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Premature Birth and Large for Gestational Age Are Associated with Risk of Barrett's Esophagus in Adults

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Abstract

Background—Birth characteristics, including weight and gestational age, may be associated with risk of Barrett's esophagus (BE), the only known precursor for esophageal adenocarcinoma; however, data are limited.

Aims—To examine associations between various birth characteristics and BE, and whether these associations are mediated by known risk factors for BE.

Methods—Data were obtained from a cross-sectional study among eligible Veterans Affairs patients scheduled for an upper endoscopy, and a sample identified from primary care clinics. Participants underwent an esophagogastroduodenoscopy and completed a survey that captured information on sociodemographic and clinical factors, as well as birth information. We compared 263 patients with histologically confirmed BE to 1,416 controls without BE on endoscopy. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated using multivariate logistic regression.

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Results—Premature birth was independently associated with risk of BE after adjusted by age, sex, race, and other birth characteristics (OR 3.28, 95% CI 1.22–8.79). On the other hand, large for gestational age was inversely associated with risk of BE (OR 0.46, 95% CI 0.21–0.98). These effects were stronger for patients with long-segment BE than short-segment BE. The associations were not mediated by gastroesophageal reflux disease symptoms, use of proton pump inhibitors, *Helicobacter Pylori* infection, waist-hip-ratio, height or presence of hiatus hernia.

Conclusions—Premature birth and large for gestational age may be associated with risk of BE in adults. These associations do not appear to be mediated through known risk factors for BE; however, additional studies are required to confirm our findings.

Keywords

Barrett's esophagus; premature birth; birth weight for gestational age; risk factors

Introduction

Esophageal cancer has two main histologic subtypes: esophageal squamous-cell carcinoma and esophageal adenocarcinoma [1]. Over the past three decades, while the incidence of esophageal squamous-cell carcinoma has declined, the incidence of esophageal adenocarcinoma has increased rapidly in many western populations [2]. In the United States, esophageal adenocarcinoma is the fastest rising cancer among white men, increasing tenfold since the early 1970s [3]. Median survival for esophageal adenocarcinoma remains less than 12 months, and the overall 5-year survival rate for patients with esophageal adenocarcinoma in the United States is approximately 17% [4].

Barrett's esophagus (BE), a specialized intestinal columnar epithelium that replaces the normal squamous epithelium of the esophagus [5], is the only known precursor for esophageal adenocarcinoma. BE develops when refluxed gastric juice induced by gastroesophageal reflux disease (GERD) damages the superficial layers of the esophageal squamous epithelium, thereby exposing stem cells in the basal layers to gastric juice that intestinal-type columnar cells replace squamous cells [6]. Patients with BE have more than 10-fold higher risk of developing esophageal adenocarcinoma compared with the general population [7]. Although the evidence is not conclusive, periodic surveillance of patients with BE may lead to detection of dysplasia and early-stage cancer and reduce morbidity and mortality associated with esophageal adenocarcinoma [1, 8–11].

Epidemiological studies indicate that pre- and perinatal factors influence risk of developing cancer later in life [12]. For example, high birth weight for gestational age is associated with increased risk for all cancers combined in men [13], while high birth weight or birth length may confer a higher risk of adult cancers in women [14]. However, the associations with various birth characteristics may differ according to cancer site, and appear strongest for hormone-related cancers [12, 15, 16].

Results from three population-based studies conducted in Sweden by the same research group suggest that babies born prematurely or small for gestational age are at increased risk of developing esophageal adenocarcinoma in adulthood [17–19]. However, these studies

involved few esophageal adenocarcinoma cases (e.g., one study included only 4 cancer cases [17], another 67 [18]) and the effect sizes varied across the three studies. This same research group also examined the role of birth characteristics in the etiopathogenesis of BE and found that infants born small for gestational age (SGA) were at increased risk for BE whereas those born large for gestational age (LGA) had lower risk for BE [20]. There were no associations between mode of delivery, premature birth and risk of BE in that study. Given the associations of premature birth and birth weight with several established risk factors for BE (e.g., gastroesophageal reflux and body size [21–24]), it remains unknown whether these factors explain (i.e., mediate the effects of) any effect of birth characteristics on BE risk.

Here, we examined the relationship between various birth characteristics and the risk of BE. We then assessed whether these associations were mediated through known risk factors for BE.

Materials and Methods

Study population

Data were obtained from a cross-sectional study conducted at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) in Houston, Texas. Details of the cross-sectional study have been described in full previously [25, 26]. In brief, we recruited consecutive ambulatory patients who were scheduled for a non-urgent, elective esophagogastroduodenoscopy for upper gastrointestinal symptoms at the MEDVAMC from 15 February 2008 to 13 August 2013. We concurrently recruited patients attending one of seven primary care clinics at the MEDVAMC between 1 September 2008 and 8 May 2012. If they agreed to participate in the study, participants recruited from the primary care clinics underwent the study endoscopy as an additional procedure at the same time as their scheduled colonoscopy. These two populations (symptomatic and asymptomatic) represent the underlying population from which BE is diagnosed at the MEDVAMC. Informed consent was obtained from all participants, and this study was approved by the Institutional Review Board at Baylor College of Medicine and by Research and Development at the MEDVAMC, both in Houston, Texas.

Inclusion and exclusion criteria

Study eligibility was based on the following: (1) for the primary care participants, age between 50 and 80 years (unless there was a reason for colonoscopy screening before age 50, then age >40), and for the elective endoscopy participants, age between 40 and 80 years; (2) no previous or current gastroesophageal surgery or cancer; (3) no active lung, colon, or breast cancer; (4) no current use of anticoagulants, which would be a relative contraindication for mucosal biopsy during endoscopy; (5) no significant liver disease indicated by platelet count <70,000, ascites, or known gastroesophageal varices; and (6) no history of major stroke or mental conditions that would limit the ability to answer questions.

Data collection

All study participants underwent an upper endoscopy with systematic recording of suspected BE [25, 26]. At least one targeted biopsy specimen was taken from suspected areas using

jumbo biopsy forceps. A patient was considered to have BE ('case') if intestinalized columnar epithelium with goblet cells (confirmed by Alcian periodic acid Schiff stain) was present in at least one biopsy sample obtained from suspected BE in endoscopy. Controls were defined as participants without suspected BE on their study endoscopy. Patients with endoscopic BE only (defined by the presence of lesions visibly suspicious for BE in the absence of specialized intestinal epithelium histologically) were excluded from this analysis. Length of BE was determined by the Prague CM classification [27] and we categorized cases as short- (<3 cm) or long-segment (≥ 3 cm) BE when data were available. Erosive esophagitis was defined as Los Angeles classification grade A or higher [28]. We classified participants as being *Helicobacter pylori* positive if (1) organisms were seen and active gastritis was identified on histopathology of any of the gastric biopsy specimens; (2) *H. pylori* was detected in culture of gastric samples; or (3) if biopsy results were not available, review of the medical record showed a previous positive biopsy, the presence of serum antibodies, or previous treatment for *H. pylori*. Hiatus hernia was categorized into three grades (none, <3cm, and ≥ 3cm).

All study participants completed a computer-assisted survey before the study endoscopy. The survey elicited information about demographics (age, gender, and race/ethnicity), lifetime history and current use of alcohol and cigarette smoking, dietary intake, physical activity, medical history, onset, frequency and severity of heartburn or regurgitation symptoms, and use of acid suppressant medications including proton pump inhibitors (PPIs), statins, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. We measured each participants' waist and hip circumferences, height, and weight using a standardized protocol [25, 26] and calculated waist-hip-ratio (WHR) and body mass index (BMI, kg/m²).

We asked participants to report their birth weight ("How much did you weigh when you were born?"), whether or not they were born prematurely ("Were you born prematurely (a "premature baby" or "premie")?") and, if so, their gestational age ("How premature were you?"; captured as months of gestation), multiple birth ("Were you born as one of a set of twins/triplets/quadruplets, etc.?"), and their birth order ("How many full brothers and how many full sisters do you have, including both living and deceased?" and "How many are older than you?"). For analysis, participants were classified into four categories of birth weight (<2500 g, 2500–2999 g, 3000–3999 g, and ≥ 4000 g) and we used the 3000–3999 g group as the referent. We used the US birth weight for gestational age reference and data collected on birth weight and gestational age to derive a variable for birth weight for gestational age [29]. We categorized participants with birth weight for gestational age ≥ 10th percentile as being SGA and those < 10th percentile as being LGA. The referent group included those that were adequate for gestational age (AGA) (10th to 90th percentile) [29]. Finally, we categorized parity as first born child, second born, third born, and fourth born or more.

Participants were asked to report average cigarette and alcohol use during different age intervals (smoking, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years; alcohol, 20–29, 30–49, 50–79 years). We defined ever smokers as those who smoked more than 100 cigarettes, cigars or pipes over their lifetime, and ever drinkers as those who consumed any alcoholic beverage at least once a month for 6 months or longer. Current and former

smokers and alcohol drinkers were defined by their status one year prior to study enrolment with the intent of capturing a sustained period of change and opportunity for change in disease risk. Standard BMI categories were used for analysis (normal, $<25 \text{ kg/m}^2$; overweight, $25\text{--}29.9 \text{ kg/m}^2$; and obese $\geq 30 \text{ kg/m}^2$) and we defined high WHR as WHR ≥ 0.9 for men and WHR ≥ 0.85 for women. We defined duration of frequent GERD symptoms as the sum of the duration of at least weekly heartburn or regurgitation symptoms.

Statistical analysis

Our primary aim was to quantify associations between birth characteristics (premature birth, birth weight, birth weight for gestational age, multiple birth, and birth order) and the risk of BE. We compared the characteristics of cases to controls using Chi-square tests for categorical variables and Student t-test for continuous variables. We first calculated odds ratios (OR) and 95% confidence intervals (CIs) for associations between birth characteristics and risk of BE using unconditional logistic regression models adjusted for age (<60 , 60 years), sex, and race/ethnicity (non-Hispanic white, African American). We excluded Hispanic white participants from the current analysis owing to low numbers of cases from this group. We then simultaneously adjusted for the birth characteristics that were associated with BE in univariate analyses ($p < 0.05$) to identify those that were independently associated with BE. Finally, we fit further models that adjusted for factors that may mediate the associations with BE, including duration of frequent GERD symptoms (none, 1–4, 5–9, and 10 years), PPI use (yes, no), *H. pylori* infection (yes, no), WHR (low, high), height (quartiles: <171 , $171\text{--}<176$, $176\text{--}<181$, $\geq 181 \text{ cm}$), and hiatus hernia (none, $<3 \text{ cm}$, and $\geq 3 \text{ cm}$). We also estimated these associations separately for long-segment BE and short-segment BE. In a series of sensitivity analyses, we compared BE cases separately with primary care controls and endoscopy controls, we excluded cases with a diagnosis of BE prior to the study endoscopy (prevalent cases), and examined the associations among white men only. A 2-tailed P value of <0.05 was considered statistically significant and all statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA).

Results

1,952 patients (301 BE cases and 1,651 controls) were recruited into the cross-sectional study. Among cases and controls, 1,747 (89.5%) answered at least one question related to birth history and 1,679 additionally had complete information for GERD symptoms, PPI use, *H. pylori* infection, WHR, height, and hiatus hernia. There were no difference of demographic and endoscopic findings between responders (1,679 patients) and non-responders to the questions pertaining to birth (273 patients); however non-responders were slightly more likely than responders to have a history of GERD symptoms (Supplementary Table 1). Therefore, we included 1,679 patients (1,237 in endoscopy group and 442 in primary care group) in this study. There were 263 cases with BE (224 from the endoscopy cohort and 39 from the primary care cohort) and 1,416 controls (1013 endoscopy controls and 403 primary care controls). The vast majority were male (91.4%) and non-Hispanic white (63.9%), and mean age of the study participants was 60.3 years (standard deviation = 8.2).

Cases were significantly older and more likely to be male and non-Hispanic white compared with controls (Table 1). As expected, a high WHR, longer duration of frequent GERD symptoms, hiatus hernia, and use of PPIs were associated with increased risk of BE. Conversely, *H. pylori* positivity was associated with lower risk of BE. BMI, height, smoking status and alcohol status were not associated with BE and there was no difference in the prevalence of erosive esophagitis between cases and controls.

The distribution of each birth characteristic in cases and controls is provided in Table 2. The prevalence of premature birth (6.2% vs. 3.9%) and low birth weight (16.7% vs. 9.5%) was higher in cases than controls although they did not reach statistical significances. On the other hand, higher birth weight was less common in cases compared with controls (18.9% vs. 24.6%). Likewise, compared with controls, SGA was more frequent and LGA less frequent in cases. Finally, cases were more likely first born than controls (42.1% vs. 36.8%).

In adjusted models among those with complete birth data (i.e., answered all birth-related questions; $n = 86$ cases and $n = 446$ controls), premature birth was independently associated with the risk of BE (OR 3.28, 95% CI 1.22 – 8.79) (Table 3). While SGA was not associated with BE, we found evidence for an inverse association with LGA (OR 0.46, 95% CI 0.21 – 0.98). The associations between premature birth and BE may be stronger for patients with long-segment BE than short-segment BE (OR 5.56, 95% CI 1.35 – 23.0 for long-segment BE, OR 2.63, 95% CI 0.77 – 9.01 for short-segment BE) (Table 3); however, these analyses involved small case numbers (33 long-segment and 50 short-segment).

We found some evidence for associations between premature birth, LGA and known risk factors for BE (Supplementary Table 2). However, when we additionally adjusted our models for these factors, we found no evidence that the associations of premature birth and LGA with BE were explained by these factors (Table 3).

In a sensitivity analysis, the association between premature birth and BE remained when we separately compared cases with primary care controls (OR 4.26, 95% CI 1.87 – 9.71) and endoscopy controls (OR 2.73, 95% CI 1.00 – 7.44) (Supplementary Table 3). In addition, when we excluded patients with BE diagnosed prior to the study endoscopy (prevalent BE), there was a strong association between premature birth and risk of incident BE (OR 3.98, 95% CI 1.21 – 13.1) (Supplementary Table 4). There remained a strong inverse association between LGA and BE in these sensitivity analyses. Furthermore, using data from only white men, premature birth was independently associated with increased risk of BE (OR 5.48, 95% CI 1.75 – 17.1) and LGA was inversely associated with BE (OR 0.33, 95% CI 0.13 – 0.83) (Supplementary Table 5).

Discussion

We found that premature birth was associated with over 3-fold higher risk of BE. On the other hand, our data suggest that infants classified as LGA have lower risk of BE in adulthood than patients born as AGA. These associations were stronger for risk of long-segment BE than short-segment BE. We found no evidence that the associations with

premature birth or LGA were mediated through known BE risk factors, including GERD symptoms, PPI use, *H. pylori*, WHR, height and presence of hiatus hernia.

Premature birth and low birth weight are associated with increased risks of coronary heart disease, stroke, type 2 diabetes mellitus, adiposity, the metabolic syndrome, and osteoporosis in adult life [30–34]. High birth weight also increases the risk of type 2 diabetes in young adult males [35]. Furthermore, high birth weight is associated with cancer, especially hormone-related cancer such as breast, prostate, and non-seminoma testicular cancer [12, 15, 16]. Few previous studies have examined the association between birth characteristics and the risks of esophageal adenocarcinoma or BE, and the results have been conflicting. A population-based study among 3364 persons in Sweden reported that infants born premature or SGA had 7-fold higher risk of developing esophageal adenocarcinoma later in life [17]. However, this result was based on only four esophageal adenocarcinoma cases and a subsequent study from the same group (a case-control study involving 67 cases of esophageal adenocarcinoma) found no association with SGA [18]. In their follow-up case-control study involving 240 esophageal adenocarcinoma cases, the same group reported an inverse association between gestational age at birth and risk of adult esophageal adenocarcinoma, and again no association with SGA [19]. The same Sweden research group examined the association between birth characteristics and BE risk using data from a population-based case-control study involving 331 BE cases and 852 controls. In contrast to our findings, they found a significant association between SGA and BE but no association with premature birth [20].

GERD is the predominant risk factor for BE, with earlier onset of frequent GERD symptoms associated with especially high risk for BE [21]. Reflux and regurgitation are considered normal physiological features among newborns, and the majority of infants regurgitate during their first year of life [36, 37], particularly those born preterm or with a low birth weight [36, 38, 39]. In infants born prematurely, abnormal acid reflux associated transient lower esophageal sphincter relaxation is common [40]. In addition, feeding with nasogastric tube is common in infants born prematurely and can impair lower esophageal sphincter [41]. While we found no evidence in our study that GERD symptoms explain the association with premature birth, history of symptom is imperfectly correlated with the occurrence of reflux and we may not have captured the most relevant period of reflux exposure. Furthermore, prematurely birth is a risk for congenital anomalies [42], including gastroschisis and hiatus hernia [43]. Although hiatus hernia was not a mediator of the association between premature birth and risk of BE in our study, it is possible that other abnormalities (present at birth or that develop in childhood or early adulthood as a result of certain birth characteristics) may explain the association with BE in adulthood. Lastly, because the esophageal mucosa of infants born prematurely may be more vulnerable [20], earlier initiation of reflux in infants born prematurely or with a low birth weight may contribute to the observed increased risk of BE in adulthood. On the other hand, LGA was inversely associated with BE, which was consistent with the only previous study [20]. The mechanisms of this inverse association are not yet elucidated.

If our findings are replicated in future studies, it is feasible that history of birth may help inform risk stratification efforts for BE. Risk stratification based on the presence of GERD

symptoms alone has been shown to have only modest discriminatory ability, which improves when GERD symptoms are combined with other risk factors (including smoking and obesity) [44]. We previously derived a model that used age, sex, race, *H. pylori*, WHR, and GERD symptoms to predict risk of BE and had reasonable predictive ability (AUC = 0.80, 95% CI, 0.75 – 0.85) [45]. Adding a multibiomarker score also improved model discrimination; however, such a score would require additional cost [45]. In contrast, capturing a patient's history of birth would add no additional cost. Clearly further work is needed to identify persons at highest risk for underlying, undiagnosed BE, and whether history of birth may help predict the presence of BE still requires additional investigation.

The major strengths of the overall cross-sectional study include the prospective enrolment of study participants and the standardized histological definition used to diagnose BE. We used a comprehensive survey to capture information on multiple birth characteristics prior to the study endoscopy to limit recall bias and interviewer bias. Study participants were not aware of the objectives of the current study. We obtained detailed data on known and suspected risk factors for BE and, for the first time, examined their role as mediators. There are several limitations to our study. First, our findings were based on birth information obtained by self-report and not birth record. The reliability of self-reported birth weight of elderly subjects is reported to be moderate to poor (the correlation between self-reported and actual birth weight was 0.64) [46]. While this may have resulted in misclassification of the exposure, we would not expect the misclassification to be differential between cases and controls as case-status was not known at the time of survey completion. Biased recall among prevalent cases is possible; however, the exclusion of these cases from the analysis did not appreciably alter our results. This study involved only a fraction of participants in the parent study due to missing data on birth-related questions. When we compared subjects with and without complete data for birth information, subjects with complete data for birth information were younger and more likely to be female and have a history of GERD symptoms (Supplementary Table 6). It is unclear how this may have affected the findings of our study. However, because we limited the potential for bias due to differential loss of data by having participants complete the questionnaire prior to their study EGD, it is unlikely to explain entirely the observed associations. Finally, because we studied predominantly male veterans, our results may not be generalizable to women and nonveterans.

In conclusion, premature birth and LGA may be independently associated with risk of BE in adults and we found no evidence that these associations were mediated through GERD symptoms, adult body size or other BE risk factors. However, further studies are needed to clarify the associations and potential mechanisms, and, if our findings are replicated, should consider the utility of birth characteristics in clinical risk stratification for BE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Sociodemographic and lifestyle factors of Barrett's esophagus cases and controls without Barrett's esophagus

	BE cases	Controls	P
N	263	1416	
Age			
Mean $\pm$ SD	61.6 $\pm$ 7.8	60.1 $\pm$ 8.2	0.01
60	187	809	(57.1%) <0.01
<60	76	607	(42.9%)
Sex			
Male	256	1278	(90.3%) <0.01
Female	7	138	(9.7%)
Race			
Non-Hispanic White	231	842	(59.5%) <0.01
African American	32	574	(40.5%)
<i>Helicobacter pylori</i>			
Positive	46	411	(29.0%) <0.01
Negative	217	1005	(71.0%)
Erosive esophagitis			
Yes	28	171	(12.1%) 0.51
No	235	1245	(87.9%)
Height			
Mean $\pm$ SD	176.4 $\pm$ 6.7	176.4 $\pm$ 8.3	0.92
<171cm	51	336	(23.7%) <0.01
171 – 176cm	75	363	(25.6%)
176–181cm	81	312	(22.0%)
181cm	56	405	(28.6%)
Body mass index (BMI)			
Mean $\pm$ SD	29.9 $\pm$ 5.3	30.0 $\pm$ 6.0	0.86
Normal (<25)	45	270	(19.1%) 0.73
Overweight (25-29)	96	515	(36.4%)
Obese (≥ 30)	122	631	(44.6%)

	BE cases	Controls	P
Waist-hip-ratio			
Mean ± SD	0.97 ± 0.07	0.95 ± 0.07	<0.01
Low	23 (8.7%)	212 (15.0%)	0.01
High	240 (91.3%)	1204 (85.0%)	
Smoking status			
Never	63 (24.0%)	400 (28.2%)	0.36
Former	116 (44.1%)	587 (41.5%)	
Current	84 (31.9%)	429 (30.3%)	
Drinking status			
Never drank	22 (8.4%)	130 (9.2%)	0.86
Former drinker	97 (36.9%)	533 (37.6%)	
Current drinker	144 (54.8%)	753 (53.2%)	
GERD symptoms			
None	97 (36.9%)	746 (52.7%)	<0.01
1 – 4 years	6 (2.3%)	15 (1.1%)	
5 – 9 years	5 (1.9%)	42 (3.0%)	
10 years	155 (58.9%)	613 (43.3%)	
Hiatus hernia			
None	36 (13.7%)	526 (37.1%)	<0.01
<3cm	111 (42.2%)	589 (41.6%)	
3cm	116 (44.1%)	301 (21.3%)	
PPI use			
Yes	183 (69.6%)	733 (51.8%)	<0.01
No	80 (30.4%)	683 (48.2%)	

* Missing category is not included in analysis.

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor;

Table 2
Birth characteristics of Barrett's esophagus cases and controls without Barrett's esophagus

	BE cases	Controls	P
N	263	1416	
Prematurely born			
Yes	16	54	0.09
No	243	1342	(96.1%)
Missing	4	20	
Birth weight (g)			
<2500	15	45	0.12
2500–2999	10	74	(15.7%)
3000–3999	48	237	(50.2%)
4000+	17	116	(24.6%)
Missing	173	944	
Birth weight for gestational age			
SGA	18	88	0.25
AGA	57	275	(60.2%)
LGA	11	94	(20.6%)
Missing	177	959	
Multiple birth			
Yes	4	22	0.62
No	257	1388	(98.4%)
Missing	2	6	
Birth order			
First born	109	508	<0.01
Second born	84	348	(25.2%)
Third born	29	204	(14.8%)
Fourth born or more	37	320	(23.2%)
Missing	4	36	

* Missing category is not included in analysis.

BE, Barrett's esophagus; SGA, small for gestational age; AGA, adequate for gestational age; LGA, large for gestational age

Table 3
ORs and 95% CIs for associations between birth characteristics and risk of Barrett's esophagus

(a)		Controls	BE cases		Crude OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR** (95% CI)
Prematurely born		N = 446 N (%)	N = 86 N (%)				
Yes		21 (4.7)	8 (9.3)		2.08 (0.89 – 4.85)	3.28 (1.22 – 8.79)	4.08 (1.38 – 12.05)
No		425 (95.3)	78 (90.7)		1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Birth weight for gestational age							
SGA		87 (19.5)	18 (20.9)		1.05 (0.59 – 1.88)	1.17 (0.63 – 2.18)	1.23 (0.62 – 2.43)
AGA		266 (59.6)	57 (66.3)		1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
LGA		93 (20.9)	11 (12.8)		0.55 (0.28 – 1.09)	0.46 (0.21 – 0.98)	0.46 (0.21 – 1.03)
Birth order							
First born		182 (40.8)	37 (43.0)		1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Second born		115 (25.8)	30 (34.9)		1.28 (0.75 – 2.19)	1.25 (0.71 – 2.20)	1.28 (0.70 – 2.33)
Third born		61 (13.7)	9 (10.5)		0.73 (0.33 – 1.59)	0.84 (0.37 – 1.89)	0.89 (0.37 – 2.15)
Fourth born or more		88 (19.7)	10 (11.6)		0.56 (0.27 – 1.18)	0.76 (0.35 – 1.65)	0.84 (0.37 – 1.92)
(b)		Controls	Long-segment BE		Short-segment BE		
		N = 446 N (%)	n = 33 N (%)	Adjusted OR* (95% CI)	n = 50 N (%)	Adjusted OR* (95% CI)	
Prematurely born							
Yes		21 (4.7)	4 (12.1)	5.56 (1.35 – 22.96)	4 (8.0)	2.63 (0.77 – 9.01)	
No		425 (95.3)	29 (87.9)	1.00 (Referent)	46 (92.0)	1.00 (Referent)	
Birth weight for gestational age							
SGA		87 (19.5)	9 (27.3)	1.61 (0.67 – 3.90)	8 (16.0)	0.86 (0.37 – 1.98)	
AGA		266 (59.6)	20 (60.1)	1.00 (Referent)	35 (70.0)	1.00 (Referent)	
LGA		93 (20.9)	4 (12.1)	0.35 (0.10 – 1.27)	7 (14.0)	0.54 (0.22 – 1.33)	
Birth order							
First born		182 (40.8)	17 (51.5)	1.00 (Referent)	18 (36.0)	1.00 (Referent)	
Second born		115 (25.8)	12 (36.4)	1.18 (0.52 – 2.68)	18 (36.0)	1.50 (0.73 – 3.05)	
Third born		61 (13.7)	2 (6.1)	0.45 (0.10 – 2.07)	6 (12.0)	1.03 (0.38 – 2.77)	

(b)	Long-segment BE		Short-segment BE	
	Controls N = 446 N (%)	n = 33 N (%)	n = 50 N (%)	Adjusted OR* (95% CI)
Fourth born or more	88 (19.7)	2 (6.1)	8 (16.0)	1.14 (0.46 – 2.83)

* ; adjusted by age, sex, race, premature born, birth weight for gestational age, and birth order

** ; adjusted by age, sex, race, premature born, birth weight for gestational age, birth order, GERD symptoms, PPI use, *H. pylori*, WHR, height, and hiatus hernia, BE, Barrett's esophagus; OR, odds ratio; CI, confidence interval; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; WHR, waist-hip-ratio, SGA, small for gestational age; AGA, adequate for gestational age; LGA, large for gestational age