Big and Small, Early and Late:
A Family-Based Study of the Health Effects of Preterm Births and Birthweight

Ken R. Smith[1], Heidi A. Hanson[1], Stacey Knight[2], Karen Curtin[1],
Jeannette Carpenter[3], Benjamin D. Horne[2], and Michael W Varner[3]

[1]Population Sciences, Huntsman Cancer Center, University of Utah, Salt Lake City, Utah
[2]Intermountain Heart Institute, Intermountain Healthcare, Salt Lake City, Utah
[3]Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah

Abstract

The contribution of preterm birth and birthweight extremes to a child's health risks, ranging from infant mortality to later onset diseases in adulthood, has been examined extensively. The direct causal relationship between gestational age, birthweight, and later life health has been questioned because they may be measures of confounding factors that are related both to birth characteristics and to later life health. With a few exceptions, this large body of work does not consider the patterns of birthweight and preterm births within a family. Additionally, the subsequent parental health impacts of bearing low-birth weight or preterm children have not been examined as extensively. To further examine the hypotheses that prematurity and birthweight adversely affect children's and parent's risk of short- and long-term health outcomes and mortality, we adopt a family-based model where we (1) compare the health outcomes of siblings throughout the life course based on differences in their gestational age and birthweight and (2) examine how gestational age and birthweight of offspring alter mortality risks of the parents. In addition, we consider how a family pattern of longevity (as a measure of familial robustness) may modify the adverse later-life health effects of gestational age and birthweight among the offspring. Key outcomes for the offspring are: infant mortality, fertility, cancer incidence, cardiovascular disease, type 2 (T2) diabetes, and adult all-cause and cause-specific mortality. These hypotheses are tested using data from nearly 400,000 births identified in the Utah Population Database for children born from 1947-1969 who have been linked to subsequent medical records and have been organized into families and whose health fortunes have been examined up to 2012. We include, for a subset of the sample, additional and unique cardiovascular outcomes based on deep phenotyping of the offspring from a clinical cohort who underwent coronary catheterization. Our findings show that preterm births and low birth weight have distinctive adverse effects on survival and key diseases including cardiovascular and T2 diabetes when examined for the entire population and that these effects persist once shared family risks are considered. Work on the role of pre-term births on parental outcomes and the catheterization-based outcomes will be provided in the final version of the paper. Assessment of how early parental death and familial longevity are described in their potentially moderating effects of the adverse effects of preterm and low birth weight births.

Introduction

Birth weight is a major public health issue (1, 2) and the percentage of U.S. children born low BW in recent decades rose from 6.8% in 1980 to 8.2% in 2009 (3, 4). Birth weight is a potentially serious risk factor for adult risks of cardiovascular disease (CVD) and for some cancers. Health risks due to preterm birth are equally important with 5-10% of young people today being born preterm (5, 6). Processes that underlie these risks are complex because they involve competing influences (e.g., low BW increases CVD risk while high BW increases some cancer risks). It is therefore critical to obtain the best evidence about the role of BW and GA and their influence on adult CVD disease, cancer risks and overall adult survival.

What are the mechanisms that may account for these associations? Fetal Origins Hypothesis (FOH) predicts that fetuses adapting to an adverse in utero environment may change the development of key organ systems (7-9), changes that predispose the child to low BW and an increased risk of CVD, diabetes and stroke as an adult. Low BW is a crucial proxy for maternal nutrition that crosses the placenta that affects fetal growth (10) or as a marker of intrauterine conditions that led to low BW (11). Some conclude that altered vascular physiology associated with low BW is largely irreversible (12). Pre-term children also face a number of adverse health outcomes as older children (13, 14) and younger adults with respect to mortality (15) and hypertension (16); pre-term births have also been identified as having similar effects as low BW on insulin sensitivity among children (17). Certainly some have cautioned the use of using absolute birthweight per se and that may this may mislead us (18-20). We take this caution seriously as described later.

Cancer has also been shown to be affected by BW and GA (21). It has been suggested that low and high BWs are associated with adult obesity, supporting the prediction that these early traits affect adult BMI obesity as well as the risk of several major cancers (22). Several studies indicate a positive association between BW and adult cancer risk owing to estrogen exposure and insulin growth factors (23-27).

One of the challenges in assessing the impact of both BW and GA and their effects on adult health is obtaining large, representative, high-quality samples where BW and GA are measured prospectively. These samples then need to be linked to high quality data on adult disease and mortality. Studies using classic natural experiments, such as the Dutch WWII famine, are based on fairly small samples (N~2500) (28-31). A long-term study of Finns born in 1924-44 (32) used a larger sample with a longer follow-up but is based on births from one hospital. A useful study of a Swedish cohort (based on more (four) hospitals) with selective survival after preterm birth, showed fetal growth restriction was the only perinatal risk factor for ischemic heart disease (33). These and other studies show differing long-term

effects of BW and they illustrate the need to adopt optimal sampling and design strategies when testing the FOH.

The use of large cohorts with high quality measures of BW and GA as well as CVD, cancer incidence and mortality is critical. To better understand specific mechanisms affecting CVD and cancer, more detailed outcome measures are needed, such as arterial functioning and cancer histology. With respect to CVD, a recent review of the association between BW and the developing vascular tree (12) demonstrated how BW affects endothelial function, aortic intima–media, and arterial elasticity. These and other cardiovascular phenotypes are difficult to measure on entire populations but are nonetheless crucial to obtain in order to complement population-based studies and will allow us to better identify specific pre/post-natal risk factors for CVD. Similarly for cancer, data on tumor traits (e.g., histology, behavior and grade) will help us better understand how BW and GA affect cancer risk.

In this paper we test hypotheses that BW and GA have enduring effects on adult health and survival through the use of an extensive assessment of these exposures while controlling for other confounder. **Most importantly, we have data on 400,000 births comprising the Baby Boom generation and from which we are able to compare siblings where one is low birth weight/preterm and the other is not. Doing direct comparisons between these sets of sibling pairs allow for powerful estimates of the effects of low birth weight/preterm status on later life health.**

This study introduces several additional designs that are advances in the literature. The analysis relies on the very large data holdings of the Utah Population Database (UPDB). The UPDB is one of the world's richest sources of linked population-based information for demographic, genetic, and epidemiological studies. Most life span epidemiological studies examining health influences of BW and GA rely on relatively modest sample sizes, a serious limitation given this complex question. For the present study, we will use the Baby Boomer Cohort of over 400,000 births (and their parents) who are linked to their adult medical and mortality records. The UPDB is unique due to extensive record linking and quality control efforts conducted by experienced Pedigree and Population Resource (PPR) staff that maintain the database.

Do BW and GA have direct effects on adult health and survival or are they moderated by circumstances arising during the adult years? Detecting even moderate interactions with adequate statistical power requires large sample sizes with sufficient variation in the main-effects measures as well as on the joint frequency of specific combinations of values. The UPDB provides large samples subjects for assessing interactions between BW/GA and mid-life characteristics. We are especially interested in the role that parental survival may have on the adverse influences of being low birth weight/preterm birth.

Many life-course studies investigating health effects of early life factors rely on adults recalling childhood conditions. These are restricted to memories that are recallable but which are subject to recall bias (34-36). Also, only adults surviving to adulthood are available to recall early events, suggesting that survival bias is a threat to the representativeness of recalled early events (37-39). The UPDB is far less susceptible to memory bias and provides key data from objective sources. The UPDB is also based on entire birth cohorts so that the extent to which there is survival bias, the nature of the bias can be quantified.

For the entire Utah (or any) population, it is impossible to obtain detailed measures of specific biologic traits. Fortunately, several thousand subjects in an important a large cardiovascular health study in the CATH Lab of the Intermountain Heart Collaborative Study has been linked to the UPDB. This project holds very rich biomarker information on cardiovascular health.

Research Questions

This paper is a comprehensive examination of the morbidity and mortality effects of Birth Weight (BW) and Gestational Age (GA). The disease end points are the leading morbid and mortal conditions of middle-aged and elderly individuals that are hypothesized to be associated with BW and GA: cardiovascular disease (CVD), type 2 diabetes (T2D), and cancer. These hypotheses will be tested with archival data from a very large cohort of Baby-Boom generation children (born 1945-1969) and their parents identified from the UPDB. It is these individuals for whom we have BW and GA information for the entire cohort. A key subset of these individuals are nearly 5,000 members enrolled in the catheterization laboratory (CATH Lab) registry of the Intermountain Heart Collaborative Study established by Intermountain Healthcare, the largest health care provider in Utah. Studying the health outcomes of Baby Boomer children in particular is important because of their large effects on the health profile of an aging nation and the demands they place on the US health care system.

This study will advance our understanding of the long-term health consequences of BW and GA because of its novel and in-depth assessment of an entire population spanning several decades that rely on high-quality socio-demographic, family, medical, and vital records linked into large multi-generational pedigrees. The data backbone of this is Utah Population Database (UPDB), which includes data from the statewide vital records and the SEER Utah Cancer Registry, along with unique biomarker data linked to members of the CATH Lab registry of the Intermountain Heart Collaborative Study.

Our questions are:

1. Do low birth weight and/or preterm births from the Baby Boomer Generation at excess risk of all-cause and cause-specific mortality, particularly cardiovascular disease, cancer, and T2D?

2. Are these effects moderated by key familial characteristics including parental survival, parental age at birth, and a familial history of longevity?
3. Do these association between health outcomes and at-risk births persist when examined within the context of the family where the at-risk and the low-risk comparisons are between same sex siblings?
4. Are there biomarkers associated with excess risk of adult mortality that are related being a birth weight and/or preterm birth?
5. Do the birth weight and/or preterm births affect the survival of the parents?

Additional measures of key early-life and mid-life circumstances (ELCs and MLCs) drawn from information within UPDB, including data contained within Utah birth certificates, genealogies, and Utah death certificates. These include whether born a twin, early/late parental age, sibship size, birth order, parental survival, and parental SES. For those who link to CATH Lab enrollees, outcomes are (1) Intermountain Risk Score based on complete blood count and basic metabolic panel (2) personal medical history including episodes of all indicators of cardiovascular disease (3) coronary angiography results including the number of arteries narrowed, maximum stenosis in each artery, number of lesions, and degree of narrowing of each lesion (4) history of diabetes, hypertension, systolic blood pressure (BP), diastolic BP, hyperlipidemia, family history of early CAD and BMI.

Data and Analysis

The identification and construction of individuals comprising the Baby Boom and Parent cohorts is based on Utah birth certificates and important record linkages within the Utah Population Database. The UPDB comprises extensive record links of comprehensive medical, demographic and vital records. Linking vital and medical records to survey samples collected years earlier (40-42) or from birth certificates (as we propose here) (43) have been used to great success to study related questions. What is novel and advantageous here is the scope of the UPDB in terms of the coverage of individuals linked into families and the breadth of healthy data about them.

An individual identified within the UPDB is a member of the Baby Boomer Cohort if they meet all of the following criteria:

1. Appear as the newborn child on a Utah birth certificate. The inclusion of all births in Utah by the Utah Office of Vital Records makes this an ideal source for identifying a population-based defined cohort.

2. Born in the years from 1947 to 1969. Children born in these years span the baby boom generation which is defined for the U.S. as those born between 1945 and 1964. In Utah, the boom lasted

longer and therefore, we include those born as late as 1969. Persons born in 1969 are age 43 in 2012, our youngest baby-boomer subjects. Birth records in 1947 and later capture the first years that both BW and GA were recorded.

3. The focus of this study is to observe the adult health consequences of BW and GA. We therefore focus on outcomes after age 18 but also starting at birth.

4. For a birth certificate to contribute to this analysis, it must be connected to other records related to that same person. For birth certificates, links exist by definition between parents and the newly born child since both appear on the same document. Here, we require that at least another record link for the child exists so that other key variables to be analyzed are available within the UPDB.

Cox proportional and non-proportional hazard models are used to estimate the full population models. **Paired-rank models are fixed-effect (within-family) models that allow us to compare the hazards of mortality for members in sibling pairs to each other as an aggressive way to rule out confounds that might affect be associated with low birth weight and preterm births and subsequent mortality risks. These are used to examine all-cause mortality differences between sib pairs who differ in terms of their gestational age and birth weight status and for whom we have survival rank (who dies first) is known.**

Early Results

Table 1 shows descriptive statistics for the full sample for key variables. The population is approximately 410,000 individuals. For this extended abstract, we report pooled-gender analyses but will include sex-specific results in the final draft.

Figures 1-4 show smoothed Kaplan Meier the effects of birth weight and gestational status as a point of reference and to lay the ground work for understanding the mortality risks for these two characteristics. The curves are shown for all ages and for those who survive to age 18.

Tables 2-11 clearly demonstrate the strong association of low birth weight and preterm birth on all-cause mortality as well as CVD and diabetes related mortality. High birth weight shows suggestive risks for cancer mortality. These findings are not generally controversial and are consistent with the literature.

Tables 12-15 show an uneven pattern of how familial longevity may protect against the adverse effects of being a low birth weight and preterm birth.

When we apply the pair rank models on a set of informative brother pairs, we show that the at-risk brother (either pre-term or low birthweight) has significantly worse survival that the healthier sib:

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	-0.9547	0.1707	31.2868	<.0001
Difference in Gestational Age	1	-0.2869	0.0278	106.6318	<.0001

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	-0.2497	0.1168	4.5684	0.0326
Difference in Birthweight	1	-0.00125	0.000113	121.4845	<.0001

These early pair rank analysis results shown above reveal negative coefficients for both gestational age and birthweight. To the extent that brothers share a common family-specific hazard rate for mortality, these negative coefficients demonstrate that increases in both gestational age and birthweight, holding all common and shared family traits constant, are associated with significantly lower risks of mortality.

Conclusions

While more work remains for this analysis, we have shown that both at the full population level and among sib pairs, there appears to be clear evidence of a protective effect of increasing gestational age and birthweight with respect to survival and cause-specific mortality. Analyses of the CATH Lab phenotypes, additional study of the moderating effects of parental survival and familial excess longevity, and the effects of bearing at-risk children on parental survival will be added and extended beyond what is shown here.

The strength of this paper is its ability to leverage an entire Baby Boomer cohort starting from birth through to the present so as to (1) explore survival to midlife and into the early senior years (2) establish associations on a range of key health outcomes for this very large cohort and (3) use the family-based nature of the data to study informative sib pairs to rule out both known and unobserved heterogeneity that might alter the risk of both being a high-risk birth and subsequent mortality.

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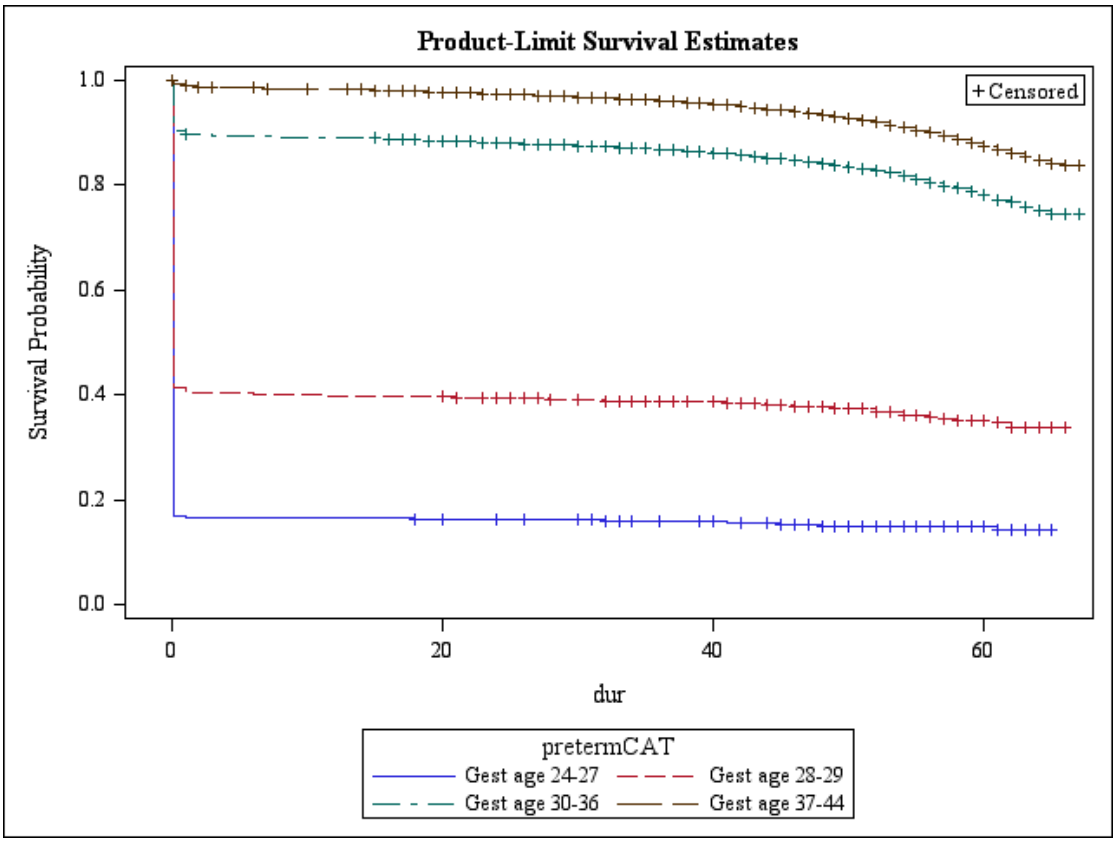
Table 1. Descriptive Statistics

Variable	Label	N	Mean	Std Dev	Minimum	Maximum
BWgtGrams	Birth weight grams	410222	3299.825	533.638	411.000	5981.000
GestAge	Gestational Age Weeks	388820	39.525	1.689	24.000	44.000
birthyr	Birth Year	410222	1958.292	6.307	1947.000	1969.000
male	1 if Male	410222	0.513	0.500	0.000	1.000
PaNPSES	NamPower SES	410222	52.112	19.969	2.000	99.000
sesmiss	1 if NP SES imputed	410222	0.217	0.412	0.000	1.000
MaAge	Mother age at birth	410222	26.972	6.069	15.000	50.000
PaAge	Father age at birth	410222	29.947	6.847	15.000	65.000
Multiplicity	Number births per pregnancy	410222	1.019	0.138	1.000	3.000
FEL	Familial Excess Longevity	330996	1.998	1.790	-15.010	20.660
padead	1 if Father dies when C<10 yo	410222	0.019	0.136	0.000	1.000
madead	1 if Mother dies when C<10 yo	410222	0.008	0.089	0.000	1.000

FIGURE 1. Kaplan Meier and Smoothed Hazard Curves by Gestational Age



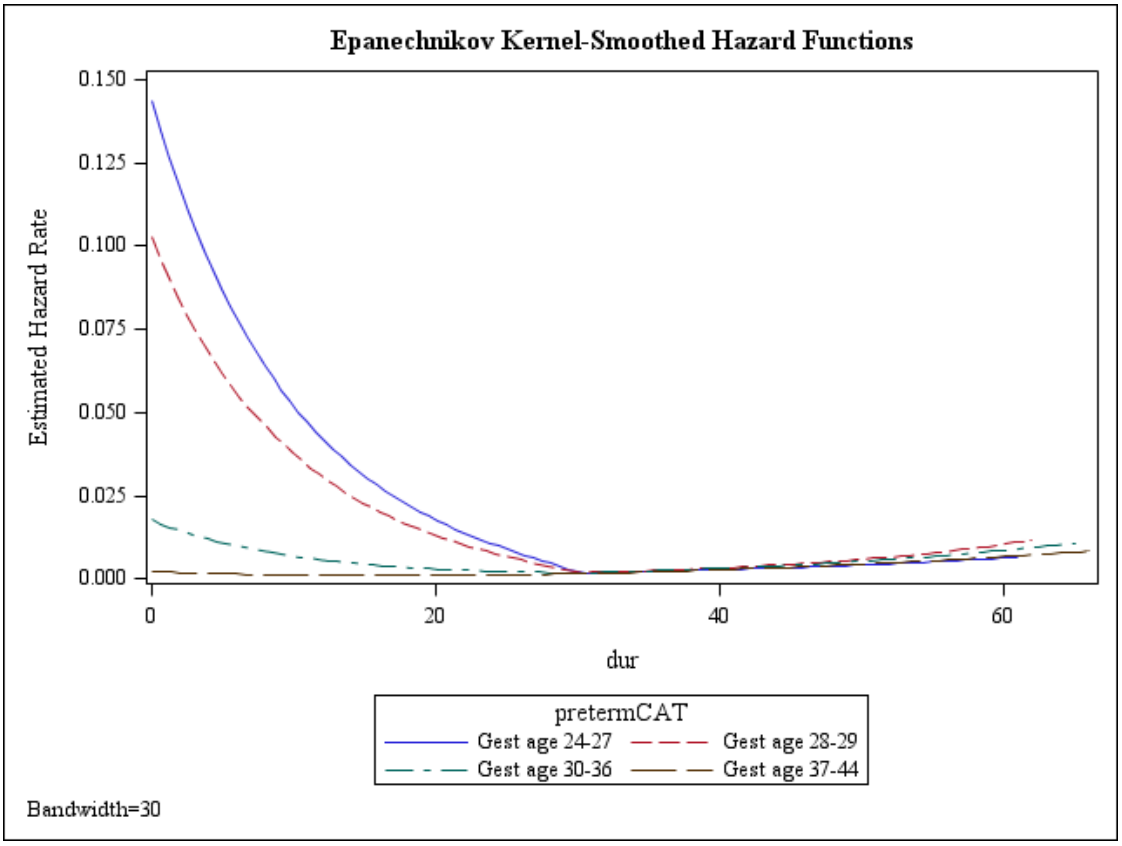
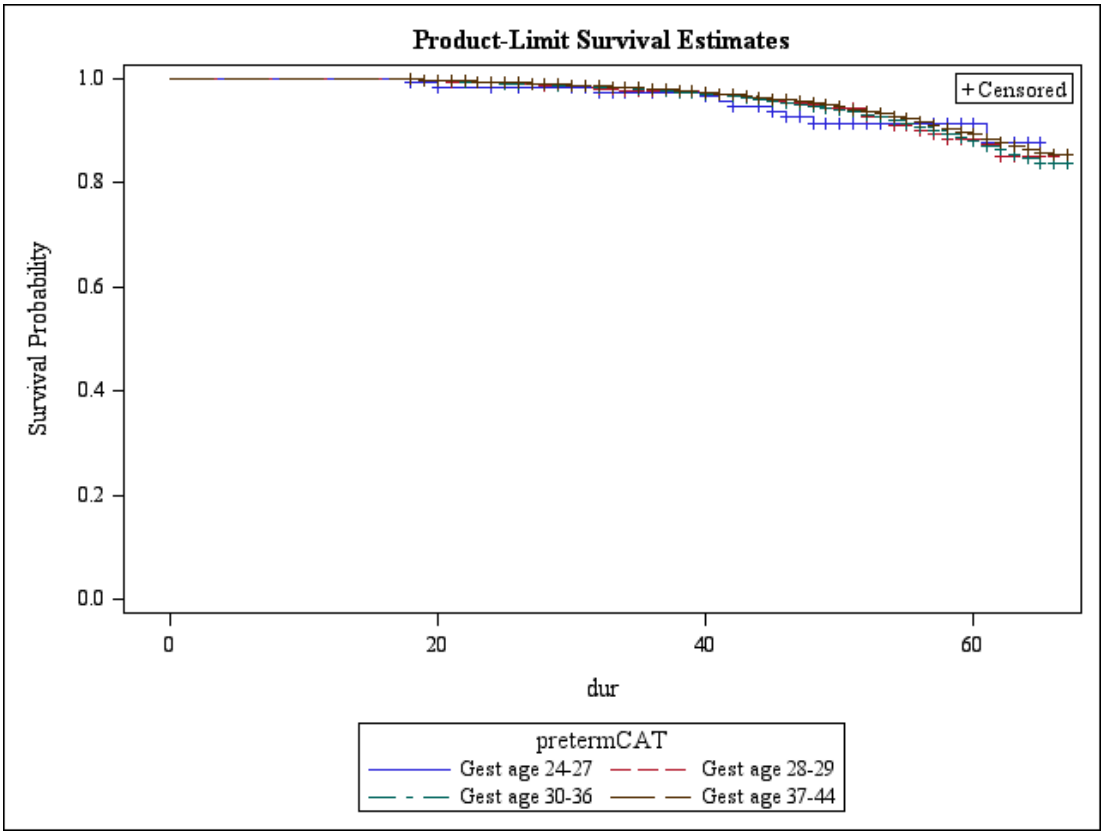


FIGURE 2. Kaplan Meier and Smoothed Hazard Curves by Gestational Age – Survived to Age 18



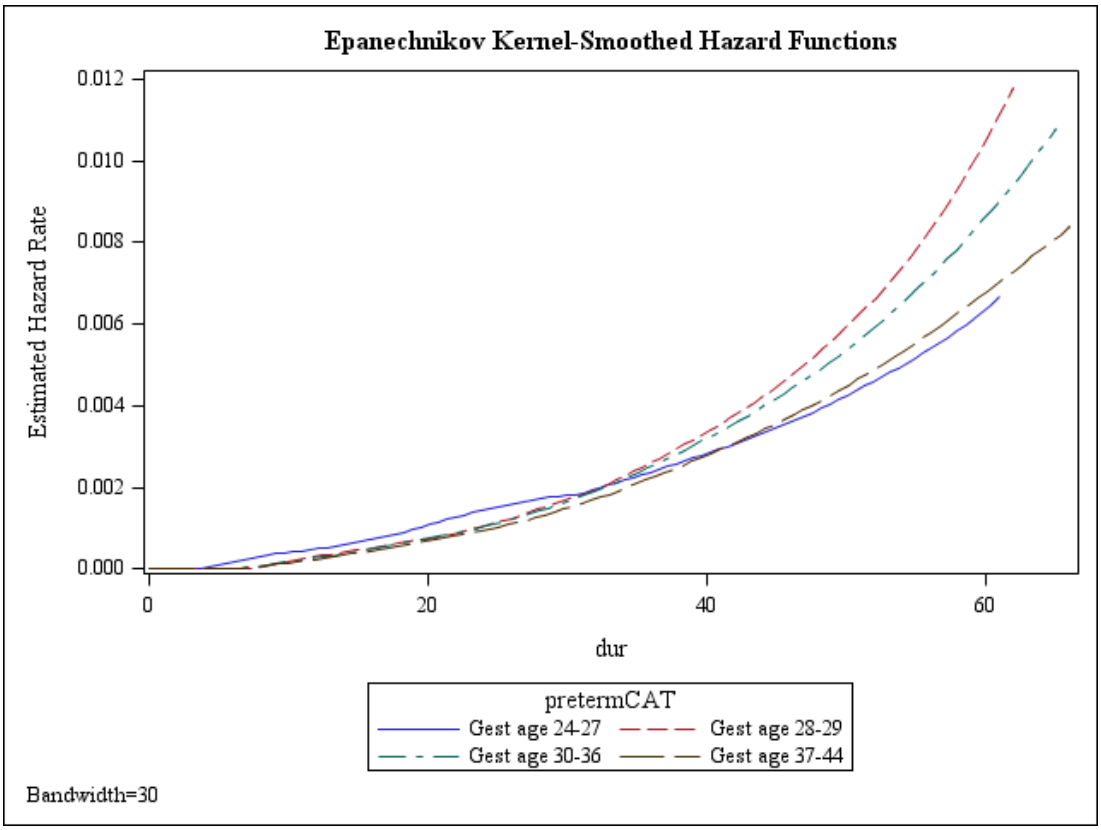
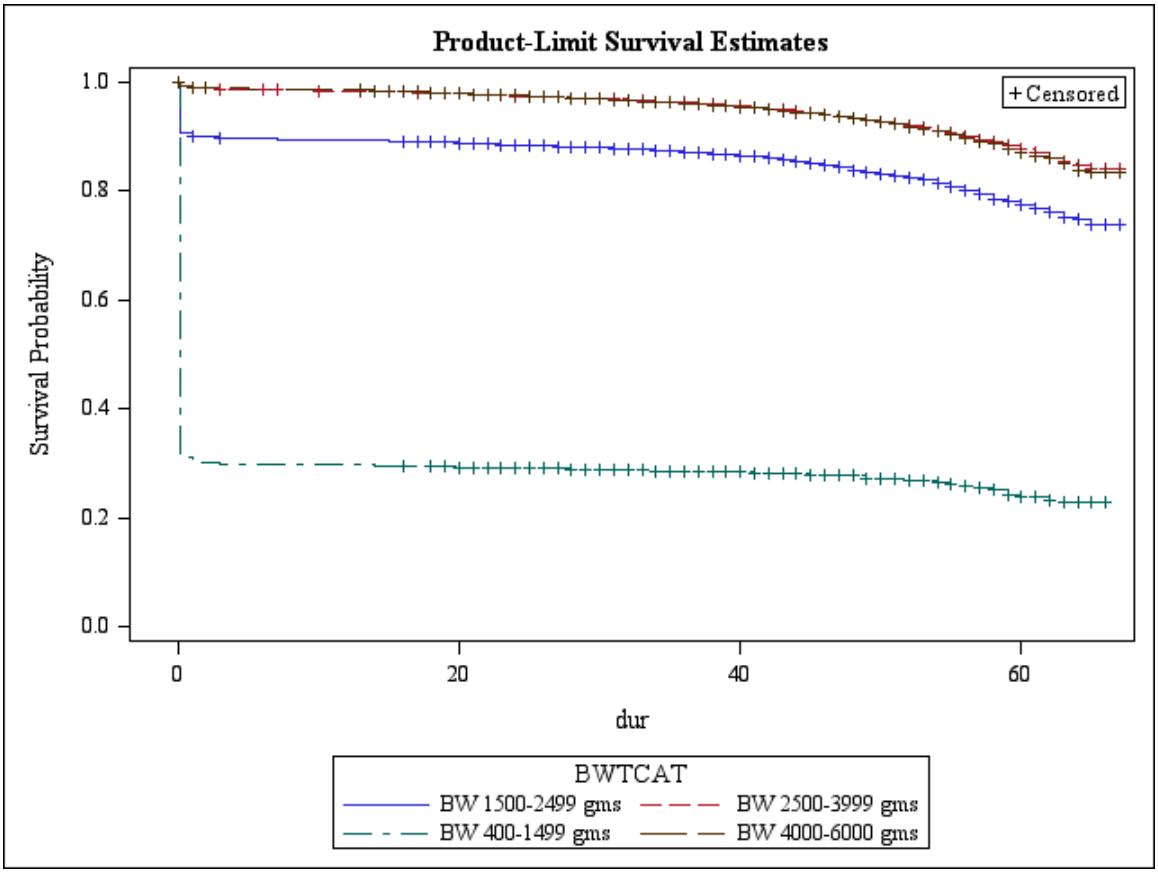


FIGURE 3. Kaplan Meier and Smoothed Hazard Curves by Birthweight



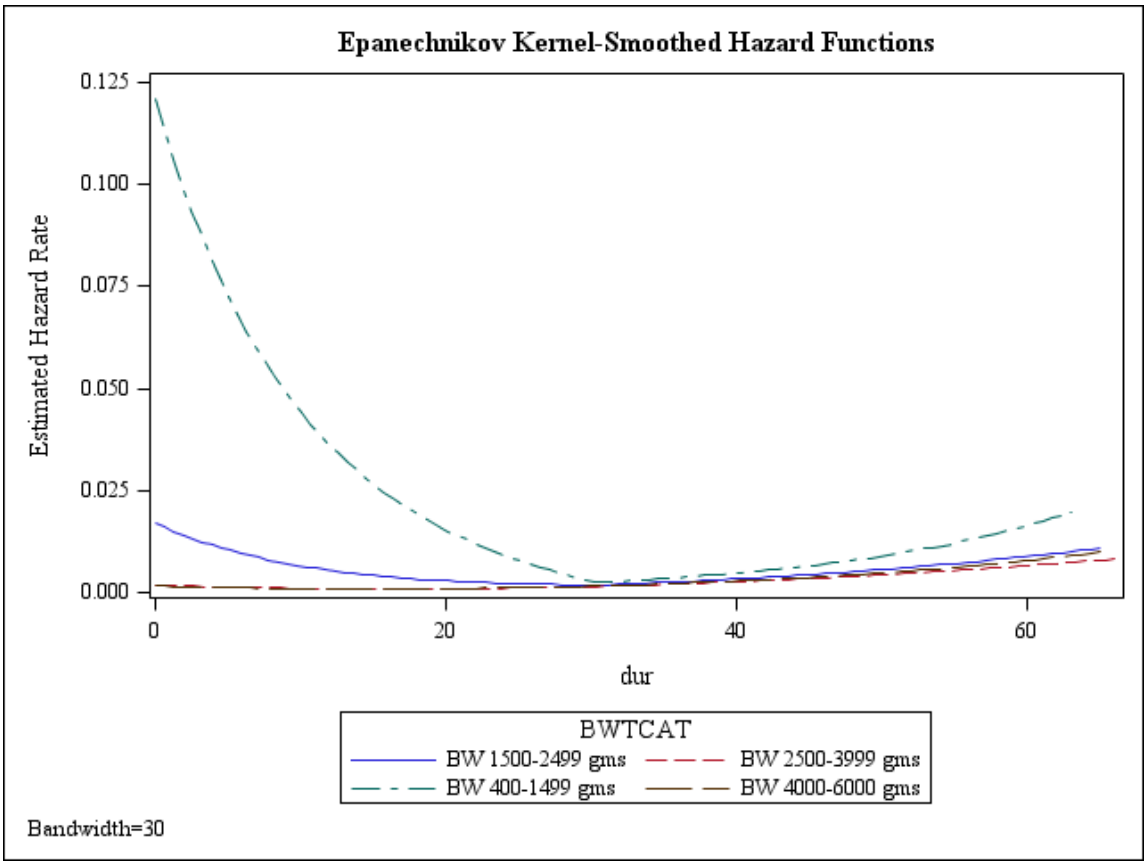
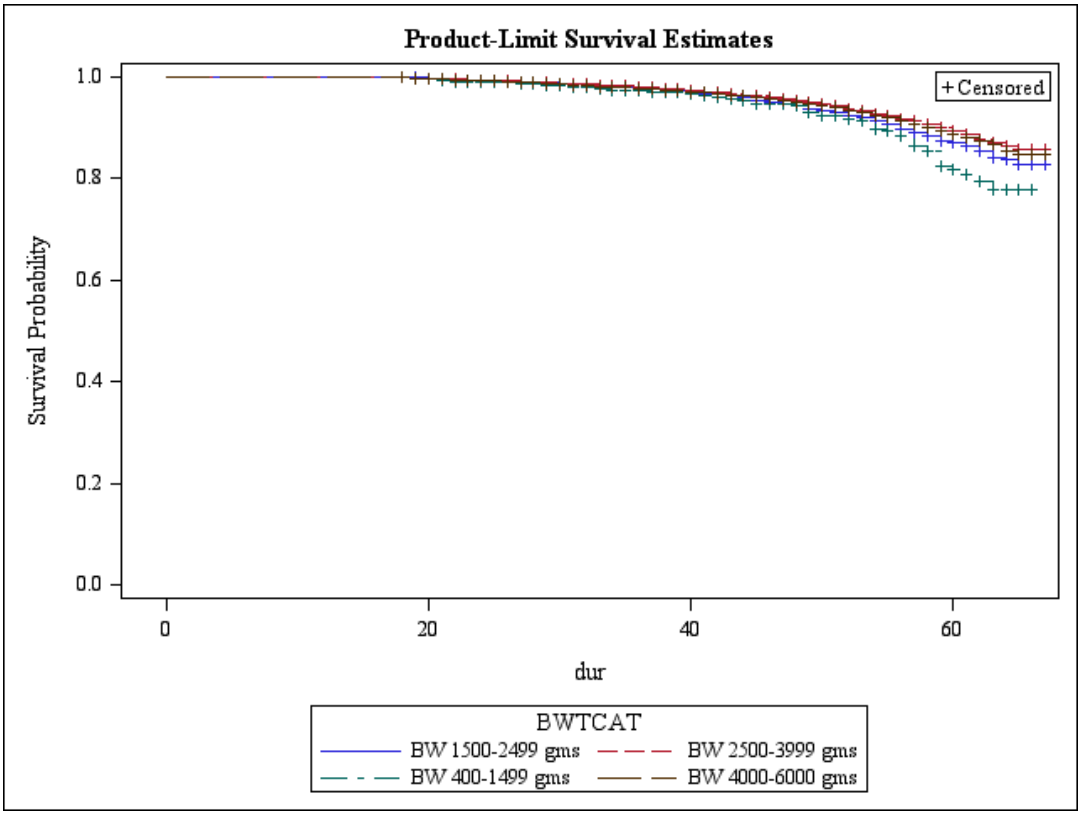


FIGURE 4. Kaplan Meier and Smoothed Hazard Curves by Birthweight, Survived to Age 18



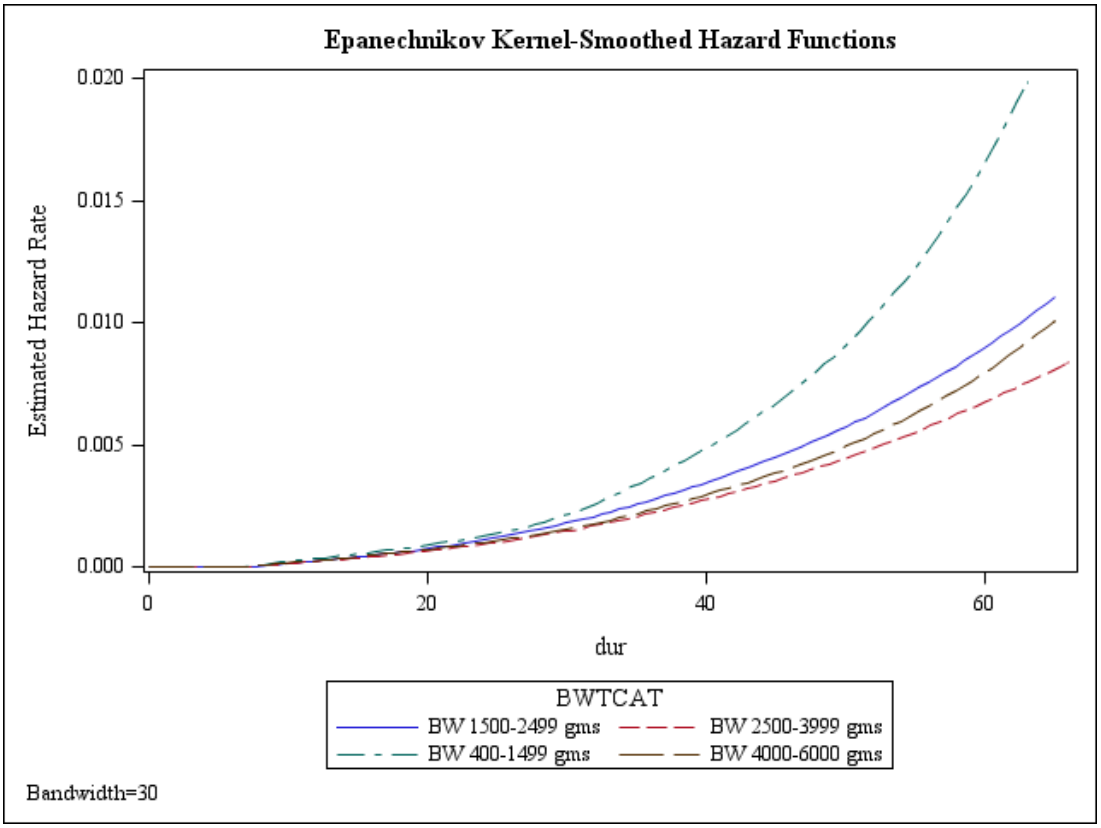


Table 2 - All Cause Mortality – Preterm Status

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
386952	32537	354415	91.59

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	803782.36	798008.70
AIC	803782.36	798024.70
SBC	803782.36	798091.82

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
preterm	1	1.02315	0.01783	1.084	3294.0055	<.0001	2.782	Gest age <37 weeks
birthyr	1	-0.00502	0.00111	1.029	20.4610	<.0001	0.995	Birth Year
male	1	0.50235	0.01174	1.017	1829.9558	<.0001	1.653	1 if Male
PaNPSES	1	-0.00436	0.0002922	1.025	222.5791	<.0001	0.996	NamPower SES
sesmiss	1	0.07038	0.01697	1.042	17.1957	<.0001	1.073	1 if NP SES imputed
MaAge	1	-0.01335	0.00190	1.090	49.5311	<.0001	0.987	Mother age at birth
PaAge	1	0.01245	0.00164	1.087	57.3719	<.0001	1.013	Father age at birth
Multiplicity	1	0.26592	0.03877	1.200	47.0571	<.0001	1.305	Number births per pregnancy

Table 3- All Cause Mortality – Preterm 2 categories

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
386952	32537	354415	91.59

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	803782.36	795269.97
AIC	803782.36	795287.97
SBC	803782.36	795363.48

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
pretermS	1	2.94370	0.04378	1.446	4520.9717	<.0001	18.986	Gest age 24-29 weeks
preterml	1	0.76113	0.01988	1.063	1465.5076	<.0001	2.141	Gest age 30-36 weeks
birthyr	1	-0.00476	0.00112	1.033	18.2084	<.0001	0.995	Birth Year
male	1	0.50326	0.01187	1.028	1798.4711	<.0001	1.654	1 if Male
PaNPSES	1	-0.00434	0.0002967	1.042	214.4162	<.0001	0.996	NamPower SES
sesmiss	1	0.06806	0.01703	1.047	15.9737	<.0001	1.070	1 if NP SES imputed
MaAge	1	-0.01330	0.00193	1.114	47.3670	<.0001	0.987	Mother age at birth
PaAge	1	0.01256	0.00168	1.116	55.7576	<.0001	1.013	Father age at birth
Multiplicity	1	0.22746	0.03845	1.188	34.9937	<.0001	1.255	Number births per pregnancy

Table 4. All Cause Mortality - Birthweight

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
408227	34345	373882	91.59

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	852043.26	843049.80
AIC	852043.26	843065.80
SBC	852043.26	843133.35

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
BWgtGrams	1	-0.0008009	0.0000131	1.331	3723.2127	<.0001	0.999	Birth weight grams
birthyr	1	-0.00648	0.00107	1.028	36.3664	<.0001	0.994	Birth Year
male	1	0.60497	0.01145	1.014	2793.5080	<.0001	1.831	1 if Male
PaNPSES	1	-0.00414	0.0002854	1.025	210.5152	<.0001	0.996	NamPower SES
sesmiss	1	0.07770	0.01619	1.035	23.0340	<.0001	1.081	1 if NP SES imputed
MaAge	1	-0.00847	0.00183	1.088	21.3588	<.0001	0.992	Mother age at birth
PaAge	1	0.01233	0.00159	1.086	60.0093	<.0001	1.012	Father age at birth
Multiplicity	1	-0.05001	0.03631	1.161	1.8970	0.1684	0.951	Number births per pregnancy

Table 5. All Cause Mortality - Very Low and Low BW

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
408227	34345	373882	91.59

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	852043.26	842208.63
AIC	852043.26	842224.63
SBC	852043.26	842292.19

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
vlbwcat	1	3.09678	0.03428	1.378	8162.2575	<.0001	22.127	BW 400-1500 gms
lbwcat	1	0.85703	0.01908	1.064	2018.0598	<.0001	2.356	BW 1500-2500 gms
birthyr	1	-0.00775	0.00109	1.041	50.8444	<.0001	0.992	Birth Year
PaNPSES	1	-0.00413	0.0002904	1.043	201.9700	<.0001	0.996	NamPower SES
sesmiss	1	0.07072	0.01642	1.052	18.5432	<.0001	1.073	1 if NP SES imputed
MaAge	1	-0.01236	0.00187	1.107	43.7199	<.0001	0.988	Mother age at birth
PaAge	1	0.01164	0.00163	1.103	51.3295	<.0001	1.012	Father age at birth
Multiplicity	1	-0.11736	0.03883	1.237	9.1330	0.0025	0.889	Number births per pregnancy

Table 6. CVD deaths - Preterm 2 categories

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
386952	2920	384032	99.25

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	70066.843	69646.409
AIC	70066.843	69664.409
SBC	70066.843	69718.223

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
pretermS	1	0.08494	0.44796	1.000	0.0360	0.8496	1.089	Gest age 24-29 weeks
preterml	1	0.23160	0.07698	1.021	9.0503	0.0026	1.261	Gest age 30-36 weeks
male	1	0.72485	0.04031	1.012	323.3472	<.0001	2.064	1 if Male
birthyr	1	-0.00407	0.00421	1.019	0.9343	0.3337	0.996	Birth Year
PaNPSES	1	-0.00583	0.0009085	0.969	41.1168	<.0001	0.994	NamPower SES
sesmiss	1	-0.06547	0.06229	1.008	1.1048	0.2932	0.937	1 if NP SES imputed
MaAge	1	-0.01389	0.00611	1.061	5.1700	0.0230	0.986	Mother age at birth
PaAge	1	0.01380	0.00532	1.063	6.7342	0.0095	1.014	Father age at birth
Multiplicity	1	0.10710	0.13322	1.021	0.6463	0.4214	1.113	Number births per pregnancy

Table 7. CVD deaths – Very Low and Low Birth Weight

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
408227	3041	405186	99.26

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	73214.344	72756.056
AIC	73214.344	72774.056
SBC	73214.344	72828.235

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
lbwcat	1	0.33258	0.07768	1.040	18.3302	<.0001	1.395	BW 1500-2500 gms
vlbwcat	1	1.07906	0.24899	0.988	18.7810	<.0001	2.942	BW 400-1500 gms
male	1	0.73686	0.03949	1.010	348.1779	<.0001	2.089	1 if Male
birthyr	1	-0.00509	0.00409	1.016	1.5542	0.2125	0.995	Birth Year
PaNPSES	1	-0.00568	0.0008941	0.970	40.3471	<.0001	0.994	NamPower SES
sesmiss	1	-0.04333	0.05994	1.007	0.5226	0.4697	0.958	1 if NP SES imputed
MaAge	1	-0.01074	0.00595	1.056	3.2545	0.0712	0.989	Mother age at birth
PaAge	1	0.01176	0.00521	1.059	5.1079	0.0238	1.012	Father age at birth
Multiplicity	1	-0.04264	0.13666	1.031	0.0973	0.7551	0.958	Number births per pregnancy

Table 8. Cancer deaths- Preterm 2 categories

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
386952	4282	382670	98.89

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	103450.74	103397.10
AIC	103450.74	103415.10
SBC	103450.74	103472.36

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
pretermS	1	0.03447	0.37748	0.998	0.0083	0.9272	1.035	Gest age 24-29 weeks
preterml	1	-0.05988	0.07151	1.001	0.7010	0.4024	0.942	Gest age 30-36 weeks
male	1	-0.03452	0.03063	1.002	1.2698	0.2598	0.966	1 if Male
birthyr	1	-0.02077	0.00329	1.001	39.7761	<.0001	0.979	Birth Year
PaNPSES	1	-0.0008706	0.0007607	0.998	1.3098	0.2524	0.999	NamPower SES
sesmiss	1	-0.01965	0.05073	1.012	0.1500	0.6985	0.981	1 if NP SES imputed
MaAge	1	-0.00434	0.00488	1.019	0.7905	0.3740	0.996	Mother age at birth
PaAge	1	0.00746	0.00427	1.016	3.0473	0.0809	1.007	Father age at birth
Multiplicity	1	-0.02999	0.11704	0.998	0.0657	0.7978	0.970	Number births per pregnancy

Table 9. Cancer deaths - Very Low and Low Birth Weight

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
408227	4447	403780	98.91

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	107809.84	107754.79
AIC	107809.84	107774.79
SBC	107809.84	107838.79

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
lbwcat	1	0.05457	0.06836	0.996	0.6374	0.4247	1.056	BW 1500-2500 gms
vlbwcat	1	-0.06762	0.35562	1.003	0.0362	0.8492	0.935	BW 400-1500 gms
hbwcat	1	0.09653	0.05508	1.004	3.0710	0.0797	1.101	BW >4000 gms
male	1	-0.03128	0.03027	1.005	1.0676	0.3015	0.969	1 if Male
birthyr	1	-0.02002	0.00322	1.003	38.7454	<.0001	0.980	Birth Year
PaNPSES	1	-0.0005531	0.0007494	1.000	0.5447	0.4605	0.999	NamPower SES
sesmiss	1	-0.02595	0.04926	1.011	0.2776	0.5983	0.974	1 if NP SES imputed
MaAge	1	-0.00449	0.00482	1.025	0.8684	0.3514	0.996	Mother age at birth
PaAge	1	0.00682	0.00422	1.022	2.6118	0.1061	1.007	Father age at birth
Multiplicity	1	-0.03957	0.11588	0.991	0.1166	0.7327	0.961	Number births per pregnancy

Table 10. Endocrine-diabetes deaths - Preterm 2 categories

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
386952	1084	385868	99.72

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	26264.580	26203.858
AIC	26264.580	26221.858
SBC	26264.580	26266.754

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
pretermS	1	1.42422	0.38117	1.004	13.9607	0.0002	4.155	Gest age 24-29 weeks
preterml	1	0.23004	0.12670	1.003	3.2964	0.0694	1.259	Gest age 30-36 weeks
male	1	0.28187	0.06199	1.006	20.6779	<.0001	1.326	1 if Male
birthyr	1	0.01029	0.00652	1.016	2.4922	0.1144	1.010	Birth Year
PaNPSES	1	-0.00673	0.00161	1.036	17.3631	<.0001	0.993	NamPower SES
sesmiss	1	0.04163	0.09554	1.024	0.1899	0.6630	1.043	1 if NP SES imputed
MaAge	1	-0.01077	0.00977	1.045	1.2143	0.2705	0.989	Mother age at birth
PaAge	1	0.01841	0.00873	1.080	4.4426	0.0351	1.019	Father age at birth
Multiplicity	1	-0.03214	0.22520	0.997	0.0204	0.8865	0.968	Number births per pregnancy

Table 11. Endocrine-diabetes deaths - Very Low and Low Birth Weight

Summary of the Number of Event and Censored Values			
Total	Event	Censored	Percent Censored
408227	1130	407097	99.72

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	27481.415	27388.760
AIC	27481.415	27408.760
SBC	27481.415	27459.060

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
lbwcat	1	0.58767	0.11611	1.047	25.6176	<.0001	1.800	BW 1500-2500 gms
vlbwcat	1	1.67593	0.37668	1.234	19.7952	<.0001	5.344	BW 400-1500 gms
hbwcat	1	0.11902	0.10831	1.011	1.2074	0.2718	1.126	BW >4000 gms
male	1	0.29526	0.06138	1.012	23.1416	<.0001	1.343	1 if Male
birthyr	1	0.01032	0.00635	1.014	2.6396	0.1042	1.010	Birth Year
PaNPSES	1	-0.00658	0.00158	1.034	17.3018	<.0001	0.993	NamPower SES
sesmiss	1	0.02606	0.09301	1.025	0.0785	0.7793	1.026	1 if NP SES imputed
MaAge	1	-0.01068	0.00950	1.037	1.2625	0.2612	0.989	Mother age at birth
PaAge	1	0.01722	0.00855	1.078	4.0584	0.0440	1.017	Father age at birth
Multiplicity	1	-0.31857	0.23750	1.031	1.7993	0.1798	0.727	Number births per pregnancy

Table 12. All Cause Mortality - FEL x Preterm

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
386952	32537	354415	91.59

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	803782.36	797480.42
AIC	803782.36	797500.42
SBC	803782.36	797584.32

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
preterm	1	1.05625	0.02356	1.103	2010.6680	<.0001	2.876	Gest age <37 weeks
birthyr	1	-0.00708	0.00111	1.029	40.3776	<.0001	0.993	Birth Year
male	1	0.50173	0.01174	1.017	1826.7437	<.0001	1.652	1 if Male
PaNPSES	1	-0.00391	0.0002926	1.023	178.0944	<.0001	0.996	NamPower SES
sesmiss	1	0.08094	0.01698	1.042	22.7209	<.0001	1.084	1 if NP SES imputed
MaAge	1	-0.01113	0.00188	1.084	34.9961	<.0001	0.989	Mother age at birth
PaAge	1	0.01202	0.00163	1.079	54.6006	<.0001	1.012	Father age at birth
Multiplicity	1	0.26387	0.03882	1.203	46.1899	<.0001	1.302	Number births per pregnancy
fellow	1	0.27219	0.01273	1.045	457.5031	<.0001	1.313	Low FEL
pretermfellow	1	-0.08300	0.03622	1.107	5.2519	0.0219	0.920	Interaction Between Low Fel and Gest Age

Table 13. All Cause Mortality - FEL x Preterm - 18+

Summary of the Number of Event and Censored Values					
Stratum	**male**	**Total**	**Event**	**Censored**	**Percent Censored**
1	Female	162930	7905	155025	95.15
2	Male	175286	14953	160333	91.47
Total		338216	22858	315358	93.24

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	525616.68	524661.93
AIC	525616.68	524679.93
SBC	525616.68	524752.26

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
preterm	1	0.05589	0.03947	1.009	2.0049	0.1568	1.057	Gest age <37 weeks
birthyr	1	0.00187	0.00137	1.000	1.8589	0.1728	1.002	Birth Year
PaNPSES	1	-0.00404	0.0003407	1.011	140.9250	<.0001	0.996	NamPower SES
sesmiss	1	-0.03368	0.02077	1.004	2.6297	0.1049	0.967	1 if NP SES imputed
MaAge	1	-0.01222	0.00221	1.072	30.4675	<.0001	0.988	Mother age at birth
PaAge	1	0.01346	0.00192	1.070	49.3828	<.0001	1.014	Father age at birth
Multiplicity	1	-0.01757	0.05149	1.022	0.1164	0.7329	0.983	Number births per pregnancy
fellow	1	0.34400	0.01451	1.046	562.0044	<.0001	1.411	Low FEL
pretermfellow	1	0.09616	0.05763	1.010	2.7841	0.0952	1.101	Interaction Between Low Fel and Gest Age

Table 14. All Cause Mortality - FEL x Birthweight

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
329389	27391	301998	91.68

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	668423.21	661166.00
AIC	668423.21	661186.00
SBC	668423.21	661268.18

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
BWgtgramsc	1	-0.0007986	0.0000148	1.337	2904.7120	<.0001	0.999	
birthyr	1	-0.00848	0.00120	1.024	49.6718	<.0001	0.992	Birth Year
male	1	0.59587	0.01281	1.014	2164.8055	<.0001	1.815	1 if Male
PaNPSES	1	-0.00335	0.0003156	1.021	112.4111	<.0001	0.997	NamPower SES
sesmiss	1	0.08694	0.01862	1.035	21.7941	<.0001	1.091	1 if NP SES imputed
MaAge	1	-0.00648	0.00202	1.079	10.2991	0.0013	0.994	Mother age at birth
PaAge	1	0.01210	0.00176	1.079	47.2937	<.0001	1.012	Father age at birth
Multiplicity	1	-0.04313	0.04025	1.157	1.1482	0.2839	0.958	Number births per pregnancy
felc	1	-0.04553	0.00344	1.100	175.0787	<.0001	0.955	Low FEL
bwtfel	1	-0.0000235	6.58526E-6	1.294	12.7421	0.0004	1.000	Interaction Between Low Fel and Birthweight

Table 15. All Cause Mortality - FEL x BW - 18+

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
289008	18945	270063	93.44

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	455655.59	453713.43
AIC	455655.59	453733.43
SBC	455655.59	453811.92

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**StdErr Ratio**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**Label**
BWgtgramsc	1	-0.0001181	0.0000156	1.050	57.5069	<.0001	1.000	
birthyr	1	0.00215	0.00151	1.001	2.0317	0.1540	1.002	Birth Year
male	1	0.59045	0.01552	1.009	1447.1361	<.0001	1.805	1 if Male
PaNPSES	1	-0.00342	0.0003702	1.009	85.2191	<.0001	0.997	NamPower SES
sesmiss	1	-0.05573	0.02341	1.004	5.6687	0.0173	0.946	1 if NP SES imputed
MaAge	1	-0.01225	0.00241	1.071	25.8140	<.0001	0.988	Mother age at birth
PaAge	1	0.01434	0.00210	1.075	46.4885	<.0001	1.014	Father age at birth
Multiplicity	1	-0.09218	0.05698	1.023	2.6172	0.1057	0.912	Number births per pregnancy
felc	1	-0.05245	0.00372	1.070	198.4320	<.0001	0.949	Low FEL
bwtfel	1	-2.6487E-6	6.81493E-6	1.043	0.1511	0.6975	1.000	Interaction Between Low Fel and Birthweight