	59 (12.1)	28 (14.7)
12 years	456 (22.4)	171 (25.3)	163 (25.2)	8 (25.8)	83 (24.6)	46 (31.1)	41 (21.9)	120 (24.7)	51 (26.7)
13 years	1297 (63.7)	419 (61.9)	403 (62.4)	16 (51.6)	219 (64.8)	86 (58.1)	112 (59.9)	307 (63.2)	112 (58.6)
Living with child's father									
Yes	1730 (84.9)	577 (85.2)	553 (85.6)	24 (77.4)	288 (85.2)	124 (83.8)	162 (86.6)	419 (86.2)	158 (82.7)
No	305 (15.0)	99 (14.6)	92 (14.2)	7 (22.6)	50 (14.8)	23 (15.5)	25 (13.4)	67 (13.8)	32 (16.8)
Unknown	2 (0.1)	1 (0.2)	1 (0.2)	0	0	1 (0.7)	0	0	1 (0.5)
Race -ethnicity									
White-nonHisp	1339 (65.7)	490 (72.4)	472 (73.1)	18 (58.1)	250 (74.0)	105 (70.9)	132 (70.6)	349 (71.8)	141 (73.8)
Hispanic	246 (12.1)	79 (11.7)	72 (11.1)	7 (22.6)	30 (8.9)	19 (12.8)	30 (16.0)	59 (12.1)	20 (10.5)
Black-nonHisp	342 (16.8)	84 (12.4)	82 (12.7)	2 (6.5)	45 (13.3)	20 (13.5)	18 (9.6)	61 (12.6)	23 (12.0)
Other	109 (5.4)	24 (3.5)	20 (3.1)	4 (12.9)	13 (3.8)	4 (2.7)	7 (3.7)	17 (3.5)	7 (3.7)
Maternal residence									
New York	568 (27.9)	212 (31.3)	202 (31.3)	10 (32.3)	100 (29.6)	56 (37.8)	54 (28.9)	156 (32.1)	56 (29.3)
North Carolina	1014 (49.8)	274 (40.5)	265 (41.0)	9 (29.0)	129 (38.2)	56 (37.8)	88 (47.1)	202 (41.6)	72 (37.7)

Descriptive Factors	Controls n=2037	Cases n=677	Isolated n=646	Multiple n=31	Bilateral n=338	Right n=148	Left n=187	Male n=486	Female n=191
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Massachusetts	455 (22.3)	191 (28.2)	179 (27.7)	12 (38.7)	109 (32.2)	36 (24.3)	45 (24.1)	128 (26.3)	63 (33.0)
Primigravida									
Yes	640 (31.4)	219 (32.3)	209 (32.4)	10 (32.3)	107 (31.7)	50 (33.8)	62 (33.2)	154 (31.7)	65 (34.0)
Primiparous									
0	814 (40.0)	326 (48.2)	313 (48.5)	13 (41.9)	170 (50.3)	65 (43.9)	90 (48.1)	224 (46.1)	102 (53.4)
Body mass index (kg/m)									
<18.5	87 (4.3)	25 (3.7)	23 (3.6)	2 (6.5)	14 (4.1)	3 (2.0)	8 (4.3)	22 (4.5)	3 (1.6)
18.5–24.9	1080 (53.0)	310 (45.8)	297 (46.0)	13 (41.9)	144 (42.6)	80 (54.1)	84 (44.9)	223 (45.9)	87 (45.5)
25.0–29.9	451 (22.1)	184 (27.2)	175 (27.1)	9 (29.0)	94 (27.8)	35 (23.6)	53 (28.3)	131 (27.0)	53 (27.7)
30.0	360 (17.7)	140 (20.7)	134 (20.7)	6 (19.4)	77 (22.8)	26 (17.6)	37 (19.8)	99 (20.4)	41 (21.5)
Unknown	59 (2.9)	18 (2.7)	17 (2.6)	1 (3.2)	9 (2.7)	4 (2.7)	5 (2.7)	11 (2.3)	7 (3.7)
Constraint-related Factors									
Oligohydramnios									
Yes	115 (5.6)	61 (9.0)	56 (8.7)	5 (16.1)	29 (8.6)	11 (7.4)	19 (10.2)	47 (9.7)	14 (7.3)
Unknown	4 (0.2)	2 (0.3)	2 (0.3)	0	1 (0.3)	1 (0.7)	0 (0.0)	2 (0.4)	0
Breech delivery									
Yes	154 (7.6)	66 (9.7)	63 (9.8)	3 (9.7)	38 (11.2)	9 (6.1)	17 (9.1)	36 (7.4)	30 (15.7)
Unknown	5 (0.2)	2 (0.3)	2 (0.3)	0	1 (0.3)	0	1 (0.5)	2 (0.4)	0
Bicornuate uterus									
Yes	32 (1.6)	14 (2.1)	14 (2.2)	0	11 (3.3)	1 (0.7)	2 (1.1)	11 (2.3)	3 (1.6)
Unknown	2 (0.1)	4 (0.6)	4 (0.6)	0	4 (1.2)	0	0	2 (0.4)	2 (1.0)
Plural birth									
Yes	73 (3.6)	40 (5.9)	40 (6.2)	0	21 (6.2)	7 (4.7)	10 (5.3)	26 (5.3)	14 (7.3)
Vascular-disruption-related Factors									
Amniocentesis									
<16 weeks	4 (0.2)	7 (1.0)	7 (1.1)	0	3 (0.9)	3 (2.0)	1 (0.5)	6 (1.2)	1 (0.5)
>16 weeks	76 (3.7)	87 (12.9)	77 (11.9)	10 (32.3)	47 (13.9)	18 (12.2)	22 (11.8)	53 (10.9)	34 (17.8)
None	1946 (95.5)	579 (85.5)	558 (86.4)	21 (67.7)	287 (84.9)	125 (84.5)	163 (87.2)	424 (87.2)	155 (81.2)
Unknown	11 (0.5)	4 (0.6)	4 (0.6)	0	1 (0.3)	2 (1.4)	1 (0.5)	3 (0.6)	1 (0.5)
Chorionic villus sampling									

Descriptive Factors	Controls n=2037	Cases n=677	Isolated n=646	Multiple n=31	Bilateral n=338	Right n=148	Left n=187	Male n=486	Female n=191
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Yes	24 (1.2)	17 (2.5)	15 (2.3)	2 (6.5)	9 (2.7)	0	8 (4.3)	14 (2.9)	3 (1.6)
Unknown	13 (0.6)	1 (0.1)	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.5)
Plural gestation w/ loss									
Yes	6 (0.3)	8 (1.2)	7 (1.1)	1 (3.2)	3 (0.9)	2 (1.4)	3 (1.6)	5 (1.0)	3 (1.6)
Unknown	1 (0.004)	0	0	0	0	0	0	0	0

Table II

Demographic and reproductive factors in relation to clubfoot cases overall and case subgroups

Descriptive factors**	Odds Ratios (95% Confidence Intervals)*							
	Overall Cases	Isolated	Multiple	Bilateral	Right	Left	Male	Female
Child's sex								
Male	2.70 (2.24–3.28)	2.78 (2.27–2.35)	2.04 (0.97–4.30)	2.90 (2.24–3.76)	2.42 (1.68–3.48)	2.64 (1.90–3.68)		
Maternal Factor								
Age(yrs)								
<20	0.52 (0.31–0.87)	0.52 (0.30–0.88)	0.62 (0.07–5.26)	0.56 (0.27–1.18)	0.26 (0.08–0.87)	0.73 (0.33–1.62)	0.56 (0.31–1.01)	0.42 (0.16–1.09)
25–29	0.90 (0.70–1.17)	0.89 (0.69–1.16)	1.11 (0.41–3.05)	1.19 (0.84–1.68)	0.51 (0.31–0.83)	0.93 (0.60–1.44)	0.96 (0.71–1.29)	0.78 (0.51–1.19)
30–34	0.83 (0.64–1.08)	0.84 (0.64–1.09)	0.69 (0.23–2.03)	0.95 (0.66–1.35)	0.59 (0.37–0.93)	0.90 (0.58–1.39)	0.90 (0.67–1.21)	0.68 (0.44–1.04)
35	0.74 (0.56–0.97)	0.75 (0.57–0.99)	0.51 (0.15–1.71)	0.88 (0.60–1.29)	0.56 (0.34–0.91)	0.72 (0.44–1.17)	0.78 (0.56–1.07)	0.64 (0.40–1.02)
Unk	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Education (yrs)								
<12	1.19 (0.88–1.60)	1.23 (0.91–1.68)	0.66 (0.24–1.85)	1.38 (0.91–2.10)	1.73 (0.96–3.11)	0.74 (0.46–1.20)	1.23 (0.87–1.74)	1.09 (0.67–1.78)
13	0.95 (0.73–1.25)	1.00 (0.76–1.32)	0.39 (0.16–0.97)	1.18 (0.80–1.72)	1.04 (0.60–1.81)	0.69 (0.46–1.05)	1.05 (0.77–1.43)	0.76 (0.49–1.18)
Living with child's father								
Yes	0.97 (0.75–1.24)	1.00 (0.78–1.29)	0.51 (0.22–1.21)	0.93 (0.67–1.29)	0.88 (0.56–1.41)	1.12 (0.72–1.75)	1.04 (0.78–1.39)	0.80 (0.53–1.20)
Unknown	1.61 (0.14–18.05)	1.72 (0.15–19.34)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	6.71 (0.57–78.60)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	5.27 (0.46–60.20)
Race / ethnicity								
Hispanic	0.89 (0.68–1.18)	0.85 (0.64–1.12)	2.24 (0.92–5.44)	0.68 (0.45–1.01)	1.02 (0.61–1.70)	1.24 (0.82–1.89)	0.94 (0.69–1.28)	0.79 (0.49–1.30)
Black-nonHisp	0.73 (0.56–0.95)	0.74 (0.56–0.96)	0.53 (0.12–2.31)	0.79 (0.56–1.12)	0.82 (0.50–1.35)	0.54 (0.33–0.90)	0.73 (0.54–0.99)	0.72 (0.45–1.14)
Other	0.59 (0.38–0.93)	0.51 (0.31–0.84)	2.62 (0.87–7.91)	0.62 (0.34–1.12)	0.48 (0.17–1.32)	0.65 (0.30–1.42)	0.59 (0.35–1.00)	0.59 (0.27–1.29)
Maternal residence								
New York	1.13 (0.89–1.42)	1.11 (0.87–1.40)	1.50 (0.64–3.50)	1.36 (1.01–1.83)	0.80 (0.52–1.24)	1.04 (0.69–1.57)	1.02 (0.79–1.33)	1.40 (0.96–2.06)
North Carolina	0.72 (0.59–0.89)	0.74 (0.60–0.91)	0.50 (0.20–1.25)	0.72 (0.55–0.96)	0.56 (0.38–0.82)	0.91 (0.64–1.30)	0.73 (0.58–0.92)	0.72 (0.50–1.04)
Primigravid								
Yes	1.05 (0.87–1.26)	1.05 (0.87–1.27)	1.04 (0.49–2.23)	1.01 (0.79–1.29)	1.13 (0.79–1.61)	1.08 (0.79–1.49)	1.02 (0.82–1.26)	1.13 (0.82–1.54)
Primiparous								
Yes	1.38 (1.16–1.65)	1.40 (1.17–1.67)	---	1.50 (1.19–1.89)	1.17 (0.84–1.65)	1.39 (1.03–1.88)	1.28 (1.05–1.56)	1.70 (1.26–2.29)
Body mass index (kg/m ²)								

Descriptive factors**	Odds Ratios (95% Confidence Intervals)*									
	Overall Cases	Isolated	Multiple	Bilateral	Right	Left	Male	Female		
<18.5	1.06 (0.67–1.68)	1.01 (0.63–1.63)	2.31 (0.51–10.54)	1.32 (0.73–2.39)	0.49 (0.15–1.60)	1.21 (0.57–2.58)	1.29 (0.79–2.11)	0.47 (0.15–1.53)		
25.0–29.9	1.44 (1.16–1.78)	1.43 (1.15–1.77)	1.72 (0.73–4.06)	1.61 (1.21–2.13)	1.05 (0.70–1.59)	1.52 (1.06–2.18)	1.42 (1.12–1.81)	1.49 (1.04–2.13)		
30.0	1.39 (1.10–1.76)	1.39 (1.09–1.76)	1.49 (0.56–3.97)	1.68 (1.24–2.27)	1.00 (0.63–1.58)	1.33 (0.89–2.00)	1.36 (1.05–1.78)	1.47 (0.99–2.18)		
Unknown	1.18 (0.68–2.03)	1.15 (0.66–2.01)	1.85 (0.23–14.59)	1.31 (0.63–2.72)	1.04 (0.37–2.95)	1.13 (0.44–2.90)	1.00 (0.51–1.93)	1.67 (0.73–3.78)		
<i>Constraint-related Factor</i>										
Oligohydramnios										
Yes	1.63 (1.18–2.26)	1.57 (1.13–2.20)	3.08 (1.15–8.23)	1.52 (0.99–2.33)	1.39 (0.73–2.65)	1.89 (1.13–3.14)	1.79 (1.25–2.55)	1.28 (0.72–2.28)		
Breech delivery										
Yes	1.31 (0.97–1.78)	1.31 (0.96–1.79)	1.32 (0.40–4.39)	1.54 (1.05–2.24)	0.80 (0.40–1.60)	1.23 (0.73–2.07)	0.98 (0.67–1.43)	2.27 (1.49–3.48)		
Bicornuate uterus										
Yes	1.41 (0.74–2.66)	1.47 (0.78–2.79)	0.00 (0.00–0.00)	2.25 (1.11–4.53)	0.47 (0.06–3.46)	0.69 (0.16–2.89)	1.53 (0.76–3.07)	1.06 (0.32–3.51)		
Plural birth										
Yes	1.82 (1.25–2.65)	1.87 (1.28–2.73)	0.84 (0.11–6.23)	1.87 (1.16–3.01)	1.50 (0.71–3.19)	1.71 (0.91–3.19)	1.66 (1.08–2.57)	2.23 (1.27–3.92)		
<i>Vascular disruption-related Factor</i>										
Amniocentesis										
<16 weeks	5.59 (1.62–19.29)	5.84 (1.69–20.15)	0.00 (0.00–0.00)	5.00 (1.10–22.83)	12.81 (2.80–58.54)	2.99 (0.33–27.01)	6.80 (1.90–24.33)	3.08 (0.34–28.15)		
>16 weeks	3.65 (2.65–5.05)	3.37 (2.42–4.70)	11.09 (5.01–24.56)	3.92 (2.66–5.77)	3.49 (2.02–6.05)	3.42 (2.07–5.66)	3.06 (2.12–4.42)	5.25 (3.38–8.15)		
Chorionic villus sampling										
Yes	2.15 (1.14–4.03)	1.96 (1.02–3.76)	5.33 (1.19–23.90)	2.21 (1.01–4.83)	0.00 (0.00–0.00)	3.70 (1.64–8.35)	2.45 (1.26–4.79)	1.25 (0.37–4.23)		
Plural gestation withloss										
Yes	4.08 (1.41–11.87)	3.67 (1.23–11.01)	11.69 (1.33–102.79)	3.06 (0.76–12.41)	4.61 (0.91–23.32)	5.45 (1.35–22.02)	3.53 (1.07–11.67)	5.27 (1.29–21.46)		

* Odds ratios are adjusted for maternal residence.

** Reference groups according to descriptive factor are: sex, female; age, 20–24 years; education, 12 years; Living with child's father, no; race/ethnicity, White-non-Hispanic; residence, Massachusetts; gravidity and parity, 1; BMI, 18.5–25.9; constraint-and vascular disruption-related factors, no.

Distribution of demographic and reproductive factors among case subgroups

Table III

Descriptive factors	Constraint Cases				Genetic Cases				Vascular Disruption Cases			
	Yes n=155	No n=522	OR (95% CI)*	n=78	Yes n=599	No n=155	OR (95% CI)*	Yes n=32	No n=645	OR (95% CI)*	n=32	
	n (%)	n (%)			n (%)	n (%)		n (%)	n (%)			
Child's sex												
Male	104 (67.1)	382 (73.2)	0.77	(0.52–1.13)	49 (62.8)	437 (73.0)	0.63	(0.39–1.04)	25 (78.1)	461 (71.5)	1.44	(0.61–3.40)
Female	51 (32.9)	140 (26.8)		Ref.	29 (37.2)	162 (27.0)		Ref.	7 (21.9)	184 (28.5)		Ref.
Maternal Factor												
Age <20	0	20 (3.8)		**	2 (2.6)	18 (3.0)	0.93	(0.19–4.46)	1 (3.1)	19 (2.9)		**
20–24	27 (17.4)	111 (21.3)		Ref.	14 (17.9)	124 (20.7)		Ref.	1 (3.1)	137 (21.2)		Ref.
25–29	39 (25.2)	150 (28.7)	1.06	(0.61–1.84)	27 (34.6)	162 (27.0)	1.51	(0.76–3.01)	9 (28.1)	180 (27.9)		**
30–34	54 (34.8)	137 (26.2)	1.53	(0.90–2.60)	20 (25.6)	171 (28.5)	1.00	(0.48–2.07)	5 (15.6)	186 (28.8)		**
35	35 (22.6)	104 (19.9)	1.30	(0.73–2.31)	15 (19.2)	124 (20.7)	1.04	(0.48–2.26)	16 (50.0)	123 (19.1)		**
Education												
<12 years	18 (11.6)	69 (13.2)	1.11	(0.59–2.09)	9 (11.5)	78 (13.0)	1.29	(0.57–2.94)	2 (6.3)	85 (13.2)	1.32	(0.25–6.95)
12 years	39 (25.2)	132 (25.3)		Ref.	22 (28.2)	149 (24.9)		Ref.	5 (15.6)	166 (25.7)		Ref.
13 years	98 (63.2)	321 (61.5)	1.10	(0.62–1.95)	47 (60.3)	372 (62.1)	1.12	(0.52–2.39)	25 (78.1)	394 (61.1)	2.93	(0.67–12.76)
Living with child's father												
Yes	136 (87.7)	441 (84.5)	1.25	(0.73–2.15)	68 (87.2)	509 (85.0)	1.21	(0.60–2.45)	29 (91.7)	548 (84.9)	1.76	(0.52–5.93)
No	19 (12.3)	80 (15.3)		Ref.	10 (12.8)	89 (14.9)		Ref.	3 (9.3)	96 (14.9)		Ref.
Unknown	0	1 (0.2)		**	0	1 (0.2)		**		1 (0.2)		**
Race/ ethnicity												
White-non- Hispanic	116 (74.8)	374 (71.6)		Ref.	58 (74.4)	432 (72.1)		Ref.	23 (71.9)	467 (72.4)		Ref.
Hispanic	13 (8.4)	66 (12.6)	0.63	(0.34–1.19)	6 (7.7)	73 (12.2)	0.62	(0.26–1.48)	4 (12.5)	80 (12.4)	1.10	(0.37–3.27)
Black-nonHispanic	20 (12.9)	64 (12.3)	1.10	(0.63–1.91)	10 (12.8)	74 (12.4)	0.97	(0.47–2.02)	4 (12.5)	75 (11.6)	0.94	(0.31–2.96)
Other	6 (3.9)	18 (3.4)	1.04	(0.40–2.69)	4 (5.1)	20 (3.3)	1.49	(0.49–4.52)	1 (3.1)	23 (3.6)		**
Maternal residence												
New York	45 (29.0)	167 (32.0)	0.68	(0.43–1.08)	19 (24.4)	193 (32.2)	0.65	(0.35–1.23)	7 (21.9)	205 (31.8)	0.62	(0.23–1.66)
NorthCarolina	56 (36.1)	218 (41.8)	0.65	(0.42–1.00)	34 (43.6)	240 (40.1)	0.94	(0.54–1.64)	15 (46.9)	259 (40.2)	1.05	(0.46–2.39)
Massachusetts	54 (34.8)	137 (26.2)		Ref.	25 (32.1)	166 (27.7)		Ref.	10 (31.3)	181 (28.1)		Ref.

<i>Descriptive factors</i>	Constraint Cases				Genetic Cases				Vascular Disruption Cases			
	Yes n=155	No n=522	OR (95% CI) *	n=78	Yes n=599	No n=155	OR (95% CI) *	n (%)	Yes n=32	No n=645	OR (95% CI) *	n=32
	n (%)	n (%)			n (%)	n (%)			n (%)	n (%)		n (%)
Primigravid												
Yes	48 (31.0)	171 (32.8)	0.94	(0.64–1.39)	21 (26.9)	198 (33.1)	0.76	(0.45–1.29)	11 (34.4)	208 (32.2)	1.12	(0.53–2.37)
Primiparous												
Yes	79 (51.0)	247 (47.3)	1.16	(0.81–1.66)	35 (44.9)	291 (48.6)	0.88	(0.54–1.41)	15 (46.9)	311 (48.2)	0.97	(0.48–2.00)
Body mass index (kg/m ²)												
<18.5	6 (3.9)	19 (3.6)	1.17	(0.45–3.06)	3 (3.8)	22 (3.7)	1.25	(0.35–4.42)	1 (3.1)	24 (3.7)	1.43	(0.18–11.75)
18.5–24.9	66 (42.6)	244 (46.7)		Ref.	31 (39.7)	279 (46.6)		Ref.	9 (28.1)	301 (46.7)		Ref.
25.0–29.9	38 (24.5)	146 (28.0)	0.97	(0.62–1.52)	17 (21.8)	167 (27.9)	0.93	(0.50–1.73)	11 (34.4)	173 (26.8)	2.17	(0.88–5.35)
30.0	44 (28.4)	96 (18.4)	1.70	(1.09–2.67)	26 (33.3)	114 (19.0)	2.03	(1.15–3.58)	10 (31.3)	130 (20.2)	2.53	(1.00–6.38)
Unknown	1 (0.6)	17 (3.3)		**	1 (1.3)	17 (2.8)		**	1 (3.1)	17 (2.6)		**

* OR (95% CI)odds ratio (95% confidence interval) adjusted for maternal residence.

** OR not estimated due to 1 observation in cell