OBSTETRICS

Are children born by cesarean delivery at higher risk for respiratory sequelae?

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BACKGROUND: Globally, the number of children born by cesarean delivery is constantly increasing. However, hormonal and physiological changes associated with labor and vaginal delivery are considered necessary for lung maturation.

OBJECTIVE: We aimed to assess whether the mode of delivery is associated with changes in respiratory and atopic outcomes during infancy and at school age.

STUDY DESIGN: We included 578 children, born at ≥37 weeks of gestation, from a prospective birth cohort study. We compared weekly respiratory symptoms throughout the first year of life and infant lung function (tidal breathing and multiple-breath washout) at 5 weeks of age between children born by cesarean delivery (N=114) and those born by vaginal delivery (N=464) after term pregnancy in healthy women. At a follow-up visit conducted at 6 years of age (N=371, of which 65 were delivered by cesarean delivery), we assessed respiratory, atopic, and lung function outcomes (spirometry, body plethysmography, and multiple-breath washout). We performed adjusted regression analyses to examine the association between cesarean delivery and respiratory and atopic outcomes. To account for multiple testing, we used the Bonferroni correction, which led to an adapted significance level of $P<.002$.

RESULTS: During infancy, children born by cesarean delivery did not have more respiratory symptoms than those born by vaginal delivery (median, 4 weeks; interquartile range, 7 weeks vs median, 5 weeks; interquartile range, 7 weeks; adjusted incidence rate ratio, 0.8; 95% confidence interval, 0.6–1.0; $P=.02$). Infant lung function was similar between the groups. Children born by cesarean delivery did not have a higher incidence of "ever wheezing" (adjusted odds ratio, 0.9; 95% confidence interval, 0.5–1.8; $P=.78$) or current asthma (adjusted odds ratio, 0.4; 95% confidence interval, 0.0–3.5; $P=.42$) at school age than those born by vaginal delivery. There was no difference in the lung function parameters between the groups.

CONCLUSION: Cesarean delivery was not associated with respiratory symptoms in the first year of life, nor with different respiratory or atopic outcomes at school age, when compared with vaginal delivery. Our results indicate that there are no long-term consequences on the respiratory health of the child associated with cesarean delivery.

Key words: asthma, atopy, infancy, lung function, mode of delivery, respiratory symptoms, school age, wheezing

Introduction

Globally, the number of children born by cesarean delivery (CD) has almost doubled over the last decades.[1] CD rates vary from 4% in west and central Africa to 25% in Western Europe and 44% in Latin America and China.[1] These differences show that indications for CD are influenced by socioeconomic factors and extend beyond medical reasons. There is an ongoing debate about the contribution of maternally requested CD on the increased rates worldwide.[2] For women and obstetricians to make informed decisions regarding the mode of delivery, evidence about the consequences of CD is needed.[2]

Although recently issued consensus statements on CD exist, there are limited data on the long-term consequences of CD on the child.[2–4] There is emerging evidence that CD alters perinatal physiology with possible long-term effects.[5,6] Different mechanisms have been hypothesized, such as changes in the neonatal gut microbiota and a subsequently altered immune system.[7] Different physical and hormonal stresses during CD might lead to suboptimal neonatal respiratory transition and impaired lung development.[8,9] Furthermore, perinatal stress experienced during vaginal delivery (VD) by activation of the hypothalamic-pituitary-adrenal axis is considered to be an important physiological trigger for epigenetic modifications.[8]

Although there is evidence for the association of CD with postnatal respiratory morbidity, little is known about the long-term respiratory outcomes.[10–12] There has been particular interest in the association of CD with asthma in children, but the results have been inconsistent.[13–16] So far, no study has examined the important developmental period during infancy and combined that with follow-ups at school age.[3]

A unique longitudinal dataset from a prospective birth cohort of term-born infants allowed us to examine short- and long-term respiratory outcomes in children born by CD. This study aimed to assess whether CD is associated with changes in respiratory symptoms and lung function in the first year of life and if CD is associated with respiratory, atopic, and lung function changes at 6 years of age when compared with children born by VD. We hypothesized that children born by CD would have more

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AJOG at a Glance

Why was this study conducted?

There is good evidence for the association between cesarean delivery (CD) and postnatal morbidity (ie, respiratory distress syndrome). The long-term impact of CD on respiratory health in children is less conclusive.

Key findings

CD was not associated with respiratory symptoms in infancy nor with asthma in school-aged children when compared with children born by vaginal delivery (VD). There was no difference in lung function during infancy or at school age between children born by CD and those born by VD.

What does this add to what is known?

Our results indicate that there are no long-term consequences related to respiratory health in infancy or at school age associated with CD. This adds essential evidence for women and obstetricians to make informed decisions about the mode of delivery.

respiratory symptoms in infancy and show a higher risk for the development of asthma at school age than children born by VD.

Materials and Methods

Study design and participants

The prospective Bern Basel Infant Lung Development birth cohort comprises a group of unselected, healthy, term-born, White neonates recruited antenatally since 1999 in the region of Bern, Switzerland.[17] The exclusion criteria were prematurity (birth at <37 weeks' gestation), congenital malformation, substantial perinatal disease, severe maternal health problems, and maternal drug abuse excluding smoking. Pre- and perinatal information was collected by interviews using standardized questionnaires. Midwives reported data on the mode of delivery, which was categorized as VD, elective CD (ie, planned, primary CD without labor), or urgent CD (ie, unplanned, secondary CD, after attempted VD).

A total of 2 study visits were completed at 5 weeks and 6 years of age during which detailed lung function measurements were collected. In addition, study nurses phoned parents weekly throughout the first year of life to assess the respiratory health status of the child by standardized questionnaires. We included children born between April 1999 and May 2019 with follow-up visits at 6 years, if available, between August 2005 and October 2019. The ethics committee of the Canton of Bern approved the study, and written consent was obtained.

Respiratory outcomes in infancy

We assessed weekly respiratory rates (RRs) and respiratory symptoms (including coughing and wheezing) prospectively throughout the first year of life by weekly phone interviews with parents. At the 5-week study site visit, parents were instructed on how to perform RR measurements weekly at home for 60 seconds during regular quiet sleep. For the assessment of respiratory symptoms, we used a standardized score with high sensitivity for lower respiratory tract symptoms.[12] Weeks with any respiratory symptoms were defined as a score of >0 and weeks with severe respiratory symptoms as a score of ≥3 (Supplemental Table 1, online supplement [OLS]). We included infants with at least 40 weeks of assessment.

Infant lung function assessments included 10 minutes of tidal breathing followed by multiple-breath washouts (MBWs) using the Exhalyzer D (Eco Medics AG, Duernten, Switzerland). Lung function measurements were performed during quiet natural sleep according to current standards.[18] For tidal breathing measurements, we analyzed the mean values of 20 consecutive breaths for tidal volume per bodyweight, RR, minute ventilation, and the ratio of time to peak tidal expiratory flow and expiratory time. MBW was performed using 4% sulfur hexafluoride (OLS). The main outcomes were functional residual capacity (FRC_{MBW}) and lung clearance index (LCI), the latter representing a sensitive marker for ventilation inhomogeneity and small airway disease.[18]

Respiratory and atopic outcomes at school age

At 6 years of age, we assessed respiratory and atopic outcomes through an interview with a clinician using a standardized questionnaire adapted from the International Study of Asthma and Allergies in Childhood.[19] We defined respiratory (ever wheezing, current asthma) and atopic outcomes (allergic rhinoconjunctivitis, atopic dermatitis) as described in Supplemental Table 2 (OLS).

Spirometry and body plethysmography were performed using the MasterLab setup (Jaeger MasterScreen, CareFusion, Hochberg, Germany) according to the guidelines.[20,21] The following spirometry parameters were investigated: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), ratio of FEV_1 to FVC, and flow when 75% of FVC has been exhaled (FEF_{75}). Main outcomes of body plethysmography were FRC_{pleth}, total lung capacity (TLC), and specific effective airway resistance (sReff). The combination of these outcomes allows the detection of obstructive and restrictive lung disease.

Nitrogen MBW (N_2 MBW) was performed according to consensus using the Exhalyzer D (OLS). The main outcomes were FRC_{MBW} and LCI.[18,22]

Fractional exhaled nitric oxide (FeNO) as a maker of eosinophilic airway inflammation was measured by the single-breath online method using 2 setups (the WBreath 3.28.0, ndd Medizintechnik AG, Zürich, Switzerland until September 2012, and the CLD88sp FeNO analyzer, Eco Medics AG, Duernten, Switzerland since September 2012).

TABLE 1
Population characteristics

Characteristic	VD N=464	CD total N=114	CD urgent N=61	CD elective N=47	*P* value[a] VD vs total CD	*P* value[a] VD vs elective CD
Birth						
Male, n (%)	243 (52)	64 (56)	39 (64)	23 (49)	.47	.65
Gestational age (wk), mean (SD)	39.8 (1.1)	39.5 (1.3)	40.2 (1.2)	38.6 (0.8)	.006	<.001
Birthweight (Z-score), mean (SD)	0.2 (0.9)	0.0 (1.0)	0.3 (0.9)	−0.3 (1.0)	.04	<.001
Birth length (Z-score), mean (SD)	0.1 (1.0)	−0.1 (1.2)	0.4 (1.1)	−0.6 (1.0)	.26	<.001
Season of birth[b] (autumn), n (%)	126 (27)	30 (26)	15 (25)	12 (26)	.93	.96
Maternal age (y), mean (SD)	33 (4)	34 (4)	34 (4)	36 (4)	.003	<.001
Transient signs of respiratory distress at birth (yes), n (%)	70 (15)	14 (12)	7 (12)	7 (15)	.45	.60
Risk factors						
Older siblings (yes), n (%)	268 (58)	59 (52)	25 (41)	31 (66)	.35	.16
Childcare (yes), n (%)	108 (23)	37 (33)	25 (41)	10 (21)	.03	.78
Exclusive breastfeeding (wk), mean (SD)	21 (13)	19 (14)	19 (14)	20 (14)	.16	.59
Maternal smoking during pregnancy[c] (yes), n (%)	79 (17)	17 (15)	9 (15)	6 (13)	.64	.49
Parental smoking (yes), n (%)	58 (13)	16 (14)	10 (16)	5 (11)	.87	.67
Educational status mother[d] (low), n (%)	112 (24)	18 (16)	9 (15)	7 (15)	.15	.32
Educational status father[d] (low), n (%)	64 (14)	12 (11)	4 (7)	5 (11)	.05	.06
Atopy mother[e] (yes), n (%)	143 (31)	36 (32)	23 (38)	12 (26)	.76	.55
Atopy father[e] (yes), n (%)	174 (38)	41 (36)	23 (38)	15 (32)	.88	.56
Study visit						
Age (d), mean (SD)	36 (5)	37 (6)	36 (6)	38 (5)	.25	.02
Bodyweight (Z-score), mean (SD)	−0.2 (0.9)	−0.5 (0.9)	−0.2 (0.8)	−0.8 (1.0)	.009	<.001
Body height (Z-score), mean (SD)	−0.1 (1.1)	−0.3 (1.1)	0.1 (0.9)	−0.8 (1.1)	.09	<.001

Data are presented as mean (SD) or number (percentage), unless otherwise indicated.

CD, cesarean delivery; *SD*, standard deviation; *VD*, vaginal delivery.

[a] Significance was determined using *t* tests or chi-square tests as appropriate; [b] Winter was defined as the period from December 21 to March 20, spring was defined as the period from March 21 to June 20, summer was from June 21 to September 20, and autumn was from September 21 to December 20; [c] Defined as active or passive smoke exposure; [d] Categorized into low (<4 years of apprenticeship), middle (≥4 years of apprenticeship), and high (tertiary education); [e] Defined as self-reported or doctor-diagnosed asthma, and atopic eczema, and hay fever.

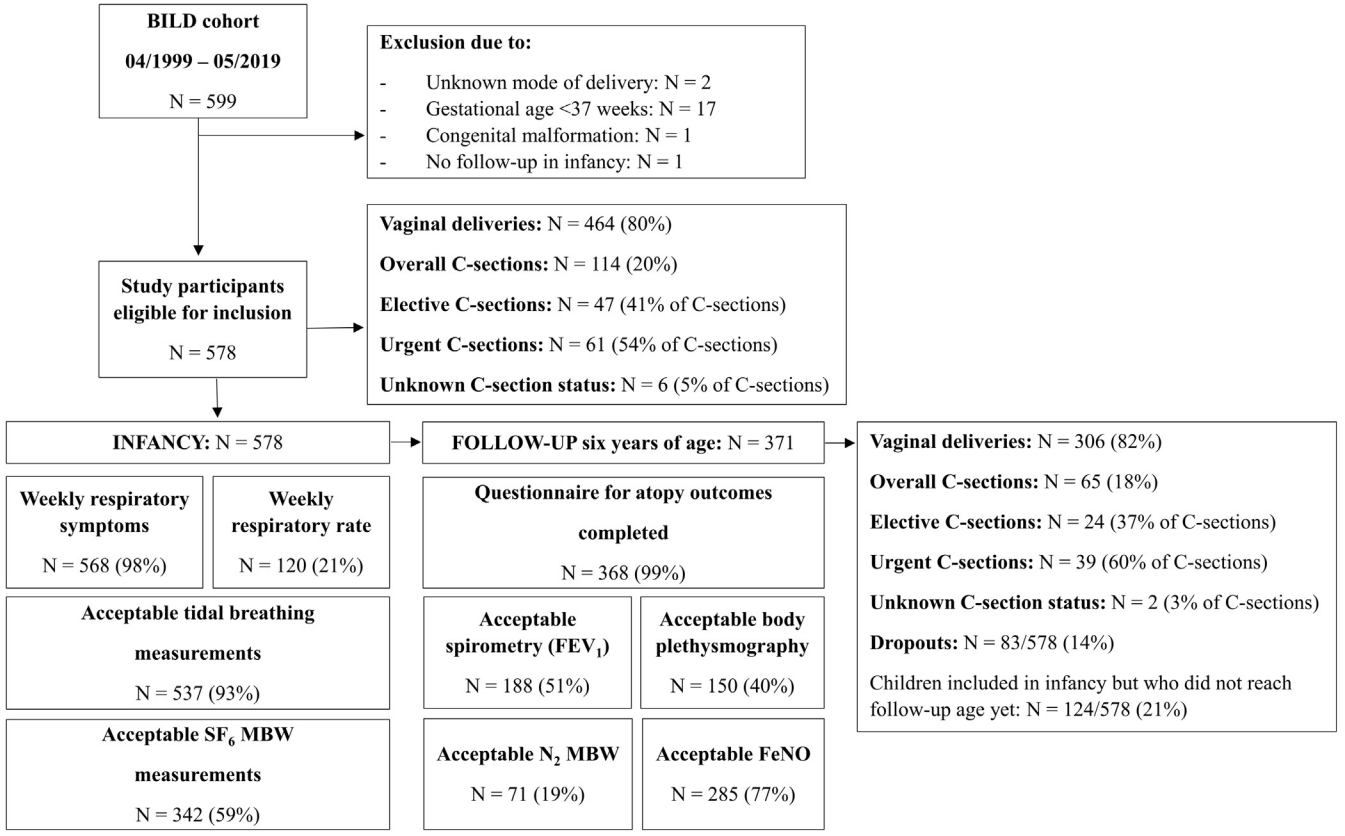
Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

Statistical analysis

We performed regression analyses to assess the differences in the outcomes between children born by CD and those born by VD. We used the analysis most appropriate for the distribution of outcome data, namely Poisson regression analysis for respiratory symptoms, linear regression analysis for lung function parameters and RR, and logistic regression analysis for respiratory and atopic outcomes. First, we performed univariable regressions. We applied multilevel linear regressions to account for multiple RR measurements in the same individual by adding a random effect term. Second, we adjusted the models for potential risk factors and included anthropometric factors distributed unequally among groups (age and body length at infant study visit) (Table 1).[12,23,24] We repeated all analyses comparing only the subgroups of elective or urgent CD with children born by VD. Finally, we performed additional analyses to rule out effect modification by birthweight, breastfeeding, transient signs of respiratory distress, and antepartum administration of antibiotics (OLS).

We aimed to detect at least a difference of 3.0 breaths per minute in the RR and a difference in FEV1 of 0.5 Z-scores between children born by CD and those born by VD. With our sample size of 578 infants, we could have detected a difference of 2.1 breaths per minute in the RR in the

FIGURE 1
Study flow



BILD, Bern Basel Infant Lung Development; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *MBW*, multiple-breath washout.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

first quarter with a power of 80% and a significance level of $P<.002$. For the follow-up at 6 years of age with a sample size of 371, we could have detected a difference of 0.4 FEV_1 in the Z-scores.

To assess differences in the anthropometric and risk factors among groups, the significance level was defined at a P value of $<.05$ for 2-sided tests. As we investigated multiple outcome variables, we used a Bonferroni correction to account for multiple testing. The Bonferroni correction led to an adjusted significance level for outcome variables at a P value of $<.002$ for 2-sided tests. All analyses were performed in Stata 16.0 (StataCorp LLC, College Station, TX). Reporting fulfills the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[25]

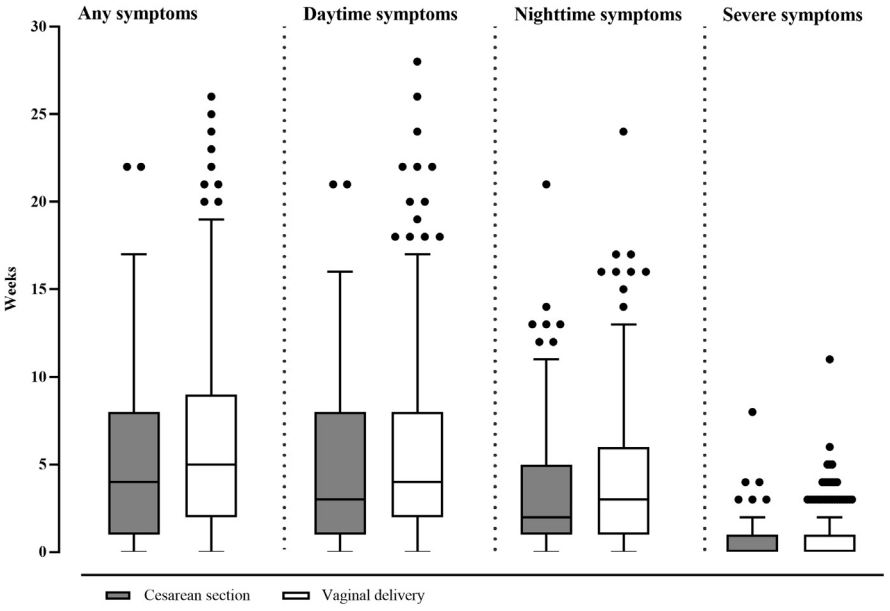
Results

We included 578 children of whom 114 (20%) were born by CD. Of all children born by CD, 47 (41%) were classified as being born by elective CD, 61 (54%) were classified as being born by urgent CD, and further classification was missing for 6 (5%) (Figure 1). Table 1 shows the anthropometric data and potential risk factors (missing data is provided in Supplemental Table 3, OLS). At birth, children born by CD had substantially lower gestational ages and birthweights and substantially older mothers, with the differences being more pronounced in the subgroup of elective CD. In addition, children born by CD showed substantially higher attendance of childcare, and at the first study visit, infants born by CD and elective CD were substantially lighter and shorter, although the infants in the elective CD subgroup were older at this first study visit. Follow-up data at 6 years of age were available for 371 children with 65 (18%) of them being born by CD and 24 (37%) of them being born by elective CD (Figure 1). The dropout rate for follow-up visits was 14%. There was no clinically relevant difference between the children included in the follow-ups and those who dropped out (Supplemental Table 4, OLS).

Respiratory outcomes in infancy

Children born by CD did not have more respiratory symptoms in the first year of life than children born by VD. Of all the children, 526 (93%) suffered from any respiratory symptoms during the first year of life, 99 (19%) of whom were born by CD. Of the 526 children with respiratory symptoms, 220 (42%) showed

FIGURE 2
Weeks with respiratory symptoms in the first year of life



Any respiratory symptoms during day- or nighttime were characterized by a score >0 and severe respiratory symptoms were characterized by a score ≥3.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

severe respiratory symptoms at least once, 36 (16%) of whom were born by CD. The median (range) number of weeks with any respiratory symptoms was 4 weeks (0−22 weeks) in the CD group and 5 weeks (0−34 weeks) in the VD group with no relevant differences between day- and nighttime symptoms (Figure 2). The median (range) number of weeks with severe respiratory symptoms was 0 weeks (0−8 weeks in the CD group and 0−11 weeks in the VD group) in both groups. The adjusted incidence rate ratio (IRR) was 0.8 (95% confidence interval [CI], 0.6−1.0; *P*=.02) among children born by CD overall and was similar in the subgroup of children born by elective CD (IRR, 0.8; 95% CI, 0.6−1.1; *P*=.10) and those born by urgent CD (IRR, 0.8; 95% CI, 0.6−1.1; *P*=.13) (Table 2). Considering the adjusted significance level of *P*<.002 after Bonferroni correction, the IRR for respiratory symptoms did not differ substantially between children born by CD and those born by VD. Older siblings and childcare were the only risk factors associated with substantially more respiratory symptoms in our final regression model (OLS).

Throughout the first year of life, there was no difference in the mean RR per quarter between children born by CD and those born by VD, with both groups showing a similar decline (Figure 3). The mean (standard deviation [SD]) RR decreased for both groups from 33 breaths per minute (5) in the first quarter to 26 breaths per minute (5) in the CD group and 25 breaths per minute (3) in the VD group, and there was no substantial difference in the adjusted linear regression analysis between the groups (Table 2). In the multilevel regression model, the RR was similar among children born by CD and those born by VD with an adjusted difference of −0.2 breaths per minute (95% CI, −1.8 to 1.3; *P*=.77).

There was no substantial association between mode of delivery and differences in infant lung function in either the tidal breathing measurements or in the MBW measurements (Table 3). The mean (SD) LCI was 8.0 (1.0) in both the groups (adjusted mean difference, 0.0; 95% CI, −0.3 to 0.3; *P*=.97).

Respiratory and atopic outcomes at school age

Children born by CD did not have a higher incidence of ever wheezing, current asthma, or atopic outcomes at 6 years of age than children born by VD. The prevalence of ever wheezing was 22% (n=14) among children born by CD and 21% (n=64) among children born by VD and the prevalence was 2% (n=1) and 3% (n=10) for current asthma, respectively (Table 4). The adjusted odds ratio (OR) for ever wheezing was 0.9 (95% CI, 0.5−1.8; *P*=.78) and for current asthma it was 0.4 (95% CI, 0.0−3.5; *P*=.42) (Figure 4, A). There was no association between CD and allergic rhinoconjunctivitis or atopic dermatitis (Table 4).

Overall, lung function parameters showed no differences between children born by CD and those born by VD. We found the most pronounced but insignificant difference for sReff. The mean (SD) sReff was 1.0 kPa×s (0.2) in the CD group and 0.9 kPa×s (0.2) in the VD group with an adjusted mean difference of 0.1 (95% CI, 0.0−0.2; *P*=.04) after additional adjustment for ever wheezing and current asthma (Table 5). Spirometry, body plethysmography, and N_2 MBW outcomes showed normal values and no adjusted difference between the groups (Table 5).

We did not observe a difference in FeNO as a marker of eosinophilic airway inflammation between children born by CD and those born by VD. The mean (SD) FeNO in parts per billion among children born by CD was 7 (4) and it was 8 (6) among children born by VD with an adjusted mean difference of −0.9 (95% CI, −2.7 to 0.9; *P*=.32) (Table 5).

Comment

Principal findings

In this birth cohort study of term-born infants, children born by CD did not have more respiratory symptoms or different physiological outcomes during the first year of life than children born by

TABLE 2
Respiratory outcomes during infancy

Association between mode of delivery and weeks with any respiratory symptoms

				Adjusted IRR (95% CI)[a]		*P* value[b]	
	VD N=464	CD total N=114	CD elective N=47	CD total	CD elective	CD total vs VD	CD elective vs VD
n (%)	457 (98)	111 (97)	45 (96)	—	—	—	—
Number of weeks, median (IQR)	5 (7)	4 (7)	3 (6)	0.8 (0.6–1.0)	0.8 (0.6–1.1)	.02	.10

Association between mode of delivery and mean respiratory rate per quarter (in breaths per minute)

				Adjusted mean difference (95% CI)[a]		*P* value[c]	
	VD N=464	CD total N=114	CD elective N=47	CD total	CD elective	CD total vs VD	CD elective vs VD
n (%)	92 (20)	28 (25)	11 (23)	—	—	—	—
1–3 mo after birth, mean (SD)	33 (5)	33 (5)	33 (4)	−0.9 (−3.3 to 1.6)	−2.0 (−5.3 to 1.4)	.47	.24
10–12 mo after birth, mean (SD)	25 (3)	26 (5)	24 (3)	0.6 (−1.4 to 2.6)	−1.5 (−3.5 to 0.5)	.54	.14

Data are presented as mean (SD) or number (percentage), unless otherwise indicated. Assessment throughout the first year of life.

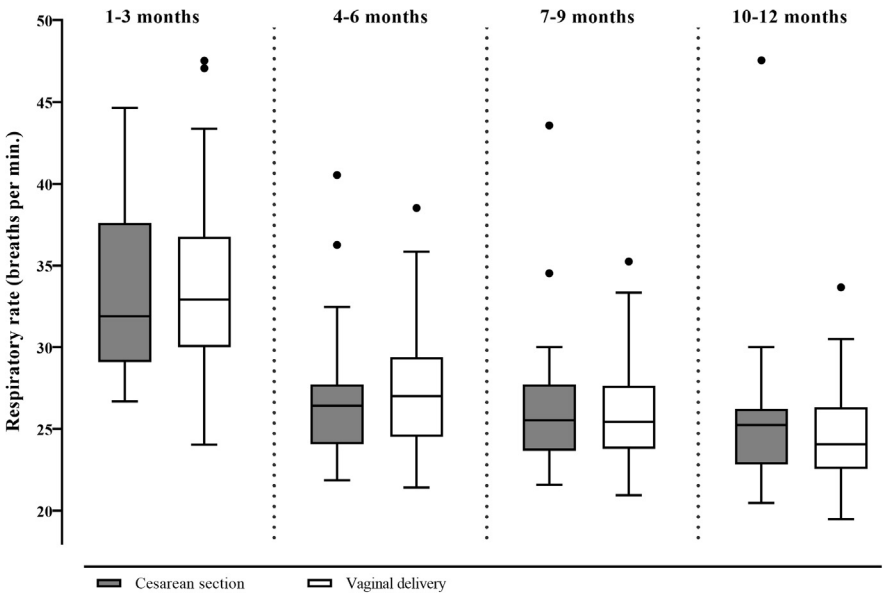
CD, cesarean delivery; *CI*, confidence interval; *IQR*, interquartile range; *IRR*, incidence rate ratio; *SD*, standard deviation; *VD*, vaginal delivery.

[a] Confounders included sex, gestational age, birthweight, maternal age at birth, duration of exclusive breastfeeding, maternal smoking during pregnancy, older siblings, attendance of childcare, atopy status of the mother, and current parental smoking; [b] Derived from Poisson regression model with children born by vaginal delivery serving as reference group; [c] Derived from linear regression model with children born by vaginal delivery serving as reference group.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

VD. At a follow-up visit at 6 years of age, we did not observe an association between CD and the incidence of ever wheezing, current asthma, allergic rhinoconjunctivitis, atopic dermatitis, or lung function abnormalities.

FIGURE 3
Mean RR per quarter in the first year of life



RR (in breaths per minute) was measured by parents on a weekly basis at home during quiet sleep.

RR, respiratory rate.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

Results in the context of what is known

In our study, CD did not affect the incidence of respiratory symptoms in infants throughout the first year of life. We found that older siblings and childcare were the only risk factors associated with substantially more respiratory symptoms during infancy. This has also been described in previous studies and was partly linked with increased exposure to respiratory infections.[23]

So far, studies assessing the effect of CD on respiratory health in term-born children focused mainly on postnatal morbidity and showed evidence of an increased risk for respiratory distress syndrome and transient tachypnea, especially in elective CDs.[7,10,11] In our cohort, substantial perinatal disease was an exclusion criterion. Nevertheless, after excluding children with transient signs of respiratory distress, the results remained unchanged. We showed comparable objective outcome measures between children born by CD and those born by VD, including a similar decline in weekly RR throughout the first year of life and similar tidal breathing parameters, FRC_{MBW}, and LCI at 5 weeks of age,

TABLE 3
Infant lung function

Association between mode of delivery and infant lung function

				Adjusted mean difference (95% CI)[a]		*P* value[b]	
	VD	CD total	CD elective	CD total	CD elective	CD total vs VD	CD elective vs VD
Tidal breathing	N=464	N=114	N=47	—	—	—	—
n (%)	439 (95)	98 (86)	39 (83)	—	—	—	—
Tidal volume (mL/kg), mean (SD)	7.5 (1.0)	7.4 (1.0)	7.3 (1.0)	0.0 (−0.3 to 0.3)	−0.1 (−0.5 to 0.4)	.92	.82
RR (breaths per minute), mean (SD)	44 (10)	44 (10)	46 (10)	−0.6 (−3.0 to 1.8)	−0.2 (−4.0 to 3.7)	.63	.93
Minute ventilation (mL/min), mean (SD)	1416 (303)	1351 (238)	1327 (245)	−49 (−113 to 15)	−72 (−174 to 30)	.14	.17
tPTEF/tE, mean (SD)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	−0.01 (−0.04 to 0.02)	−0.01 (−0.06 to 0.03)	.61	.58
MBW	N=464	N=114	N=47	—	—	—	—
n (%)	272 (59)	70 (61)	30 (64)	—	—	—	—
LCI, mean (SD)	8.0 (1.0)	8.0 (1.0)	8.0 (1.0)	0.0 (−0.3 to 0.3)	0.1 (−0.3 to 0.5)	.97	.65
FRC (mL/kg), mean (SD)	22 (4)	22 (4)	22 (4)	−0.1 (−1.1 to 0.8)	−0.5 (−2.0 to 0.9)	.77	.48

Data are presented as mean (SD) or number (percentage), unless otherwise indicated.

CD, cesarean delivery; *CI*, confidence interval; *FRC*, functional residual capacity; *LCI*, lung clearance index; *MBW*, multiple-breath washout; *RR*, respiratory rate; *SD*, standard deviation; *tPTEF/tE*, ratio of time to peak tidal expiratory flow and expiratory time; *VD*, vaginal delivery.

[a] Confounders included sex, gestational age, birthweight, maternal age at birth, duration of exclusive breastfeeding, maternal smoking during pregnancy, older siblings, attendance of childcare, atopy status of the mother, parental smoking, age, and body length at study visit; [b] Derived from the linear regression model with children born by vaginal delivery as reference group.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

the latter representing a sensitive marker of ventilation inhomogeneity. Our data indicate that birth by CD does not influence respiratory outcomes in infancy.

Most of the studies in which the impact of CD on the respiratory health of offspring have been evaluated have focused on childhood asthma with inconsistent results, with them describing a small positive association between CD and asthma (OR, 1.1−1.3).[13,15,16,24] We did not find any association between CD and asthma. Despite the low asthma prevalence of 3% in our cohort, our results are in line with other large studies with higher asthma prevalence rates of between 7% and 16% that found no association between birth

TABLE 4
Respiratory and atopic outcomes at early-school age

Association between mode of delivery and respiratory and atopic outcomes

	VD N=306	CD total N=65	CD elective N=24	Adjusted OR (95% CI)[a]		*P* value[b]	
				CD total	CD elective	CD total vs VD	CD elective vs VD
n (%)	304 (99)	64 (98)	24 (100)	—	—	—	—
Ever wheezing (yes), n (%)	64 (21)	14 (22)	5 (21)	0.9 (0.5−1.8)	1.1 (0.4−3.4)	.78	.88
Current asthma (yes), n (%)	10 (3)	1 (2)	1 (4)	0.4 (0.0−3.5)	0.8 (0.1−7.9)	.42	.83
Allergic rhinoconjunctivits (yes), n (%)	15 (5)	3 (5)	0 (0)	1.0 (0.3−3.7)	0.6 (0.0−11.9)	.99	.75
Atopic dermatitis (yes), n (%)	27 (9)	3 (5)	1 (4)	0.4 (0.1−1.6)	0.3 (0.0−2.4)	.20	.24

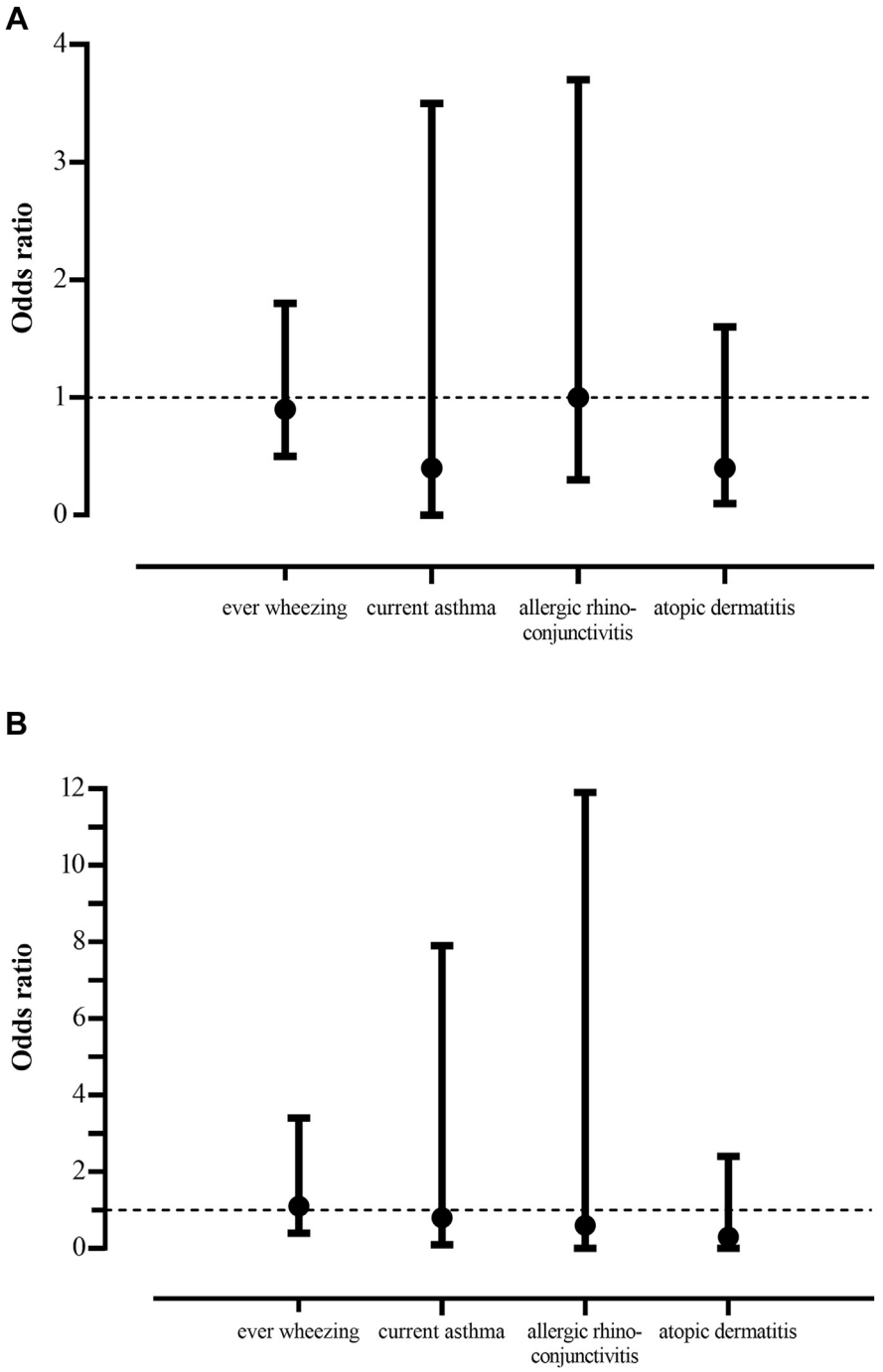
Data are presented as number (percentage), unless otherwise indicated.

CD, cesarean delivery; *CI*, confidence interval; *OR*, odds ratio; *VD*, vaginal delivery.

[a] Confounders included sex, gestational age, birthweight, maternal age at birth, duration of exclusive breastfeeding, maternal smoking during pregnancy, older siblings, attendance of childcare, atopy status of the mother, and current parental smoking; [b] Derived from the logistic regression model with children born by vaginal delivery as reference group.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

FIGURE 4
OR for respiratory and atopic outcomes among school-aged children



A, OR (95% CI) for outcomes in children born by CD overall compared with children born by VD as reference group. **B,** OR (95% CI) for outcomes in children born by elective CD compared with children born by VD as reference group.

CD, cesarean delivery; *CI*, confidence interval; *OR*, odds ratio; *VD*, vaginal delivery.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

by CD and an increased risk for asthma.[15,24] Thus, different definitions and timings of asthma diagnosis might hamper the comparison of various studies and partly explain different results. Similar to other studies, we found no association between CD and a higher incidence of adverse respiratory and atopic outcomes including ever wheezing (21%), allergic rhinoconjunctivitis (5%), or atopic dermatitis (8%).[16,26] Overall, in our cohort, children born by CD did not show different respiratory or atopic outcomes at school age than children born by VD.

We did not find any association between CD and lung function outcomes in line with other studies examining spirometry outcomes in older children ranging from 8 to 17 years of age.[24,27,28] The lack of association between CD and a wide spectrum of lung function outcomes supports our findings as objective markers.

Our results did not change when examining the subgroups of children born by elective or urgent CD. Infants born by elective CD are of particular interest, because their microbiome probably differs the most.[7] In addition, the absence of labor-induced stress might hamper neonatal respiratory transition and alter epigenetic modification.[8,9] We adjusted for factors indicative of increased (older siblings, childcare) or altered (breastfeeding) microbial load and found no evidence for any alteration in the association between mode of delivery and respiratory outcome. In addition, after exclusion of children with antepartum administration of maternal antibiotics the results remained the same. Some studies reported a stronger association between urgent instead of elective CD and an increased risk for asthma.[29] However, we did not find any association between urgent CD and asthma in our cohort. This suggests that causal mechanisms may be even more complex and not yet fully understood.

Clinical implications

Our results are relevant for current population health in view of the globally rising rates of CD.[1] Our data add important information regarding the long-term consequences of CD on the respiratory health of the child. In the absence of a clear medical indication, the decision to perform a CD, such as on maternal request, requires consideration of all the potential risks and benefits.

TABLE 5
Lung function at early-school age

Association between mode of delivery and lung function at school age

				Adjusted mean difference (95% CI)[a]		*P* value[b]	
	VD	CD total	CD elective	CD total	CD elective	CD total vs VD	CD elective vs VD
Spirometry, n (%)	150 (49)	38 (58)	17 (71)	—	—	—	—
FEV_1 (Z-score), mean (SD)	0.1 (0.9)	−0.1 (0.6)	−0.3 (0.6)	−0.2 (−0.5 to 0.1)	−0.2 (−0.7 to 0.3)	.28	.40
n (%)	65 (21)	14 (22)	—[c]	—	—	—	—
FVC (Z-score), mean (SD)	0.2 (1.0)	0.03 (0.7)	—[c]	−0.2 (−0.8 to 0.3)	—[c]	.43	—[c]
FEV_1/FVC (Z-score), mean (SD)	−0.1 (0.9)	−0.4 (0.7)	—[c]	−0.3 (−0.8 to 0.3)	—[c]	.28	—[c]
FEF_{75} (Z-score), mean (SD)	−0.2 (0.8)	−0.3 (0.5)	—[c]	−0.3 (− 0.8 to 0.2)	—[c]	.17	—[c]
Body plethysmography	N=306	N=65	N=24	—	—	—	—
n (%)	124 (41)	26 (40)	11 (46)	—	—	—	—
FRC_{pl} (L), mean (SD)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	−0.1 (−0.1 to 0.0)	−0.1 (−0.2 to 0.0)	.19	.24
TLC (L), mean (SD)	2.1 (0.3)	2.1 (0.4)	2.0 (0.3)	0.0 (−0.1 to 0.1)	−0.1 (−0.2 to 0.1)	.77	.60
sReff (kPa×s), mean (SD)	0.9 (0.2)	1.0 (0.2)	1.1 (0.2)	0.1 (0.0−0.2)	0.2 (0.1−0.4)	.04	.004
N_2 MBW	N=306	N=65	N=24	—	—	—	—
n (%)	54 (18)	17 (26)	5 (21)	—	—	—	—
LCI, mean (SD)	7.1 (0.5)	7.0 (0.6)	6.8 (0.7)	−0.1 (−0.4 to 0.3)	−0.2 (−1.0 to 0.4)	.62	.50
FRC (L), mean (SD)	0.9 (0.2)	0.9 (0.1)	0.9 (0.2)	0.0 (−0.1 to 0.1)	0.0 (−0.2 to 0.2)	.83	.98
FeNO	N=306	N=65	N=24	—	—	—	—
n (%)	234 (76)	51 (78)	16 (67)	—	—	—	—
FeNO (ppb), mean (SD)	8 (6)	7 (4)	7 (4)	−0.9 (−2.7 to 0.9)	−1.3 (−4.6 to 2.1)	.32	.46

Data are presented as mean (SD) or number (percentage), unless otherwise indicated.

CD, cesarean delivery; *CI*, confidence interval; *FEF_{75}*, flow when 75% of FVC has been exhaled; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FRC*, functional residual capacity; *FVC*, forced vital capacity; *LCI*, lung clearance index; *MBW*, multiple-breath washout; *ppb*, parts per billion; *SD*, standard deviation; *sReff*, specific effective airway resistance; *TLC*, total lung capacity; *VD*, vaginal delivery.

[a] Confounders included sex, gestational age, birthweight, maternal age at birth, duration of exclusive breastfeeding, maternal smoking during pregnancy, older siblings, attendance of childcare, atopy status of the mother, and current parental smoking status; [b] Derived from linear regression model with children born by vaginal delivery as reference group; [c] Number of children born by elective CD were too low (because of quality or technical reasons) to perform subgroup analysis.

Salem et al. Cesarean delivery and respiratory morbidity in term-born children. Am J Obstet Gynecol 2021.

Further studies are needed to provide more evidence for women and obstetricians to make informed decisions about the mode of delivery.[3,4]

Research implications

Replicating our findings in other populations, especially among those with a higher prevalence of asthma and different socioeconomic standards, will be important. Future studies should include detailed information on the classification of the women during delivery, the exact indication for CD, and the clinical practices applied during childbirth and newborn care.[30,31] Ideally, future research should combine multiple outcome measures (clinical, functional, and biological such as microbiome data) to better understand the underlying pathophysiological mechanisms that link CD with adverse childhood outcomes.

Strengths and limitations

One strength of our prospective study was the detailed information on perinatal risk factors. Moreover, we could clearly distinguish between elective and urgent CD, information that has been missing in many previous studies.[13,16,24] The combined assessment of respiratory outcomes in infancy and at school age by multiple outcome measures, including detailed lung function measurements, improves the robustness of our findings.

Among the limitations of our study was the lack of information on the medical indications for CD and on clinical practices related to childbirth and newborn care. Another limitation was the low prevalence of asthma in our cohort, which was 3%, when compared with the asthma prevalence of around 10% among Swiss and European school children.[32,33] This could have hampered our ability to detect small but clinically relevant differences. However, prevalence of the other respiratory and atopic outcomes was high and comparable with other studies. Furthermore, the

proportion of CD in our study population (20%) was lower than the incidence of CD in the general Swiss population (32% in 2018).[34] Care should be taken when generalizing our results when taking the sample size into account.

Conclusions

We found no clinically relevant association between CD and the occurrence of respiratory symptoms in infancy or respiratory and atopic outcomes at school age. Our findings were supported by normal lung function measurements among children born by CD. The results from our study contribute important evidence about the long-term consequences of CD with further studies being needed. Data on the long-term consequences of CD are essential for women and obstetricians to make informed decisions about the mode of delivery. ■

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References

1. Boerma T, Ronsmans C, Melesse DY, et al. Global epidemiology of use of and disparities in caesarean sections. Lancet 2018;392:1341–8.

2. Loke AY, Davies L, Mak YW. Is it the decision of women to choose a cesarean section as the mode of birth? A review of literature on the views of stakeholders. BMC Pregnancy Childbirth 2019;19:286.

3. National Institute for Health and Care Excellence (NICE). Caesarean section clinical guideline (CG132). 2011. Available at: https://www.nice.org.uk/guidance/cg132. Accessed November 2, 2020.

4. ACOG Committee Opinion no. 761: cesarean delivery on maternal request. Obstet Gynecol 2019;133:e73–7.

5. Sandall J, Tribe RM, Avery L, et al. Short-term and long-term effects of caesarean section on the health of women and children. Lancet 2018;392:1349–57.

6. Gillman MW. Mothers, babies, and disease in later life. BMJ 1995;310:68–9.

7. Jakobsson HE, Abrahamsson TR, Jenmalm MC, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. Gut 2014;63:559–66.

8. Tribe RM, Taylor PD, Kelly NM, Rees D, Sandall J, Kennedy HP. Parturition and the perinatal period: can mode of delivery impact on the future health of the neonate? J Physiol 2018;596:5709–22.

9. Ramachandrappa A, Jain L. Elective cesarean section: its impact on neonatal respiratory outcome. Clin Perinatol 2008;35:373–93.

10. Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. BMJ 2008;336:85–7.

11. Li Y, Zhang C, Zhang D. Cesarean section and the risk of neonatal respiratory distress syndrome: a meta-analysis. Arch Gynecol Obstet 2019;300:503–17.

12. Gorlanova O, Thalmann S, Proietti E, et al. Effects of breastfeeding on respiratory symptoms in infancy. J Pediatr 2016;174:111–7.e5.

13. Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: systematic review and meta-analysis. PLoS Med 2018;15:e1002494.

14. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between caesarean section and childhood asthma. Clin Exp Allergy 2008;38:629–33.

15. van Berkel AC, den Dekker HT, Jaddoe VW, et al. Mode of delivery and childhood fractional exhaled nitric oxide, interrupter resistance and asthma: the Generation R study. Pediatr Allergy Immunol 2015;26:330–6.

16. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. Clin Exp Allergy 2008;38:634–42.

17. Fuchs O, Latzin P, Kuehni CE, Frey U. Cohort profile: the Bern infant lung development cohort. Int J Epidemiol 2012;41:366–76.

18. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single-breath tests. Eur Respir J 2013;41:507–22.

19. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733–43.

20. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med 2019;200:e70–88.

21. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–22.

22. Singer F, Houltz B, Latzin P, Robinson P, Gustafsson P. A realistic validation study of a new nitrogen multiple-breath washout system. PLoS One 2012;7:e36083.

23. Latzin P, Frey U, Roiha HL, et al. Prospectively assessed incidence, severity, and determinants of respiratory symptoms in the first year of life. Pediatr Pulmonol 2007;42:41–50.

24. Liao Z, Lamb KE, Burgner D, et al. No obvious impact of caesarean delivery on childhood allergic outcomes: findings from Australian cohorts. Arch Dis Child 2020;105:664–70.

25. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.

26. Park YH, Kim KW, Choi BS, Jee HM, Sohn MH, Kim KE. Relationship between mode of delivery in childbirth and prevalence of allergic diseases in Korean children. Allergy Asthma Immunol Res 2010;2:28–33.

27. Brüske I, Pei Z, Thiering E, et al. Caesarean section has no impact on lung function at the age of 15 years. Pediatr Pulmonol 2015;50:1262–9.

28. Kotecha SJ, Watkins WJ, Lowe J, Henderson AJ, Kotecha S. Effect of early-term birth on respiratory symptoms and lung function in childhood and adolescence. Pediatr Pulmonol 2016;51:1212–21.

29. Tollånes MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe childhood asthma: a population-based cohort study. J Pediatr 2008;153:112–6.

30. Wellmann S, Manegold-Brauer G, Fischer T, et al. Improving neonatal and maternal outcome by inducing mild labor before elective cesarean section: the Lacarus randomized controlled trial. Neonatology 2021;118:116–21.

31. Edmond KM, Zandoh C, Quigley MA, Amenga-Etego S, Owusu-Agyei S, Kirkwood BR. Delayed breastfeeding initiation increases risk of neonatal mortality. Pediatrics 2006;117:e380–6.

32. Braun-Fahrlander C, Gassner M, Grize L, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. Eur Respir J 2004;3:407–13.

33. Mallol J, Crane J, von Mutius E, et al. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global

synthesis. Allergol Immunopathol (Madr) 2013;41:73–85.

34. The Swiss Federal Statistical Office. Reproductive health. 2018. Available at: https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/gesundheitszustand/reproduktive.html. Accessed November 2, 2020.

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