Invited Commentary

Invited Commentary: The Causal Association Between Obesity and Stillbirth—Strengths and Limitations of the Consecutive-Pregnancies Approach

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There has been a resurgence in analyses of consecutive pregnancies (or similarly, sibling designs) in perinatal and pediatric epidemiology. These approaches have attractive qualities for estimating associations with complex multifactorial exposures like obesity. In an article appearing in this issue of the *Journal*, Yu et al. (*Am J Epidemiol.* 2019;188(7):1328–1336) apply a consecutive-pregnancies approach to characterize the risk of stillbirth among women who develop obesity between pregnancies (“incident obesity”). Working within a causal framework and using parametric and nonparametric estimation techniques, the authors find an increase in stillbirth risk associated with incident obesity. Risk differences varied between 0.4 per 1,000 births (95% confidence interval (CI): 0.1, 0.7) and 6.9 per 1,000 births (95% CI: 3.7, 10.0), and risk ratios ranged from 1.12 (95% CI: 1.02, 1.23) to 2.99 (95% CI: 2.19, 4.08). The strengths of this approach include starting from a clearly defined causal estimand and exploring the sensitivity of parameter estimates to model selection. In this commentary, we put these findings in the broader context of research on obesity and birth outcomes and highlight concerns regarding the generalizability of results derived from within-family designs. We conclude that while causal inference is an important goal, in some instances focusing on formulation of a causal question drives results away from broad applicability.

birth outcomes; causal inference; generalizability; obesity; pregnancy; stillbirth

Abbreviation: BMI, body mass index.

Numerous challenges face researchers studying the health effects of obesity. These include defining and measuring the most meaningful physiological features of the condition (e.g., adiposity, metabolic dysregulation, related comorbidity) and the social and clinical factors that both pattern obesity and are affected by it (e.g., socioeconomic status, health-care access and quality). A central challenge is that this complex and multifactorial condition cannot be assigned, let alone randomized. The challenges are compounded when studying obesity in pregnancy, another health-related state that cannot be randomly assigned. Thus, there is a need to rely on diverse observational data sources and analytical approaches, and estimating a causal effect of obesity in pregnancy requires particular creativity.

CONSECUTIVE PREGNANCIES AND WITHIN-PERSON VARIABILITY

This is the challenge that Yu et al. (1) take on in their contribution to this issue of the *Journal*. Specifically, they focus on

within-person changes in obesity status, not just differences between individuals, to estimate an effect that is more causal in nature. Many understandings of causal inference exist, but most invoke the concept of assessing effects of *changes in exposure*, not merely comparing different exposure states (2–6). The authors focus on this type of variation by using a study design that exploits exposure differences between consecutive pregnancies. Although within-person and within-family study designs are not new (7–9), they have experienced a resurgence in recent years (10–15).

This study follows prior research that attempted to isolate causal effects of obesity on stillbirth by focusing on within-person changes in prepregnancy body mass index (BMI; weight (kg)/height (m)²). These studies found an increased risk of stillbirth associated with an interpregnancy increase in BMI (16, 17). It has been argued that this association provides stronger evidence for a biological effect of BMI increases on stillbirth than do studies that examine single pregnancies, because such studies cannot rule out common causes shared between BMI and stillbirth

(16). The present study builds on these initial approaches by analyzing the onset of obesity between consecutive pregnancies (i.e., “incident obesity”) as the exposure of interest in studying the risk of stillbirth. The comparison (unexposed) group is women who were not obese during their earlier pregnancy and remained so in a subsequent pregnancy.

The authors present their analysis plan within an explicit causal framework that clarifies the ideal experiment for the causal question of interest, necessary departures from this given the use of real observational data, and the estimand used to define the target causal parameter. They estimate the association of interest using parametric, semiparametric, and nonparametric approaches, rigorously checking causal assumptions. They find consistent evidence of an increase in stillbirth associated with incident obesity, generally of the magnitude of 2 per 1,000 births (risk difference) and 1.50 (risk ratio). Equally important from a methodological standpoint, they find that effect estimates are more variable in approaches that involve modeling the propensity score, in contrast to those that rely on the outcome model alone.

In this commentary, we build upon the article by Yu et al. and explore in greater detail issues of exposure definition, outcome considerations, and generalizability. We analyze a similar population-based data set of births from California (2007–2011; $n = 2,375,447$ singleton pregnancies) for demonstration. Throughout, we highlight connections between these study design features and practical implications of study results. We conclude by weighing the trade-offs between asking a question that is more causal and asking one that is most broadly applicable.

EXPOSURE CONSIDERATIONS: IMPLICATIONS OF ANALYZING INCIDENT OBESITY

Although analysis of incident obesity as the exposure enables analysis of within-person exposure changes, this exposure definition also limits the scope of the obesity effects estimated, as the authors acknowledge (1). First, the duration of the study time period ensures that women experiencing incident obesity will be exposed for a relatively short duration of time—not a small consideration given that longer durations of obesity are associated with worse outcomes (18–20), particularly obesity that is established during childhood or adolescence (21–23). Second and relatedly, the definition of a binary obesity exposure using the traditional threshold of BMI ≥ 30 imposes a restriction on the range of BMI values analyzed. One could reasonably ask whether women who transitioned from nonobese status to obese status between pregnancies experienced a meaningful change in BMI.

To illustrate this point, we identified pairs of first and second singleton births (including live births and stillbirths) that took place between 2007 and 2011 in the California data set. Following the approach of Yu et al. (1), we restricted the available population to pairs in which the mother had a BMI value less than 30 (“nonobese”) at the start of the first pregnancy, and further restricted the population to mothers who had a BMI value greater than or equal to 30 (“obese”) at the start of the second pregnancy (throughout, we use “first” and “second” pregnancy to refer to the order of the births within the study years). In this subpopulation, women tended to begin the first pregnancy with

Table 1. Distribution of Prepregnancy Body Mass Index Values and Interpregnancy Change in Body Mass Index Among Women Who Became Obese Between 2 Consecutive Pregnancies ($n = 21,432$), California, 2007–2011^a

BMI ^b Variable	Mean (SD)	Median (IQR)
Prepregnancy BMI		
First pregnancy	26.8 (2.5)	27.4 (25.4–28.8)
Second pregnancy	32.8 (2.9)	31.9 (30.8–33.8)
Interpregnancy BMI change	6.0 (3.9)	5.2 (3.3–7.8)

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.

^a Data were restricted to first and second singleton pregnancies occurring during 2007–2011 for which there was no missing information on stillbirth indicator, prepregnancy BMI, or date of birth.

^b Weight (kg)/height (m)².

a BMI in the overweight category (BMI 25–29.9) and begin the second pregnancy with a BMI in the class 1 obesity category (BMI 30–34.9) (Table 1).

Notably, the mean interpregnancy increase in BMI of 6.0 units that we observed in this subpopulation is substantial; in a woman of average height (5 feet, 4 inches (163 cm)), such an increase would be from 156 pounds (71 kg) to 191 pounds (87 kg). However, the obesity threshold used, while supporting the focused causal analysis proposed by Yu et al., comes at the cost of excluding women who begin their first pregnancy already obese. The longer exposure period of these women likely puts them at higher risk of poor outcomes. Similarly, the composition of obesity (by class) among women with incident obesity was different from the composition of obesity among all women with obesity. Whereas 14.3% of all women with obesity in California had class 3 obesity (BMI ≥ 40), only 3.1% of women with incident obesity had a BMI in this upper range (Table 2). The prevalences of diabetes and hypertension were also higher among all women than among women with incident obesity (Table 2), since these metabolic conditions are closely related to severity of obesity. Using a longer study period as Yu et al. did would probably increase the proportion of the sample with very high BMI, but this exposure definition necessarily limits the severity of obesity studied. This is especially noteworthy given that persons with prepregnancy obesity in classes 2 and 3 are the fastest-growing segment of the childbearing population and experience the highest risks of stillbirth (24, 25).

Collectively, these facts suggest that the obesity phenotype being analyzed in the paper by Yu et al. is obesity of lower severity, shorter duration, and better metabolic health than the full range of obesity that exists among pregnant women in the United States as a whole.

OUTCOME CONSIDERATIONS: STILLBIRTH RISK IN FIRST PREGNANCIES

Stillbirth is a devastating outcome, and despite recent advances in understanding its etiology, a substantial share of stillbirths do not have a known cause (26, 27). The chosen study design helps confirm the causal basis of obesity as a risk factor for stillbirth, but it also requires restriction of this analysis to multiparous women. Although it is dictated by the

Table 2. Characteristics of Pregnancies After Selection of a Sample for Within-Family Incident Prepregnancy Obesity, California, 2007–2011

Pregnancy Outcome or Characteristic	All Pregnancies ^a (n = 2,375,447)		Second Pregnancies Occurring During 2007–2011 (n = 274,174)		Second Pregnancies With Nonobese BMI ^b in First Pregnancy (n = 224,532)	
	No. of Pregnancies	%	No. of Pregnancies	%	No. of Pregnancies	%
<i>Outcome</i>						
Stillbirth	11,201	0.5	891	0.3	671	0.3
<i>Obesity-Related Characteristics (All Women)</i>						
Prepregnancy BMI group						
Underweight (BMI <18.5)	97,478	4.1	9,930	3.6	9,849	4.4
Normal weight (BMI 18.5–24.9)	1,185,203	49.9	131,815	48.1	130,013	57.9
Overweight (BMI 25.0–29.9)	611,053	25.7	69,611	25.4	63,238	28.2
Obese (BMI ≥30.0)	481,713	20.3	62,818	22.9	21,432	9.5
Prepregnancy diabetes mellitus	25,781	1.1	2,715	1.0	1,318	0.6
Prepregnancy hypertension	38,117	1.6	4,298	1.6	2,188	1.0
<i>Obesity-Related Characteristics (Women With Obesity)</i>						
Total no. of women with obesity	481,713		62,818		21,432	
Prepregnancy obesity group						
Class 1 (BMI 30.0–34.9)	293,967	61.0	36,391	57.9	18,005	84.0
Class 2 (BMI 35.0–39.9)	119,048	24.7	16,303	25.9	2,767	12.9
Class 3 (BMI ≥40.0)	68,698	14.3	10,124	16.1	660	3.1
Prepregnancy diabetes mellitus	13,316	2.8	1,541	2.5	279	1.3
Prepregnancy hypertension	20,020	4.2	2,380	3.8	453	2.1
<i>Demographic and Pregnancy-Related Characteristics^c (All Women)</i>						
Parity ^d						
1	941,006	39.7	0	0.0	0	0.0
2	743,439	31.4	167,123	61.1	143,552	64.1
≥3	685,023	28.9	106,386	38.9	80,477	35.9
Maternal age at delivery, years ^e	28.2 (6.3)		29.0 (5.8)		29.0 (5.9)	
Maternal race/ethnicity						
Hispanic/Latina	1,214,623	52.0	114,721	42.5	86,853	39.4
Non-Hispanic white	621,853	26.6	92,148	34.2	79,334	35.9
Asian/Pacific Islander	277,481	11.9	34,448	12.8	32,108	14.5
Non-Hispanic black	120,525	5.2	15,197	5.6	11,445	5.2
Other	101,025	4.3	13,201	4.9	10,937	5.0
Expected delivery payment method						
Private insurance	1,103,537	46.5	153,444	56.0	131,285	58.5
Medicaid	1,105,565	46.6	107,407	39.2	82,379	36.7
Other	162,249	6.8	12,958	4.7	10,585	4.7
Maternal education						
Less than a college degree	1,727,428	75.1	184,006	69.0	142,852	65.5
College degree or higher	572,465	24.9	82,601	31.0	75,221	34.5

Abbreviation: BMI, body mass index.

^a Singleton pregnancies occurring during the years 2007–2011 and not missing information on stillbirth indicator, prepregnancy BMI, or date of birth.^b Weight (kg)/height (m)².^c Numbers within subgroups may not sum to the total sample size because of missing values.^d Number of previous live births and stillbirths.^e Values are expressed as mean (standard deviation).

Table 3. Comparison of Stillbirth Prevalences Between Pregnancies With Obesity and Pregnancies Without Obesity Following Selection of the Study Population,^a California, 2007–2011

Population Analyzed	Prevalence of Stillbirth				Obesity Risk Ratio	Obesity Risk Difference (per 10,000 Pregnancies)
	Prepregnancy BMI ^b ≥30 (Obese)		Prepregnancy BMI <30 (Nonobese)			
	No. of Stillbirths	%	No. of Stillbirths	%		
All pregnancies	3,189	0.66	8,012	0.42	1.57	24
All second pregnancies	277	0.44	614	0.29	1.52	15
Second pregnancies with prepregnancy BMI <30 in first pregnancy	93	0.43	578	0.28	1.54	15

Abbreviation: BMI, body mass index.

^a Restricted to first and second singleton pregnancies occurring during the years 2007–2011 and not missing information on stillbirth indicator, prepregnancy BMI, or date of birth.^b Weight (kg)/height (m)².

chosen causal effect definition, this restriction comes at the cost of analyzing a portion of the population that is of great interest as relates to stillbirth: primiparous women.

Primiparity (no prior births) is one of the most important and prevalent risk factors for stillbirth, on par with obesity (28). Primiparous women make up a large share of the childbearing population—39.7% in California (Table 2). Being primiparous is associated with a 42% increase in the odds of stillbirth and contributes to approximately 15% of all stillbirths in high-income countries (28). Stillbirth etiology may also differ between primiparous women and multiparous women, with a greater share of unexplained risk in primiparous women (28, 29).

The lower stillbirth risk borne by multiparous women is evidenced in the population of childbearing women in California. The prevalence of stillbirth was substantially lower in second pregnancies (multiparous by definition) than in all pregnancies (primiparous and multiparous) among both women with prepregnancy obesity and women without prepregnancy obesity (Table 3). Consequently, although the crude risk ratio quantifying the obesity–stillbirth association was fairly consistent between second pregnancies (i.e., multiparous women) and all pregnancies (i.e., approximately 1.5), the crude risk difference was much lower owing to lower overall occurrence of the outcome (i.e., 15/10,000 in second pregnancies vs. 24/10,000 overall). These population differences in outcome frequency should be taken into account when interpreting results from consecutive-pregnancy studies, especially as they relate to measures of association on absolute scales. Although the parity-based restriction is the most profound difference between the study population and the overall population when studying incident obesity, the issue of generalizability should be considered more broadly.

GENERALIZABILITY CONSIDERATIONS

Internal validity is critical, and Yu et al. demonstrate how investigators can thoughtfully design research that optimizes a study for this consideration. However, in putting results into practice, we also must consider external validity, or the extent to which the results are generalizable outside of the study population. This becomes especially salient when excluding large

proportions of the potential study population when motivated by a causal effect definition rather than an a priori interest in the population that is retained in the study. Yu et al. report that they included 363,610 pregnancies occurring during 2003–2013 in their analysis, from an available 1,551,919—approximately 23% (1). Using data from all births taking place in California during 2007–2011, we followed the authors' process of restricting the study population to examine how those exclusions changed the study population (Table 2). To illustrate how the study population changes with successive restrictions, in Table 2 we present outcome, exposure, and covariate data for all pregnancies, second pregnancies, and second pregnancies in which the mother was nonobese in the first pregnancy (analogous to Yu et al.'s study population). Owing to a shorter study period and inclusion of only second pregnancies (in contrast with Yu et al., who included third pregnancies (1)), our available study population decreased by over 90%, from 2.4 million births to approximately 225,000 births.

The restricted population of second pregnancies occurring after a nonobese first pregnancy differed from the full population in terms of a number of characteristics, in addition to degree of obesity and parity: A higher proportion of such women were non-Hispanic white, had private health insurance, and had a college degree (Table 2). Whether these population differences affect the association of interest and whether they affect generalizability are open areas of research and debate, but the severity of these restrictions should be considered when investigators consider consecutive-pregnancy designs, if their goal is to make inferences about the full population.

CONCLUSION

The benefits of consecutive-pregnancy study designs are clear: By exploiting exposure variation within an individual, they reveal important causal information regarding the effects of exposures incurred during pregnancy. This approach is useful for pregnancy-related variables that are often difficult to study in a causal framework, especially complex multifactorial exposures like obesity. The advantage of such an estimand is that the effect is well-defined and is more likely to be identifiable in the data than one chosen without these restrictions.

Still, we have highlighted a trade-off between estimating causal effects and estimating associations that apply broadly at the population level. The process of defining this causal effect also shapes the research question in meaningful ways that must be considered in interpreting study results and applying them in practice. In the study by Yu et al., this results in studying associations with a relatively healthier obesity phenotype in a population of multiparous women whose stillbirth risk is lower than that in the overall population, and who probably differ from the overall population in other ways as well. In light of these exposure and outcome considerations, the chosen effect definition is perhaps a conservative one.

We believe that this tension is widespread—that is, between estimating a more causal association that applies to a narrower target population (and is perhaps one of less a priori interest) and estimating associations that are less clearly causal but apply to 1) a broader population or 2) a population of greater relevance. Of course, the decision as to which results are most important and broadly applicable is subjective and depends on the specific stakeholder. Nonetheless, we argue that as epidemiologists we should focus on rigorously defining our question of interest (whether causal or noncausal) as Yu et al. have done (1), and also making explicit how the exposure, outcome, and target population are defined within that question definition.

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