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METHODOLOGY ARTICLE

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Short interpregnancy interval and pregnancy outcomes: How important is the timing of confounding variable ascertainment?

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Abstract

Background: Estimation of causal effects of short interpregnancy interval on pregnancy outcomes may be confounded by time-varying factors. These confounders should be ascertained at or before delivery of the first ("index") pregnancy, but are often only measured at the subsequent pregnancy.

Objectives: To quantify bias induced by adjusting for time-varying confounders ascertained at the subsequent (rather than the index) pregnancy in estimated effects of short interpregnancy interval on pregnancy outcomes.

Methods: We analysed linked records for births in British Columbia, Canada, 2004-2014, to women with ≥2 singleton pregnancies (n = 121 151). We used log binomial regression to compare short (<6, 6-11, 12-17 months) to 18-23-month reference intervals for 5 outcomes: perinatal mortality (stillbirth and neonatal death); small for gestational age (SGA) birth and preterm delivery (all, early, spontaneous). We calculated per cent differences between adjusted risk ratios (aRR) from two models with maternal age, low socio-economic status, body mass index, and smoking ascertained in the index pregnancy and the subsequent pregnancy. We considered relative per cent differences <5% minimal, 5%-9% modest, and ≥10% substantial.

Results: Adjustment for confounders measured at the subsequent pregnancy introduced modest bias towards the null for perinatal mortality aRRs for <6-month interpregnancy intervals [−9.7%, 95% confidence interval [CI] −15.3, −6.2). SGA aRRs were minimally biased towards the null (−1.1%, 95% CI −2.6, 0.8) for <6-month intervals. While early preterm delivery aRRs were substantially biased towards the null (−10.4%, 95% CI −14.0, −6.6) for <6-month interpregnancy intervals, bias was minimal for <6-month intervals for all preterm deliveries (−0.6%, 95% CI −2.0, 0.8) and spontaneous preterm deliveries (−1.3%, 95% CI −3.1, 0.1). For all outcomes, bias was attenuated and minimal for 6-11-month and 12-17-month interpregnancy intervals.

Conclusion: These findings suggest that maternally linked pregnancy data may not be needed for appropriate confounder adjustment when studying the effects of short interpregnancy interval on pregnancy outcomes.

KEYWORDS

causal inference, confounding adjustment, interpregnancy interval, pregnancy spacing, time-varying confounding, vital statistics

1 | BACKGROUND

There has been substantial debate in the interpregnancy interval literature on whether observed associations between short interpregnancy interval and adverse pregnancy outcomes[1,2] are causal or are due to confounding.[3] Researchers estimating the causal effect of interpregnancy interval on adverse pregnancy outcomes in observational studies are advised to identify potential confounding variables using *a priori* substantive expertise and control for confounding in study design and/or analysis.[4,5] The delivery of the first ("index") pregnancy indicates the start of the interpregnancy interval and serves as the baseline for interpregnancy interval analyses;[5] this is the time at which exposure groups should ideally be balanced with respect to confounding variable distributions.

Confounders that can change values between pregnancies (time-varying confounders) warrant particular consideration in studies of interpregnancy interval. Time-varying confounders include maternal age,[6-9] prepregnancy body mass index (BMI; kg/m^2),[10-12] smoking,[10,13-15] and socio-economic status.[16-18] In addition to these confounders changing status between pregnancies, the interpregnancy interval length may affect some of these variables directly such that the extent to which these values are discordant at the index and subsequent pregnancies will differ based on the interpregnancy interval length. For example, longer interpregnancy interval deterministically leads to older maternal age at start of next pregnancy. For other confounders, the relationship between short interpregnancy interval and the variable values over time may be more complex. For example, short interpregnancy intervals may lead to higher prepregnancy BMI, because 75% of women do not return to their prepregnancy weight by 12 months postpartum.[12] On the other hand, longer interpregnancy intervals may also lead to higher BMI, because BMI tends to increase with age, including within the reproductive years.[19] Many large databases that capture interpregnancy interval and pregnancy outcome data, such as the national-level US vital statistics natality data, do not link successive pregnancies to the same mother.[20] Rather, these databases include interpregnancy interval as a covariate on the post-interval pregnancy record, along with values for confounding variables measured at the time of the subsequent pregnancy. Thus, researchers using such data sets are unable to use time-varying confounding variables ascertained at baseline, that is delivery of the index pregnancy. Of 27 studies included in a recent systematic review of short interpregnancy interval and perinatal outcomes, at least 23 studies adjusted for one or more time-varying confounders measured at the start of the subsequent pregnancy.[1]

Adjustment for confounders ascertained at the subsequent pregnancy could theoretically induce mediator overadjustment bias[21] and/or collider-stratification bias,[22] as illustrated in the causal diagram (Directed Acyclic Graph, or DAG; Figure 1).[23] These biases could preclude the use of databases that do not link across pregnancies for research examining associations between interpregnancy interval and subsequent pregnancy outcomes.[24] Although the structure of the bias induced by this adjustment is well understood, the magnitude and direction of this bias for research on short interpregnancy interval is unknown. In this study, we quantified the bias induced by adjusting for time-varying confounders ascertained at the subsequent (rather than the index) pregnancy in estimating the effects of short interpregnancy interval on pregnancy outcomes. We aimed to provide pragmatic guidance to researchers working with data that are not linked across pregnancies on the potential magnitude of bias due to using incorrect ascertainment timing for time-varying confounders in their analyses.

Synopsis

Study question

Does incorrect timing of ascertainment for time-varying confounders bias observed associations between short interpregnancy interval and pregnancy outcomes?

What's already known

Studies examining the association between short interpregnancy interval and adverse pregnancy outcomes should control for confounders as ascertained at the start of the interpregnancy interval (ie delivery of the index, pre-interval, pregnancy). However, many databases are not linked across pregnancies; in these databases, time-varying confounders can only be ascertained at the time of the subsequent pregnancy.

What this study adds

Adjusting for time-varying confounders ascertained at the subsequent, rather than index, pregnancy induced minimal-to-modest bias (<5% - 5-9%). Maternally linked pregnancy data may not be needed for appropriate confounder adjustment when studying the effects of short interpregnancy interval on pregnancy outcomes.

2 | METHODS

2.1 | Study population

Our study population was drawn from a population-based cohort of linked records for all pregnancies to women with ≥2 consecutive singleton deliveries ≥20 weeks of gestational age in British Columbia (BC), Canada, 1 April 2004 to 31 March 2014. Eligible deliveries were identified using the BC Perinatal Data Registry, a validated[25] birth registry which contains detailed demographic and clinical data for over 99% of births in the province. Registry data are abstracted

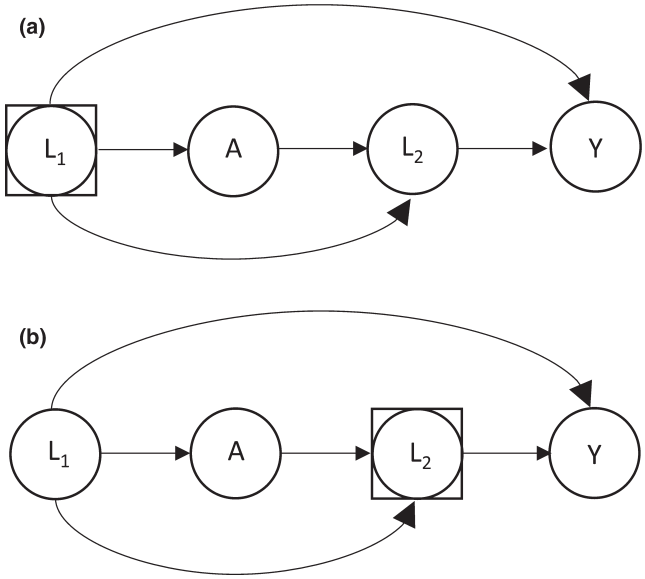

FIGURE 1 Directed acyclic graph representing relationships between interpregnancy interval (A), outcomes of the subsequent pregnancy (Y), and adjustment variables (L): a, correct adjustment for time-varying confounders measured at the index pregnancy (L_1), b, incorrect adjustment for time-varying confounders measured at the subsequent pregnancy (L_2), which induces collider stratification bias at L_2 in addition to adjusting for a causal intermediate (overadjustment bias)

from maternal and infant medical records by trained abstracters using provincially standardized forms.[26] Successive pregnancies to the same woman were linked using a probabilistic linkage based on personal health number (a unique health care identifier for all BC residents), name, and date of birth.

The Perinatal Data Registry files were linked to 5 other provincial databases by Population Data BC (a multi-university platform that facilitates linkages of population-based administrative health data)[27] using personal identifiers and mathematical linkage techniques. The linked provincial databases included physician billing records (Medical Service Plan payment file),[28] hospital discharge summaries (Canadian Institute for Health Information's Discharge Abstract Database),[29] outpatient prescription records (PharmaNet),[30] census neighbourhood-level income[31] and community size records (Consolidation File),[32] and Vital Statistics death records.[33] We restricted this analysis to index pregnancies ending in live birth to be consistent with previous interpregnancy interval studies.[5,34,35] We further restricted this analysis to subsequent pregnancies that continued to ≥20 weeks' gestation because the study outcomes examined cannot occur before 20 weeks' gestation, by definition. The University of British Columbia and Children's and Women's Heath Centre of British Columbia Research Ethics Board approved this study (#H15-01208).

2.2 | Exposure

We calculated interpregnancy interval as the time between delivery dates minus the gestational age at delivery for the subsequent pregnancy. Gestational age was calculated using a hierarchical gestational age algorithm based on last menstrual period confirmed, or revised with early pregnancy ultrasound, or newborn examination.[36] We categorized interpregnancy interval using standard thresholds, with short intervals defined as <6, 6-11, and 12-17 months and a reference interval of 18-23 months.[5]

2.3 | Outcomes

We examined the following five perinatal health outcomes: (a) perinatal mortality (stillbirth and neonatal death within 28 days after birth), (b) small for gestational age (SGA) birth, defined as birthweight <10th percentile for gestational age and sex using a Canadian birthweight reference chart,[37] (c) preterm delivery, defined as birth of a live infant before 37 weeks of gestation, (d) early preterm delivery (birth of a live infant before 28 weeks of gestation), and (e) spontaneous preterm delivery, defined as preterm delivery after either the spontaneous onset of labour or membrane rupture (recorded in the labour and delivery record by the attending provider).

2.4 | Confounders

We used causal diagrams to identify potential confounding variables, defined as shared causes of short interpregnancy interval and the study outcomes. For all five study outcomes, potential time-varying confounding variables included maternal age, low socio-economic status (SES, using a proxy of median neighbourhood income <3rd decile), prepregnancy body mass index (BMI: weight in kg/height in m^2, categorized as: underweight [<18.5], normal weight [18.5-24.9], overweight [25-29.9], and obese [≥30]), and smoking before or during pregnancy.[7] For studies of interpregnancy interval, the correct ascertainment of time-varying confounders is at the delivery of the index live birth (baseline), the time at which exposure groups should be exchangeable. The linkage of successive pregnancies to the same woman ensured that we had confounding variable information at the time of the index and subsequent pregnancies.

2.5 | Missing data

For simplicity, we used the missing indicator method to account for missing values for all confounding variables (missingness 31.1% for pre-index pregnancy BMI and 32.3% for presubsequent pregnancy BMI, 5.1% for pre-index pregnancy SES and 10.0% for presubsequent pregnancy SES). We conducted a sensitivity analysis with missing values imputed using multiple imputation. The multiple imputation models used all outcome variables, confounders without missing values, and interpregnancy interval values as predictor variables, with

20 imputations. We used chained equations modelling and selected a conditional binomial distribution for SES and conditional multinomial for BMI categories.[38]

2.6 | Statistical analysis

We used log binomial regression to estimate risk ratios of each outcome comparing short (<6, 6-11, 12-17 month) interpregnancy intervals to the reference 18-23-month interval. We estimated three sets of risk ratios: crude, adjusted for confounders measured at the start of the interpregnancy interval (at or before the delivery of the index pregnancy), and adjusted for confounders measured at the time of the subsequent pregnancy. We compared adjusted risk ratios (aRR) from two models with maternal age, low SES, BMI, and smoking ascertained in the (a) index pregnancy, aRR_1, and (b) subsequent pregnancy, aRR_2. We calculated per cent difference in aRR as $100^*(aRR_2 - aRR_1)/aRR_1$ and used bootstrapping to estimate 95% confidence intervals around these per cent differences (using 200 samples drawn with replacement for each estimate). We considered per cent differences in aRR <5% minimal, 5%-9% modest, and ≥10% substantial. All models used robust variance estimates to account for non-independence due to multiple interpregnancy intervals to the same woman.

TABLE 1 Time-varying confounder distributions at the time of index and subsequent pregnancy according to interpregnancy interval categories

		Interpregnancy interval length (mo)					
		All	<6	6-11	12-17	18-23	≥24
n		121 151	5469	20 065	28 594	22 643	44 380
Maternal age (y)							
Index pregnancy	<20	4.1	8.5	4.4	3.0	3.2	4.6
	20-34	85.2	82.3	83.8	84.7	85.1	86.5
	≥35	10.7	9.2	11.8	12.3	11.7	8.9
Subsequent pregnancy	<20	0.9	4.6	1.7	0.8	0.6	0.3
	20-34	73.7	82.5	79.5	76.0	73.4	68.3
	≥35	25.4	12.9	18.8	23.2	26.0	31.1
Smoking during or before pregnancy							
Index pregnancy	Any smoking	9.1	19.6	10.3	7.0	7.0	9.6
Subsequent pregnancy	Any smoking	7.5	16.6	8.6	5.7	5.6	8.0
BMI (kg/m^2)							
Index pregnancy	<18.5	4.6	4.8	4.3	4.1	4.2)	5.2
	18.5-24.9	43.7	33.9	41.9	45.7	45.7	43.6
	25-29.9	13.8	14.4	14.6	13.6	13.9	13.5
	≥30	7.8	10.6	8.1	(7.4	7.5	7.6
	Missing	30.1	36.3	31.1	29.3	28.8	30.2
Subsequent pregnancy	<18.5	3.2	2.3	3.1	3.3	3.4	3.2
	18.5-24.9	39.0	26.0	36.1	41.1	41.4	(39.2
	25-29.9	15.3	14.9	15.1	14.5	15.2	16.1
	≥30	10.2	12.8	9.7	8.9	9.4	11.3
	Missing	32.4	44.0	36.1	32.2	30.6	30.2
Socio-economic status (Neighbourhood income decile[a])							
Index pregnancy	Mid-high	74.9	64.6	72.5	76.1	76.5	75.5
	Low	20.1	26.1	19.7	18.0	18.8	21.6
	Missing	5.1	9.3	7.8	6.0	4.7	2.9
Subsequent pregnancy	Mid-high	71.1	62.1	70.5	73.0	72.9	70.5
	Low	18.9	26.1	18.9	17.1	17.7	19.8
	Missing	10.0	11.9	10.7	10.0	9.5	9.8

Note: Cells show column percentages.

[a]Low income is defined as neighbourhood income <3rd decile; mid-high income is defined as neighbourhood income 3-10th decile.

2.7 | Sensitivity analyses

To examine the role of individual confounders, we identified the within-woman change in values for each confounder; we report the median change for continuous maternal age and BMI values and the proportion of observations that changed categories for smoking and low income. We also examined the per cent difference in aRR resulting from adjusting for one subsequent pregnancy confounder at a time.

All analyses were conducted using Stata 16.0.[39]

3 | RESULTS

The study population included 144 542 interpregnancy intervals following a livebirth from 2004 to 2014 in British Columbia. After restricting to subsequent pregnancies continuing to ≥20 weeks, our cohort included 121 151 interpregnancy intervals to 102 546 women. Interpregnancy intervals shorter than 6 months were uncommon (4.5%), intervals of 6-11 months were more common (16.6%), and those 12-17 months were most common (23.6%) followed by the reference 18-23-month interval category (18.7%); the remainder of the cohort had intervals ≥24 months (36.6%).

Distributions of the time-varying confounders of interest (maternal age, smoking status, BMI, SES) according to interpregnancy interval categories are presented in Table 1. Comparing the values of each confounder at the index vs subsequent pregnancy shows the extent to which these changed between pregnancies. The frequency of maternal age <20 or ≥35 was substantially different at the index and subsequent pregnancies, respectively. Maternal age younger than 20 was 4 times as common at the time of the index pregnancy than the subsequent pregnancy. Similarly, while just over one tenth of the study population was ≥35 years of age at the index pregnancy, more than one quarter of the population was ≥35 at the subsequent pregnancy. Smoking was more common at the time of the index pregnancy than the subsequent; similarly, low SES was slightly more common at the index than subsequent pregnancy. Overweight and obesity were more common at the time of the subsequent pregnancy than at the index pregnancy. Not surprisingly, confounder values changed the most with interpregnancy intervals 24 months or longer. Because the focus of this paper is to examine bias in estimated associations between short interpregnancy interval and pregnancy outcomes, the long interpregnancy interval category is presented only descriptively in Table 1. Despite differences in the frequency of each characteristic based on the ascertainment timing, the distributions according to interpregnancy interval categories were

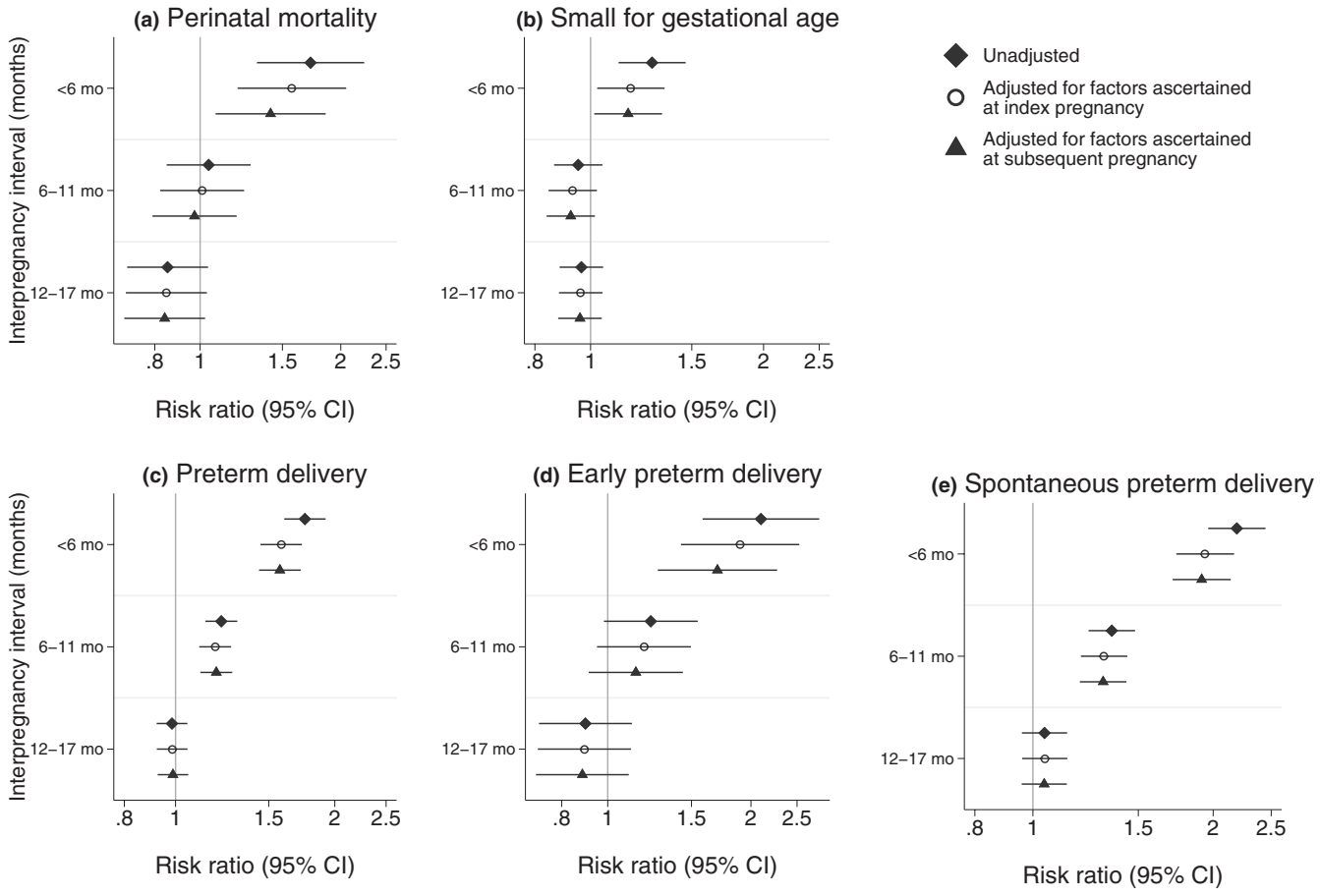

FIGURE 2 Risk ratios with 95% confidence intervals for adverse pregnancy outcomes comparing short vs reference interpregnancy intervals according to confounder ascertainment timing. A, Perinatal mortality, B. Small for gestational age C. Preterm delivery, D. Early preterm delivery, E. Spontaneous preterm delivery

fairly consistent between index and subsequent pregnancies. Smoking and low income were most common at intervals <6 months and least common at 12-17 and 18-23 months.

Figure 2 displays risk ratios and 95% confidence intervals for each outcome comparing short interpregnancy interval categories to the reference 18-23-month interval according to the following adjustment strategies: (i) crude (unadjusted), (ii) adjusted for all confounding variables measured at the time of the index pregnancy, and iii) adjusted for all confounding variables measured the time of the subsequent pregnancy. The corresponding risk ratios are shown as numeric estimates in Table S1. As expected, short interpregnancy interval categories were associated with increased risks of all outcomes we examined. Intervals shorter than 6 months were associated with the greatest degree of increased risk for all outcomes and risk ratios decreased progressively at 6-11-month and 12-17-month intervals. Either type of adjustment attenuated risk ratios for all interval categories.

The per cent difference in aRR comparing models adjusted for confounders measured at the index and subsequent pregnancies are presented in Table 2. Adjustment for confounders measured at the subsequent pregnancy modestly biased the perinatal mortality aRR towards the null for interpregnancy interval <6 months and minimally biased the aRRs towards the null for interpregnancy intervals 6-11 and 12-17 months. All risk ratios for SGA were minimally biased towards the null. While early preterm delivery aRRs were substantially biased towards the null for <6-month interpregnancy intervals, bias was minimal for <6-month intervals for all preterm and spontaneous preterm deliveries. For all preterm delivery outcomes, bias was attenuated and was minimal for 6-11-month and 12-17-month interpregnancy intervals.

3.1 | Sensitivity analyses

As shown in Table S2, changes in BMI, smoking, and low SES between index and subsequent pregnancies were most pronounced at short interpregnancy intervals, though the maternal age differences increased with increasing intervals and showed little variability within interpregnancy interval categories. Adjustment for BMI ascertained at the incorrect time (the subsequent pregnancy) induced the greatest degree of bias (Table S2).

3.2 | Missing data

Missing (presubsequent or pre-index pregnancy) BMI values were more common among those with short interpregnancy interval, young maternal age, smoking, low income, preterm delivery, and spontaneous preterm delivery (shown in Table S3). Despite these associations, per cent differences in aRR estimated using multiple imputation for missing values were similar to those estimated in our primary analysis (shown in Table S4).

4 | COMMENT

4.1 | Principal findings

We found that bias induced by adjusting for confounding variables ascertained at the incorrect time (subsequent pregnancy) rather than the correct time (index pregnancy) resulted in minimal

TABLE 2 Per cent differences in adjusted risk ratios (aRR, with 95% confidence intervals) for short interpregnancy intervals: (i) adjusted for confounders ascertained at the index delivery and (ii) adjusted for confounders ascertained at the subsequent delivery

	Interpregnancy interval (mo)			
	<6	6-11	12-17	18-23
	n = 5468	n = 20 071	n = 28 583	n = 22 638
Perinatal mortality	77	171	199	185
Per cent difference in aRR (95% CI)	−9.7% (−15.3, −6.2)	−3.7% (−5.3, −2.2)	−0.8% (−1.9, 0.1)	0.0 (Reference)
Small for gestational age[a]	271	740	1069	878
Per cent difference in aRR (95% CI)	−1.1% (−2.6, 0.8)	−0.8% (−1.6, 0.0)	−0.3% (−0.9, 0.2)	0.0 (Reference)
Preterm delivery	616	1568	1803	1,450
Per cent difference in aRR (95% CI)	−0.6% (−2.0, 0.8)	0.5% (−0.1, 1.2)	0.4% (−0.1, 0.7)	0.0 (Reference)
Early preterm delivery	72	155	161	142
Per cent difference in aRR (95% CI)	−10.4% (−14.0, −6.6)	−3.9% (−5.7, −2.3)	−1.0% (−2.3, −0.1)	0.0 (Reference)
Spontaneous preterm delivery	454	1030	1133	858
Per cent difference in aRR (95% CI)	−1.3 (−3.1, 0.1)	−0.4 (−1.1, 0.5)	−0.2 (−0.7, 0.2)	0.0 (Reference)

[a]Restricted to 22-24 wk due to birthweight reference chart availability.

to modest bias in the associations between short interpregnancy interval and adverse perinatal outcomes. These findings indicate that, for this specific context, the theoretical bias introduced by incorrect time-varying confounder ascertainment did not have a meaningful impact on substantive conclusions on observed effects of short interpregnancy interval on adverse outcome.[24] Therefore, it is not unreasonable for researchers to study short interpregnancy interval and with pregnancy outcomes using unlinked data sets.

4.2 | Strengths of the study

The key strength of this study is its use of a cohort with within-woman pregnancy linkages containing detailed clinical information, which enabled this empirical consideration of the importance of violations of causal DAGs for controlling confounding in studies of short interpregnancy interval and adverse pregnancy outcomes.

4.3 | Limitations of the data

Several limitations of our study must be considered. Our measure of SES was limited to neighbourhood-level information (income decile), rather than individual- or household-level income information, which may misclassify low SES for some women.[40] Neighbourhood-level income values may also be more stable over the interpregnancy period than individual-level income, which would limit the conclusions of our analysis for this confounding variable. Administrative health databases lack information on other time-varying variables that potentially confound estimated effects of short interpregnancy interval on adverse pregnancy outcomes, such as pregnancy intention, maternal stress, or financial difficulties not reflected in neighbourhood income deciles. Our study could not adjust for these or examine the potential limitations of ascertaining these confounders at the incorrect time. Furthermore, population-based administrative health data from BC do not include race or ethnicity. Although race or ethnicity may confound or modify associations between short interpregnancy interval and adverse pregnancy outcomes,[41] these values would not change over time and thus would not be of interest for this particular methodological question. Finally, because the thresholds we used to define minimal, modest, and substantial bias are subjective, investigators seeking to apply these findings to their own research contexts may find the specific per cent differences in aRR more useful than the categorized summary.

4.4 | Interpretation

The magnitude of bias induced by incorrect timing of confounder ascertainment is bounded by the degree to which time-varying confounders change between successive pregnancies. For some confounders, the relatively short time frame of women's reproductive histories may limit the extent to which characteristics that *can* change over time actually *do* change. For example, change in smoking status over a 12-month period is uncommon, occurring in <10% of current daily smokers in previous research[42] and 6.3% in our cohort. Transitions into or out of low-income SES over a 24-month period are similarly uncommon, occurring in only 5.1%-13.5% of Canadians in previous reports[43] and 17.4% in our cohort. However, for other confounders (such as BMI), substantial variation between pregnancies at short intervals is expected due to insufficient time to lose pregnancy weight gain during a short interpregnancy interval, with most women still retaining weight gained in pregnancy at 12 months postpartum.[12] In this analysis, we found that the time-varying confounder that changed the most between pregnancies was maternal age category. Because maternal age changes deterministically with interpregnancy interval, researchers aiming to examine associations between short interpregnancy interval and pregnancy outcomes can calculate maternal age at the time of the index pregnancy even when using data sets that are not linked across pregnancies (by subtracting time since last live birth from age at subsequent delivery). This calculation can yield a reasonably accurate approximation even when using data sets that report age only in whole integers, as some authors have previously done.[44] On the other hand, while the values for smoking and low SES at the time of the index pregnancy cannot be inferred or calculated based on the value at the subsequent pregnancy, the finding that these vary less across successive pregnancies is reassuring for researchers aiming to study short interpregnancy interval and pregnancy outcomes in data sets that are not linked across pregnancies. However, our findings of modest to minimal bias induced by ascertainment of time-varying confounders at the incorrect time may not apply to studies examining long interpregnancy interval, as the longer interval allows greater opportunity for confounder values to change between successive pregnancies and may have distinct confounder sets. For example, BMI discordance may increase with longer interpregnancy intervals, given that 25% of reproductive aged women gain ≥10 pounds in a 4-year period.[45]

The bias induced by incorrect ascertainment timing of time-varying confounders may differ by the strength of association between these confounders and both short interpregnancy interval and adverse outcomes. Thus, the bias induced could vary by setting or population. If so, our findings may not be generalizable to settings with more or less variability in these characteristics across successive pregnancies. However, generalizability of our findings is bolstered by the fact that the magnitude of interpregnancy change we found for these confounding variables appears similar to that reported in previous studies. We found comparable changes in BMI category across pregnancies as two previous studies from the United States (Texas[46] and Ohio[47]), and similar interpregnancy smoking status and SES change as previous studies from Sweden[48] and Australia.[49]

Several recent studies that used matched, within-woman designs reported attenuated effect estimates compared with between-woman designs, which reignited debate about the importance of confounding in studies estimating causal effects of short

interpregnancy interval.[49-51] By design, this approach controls for all time-invariant confounders, both measured and unmeasured, which may theoretically improve the internal validity of estimated associations. However, because matched designs do not account for time-varying confounders (those that vary between pregnancies within the same woman) and may have poor external validity (due to restriction to women with at least three pregnancies with discordant interpregnancy intervals and discordant outcomes across matched pairs),[4,52,53] these papers have not resolved the concern regarding the role of confounding in studies of interpregnancy interval.

While DAGs can be used to identify the potential presence of confounding, overadjustment, or collider-stratification biases,[23] including the direction of bias,[54] the magnitude of this bias cannot be inferred from DAGs alone. Our finding that violation of the causal DAG for short interpregnancy interval studies induces only minimal to modest bias for perinatal health outcomes does not necessarily lead to the conclusion that violation of causal DAGs includes minimal to modest bias in general, even for studies of short interpregnancy interval and maternal health outcomes (which may have different confounders or causal structures) or other research questions with relatively short exposure windows. Our findings do indicate the importance of empirical work to determine the magnitude and direction of bias induced when assumptions embedded in causal diagrams (DAGs) are intractably violated by the nature of data collection or database construction methods that cannot be prevented or mitigated by the researchers. Applications of this approach to determine the magnitude of bias induced by DAG violations to other areas of epidemiologic research may be worthwhile to inform valid and pragmatic decisions for study design and data analysis.

5 | CONCLUSIONS

This study found that adjusting for time-varying confounding variables ascertained at the subsequent, rather than index, pregnancy induced modest to substantial bias for the shortest interpregnancy intervals for perinatal mortality and early preterm birth, and otherwise induced minimal bias on estimated effects of short interpregnancy interval on pregnancy outcomes. These findings suggest that maternally linked pregnancy data may not be needed for appropriate confounder adjustment when studying the effects of short interpregnancy interval on pregnancy outcomes. Findings provide practical guidance to researchers seeking to estimate valid causal effects between interpregnancy interval and perinatal outcomes of the subsequent pregnancy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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