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IN UTERO EXPOSURES AND ENDOMETRIOSIS, THE ENDO STUDY

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Abstract

Objective—To assess *in utero* exposures and the odds of an endometriosis diagnosis.

Design—Matched cohort design.

Setting—Fourteen participating clinical centers in geographically defined areas in Utah and California.

Study cohorts—The operative cohort comprised 473 women undergoing laparoscopy/laparotomy, and was matched on age and residence to a population cohort comprising 127 women undergoing pelvic magnetic resonance imaging (MRI), 2007–2009.

Interventions—None

Main outcome measures—Women completed standardized interviews prior to surgery or MRI regarding in utero exposures: mothers' lifestyle during the index pregnancy, and the index woman's gestation and birth size. Endometriosis was defined as visually confirmed disease in the operative cohort, and MRI visualized disease in the population cohort. The odds of an endometriosis diagnosis and corresponding 95% confidence intervals (AOR; 95% CI) were estimated for each exposure by cohort using logistic regression and adjusting for current smoking, age at menarche, body mass index, and study site.

Results—Endometriosis was diagnosed in 41% and 11% of women in the operative and population cohorts, respectively. In the primary analysis, AORs were elevated for maternal vitamin usage (1.27; 95% CI =0.85–1.91), maternal cigarette smoking (1.16; 95% CI=0.61–2.24), and low birth weight (1.1; 95% CI=0.92–1.32). Reduced odds were observed for maternal usage

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of caffeine (0.99; 95% CI=0.64–1.54), alcohol (0.82; 95% CI=0.35–1.94), paternal cigarette smoking (0.72; 95% CI=0.43–1.19) and preterm delivery (0.98; 95% CI=0.47–2.03). Sensitivity analyses mostly upheld the primary results except for a decreased AOR for preterm birth (0.41; 95% CI=0.18–0.94) when restricting to visualized and histologically-confirmed endometriosis in the operative cohort.

Conclusions—*In utero* exposures were not significantly associated with the odds of an endometriosis diagnosis in either cohort.

Keywords

endometriosis; epidemiology; *in utero*; ovarian dysgenesis hypothesis

BACKGROUND

The Barker hypothesis (1) sparked considerable interest in the potential early origins of health and disease (2). This hypothesis posits that early exposures, including those arising from parents' lifestyles during sensitive windows of human development such as pregnancy, may permanently reprogram the developing embryo or fetus for extrauterine life. This reprogramming is speculated to occur largely through epigenetic mechanisms (3). Such reprogramming of human fecundity, defined as the biologic capacity of men and women for reproduction, irrespective of pregnancy intentions, has also been observed including for early environmental exposures with trans-generational effects (4, 5).

In response to the early origins of health and disease hypothesis, investigators have assessed *in utero* exposures with endometriosis in adult women. A higher odds of an endometriosis diagnosis was associated with *in utero* diethylstilbestrol (DES) (6), and a lower odds of diagnosis with *in utero* exposure to cigarette smoking (7) and increasing birth weight (6). Other evidence suggestive of an early origin for endometriosis includes body size. Hediger and colleagues first reported that women eventually diagnosed with endometriosis tracked leaner from childhood through diagnosis relative to women without endometriosis (8). This finding was subsequently corroborated in the large Nurses Health III Cohort Study (9). Despite an evolving body of evidence suggestive of an early origin for endometriosis, current studies are limited by the fact that endometriosis was only self-reported (instead of the gold standard of visualized disease) (6) and that a woman with endometriosis had to retrospectively recall her mother's exposures and behaviors during pregnancy (6, 7). We designed the Endometriosis, Natural History, Disease, Outcome (ENDO) Study, in part, to specifically assess *in utero* exposures, gestation and birth size and endometriosis, while attempting to address some of the methodological challenges of endometriosis research (10).

MATERIALS AND METHODS

Study design and cohorts

Full human subjects approval (Committee of Human Research, University of California, San Francisco; Institutional Review Board, University of Utah; Intermountain Healthcare Office of Research, Utah; and the National Institutes of Health Institutional Review Board Reliance) was obtained for the conduct of this study; each of the women provided informed consent before any data collection. The ENDO Study used a matched exposure cohort design in which an operative cohort was matched to a population cohort. The operative cohort comprised women scheduled for laparoscopy or laparotomy at one of 14 participating clinical sites in the Salt Lake City and San Francisco areas. Subsequently, the operative cohort was matched to the population cohort comprising women residing within a 50-mile radius surrounding the 14 participating centers. By design, the population cohort was not

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seeking surgery but was at risk for endometriosis and its diagnosis, in that eligible women had to be currently menstruating and residents in the geographical areas served by the clinical sites. Given the absence of uniform sampling frameworks to find women at risk for endometriosis and its diagnosis, we utilized the Utah Population registry for our Utah clinical sites, in that this sampling framework represents approximately 95% of State residents (11), and a well-established household sampling database for California (12). Letters were sent to all women in the population sampling frameworks introducing the study, followed by telephone calls to screen women for eligibility: 1) no history of laparoscopically-confirmed endometriosis; 2) currently menstruating; 3) residence within the geographic clinical catchment areas; 4) aged 18–44 years; 5) not currently breastfeeding for ≥6 months; 6) no injectable hormonal treatment within the past 2 years; and 7) no history of cancer (except non-melanomatous skin cancer). The same criteria were used for the operative cohort. The age criterion intended to reflect the female reproductive age distribution with the exception of age-extremes (adolescents and perimenopausal women) and to allow sufficient time for women to become exposed to environmental agents, while the breastfeeding criterion was intended to prevent reduction in women's serum concentrations of lipophilic environmental chemicals via lactational transfer. All women in the operative cohort underwent surgery, while all women in the population cohort underwent pelvic magnetic resonance imaging (MRI) for the diagnosis of endometriosis using a standardized protocol. The operative and population cohort comprised 473 and 127 women with complete information on endometriosis status, respectively. Complete details of the ENDO Study methodology are provided elsewhere (10).

Data collection

Upon enrollment, all women were interviewed prior to surgery or MRI regarding their knowledge of exposures while *in utero.* Specifically, women were asked about parental smoking during pregnancy (yes/no), mother's use of alcohol (yes/no), caffeinated beverages (yes/no), and vitamins (yes/no), and whether the mother received diethylstilbestrol (DES) or infertility treatment for the index woman's pregnancy. In addition, women were asked the plurality of their birth (singleton/multiple) along with their birth weight (pounds and ounces), birth length (inches), and length of gestation (categorized as <37, 37–42, or >42 weeks). Standardized anthropometric protocols were used to measure height and weight (13). Surgeons completed standardized operative reports for all women in the operative cohort to capture the primary postoperative diagnosis and any other operative findings. Endometriosis was defined as consistent with the gold standard for surgically visualized disease (14). Given the observational study design, endometrial implants were removed for histologic assessment per the surgeon's standard of practice. Histologically-confirmed disease was assessed in the sensitivity analyses. Severity of endometriosis was utilized using the rASRM criteria (15). A primary MRI endometriosis diagnosis, largely comprised ovarian endometriomas, as determined and corroborated by the study's two radiologists who were blinded to exposure and disease status. All other MRI findings were noted as well including adenomyosis. As defined *a priori*, we restricted endometriosis in the population cohort to represent the primary diagnosis.

Statistical analysis

Descriptive analyses included the inspection of missing data by cohort, exposure and disease status followed by comparison of *in utero* exposures and endometriosis status in each cohort to assess potential confounders. The Chi-squared (χ^2) Statistic was used to assess significance for categorical and the nonparametric Wilcoxon test for continuous data by *in utero* exposure status. Logistic regression techniques were used to estimate unadjusted and adjusted odds ratios (OR/AOR) and corresponding 95% confidence intervals (CIs). *A priori*, we defined our models to be inclusive of all *in utero* exposures along with potential

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confounders as suggested by the literature: age at menarche (years); body mass index (weight in kg/height in m^2); woman's current smoking (yes/no); and clinical site (California/Utah) to account for any residual confounding. We also ran models adjusting for woman's birth weight to permit comparison of our findings with past research reporting such an effect (6). In addition, a number of sensitivity analyses were performed for the operative cohort to assess the robustness of the primary findings by diagnostic classifications: 1) restricting endometriosis diagnosis to visually and histologically confirmed disease; 2) restricting endometriosis to stages 3–4; and 3) restricting the comparison of unaffected women to those with a postoperative diagnosis of a normal pelvis. Statistically significant findings are those with p-values less than 0.05 or 95% confidence intervals exclusive of 1.0.

RESULTS

The two cohorts were similar, except for a significantly higher percentage of married women in the operative versus population cohort (76% versus 60%, respectively) as previously reported (10). The mean ages of women in the operative and population cohorts were comparable, 32±7 (18–44) and 33±8 (19–44) years, respectively, reflecting the success of matching the population cohort to the operative cohort. Also as previously noted, the incidence of endometriosis in the operative and population cohorts was 40% and 11%, respectively, largely skewed (70%) toward stage 1–2 versus stage 3–4 disease (30%). (10) Among the 143 women with endometrial implants available for histologic analysis, endometriosis was histologically diagnosed in 68 (48%) women. All but two of these women had surgically visualized disease. Of note is that in addition to the 14 women with MRI diagnosed endometriosis in the population cohort, 9 (7%) women had adenomyosis as a primary diagnosis. As described, women with only histologically-diagnosed endometriosis in the operative cohort or MRI diagnosed adenomyosis in the population cohort were not reclassified as endometriosis for analysis.

Table 1 presents the distribution of *in utero* exposures and birth size by endometriosis status in each cohort, and reflects relatively complete data with only one significant finding. Specifically, a higher percentage of women without than with endometriosis reported exposure to paternal smoking but only in the operative cohort, i.e., 35% and 26%, respectively. Of note is the reverse pattern for women in the population cohort (i.e., 24% and 36%, respectively). While not significant, women with endometriosis were less likely to report having been exposed to cigarettes or alcohol while *in utero* than women without endometriosis. None of the women in the population cohort reported DES exposure in contrast to 2% of women reporting such exposure in the operative cohort. However, DES exposure did not vary by endometriosis status in the operative cohort. No clear patterns were observed between any *in utero* exposures or birth size and endometriosis status irrespective of cohort (Table 2). The absence of women with endometriosis in the population cohort reporting no maternal smoking or alcohol exposure or having been born preterm precluded further analysis. A higher odds of an endometriosis diagnosis was observed for vitamin use (AOR=1.27), maternal cigarette smoking (AOR=1.16) and low birth weight (AOR=1.10) in the operative cohort only, but all confidence intervals included one. Paternal cigarette smoking (AOR=3.43) was associated with a higher odds of endometriosis diagnosis in the population cohort; however, the confidence intervals included one. Decreased odds of diagnosis were observed for caffeine (AOR=0.99), alcohol (AOR=0.82), preterm birth (AOR=0.98) and paternal cigarette smoking (AOR=0.72) in the operative cohort, though all confidence intervals included one. We did not further analyze multiple birth or DES exposure relative to endometriosis, given the low prevalence in each cohort. We also did not further assess birth length, given the high percentage of missing information (48% and 67% in the operative and population cohorts, respectively) that did not systematically vary by endometriosis status. Birth weight was missing in 17 and 20% in the operative and

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population cohorts, respectively, and did not vary by endometriosis status. Missing data for other in utero exposures was minimal ranging from 0 to 10 % for preterm birth and maternal vitamin usage, respectively, and did not vary by endometriosis status.

In sensitivity analysis examining the associations by various definitions of endometriosis or the comparison women, none of the *in utero* exposures were significantly associated with endometriosis with one exception. Preterm birth was associated with a decreased odds (AOR=0.41; 95% CI 0.18, 0.94) of diagnosis in the operative cohort when restricting to visual and histologically confirmed endometriosis in the operative cohort. Other important findings from the sensitivity analyses included rather consistent findings with the primary analysis except for a reverse in the direction of AORs for maternal caffeine consumption in all three sensitivity analyses and maternal cigarette smoking and low birth weight when restricting the comparison women in the operative cohort to those with a normal pelvis. All these reversals in the direction of the AORs may be due to randomness in the data as these effects are not statistically significant in either the primary or the sensitivity analyses.

DISCUSSION

We found no evidence of an association between *in utero* exposures and increased odds of an endometriosis diagnosis irrespective of study cohort in our primary analysis. In fact, most exposures (parental cigarette smoking, maternal consumption of alcohol or caffeine during pregnancy, and women's gestation) were associated with reduced AORs, while maternal vitamin usage, maternal cigarette smoking and birth weight elevated AORs. However, one significant finding emerged in the operative cohort for reduced odds of a preterm birth in our sensitivity analyses when restricting the diagnosis of endometriosis to those women who had both visual and histological confirmation.

Our findings are inconsistent with previous findings reported for the Nurses' Health Study II (NHS II). This well characterized cohort previously reported that decreased birth weight, multiple gestation and DES (but not preterm delivery) were associated with a diagnosis of endometriosis (6). The NHS II recorded birth weight categories and detected a trend in the RR of the categories, while we captured weight in pounds and ounces. We performed an additional model controlling for birth weight categories consistent with the NHS II, but failed to corroborate the association. One possible explanation for the difference in findings maybe reliance on self-reported endometriosis (or its absence) in the NHS II versus the ENDO Study's reliance on the diagnostic gold standard of visualized disease. Other plausible explanations include possible measurement error introduced by the index woman's proxy reporting on behalf of their mothers, or differing characteristics of the study populations stemming from changes in public perception about behaviors during pregnancy (e.g., drinking during pregnancy) or changes in clinical practices (e.g., DES and infertility treatment). The low prevalence of exposures in the ENDO Study underscores the importance of Type 2 errors, particularly with the potential for measurement error stemming from proxy reporting. We believe a reduction in power in the ENDO Study stemmed from a lower prevalence for exposures, given all the clinical and public health guidance targeting women of reproductive age to avoid smoking, drinking alcohol and caffeinated beverages during pregnancy.

The consistency of our findings by diagnostic criteria and choice of comparison group were largely upheld with the exception of a single significant finding for preterm birth. This finding may be a chance finding, given the number of comparisons made. The reversal in direction for maternal caffeine consumption and cigarette smoking during pregnancy and women's preterm birth status is perplexing. Possible explanations include these exposures being associated with more severe disease when restricting to stages 3–4 or histologically

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and visualized disease, or indicative of the fragility of our modeling techniques in the context of potential measurement error stemming from proxy reporting. Another limitation of our current study is that we did not include adolescents. An important consideration is the exclusion of women at the age extremes, if one posits that *in utero* exposures may disproportionately affect younger or older women. However, we know of no evidence to support this assumption in light of a relatively scant literature focusing on an *in utero* origin for endometriosis. Since women were not aware of their postoperative diagnosis at the baseline interview, we do not believe there are any systematic differences in the reporting of *in utero* exposures by endometriosis status in either cohort. Lastly, we recognize that the potential for residual confounding or misclassification bias on disease status stemming from our adherence to the gold standard of visualized disease in the operative cohort and MRI visualized endometriosis as the primary diagnosis in the population cohort. The extent to which undiagnosed disease impacts our results remains to be established. However, any bias introduced would suggest that misdiagnosed disease is systematically associated (or not) with the study's in utero exposures. Still, it is reassuring that our findings were generally consistent in sensitivity analyses.

The detection, diagnosis and staging of endometriosis remain very difficult. We attempted to compare the different modalities of staging endometriosis in the ENDO study by looking at both surgical as well as MRI diagnosis in order to compare them, while recognizing that there are no established MRI criteria to diagnosis the disease. An interesting finding when performing the sensitivity analyses by method of diagnosis of endometriosis (i.e. MRI or surgery) was the 7 women who had MRI-diagnosed endometriosis, but no endometriosis visualized at surgery. Two possibilities exist; first, these could be attributed to endometriomas, as endometriomas automatically upstage a woman to Stage III. In this way, MRI could be more sensitive at detecting small endometriomas which could theoretically be missed at the time of surgery. Because of the ASRM staging guidelines on endometriomas, MRI does in some ways detect more severe disease, albeit disease that might not be clinically evident at surgery. Alternatively, MRI could be overcalling other forms of endometriosis that is not confirmed at the time of surgery.

Similarly, evidence of adenomyosis is likely easier to detect in the MRI cohort, while mild peritoneal disease detection is likely higher in the surgical cohort. We hope to shed light on the difficultly in diagnosing endometriosis with different methods as part of the main study to attempt to clarify strengths and weakness of different modalities of detection. For our analysis here, it was reassuring that our findings of a lack of association of in utero exposures with endometriosis were consistent regardless of the method of diagnosing endometriosis.

The decreased odds of endometriosis associated with paternal cigarette smoking while the ENDO study participant was in utero is interesting, and to our knowledge has not been previously reported. While speculative, this finding may suggest a role for in utero environmental (aka second hand) tobacco smoke and endometriosis. Pregnant women's exposure to cigarette smoke is a function of both her active smoking and passive exposure from environmental sources. Irrespective of route of exposure, women's biologic dose of tobacco chemicals and metabolites may be the relevant exposure.

Our findings are consistent with a more recent study that also did not observe evidence in support of a developmental origin for surgically diagnosed endometriosis (16). Despite an equivocal literature, albeit a very limited knowledge base, it is important to continue to explore the etiology and timing of onset of endometriosis across the lifespan, i.e., preadolescence through menopause. This approach may require sampling frameworks inclusive of clinical and population cohorts; possibly utilizing a diad (mother-daughter) or

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triad (grandmother-mother-daughter) design to minimize reliance on proxy reporting of in utero exposures. Other data sources such as birth certificates, pregnancy diaries or journals mothers may have kept, women's baby books, or medical records would be extremely helpful in corroborating self-reported exposures such as gestation and birth size in future research focusing on the early origins of endometriosis hypothesis. Given the number of pregnancy cohorts conducted to date with maternal exposure characterization collectively prospectively throughout pregnancy, it may be possible to follow up daughters for the evaluation of endometriosis. We also encourage investigators to design research that can accommodate sensitivity analyses to ensure the detection of signals that may only be apparent for subgroups of women with endometriosis such as those with more severe disease.

In summary, endometriosis remains an elusive disease to diagnose and to study at the population level. We found no evidence of a relation between *in utero* exposures and endometriosis diagnosis in either of our two cohorts, though a relation for preterm birth decreased the odds of disease in analyses restricted to visually and histologically confirmed endometriosis in the operative cohort.

CONCLUSIONS

We found no consistent evidence that maternal behaviors during pregnancy significantly increased the odds of endometriosis in adult female offspring during adulthood. A more definitive answer awaits a careful measurement of developmental exposures, possibly from women's mothers themselves, combined with surgical diagnosis of endometriosis

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Table 1

Comparison of *in utero* exposures and endometriosis diagnosis by cohort, The ENDO Study.

	Operative Cohort (n=473)		Population Cohort (n=127)	
In Utero Exposure:	**None (n=283) # (%)**	**Endometriosis (n=190) # (%)**	**None (n=113) # (%)**	**Endometriosis (n=14) # (%)**
Maternal Behavior at/during Pregnancy (yes/no)				
Vitamin usage	135 (51%)	106 (58%)	56 (55%)	6 (46%)
Fertility treatment	4 (1%)	3 (2%)	3 (3%)	0 (0%)
Caffeine consumption	176 (64%)	102 (56%)	68 (64%)	8 (62%)
Cigarette consumption	48 (17%)	25 (13%)	15 (13%)	0 (0%)
Alcohol consumption	23 (8%)	10 (5%)	12 (11%)	0 (0%)
DES treatment	6 (2%)	3 (2%)	0 (0%)	0 (0%)
Paternal Behavior during Pregnancy (yes/no)				
Cigarette consumption	96 (35%)	48 (26%) *	27 (24 %)	5 (36%)
Index Woman				
Preterm birth	22 (8%)	15 (8%)	12 (11%)	0 (0%)
Multiple birth	5 (2%)	2 (1%)	1 (1%)	0 (0%)
Birth weight (pounds) [Mean (SD)]	7.1 (1.2)	7.0 (1.2)	7.3 (1.4)	7.6 (1.3)
Birth length (inches) [Mean (SD)]	20.0 (1.4)	19.8 (1.5)	20.1 (1.5)	18 (4.6)

* $p<0.05$

DES, denotes diethylstilbestrol

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Table 2

In utero exposures and the odds of an endometriosis diagnosis by cohort, The ENDO Study.

	Operative Cohort (n=473)		Population Cohort (n=127)	
In Utero Exposures	**Unadjusted OR (95% CI)**	**Adjusted OR[1] (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR[1] (95% CI)**
Maternal Behavior				
Vitamins	1.29 (0.87, 1.91)	1.27 (0.85, 1.91)	0.62 (0.18, 2.10)	0.60 (0.16, 2.15)
Caffeine	0.82 (0.54, 1.25)	0.99 (0.64, 1.54)	0.86 (0.22, 3.32)	0.76 (0.19, 3.03)
Cigarettes	1.15 (0.61, 2.16)	1.16 (0.61, 2.24)	--	--
Alcohol	0.76 (0.33, 1.75)	0.82 (0.35, 1.94)	--	--
Paternal Behavior				
Cigarettes	0.72 (0.44, 1.18)	0.72 (0.43, 1.19)	3.41 (0.82, 14.3)	3.43 (0.75, 15.7)
Index Woman	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Preterm	1.00 (0.50, 1.99)	0.98 (0.47, 2.03)	--	--
Low Birth Weight[2]	1.09 (0.92, 1.30)	1.10 (0.92, 1.32)	0.80 (0.50, 1.28)	0.81 (0.50, 1.32)

NOTE: *In utero* exposures were simultaneously included in model.

[1]Model adjusted for clinical site (California/Utah), currently smoking (yes/no), age at menarche (years) and BMI (weight in kg/height in m^2).

[2]As lower birth is associated with increased risk of endometriosis in previous studies, birth weight entered the model so that the estimated OR/AOR confers the effect of every pound less in weight.

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Table 3

In Utero exposures and odds of an endometriosis diagnosis, The ENDO Study – sensitivity analyses.

Exposures	**Visualized & Histologically-Confirmed Endometriosis vs. No Endometriosis (n=473)**	**Endometriosis Stages 3–4 vs. No Endometriosis (n=339)**	**Endometriosis vs. Women with Postoperative Diagnosis of Normal Pelvis (n=320)**
	Adjusted OR[1] (95% CI)	**Adjusted OR[1] (95% CI)**	**Adjusted OR[1] (95% CI)**
Maternal Behavior			
Vitamins	1.68 (0.92, 3.05)	1.63 (0.86, 3.08)	1.51 (0.92, 2.48)
Caffeine	1.17 (0.43, 3.20)	1.13 (0.40, 3.18)	1.22 (0.59, 2.53)
Cigarettes	2.84 (0.94, 8.60)	1.88 (0.58, 6.09)	0.82 (0.30, 2.25)
Alcohol	0.63 (0.33, 1.19)	0.97 (0.49, 1.92)	0.71 (0.40, 1.23)
Paternal Behavior			
Cigarettes	0.74 (0.34, 1.60)	0.91 (0.41, 2.03)	0.63 (0.35, 1.14)
Index Woman			
Preterm	0.41 (0.18, 0.94)	0.47 (0.19, 1.15)	0.98 (0.42, 2.25)
Low Birth Weight[2]	1.19 (0.93, 1.52)	1.03 (0.79, 1.33)	0.95 (0.77, 1.16)

NOTE: *In utero* exposures were simultaneously included in model.

[1] Model adjusted for clinical site (California/Utah), currently smoking (yes/no), age at menarche (years) and BMI (weight in kg/height in m^2).

[2] As lower birth is associated with increased risk of endometriosis in previous studies, birth weight entered the model so that the estimated OR/AOR confers the effect of every pound less in weight.