



Associations of Preeclampsia with Expiratory Airflows in School-Age Children Born Either at <28 Weeks or Weighing <1000 g

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Objectives To assess whether preeclampsia was associated with expiratory airflow at school-age in children born either extremely preterm (<28 weeks of gestation) or extremely low birthweight (ELBW; <1000 g birth weight).

Study design Participants comprised 3 cohorts of children born extremely preterm/ELBW in the state of Victoria, Australia, in 1991-1992, 1997, or 2005. Expiratory airflows were measured at age 8 years, and results converted to z scores. Data were compared between those exposed to preeclampsia with those unexposed to preeclampsia; analyses were then adjusted for confounding perinatal variables. Analyses were repeated within subgroups of extremely preterm only and ELBW only.

Results Respiratory data were available for 544 of 717 (76%) survivors, of whom 95 (17%) had been exposed to preeclampsia. On univariable analysis, those exposed to preeclampsia had better z scores for flows for the forced expired volume in 1 second (zFEV₁) (mean difference 0.29, 95% CI 0.04-0.53; *P* = .022) and zFEV₁/forced vital capacity (mean difference 0.33, 95% CI 0.04-0.61; *P* = .025); the difference persisted for zFEV₁ after adjustment for confounding perinatal variables. Analyses confined to those born extremely preterm revealed little evidence for associations between preeclampsia and airflow. In analyses confined to those born ELBW, preeclampsia was associated with better zFEV₁, which persisted after adjustment (mean difference 0.33, 95% CI 0.04-0.63; *P* = .025).

Conclusions Exposure to maternal preeclampsia was not associated with worse expiratory airflow in children born extremely preterm/ELBW; in fact, some airflows were better. (*J Pediatr* 2019;209:39-43).

It is uncertain whether maternal preeclampsia increases the risk of bronchopulmonary dysplasia (BPD) in infants born preterm or with low birth weight. Some studies report that preeclampsia is associated with a decrease in BPD,¹⁻³ some report an increase,^{4,5} and others report similar rates.⁶⁻⁸ We reported that BPD was not associated with preeclampsia exposure in infants born either extremely preterm (<28 weeks of gestational age) or extremely low birth weight (ELBW, <1000 g birth weight). These conclusions were unaltered if the cohort was restricted to extremely preterm survivors only, or ELBW survivors only.⁸

Regardless of whether preeclampsia is associated with BPD, it remains of interest whether preeclampsia is associated with long-term lung function. Although 3 studies have reported associations between preeclampsia and lung function in childhood, results have been inconsistent.⁹⁻¹¹ In these studies, most children were born at term, and the exposure to preeclampsia would have been predominantly at the end of the third trimester. These observations may not be relevant to babies born preterm because the potentially adverse effect of preeclampsia exposure occurs at a different stage of lung development. As lung function may be deteriorating in cohorts born extremely preterm in more recent eras,¹² it is important to determine whether preeclampsia is a contributing factor.

The aim of this study was to determine the associations between maternal preeclampsia and measures of expiratory airflow at school age in 3 large geographical cohorts of infants born either extremely preterm or ELBW in the postsurfactant era. Because we previously did not demonstrate an association of preeclampsia with BPD within these cohorts,⁸ we hypothesized that measures of expiratory flows in childhood would not be associated with preeclampsia.

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BPD	Bronchopulmonary dysplasia
ELBW	Extremely low birth weight
FEF _{25%-75%}	Forced expiratory flow between 25% and 75% of vital capacity
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity

Methods

Participants comprised 3 cohorts of consecutive infants born extremely preterm/ELBW born in the state of Victoria, Australia, during the calendar years 1991-1992, 1997, and 2005. Over this time, there have been 4 neonatal intensive care units in the state, 3 of which are located in high-risk maternity hospitals. Details of these cohorts have been reported elsewhere.¹²

Maternal details collected included the presence or absence of an obstetric diagnosis of preeclampsia, based on hypertension and proteinuria or nondependent edema. The preeclampsia had to be of sufficient severity to warrant delivery of the fetus, for either maternal or fetal indications. BPD was defined as an oxygen requirement at 36 weeks of postmenstrual age. Other perinatal data were collected as part of the overall follow-up assessments of the 3 cohorts, as previously described.^{8,12,13}

At 8 years of age, corrected for preterm birth, spirometry was measured according to American Thoracic Society guidelines¹⁴ or equivalent at the time of testing by respiratory scientists who were blinded to clinical details of the subjects. Maximum expiratory flow-volume curves were recorded while the child sat in a body plethysmograph with the door open. Flow was measured with a pneumotachograph, and volume obtained by integration of flow. Variables reflecting airflow included forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and forced expiratory flow from 25% to 75% of vital capacity (FEF_{25%-75%}). Results at body temperature and pressure saturated with water vapor were expressed as z scores for height, sex, ethnicity, and age.¹⁵

All aspects of the study were approved by the Human Research Ethics Committees at the Royal Women's Hospital, Mercy Hospital for Women, Monash Medical Centre, and the Royal Children's Hospital, Melbourne.

Statistical Analyses

Data were analyzed using Stata 15.1 (StataCorp LP, College Station, Texas). Data were compared between children exposed and those unexposed to preeclampsia by linear and logistic regression, fitted using generalized estimating equations with robust error estimates to account for clustering

within multiple births. Differences in expiratory airflows between groups were first calculated unadjusted, then adjusted for perinatal variables, including antenatal corticosteroids, multiple births, cesarean delivery, gestational age, birthweight z score, sex, and era of birth, with 2005 as the baseline. Data on maternal smoking in pregnancy were incomplete so could not be added to the multivariable models. Postdelivery events, including treatment with exogenous surfactant, BPD, or respiratory health after discharge home, were not included in the multivariable models as they might lie along the causal pathway leading from exposure to preeclampsia through to aberrant expiratory flows in later childhood. Mean differences or OR and 95% CI were calculated from regression coefficients, where appropriate.

Results

The 3 cohorts combined totaled 1190 live-born infants free of lethal anomalies who were either extremely preterm or ELBW, 717 (60.3%) of whom survived to 8 years of age. There were no data on preeclampsia for 2 of the mothers. Expiratory flow rates were measured on 544 of the 715 survivors (76%) with preeclampsia data, of whom 95 (17%) had mothers who had preeclampsia; rates of preeclampsia were similar across the 3 cohorts in those with expiratory flow data, at 18% (43/240) in the 1991-1992 cohort, 18% (27/146) in the 1997 cohort, and 16% (25/158) in the 2005 cohort. Comparing those exposed to preeclampsia with those who were not, there were fewer multiple births, more were delivered by cesarean, and more were female, and they were more mature but had lighter birth weights and lower birth weight SD scores (Table I). Similar proportions were treated with antenatal corticosteroids and exogenous surfactant, and there was a trend for a lower rate of BPD in the preeclampsia group.

On univariable analysis, children exposed to preeclampsia had evidence of better expiratory flow z scores for FEV₁ and FEV₁/FVC than those not exposed when extremely preterm/ELBW children were combined (Table II). When the analyses were restricted just to those who were extremely preterm, the evidence weakened, but when analyses were restricted just to those who were ELBW, the evidence

Table I. Perinatal characteristics compared between groups

Perinatal characteristics	Preeclampsia	No preeclampsia	OR or mean difference (95% CI), P value
No. survivors to 8 y with data	95	449	
Antenatal corticosteroids, n (%)	80 (84%)	365 (81%)	1.23 (0.67-2.24), P = .50
Multiple birth, n (%)	9 (9%)	145 (32%)	0.22 (0.11-0.45), P < .001
Cesarean delivery, n (%)	87 (92%)	203 (45%)	13.2 (6.2-27.8), P < .001
Gestational age, completed weeks, mean (SD)	27.8 (1.6)	26.4 (1.9)	1.4 (1.0-1.8), P < .001
Birth weight, g, mean (SD)	824 (139)	877 (172)	-53 (-90 to -16), P = .005
Female, n (%)	64 (67%)	233 (52%)	1.91 (1.20-3.05), P = .006
Birth weight z score, mean (SD)	-1.68 (0.88)	-0.58 (1.11)	-1.10 (-1.33 to -0.86), P < .001
Exogenous surfactant, n (%)	65 (68%)	272 (61%)	1.41 (0.88-2.26), P = .15
BPD	30 (32%)	188 (42%)	0.64 (0.40-1.03), P = .06

BPD defined as oxygen requirement at 36 weeks.

Table II. Expiratory airflows compared between groups

	Preeclampsia		No preeclampsia		Univariable		Multivariable	
	Mean (SD)	n	Mean (SD)	n	Mean difference (95% CI) P value*	P value*	Mean difference (95% CI) P value†	P value†
Extremely preterm or ELBW		n = 95		n = 449				
zFEV ₁	-0.65 (1.09)		-0.95 (1.20)		0.29 (0.04-0.53) P = .022		0.29 (0.01-0.56) P = .044	
zFVC	-0.61 (1.17)		-0.73 (1.24)		0.09 (-0.17 to 0.35) P = .50		0.10 (-0.19 to 0.38) P = .50	
zFEV ₁ /FVC	0.04 (1.27)		-0.29 (1.45)		0.33 (0.04-0.61) P = .025		0.28 (-0.05 to 0.62) P = .09	
zFEF _{25%-75%}	-1.14 (0.98)		-1.32 (1.10)		0.19 (-0.05 to 0.42) P = .12		0.21 (-0.07 to 0.49) P = .14	
ELBW only		n = 90		n = 355				
zFEV ₁	-0.63 (1.11)		-0.98 (1.19)		0.34 (0.08-0.60) P = .01		0.33 (0.04-0.63) P = .025	
zFVC	-0.62 (1.19)		-0.78 (1.25)		0.14 (-0.13 to 0.42) P = .31		0.13 (-0.17 to 0.42) P = .39	
zFEV ₁ /FVC	0.08 (1.27)		-0.25 (1.48)		0.32 (0.01-0.62) P = .042		0.30 (-0.05 to 0.65) P = .09	
zFEF _{25%-75%}	-1.15 (0.99)		-1.33 (1.13)		0.19 (-0.06 to 0.44) P = .13		0.21 (-0.08 to 0.50) P = .16	
Extremely preterm only		n = 47		n = 371				
zFEV ₁	-0.90 (1.20)		-0.97 (1.20)		0.08 (-0.29 to 0.44) P = .68		0.05 (-0.36 to 0.47) P = .80	
zFVC	-0.81 (1.33)		-0.73 (1.24)		-0.10 (-0.50 to 0.29) P = .60		-0.17 (-0.59 to 0.26) P = .45	
zFEV ₁ /FVC	-0.07 (1.34)		-0.37 (1.41)		0.32 (-0.09 to 0.73) P = .12		0.42 (-0.04 to 0.87) P = .07	
zFEF _{25%-75%}	-1.28 (1.01)		-1.37 (1.07)		0.11 (-0.21 to 0.43) P = .66		0.22 (-0.14 to 0.57) P = .24	

Bolded values P < .05.

*Univariable values obtained from generalized estimating equations.

†Multivariable values obtained from generalized estimating equations, adjusted for antenatal corticosteroids, multiple births, cesarean delivery, gestational age, birthweight z score, sex, and era of birth.

persisted. Of note, in the analysis restricted to children born extremely preterm, the number of children exposed to preeclampsia was halved, reducing the power to find differences if they existed.

On multivariable analysis, several other variables were independently associated with improved airflows. Gestational age and birthweight z score were both positively associated with zFEV₁ and zFVC. In addition, gestational age was also positively associated with zFEF_{25%-75%} (Table III). Of the other variables, multiple birth was associated with greater zFEV₁/FVC. Some airflows were better in earlier eras compared with 2005, although zFVC was lower in 1991-1992 compared with 2005. Conclusions were similar if the analyses were confined to those who were extremely preterm only or to those who were ELBW only, although there was more evidence for associations with some variables within the ELBW subgroup than within the extremely preterm subgroup (Tables IV and V; available at www.jpeds.com).

When we adjusted for all the variables, the associations with preeclampsia were marginally attenuated and the CIs were slightly wider, the combination leading to a weakening of the evidence for associations between preeclampsia and expiratory flows where it existed (Tables II-V). The previously reported associations of worse expiratory airflow in the 2005 cohort born extremely preterm compared with earlier eras¹² persisted when preeclampsia was included in the multivariable models (Table IV).

Discussion

The major finding of the current study was that there was little evidence of an adverse association of preeclampsia with expiratory airflows at 8 years of age in children who were born either extremely preterm or ELBW; if anything, airflows were better in those exposed to preeclampsia, particularly if the analyses were restricted to those who were born ELBW in contrast with those who were born extremely preterm.

Table III. Variables associated with expiratory airflows—multivariable analyses using a single model for each dependent variable

	Expiratory flow variable			
	zFEV ₁	zFVC	zFEV ₁ /FVC	zFEF _{25%-75%}
Preeclampsia	0.29 (0.01-0.56) P = .044	0.10 (-0.19 to 0.38) P = .50	0.28 (-0.05 to 0.62) P = .09	0.21 (-0.07 to 0.49) P = .14
Antenatal corticosteroids	0.02 (-0.25 to 0.28) P = .91	-0.04 (-0.31 to 0.24) P = .80	0.09 (-0.22 to 0.40) P = .56	0.11 (-0.14 to 0.36) P = .39
Multiple birth	-0.02 (-0.27 to 0.22) P = .85	-0.24 (-0.49 to 0.01) P = .06	0.39 (0.10-0.69) P = .01	0.04 (-0.20 to 0.28) P = .76
Cesarean delivery	-0.06 (-0.30 to 0.18) P = .64	-0.02 (-0.28 to 0.24) P = .87	-0.04 (-0.33 to 0.24) P = .76	-0.12 (-0.33 to 0.10) P = .30
Gestational age – per week	0.14 (0.07-0.21) P ≤ .001	0.15 (0.08-0.22) P < .001	0.00 (-0.08 to 0.08) P = 1.00	0.10 (0.03-0.17) P = .004
Birthweight z-score – per SD	0.19 (0.07-0.31) P = .002	0.25 (0.13-0.37) P < .001	-0.09 (-0.23 to 0.04) P = .18	0.10 (-0.01 to 0.21) P = .08
Female sex	0.17 (-0.03 to 0.37) P = .09	0.07 (-0.13 to 0.27) P = .50	0.08 (-0.15 to 0.31) P = .50	0.02 (-0.17 to 0.21) P = .83
1991-92 cohort*	0.12 (-0.13 to 0.36) P = .35	-0.27 (-0.52 to -0.01) P = .038	0.87 (0.59-1.14) P < .001	-0.15 (-0.39 to 0.10) P = .25
1997 cohort*	0.56 (0.27-0.85) P < .001	0.30 (0.02-0.59) P = .037	0.53 (0.24-0.82) P < .001	-0.01 (-0.26 to 0.25) P = .95

Data are mean difference, 95% CI, and P value.

*Compared with the 2005 cohort.

Although the debate over the potential adverse effect of vascular problems in preeclampsia in the mother on fetal lung development and subsequent predisposition for developing BPD remains unresolved, our findings are reassuring with respect to the effects of preeclampsia on long-term lung function, at least in children born extremely preterm/ELBW.

In the same cohorts of infants born either extremely preterm/ELBW in the 3 eras in Victoria in 1991-1992, 1997, and 2005, we reported that preeclampsia was not related to the presence of BPD.⁸ In a review of the literature at the time, we were unable to find definitive evidence for the associations between preeclampsia and BPD.⁸ Since that time, there have been several other reports of associations between preeclampsia and BPD in infants born preterm, still with conflicting results. One reported lower rates of BPD with preeclampsia in a cohort of >5000 infants selected by birthweight <1501 g in Taiwan.¹⁶ In contrast, in a population-based French study of 2697 singletons born before 32 weeks of gestation, moderate-to-severe BPD was associated with maternal disorders, including preeclampsia, when accompanied by fetal growth restriction.¹⁷ In a case-control study of infants born <32 weeks from a single hospital, 102 of whom were exposed to preeclampsia, BPD was not associated with preeclampsia,¹⁸ but the study may have been underpowered to find associations compared with the 2 population-based studies from Taiwan and France. We specifically reported our data not only for extremely preterm/ELBW combined, but also extremely preterm alone and ELBW alone, to observe the effects of the different selection filters. Selecting by birth weight will inevitably lead to the inclusion of more growth-restricted infants, whose outcomes will differ systematically from those who are not growth-restricted. Selecting by gestational age alone will avoid the problem of over-representation of growth-restricted infants, but it will lead to a reduction in study power; in our study, the number of children exposed to preeclampsia was halved by selecting infants born extremely preterm only. A possible explanation for the different conclusions about the association between preeclampsia and BPD in the literature relates to the different selection criteria, ie, either by gestation or birth weight. Regardless of the different denominators in the current study, we could find no evidence for adverse associations between preeclampsia and airflow in children born extremely preterm or ELBW. We recognize that our study sample is relatively small, and our findings need to be replicated in other studies.

The relationship between lung function in childhood in survivors born extremely preterm/ELBW with preeclampsia has not specifically been reported before. Several studies have reported associations between preeclampsia and lung function in childhood across all gestations and birth weights. In a longitudinal study of children born in 1991-1992 in Avon, England, lung function at 8-9 years of age was measured in 5461 of 13 758 (40%) of the original cohort recruited in the newborn period.⁹ They reported a small reduction of expiratory flow variables but little evidence for a difference in 138 children where pregnancy was complicated

by preeclampsia compared with 5323 children whose mothers were normotensive in pregnancy, eg, zFEV₁ mean difference -0.14 (95% CI -0.33 to 0.06); zFEF_{25%-75%} -0.15 (95% CI -0.34 to 0.04). On average, pregnancies complicated by preeclampsia were delivered 2 weeks earlier, and the infants were 457 g lighter at birth; adjustment for gestational age and birthweight attenuated the differences further (zFEV₁ mean difference -0.08 [95% CI -0.27 to 0.11]; zFEF_{25%-75%} -0.09 [95% CI -0.28 to 0.10]).

In another case-control study from a single hospital in Norway, expiratory airflows were measured at 12.8 years in children born between 1993 and 1995.¹⁰ There was little evidence for differences in expiratory airflow related to preeclampsia and its severity. The mean FEV₁ (% predicted) in children exposed to severe preeclampsia was 89.7% (n = 45) compared with 91.0% (n = 126) in the mild/moderate preeclampsia group and 91.1% (n = 272) in the no preeclampsia group. A limitation of that study was the poor retention rates; fewer than 50% of the original 366 preeclampsia and 659 controls with no preeclampsia initially recruited had expiratory flows measured. Moreover, most participants would have been born at term as the mean gestational age of the children was 39.3 weeks.

A prospective clinical birth cohort study sought to establish the associations between preeclampsia and systemic inflammatory conditions in their offspring, including asthma. The study included 411 Danish children born in 1998-2001 to mothers with doctor-diagnosed asthma and excluded children with gestational ages <36 weeks.¹¹ Preeclampsia was not associated with any changes in expiratory airflow measurements at either 1 month or 7 years of age, eg, mean difference in zFEV₁ at 7 years in children exposed to preeclampsia compared with controls was 0.17 (95% CI -0.32 to 0.67); *P* = .49. Preeclampsia was, however, associated with increased bronchial responsiveness to methacholine at 7 years.

In these 3 studies of predominantly children born at term, it would be reasonable to conclude that many cases of preeclampsia would not have been as severe as in our study, where the severity of preeclampsia led to very preterm delivery. Moreover, the exposure to preeclampsia would have been predominantly at the end of the third trimester, whereas in our study it would have been predominantly at the end of the second trimester, or early in the third trimester. As exposure to preeclampsia at a different stage of lung development may result in different effects, timing of exposure could be an important determinant of later lung function.

The strengths of the current study include the complete geographic cohorts selected, which avoids referral biases that occur in more restricted cohorts, the high proportion with both data on exposure to preeclampsia and on expiratory airflow, and the ability to adjust for potential early confounding variables due to the prospective nature of the study design and data collection. Limitations include a lack of biochemical data supporting a diagnosis of preeclampsia because women were sometimes delivered outside of high-risk maternity hospitals, and that the cohorts were born over a 15-year period, during which obstetric and neonatal

care may have changed over time. We have reported previously that expiratory airflows had worsened over time for our cohorts¹² but in the current study we have been able to demonstrate that preeclampsia was not a contributing factor to this decline. The search for an explanation for the worsening respiratory outcomes over time of children born extremely preterm/ELBW needs to focus elsewhere.¹⁹

In conclusion, we could not find evidence to support an association between exposure to maternal preeclampsia with worse expiratory airflow in school-age children born extremely preterm or ELBW. ■

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Appendix

Additional members of the Victorian Infant Collaborative Study Group

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Table IV. Variables associated with expiratory airflows—multivariable analyses using a single model for each dependent variable: children born extremely preterm only

	Expiratory flow variable			
	zFEV ₁	zFVC	zFEV ₁ /FVC	zFEF _{25%-75%}
Preeclampsia	0.05 (−0.36 to 0.47) <i>P</i> = .80	−0.17 (−0.59 to 0.26) <i>P</i> = .45	0.42 (−0.04 to 0.87) <i>P</i> = .07	0.22 (−0.14 to 0.57) <i>P</i> = .24
Antenatal corticosteroids	−0.03 (−0.34 to 0.29) <i>P</i> = .87	−0.08 (−0.40 to 0.25) <i>P</i> = .65	0.11 (−0.23 to 0.45) <i>P</i> = .52	0.10 (−0.19 to 0.38) <i>P</i> = .51
Multiple birth	−0.01 (−0.29 to 0.27) <i>P</i> = .96	−0.18 (−0.47 to 0.10) <i>P</i> = .21	0.33 (−0.01 to 0.66) <i>P</i> = .06	0.08 (−0.20 to 0.35) <i>P</i> = .59
Cesarean delivery	−0.03 (−0.29 to 0.24) <i>P</i> = .85	0.03 (−0.25 to 0.31) <i>P</i> = .83	−0.06 (−0.36 to 0.24) <i>P</i> = .71	−0.12 (−0.35 to 0.12) <i>P</i> = .33
Gestational age – per week	0.16 (0.05-0.27) <i>P</i> = .005	0.21 (0.09-0.33) <i>P</i> < .001	−0.09 (−0.21 to 0.04) <i>P</i> = .17	0.07 (−0.03 to 0.17) <i>P</i> = .20
Birthweight z-score – per SD	0.11 (−0.04 to 0.26) <i>P</i> = .16	0.15 (−0.01 to 0.31) <i>P</i> = .057	−0.05 (−0.21 to 0.12) <i>P</i> = .58	0.09 (−0.05 to 0.22) <i>P</i> = .20
Female sex	0.14 (−0.08 to 0.37) <i>P</i> = .22	0.09 (−0.14 to 0.33) <i>P</i> = .43	0.00 (−0.26 to 0.25) <i>P</i> = .99	−0.06 (−0.28 to 0.16) <i>P</i> = .58
1991-92 cohort*	0.18 (−0.10 to 0.47) <i>P</i> = .20	−0.16 (−0.46 to 0.13) <i>P</i> = .28	0.77 (0.45-1.08) <i>P</i> < .001	−0.17 (−0.45 to 0.10) <i>P</i> = .22
1997 cohort*	0.66 (0.33-1.00) <i>P</i> < .001	0.38 (0.05-0.71) <i>P</i> = .025	0.54 (0.21-0.87) <i>P</i> = .001	0.04 (−0.25 to 0.34) <i>P</i> = .77

Data are mean difference, 95% CI, and *P* value.

*Compared with the 2005 cohort.

Table V. Variables associated with expiratory airflows—multivariable analyses using a single model for each dependent variable: children with ELBW only

	Expiratory flow variable			
	zFEV ₁	zFVC	zFEV ₁ /FVC	zFEF _{25%-75%}
Preeclampsia	0.33 (0.04-0.63) <i>P</i> = .025	0.13 (−0.17 to 0.42) <i>P</i> = .39	0.30 (−0.05 to 0.65) <i>P</i> = .09	0.21 (−0.08 to 0.50) <i>P</i> = .16
Antenatal corticosteroids	0.00 (−0.31 to 0.31) <i>P</i> = .99	−0.06 (−0.37 to 0.25) <i>P</i> = .71	0.12 (−0.25 to 0.49) <i>P</i> = .54	0.13 (−0.18 to 0.43) <i>P</i> = .42
Multiple birth	−0.01 (−0.26 to 0.24) <i>P</i> = .94	−0.26 (−0.52 to 0.01) <i>P</i> = .06	0.40 (0.09-0.71) <i>P</i> = .011	0.03 (−0.21 to 0.28) <i>P</i> = .80
Cesarean delivery	−0.01 (−0.27 to 0.25) <i>P</i> = .93	0.03 (−0.25 to 0.31) <i>P</i> = .83	−0.08 (−0.41 to 0.25) <i>P</i> = .65	−0.11 (−0.36 to 0.14) <i>P</i> = .37
Gestational age – per week	0.17 (0.09-0.26) <i>P</i> ≤ .001	0.20 (0.11-0.28) <i>P</i> < .001	0.00 (−0.10 to 0.10) <i>P</i> = .97	0.13 (0.05-0.22) <i>P</i> = .002
Birthweight z-score – per SD	0.31 (0.14-0.48) <i>P</i> < .001	0.38 (0.20-0.57) <i>P</i> < .001	−0.09 (−0.30 to 0.12) <i>P</i> = .40	0.17 (0.004-0.34) <i>P</i> = .044
Female sex	0.11 (−0.11 to 0.33) <i>P</i> = .32	−0.04 (−0.26 to 0.19) <i>P</i> = .74	0.15 (−0.11 to 0.42) <i>P</i> = .26	0.03 (−0.18 to 0.25) <i>P</i> = .76
1991-q992 cohort*	0.01 (−0.25 to 0.28) <i>P</i> = .92	−0.39 (−0.67 to −0.11) <i>P</i> = .006	0.93 (0.61-1.25) <i>P</i> < .001	−0.16 (−0.44 to 0.13) <i>P</i> = .28
1997 cohort*	0.40 (0.09-0.72) <i>P</i> = .013	0.21 (−0.10 to 0.52) <i>P</i> = .18	0.45 (0.12-0.77) <i>P</i> = .007	−0.13 (−0.42 to 0.15) <i>P</i> = .35

Data are mean difference, 95% CI, *P* value.

*Compared with the 2005 cohort.