Prevalence and Risk Factors for Microcephaly at Birth in Brazil in 2010

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abstract

OBJECTIVES: To estimate the baseline prevalence and risk factors for microcephaly at birth before the Zika virus epidemic in 2 Brazilian cities.

METHODS: We used population-based data from the Brazilian Ribeirão Preto (RP) and São Luís (SL) birth cohort studies of 2010 that included hospital deliveries by resident mothers. The final sample was 7376 live births in RP and 4220 in SL. Gestational age was based on the date of the mother's last normal menstrual period or obstetric ultrasonography, if available. Microcephaly at birth was classified according to the criteria of the International Fetal and Newborn Growth Consortium for the 21st Century and the Brazilian Ministry of Health. Risk factors for microcephaly, proportionate and disproportionate microcephaly, and severe microcephaly were estimated in a hierarchized logistic regression model.

RESULTS: According to the International Fetal and Newborn Growth Consortium for the 21st Century definition, the prevalence of microcephaly (>2 SDs below the mean for gestational age and sex) was higher in SL (3.5%) than in RP (2.5%). The prevalence of severe microcephaly (>3 SDs below the mean) was higher in SL (0.7%) than in RP (0.5%). Low maternal schooling, living in consensual union or without a companion, maternal smoking during pregnancy, primiparity, vaginal delivery, and intrauterine growth restriction were consistently associated with microcephaly. The number of cases of microcephaly is grossly underestimated, with an underreporting rate of ~90%.

CONCLUSIONS: The prevalence of severe microcephaly was much higher than expected in both cities. Our findings suggest that microcephaly was endemic in both municipalities before the circulation of the Zika virus.

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WHAT'S KNOWN ON THIS SUBJECT: Baseline estimates of the prevalence of microcephaly at birth before the Zika virus epidemic are not population based. Risk factors for microcephaly have been little researched to date.

WHAT THIS STUDY ADDS: The baseline prevalence of severe microcephaly was much higher than expected. Before the circulation of the Zika virus, microcephaly was endemic in 2 Brazilian cities and was associated with intrauterine growth restriction and sociodemographic, reproductive, and lifestyle variables.

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The Zika virus was first noticed in Brazil in May 2015.[1] Shortly thereafter, in October, increasing notification of microcephaly at birth was reported, and a possible link with the Zika virus was announced.[2] The prevalence rate of severe microcephaly based on the Brazilian Live Birth Information System (SINASC, Portuguese acronym) increased from 0.57 per 10 000 livebirths in 2010 to 5.5 per 10 000 livebirths in 2015.[3]

Prevalence rates of severe microcephaly at birth in Brazil based on the SINASC are underestimated,[4] and the Latin American Collaborative Study of Congenital Malformations (ECLAM) estimated that the rate of underreporting is 66%.[5] However, the degree of underascertainment of cases has been only poorly measured to date. Thus, baseline estimates of the prevalence of microcephaly before the Zika virus epidemic are confined to a few geographical areas and are not population based.

Risk factors for microcephaly have been little researched to date. The primary causes of microcephaly, including congenital infections, are relatively well known,[6,7] but other social, reproductive, demographic, and lifestyle risk factors are poorly known. Maternal smoking, alcohol and illicit drug use during pregnancy, inadequate weight gain during pregnancy, inadequate prenatal care, black race, nulliparity, maternal age of <20 years or ≥40 years, very low birth weight, very preterm birth, twinning, and low maternal schooling have been identified as risk factors for microcephaly at birth.[8–11]

Thus, we looked at head circumference (HC) at birth using data from 2 population-based birth cohorts performed in 2 Brazilian municipalities in 2010. Our objective in this study was to estimate the baseline prevalence and risk factors for microcephaly at birth in 2 Brazilian cities before the Zika virus epidemic in Brazil. The number of cases of microcephaly that should have been reported and the rate of underascertainment of cases were also estimated.

METHODS

We used population-based data from the Brazilian Ribeirão Preto (RP) and São Luís (SL) birth cohort studies, including hospital deliveries by resident mothers from January 2010 to December 2010. The RP birth cohort comprised 7798 newborns. Losses because of refusal or early discharge amounted to 3.8%.

The SL birth cohort consisted of a random sample of 1 of 3 hospital births. Sampling was stratified according to hospital, and probability of selection was proportional to the number of deliveries in each hospital. The sample included 5236 hospital births. Losses because of refusal or early discharge amounted to 4.6%.[12]

The mothers were interviewed during the first 24 hours postpartum. Two standardized questionnaires were used.

In RP, 2 criteria were employed to estimate gestational age (GA): the first took into account the date of the mother's last normal menstrual period (LNMP) reported by the mother, and the second used an algorithm based on the LNMP date and obstetric ultrasonography (OU), if available. If the difference between the GA calculated by the LNMP and the OU was up to 10 days more or less, the GA was estimated on the basis of the LNMP date; otherwise, it was estimated on the basis of the OU.[13] GA was only based on the date of LNMP in SL because in this city, few case patients had OU available.

Flowcharts of the Brazilian Ribeirão Preto and São Luís birth cohort studies (BRISA) showing exclusions are illustrated in Fig 1. The exclusion of newborns whose GA was <24 weeks or ≥43 weeks was necessary because *z* score reference standards for those GA values were not available in the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st).[14] Multiple births were not excluded. The final sample included 6174 live births in RP and 4220 live births in SL when only the LNMP date was used to estimate GA. When the LNMP date or OU was used to estimate GA in RP, 7376 cases were left for analysis.

Newborns were weighed naked by using electronic scales that are accurate to 5 g. Length was measured with the infant laid in the supine position on a neonatometer, with the head kept in line with the body and supported against the fixed vertical headpiece of the device; the legs were stretched, and the heels touched the vertical, sliding footpiece. The measurement was recorded to the last completed 1 mm. HC was measured within 12 hours of birth with a nonextensible metric tape passed around the head and anchored above the eyebrows and over the occiput. The tape was then pulled tightly to compress the hair, and the reading was recorded to the last completed millimeter.[15] Trained personnel supervised by the research team performed the HC measures. A 5% random sample was drawn, and a second HC measurement was obtained. Reliability, as measured by κ, was >80% at both sites. Microcephaly at birth was classified according to the INTERGROWTH-21st standards[14] and the Brazilian Ministry of Health criterion.[16] Microcephaly was defined as HC >2 SDs below the mean for GA and sex based on the INTERGROWTH-21st standards. Severe microcephaly was defined as HC >3 SDs below the mean. Birth weight and length *z* scores were also classified according to the INTERGROWTH-21st criterion[14] by using the INTERGROWTH-21st application for calculating *z* scores for weight, length, and HC at birth.[17]

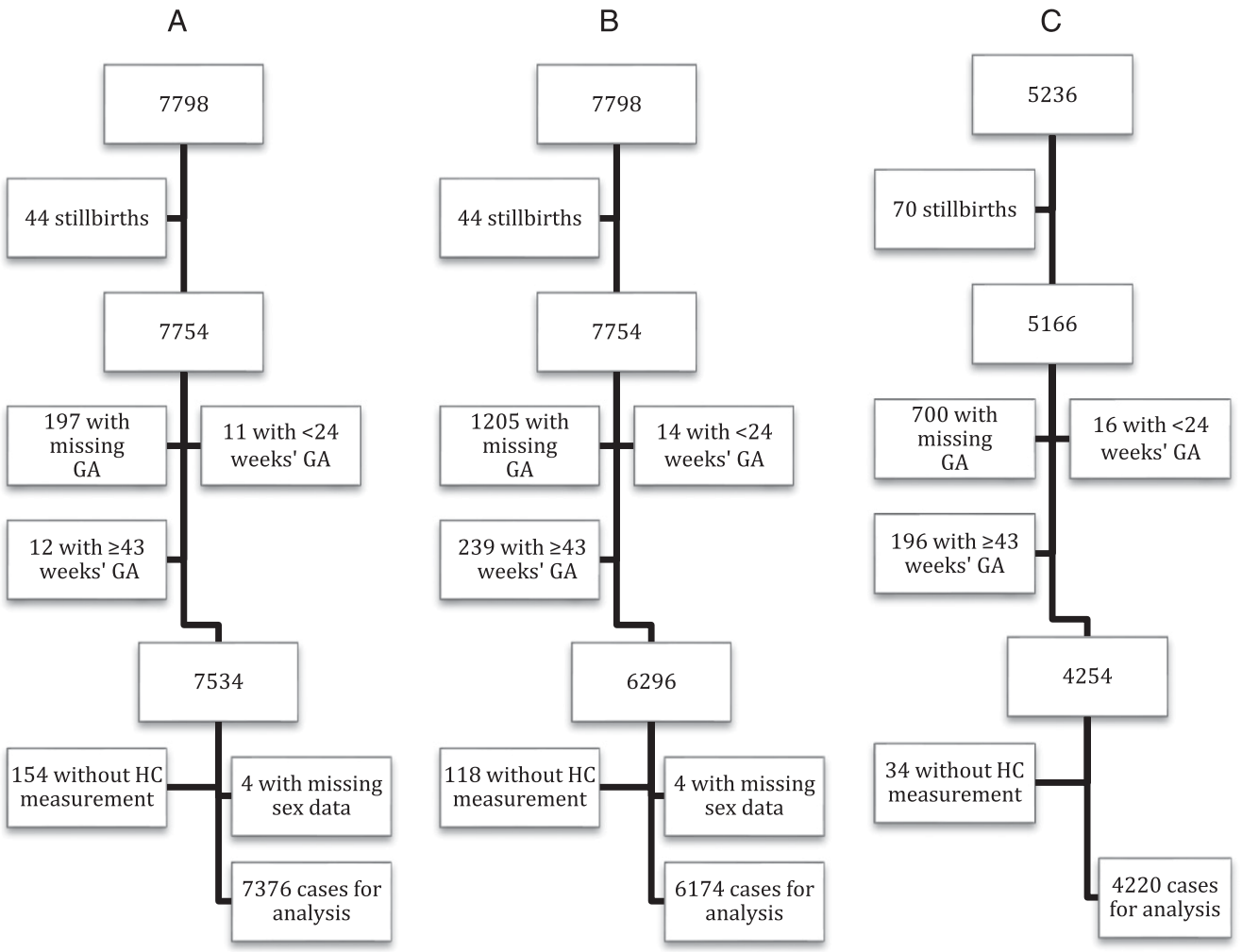

FIGURE 1
Flowchart of the BRISA cohort study (Brazil, 2010). A, RP exclusions by using GA estimated by an algorithm based on the LNMP date or OU. B, RP exclusions by using GA estimated by the LNMP date. C, SL exclusions by using GA estimated by the LNMP date.

According to the Brazilian Ministry of Health criterion, microcephaly for preterm infants is defined by taking into account the INTERGROWTH-21st standards. For term infants, microcephaly was considered as HC ≤31.5 cm for girls and ≤31.9 cm for boys,[16] values that correspond to >2 SDs below the mean for each sex in the World Health Organization (WHO) growth standards.[18] For severe microcephaly, the cutoff point adopted for term births was ≤30.3 cm for girls and ≤30.7 cm for boys, values that correspond to >3 SDs below the mean for each sex in the WHO growth standards.[18]

Analyses were based on the best available estimate for each city: for SL by using GA estimated by the LNMP date and for RP by using GA estimated by a previously described algorithm by using the LNMP date or the OU.[13] However, to determine if the measurement of GA would bias the estimation of the prevalence of microcephaly and severe microcephaly, these prevalences were also calculated only on the basis of the LNMP date for RP.

Data Processing and Statistical Analysis

We derived estimates of the number of cases of microcephaly and severe microcephaly for Brazil in 2010. We applied the prevalence rates according to various estimates derived from the SINASC,[3] ECLAM,[5] European Surveillance of Congenital Anomalies (EUROCAT),[19] a meta-analysis using data from India,[20] surveillance data from the United States,[11] data from Simmins,[4] and data from our own study to the total number of live births from that year (2 861 868), which was obtained from the SINASC Web page.[21] From our study, we derived estimates by using data from each city extrapolated for the whole country, and we pooled data by using the data from RP to derive estimates for the South, Southeast, and Central-West regions and the data from SL to derive estimates for the North and Northeast regions.

A measure of proportionality between HC and weight or length *z* scores was calculated to find if head growth lagged behind somatic growth or weight accretion. Microcephaly was considered disproportionate if HC was >2 SDs below the mean for GA and sex, but birth length or weight were not >2 SDs above the mean; it was considered proportionate if HC, length, and weight at birth were all >2 SDs below the mean for GA and sex.[22]

Data were analyzed with Stata 14.0 software (StataCorp, College Station, TX). To study the associations between the independent variables and the prevalence of microcephaly in each city, odds ratios (ORs) were estimated by using a hierarchized logistic regression model. The first level included demographic and socioeconomic variables: maternal schooling in years (≥12, 9–11, 5–8, and ≤4) and mother's marital status (married, consensual union, or without a companion). The second level included variables from the first level plus lifestyle and reproductive variables: parity (2–4, 1, and ≥5), alcohol consumption during pregnancy (yes [if at least 1 dose of alcoholic beverage was consumed per week] or no [otherwise]), and maternal smoking during pregnancy (yes [regardless of the number of cigarettes smoked] or no). The third level included variables from the second level plus health services variables: type of delivery (vaginal or cesarean) and type of hospital (private, public, or mixed, which covers both public and private patients). The fourth level included variables from the third level plus the newborn variable intrauterine growth restriction (IUGR; classified according to the INTERGROWTH-21st criterion[14] into yes [if birth weight was >2 SDs below the mean for GA and sex] or no [otherwise]).

We reported separate logistic regression models of risk factors for microcephaly and severe microcephaly. We also presented separately for each city risk factors for proportionate and disproportionate microcephaly according to birth length estimated by multinomial logistic regression.

TABLE 1 Prevalence of Microcephaly and Severe Microcephaly at Birth According to the Cutoff Points Proposed by the Brazilian Ministry of Health and INTERGROWTH-21st Criteria (BRISA Cohort Study, RP and SL, Brazil, 2010)

Criterion[a]	RP[b] (*n* = 7376)		RP[c] (*n* = 6174)		SL[c] (*n* = 4220)	
	n	%	*n*	%	*n*	%
INTERGROWTH-21st						
Microcephaly[d]	187	2.5	198	3.2	148	3.5
Severe microcephaly[e]	37	0.5	46	0.8	28	0.7
Brazilian Ministry of Health						
Microcephaly[f]	232	3.2	209	3.4	174	4.1
Severe microcephaly[g]	55	0.8	54	0.9	33	0.8

[a] Newborns whose GA was <24 wk or ≥43 wk were excluded because INTERGROWTH-21st *z* score reference standards were not available for these case patients.[14]
[b] Estimation of GA was based on the LNMP date or OU, if available, according to an algorithm described in the text.[13]
[c] Estimation of GA was based on the LNMP date.
[d] HC 2 SDs below the mean for GA and sex.[14]
[e] HC 3 SDs below the mean for GA and sex.[14]
[f] HC 2 SDs below the mean for preterm births[14] and ≤31.5 cm for term girls and ≤31.9 cm for term boys.[18]
[g] HC 3 SDs below the mean for preterm births[14] and ≤30.3 cm for term girls and ≤30.7 cm for term boys.[18]

Ethical Aspects

Mothers who agreed to participate in the study gave written, informed consent. The ethics research committees in both cities approved the project (4771/2008-30 for SL and 4116/2008 for RP).

RESULTS

According to the INTERGROWTH-21st definition, the prevalence of microcephaly was a little higher in SL (3.5%) than in RP (3.2%) in 2010 when using only the LNMP date for the estimation of GA. However, when we used an algorithm based on the LNMP date or the OU, the prevalence of microcephaly was substantially reduced in RP to 2.5%. The prevalence of severe microcephaly was also higher in SL (0.7%) compared with RP (0.5%) when we used the algorithm for the estimation of GA. By using the Brazilian Ministry of Health criterion, the prevalence of microcephaly was higher in SL independent of the method used to estimate GA (Table 1).

Among newborns with microcephaly, 62.8% had disproportionate microcephaly in relation to length and 71.1% in relation to weight in RP, whereas in SL, these figures were higher (ie, 78.2% and 83.8%; Table 2).

In both cities, mothers with maternal schooling ≤11 years, living without a companion or in consensual union, who smoked during pregnancy, had primiparity, vaginal delivery, and IUGR were associated with a higher prevalence of microcephaly. In SL, delivery in a public hospital and alcohol consumption during pregnancy were also associated with an increased prevalence of microcephaly. Having had 5 or more deliveries was protective against microcephaly in both cities (Table 3).

Risk factors that were consistently associated with severe microcephaly in both cities were low maternal schooling, living in consensual union or without a companion, and IUGR. The magnitude of the association of IUGR was greater for severe microcephaly than for microcephaly (Table 3).

The same risk factors were consistently associated with proportionate and disproportionate

TABLE 2 Proportionality Between HC at Birth and Birth Weight or Length *z* Scores in the BRISA Cohort Study (RP and SL, Brazil, 2010)

City and HC at Birth	Birth Length *z* Score >2 SDs Below the Mean for GA and Sex[a]				*P*
	No		Yes		
	n	%	*n*	%	
RP (*n* = 7338)[b]					
HC at birth >2 SDs below the mean for GA and sex[a]					<.001
No	6837	95.6	318	4.4	
Yes	115	62.8	68	37.2	
SL (*n* = 4210)[b]					
HC at birth >2 SDs below the mean for GA and sex[a]					<.001
No	3911	96.3	152	3.7	
Yes	115	78.2	32	21.8	
	Birth wt *z* score >2 SDs below the mean for GA and sex[a]				
RP (*n* = 7376)					
HC at birth >2 SDs below the mean for GA and sex[a]					<.001
No	7071	98.4	118	1.6	
Yes	133	71.1	54	28.9	
SL (*n* = 4220)					
HC at birth >2 SDs below the mean for GA and sex[a]					<.001
No	4006	98.4	66	1.6	
Yes	124	83.8	24	16.2	

[a] Based on the INTERGROWTH-21st standards.

[b] Thirty-eight newborns in RP and 10 in SL were excluded because their birth lengths were not measured.

microcephaly in both cities: low maternal schooling, living without a companion, and IUGR. The magnitude of the associations of maternal smoking and IUGR were greater for proportionate than for disproportionate microcephaly. Maternal smoking was a protective factor against disproportionate microcephaly but a risk factor for proportionate microcephaly in SL (Table 4).

Table 5 presents the estimates of the number of cases of severe microcephaly and microcephaly expected for Brazil in 2010. For severe microcephaly, numbers ranged from 163 (based on SINASC data) to 20 033 (based on our estimate by using data from SL). Our pooled estimate indicated that the expected number of cases of severe microcephaly would be 16 605 for 2010. For microcephaly, the estimates ranged from 71 547 to 100 165. Our pooled estimate from population-based data indicated that there would be 83 023 cases in 2010 in Brazil before the Zika virus epidemic (Table 5).

DISCUSSION

When using data from 2 population-based birth cohorts performed in 2 Brazilian municipalities with contrasting socioeconomic indicators before the Zika epidemic began in 2010, the prevalence of microcephaly at birth was higher than previous estimates, especially in the less developed city, SL (3.5%), compared with the more developed city, RP (2.5%). The prevalence of severe microcephaly was also much higher than previous estimates (0.7% in SL and 0.5% in RP).

The method used to estimate GA affected the prevalence of microcephaly. We used sensitivity analysis to address this issue in RP. When we used only the LNMP date to estimate GA, the prevalence of microcephaly was higher (3.2%) than that calculated by using either the LNMP date or the OU (2.5%), indicating that when GA was measured only with the LNMP date, the prevalence of microcephaly was overestimated. This finding also suggests that our estimate of the prevalence of microcephaly for SL may be an overestimate of the true prevalence. In the situation of a Zika virus epidemic, because in many places access to OU is restricted, the prevalence of microcephaly probably would be overestimated.

Current estimates of the prevalence of microcephaly at birth are ∼0.55%. Ashwal et al[23] pointed out that a 2.3% prevalence of microcephaly would be expected normally. Our estimate for RP (2.5%) indicates that in this city, the prevalence of microcephaly is higher than previous estimates and slightly higher than expected. In SL, the estimate (3.5%) suggests that the prevalence of microcephaly is ∼1.5 times the expected rate.

The prevalence of severe microcephaly at birth is expected to be 0.14%.[23] In both cities, the prevalence of severe microcephaly (0.5% in RP and 0.7% in SL) was much higher than expected and higher than previously reported in various national[3–5] and international[19,20] studies.

To date, few researchers have reported factors associated with microcephaly at birth. Källén[9] reported that maternal smoking during pregnancy was associated with small HC at birth, which is in agreement with our data from both cities. In another study, Krauss et al[10] identified alcohol use during pregnancy, low education, nulliparity, and black race as risk factors for microcephaly. In our study, primiparity and low maternal schooling were associated with a higher risk for microcephaly in both cities, whereas alcohol consumption

TABLE 3 Hierarchized Analysis of the Variables Associated With Microcephaly and Severe Microcephaly at Birth According to the INTERGROWTH-21st Criterion (RP and SL, 2010)

Level	Variable	*n*	%	Microcephaly RP	%	Severe Microcephaly RP	*n*	%	Microcephaly SL	%	Severe Microcephaly SL
				OR (95% CI)		OR (95% CI)			OR (95% CI)		OR (95% CI)
1: Demographic and socioeconomic variables	Maternal schooling, y										
	≥12	1713	1.23	1.00	0.18	1.00	635	1.89	1.00	0.31	1.00
	9–11	3767	2.23	1.51 (1.33–1.73)	0.56	2.39 (2.29–2.50)	2500	3.68	1.70 (1.35–2.14)	0.72	1.85 (1.51–2.27)
	5–8	1584	4.17	2.59 (2.08–3.22)	0.57	2.10 (1.96–2.24)	917	3.82	1.69 (1.25–2.29)	0.76	1.83 (1.72–1.95)
	≤4	308	5.19	3.21 (2.51–4.11)	1.30	4.72 (4.55–4.90)	157	5.73	2.59 (1.78–3.77)	0.64	1.55 (1.52–1.57)
	Marital status										
	Married	3515	1.54	1.0	0.26	1.0	918	2.18	1.0	0.33	1.0
	Consensual union	2895	3.25	1.65 (1.52–1.78)	0.66	2.09 (2.00–2.18)	2504	4.03	1.63 (1.26–2.11)	0.72	1.91 (1.53–2.39)
	Without a companion	964	4.05	2.09 (2.00–2.19)	0.93	2.95 (2.91–2.99)	798	3.38	1.37 (1.31–1.43)	0.88	2.35 (2.33–2.38)
2: Level 1 variables plus lifestyle and reproductive variables	Alcohol consumption during pregnancy										
	No	5699	2.37	1.00	0.44	1.00	3641	3.41	1.00	0.60	1.00
	Yes	1672	3.05	1.06 (0.94–1.19)	0.72	1.16 (1.13–1.18)	579	4.15	1.08 (1.05–1.10)	1.04	1.31 (0.83–2.04)
	Maternal smoking during pregnancy										
	No	6534	2.17	1.00	0.37	1.00	4081	3.41	1.00	0.61	1.00
	Yes	841	5.23	1.86 (1.74–2.00)	1.55	3.18 (3.09–3.27)	139	6.47	1.90 (1.35–2.67)	2.16	3.28 (0.90–11.95)
	Parity										
	2–4	3450	2.20	1.00	0.55	1.00	2043	2.79	1.00	0.49	1.00
	1	3700	2.81	1.69 (1.57–1.81)	0.43	0.94 (0.93–0.95)	2045	4.30	1.79 (1.66–1.93)	0.88	2.01 (1.42–2.83)
	≥5	215	3.26	0.80 (0.70–0.92)	0.93	0.91 (0.74–1.11)	132	2.27	0.59 (0.47–0.74)	0.00	—[a]
3: Level 2 variables plus health services variables	Type of delivery										
	Cesarean	4374	1.53	1.00	0.39	1.00	1999	1.60	1.00	0.35	1.00
	Vaginal	3002	4.00	2.11 (2.10–2.11)	0.67	0.95 (0.91–0.99)	2221	5.22	2.74 (1.85–4.08)	0.95	1.92 (1.23–3.00)
	Type of hospital										
	Private	2999	1.33	1.00	0.13	1.00	655	0.61	1.00	0.00	1.00
	Mixed[b]	1279	3.60	1.25 (0.98–1.58)	1.17	6.00 (5.71–6.31)	—	—	—	—	—
	Public	3094	3.26	1.01 (0.82–1.24)	0.58	2.98 (2.85–3.13)	3565	4.04	3.65 (2.14–6.24)	0.79	—[c]
4: Level 3 variables plus newborn variable	IUGR										
	No	7204	1.85	1.00	0.26	1.00	4130	3.00	1.00	0.39	1.00
	Yes	172	31.40	22.20 (21.76–22.66)	10.47	40.01 (35.08–45.83)	90	26.7	11.15 (10.22–12.16)	13.33	35.79 (33.87–37.81)

CI, confidence interval; —, not applicable.

[a] OR could not be calculated because there were no cases of microcephaly in this category.

[b] There were no hospitals in the mixed category in SL.

[c] OR could not be calculated because there were no cases of severe microcephaly in the reference category.

TABLE 4 Hierarchized Analysis of the Variables Associated With Proportionate and Disproportionate Microcephaly at Birth in Relation to Birth Length According to the INTERGROWTH-21st Criterion, RP and SL, Brazil, 2010

Level	Variable	*n*	%	Proportionate Microcephaly RP	%	Disproportionate Microcephaly RP	*n*	%	Proportionate Microcephaly SL	%	Disproportionate Microcephaly SL
				OR (95% CI)		OR (95% CI)			OR (95% CI)		OR (95% CI)
1: Demographic and socioeconomic variables	Maternal schooling, y										
	≥12	1712	0.35	1.00	0.82	1.00	635	0.31	1.00	1.57	1.00
	9–11	3765	0.80	1.79 (0.70–4.53)	1.38	1.44 (1.18–1.75)	2500	0.60	1.73 (0.94–3.19)	3.08	1.70 (1.15–2.51)
	5–8	1583	1.39	2.82 (1.04–7.64)	2.72	2.59 (2.35–2.86)	917	1.42	3.95 (3.81–4.10)	2.29	1.20 (0.77–1.87)
	≤4	308	3.25	6.51 (2.33–18.21)	1.95	1.87 (1.74–2.00)	157	1.27	3.63 (2.87–4.60)	4.46	2.38 (1.60 –3.56)
	Marital status										
	Married	3513	0.48	1.0	1.00	1.0	918	0.44	1.0	1.74	1.0
	Consensual union	2894	1.04	1.57 (1.34–1.84)	2.18	1.74 (1.65–1.84)	2504	0.84	1.39 (0.63–3.07)	3.19	1.71 (1.48–1.97)
	Without a companion	963	2.18	3.36 (3.22–3.50)	1.77	1.44 (1.31–1.59)	798	0.88	1.45 (1.42–1.49)	2.38	1.28 (1.19–1.37)
2: Level 1 variables plus lifestyle and reproductive variables	Alcohol consumption during pregnancy										
	No	5697	0.84	1.00	1.49	1.00	3641	0.69	1.00	2.72	1.00
	Yes	1670	1.14	0.94 (0.77–1.14)	1.80	1.10 (1.02–1.18)	579	1.21	1.16 (1.10–1.23)	2.77	1.01 (1.01–1.02)
	Maternal smoking during pregnancy										
	No	6532	0.67	1.00	1.47	1.00	4081	0.66	1.00	2.74	1.00
	Yes	839	2.74	3.22 (2.89–3.58)	2.26	1.17 (1.11–1.23)	139	3.62	4.50 (3.03–6.69)	2.17	0.85 (0.84–0.86)
	Parity										
	2–4	3448	0.78	1.00	1.36	1.00	2043	0.49	1.00	2.30	1.00
	1	3698	1.03	1.86 (1.69–2.05)	1.73	1.62 (1.52–1.73)	2045	0.98	2.70 (1.04–7.02)	3.28	1.58 (1.45–1.71)
	≥5	215	1.40	0.73 (0.57–0.92)	1.86	0.90 (0.83–0.98)	132	1.52	1.91 (0.71–5.18)	0.76	0.26 (0.24–0.27)
3: Level 2 variables plus health services variables	Type of delivery										
	Cesarean	4370	0.66	1.00	0.78	1.00	1999	0.50	1.00	1.10	1.00
	Vaginal	3002	1.30	1.53 (1.42–1.64)	2.70	3.09 (2.93–3.26)	2221	0.99	1.44 (0.50–4.16)	4.19	3.34 (3.16–3.52)
	Type of hospital										
	Private	2999	0.53	1.00	0.80	1.00	655	0.15	1.00	0.46	1.00
	Mixed[a]	1279	1.17	0.85 (0.84–0.86)	2.42	1.32 (0.93–1.86)	—	—	—	—	—
	Public	3090	1.20	0.78 (0.71–0.85)	1.94	0.91 (0.64–1.29)	3565	0.87	3.47 (1.63–7.42)	3.14	3.57 (2.53–5.04)
4: Level 3 variables plus newborn variable	IUGR										
	No	7203	0.35	1.00	1.49	1.00	4130	0.44	1.00	2.54	1.00
	Yes	169	25.44	88.30 (77.38–100.76)	4.73	4.19 (3.38–5.20)	90	15.56	39.02 (35.56–42.81)	11.11	5.70 (4.89–6.64)

CI, confidence interval; —, not applicable.

[a] There were no hospitals in the mixed category in SL.

TABLE 5 Estimated No. Cases of Severe Microcephaly and Microcephaly at Birth According to Figures Derived From Various Studies (Brazil, 2010)

Source	Prevalence of Microcephaly per 10 000 Births	Estimated No. Cases
Severe microcephaly (>3 SDs below the mean)		
SINASC[3,a]	0.57	163
EUROCAT (all registries)[19,b]	1.53	438
ECLAM[5,c]	1.98	567
EUROCAT, including genetic conditions[19,b]	2.00	572
India[20,d]	2.30	658
EUROCAT (highest rate, Hungary)[19,b]	4.25	1216
Unites States (30 registries)[11,e]	8.70	2490
Simmins[4,f]	9.20	2633
RP[g]	50.0	14 309
Pooled estimate[h]	62.0	16 605
SL[g]	70.0	20 033
Microcephaly (>2 SDs below the mean)		
RP[i]	250	71 547
Pooled estimate[j]	290	83 023
SL[i]	350	100 165

[a] SINASC's microcephaly definition was not standardized, but recommendations are to include only infants whose HC was >3 SD below the mean for GA and sex.
[b] EUROCAT microcephaly is defined as a reduction in the size of the brain with a skull circumference >3 SDs below the mean for sex, age, and ethnic origin, but not all reported cases follow this definition.
[c] ECLAM microcephaly is defined as congenital small head defined by an HC >3 SDs below the average in appropriate charts for sex and age, but many registries do not enforce this definition.
[d] Meta-analysis estimate derived from hospital data from 10 studies. No standardized definition of microcephaly was used.
[e] Cases were identified by the presence of an *International Classification of Diseases, Ninth Revision, Clinical Modification* hospital discharge code for microcephaly or mention of microcephaly in the medical record regardless of HC size.
[f] Estimate was based on registry data. Registries commonly use the definition of microcephaly as an HC >3 SDs below the mean for sex and GA.
[g] Severe microcephaly was defined as an HC >3 SDs below the mean for sex and GA based on the INTERGROWTH-21st standards.
[h] Severe microcephaly was defined as an HC >3 SDs below the mean for sex and GA based on the INTERGROWTH-21st standards. The pooled estimate was calculated by using data from RP to derive estimates for the South, Southeast, and Central-West regions and data from SL to derive estimates for the North and Northeast regions.
[i] Microcephaly was defined as an HC >2 SDs below the mean for sex and GA based on the INTERGROWTH-21st standards.
[j] Microcephaly was defined as an HC >2 SDs below the mean for sex and GA based on the INTERGROWTH-21st standards. The pooled estimate was calculated by using data from RP to derive estimates for the South, Southeast, and Central-West regions and data from SL to derive estimates for the North and Northeast regions.

during pregnancy was associated with a higher risk of microcephaly in SL, which is in agreement with their findings.[10] We also observed that living without a companion or having IUGR was associated with higher prevalence rates of microcephaly.

Vaginal delivery was associated with a higher prevalence of microcephaly in our study, which is in agreement with 1 African study.[24] Lower HC among those delivered vaginally is explained by head molding.[25]

Consistent risk factors were associated with microcephaly in both cities: low maternal schooling, living in consensual union or without a companion, maternal smoking during pregnancy, primiparity, vaginal delivery, and IUGR. Our findings suggest that before the Zika virus epidemic, there was a silent endemic of microcephaly associated with these variables closely linked to poverty but also because of other causes, such as undiagnosed congenital infections.

Most newborns had disproportionate microcephaly at birth (ie, HC at birth was small in proportion to birth length or weight). Whichever caused their brain growth to lag behind their somatic growth or weight accretion, most of these newborns with microcephaly were not able to preserve their brain growth (brain-sparing).[26] It is worth noting that disproportionate microcephaly was more prevalent in the less developed city (SL) than in the more developed city (RP).

It was not possible to clearly identify risk factors that were associated only with proportionate or disproportionate microcephaly, but some risk factors were consistently associated with these conditions in both cities. Maternal smoking and IUGR were consistently associated with a higher risk of proportionate than disproportionate microcephaly.

Our findings strongly suggest that current rates of microcephaly and severe microcephaly are grossly underestimated, probably because of an underascertainment of cases. From November 8, 2015, to October 8, 2016, 9814 suspected cases of microcephaly were reported to the Brazilian Ministry of Health.[27] Compared with our pooled estimate of 83 023 cases of microcephaly, this number is a little >10% of what should have been reported and represents 59.1% of the estimated number of severe microcephaly cases, which are also based on our pooled estimate.

Victora et al[28] estimated that ~63 000 cases of microcephaly >2 SDs below the mean for GA and sex should be reported. Our pooled estimate is 32% higher than their estimate, and our estimate for the number of severe cases of microcephaly is also higher (16 605 compared with 3000).

In view of the severity of the epidemic of congenital Zika syndrome,[29–31] it is highly advisable that countries set up HC monitoring systems to detect early signs of this syndrome. Accurate surveillance of congenital anomalies is a necessity. However, the number of cases not ascertained in Brazil is currently high. If the policy is reporting all HC >2 SDs below the mean for GA and sex, the current number of reported cases is low[27] compared with our

population-based estimates, with underreporting estimated at ~90%.

Our study has some strengths. It is population based and derived from 2 cities located in 2 Brazilian regions with different development levels. We used standardized criteria to identify microcephaly on the basis of the Brazilian Ministry of Health[22] and the INTERGROWTH-21st study.[14] Among the limitations, HC was measured within 12 hours after birth, and head molding after vaginal birth may have produced some measurement error. However, because head shrinkage and biparietal flattening continue postnatally in the first week after birth because of gravity,[25] even if we had measured HC 24 hours after birth, we would not have been able to reduce this limitation. On the other hand, the timing of the measurement of HC was the same as was used in the INTERGROWTH-21st reference,[14] as recommended by the WHO.[32] We used data from only 2 cities to derive estimates of microcephaly for the whole country. There are few estimates available, and all are based on registry data.[28] In contrast, our estimates are population based. Our estimates are not accurate but represent approximations by using the best available data.

Our aim in this study was not to make a microcephaly diagnosis but to screen for microcephaly. Therefore, newborns with >3 SDs below the mean for gestational age and sex should be referred to neuropediatricians for diagnosis of microcephaly, whereas those between 2 SDs and 3 SDs should be closely monitored by pediatricians or general practitioners, and HC should be continuously monitored during early infancy for a definitive diagnosis of microcephaly.

ABBREVIATIONS

BRISA: Brazilian Ribeirão Preto and São Luís birth cohort studies
ECLAM: Latin American Collaborative Study of Congenital Malformations
EUROCAT: European Surveillance of Congenital Anomalies
GA: gestational age
HC: head circumference
INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century
IUGR: intrauterine growth restriction
LNMP: last normal menstrual period
OR: odds ratio
OU: obstetric ultrasonography
RP: Ribeirão Preto
SINASC: Brazilian Live Birth Information System
SL: São Luís
WHO: World Health Organization

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