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It′s About Time:

A Survival Approach to Gestational Weight Gain and Preterm Delivery

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Abstract

There is substantial interest in understanding the impact of gestational weight gain on preterm delivery (delivery <37 weeks). The major difficulty in analyzing the association between gestational weight gain and preterm delivery lies in their mutual dependence on gestational age, as weight naturally increases with increasing pregnancy duration. In this study, we untangle this inherent association by reframing preterm delivery as time to delivery and assessing the relationship through a survival framework, which is particularly amenable to dealing with time-dependent covariates, such as gestational weight gain. We derive the appropriate analytical model for assessing the relationship between weight gain and time to delivery when weight measurements at multiple time points are available. Since epidemiologic data may be limited to weight gain measurements taken at only a few time points or at delivery only, we conduct simulation studies to illustrate how several strategically timed measurements can yield unbiased risk estimates. Analysis of the study of successive small-for-gestational-age births demonstrates that a naive analysis that does not account for the confounding effect of time on gestational weight gain suggests a strong association between higher weight gain and later delivery (hazard ratio: 0.89, 95% confidence interval = 0.84, 0.93). Properly accounting for the confounding effect of time using a survival model, however, mitigates this bias (hazard ratio: 0.98, 95% confidence interval = 0.97, 1.00). These results emphasize the importance of considering the effect of gestational age on time-varying covariates during pregnancy, and the proposed methods offer a convenient mechanism to appropriately analyze such data.

Maternal weight gain is a potentially modifiable determinant of maternal and child health outcomes. Current Institute of Medicine recommendations concerning optimal weight gain are designed to minimize maternal and child risk of adverse short- and long-term outcomes.[1] However, available evidence surrounding the association between weight gain and preterm delivery, arguably one of the most important predictors of neonatal morbidity and mortality,[2] is critically lacking. Existing research surrounding this association is potentially biased due to methodologic challenges in dealing with the inherent correlation between pregnancy weight gain and length of gestation.

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Previous studies have reported a modest U-shaped relation between total gestational weight gain and preterm delivery, where both low and high weight gain are associated with increased risk.[1] As demonstrated by Hutcheon et al,[3] using a single measure of total weight gain at delivery can lead to a biased estimate of the risk of preterm, where low weight gain is ostensibly associated with increased risk, as women who delivered earlier had less time to gain weight. Some investigators have attempted to avoid this issue by calculating an average rate of weight gain or an adequacy ratio relative to the Institute of Medicine recommendations.[4–8] These methods, however, rely on additional assumptions concerning the weight gain trajectory and may not completely eliminate this potential source of bias.[3] One major issue with using a single measure of total weight gain as the exposure is that, among the women who deliver at term, some of the weight is gained after 37 weeks, when they are no longer at risk for preterm delivery.

We propose an alternative means to address the correlation between weight gain and gestational age at delivery by reframing the binary outcome of preterm (<37 vs. ≥37 weeks of gestation) as time to delivery (i.e., gestational age at delivery), and incorporating this semicontinuous outcome of interest into a survival framework. Studies of preterm delivery rarely use time-to-event analysis, despite its methodological advantages.[9–11] The survival approach has the additional advantage of discriminating week-specific delivery risk across the continuum of gestational age. This could prove particularly useful in light of recent research suggesting that neonatal morbidities are differential even within the “term” period, [12] reflecting important distinctions that would be missed under the dichotomous outcome of preterm delivery. Furthermore, survival models are compatible with repeated measurements and time-dependent exposures, such as gestational weight gain. By simulating nonlinear trajectories of weight gain during pregnancy, we evaluate the performance of this survival approach with time to delivery as the outcome of interest, and compare it with a binomial model of preterm delivery. In addition, we demonstrate that using repeated measures of gestational weight gain, instead of weight gain at delivery, can improve precision.

METHODS

When quantifying the association between a time-independent predictor, X, and preterm delivery, the following regression model may be applied, where preterm delivery is represented by a binary indicator, or equivalently, by gestational age at delivery (t) being less than 37 weeks:

$$g[\Pr(preterm \mid X)] = g[\Pr(t < 37 \mid X)] = \alpha + X\beta,$$

where g is the link function (e.g., log for Poisson regression, logit for logistic regression) and calculation of the risk or odds (e^{β}) associated with X is straightforward. Comparatively, when X is time-dependent and varies with gestational age, such as weight gain, bias can be induced if gestational age is not accounted for. Simple adjustment for gestational age at delivery when modeling preterm delivery as the outcome will result in numerical instability, since preterm delivery is a deterministic function of gestational age at delivery.[13,14] Even if convergence appears successful, the interpretation of the estimated risk can be misleading. Later, we return to this issue to discuss alternative measures to total gestational weight gain

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that can effectively eliminate this confounding effect of time. First, however, we propose an alternate and more powerful structure to assess the risk associated with gestational weight gain.

Survival Analysis

As an alternative to the binary outcome of preterm delivery, we propose application of the Cox proportional hazards model, where the outcome of interest is time to delivery. Survival models are naturally suited to incorporate the time-dependent nature of the outcome as well as any time-varying covariates. In addition, they are conducive to handling measurements of weight gain at multiple time points. Under a proportional hazards model:

$$\log h(t \mid X_t) = \log h_0(t) + X_t\beta,$$

where $h(t|X_t)$ represents the hazard of delivering at time t, given the value of the predictor X at time t, and $h_0(t)$ is the baseline hazard function, which captures the natural time course of the hazard of delivery. More details on the implementation of this method are provided in the section describing the simulation studies.

Binomial Regression

There may be circumstances in which the outcome of preterm delivery as a binary event, as opposed to time to delivery, remains of interest. While a survival model will estimate the instantaneous hazard of delivering at any given gestational week per one-unit increase in the exposure (e.g., 1 extra kilo of weight), a binomial model will estimate the risk of delivering before 37 weeks given a one-unit increase in the exposure. Although the risk of delivering preterm can be derived from the survival model, the binomial model can directly estimate the relative risk, so long as all exposure measurements included in the model occur before 37 weeks, when women are still at risk for preterm delivery. The following model can be fit:

$$\begin{aligned} g[\Pr(preterm \mid X)] &= g[\Pr(t < 37 \mid GWG_{GA})] \\ &= \alpha + (GWG_{GA})\beta + (GA)\gamma, \end{aligned}$$

where $\mathrm{GWG_{GA}}$ is the gestational weight gain recorded at gestational age GA. Note that under a proportional hazards model with a time-fixed covariate, the probability of delivering preterm is given by

$$\begin{aligned} p &= \Pr(t < 37 \mid X) = 1 - S(37 \mid X) = 1 - \exp(-H(37 \mid X)) \\ &= 1 - \exp(-\exp(\alpha + X\beta)), \end{aligned}$$

where S represents the survival function, and H the cumulative hazard. Thus, a binomial model with a complementary log–log link is directly comparable to the survival model, since estimates of β under this model are equivalent to the log-hazard ratio estimated under a survival model (see Ref. 15 for more details). This model can be extended to directly estimate the relative risk or odds ratio of preterm delivery using a log or logit link, respectively. In the following simulation studies, we compare hazard ratio estimates from a

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survival model on time to delivery with those from model (2) using the complementary log-log link and the binary outcome of preterm delivery.

Simulation Study

We performed a simulation study to compare the performance of the survival and binomial models in estimating the hazard ratio, as well as to determine the extent to which hazard ratio estimates are affected when only a limited number of weight measurements are available. To do this, nonlinear weight gain trajectories across gestation and time to delivery were simulated for 1,000 women. The dataset was then reduced to resemble more realistic scenarios of intermittent weight gain collection in cohort studies. These datasets were generated to resemble the study of successive small-for-gestational-age births described below. Gestational weight gain was generated to mimic minimal weight gain in the first trimester, followed by linear weight gain in the second and third trimesters.[1] While existing strategies to generate time-dependent covariates in a survival setting focus on binary predictors (such as treatment switching) or a known function of time (e.g., cumulative dose),[16–18] we explicitly incorporated a random component into the simulated weight gain trajectories to better resemble actual weight gain data.

After simulating gestational weight gain trajectories for each participant, we simulated time to delivery based on various levels of a prespecified hazard ratio. To do this, we generated the hazard of delivery at each week as a Weibull random variable with shape ν and scale = $\lambda\exp(X_t\beta)$, to mimic the nonconstant hazard of delivery, where

$$h\left(t \mid X_t\right) = \nu t^{\nu-1}\lambda\exp(X_t\beta)$$

The cumulative hazard at time T is then given by

$$\begin{aligned} H\left(T \mid X_t\right) &= \int_0^T h\left(t \mid X_t\right)\mathrm{dt} \\ &= \int_0^T \nu t^{\nu-1}\lambda\exp\left(X_t\beta\right)\mathrm{dt} \approx \sum_{j=1}^{k}\left(t_j^{\nu} - t_{j-1}^{\nu}\right)\lambda\exp\left(X_{t_{j-1}}\beta\right), \end{aligned}$$

where $T = t_k$ represents gestational age at time point k. This approximation to the integral is equivalent to a Riemann sum, where the time intervals $\left(t_j^{\nu} - t_{j-1}^{\nu}\right)$ can be arbitrarily small. In our study, we choose each time interval to represent 1 week of gestation. Next, the gestational age at delivery was selected based on inverse transform sampling, where U is generated from a uniform distribution between 0 and 1, and t is found by solving the equation $U = S(t) = \exp[-H(t)]$.[19] This simulation process was conducted for hazard ratios (i.e., e^{β}) of 0.7, 0.9, 1.0, 1.1, and 1.3, corresponding to a 1 kg increase of weight gain. The shape and scale parameters of the Weibull distribution were altered accordingly to maintain an expected preterm prevalence of 12%–13%. Each simulation scenario was repeated 5,000 times.

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Intermittent Visits

In most epidemiologic studies, it is rare to have weight measured at each week during pregnancy. To approximate a scenario where participants are observed at intermittent time points, the simulated dataset was reduced to contain weight gain measurements at four visits, randomly selected for each individual to coincide with a first (10 to 12 weeks), second (18 to 23 weeks), and third trimester visit (25 to 36 weeks), as well as weight recorded at delivery. For this simulation, the exact week of measurement for each woman was randomly selected to fall within the prespecified range, and weight at delivery was retained for each woman. Under this realistic scenario of intermittent weight gain measurements, one crucial step for appropriate estimation under the survival model is that weight gain must be linearly interpolated between the observed time points, to approximate weight gain at each week. If weight gain were not interpolated, the default model in most standard software packages (e.g., SAS and R) would treat the weight observed at each time point as being constant over the entire interval between measurements, and the resulting trajectory would resemble a step function. While any weight gain measurements before the first event or censoring time will not affect hazard ratio estimates, these values can inform the linear interpolation strategy, particularly if later weight gain measurements are unavailable.

In addition to assessing the performance of the survival model on intermittent time points, the binary regression model with complementary log–log link is also considered, where the outcome is preterm delivery (<37 weeks) and weight gain measurements after 37 weeks are excluded. Table 1 provides the average hazard ratio estimate, standard error, and coverage rates for each of these models.

The results of the simulations suggest that the survival model with interpolated gestational weight gain performs extremely well under various effect sizes, with no discernable bias and nominal coverage. This result implies that even when weight is measured only intermittently, an unbiased and precise hazard ratio estimate can be achieved. Since the success of this interpolation strategy depends on the approximate linear trajectory of weight gain between observed time points, adequate spacing of weight measurements can greatly improve estimation by providing a more precise representation of the weight gain trajectory.

If only one measurement of weight is available, the hazard ratio can still be effectively estimated using a binomial model with complementary log–log link, so long as weight is measured at a time point before 37 weeks for each woman. In general, estimates under these models are approximately unbiased, with close to nominal coverage. In particular, the model fit with the third trimester visit weight performs remarkably well, although this model does not achieve the level of precision of the survival model, which is able to incorporate weight gain measurements at multiple time points for each woman. Thus, the binomial model performance tends to improve with a weight measurement taken later in pregnancy. Thus, so long as weight gain is measured before 37 weeks, a binomial model adjusted for the gestational age at measurement can effectively untangle the inherent time dependency between weight gain and preterm delivery. This performance extends readily to log-linear models to directly estimate the relative risk.

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Total Weight Gain at Delivery

For this simulation, we reduce the dataset to include only the observation at the time of delivery, as is common in many cohorts or vital records data. These results illustrate the potential consequences of naively estimating the risk of preterm delivery using only total gestational weight gain, and help determine whether the proposed survival model can effectively mitigate the potential effect of time when weight gain is linearly interpolated at every gestational week. Since weight gain, and not total weight (where total weight = prepregnancy weight + weight gain), is the exposure of interest, weight gain at conception is assumed to be 0. Weight gain can then be interpolated assuming linear gain from conception until delivery. For this simulation, the binomial model with complementary log–log link is also fit to assess the potential bias of failing to account for the intrinsic correlation between total weight gain and preterm delivery. Results from these models are provided in Table 2.

The binomial model with complementary log–log link produces biased estimates of the true hazard ratio. Coverage is poor for this naive model, and the effect of higher weight gain appears to be protective when it is actually not (e.g., when HR = 1.1). Alternatively, when weight gain is interpolated in a survival model, risk estimates are close to the true hazard ratio. Even though the interpolated weight gain trajectory was misspecified by assuming a constant linear rate of weight gain instead of minimal gain in the first trimester, coverage is still fairly high, surpassing 86% in all scenarios. Thus, when only gestational weight gain at delivery is available, a linear interpolation of weight gain could still prove useful, particularly with respect to point estimation. Improvements on the standard error estimates (and subsequently, coverage) could be achieved by obtaining at least one additional time point, preferably around the end of the first trimester, when previous evidence suggests that the rate of weight gain is likely to change.

Application to Motivating Dataset

We applied these methods to the study of successive small-for-gestational-age births, a longitudinal cohort study of mothers in Norway and Sweden (1986–1988).[20] Women were eligible if they had parity of 1 or 2, were of Caucasian origin, spoke one of the Scandinavian languages, had a singleton gestation, and were <20 weeks gestation by enrollment (n = 561). All participants provided signed informed consent, and institutional review board approval was arranged at each participating hospital for primary and secondary hypotheses.

Antenatal study visits were targeted at 17, 25, 33, and 37 gestational weeks. Gestational age was calculated based on the first day of the last menstrual period and confirmed with ultrasound estimate.[20] At the first visit, women reported their prepregnancy weight and height. Subsequent weight measurements were extracted by study midwives based on personal health records of regular prenatal visits provided by the participants.

After removing any observations with missing data, the dataset contained information on 540 women, each of which had weight recorded at least 5, and up to 22 times, during gestation. The median time to delivery was 39 weeks, with 11% delivering preterm (<37 weeks). To determine whether gestational weight gain was associated with time to delivery, a survival model with interpolated weight gain values was fit. In addition, the hazard ratio

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from a binomial model with complementary log–log link was also estimated, where the most recent weight measurement before 37 weeks (between 30 and 36) was the main exposure, and the gestational age of that measurement was included as a covariate.

Hazard ratio estimates and 95% confidence intervals are given in Table 3. Based on these analyses, the survival model with interpolated weight gain suggests that a higher weight gain may have a weak protective association with time to delivery. Results from the binomial model concur with this inference, although, consistent with the simulation studies, the precision of this estimate is slightly lower.

To assess the hazard ratio estimates assuming that only weight gain at delivery was available, we fit a survival model with a linearly interpolated weight gain, as well as the naive binomial model with total weight gain at delivery as the predictor variable. These models disregard all weight measurements before delivery. Results from the survival model with interpolated weight gain using only weight measured at delivery (Table 3) are almost identical to the results when multiple weight measurements for each woman were included in the model. Both survival models suggest only a weak association between weight gain and time to delivery in this cohort.

Comparatively, the hazard ratio estimate under the naive binomial model implies a strong protective association with higher weight gain. This estimate corresponds almost exactly to those from the simulation results in Table 2, where, under a null effect, the binomial model based on total weight gain is biased downwards, estimating a risk of around 0.88 when the true hazard ratio is 1. The results from this example emphasize the importance of accounting for the confounding effect of time. As demonstrated in the simulation studies and reflected in the data analysis, not doing so could result in misleading inference, indicating a protective effect where none exists or, worse, in the presence of a harmful effect.

DISCUSSION

In this article, we have demonstrated an innovative survival approach to examine the association between gestational weight gain and time to delivery. We have demonstrated that hazard ratio estimates can be accurately and precisely estimated under a survival model with linear interpolation of weight gain, particularly when multiple intermittent time points are available for each participant. In addition, a binomial model with preterm delivery as the outcome can effectively estimate risk, as long as all exposure measurements are taken before 37 weeks, and adjusted for gestational age at measurement. Finally, in the scenario with only total weight gain at delivery, the survival model with interpolated weekly weight gain can supply valid point estimates, but coverage may not be ideal. While minimal weight gain data can provide reasonable point estimates, the findings of this article stress the benefit of allocating resources to collect strategically timed weight gain measurements to improve overall inference.

While modeling preterm delivery as a dichotomous outcome may facilitate interpretation, more precision can be gained by retaining the original scale of time to delivery. Since preterm is a direct dichotomization of this time-dependent variable, even the step of

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redefining time to delivery as preterm delivery ignores valuable information. If the goal is to directly estimate the relative risk as opposed to the hazard ratio, it is worth noting that when the outcome prevalence is small (~10%), these two values are approximately equivalent.[21] Thus, even when estimating the association between a time-fixed exposure and preterm delivery, retaining the original time-scale and fitting a survival model on time to delivery can improve precision, and translating the hazard ratio to the relative risk is straightforward.[22]

When longitudinal measurements on time-varying covariates are available, a survival analysis on time to delivery is arguably the optimal approach. While previous studies have successfully eliminated the confounding effect of gestational age by omitting weight gain measurements taken after 28 weeks,[23] the proposed survival model easily incorporates multiple measurements of weight gain, thus improving precision by retaining all available data up to delivery. In addition, survival models are more effective than the binomial model at handling truncation, competing risks, and censoring.[24–27] For instance, adjusting for left truncation when participants enter the study at later gestational ages is straightforward in a survival framework. In addition, competing risks to delivery, such as pregnancy loss, can be accounted for using existing methods in the survival framework. The binomial model, on the other hand, does not enjoy such flexibility.

Of note, the proposed methods are relevant to other time-varying exposures, such as maternal exercise or medication use. In addition, a quadratic version of weight gain or a spline regression could be tested to capture potential nonlinear associations with weight gain and earlier delivery. It is important to note, however, that Cox proportional hazards models can be susceptible to bias when predictors of the outcome are not included in the model. If this issue is a concern, parametric techniques such as accelerated failure time models can be employed, or more advanced causal mediation methods such as g-estimation or marginal structural models may be useful.[28–30]

In some cases, such as with vital records, only a single data point of total weight gain at delivery is available. In this situation, estimation of the association with time to delivery is possible, but care must be taken when interpreting the results. While a binomial model with preterm delivery as the outcome will give statistically biased estimates, the survival model with an interpolated weight gain can give reliable point estimates of the hazard ratio. Although coverage was not ideal under mis-specification of the weight gain trajectory, improvements could be made by applying a joint longitudinal and survival model, where weight gain values are approximated by individual level predictors.[31] The weight-gain-for-gestational-age z-score has been proposed as another means to estimate the association between total weight gain and preterm delivery.[3] However, the utility of this method relies on additional assumptions concerning the development of the reference z-score chart, and may not adequately mitigate the correlation between gestational age at delivery and weight gain when these assumptions are not met (Hinkle et al., unpublished, 2015).

As demonstrated in the simulations, obtaining multiple measurements on pregnant women will give the most precise estimates and avoid the potential difficulty of estimating a weight gain trajectory when gestational weight gain is measured only at delivery. Intermittent prenatal visits are common among pregnant women. Advances in data collection methods,

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such as electronic medical record abstraction and mobile-based data collection, can facilitate attainment of repeated measures during pregnancy. When only two measures are feasible, the optimal timing for measurements is at the expected change point in the rate of weight gain (around the end of the first trimester), and again late in pregnancy but before 37 weeks.

There is tremendous interest in understanding the impact of gestational weight gain on maternal and child health. While low weight gain has been associated with an increased risk for small-for-gestational-age birth weight and high weight gain with macrosomia and child obesity,[1] there is a substantial data gap related to preterm delivery, one of the most important outcomes. The methods demonstrated in this study have the potential to enhance studies of the relationship between weight gain and time to delivery with the ultimate goal of refining recommendations for gestational weight gain.

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TABLE 1.

Simulated HR When Gestational Weight Gain Is Measured at Intermittent Visits

True HR	Model	Predictors	Estimated HR	Standard Error	95% CI Coverage (%)
1.3	Survival	Intermittent visits[a]	1.30	0.02	94
	Binomial	1 st trimester[b]	1.29	0.08	95
		2nd trimester[c]	1.29	0.05	94
		3rd trimester[d]	1.30	0.04	95
1.1	Survival	Intermittent visits	1.10	0.01	95
	Binomial	1 st trimester	1.10	0.07	95
		2nd trimester	1.10	0.04	95
		3rd trimester	1.10	0.03	95
1.0	Survival	Intermittent visits	1.00	0.01	95
	Binomial	1 st trimester	1.00	0.06	95
		2nd trimester	1.00	0.04	95
		3rd trimester	1.00	0.03	95
0.9	Survival	Intermittent visits	0.90	0.01	95
	Binomial	1 st trimester	0.90	0.05	95
		2nd trimester	0.90	0.04	95
		3rd trimester	0.90	0.03	95
0.7	Survival	Intermittent visits	0.70	0.01	94
	Binomial	1 st trimester	0.73	0.05	91
		2nd trimester	0.72	0.04	90
		3rd trimester	0.71	0.03	93

[a]Four visits at 1st trimester, 2nd trimester, 3rd trimester, and delivery. Weight gain values are linearly interpolated between visits.

[b]Between 10 and 12 weeks.

[c]Between 18 and 23 weeks.

[d]Between 25 and 36 weeks.

HR indicates hazard ratio; 95% CI, 95% confidence interval.

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TABLE 2.

Simulated HRs When Gestational Weight Gain Is Measured at Delivery Only

True HR	Model	Estimated HR	Standard Error	95% CI Coverage (%)
1.3	Survival[a]	1.29	0.02	86
	Binomial[b]	1.13	0.04	1
1.1	Survival	1.09	0.01	87
	Binomial	0.94	0.03	0
1.0	Survival	0.99	0.01	90
	Binomial	0.88	0.02	0
0.9	Survival	0.89	0.01	91
	Binomial	0.81	0.02	1
0.7	Survival	0.70	0.01	95
	Binomial	0.68	0.02	86

[a]Weight gain linearly interpolated from baseline (weight gain = 0) to total weight gain at delivery.

[b]Total gestational weight gain as measured at delivery.

HR indicates hazard ratio; 95% CI, 95% confidence interval.

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TABLE 3.

Data Analyses When Gestational Weight Gain Is Measured at Intermittent Visits and at Delivery Only

Model	Predictor	Hazard Ratio (95% CI)
Survival	Weight gain at multiple visits[a]	0.98 (0.97, 1.00)
Binomial	Weight gain between 30 and 36 weeks	0.95 (0.89, 1.01)
Survival	Total gestational weight gain[b]	0.99 (0.97, 1.01)
Binomial	Total gestational weight gain[c]	0.89 (0.84, 0.93)

[a]Weight gain linearly interpolated between visits.

[b]Weight gain linearly interpolated from baseline (weight gain = 0) to total weight gain at delivery.

[c]Total gestational weight gain as measured at delivery.

95% CI indicates 95% confidence interval.