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Fetuses-at-risk, to avoid paradoxical associations at early gestational ages: extension to preterm infant mortality

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Abstract

Background: Fetuses-at-risk denominators are commonly used in research on preterm stillbirth, but applications to postnatal outcomes such as preterm infant mortality are controversial. We evaluated whether biased associations between maternal risk factors and preterm infant mortality caused by stratification by preterm birth could be avoided using fetuses-at-risk risk ratios.

Methods: Data included 3 277 570 births drawn from the linked live birth-death file for Canada from 1990 through 2005. We used maternal age as the risk factor, and estimated the association with stillbirth, early neonatal, late neonatal and postneonatal mortality by gestational interval (22–24, 25–27, 28–31, 32–36, $\geq$37 weeks). Models were run using (i) log-binomial regression stratified by preterm gestational age, and (ii) unstratified log-binomial regression using fetuses-at-risk denominators.

Results: Extremes of maternal age were associated with higher mortality among term births. Among preterm births, the stratified model suggested a protective, null or attenuated association of extremes of maternal age with stillbirth, early, late and post neonatal mortality. The unstratified fetuses-at-risk model, however, resulted in the expected higher risk of mortality at extremes of maternal age for all outcomes.

Conclusions: Fetuses-at-risk regression can avoid paradoxical associations between maternal exposures and mortality of infants born early in gestation, caused by preterm birth stratification bias. The fetuses-at-risk approach can be extended through the first year of life, or potentially beyond, depending on the outcome and presence of unmeasured confounders associated with preterm birth.

Key words: Bias (epidemiology), gestational age, infant mortality, maternal age, premature birth

Key Messages

- Associations between risk factors and postnatal outcomes may be biased for infants born preterm.
- Fetuses-at-risk denominators have been used to avoid bias for preterm stillbirth, but extension to outcomes after the perinatal period is controversial.
- We demonstrate how fetuses-at-risk denominators can overcome paradoxical associations between maternal age and preterm infant mortality in a Canadian cohort of births.
- Fetuses-at-risk denominators can be used past the perinatal period to assess risk factors for outcomes in infants born at low gestational ages.

Introduction

Interest in identifying risk factors for adverse outcomes in preterm infants is growing,[1] partly because of paradoxical associations of harmful exposures at low gestational ages. A wide range of maternal risk factors are harmful to infants at term, but are unusually protective against preterm adverse outcomes.[2–8] A similar problem underlies the birthweight paradox, where mortality of low birthweight infants is lower in groups with harmful exposures (e.g. smokers vs non-smokers).[9,10] Paradoxical results such as these have been shown to be biased by faulty analyses that rely on data stratified by preterm birth.[11] Stratification bias typically occurs because of unknown or unmeasured confounders that are causes of both preterm birth and the outcome.[12,13] In data stratified by gestational age, the confounders make preterm infants without known risk factors appear worse off than preterm infants with the risk factors. Stratification bias often goes unrecognized, and may be the source of erroneous observations published in many prominent medical journals.[2–6,8]

Researchers therefore propose avoiding stratification by gestational age,[14] but this solution precludes studies of risk factors for adverse outcomes in preterm infants, an important research and policy issue.[1] Understanding the relations between risk factors and outcomes at low gestational ages is necessary for clinical management of infants born preterm. The fetuses-at-risk (FAR) approach recently emerged for its potential to assess associations between risk factors and preterm stillbirth without relying on stratified data,[15] and researchers have called for studies on this potential research tool.[14] FAR denominators consist of ongoing pregnancies rather than preterm births, and were originally developed to estimate the remaining risk of stillbirth early in gestation.[16–18] Regression models containing FAR denominators correct paradoxically protective associations between maternal risk factors and preterm stillbirth.[19] Extension to outcomes in the neonatal or post neonatal periods is, however, controversial and has received less attention,[20,21] perhaps because risk of infant death is difficult to envisage for fetuses that have yet to be born. Nonetheless, scattered studies have used FAR denominators in analyses of preterm small-for-gestational-age birth[22] and perinatal mortality.[23]

We evaluated the impact of FAR denominators on relationships between maternal risk factors and preterm infant mortality. We sought to (i) determine how FAR regression compared with stratified regression to estimate associations between risk factors and infant mortality across increasing severity of preterm birth; and (ii) assess how far into the postnatal period FAR regression could be used (as the influence of preterm birth on infant mortality may persist after delivery, potentially causing stratification bias up to or even past 1 year of age). We chose maternal age as the exposure because paradoxical associations at low gestational ages have recently been identified.[5] Extremes of maternal age are associated with fetal-infant mortality,[24,25] and advancing age during pregnancy is of public health importance.[26,27]

Methods

Data

We used data from the linked live birth-death file of the Public Health Agency of Canada's Canadian Perinatal Surveillance System. The file is a prospective study of all births from 1991 to 2005 in Canada except Ontario, followed for mortality up to 1 year after delivery (i.e. <365 days).[26] Stillbirths meeting mandatory registration criteria (i.e. weight $\geq$500 g or $\geq$20 gestational weeks) are included.[26] Births with unknown maternal or gestational age, births <22 weeks of gestation, multiple births and pregnancy terminations were excluded. The final sample consisted of 3 195 996 singleton births, including 28 457 fetal-infant deaths.

Four mortality outcomes were evaluated, including 14 092 stillbirths and 7109 early neonatal (0–6 days), 1861 late neonatal (7–27 days) and 5395 post neonatal

(28–364 days) deaths. Preterm birth was defined as <37 completed weeks of gestation, and gestational age-specific intervals were specified as 22–24, 25–27, 28–31, 32–36 and ≥37 weeks. The method for determining gestational age was not recorded, but ultrasound estimates are common in Canada.

Maternal age was evaluated in five categories (<20, 20–24, 25–29, 30–34, ≥35 years). Covariates included legal marital status (yes, no), parity (0, 1, ≥2 previous deliveries), period (1991–95, 1996–2000, 2001–05) and provincial region (Maritimes, Québec, Prairies, British Columbia, Territories). These covariates were selected for their potential to influence the relation between maternal age and fetal-infant mortality.

Denominators for mortality rates

Gestational age-specific mortality rates were computed for each mortality outcome using both conventional and FAR denominators. Conventional denominators are stratified and consist of births in a specific gestational interval only. For stillbirths, conventional denominators were defined as all live births and stillbirths in a given gestational interval. For infant mortality, these denominators consisted of infant survivors and deaths at each gestational interval, by early, late or post neonatal window (i.e. 0–6, 7–27 or 28–364 days, respectively). For example, the denominator for late neonatal mortality at 22–24 gestational weeks consisted of all infants born at 22–24 weeks who survived at least 7 days, including those that died between 7 and 27 days. Mortality rates that use conventional denominators are higher at low gestational ages, because of the relatively low number of extreme preterm births that survive.[16,18]

FAR denominators, however, include the population born later in gestation and do not inflate mortality rates at preterm gestational ages.[16,18] These denominators are gestational age-specific without being stratified by gestational interval. For example, FAR denominators for late neonatal mortality consist of births that survived at least 7 days in any given gestational interval plus births in all later intervals. Similarly, FAR denominators for post neonatal mortality consist of births that survived at least 28 days in any given gestational interval plus survivors of all later intervals. Fetal mortality rates that use FAR denominators are U-shaped with peaks at very low and high gestational ages.[16,18]

Statistical analysis

Conventional and FAR risk ratios (RRs) and 95% confidence intervals (CIs) for the association between high or low (vs intermediate) maternal age and mortality were estimated in generalized linear regression models for binary outcomes, adjusted for marital status, parity, period and region. Conventional RRs were obtained using data stratified by gestational interval, with the denominator of stillbirth risks equivalent to the denominator of conventional mortality rates. These RRs may be biased early in gestation if there are unmeasured confounders associated with preterm birth and mortality. To obtain RRs not stratified by gestational age, FAR denominators were used in regression models such that all pregnancies in any given plus all later intervals were analysed. This was done by recoding deaths in later gestational intervals as survivors (i.e. data were not stratified, although births in earlier gestational intervals were not included). For stillbirth, this meant that fetal deaths at later gestational intervals were re-coded as survivors. For early and late neonatal mortality, fetal-infant deaths at later gestational intervals were re-coded as survivors, and for post neonatal mortality, infant deaths in subsequent gestational intervals were re-coded as survivors.

To compare the magnitude of the difference between conventional and FAR RRs, we calculated the absolute difference in the log(RR) of both estimates.[28] A large difference between log(RR)s reflects a potentially greater impact of stratification bias due to unmeasured confounders associated with preterm birth and fetal-infant mortality.

In sensitivity analyses, we verified that exclusion of infants with potentially implausible gestational ages did not impact on results.[29] Statistical analyses were undertaken with SAS v9.1 (SAS Institute, Cary, NC). The linked live birth-death file was created with approval of vital statistics registrars of provincial and territorial jurisdictions in Canada. Ethical review was waived by the University of Montreal Hospital Centre, as data were anonymized and conformed to requirements for research involving humans in Canada.

Results

There were 4.7 stillbirths per 1000 total births and 5.0 infant deaths per 1000 live births during the study (Table 1). Stillbirth rates were highest for women aged <20 and ≥35 years (6.1 per 1000), whereas infant mortality was highest at age <20 years. As expected, conventional mortality rates were higher for earlier gestational intervals at all maternal ages, although the gradient over gestation was more pronounced for stillbirth and early neonatal mortality (Table 2). FAR denominators resulted in a U-shaped gradient, with higher rates early in gestation that gradually declined and increased again at term for stillbirth and early (but not late or post) neonatal mortality.

Table 1. Fetal and infant mortality rates according to maternal characteristics[a]

Characteristics	Total births	Stillbirth		Early neonatal mortality		Late neonatal mortality		Post-neonatal mortality	
		n	Rate	*n*	Rate	*n*	Rate	*n*	Rate
Maternal age, years									
<20	198 717	1152	5.8	664	3.4	181	0.9	816	4.1
20–24	648 657	2884	4.4	1537	2.4	437	0.7	1568	2.4
25–29	1 061 092	4067	3.8	2113	2.0	546	0.5	1446	1.4
30–34	888 746	3692	4.2	1745	2.0	426	0.5	1045	1.2
≥35	398 784	2297	5.8	1050	2.6	271	0.7	520	1.3
Gestational age, weeks									
22–24	6 317	2926	463.2	2360	696.0	175	169.7	95	111.0
25–27	7 224	1423	197.0	929	160.1	248	50.9	259	56.0
28–31	17 317	1844	106.5	678	43.8	149	10.1	206	14.1
32–36	170 864	3217	18.8	1144	6.8	311	1.9	823	5.0
≥37	2 994 274	4682	1.6	1998	0.7	978	0.3	4012	1.3
Legally married									
Yes	1 928 507	7562	3.9	3721	1.9	961	0.5	2296	1.2
No	1 158 711	5708	4.9	2861	2.5	769	0.7	2782	2.4
Parity									
0	1 383 338	6424	4.6	3201	2.3	813	0.6	1889	1.4
1	1 076 932	3352	3.1	1927	1.8	520	0.5	1709	1.6
≥2	436 564	1823	4.2	1011	2.3	270	0.6	848	2.0
Region									
Maritimes	369 204	1705	4.6	814	2.2	209	0.6	574	1.6
Québec	1 169 115	4283	3.7	2455	2.1	646	0.6	1528	1.3
Prairies	997 794	5201	5.2	2610	2.6	704	0.7	2236	2.3
British Columbia	635 822	2760	4.3	1177	1.9	285	0.5	947	1.5
Territories	24 061	143	5.9	53	2.2	17	0.7	110	4.6
Period									
1991–1995	1 177 092	5591	4.7	3065	2.6	732	0.6	2478	2.1
1996–2000	1 031 452	4502	4.4	2166	2.1	586	0.6	1650	1.6
2001–2005	987 452	3999	4.0	1878	1.9	543	0.6	1267	1.3
Total	3 195 996	14 092	4.4	7109	2.2	1861	0.6	5395	1.7

[a]Per 1000 total births or infant survivors.

Both very low and high maternal ages were associated with greater risk of infant mortality relative to intermediate age (Table 3). Older age was however more strongly associated with stillbirth, whereas younger age was more strongly associated with late and post neonatal mortality.

In conventional regression models stratified by gestational interval, older maternal age appeared more strongly associated with term than preterm stillbirth or early neonatal mortality, and risks were paradoxically protective at extremely low gestational ages (Table 4, relative to intermediate maternal age). Risks of preterm post neonatal mortality were also protective for women ≥35 years. In contrast, the magnitude of FAR RRs was higher preterm, and none was protective. The difference in log(RR) between FAR and conventional estimates increased progressively with lower gestational age for all four outcomes, suggesting that unmeasured confounders associated with preterm birth and mortality were a more important source of stratification bias at extremely low gestational ages. Findings were similar for younger women, although the difference in log(RR) between FAR and conventional estimates was less pronounced, suggesting that unmeasured confounders were a less important cause of stratification bias for this age group.

Discussion

This study made two contributions to literature on gestational age-specific associations between maternal exposures and infant outcomes. First, compared with paradoxically protective RRs from conventional stratified analyses, we demonstrated that FAR RRs at preterm gestational ages more closely resembled associations at term. This occurred across the early, late, and post neonatal periods, suggesting that FAR regression yields more appropriate estimates at low gestational ages and can be used into

Table 2. Gestational age-specific mortality rates according to maternal age

Age	Total births	Conventional mortality rate[a]				Fetuses-at-risk mortality rate[b]			
		Stillbirth	Neonatal			Stillbirth	Neonatal		
			Early	Late	Post		Early	Late	Post
Maternal age-by-gestational week[c]									
<20 years									
22–24	598	456.52	723.08	188.89	136.99	1.37	1.18	0.09	0.05
25–27	688	171.51	208.77	62.08	75.65	0.60	0.60	0.14	0.16
28–31	1 637	98.35	48.78	9.26	16.53	0.82	0.36	0.07	0.12
32–36	12 849	19.07	7.14	2.16	10.33	1.25	0.46	0.14	0.66
≥37	182 945	1.94	0.81	0.53	3.41	1.94	0.81	0.53	3.41
25–29 years									
22–24	1 788	454.70	699.49	150.17	116.47	0.77	0.64	0.04	0.03
25–27	2 048	197.75	157.64	49.86	57.79	0.38	0.24	0.07	0.07
28–31	4 954	108.40	42.79	10.64	12.67	0.51	0.18	0.04	0.05
32–36	53 233	17.34	6.65	1.85	4.15	0.88	0.33	0.09	0.21
≥37	999 069	1.39	0.64	0.29	1.08	1.39	0.64	0.29	1.08
≥35 years									
22–24	1 015	435.47	664.92	187.50	108.97	1.11	0.96	0.09	0.03
25–27	1 121	224.80	124.28	60.45	44.76	0.63	0.27	0.12	0.08
28–31	2 595	110.98	39.45	10.38	10.94	0.73	0.23	0.06	0.06
32–36	24 173	21.47	7.95	2.22	3.72	1.32	0.48	0.13	0.22
≥37	369 880	2.15	0.76	0.31	0.98	2.15	0.76	0.31	0.98

[a]Per 1000 total births or infant survivors.
[b]Per 1000 fetuses-at-risk.
[c]Not all age categories are shown, to conserve space.

Table 3. Association between maternal age and fetal/infant mortality

Age	Risk ratio (95% confidence interval)[a]			
	Stillbirth	Neonatal		
		Early	Late	Post
Maternal age, years				
<20	1.18 (1.09–1.27)	1.36 (1.22–1.52)	1.70 (1.37–2.09)	3.26 (2.89–3.66)
20–24	1.05 (0.99–1.10)	1.08 (1.00–1.17)	1.23 (1.05–1.44)	1.93 (1.75–2.12)
25–29	Referent	0.98 (0.91–1.05)	1.03 (0.90–1.19)	1.14 (1.04–1.25)
30–34	1.11 (1.06–1.17)	Referent	Referent	Referent
≥35	1.48 (1.39–1.58)	1.26 (1.14–1.38)	1.36 (1.13–1.64)	1.04 (0.91–1.19)

[a]Association for data pooled across all gestational intervals, and adjusted for marital status, parity, region, and period. These results are not gestational age-specific and are not subject to stratification bias.

the first year of life to identify risk factors for preterm infant outcomes. Second, we showed that the difference between conventional and FAR RRs was larger for extremely early (vs late) preterm intervals, and for older (vs younger) women. These findings suggest that unmeasured confounders associated with mortality and extremely early preterm birth may play a greater role in biasing associations for older women, or that advanced age is a stronger risk factor for preterm live birth than for mortality, compared with intermediate age. Extremes of maternal age are established risk factors for fetal-infant mortality,[24,25] and it is counter-intuitive when conventional studies report protective or low associations before term.[5]

Conventional and FAR regression differ in two important ways. First, FAR regression more appropriately accounts for the temporal dimension of gestational age,[30] resolving paradoxical associations early in gestation by comparing preterm infant deaths with ongoing pregnancies rather than preterm survivors, an inappropriate comparison group that appears relatively sicker than deaths.

Table 4. Gestational-age specific association between maternal age and fetal/infant mortality

Offspring age	Conventional risk ratio, maternal age (95% CI)[a]		Fetuses-at-risk risk ratio, maternal age (95% CI)[a]		Change log (RR)[b]	
	<20 years	≥35 years	<20 years	≥35 years	<20 years	≥35 years
Stillbirth, wk						
22–24	1.06 (0.90–1.25)	0.94 (0.81–1.09)	1.32 (1.12–1.56)	1.43 (1.23–1.65)	0.22	0.42
25–27	0.89 (0.70–1.13)	1.14 (0.94–1.39)	1.21 (0.95–1.54)	1.69 (1.38–2.05)	0.30	0.39
28–31	0.92 (0.75–1.13)	1.04 (0.86–1.24)	1.23 (1.00–1.50)	1.50 (1.25–1.80)	0.29	0.37
32–36	1.03 (0.88–1.21)	1.12 (0.97–1.29)	1.10 (0.94–1.30)	1.41 (1.23–1.63)	0.07	0.23
≥37	1.12 (0.98–1.28)	1.53 (1.37–1.71)	1.12 (0.98–1.28)	1.53 (1.37–1.71)	0	0
Early neonatal, wk						
22–24	1.04 (0.96–1.12)	0.95 (0.89–1.02)	1.29 (1.07–1.55)	1.40 (1.19–1.65)	0.22	0.39
25–27	1.47 (1.15–1.89)	0.85 (0.66–1.11)	2.06 (1.56–2.73)	1.14 (0.86–1.51)	0.34	0.29
28–31	1.26 (0.90–1.76)	0.92 (0.66–1.27)	1.63 (1.15–2.31)	1.14 (0.81–1.59)	0.26	0.22
32–36	1.31 (0.99–1.75)	1.13 (0.89–1.43)	1.43 (1.06–1.91)	1.37 (1.08–1.75)	0.08	0.20
≥37	1.03 (0.83–1.29)	1.15 (0.96–1.37)	1.03 (0.83–1.29)	1.15 (0.96–1.37)	0	0
Late neonatal, wk						
22–24	0.90 (0.51–1.61)	1.09 (0.67–1.76)	0.84 (0.43–1.66)	1.92 (1.13–3.26)	−0.07	0.56
25–27	1.22 (0.72–2.06)	1.36 (0.86–2.14)	1.82 (1.46–2.28)	1.30 (1.06–1.59)	0.40	−0.04
28–31	0.99 (0.46–2.12)	1.21 (0.65–2.26)	1.21 (0.55–2.62)	1.52 (0.82–2.85)	0.20	0.23
32–36	1.96 (1.14–3.36)	1.58 (1.01–2.49)	2.12 (1.22–3.67)	1.90 (1.21–2.99)	0.08	0.18
≥37	1.98 (1.48–2.64)	0.99 (0.74–1.31)	1.98 (1.48–2.64)	0.99 (0.74–1.31)	0	0
Post neonatal, wk						
22–24	1.34 (0.60–2.98)	1.14 (0.59–2.23)	1.44 (0.59–3.55)	2.00 (0.99–4.06)	0.07	0.56
25–27	1.63 (0.96–2.78)	0.88 (0.51–1.54)	2.00 (1.14–3.51)	1.21 (0.68–2.13)	0.21	0.32
28–31	1.27 (0.70–2.28)	0.96 (0.52–1.79)	1.59 (0.86–2.92)	1.22 (0.65–2.28)	0.23	0.24
32–36	2.39 (1.78–3.19)	0.81 (0.57–1.14)	2.73 (2.02–3.69)	0.97 (0.68–1.38)	0.13	0.19
≥37	3.75 (3.27–4.30)	1.02 (0.87–1.20)	3.75 (3.27–4.30)	1.02 (0.87–1.20)	0	0

[a]Relative to maternal age 25–29 years (stillbirth) and 30–34 years (early, late and post neonatal mortality), adjusted for marital status, parity, region and period; other age categories not shown, to conserve space.

[b]Fetuses-at-risk log(risk ratio) minus conventional log(risk ratio).

This approach has elicited controversy,[20,21] partly because of difficulty in identifying the correct population comparison for preterm infant deaths. FAR denominators include ongoing pregnancies in the underlying risk set, considering fetuses as 'unseen' but still at risk. From this standpoint, the intrauterine environment is merely a location for physical development; preterm delivery simply 'moves' fetuses from the uterus to an external environment where the process of growth and development continues.

Second, conventional regression stratified by gestational age, unlike FAR, is subject to bias when (i) another unknown cause for leaving the uterus early is present, (ii) the unknown cause also causes death outside the uterus and (iii) the known risk factor, maternal age in this case, is associated with leaving the uterus early. Bias is introduced when infants who died after leaving the uterus early are compared with those who left early but survived (i.e. when analyses are stratified by preterm birth without considering fetuses still *in utero*), depending on how strongly the unknown cause is associated with the move/death compared with the known risk factor. If the unknown cause is more strongly associated with the move/death, infants who left early and who have the risk factor will appear less likely to die than those without the risk factor, resulting in a paradoxically protective association. If the unknown cause is weakly associated with moving/death, the association will be attenuated. Among late movers (≥37 weeks), the association between the risk factor and mortality is not affected because the unknown cause cannot lead to an early move (i.e. preterm birth by definition cannot occur at term). In causal literature, this bias has been illustrated using directed acyclic graphs, with preterm birth labelled a 'collider'.[10,31] The FAR approach essentially avoids collider stratification by including fetuses still in the uterus in the population at risk of death. The FAR approach can be used with any infant outcome, not only death, as long as the aforementioned conditions (unknown cause affecting both preterm birth and mortality) are present. It is important to point out that FAR regression circumvents stratification bias, but not bias from other sources. Neither FAR nor conventional RRs can account for mis-specified models or other confounders, including any arising after delivery.

We found a greater difference between conventional and FAR RRs among older women, implying that

stratification bias was more prominent at advanced ages. These findings suggest that unmeasured confounders potentially more prevalent at older maternal ages, such as hypertension or diabetes, account for the some of the bias.[5] The difference between conventional and FAR RRs gradually diminished over the first year of infant life, suggesting that these confounders are stronger risk factors for stillbirth than post neonatal mortality. However, the difference was greater at extremely low gestational ages, implying that other rare confounders strongly associated with extreme preterm birth and fetal-infant mortality may be present (e.g. congenital anomalies).[32] If so, the paradoxical associations suggest that congenital anomalies are more prevalent among women of intermediate age, as their risk of preterm fetal-infant mortality appeared to be higher than that of older women (a plausible hypothesis since screening for congenital anomalies is not systematic below maternal age 35 years in Canada). An alternative explanation could simply be that, compared with moderate age, older women are at greater risk of preterm live birth than fetal-infant mortality.

The FAR approach can be extended to other correlates of gestational age, such as birthweight[9] or maternal weight gain.[33] For birthweight, the denominator would include live births and stillbirths (or deaths) in any given birthweight interval plus all heavier infants. It has already been demonstrated that the birthweight paradox is resolved using FAR denominators in birthweight-specific rates.[23] For maternal weight gain, the denominator would include live births and stillbirths (or deaths) at any given plus all higher weight gain categories, and so on for other variables correlated with gestational age.

This study has implications for future research. Use of FAR denominators is related to survival or time-to-event analyses where, at any given gestational age, individuals at risk for the event are included in the risk-set (including events occurring at later gestational ages). Indeed, some researchers have used survival analysis to address stratification bias at low gestational ages.[30] Survival models may help clarify certain challenges of FAR regression, such as counterintuitive situations where early neonatal deaths of infants born at 28 weeks of gestation are included in the risk-set for post neonatal deaths of infants born at 25–27 weeks. FAR regression may also be related to nested Cox[34] or structural nested failure time models,[35] which may further prove useful to address bias in the stratified approach.[36] These methods adjust for confounding by not conditioning on preterm birth, a collider with low probability of occurrence, and instead conditioning on almost all fetuses, a stratum that more closely mirrors the entire population.

Relevance of evaluating gestational age-specific associations remains a question. Some researchers recommend abandoning gestational age entirely in research on maternal exposures and infant outcomes.[14] Others recommend decomposing causal effects of exposures,[37–39] and propose that we might best rely on methods that isolate direct effects of exposures not mediated through preterm birth.[12,37] This may indeed be the goal in epidemiologic research, but for clinical purposes it is often necessary to understand gestational age-specific associations, especially if sensitivity to exposures depends on timing of fetal development. Some infectious exposures, for example, disproportionately cause fetal loss or congenital syndromes early during pregnancy.[40,41] It is also natural to seek to optimize the timing of delivery for women at risk. FAR regression is an added tool towards achieving a better understanding of gestational age-specific risk factors, and potentially avoids missing risk factors during early gestational windows.

This study was limited by lack of data in administrative files, including markers of individual socioeconomic status and behavioural factors. Adjustment for such factors is however unlikely to affect the trend observed when conventional RRs are compared with FAR RRs. Recording of stillbirths and infant deaths very early in gestation may vary between Canadian provinces, but differences are unlikely to affect the study conclusion as there is no evidence that under-recording varies with maternal age. Gestational age may be misclassified if the ascertainment method (ultrasound vs menstrual dating) differs between provinces, which may further attenuate results towards the null since there again is no reason to suspect systematic differences by maternal age.

This study demonstrates that FAR regression can be used to estimate associations between maternal exposures and preterm infant outcomes, extending beyond the perinatal period into infancy. This approach can potentially be applied past the first year of life until such time as preterm delivery no longer is in the pathway to later health outcomes. Preterm birth can however affect a spectrum of health outcomes well after the first year of life,[42,43] making it possible for studies of preterm individuals to underestimate, find null or even protective associations with risk factors if conventional stratification is used. Studies of preterm cohorts that do not contain a term comparison group should be aware of the potential for gestational age stratification bias. Preterm cohorts are simple to design, and can for instance simply consist of infants admitted to neonatal intensive care units, where preterm births are commonly found. FAR denominators can potentially avoid paradoxical associations between exposures and preterm outcomes, thus providing a valuable tool for identifying risk factors and improving survival of extremely preterm infants.

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