

## **eAppendix 1**

### **Québec Birth File Data**

We used the Québec birth file data to estimate exposure-response curves for the relation between inter-pregnancy interval and the risk of preterm birth. Québec is the second most populous province in Canada, and registration of live births is mandatory. We extracted information from over one million live singleton births between 1989 and 2008 (inclusive), including: gestational age at birth (in completed weeks); maternal and paternal date and country of birth; marital status in six categories; language spoken at home (English, French, Other); parity (total number of previous deliveries); maternal educational status (integer years from 0 to 30); and six-digit postal code. We used postal code information to assign to each individual two area-level measures of social and material deprivation based on the quinquennial Census.<sup>1</sup> These indices were coded at the Census dissemination area, small neighbourhoods containing an average of 400-700 inhabitants.<sup>1</sup> Maternal and paternal country of birth was used to create an 11-category variable for region of birth, with categories defined as: Canada, Western Europe, Eastern Europe, Sub-Saharan Africa, Middle East, Latin America, East Asia-Pacific, South Asia, Caribbean, USA, and foreign unspecified. Gestational age at birth was obtained using first- or second-trimester ultrasounds which are not subject to recall bias common to estimates based on last menstrual period. Preterm birth was defined as an indicator of less than 37 weeks completed gestation. We defined inter-pregnancy interval as the difference (in years) between the conception date of the index child and the date of birth of the previous child. Of the over one million births available, information from a total of 726,294 multiparous women was extracted.

## Statistical Analysis

### Stabilized Inverse Probability Weights

We used the quantile binning method<sup>2</sup> to construct stabilized inverse probability weights ( $\widehat{sw}$ ) for inter-pregnancy interval, defined as:

$$\widehat{sw} = \frac{\hat{f}_X(X; \theta_1)}{\hat{f}_{X|C}(X | \mathbf{C} = \mathbf{c}; \theta_2)} \quad (1)$$

where  $f_{\bullet}(\bullet)$  denotes the probability density function for inter-pregnancy interval with parameter vector  $\theta$ . The quantile binning approach requires that one first rank the exposure variable into quantiles (e.g., deciles) and fit a cumulative logistic model to estimate the predicted probability of being in each category. These probabilities are then used to construct the weights in (1). To obtain marginal exposure response curves, we avoid conditioning the numerator on elements of  $\mathbf{C}$ .<sup>3</sup> For the denominator model in  $\widehat{sw}$ , the set of confounders  $\mathbf{C}$  included maternal year of birth, year of birth of the index child, neighborhood-level social and material deprivation indices, maternal and paternal age (in years), maternal education, parity, and maternal and paternal country of birth. Interactions between maternal and paternal age, social and material deprivation indices, and maternal education and maternal age were also included in the model. Continuous covariate main terms and interaction terms were fit using natural cubic splines with eight and three degrees of freedom, respectively.

### Regression Models

We fit a marginally adjusted (weighted) model defined as:

$$\log \left\{ \frac{P^*(Y = 1 | X = x)}{1 - P^*(Y = 1 | X = x)} \right\} = \beta_0^* + s^*(x), \quad (\text{Marginal})$$

where the superscript asterisk reflects probabilities, parameters, and functions in the pseudo-data (i.e., weighted).

### **Interaction Models**

To explore the exposure response curves for the relation between interpregnancy interval and the risk of preterm birth in mothers of parity = 1 and mothers of parity  $\geq 2$ , we fit a marginally adjusted interaction model, defined as:

$$\log \left\{ \frac{P^*(Y = 1 | X = x)}{1 - P^*(Y = 1 | X = x)} \right\} = \beta_0^* + s^*(x, z),$$

where  $s(x, z)$  represents a separate penalized smoothing spline expansion for mothers with parities  $z = 1$  and  $z \geq 2$ .

## References

1. Pampalon R, Hamel D, Gamache P, and Raymond G. A deprivation index for health planning in Canada. *Chronic Dis Can.* 2009; **29**:178–191.
2. Naimi AI, Moodie EEM, Auger N, and Kaufman JS. Constructing Inverse Probability Weights for Continuous Exposures: A Comparison of Methods. *Epidemiol.* 2014; **25**:292–299.
3. Cole SR and Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol.* 2008; **168**:656–64.

## eAppendix 2

There are well known relations between linear models fit with penalized smoothing splines and mixed effects regression models.<sup>1(p108,p288),2(p316),3(p608)</sup> Consequently, one can make use of existing mixed model (MM) routines in standard software packages to estimate regression models with penalized smoothing splines. Moreover, because MM routines in packages such as SAS (SAS Institute, Cary, NC) and Stata (StatCorps, College Station, TX) accommodate weighting, one can fit weighted penalized smoothing spline regression models. In SAS, the approach can be accomplished by first building a set of spline basis functions using the `transreg` procedure, and fitting a penalized likelihood using the `glimmix` procedure:

```
proc transreg data=w design;
    model pspline(m / degree=3 nknots=20);
    id ptb_i id sw;
    output out=wspline;
run;

proc glimmix data=wspline method=LAPLACE;
    weight swQB;
    model ptb = m_1 m_2 m_3 / link=logit dist=bin s;
    random m_4-m_23 / type=toep(1) s;
    output out=spl pred(blup ilink)=p;
run;
```

where `swQB` is the inverse probability weight estimated with the quantile binning approach outlined in eAppendix 1, `ptb` is an indicator of preterm birth, and `m` is a centred and scaled inter-pregnancy interval variable. Importantly, using `pred(blup ilink)=p` allows one to plot the predicted risk as a smoothed functional inter-pregnancy because the `ilink` request outputs predicted probabilities. An alternative to this code would be to remove `m_1-m_13` from the `random` statement, add `m` to the `random` statement, and replace `type=toep(1)` with `type=pspline` or `type=rsmooth` to implement  $B$ -splines and radial smoothing splines, respectively. This approach would not require that the user build their own set of spline basis functions, but, in our experience, is more prone to convergence issues.

Pointwise bootstrap confidence intervals for exposure-response curves from the above process can be obtained as follows:<sup>4</sup>

1. Fit the weighted generalized linear mixed model to obtain parameter estimates  $\hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3$  for the fixed effects, and a variance estimate  $\hat{\sigma}_u$  for the random effects.
2. Sample (with replacement)  $n$  individuals  $B$  times from the original data, where  $n$  is the original sample size, and  $B = 1000$  is the number of bootstrap resamples. Then, for each of the  $n$  individuals in each of the  $B$  resamples,
3. Construct stabilized inverse probability weights for the exposure.
4. Generate a bootstrapped random effects component of the linear predictor,  $Zu^*$ , where  $u^* \sim \mathcal{N}(0, \hat{\sigma}_u)$ , and where  $Z$  is the vector of spline variables in the random effects statement of the `glimmix` code above (m\_4-m\_23).
5. Generate a fixed effects component of the linear predictor,  $X\beta$ , as  $\hat{\beta}_0 + \hat{\beta}_1 m_1 + \hat{\beta}_2 m_2 + \hat{\beta}_3 m_3$ .
6. Generate a bootstrapped outcome,  $Y^*$ , drawn from a binomial distribution with probability  $p = \{1 + \exp(-X\beta - Zu^*)\}^{-1}$
7. Re-fit the generalized linear mixed model in Step 1 to obtain  $B$  exposure response curves. Each curve provides a different predicted probability of the response as a function of the exposure.
8. For each unique exposure value, calculate the standard deviation of the predicted probability of the response, denoted  $\widehat{se}_B$ . For each unique exposure value, the pointwise upper and lower 95% confidence interval can be computed as  $\hat{p} \pm 1.96 \times \widehat{se}_B$ . Alternatively, one can choose the 97.5<sup>th</sup> and 2.5<sup>th</sup> percentile of the distribution of predicted probabilities for each unique exposure value as the pointwise 95% confidence bounds. This latter method, however, may require smoothing of the pointwise confidence bands.

We applied the above procedure using the 97.5<sup>th</sup> and 2.5<sup>th</sup> percentile of the distribution of predicted probabilities for each unique exposure value as the pointwise 95% confidence bounds to a random sub-sample of 12,145 live births between 2009 and 2010 from the Québec birth file, yielding the curves shown in Figure 1.

## References

1. Ruppert D, Wand M, and Carroll R. *Semi-parametric Regression*. New York: Cambridge University Press. 2003.
2. Wood SN. *Generalized Additive Models: An Introduction with R*. Chapman & Hall/CRC. 2006.
3. Wakefield J. *Bayesian and Frequentist Regression Methods*. Springer series in statistics, Springer. 2013.
4. Kauermann G, Claeskens G, and Opsomer JD. Bootstrapping for penalized spline regression. *J Comput Graph Stat*. 2009; **18**:126–146.

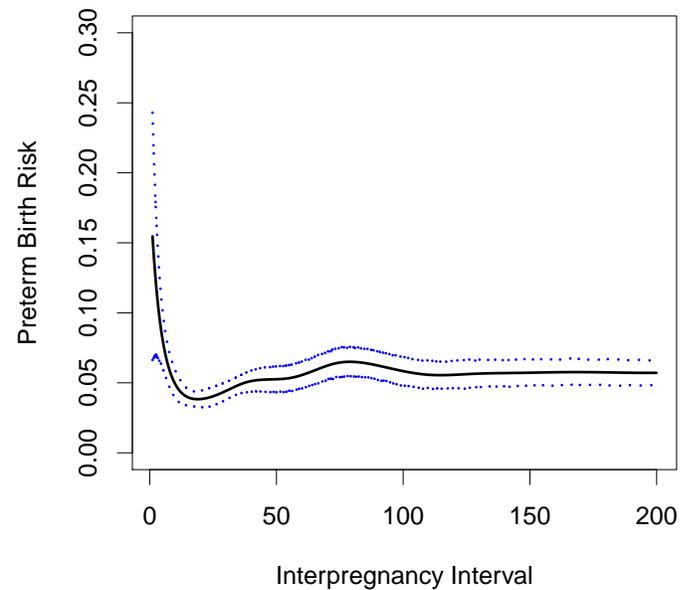


Figure 1: Exposure response curve and 95% pointwise bootstrap confidence bands for the relation between interpregnancy interval and the risk of preterm birth in 12,145 live births in Québec, Canada, 2009-2010.