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Original Contribution

Conditions for Bias from Differential Left Truncation

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Spontaneous abortion studies that recruit pregnant women are left truncated because an unknown proportion of the source population experiences losses prior to enrollment. Unconditional logistic regression, commonly used in such studies, ignores left truncation, whereas survival analysis can accommodate left truncation and is therefore more appropriate. This study assessed the magnitude of bias introduced by fitting logistic versus Cox models using left-truncated data from a 1998 US pregnancy cohort study (n = 5,104) of trihalomethanes and spontaneous abortion. In addition, the conditions producing bias were explored by using simulated exposure data. The odds ratios and hazard ratios from the actual study differed by 10% or less. However, when the exposed women entered observation earlier on average than those unexposed, the hazard ratio was closer to the null than the odds ratio, whereas the reverse was true when the exposed entered later. The simulation suggests that bias in the odds ratio will exceed 20% when average gestational age at entry for the exposed versus the unexposed differs by 10 days or more, as has been observed regarding some socioeconomic factors, such as education and ethnicity. Cox regression can correct for left truncation and is no more difficult to perform than logistic regression.

abortion, spontaneous; bias (epidemiology); logistic models; survival analysis; trihalomethanes

Abbreviation: TTHM, total trihalomethane.

Most studies of spontaneous abortion are left truncated because women are recruited from prenatal clinics after conception (1–5). Thus, women enter the study at different gestational ages, and, more importantly, an unknown proportion of the source population is missing because of pregnancy losses prior to enrollment. This situation gives women whose pregnancies end in livebirths a greater opportunity to enter the study. Left truncation occurs in other types of studies whenever time zero (in this case, conception) is not observed on the relevant timeline (here, gestational age). Calculating effect estimates without accounting for left truncation may introduce bias because entry into the study is differential by outcome and may be differential by exposure status as well.

Unconditional logistic regression is a common analytic method that does not allow for left truncation. In contrast, survival analysis is able to account for time under observation, and hence left truncation, through a series of risk sets that include only those women who have entered the study by the time of each observed pregnancy loss (4). The underlying assumption is that the women who have entered observation by a given gestational age are representative of all pregnancies surviving to that gestational age in the source population (including those who never come under observation, those who have not yet come under observation by that gestational age, and those who are already under observation). Given modern computing abilities, Cox regression is no more difficult to perform than logistic regression.

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In this study, we sought to determine the level of bias introduced by fitting logistic models versus Cox models using left-truncated data from a 1998 paper that examined the relation between trihalomethanes in drinking water and spontaneous abortion (6). In addition, we performed simulations with hypothetical exposure data to characterize the conditions under which left truncation results in biased effect measure estimates. The hazard ratio was assumed to be the ''gold standard'' because it addresses left truncation and the odds ratio does not. However, even in the absence of left truncation, the two effect measure estimates would not be identical; the hazard ratio would be closer to the null than the incidence odds ratio. This relation can be derived from the mathematical expressions of the measures (7, 8) and has been observed in both actual (8–15) and simulated (12, 16) studies. The magnitude of the difference between the incidence odds ratio and the hazard ratio is a function of the prevalence of the outcome, the length of follow-up, and the magnitude of the true effect; uncommon outcomes, short follow-up periods, and small effects lead to negligible differences between the measures (7, 12, 14, 17). The magnitude of the difference is also affected by whether censoring is differential by exposure status; differential censoring introduces greater bias to the odds ratio (12).

Several papers mention left truncation (12, 16) but do not specifically examine how it alters the relation between the odds ratio and the hazard ratio. In Cox analyses that accommodate left truncation, pregnancies contribute to the likelihood conditional on having entered observation at that time, as opposed to traditional Cox regression, where all pregnancies contribute to the likelihood at the start of the study. This modification of the likelihood may also affect the relation of the hazard ratio to the odds ratio. We explored this possibility by using actual and simulated data.

MATERIALS AND METHODS

Background

The study population was recruited from three Northern California Kaiser Permanente Medical Care Program facilities from 1989 to 1991. The original investigators describe the cohort in greater detail elsewhere (6, 18, 19), but we summarize key details here. Women were recruited when they called to make their first prenatal care appointment after having had a positive pregnancy test. Entry into the study was defined as the date of a computer-assisted telephone interview that took place, on average, 8 days after the initial contact. Of the 7,881 women evaluated for recruitment, 6,179 were eligible and were willing to be interviewed; 5,342 completed the interview. At the time of the interview, 268 women were no longer pregnant, of whom 186 had already experienced a spontaneous abortion. Only women who were still pregnant were interviewed (6, 18); no exposure information was collected for those not interviewed.

Pregnancy outcomes were ascertained from hospital and medical records (91 percent), follow-up telephone interviews, mailed questionnaires, or matches to California vital records. The outcome could not be determined for 35 women who were therefore dropped from the study. In addition, 163 women were excluded for reasons such as elective termination, ectopic pregnancy, and molar pregnancy. Multiple births ($n = 55$) were considered a single outcome. Gestational age was calculated based on the first day of the last menstrual period, as reported during the interview. Extreme gestational ages at outcome ($<$4 weeks or $>$45 weeks) were verified against medical records when possible and corrected as appropriate. Spontaneous abortions were originally defined as fetal deaths prior to 21 completed weeks of gestation. Eighty-four percent of the spontaneous abortions were validated by medical records (6, 18).

The original investigators assigned total trihalomethane (TTHM) exposures based on the average TTHM level of each woman's residential water utility. In a later analysis, they assigned each woman a TTHM measurement from the utility site closest to her residence instead of the utility-wide average. The authors concluded that there was no advantage to the closest-site method because the results did not change much and because a residence is not necessarily served by the closest utility site. Thus, we were able to use original exposure assignment data (19). Other covariates were reported during computer-assisted interviews.

Model comparison using real data

Our analysis compared logistic regression ignoring left truncation with Cox regression accounting for left truncation. For this study, we defined spontaneous abortion as the involuntary loss of an intrauterine pregnancy between gestational ages 5 and 20 completed weeks inclusive; there were no reported pregnancy losses prior to week 5, so no early losses were excluded by this definition. We did exclude 21 livebirths and two spontaneous abortions that appeared to have entered observation prior to day 35 because we believed their gestational age data to be in error (38 percent of the livebirths were preterm among women who apparently entered before day 35 vs. 7 percent among women who entered on day 35 or later). We also dropped data for nine livebirths and eight spontaneous abortions because of other errors in their gestational age data. Thus, of 5,144 pregnancies in the original analysis, 5,104 met our inclusion criteria for the reanalysis. In both the original analysis and the reanalysis, additional women had to be dropped from specific models because of missing data for the main exposure or the covariates (table 1).

We focused on comparing results from logistic and Cox models for TTHM as defined in table 4 of the original paper (6). However, we also compared the effect measure estimates for each covariate from the original model to better understand the effect of left truncation in different contexts. The original investigators first compared all women exposed to high average TTHM concentrations, defined as 75 μg/liter or higher, with all women with low average exposure ($<$75 μg/liter) in a logistic model with no covariates. They also performed this analysis stratified by cold tap water consumption (separate models for those who consumed fewer than five glasses per day and for those consuming five glasses or more per day). Next, they compared women with high TTHM exposure and high cold tap water consumption with all other women. Then, all analyses were repeated

TABLE 1. Number of spontaneous abortions and sample size by strata of total trihalomethane exposure from drinking water (μg/liter) in a cohort of women recruited from Kaiser Permanente Medical Care Program facilities in Northern California from 1989 to 1991

Main exposure	Logistic analysis and survival analysis closed left*		Survival analysis open left			
			Unit = weeks		Unit = days	
	SAB†	No.	SAB	No.	SAB	No.
All women						
TTHM† <75‡	327	3,636	304	3,613	326	3,635
TTHM ≥75	105	940	100	935	103	938
Women consuming <5 glasses of cold tap water/day						
TTHM <75‡	278	3,072	260	3,054	278	3,072
TTHM ≥75	86	818	83	815	85	817
Women consuming ≥5 glasses of cold tap water/day						
TTHM <75‡	48	562	43	557	47	561
TTHM ≥75	19	121	17	119	18	120
All women						
TTHM <75 or <5 glasses of cold tap water/day‡	462	4,935	434	4,907	460	4,933
TTHM ≥75 and ≥5 glasses of cold tap water/day	19	121	17	119	18	120

* Risk intervals used in the survival analysis are closed left as opposed to open left.
† SAB, spontaneous abortions; TTHM, total trihalomethane.
‡ Reference group.

adjusting for maternal age at interview (≥35, <35 years), history of pregnancy loss (≥2, <2 prior spontaneous abortions), cigarette smoking in the week before the interview (any, none), maternal race (Black or Asian, White or Hispanic), and employment during pregnancy (yes, no). The authors also coarsely accounted for left truncation by including the dichotomous variable gestational age at entry (≤8, >8 weeks).

We started by fitting adjusted logistic regression models both including and excluding the dichotomous entry time variable using data for only those women who met our inclusion criteria. Next, we compared histograms of gestational age at entry for the exposed and the unexposed for each variable and fit Cox models to address left truncation. The choice of the unit of time used in a life table may bias the estimated risk of spontaneous abortion if entries into observation violate the uniformity assumption within long intervals (i.e., that censoring occurs uniformly throughout the interval or equivalently, that mean censoring time occurs at the midpoint of the interval) (2, 20). Although Cox regression does not use intervals per se, the issue of the choice of the unit of time could influence the estimated hazard ratio. Because we were able to calculate gestational ages in completed weeks as well as in days, we constructed and compared separate Cox models by using both of these time scales. We assumed that tied event times were caused by an imprecise measurement of time (as is the case when weeks are used instead of days and when days are used instead of hours or minutes) and therefore calculated the exact conditional probabilities.

Another issue of concern in survival analysis is that for a given event, the risk set used by the likelihood function includes only individuals who are at risk because they have entered observation prior to the interval (21). Thus, a woman who experiences a loss during the same interval she enters observation is dropped from the analysis. In statistical terms, the risk interval is "open left" (22). The interval can be closed artificially by subtracting a small number (a fraction of one unit of time, such as 0.002) from the entry time of all women (essentially, treating women as if they enter observation slightly before they actually do) to enable those who enter and exit the study in the same time interval to contribute to the analysis (22, 23). This rescaling of the entry time seems particularly appropriate for spontaneous abortion studies, where the data are left truncated and the time between entry and loss can be short. For comparison, we fit all the Cox models with the intervals both open and closed left. The survival models included the same variables as were used in the original analysis except for the dichotomous indicator of gestational age at entry, which was excluded because the survival models account for gestational age at entry directly.

Model comparison using simulated data

We also performed a simulation study to assess the conditions under which the odds ratio would differ meaningfully from the hazard ratio. We used the outcome and

TABLE 2. Adjusted* odds ratios and hazard ratios with 95% confidence intervals for the estimated effect of total trihalomethane exposure from drinking water (μg/liter) on spontaneous abortion in a cohort of women recruited from Kaiser Permanente Medical Care Program facilities in Northern California from 1989 to 1991

Main exposure	Logistic regression				Survival analysis unit = weeks				Survival analysis unit = days			
	No adjustment for entry		Adjustment for entry†		Open left‡		Closed left		Open left‡		Closed left	
	OR§	95% CI§	OR	95% CI	HR§	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All women												
TTHM§ <75¶	1.00		1.00		1.00		1.00		1.00		1.00	
TTHM ≥75	1.26	0.99, 1.59	1.22	0.96, 1.55	1.21	0.96, 1.52	1.20	0.96, 1.50	1.17	0.94, 1.46	1.19	0.96, 1.49
Women consuming <5 glasses of cold tap water/day												
TTHM <75¶	1.00		1.00		1.00		1.00		1.00		1.00	
TTHM ≥75	1.16	0.90, 1.50	1.12	0.87, 1.46	1.14	0.89, 1.46	1.12	0.88, 1.43	1.10	0.86, 1.40	1.11	0.87, 1.42
Women consuming ≥5 glasses of cold tap water/day												
TTHM <75¶	1.00		1.00		1.00		1.00		1.00		1.00	
TTHM ≥75	1.99	1.11, 3.58	1.98	1.10, 3.56	1.76	1.00, 3.11	1.83	1.07, 3.13	1.74	1.01, 3.01	1.81	1.06, 3.10
All women												
TTHM <75 or <5 glasses of cold tap water/day¶	1.00		1.00		1.00		1.00		1.00		1.00	
TTHM ≥75 and ≥5 glasses of cold tap water/day	1.84	1.11, 3.04	1.83	1.10, 3.03	1.66	1.02, 2.70	1.76	1.11, 2.78	1.67	1.04, 2.67	1.75	1.11, 2.78

* Adjusted for maternal age at interview (≥35 vs. <35 years), cigarette smoking (any vs. none), history of spontaneous abortion (≥2 or <2 prior losses), maternal race (Black or Asian vs. White or Hispanic), and employment during pregnancy (yes vs. no).
† Adjusted for gestational age at interview (≤8 vs. >8 weeks).
‡ Risk intervals used in the survival analysis are open left as opposed to closed left.
§ OR, odds ratio; CI, confidence interval; HR, hazard ratio; TTHM, total trihalomethane.
¶ Reference group.

gestational age data from the actual data set but assigned each pregnancy a hypothetical exposure status by randomly drawing from a Bernoulli distribution. In each scenario, the probability of exposure could vary for women who entered at different gestational weeks, but we forced the prevalence of exposure among the spontaneous abortions to be a constant multiple of the prevalence of exposure among the livebirths at each gestational week of entry. By allowing the probability of exposure to vary across entry, we were able to create a variety of scenarios in which entry into observation was differential by exposure status but the true effect size remained constant. We examined effect sizes of 2.0, 1.5, 1.2, and 1.0 for each scenario.

RESULTS

Overall, the results in which the actual data were used differed by 10 percent or less (usually by less than 5 percent) regardless of the analytic method used. For TTHM, the odds ratios were consistently farther from the null than the corresponding hazard ratios (table 2). Women exposed to high TTHM levels entered slightly earlier on average than women in the reference group (figure 1). The elevation in the odds ratio was most pronounced in the models limited to women who consumed five or more glasses of cold tap water a day and the models comparing women with high TTHM exposure and high tap water consumption with all others. These models had the largest effect measure estimates, but they also had sparse strata, particularly among the exposed (table 1). The confidence intervals for the hazard ratios were

FIGURE 1. Gestational age at entry into the spontaneous abortion study by total trihalomethane (TTHM) exposure. Of women recruited from Kaiser Permanente Medical Care Program facilities in Northern California from 1989 to 1991, those consuming high levels of TTHM tended to enter earlier.

TABLE 3. Adjusted* odds ratios and hazard ratios with 95% confidence intervals for the effect of total trihalomethanes, maternal age, smoking, history of spontaneous abortion, maternal race, and maternal employment on spontaneous abortion among a cohort of women recruited from Kaiser Permanente Medical Care Program facilities in Northern California from 1989 to 1991

Variable	SAB†	No.	Mean gestational age at entry (days)	Logistic regression				Cox regression‡			
				No adjustment for entry		Adjustment for entry§		Unit = weeks		Unit = days	
				OR†	95% CI†	OR	95% CI	HR†	95% CI	HR	95% CI
TTHM† exposure											
<75 μg/liter¶	327	3,636	59.8	1.00		1.00		1.00		1.00	
≥75 μg/liter	105	940	57.9	1.26	0.99, 1.59	1.22	0.96, 1.55	1.20	0.96, 1.50	1.19	0.96, 1.49
Maternal age at interview											
<35 years¶	348	4,070	59.3	1.00		1.00		1.00		1.00	
≥35 years	84	506	59.9	2.03	1.56, 2.64	2.05	1.57, 2.66	1.94	1.53, 2.47	1.95	1.53, 2.48
Cigarette smoking											
None¶	375	4,090	59.4	1.00		1.00		1.00		1.00	
Any	57	486	59.1	1.35	1.00, 1.82	1.36	1.00, 1.83	1.31	0.99, 1.73	1.31	0.99, 1.73
History of spontaneous abortions											
<2 prior losses¶	396	4,370	59.5	1.00		1.00		1.00		1.00	
≥2 prior losses	36	206	58.1	1.89	1.29, 2.76	1.85	1.26, 2.71	1.74	1.23, 2.46	1.73	1.22, 2.44
Maternal race											
White or Hispanic¶	342	3,837	59.0	1.00		1.00		1.00		1.00	
Black or Asian	90	739	61.4	1.43	1.11, 1.83	1.49	1.16, 1.92	1.45	1.15, 1.84	1.47	1.17, 1.86
Employed during pregnancy											
No¶	74	929	58.2	1.00		1.00		1.00		1.00	
Yes	358	3,647	59.7	1.27	0.97, 1.65	1.30	1.00, 1.69	1.28	0.99, 1.64	1.29	1.00, 1.65

* Adjusted for all variables listed.
† SAB, spontaneous abortion; OR, odds ratio; CI, confidence interval; HR, hazard ratio; TTHM, total trihalomethane.
‡ Risk intervals are closed left.
§ Adjusted for gestational age at interview (≤8 vs. >8 weeks).
¶ Reference group.

consistently tighter than the confidence intervals for the odds ratios in all models.

Table 3 shows the results for all the variables from the basic TTHM model among all women. Generally, if the exposed group entered earlier on average than the unexposed group, the hazard ratio was smaller than the odds ratio. If the average gestational age at entry for the exposed group was at least a day later than the average gestational age at entry for the unexposed group, the hazard ratio was larger than the odds ratio. The effect measure estimates for maternal age behaved slightly differently. Older women (the exposed group) entered approximately half a day later than younger women on average, but the odds ratio for maternal age was approximately 5 percent greater than the hazard ratio. The percent difference between the odds ratio and the hazard ratio [(odds ratio – hazard ratio)/hazard ratio] seems to be a function of the magnitude of the effect measure estimate and the difference in average gestational age at entry for the exposed and unexposed (figure 2).

Coarsely accounting for left truncation by using a dichotomous variable for gestational age at entry moved the odds ratios for TTHM exposure toward the corresponding hazard ratios and widened the confidence intervals (table 2). The crude approach was least effective in the TTHM models with the largest effect measure estimates and sparsest data for the exposed even though these models had the greatest difference between the odds ratios and the hazard ratios. Generally, the dichotomous entry variable seemed to move the odds ratio toward the hazard ratio for variables in which the exposed entered earlier than the unexposed, but only part way, as might be expected (table 3). For variables in which the exposed entered later than the unexposed, including the entry variable seemed to move the odds ratios in the expected direction (away from the null), but the resulting odds ratios were greater than the hazard ratios. Coarsely addressing gestational age at entry moved the odds ratio in the wrong direction for smoking and maternal age because the dichotomized version of gestational age was not representative of the overall relation between entry times for the exposed and the unexposed groups. For example, older women were more likely than younger women to enter observation at weeks 7–10, whereas younger women were more likely than

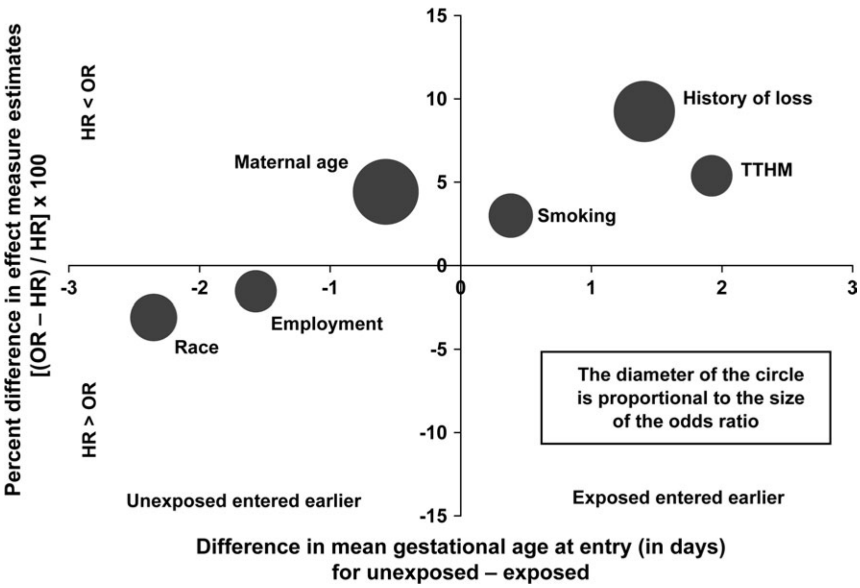

FIGURE 2. Percent difference in effect estimates comparing odds ratios (ORs) and hazard ratios (HRs) in a reanalysis of a study of spontaneous abortion and total trihalomethanes (TTHMs). The percent difference in the effect estimates is presented as a function of the average difference in gestational age at entry for the exposed and the unexposed and the magnitude of the odds ratio for several binary variables, including TTHM, maternal age, maternal smoking, history of spontaneous abortion (loss), maternal race, and maternal employment. The cohort of women was recruited from Kaiser Permanente Medical Care Program facilities in Northern California from 1989 to 1991. TTHM, total trihalomethane.

older women to enter at the tails (weeks 5, 6, 11, and 13). Therefore, dichotomizing entry time was misleading with respect to maternal age.

The TTHM results varied by 5 percent or less across the survival models regardless of whether days or weeks were used as the unit of time and regardless of whether the models had risk intervals that were open or closed left. The open models included fewer observations than the closed models because data for women who entered and terminated in the same time interval were dropped (table 1). The differences in the effect measure estimates were more pronounced in the sparser models (table 2). In addition, the confidence intervals for the open models were wider than the confidence intervals for the corresponding closed models, reflecting the sample size. For the closed models (which had the same sample size across a given model), the hazard ratios from models in which weeks were used as the unit of time were generally closer to the odds ratio than the models in which days were used. In addition, the models in which days were used had narrower confidence intervals.

The percent differences between odds ratios and the hazard ratios for the actual data were all less than 10 percent. However, by creating more extreme differences in entry time between the exposed and the unexposed, the odds ratios from the simulation study were biased by as much as 35 percent (figure 3). When the exposed entered as few as 6 days earlier on average than the unexposed, the odds ratio was inflated by 20 percent. However, the unexposed had to enter an average of 10 days earlier than the exposed for the odds ratio to be 20 percent smaller than the hazard ratio. There is evidence that when the exposed entered earlier than the unexposed on average, large true effects introduced more bias than smaller true effects, but the opposite was true when the unexposed entered earlier (i.e., the bias in the odds ratio was greater with smaller true effects).

DISCUSSION

Mathematically, in the absence of left truncation, the odds ratio is expected to be further from the null than the hazard ratio, which in turn is expected to be further from the null than the risk ratio (7, 8). Both simulations (12, 16) and studies using actual data (8–15) have confirmed these expectations. The magnitude of the difference between the odds ratio and the hazard ratio has been reported to be a function of the prevalence of the outcome, the length of the follow-up period, and the magnitude of the true effect size (7, 10, 11, 14, 15, 17). Previous publications have suggested that the odds ratio approximates the hazard ratio when the prevalence of the outcome is anywhere from less than 5 percent to less than 20 percent among the study population or among the unexposed (7–9, 12, 16). Because the prevalence of the outcome does not affect the difference between effect measure estimates in isolation, there is no firmly established rule. It has been argued that the length of the follow-up period affects the difference between the estimates by increasing the prevalence of the outcome with increasing follow-up (7, 12). In fact, Callas et al. (16) did not find the length of the follow-up period to be substantively important. Larger effects are associated with greater divergence between the measures; simulation studies have indicated substantial differences between

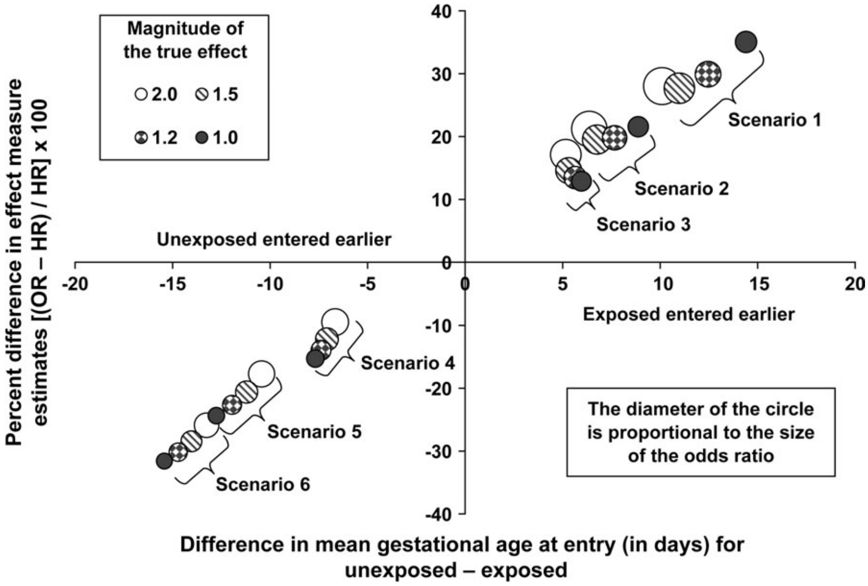

FIGURE 3. Simulation results for a spontaneous abortion study. The percent difference between the odds ratio (OR) and the hazard ratio (HR) is presented in relation to the average difference in gestational age at entry for the trihalomethane exposed versus the unexposed and the magnitude of the observed odds ratio. Scenario 1: prevalences of exposure for the spontaneous abortions—0.80, 0.60, and 0.10 for entry at gestational weeks 5–7, 8, and 9–13, respectively. Scenario 2: respective prevalences of 0.80, 0.60, 0.20, and 0.10 for weeks 5, 6–9, 10, and 11–13. Scenario 3: prevalences of 0.40, 0.25, and 0.10 for weeks 5–7, 8–10, and 11–13. Scenario 4: prevalences of 0.10, 0.25, and 0.40 for weeks 5–7, 8–10, and 11–13. Scenario 5: prevalences of 0.10, 0.20, 0.60, and 0.80 for weeks 5–7, 8, 9–12, and 13. Scenario 6: prevalences of 0.10, 0.60, and 0.80 for weeks 5–9, 10, and 11–13.

the odds ratio and the hazard ratio when the true effect size was greater than 2.0 or 3.0 (7, 8, 12, 16).

Ingram and Kleinman (12) point out that differential censoring by exposure status introduces bias to the odds ratio. However, the relation between the odds ratio and the hazard ratio when left truncation is present does not appear to have been previously evaluated. Theoretically, if left truncation is differential by exposure, the logistic regression results will be biased because one exposure group is observed for a larger portion of the risk period than the other, as with censoring. In such a situation, the survival models would be more correct than the logistic models because they take into account the time that each pregnancy is under observation. In this study, women who were exposed to high levels of TTHM entered observation 2 days earlier on average than women who were unexposed (figure 1). Therefore, the logistic estimates should be greater than the survival analysis estimates. In fact, our empirical results bear this out. Because the difference in entry time was small, the difference in the estimates was also small. Generally, in this study, the magnitude of the percent difference between the odds ratio and the hazard ratio seemed to be a function of two factors: 1) the difference in average gestational age at entry between the exposed and the unexposed women and 2) the magnitude of the effect measure estimate of the variable of interest (figures 2 and 3).

If the exposed women entered earlier, on average, than the unexposed, then the odds ratio was larger than the hazard ratio, with bigger differences in time under observation resulting in bigger differences between the odds ratio and the hazard ratio. When the exposed entered later than the unexposed by an average of at least a day, the odds ratio was smaller than the hazard ratio. Presumably when the difference was less than a day, the differential truncation was trivial and therefore the hazard ratio was less than the odds ratio for the same reason that the hazard ratio is smaller than the odds ratio when there is no left truncation (7). The odds ratios and the hazard ratios differed by 10 percent or less for the actual data in this study, but the differences in the time under observation by exposure status were also quite small (<2.5 days). In the simulation study, the odds ratios differed from the hazard ratios by more than 20 percent when entry was differential by as few as 6 days.

The larger odds ratios from the actual data seemed to be more biased than odds ratios that were near 1.0 even when the difference in time under observation was quite small, as with maternal age. In the simulation study, the larger the effect size, the more biased the odds ratio when the exposed entered earlier than the unexposed, but magnitude of the true effect size did not appear to be important when the unexposed entered earlier. This finding suggests that bias introduced to the odds ratio by left truncation competes with the bias introduced by the effect size. For left-truncated studies, as the magnitude of the difference in entry time increases, it appears to become the dominant factor in determining the divergence of the effect measure estimates.

A number of social characteristics (such as socioeconomic status, ethnicity, depression, marital status, maternal age) have been associated with delayed entry into prenatal care (24–30). For California births in 2000 where the mother started prenatal care by month 5, women with health insurance entered care approximately a week prior to women without insurance, women with less than 12 years of education entered care approximately 2 weeks later than women with at least 16 years of education, and Hispanic women entered approximately a week after non-Hispanic women (31). Thus, differences of 6 or 10 days in mean gestational age at entry are plausible for certain exposures, and whereas Cox regression would be preferable to logistic regression for any study of spontaneous abortion, it would be particularly important for reducing bias when studying exposures associated with social factors.

In the original paper on trihalomethanes (6), the authors attempted to address left truncation coarsely by including a dichotomous variable indicating younger versus older gestational age at entry into the study. Our reanalysis results suggest that a dichotomous entry variable is not a reliable method of accounting for left truncation. The dichotomous entry variable seemed to underadjust in some cases, overadjust in others, and even move the odds ratio in the wrong direction for some variables. Collectively, these results suggest that addressing gestational age at entry crudely is not adequate and may in fact be misleading.

The survival analysis models were robust to the choice of scale (i.e., weeks or days), although the hazard ratios from the models in which weeks were used tended to be closer to the odds ratio than those from the models using days. Using days is preferable because it accounts for left truncation more finely and uses more of the available information. We also found that whether the risk intervals were open or closed left, the hazard ratios changed by 5 percent or less. Because data for fewer women are dropped from the analyses when the risk intervals are closed left, closed intervals improved precision slightly compared with open intervals, especially when the analysis was based on weeks. Thus, using closed risk sets is desirable to avoid losing information unnecessarily.

Overall, left truncation in the actual data set introduced bias less than or equal to 10 percent, but, in the simulation, some odds ratios were biased by 20 percent or more when the difference in mean gestational age at entry was assumed to be 6 days or more comparing the exposed with the unexposed. Although left truncation dramatically affects the estimates for risk of spontaneous abortion (1–3, 5), the issue may be less important for relative measures of effect. Nevertheless, for variables where exposure status is associated with entry time, as may be the case for some social variables (24–30), logistic regression could be subject to more substantial bias. Given that left truncation may be related to exposure or important covariates and that Cox regression models may easily be fit in most statistical packages today, there is no reason not to use it in cohort studies and nested case-control studies, where the sampling fractions are available. A different approach is required for case-control studies in which no sampling fractions are available.

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