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Gestational age-dependent risk factors for preterm birth: associations with maternal education and age early in gestation

Nathalie Auger [a,b,c,*], Michal Abrahamowicz [d], Willy Wynant [d], Ernest Lo [a,d]

[a] Institut national de santé publique du Québec, Montréal, Canada
[b] Research Centre of the University of Montréal Hospital Centre, Montréal, Canada
[c] Department of Social and Preventive Medicine, University of Montréal, Montréal, Canada
[d] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, Canada

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ABSTRACT

Objectives: Preterm birth (PTB) before 37 weeks can occur over a wide range of gestational ages, but few studies have assessed if associations between risk factors and PTB vary over the duration of gestation. We sought to evaluate if associations between two major risk factors (maternal education and age) and PTB depend on gestational age at delivery.
Study design: We estimated hazard ratios of PTB for education and age in a time-to-event analysis using a retrospective cohort of 223,756 live singleton births from the province of Québec, Canada for the years 2001–2005. Differences in hazards of maternal education and age with PTB were assessed over gestational age in a Cox proportional hazards model using linear and nonlinear time interaction terms, adjusting for maternal characteristics.
Results: Associations of PTB with lower (vs. higher) education and older (vs. younger) age strengthened progressively at earlier gestational ages, such that the risk of PTB for maternal education and age was not constant over the course of gestation.
Conclusions: Associations of PTB with risk factors such as maternal low education and older age may be stronger early in gestation. Models that capture the time-dependent nature of PTB may be useful when the goal is to assess associations at low gestational ages, and to avoid masked or biased associations early in gestation.

1. Introduction

Preterm birth (PTB) is an important contributor to neonatal morbidity and mortality [1,2], especially when delivery occurs at very early gestational ages [3,4]. Although the causes of PTB are poorly understood [5], maternal socio-demographic characteristics such as low education and older age are known risk factors [6–10]. Few studies, however, have examined how maternal characteristics are associated with very early (e.g., <32 gestational weeks) as opposed to later PTB. PTB is frequently analyzed dichotomously with early and late cases combined, an approach which does not account for the fact that preterm delivery is the consequence of a dynamic process resulting in an event (birth) at a specific time [11], and that potentially pathologic PTBs at earlier gestational ages may be more strongly associated with maternal risk factors than PTBs at later gestational ages. A natural way to determine if associations vary by gestational age is to test for non-proportional hazards of risk factors in a time-to-event (survival) analysis. A particular advantage of time-to-event analysis is that associations between risk factors and PTB can be expressed at specific gestational ages if there are differences over gestation (i.e., non-proportional hazards), or summarized as one overall measure of association if there are no differences by gestational age (i.e., proportional hazards).

Our objective was to determine if the association between PTB and maternal risk factors varies by gestational age at delivery using time-to-event analysis. We evaluated two risk factors for PTB, maternal education and age [12–17], both relevant to future research on determinants of perinatal outcomes over the range of gestational age, and to guiding clinical prevention [18].

* Corresponding author at: Institut national de santé publique du Québec, 190, boulevard Crémazie Est, Montréal, Québec H2P 1E2, Canada.
Tel.: +1 514 864 1600 x3717; fax: +1 514 864 1616.
E-mail address: nathalie.auger@inspq.qc.ca (N. Auger).

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2. Materials and methods

Data included 223,892 live singleton births to Canadian-born mothers aged ≥25 years in Québec, Canada for 2001–2005. Births to women aged <25 years were not included because very young women are at higher risk of PTB in Québec compared with women in their late 20 s [7,19], and we sought to compare older women to an age group with low risk. In addition, education is more likely to be in progress before 25 years of age. To increase homogeneity of associations, we excluded births to foreign-born women ($N = 55,675$), for whom effects of education and age may be systematically weaker compared with Canadian-born women [19–21]. The live birth file in Québec is compiled from birth certificates and is considered complete.

Infants born at <37 completed weeks of gestation were defined as preterm. Gestational age estimates in Québec were available in completed weeks based on ultrasound examinations. For descriptive statistics, PTB was expressed as extreme (22–27 weeks), very (28–31 weeks), or moderate (32–36 weeks) [22]. PTBs at <22 weeks ($N = 136$) were excluded as gestational age may be misclassified, and these outliers may unduly influence associations between maternal characteristics and PTB extremely early in gestation. The final sample contained 223,756 live singleton births.

Maternal education (range 1–30 years) was ranked continuously such that the least educated women were compared to the most educated. Maternal age (range 25–51 years) was also evaluated continuously, comparing the oldest to the youngest women. As our primary objective was to determine if associations varied by gestational age, we used continuous variables to capture the distribution of education and age in summary measures scaled from 0 to 1 [13,14], rather than categorical variables that have lower statistical power [23]. Linearity of maternal education and age with the logarithm of the PTB hazard was verified.

Covariates included marital status (legally married, not legally married), language spoken at home to proxy ethnicity (French, English, other), and parity (0, 1, ≥2 previous deliveries). Births missing data on education ($N = 15,618$; 7.0%), gestational age ($N = 30$; 0.0001%), and language ($N = 5474$; 2.4%) were assumed to be missing at random, and were imputed five times based on the distribution of observed covariates using multiple imputation [24].

2.1. Statistical analysis

Mean maternal education and age were calculated by severity of gestational age. Continuous gestational age was the time axis for the time-to-event analysis, and births were censored at ≥37 weeks (when they were no longer at risk of PTB). Initially, Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of PTB for continuous maternal education and age in separate unadjusted models, and in models adjusted for maternal education, age, marital status, language, and parity. The HR is conceptually similar to a relative risk, rather than an odds ratio [25]. Cox proportional hazards regression provides HRs averaged over all preterm gestational ages, thus estimates will be misleading if HRs vary substantially at specific points in gestation (i.e., if the proportional hazards assumption is not satisfied due to differences over gestational age) [25]. We therefore determined if hazards of maternal education and age were not proportional over gestation by testing gestational age-dependent interaction terms in the Cox model using two approaches: (1) conventional linear interaction terms, and (2) spline-based interaction terms. In the first approach, the linear interaction terms (gestational age-by-education, gestational age-by-maternal age) contained gestational age as a continuous variable. These interaction terms assume that the hazard varies linearly over gestation. Gestational age-specific HRs and 95% CIs were derived from these interaction terms. We also used gestational age as a categorical variable in the interaction terms – categorical interaction terms are less likely to detect non-proportionality because they do not use the entire range of data and have less power [23].

In the second approach, we used spline-based interaction terms as the hazard ratio for maternal education or age may change nonlinearly over gestation. Spline terms do not force the hazard to be linear, but rather allow the shape of the hazard to vary flexibly over gestational age [26]. We used a flexible extension of the Cox model employing quadratic splines for the gestational age-by-covariate interactions to evaluate nonlinear changes in the proportionality of hazards of maternal education and age over the duration of gestation [27]. Gestational age-specific HRs were derived from these interaction terms, and HRs were plotted against continuous gestational age. A nonparametric likelihood ratio test that compared the nonlinear model with the initial proportional hazards model was used to test non-proportionality of hazards (a P-value <0.05 was evidence that hazards were non-proportional) [27].

In sensitivity analyses, models were run using cubic splines, excluding births missing data, including births <22 gestational weeks and mothers aged 20–24 years ($N = 57,107$). Cox models with conventional linear interaction terms were run using SAS 9.2 (SAS Institute Inc., Cary, NC). Flexible Cox models with nonlinear interactions were estimated with Revolution R Enterprise 4.2 (http://www.revolutionanalytics.com). Data were anonymized, and ethical approval was waived by the institutional review board of the University of Montreal Hospital Centre.

3. Results

Overall, 6.0% of births were preterm. Mean education was lower at extreme preterm gestational ages, whereas maternal age was significantly higher ($P = 0.002$; Table 1).

In Cox models that assumed proportional hazards, the adjusted risk of PTB was 92% higher for the least educated mothers relative to most educated (95% CI 1.78, 2.06), and 21% higher for the oldest mothers relative to the youngest (95% CI 1.13, 1.28; Table 2). Linear gestational age-by-education and gestational age-by-maternal age interaction terms were statistically significant ($P < 0.001$), indicating that hazards were non-proportional for both maternal

Table 1
Mean maternal education and age according to gestational age, singletons, Québec, 2001–2005.

	Education, years		Age, years		No. births
	Mean (95% CI)	IQR	Mean (95% CI)	IQR	
Gestational age, weeks[a]					
Extreme, 22–27	14.3 (14.0, 14.5)	12–16	31.0 (30.6, 31.3)	27–34	614
Very, 28–31	14.2 (14.0, 14.5)	12–16	31.0 (30.4, 31.0)	27–34	879
Moderate, 32–36	14.4 (14.3, 14.4)	12–17	30.4 (30.3, 30.4)	27–33	11,933
Term, ≥37	14.9 (14.8, 14.9)	13–17	30.4 (30.3, 30.4)	27–33	210,398

CI, confidence interval; IQR, interquartile range.
[a] Descriptive statistics for unimputed data