**Title of proposed project: Exposure of Maternal Gestational Diabetes on Time to Obesity in the Exploring Perinatal Outcomes among Children (EPOCH) Study**

**Name & affiliation: Sarah Bird, Department of Biostatistics and Informatics + LEAD Center**

1. Which of the following most closely aligns with your affiliation to the LEAD center?
   * LEAD trainee (Graduate student)
2. What services are you requesting
   * Data
3. Do you have funding to support this request?
   * No, this is for a class project
     + - 1. **Background (**<1 page):

In the United States, the rates of obesity have been steadily rising, including among the population of children and prepregnant women1. This increase in obesity has been accompanied by a growing prevalence of diabetes, both of which are now being diagnosed at increasingly younger ages2,3. Researchers are becoming more interested in investigating the physiological, biological, and sociological factors that contribute to this concerning surge in childhood obesity. Recent studies have been exploring these factors which include 1) physiological factors (such as genetics, basal metabolic rate, exposure to diseases), 2) socio-economic influences (like access to affordable, healthy food), 3) physical activity levels (including time spent being physically active and sedentary), and 4) dietary habits (such as portion size, intake of sugary beverages and fast food)4. One avenue of particular interest is the relationship between exposure to gestational diabetes in utero and the development of obesity during puberty.

Previous studies have linked exposure to gestational diabetes during intrauterine life with increased fetal growth, adiposity, fetal overnutrition, increased offspring body mass, and risk for overweight or obesity5–7. However, to our knowledge, there are no studies that examine for a potential association between exposure of gestational diabetes and the time it takes for an individual to become overweight or obese. This study aims to leverage survival data analysis to explore the relationship between exposure in utero to gestational diabetes and time to obesity and overweight.

* + - * 1. **Biological plausibility (1/2 page):**
* This can be drawn out as a diagram showing mechanistic pathways, or could be a brief text description.

There is an increase in the prevalence of diabetes across the United States. Obesity is trending to occur much earlier in life, which points to a shift in the environment that could lend to this increase in childhood obesity that is being observed. Gestational diabetes has been associated with increased fetal adiposity, growth, and overnutrition in prior studies8,9. Because of this, it is plausible to believe that exposure to gestational diabetes could have implications for higher overall trajectories of BMI across childhood, specifically time to becoming overweight or obese.

* + - * 1. **Specific Aims (1/2 page):**
* List specific aims and hypotheses

Aim 1: Evaluate the relationship between time to obesity and exposure to gestational diabetes.

Hypothesis: Children who have been exposed to gestational diabetes during pregnancy will have a higher hazard of becoming obese.

Aim 2: Evaluate the relationship between time to becoming overweight and exposure to gestational diabetes.

Hypothesis: Children who have been exposed to gestational diabetes during pregnancy will have a higher hazard of becoming overweight.

* + - * 1. **Conceptual models (no page limit):**

**A diagram of a diagram

Description automatically generated**

A conceptual model is presented in the above image. Note: there are two aims. The same conceptual model is used for both aims.

* + - * 1. **Approach**

**Study sample**

* Include exclusion criteria.
  + Inclusion Criteria: All participants who have present BMI data will be included in the analysis

**Variables of interest**

**Exposure:** Exposure to gestational diabetes in utero

Variable in Data: DMExposureC (I figured I would use the clinical classification for exposure instead of self-reported?)

**Outcome(s):**

The outcome is time to obesity for the first aim, and time to becoming overweight for the secondary hypothesis. I will create the obesity and overweight covariates using the following methods:

* Both outcomes will be generated using the CDC growth charts. The methods are as follows:
  + Obesity will be classified as a BMI of >= 95th percentile
  + Overweight will be classified as a BMI of >= 85th percentile and < 95th percentile
  + Reference: <https://www.cdc.gov/bmi/child-teen-calculator/bmi-categories.html>

**Variables in data:**

* BMIPCT at Epoch 1 Visit: Unit = percentile
* BMIPCT at Epoch 2 Visit: Unit = percentile
* mra\_weightkgX: X indicates the specific MRA visit, Unit = kg
* mra\_heightcmX: X indicates the specific MRA visit, Unit = cm
* mra\_visit\_dateX: X indicates the specific MRA visit, Unit = date
* DOB: Participant DOB so I can calculate age at MRA visit, Unit = date

**Covariates(s):**

* List the covariates of interest (this includes potential confounders, mediators, and effect modifiers), how they were assessed, units, and the actual name of the variables in the codebook.

I am primarily interested in adjusting for potential sociodemographic covariates. I am also interested in potentially stratifying the analysis by sex. That will be an analysis choice made after evaluating assumptions of the proportional hazards model.

Possible stratification variables:

* Child\_sex (M/F): Sex of the child assigned at birth

Potential covariates:

* FH33 OR FH34: (categorical, 6 levels that characterize household income at birth and income at visit)
* FH28 OR FH29: (categorical, 16 levels that characterize education of parents at child’s birth)
  + If I use this in the analysis, I will obviously have to collapse some of these levels

**Data analysis (**no page limit**):**

**Data Cleaning**

I plan to not perform any univariate analyses to assess the distributions. I plan on creating the two derived outcome variables: time to obesity and time to overweight. I plan on visualizing the data with histograms to check distributions and make sure no major outliers are present within the data. I also plan on generating summary statistics in a report form to further investigate the distributions of the data. I will be performing a complete case analysis—no imputation will be performed.

**Data Analysis**

Kaplan Meier curves will also be generated to visualize the survival curves of the exposed and unexposed populations as a descriptive. A cox proportional hazards model will be used to investigate both aims. The main predictor to be assessed will be exposure to gestational diabetes during pregnancy. A Wald test will be conducted to assess a difference in the hazards at an level. Sociodemographic features will be selected for inclusion into the model based on domain knowledge and constructive feedback from this proposal document.

The assumption of the proportionality of hazards will be assessed through multiple checks. First, log-log and log plots of the survival functions will be generated and checked for proportionality and linearity respectively. Second, Schoenfeld residuals will be examined. Score residuals, deviance residuals, and martingale residuals will also be assessed for influential points, outliers, and to ensure that the model has a correct functional form for the covariates.

I will also investigate stratifying the cox proportional hazards model by gender. I will first see if this makes sense by examining the survival curves by gender. If there is a large difference between the two shapes, which could also indicate violation of the proportional hazards assumption, I will stratify by gender which will modify the baseline hazards for each group to make them more flexible.

\*\*We may need to consider accounting for left truncation, if that exists within this data. \*\*

**Questions for discussion:**

* I am interested in leveraging data from EPOCH. The following are questions I have about the study design:
  1. How were women and children recruited?
  2. When were women and children recruited into the study?

\*\*I am happy to adjust any piece of the analytical framework or to include/exclude covariates into the model as deemed important by the subject matter experts (you!)\*

**Proposed author list:**

The proposed deliverable is intended to be for a short manuscript submitted for coursework, not for a journal. Thus, just myself and Dr. Dabelea.

**Proposed avenue for publication:**

Submission for a final project for my coursework.

**Proposed Timeline**

Preliminary Tables/Results: November 14th

First Draft of Limited Paper (5 page maximum!): November 25th

Presentations Begin (not sure when I’ll present): November 27th

Final Project Due: December 6th

**References**

1. Yeh J, Shelton JA. Increasing prepregnancy body mass index: analysis of trends and contributing variables. *Am J Obstet Gynecol*. 2005;193(6):1994-1998. doi:10.1016/j.ajog.2005.05.001

2. Kim J, Peterson KE, Scanlon KS, et al. Trends in overweight from 1980 through 2001 among preschool-aged children enrolled in a health maintenance organization. *Obes Silver Spring Md*. 2006;14(7):1107-1112. doi:10.1038/oby.2006.126

3. Ogden CL, Carroll MD, Lawman HG, et al. Trends in Obesity Prevalence Among Children and Adolescents in the United States, 1988-1994 Through 2013-2014. *JAMA*. 2016;315(21):2292-2299. doi:10.1001/jama.2016.6361

4. Sahoo K, Sahoo B, Choudhury AK, Sofi NY, Kumar R, Bhadoria AS. Childhood obesity: causes and consequences. *J Fam Med Prim Care*. 2015;4(2):187. doi:10.4103/2249-4863.154628

5. Hockett CW, Harrall KK, Moore BF, et al. Persistent effects of in utero overnutrition on offspring adiposity: the Exploring Perinatal Outcomes among Children (EPOCH) study. *Diabetologia*. 2019;62(11):2017-2024. doi:10.1007/s00125-019-04981-z

6. Crume TL, Ogden L, West NA, et al. Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes among Children (EPOCH) Study. *Diabetologia*. 2010;54(1):87. doi:10.1007/s00125-010-1925-3

7. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics*. 2003;111(3):e221-226. doi:10.1542/peds.111.3.e221

8. Venkataraman H, Ram U, Craik S, Arungunasekaran A, Seshadri S, Saravanan P. Increased fetal adiposity prior to diagnosis of gestational diabetes in South Asians: more evidence for the “thin-fat” baby. *Diabetologia*. 2017;60(3):399-405. doi:10.1007/s00125-016-4166-2

9. Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes*. 1980;29(12):1023-1035. doi:10.2337/diab.29.12.1023

10. Windham S, Hirsch K, Peterson R, et al. The Predictive Potential of Elevated Serum Inflammatory Markers in Determining the Need for Intubation in CoVID-19 Patients. *J Crit Care Med*. 2021;8(1):14. doi:10.2478/jccm-2021-0035

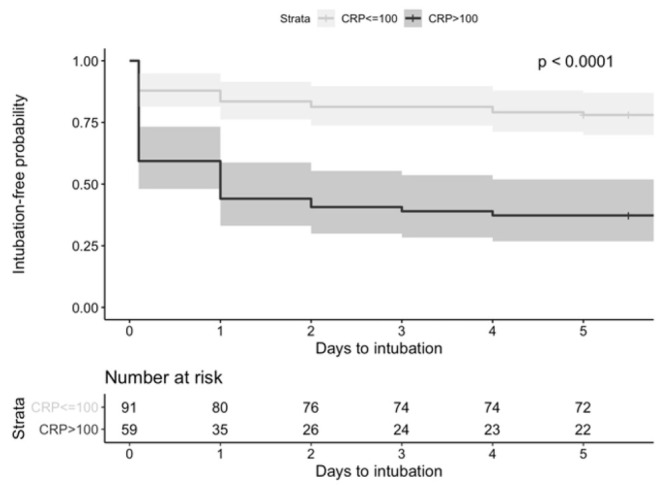
**Table shells**

Table Participant Characteristics

|  |  |  |
| --- | --- | --- |
|  | Exposure to Gestational Diabetes  (N = XX) | No Exposure to Gestational Diabetes  (N = XX) |
| Gender |  |  |
| Male |  |  |
| Female |  |  |
|  |  |  |
| Race |  |  |
| Categories |  |  |
|  |  |  |
| Ethnicity |  |  |
| Categories |  |  |
|  |  |  |
| Age |  |  |
| ……. |  |  |
|  |  |  |

This table presents participant characteristics of those included in the study. Numeric variables are presented as mean (SD), while categorical variables are presented as N (%).

Figure Kaplan Meier Curve, Time to Obesity



This figure will show the survival curves of the exposed and unexposed participants in the study population. This caption will discuss how dramatically the two curves differ OR will discuss that the curves do NOT look like they differ.

10

Table Model Results

|  |  |  |
| --- | --- | --- |
|  | Aim 1 Model:  Time to Obesity | Aim 2 Model:  Time to Overweight |
| Exposure to GDM | XX\* | XX |
| Age | XX | XX |
| (other covariates) | XX | XX |

This table presents exponentiated coefficients that represent the hazard of obesity or overweight associated with a one unit increase (or categorical increase) in the covariate. Significant effects are presented by a \*.