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Practice of Epidemiology

Stochastic Mediation Contrasts in Epidemiologic Research: Interpregnancy Interval and the Educational Disparity in Preterm Delivery

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Low maternal education is consistently associated with increased risk of preterm delivery (PTD). The interpregnancy interval (IPI), defined as the time between the date of a previous birth and the conception date of the index pregnancy, may mediate this relationship. We estimated controlled direct effects to assess whether hypothetical interventions designed to increase IPIs would reduce the educational disparity in PTD. We introduce a technique for estimating controlled direct effects under interventions that set only some persons in the population to a specific mediator value. We used data from 847,618 singleton livebirths occurring in Quebec, Canada, between 1989 and 2010. Compared with mothers with some university education (≥14 years), mothers with less than high school (<11 years), high school (11 years), and some college (12–13 years) had excess PTD risks of 2.6% (95% confidence interval (CI): 2.4, 2.8), 1.5% (95% CI: 1.4, 1.7), and 1.0% (95% CI: 0.9, 1.1), respectively. Risk differences under an intervention corresponding to the Healthy People 2020 objective of reducing the number of mothers with IPIs less than 18 months by 3% were no different from those for the total relationship. Our results suggest that interventions designed to increase the length of short IPIs will yield no important change in the PTD disparity by maternal educational level.

controlled direct effect; interpregnancy interval; maternal education; mediation analysis; perinatal epidemiology; pregnancy; preterm delivery; social epidemiology

Abbreviations: CDE, controlled direct effect; CI, confidence interval; IPI, interpregnancy interval; ME, maternal education; PTD, preterm delivery.

Preterm delivery (PTD) is a leading cause of infant mortality (1) and morbidity (2), and its prevalence is increasing in many countries (3). The relationship between socioeconomic factors and PTD is well established (4–10). Lower maternal education (ME) is consistently associated with an elevated risk of PTD across time (11), racial/ethnic subgroups (12), and geographic regions (6, 7, 13). ME is more strongly related to PTD than are other measures of socioeconomic status, such as occupation or income (7, 8, 11).

While research findings in social epidemiology are often used to reason about effects of interventions designed to mitigate social disparities in health, the usefulness of this approach has been debated extensively (14–20). A central feature of this debate is the nature of social class variables (21). It is doubtful that the estimated associations between ME and PTD directly equate with the impact of policies designed to increase education in a population (22). That is, the difference in PTD risk between mothers with a university education and mothers with less than a high school education is not likely to reflect the effect of, say, a scholarship or conditional cash-transfer program encouraging high school dropouts to obtain university degrees. As a proxy for a complex set of social conditions that act as fundamental causes (23, 24), however, ME is probably related to downstream risk factors or mediators that are themselves associated with PTD and that may be more suitable targets for intervention (25).

The interpregnancy interval (IPI), or the elapsed duration between the birth date of the previous pregnancy and the conception date of the current (index) pregnancy, may be one such mediator (26). IPI is associated with PTD (27), and

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low levels of ME are associated with shorter IPIs (28–30). IPI is a modifiable risk factor (28), and the optimal timing of conception following a previous delivery falls between 18 and 60 months (27).

Information on whether increasing the length of short IPIs will yield reductions in the educational disparity in PTD would be useful in prioritizing risk factors to mitigate socioeconomic disparities in adverse birth outcomes (31, 32). In this paper, we illustrate the use of a mediation analysis technique (33, 34) to assess whether interventions to prevent short IPIs will also reduce educational disparities in PTD and, if so, by how much. The technique employs standard regression models, and like Robins' G-methods (35), it can be used to assess unmediated effects when confounders of the mediator-outcome relationship are affected by the exposure (36, 37) and when exposure-mediator interactions are present. Furthermore, unlike standard controlled direct effects (CDEs), which force the mediator to take on the same value for all subjects in a population (37), we introduce a method to estimate stochastic mediation contrasts, corresponding to effects that would be observed under (possibly hypothetical) mediator interventions in which only a portion of the population's mediator value is altered. We estimated associations between ME and PTD under hypothetical interventions that changed the distribution of IPIs in Quebec, Canada.

METHODS

Quebec Birth File data

We used data from the Quebec Birth File to assess the mediating role of IPI in the relationship between ME and PTD. We extracted data on 1,879,986 singleton livebirths occurring between 1989 and 2010 (11). We restricted analyses to mothers with ≥1 previous birth, leaving 847,618 livebirths. IPI was defined as the number of months between the birth date of the previous pregnancy and the conception date of the current (index) pregnancy.

ME, in integer years attained, was used to create a categorical variable following the Quebec educational system (6): "less than high school" (<11 years, or not graduating from high school); "high school" (11 years, or attainment of a high school diploma); "some college" (12–13 years, representing pre-university studies); and "some university" (≥14 years, representing at least some university studies). The referent category was "some university." IPI was categorized as short (<18 months), optimal short (18–<24 months), moderate (24–<60 months), or long (≥60 months) (27, 29). The referent category for IPI was "optimal short." We used postal codes to assign area-level measures of social and material deprivation coded according to census dissemination area (38). We used gestational age at birth obtained from first- or second-trimester ultrasonography to create an indicator of PTD, defined as delivery at <37 completed weeks' gestation.

Causal pathways

Figure 1 depicts the scenario under study. In this figure, ***C*** denotes exposure-outcome confounders, including maternal year of birth, maternal and paternal age, country of birth, native language, and 2 area-level measures of material and social deprivation. Similarly, ***L*** denotes mediator-outcome confounders, including infant year of birth, maternal marital status, and parity. We distinguish between ***C*** and ***L*** because, by definition, infant year of birth cannot confound the relationship between ME and PTD, and ME may be causally related to parity and other (possibly unmeasured) mediator-outcome confounders. This latter point is the reason why Figure 1 includes an arrow from ME to ***L***. The figure shows that the total relationship between ME and PTD is divided into at least 4 different paths:

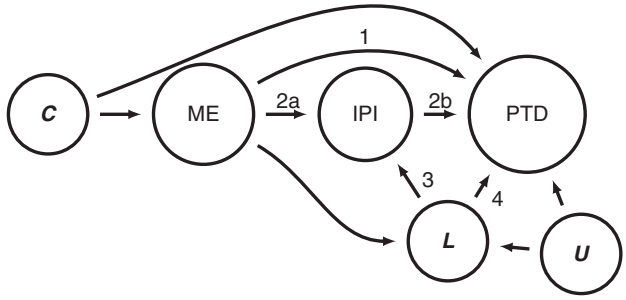

Figure 1. Assumed relationships between maternal education (ME), interpregnancy interval (IPI), and preterm delivery (PTD), including confounders of the exposure-outcome relationship (***C***), the mediator-outcome relationship (***L***), and an unmeasured confounder of the relationship between variables in ***L*** and PTD (***U***).

Path 1. The direct path from ME to PTD.
Path 2. The indirect path from ME to IPI to PTD.
Path 3. The indirect path from ME to ***L*** to IPI to PTD.
Path 4. The indirect path from ME to ***L*** to PTD.

Furthermore, for clarity we divide path 2 into subpaths:

Path 2a. The portion of path 2 from ME to IPI.
Path 2b. The portion of path 2 from IPI to PTD.

As with each of the 3 G-methods, the approach employed here requires no uncontrolled exposure-outcome confounding (path 1) and no uncontrolled mediator-outcome confounding (path 2b). To estimate stochastic mediation contrasts, we additionally require no uncontrolled exposure-mediator confounding. Under additional assumptions required for causal inference, including counterfactual consistency, positivity, and no interference, this approach provides an estimate of the CDE.

Standard regression models

In the main text, we use simplified equations for a binary outcome, mediator, and exposure. In the accompanying Appendix, we present statistical software code for this simplified scenario. In Web Appendix 1 (available at http://aje.oxfordjournals.org/), we provide more explicit equations for situations where the exposure and mediator have multiple categories. We first assessed the total relationship between ME and

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PTD (through paths 1–4). To obtain risk differences, we fitted a binomial regression model with an identity link function, defined as

$$\mathbb{E}(\text{PTD}|\text{ME}, \boldsymbol{C}) = \alpha_0 + \alpha_1\text{ME} + \boldsymbol{\alpha}'\boldsymbol{C}. \qquad \text{(Model 1a)}$$

To assess the relationship between IPI and PTD (path 2b), we added IPI (in categories) to model 1a and included the additional confounder vector $\boldsymbol{L}$. This yielded a binomial regression model with an identity link function for the relationship between IPI and PTD, adjusted for $\boldsymbol{C}$, $\boldsymbol{L}$, and ME, defined as

$$\begin{aligned}&\mathbb{E}(\text{PTD}|\text{ME}, \text{IPI}, \boldsymbol{L}, \boldsymbol{C})\\ &\quad = \theta_0 + \theta_1\text{IPI} + \theta_2\text{ME} + \boldsymbol{\theta}'_l\boldsymbol{L} + \boldsymbol{\theta}'_c\boldsymbol{C}.\end{aligned} \qquad \text{(Model 1b)}$$

We also fitted a binomial model with an identity link function regressing PTD against categorical ME, categorical IPI, the interaction between them, and the confounding vectors $\boldsymbol{C}$ and $\boldsymbol{L}$ (model 1c; see Web Appendix 1) to estimate departures from additivity on the risk difference scale. Thus, models 1a–1c provided estimates of the risk difference for the total relationship between ME and PTD (paths 1–4), the total relationship between IPI and risk of PTD (path 2b), and an assessment of departures from risk difference additivity, respectively. To assess corresponding risk ratios, we fitted models 1a–1c using a log link function.

Controlled direct effect

Our interest lies in the relationship between ME and PTD under hypothetical interventions that change the distribution of IPI to the value "ipi." For example, if IPI is a random categorical variable with the categories defined above, "ipi" might correspond to the value of IPI under a hypothetical intervention that shifts all persons with intervals of <18 months or ≥24 months to intervals of 18–<24 months. Estimating the relationship between ME and PTD under a hypothetical intervention setting the mediator to a single specified value yields the CDE (37, 39). We used a regression-based approach (33, 34) to estimate the CDE on the risk difference (RD) scale, defined as

$$\text{CDE}_{\text{RD}} = \mathbb{E}\{\text{PTD}(\text{me}, \text{ipi}) = 1\} - \mathbb{E}\{\text{PTD}(\text{me}^*, \text{ipi}) = 1\},$$

or on the risk ratio (RR) scale, defined as

$$\text{CDE}_{\text{RR}} = \frac{\mathbb{E}\{\text{PTD}(\text{me}, \text{ipi}) = 1\}}{\mathbb{E}\{\text{PTD}(\text{me}^*, \text{ipi}) = 1\}},$$

where PTD(me, ipi) is the outcome that would be observed under ME = me and IPI = ipi. These equations describe contrasts (on the difference and ratio scales) between the proportions of PTDs in our sample among mothers with educational levels "me" and "me*" that would be observed under an intervention that set the value of IPI for both ME groups to 18–<24 months. In our analyses, "me*" was the referent educational level (some university); thus, "me" could be "less than high school," "high school," or "some college."

To estimate CDE_{RD}, we first fit a binomial regression model with an identity link function for the outcome defined as

$$\begin{aligned}&\mathbb{E}(\text{PTD}|\text{ME}, \text{IPI}, \boldsymbol{C}, \boldsymbol{L})\\ &\quad = \beta_0 + \beta_{\text{me}}\text{ME} + \beta_{\text{ipi}}\text{IPI} + \beta_{\text{me}\times\text{ipi}}\text{ME}\times\text{IPI}\\ &\qquad + \boldsymbol{\beta}'_c\boldsymbol{C} + \boldsymbol{\beta}'_l\boldsymbol{L}\end{aligned} \qquad \text{(Model 2)}$$

with estimates obtained using maximum likelihood. The purpose of fitting model 2 is not to interpret parameter estimates (since an estimate of β_{me} would be subject to collider-stratification bias (40)) but to obtain estimates to create a transformed outcome needed to estimate CDE_{RD} or CDE_{RR}. Conceptually, the average of this transformed outcome can be thought of as the average outcome with the effect of the mediator removed (34). Using the parameter estimates from model 2, we create the transformed outcome, denoted $\widetilde{\text{PTD}}$, as

$$\widetilde{\text{PTD}} = \text{PTD} - \hat{\beta}_{\text{ipi}}\text{IPI} - \hat{\beta}_{\text{me}\times\text{ipi}}\text{ME}\times\text{IPI},$$

and fit a second regression model using the transformed outcome, defined as

$$\mathbb{E}(\widetilde{\text{PTD}}\,|\text{ME}, \boldsymbol{C}) = \gamma_0 + \gamma_{\text{me}}\text{ME} + \boldsymbol{\gamma}'_c\boldsymbol{C}. \qquad \text{(Model 3)}$$

Because the transformed outcome is no longer binary, we use ordinary least squares to obtain parameter estimates for model 3. The sandwich variance estimator (41, 42) or the nonparametric percentile bootstrap (43) with 1,000 resamples can be used to obtain 95% confidence intervals. An estimate of CDE_{RR} can be obtained by replacing the identity link function in model 2 with a log link, computing

$$\widetilde{\text{PTD}} = \text{PTD}\,\exp(-\hat{\beta}_{\text{ipi}}\text{IPI} - \hat{\beta}_{\text{me}\times\text{ipi}}\text{ME}\times\text{IPI}),$$

and fitting model 3 with a log link and normal distribution generalized linear model (34). Sandwich or bootstrap variance estimators must again be used for standard errors.

Because the referent category for IPI was 18–<24 months, the estimate of γ_{me} can be interpreted as the magnitude of the relationship between ME and PTD under a hypothetical intervention that would set *everyone*'s interval (including mothers with IPIs of ≥24 months) to 18–<24 months' duration. This value corresponds to paths 1 and 3 in Figure 1 and represents the relationship between ME and PTD that would remain if the intervention aimed at setting every mother's IPI to 18–<24 months was 100% effective.

Stochastic mediator interventions

Given the complex nature of pregnancy spacing (28), interventions that result in all IPIs falling exactly between 18 and 24 months are unrealistic. We therefore modified the above approach to estimate the relationship between ME and PTD that would be observed under a more realistic intervention that increased only a fraction the population's intervals to 18 months or more. We denote the contrast a *stochastic*

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mediation contrast. This contrast is similar to those based on "representative regimes," previously implemented via the parametric G-formula (44), in which persons who fall below a prespecified exposure (or mediator) cutpoint are redistributed to somewhere above the cutpoint based on the exposure's (or mediator's) conditional distribution. Stochastic intervention (or mediator) contrasts go a step further by redistributing only a portion of the persons who fall below a preselected cutpoint.

To implement the approach, we add back to the transformed outcome a portion of the mediator's effect by defining a new IPI variable, IPI*, that represents the hypothetical distribution of intervals under a stochastic intervention. The redefined transformed outcome when all variables are binary indicators is

$$\widetilde{\text{PTD}} = \text{PTD} - \hat{\beta}_{\text{ipi}}(\text{IPI} - \text{IPI}^*) - \hat{\beta}_{\text{me}\times\text{ipi}}(\text{ME}\times\text{IPI} - \text{ME}\times\text{IPI}^*)$$

for CDE_{RD} and

$$\widetilde{\text{PTD}} = \text{PTD}\,\exp[-\hat{\beta}_{\text{ipi}}(\text{IPI} - \text{IPI}^*) - \hat{\beta}_{\text{me}\times\text{ipi}}(\text{ME}\times\text{IPI} - \text{ME}\times\text{IPI}^*)]$$

for CDE_{RR}. We might be interested in what would happen if 3% of the 282,066 mothers with intervals of <18 months (to the left of the dashed line in Figure 2) were shifted (e.g., through family planning initiatives) to intervals of 18 months or more. Such a shift is equivalent to the Healthy People 2020 objective of decreasing the proportion of US pregnancies conceived within 18 months of a previous birth from 33% to 30% (45).

To estimate the effect of such a shift, we first select a conditional 3% of mothers with IPIs of <18 months to be redistributed, with the probability of being selected defined by

$$P(R = 1|\text{ME}, L) = \{1 + \exp[-(\delta_0 + \delta_1\text{ME}^* + \delta_2\text{Age}^*)]\}^{-1},$$

where δ_0 is chosen such that the marginal probability of R is approximately 0.03 among mothers with intervals of <18 months. We set $\delta_1 = \log(1.5)$ with ME* = 1 if ME is less than high school (0 otherwise), and $\delta_2 = \log(1.25)$ with Age* = 1 if maternal age is less than 20 (0 otherwise). For all other mothers, R is set equal to 0. Using this model implies that intervention efforts will prioritize young mothers with less than a high school education, but alternative choices are possible.

Next, we redistribute selected mothers. For each selected mother (i.e., with $R = 1$), we draw a realization from a log-normal distribution based on the following model estimated from the data:

$$\text{IPI}^* \sim f_{\text{LN}}(\text{IPI}|\text{ME}, \boldsymbol{L}, \boldsymbol{C}, \text{IPI} \geq 18, R = 1; \zeta),$$

where $f_{\text{LN}}(\cdot)$ represents the log-normal distribution with homoscedastic variance. For all other mothers, we let IPI* = IPI. Additional details, including an assessment of the adequacy of this model (Web Figure 1), are provided in Web Appendix 2. We explored scenarios in which 3%, 10%, 20%, and 100% of the persons with IPIs of <18 months were redistributed to IPIs of ≥18 months.

An intervention in which 100% of mothers with short intervals are redistributed differs from the fully effective intervention in that mothers to the left of the dashed line in Figure 2 are redistributed to *anywhere* above the dashed line (as determined by the model for IPI*). In the fully effective intervention initially described (the standard CDE), all mothers with IPIs of <18 months *and* ≥24 months are set to have IPIs of 18–<24 months.

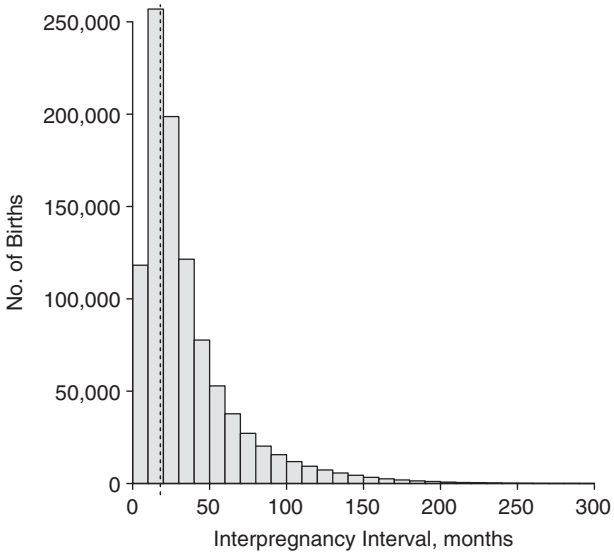

Figure 2. Distribution of interpregnancy intervals among 847,618 singleton livebirths in Quebec, Canada, 1989–2010. The dashed vertical line at 18 months shows the 33rd percentile.

Quantitative bias analysis

We lacked information on prior pregnancy outcome, which may confound the relationship between IPI and preterm birth (46). To assess the sensitivity of our results to missing $\boldsymbol{L}$ information (Figure 1), we performed a quantitative bias analysis (47) by bootstrap resampling our data 10,000 times, simulating an unmeasured binary confounder representing prior pregnancy outcome for each bootstrap resample, and estimating CDE_{RD} while adjusting for the simulated confounder. Details are provided in Web Appendix 3.

Analyses were carried out with SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). We present risk differences and risk ratios as measures of association and 95% confidence intervals as measures of precision. In the main text, we present 95% sandwich variance confidence intervals, and we report 95% bootstrap confidence intervals in Web Appendix 4. For all models, categorical confounders were entered as indicator variables, and continuous confounders were entered using restricted quadratic splines with knots at the 5th, 23rd, 41st, 59th, 77th, and 95th percentiles. Example SAS code is provided in the Appendix.

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Table 1. Characteristics (Median and Interquartile Range[a]) of 847,618 Livebirths in the Quebec Birth File According to Preterm Delivery Status,[b] Quebec, Canada, 1989–2010

Characteristic	Preterm Delivery ($n = 43,231$)	Term Delivery ($n = 804,387$)
Maternal age, years	30 (26–33)	30 (27–33)
Paternal age, years	32 (28–36)	32 (29–36)
Maternal education, completed years	12 (11–15)	14 (11–16)
Interpregnancy interval, months	27.0 (14.7–51.0)	24.9 (14.9–43.1)
Gestational age at birth, completed weeks	35 (34–36)	39 (38–40)
Year of birth	2000 (1994–2006)	1999 (1994–2006)

[a] 25th–75th percentiles.
[b] Preterm delivery was defined as delivery at <37 completed weeks' gestation.

Table 2. Distribution of Pregnancy-Related Characteristics According to Decade of Birth Among 847,618 Livebirths in the Quebec Birth File, Quebec, Canada, 1989–2010

Characteristic	Decade of Birth			
	1989–2000 ($n = 456,954$)		2001–2010 ($n = 390,664$)	
	No.	%	No.	%
Maternal educational level[a]				
Less than high school	66,864	14.6	36,197	9.3
High school	56,136	12.3	70,269	18.0
Some college	137,113	30.0	47,691	12.2
Some university	196,841	43.1	236,507	60.5
Interpregnancy interval, months				
<18	156,115	34.2	128,460	32.9
18–<24	62,967	13.8	58,272	14.9
24–<60	172,932	37.8	142,663	36.5
≥60	64,940	14.2	61,269	15.7
Gestational age, completed weeks				
<25	389	0.1	539	0.1
25–<32	2,084	0.5	1,721	0.4
32–<34	2,096	0.5	1,765	0.5
34–<37	18,287	4.0	16,350	4.2
≥37	434,098	95.0	370,289	94.8

[a] Less than high school, <11 years (no graduation); high school, 11 years (high school diploma); some college, 12–13 years (pre-university studies); some university, ≥14 years (at least some university studies).

RESULTS

Tables 1 and 2 provide descriptive information on our cohort stratified by PTD status. Overall, 5.1% of mothers with parity ≥1 ($n = 43,231$) had fewer than 37 completed weeks of gestation. Of these, 17.7% ($n = 7,641$) had less than a high school education, and 32.6% ($n = 14,101$) had IPIs of <18 months. In comparison, 11.8% ($n = 94,729$) of mothers with ≥37 weeks of gestation had less than a high school education, and 33.3% ($n = 267,965$) had IPIs of <18 months.

Table 3 presents risk differences, risk ratios, and 95% confidence intervals for the total relationship between ME and PTD and the total relationship between IPI and PTD. Compared with mothers with some university education, mothers with less than high school, high school, and some college had excess PTD risks of 2.6% (95% confidence interval (CI): 2.4, 2.8), 1.5% (95% CI: 1.4, 1.7), and 1.0% (95% CI: 0.9, 1.1), respectively. Compared with mothers with IPIs of 18–<24 months, mothers with intervals of <18 months, 24–<60 months, and ≥60 months had excess PTD risks of 0.4% (95% CI: 0.3, 0.5), 0.5% (95% CI: 0.4, 0.7), and 2.0% (95% CI: 1.8, 2.2), respectively. Patterns were similar on the risk ratio scale for both ME and IPI (Table 3).

Figure 3 displays total and CDE estimates for the relationship between ME and PTD on the risk difference (part A) and risk ratio (part B) scales. Web Table 1 presents these results including bootstrap and sandwich variance confidence intervals. As demonstrated in Figure 3, under a perfect intervention in which all mothers with IPIs of <18 months or ≥24 months were set to IPIs of 18–<24 months, mothers with less than high school, high school, and some college education had excess PTD risks of 2.4% (95% CI: 2.2, 2.6), 1.4% (95% CI: 1.2, 1.5), and 0.9% (95% CI: 0.8, 1.0), respectively, on the risk difference scale. This perfect intervention corresponds to the CDE. Stochastic mediation contrasts in which 3%, 10%, 20%, and 100% of mothers with intervals of <18 months were redistributed to intervals of ≥18 months yielded an excess risk of PTD that was no different from the total relationship presented in Table 3 (Figure 3, Web Table 2). Restricting analyses to mothers with intervals less than 84 months ($n = 776,440$) yielded negligible changes, as did restricting analyses to mothers who gave birth at 30 years of age ($n = 82,574$) or mothers with a parity of 2 who gave birth at 30 years of age ($n = 20,085$). Similar patterns were observed on the risk ratio scale.

Table 4 shows the distribution (median value and 2.5th and 97.5th percentiles) of 10,000 CDE_{RD} estimates for the 3% and 100% stochastic mediation contrasts obtained from our Monte Carlo sensitivity analysis. This table shows that accounting for possible confounding due to unmeasured prior pregnancy outcome yields negligible changes in the stochastic mediation contrast estimates.

DISCUSSION

We estimated the magnitude of the relationship between ME and PTD that would remain under hypothetical interventions designed to increase IPIs in Quebec. We found that for every 1,000 livebirths, mothers with less than a high school education had 26 more preterm births than did mothers with a university education. Under an unrealistic intervention in which all mothers were set to IPIs of 18–<24 months, mothers with less than high school would have 24 more preterm births than mothers with a university education. Under a

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Table 3. Associations of Maternal Education and Interpregnancy Interval With Preterm Delivery Among 847,618 Livebirths in the Quebec Birth File, Quebec, Canada, 1989–2010

Characteristic	Risk Difference[a]	95% CI	Risk Ratio[a]	95% CI
Maternal educational level[b]				
Less than high school	0.026	0.024, 0.028	1.61	1.57, 1.66
High school	0.015	0.014, 0.017	1.37	1.34, 1.41
Some college	0.010	0.009, 0.011	1.26	1.23, 1.29
Some university	0	Referent	1	Referent
Interpregnancy interval, months				
<18	0.004	0.003, 0.005	1.11	1.08, 1.15
18–<24	0	Referent	1	Referent
24–<60	0.005	0.004, 0.007	1.13	1.09, 1.16
≥60	0.020	0.018, 0.022	1.45	1.40, 1.50

Abbreviation: CI, confidence interval.

[a] Adjusted for maternal year of birth, maternal and paternal age, maternal and paternal country of birth, maternal and paternal native language, and area-level measures of material and social deprivation.

[b] Less than high school, <11 years (no graduation); high school, 11 years (high school diploma); some college, 12–13 years (pre-university studies); some university, ≥14 years (at least some university studies).

more realistic intervention in which 3%, 10%, 20%, or 100% of short IPIs were set to IPIs of ≥18 months, mothers with less than a high school education would still have 26 more preterm births than mothers with a university degree. Our results suggest that interventions designed to increase short IPIs will have a negligible impact on the educational disparity in PTD. It is possible that IPI is too far downstream to be of any consequence in mitigating educational disparity (23, 24) or that IPIs of <18 months confer a low overall risk of PTD in Western societies, where standards of living are high. Our results should be considered in light of certain limitations, including an inability to differentiate spontaneous PTD from induced PTD and to account for clustering of birth outcomes.

We combined a simple approach to estimate CDEs in the presence of exposure effects that confound the mediator-outcome relationship (33) with a simulation-based approach to assess "representative regimes" (44) to obtain stochastic mediation contrasts. The approach can be used to estimate risk differences or risk ratios, but estimating odds ratios is not straightforward (34). To implement the approach, we had to select a subset of mothers with IPIs of <18 months to redistribute. Our selection was based on a model for the relationships between age, ME, and the probability of being redistributed under a hypothetical intervention. This approach requires the analyst to consider the specific mechanisms by which interventions may impact the population, and a range of scenarios can be explored. In this analysis, the results did not differ regardless of whether we chose a random subset of mothers with IPIs less than 18 months or a conditional subset.

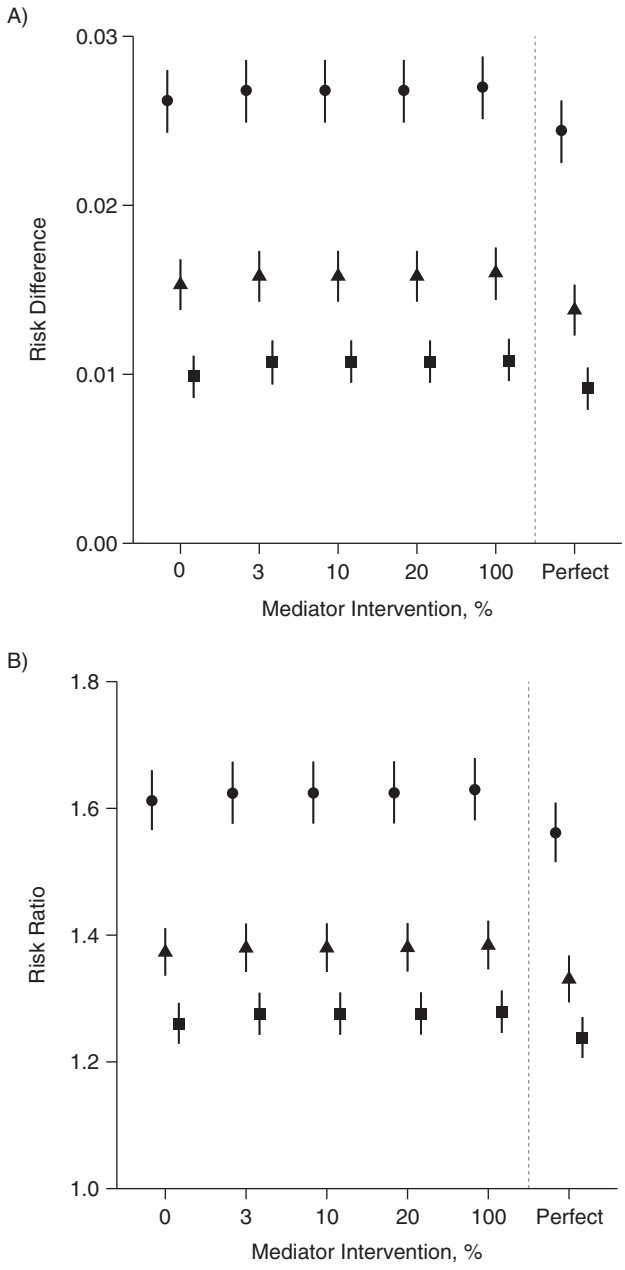

Figure 3. Associations between maternal education and preterm delivery (PTD) under hypothetical interventions that change the distribution of interpregnancy intervals (IPIs) among 847,618 singleton livebirths in Quebec, Canada, 1989–2010. All associations were adjusted for maternal year of birth, maternal and paternal age, maternal and paternal country of birth, maternal and paternal native language, and area-level measures of material and social deprivation. Circles, less than high school (<11 years); triangles, high school (11 years); squares, some college (12–13 years). The referent category for all comparisons was some university education (≥14 years). Percentages on the *x*-axes refer to the relationship between maternal education and PTD under interventions in which 0%, 3%, 10%, 20%, and 100% of mothers with short IPIs, respectively, are redistributed to have IPIs of ≥18 months. A 0% intervention on IPI corresponds to the total relationship between maternal education and PTD. "Perfect" represents the relationship between maternal education and PTD under an intervention in which all mothers have IPIs of 18–<24 months (i.e., standard controlled direct effect). Vertical lines, 95% confidence intervals.

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Table 4. Distribution of 10,000 Controlled Direct Effect Risk Differences for the 3% and 100% Stochastic Mediation Contrasts Obtained From a Monte Carlo Quantitative-Bias Analysis of Quebec Birth Data, Quebec, Canada, 1989–2010

Contrast and Maternal Educational Level[a]	Median	2.5th Percentile	97.5th Percentile
3% of women with short IPIs redistributed			
Less than high school	0.0266	0.0254	0.0277
High school	0.0158	0.0141	0.0173
Some college	0.0109	0.0095	0.0120
Some university		Referent	
100% of women with short IPIs redistributed			
Less than high school	0.0268	0.0257	0.0279
High school	0.0160	0.0144	0.0176
Some college	0.0110	0.0096	0.0122
Some university		Referent	

Abbreviation: IPI, interpregnancy interval.

[a] Less than high school, <11 years (no graduation); high school, 11 years (high school diploma); some college, 12–13 years (pre-university studies); some university, ≥14 years (at least some university studies).

Other methods for estimating CDEs in situations where exposure effects confound the mediator-outcome relationship include inverse probability-weighted marginal structural models (48), targeted maximum likelihood estimation (49), G-estimation of a structural nested model (33), and the parametric G-formula (50). Inverse probability-weighted marginal structural models are easy to implement, but they have not, to our knowledge, been used to estimate realistic (or stochastic) intervention effects. Targeted maximum likelihood estimation can be used to calculate stochastic intervention effects (51) but has not been used to do so in a mediation framework. The G-formula can be used to estimate the CDE in the presence of exposure effects that confound the mediator-outcome relationship, and it easily accommodates estimation of stochastic or "representative" regimes (44, 52). However, in typical epidemiologic data, the parametric G-formula requires strong modeling assumptions (53). Our results depend on correct specification of the model for the mean of PTD as a function of ME, IPI, and relevant confounders (model 2), as well as correct specification of the model for the transformed outcome as a function of ME and relevant confounders (model 3). This is fewer than what would have been required for the G-formula.

Throughout the main text, we presented 95% confidence intervals obtained using the sandwich variance estimator (41, 42). While robust to model misspecification, these variance estimators do not account for the additional variation induced by the models to generate our transformed outcome and to create an IPI variable that would have been observed under a hypothetical distribution (IPI*). We used the nonparametric bootstrap to account for this additional variation, but found no difference in our confidence interval estimates (Web Table 2). This was undoubtedly the result of our large sample size. In future research, investigators using stochastic mediation contrasts in smaller samples should consider the use of bootstrap confidence interval estimators to better capture the variability introduced by each step of the estimation process.

Epidemiologists have done much to establish that adverse birth outcomes are differentially distributed across social categories (31), often defined using attributes such as education, occupation, race/ethnicity, and sex (54). Such attributes are critical to understanding how adverse birth outcomes are distributed socially. However, their causal effects are difficult to formalize using potential outcomes, largely because they cannot be construed as characteristics that correspond to well-defined interventions (21, 55). Thus, the conditions necessary for causal inference (e.g., exposure variation irrelevance (56)) are violated, and our use of potential outcomes to define CDE_{RD} and CDE_{RR} represents a slight abuse of notation. Because university attendance is the result of a complex sequence of experiences and decisions made in a wide range of social contexts during critical periods of life (54), it is difficult to conceive of education-related interventions that would yield comparable effects on birth outcomes. Even if CDE estimates in this study cannot be interpreted as causal effects defined using potential outcomes, under the assumptions necessary for causal inference for the relationship between IPI and PTD, our estimates can be interpreted as the magnitude of the relationship between ME and PTD that would remain under the specified interventions to increase IPIs.

A central objective of epidemiologic research is to yield scientifically informed improvements in population health (57). Stochastic mediation contrasts provide a useful means of estimating the effects of realistic interventions geared towards this end.

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APPENDIX

Example of SAS Code for Estimating the Controlled Direct Effect

```
*Step 1: Fit a model for the outcome conditional on the exposure, mediator, exposure-
mediator interaction, and confounders of the exposure-outcome and mediator-outcome
relationship;
proc genmod data=ipi desc;
model ptd_ind = ipi me ipi*me c l / link=identity dist=bin;
ods output ParameterEstimates=parms0(keep= parameter level1 level2 estimate);
run;

*Step 2: Keep parameter estimates for the mediator (ipi) and exposure-mediator
interactions (ipi*me);
data parms;
set parms0;
if parameter = "ipi" | parameter = "me*ipi";
name = cats("p_",parameter);
drop parameter;
run;
proc transpose data=parms out=parms2;id name;
data parms2;set parms2;merg=1;drop _name_;
run;

*Step 3: Fit a model for continuous IPI to generate a distribution of IPI*;
proc lifereg data=ipi outest=parms(drop = _model_ _name_ _type_ _dist_ _status_
_lnlike_ ipimo);
model ipimo*merg(0) = me c l / dist=lnormal;
*nb: merg = 1 for all individuals;
run;quit;run;
proc transpose data=parms out=parms2;run;quit;run;
proc transpose data=parms2 out=parms prefix=pp_;id _name_;run;
data parms;set parms; merg=1;drop _name_;run;
```

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```
*Step 4: generate necessary variables;
data ipi;
merge parms parms2 ipi;
by merg;
call streaminit(6435);
*perfect mediator intervention;
ytilde = ptd_ind - ipi*p_ipi - me*ipi*p_me_ipi;

*stochastic mediator intervention;
r=0;
if ipimo < 18 then do;
r = rand("bernoulli",1/(1+exp(-(-log(1/0.03 - 1) - log(1.5)*.12 - log(1.25)*.12 +
log(1.5)*(meduc<11) + log(1.25)*(mage<20)))));
*ipimo is continuous IPI, meduc is integer maternal education, and mage is continuous
maternal age;
*.12 = proportion of mothers with meduc<11 and proportion of mothers with mage<20;
*-log(1/.03 - 1) sets marginal proportion of r;
end;

*generate ipistar variable;
ipistar0 = ipimo;
if r = 1 then do;
  do until (ipistar0 ge 18 and ipistar0 < 300);
ipistar0 = exp(pp_intercept + pp_me*me + pp_c*c + pp_l*l +
rand("normal",0,pp__scale_));
  end;
end;


ipistar = (ipistar0<18);

ytilde1 = ptd_ind - (ipi - ipistar)*p_ipi - me*(ipi - ipistar)*p_me_ipi;

*Step 5: Fit Model for Controlled Direct Effect;

proc genmod data=ipi;

class id;

model ytilde = me c / link=identity dist=normal;

*replace ytilde with ytilde1 for stochastic mediation;

repeated subject = id / type = ind;

*use above to obtain sandwich variance CIs;

run;quit;run;
```

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