


# Diabetes in Relation to Barrett's Esophagus and Adenocarcinomas of the Esophagus: A Pooled Study From the International Barrett's and Esophageal Adenocarcinoma Consortium

Jessica L. Petrick, PhD, MPH <sup>1</sup>; Nan Li, PhD<sup>2</sup>; Lesley A. Anderson, PhD, MPHE<sup>3</sup>; Leslie Bernstein, PhD<sup>4</sup>; Douglas A. Corley, MD, PhD<sup>5</sup>; Hashem B. El Serag, MD, MPH<sup>6</sup>; Sheetal Hardikar, PhD, MBBS<sup>7,8</sup>; Linda M. Liao, PhD, MPH<sup>1</sup>; Geoffrey Liu, MD, MSc<sup>9</sup>; Liam J. Murray, MD<sup>3</sup>; Joel H. Rubenstein, MD, MSc<sup>10,11</sup>; Jennifer L. Schneider, MPH<sup>5</sup>; Nicholas J. Shaheen, MD, MPH<sup>12</sup>; Aaron P. Thrift, PhD<sup>13,14</sup>; Piet A. van den Brandt, MD<sup>15</sup>; Thomas L. Vaughan, MD, MPH<sup>16</sup>; David C. Whiteman, PhD<sup>17</sup>; Anna H. Wu, PhD<sup>18</sup>; Wei K. Zhao, MPH<sup>5</sup>; Marilie D. Gammon, PhD<sup>19</sup>; and Michael B. Cook, PhD<sup>1</sup>

**BACKGROUND:** Diabetes is positively associated with various cancers, but its relationship with tumors of the esophagus/esophago-gastric junction remains unclear. **METHODS:** Data were harmonized across 13 studies in the International Barrett's and Esophageal Adenocarcinoma Consortium, comprising 2309 esophageal adenocarcinoma (EA) cases, 1938 esophagogastric junction adenocarcinoma (EGJA) cases, 1728 Barrett's esophagus (BE) cases, and 16,354 controls. Logistic regression was used to estimate study-specific odds ratios (ORs) and 95% CIs for self-reported diabetes in association with EA, EGJA, and BE. Adjusted ORs were then combined using random-effects meta-analysis. **RESULTS:** Diabetes was associated with a 34% increased risk of EA (OR, 1.34; 95% CI, 1.00-1.80;  $I^2 = 48.8%$  [where 0% indicates no heterogeneity, and larger values indicate increasing heterogeneity between studies]), 27% for EGJA (OR, 1.27; 95% CI, 1.05-1.55;  $I^2 = 0.0%$ ), and 30% for EA/EGJA combined (OR, 1.30; 95% CI, 1.06-1.58;  $I^2 = 34.9%$ ). Regurgitation symptoms modified the diabetes-EA/EGJA association ( $P$  for interaction = .04) with a 63% increased risk among participants with regurgitation (OR, 1.63; 95% CI, 1.19-2.22), but not among those without regurgitation (OR, 1.03; 95% CI, 0.74-1.43). No consistent association was found between diabetes and BE. **CONCLUSIONS:** Diabetes was associated with increased EA and EGJA risk, which was confined to individuals with regurgitation symptoms. Lack of an association between diabetes and BE suggests that diabetes may influence progression of BE to cancer. *Cancer* 2019;125:4210-4223. © 2019 American Cancer Society.

**KEYWORDS:** Barrett esophagus, diabetes, epidemiology, esophageal adenocarcinoma, meta-analysis.

## INTRODUCTION

Esophageal adenocarcinoma (EA) incidence has increased approximately 600% over the last 35 years and, until the recent time period, was one of the most rapidly increasing cancer types in the United States and other Western countries.<sup>1-3</sup> The incidence of the anatomically linked esophagogastric junction adenocarcinoma (EGJA) has also increased but less rapidly than EA.<sup>4</sup> EA and EGJA are often considered as similar clinical entities because both are cancers at or near the gastroesophageal junction, have similar 5-year survival rates, and have comparable survival according to tumor stage.<sup>5</sup> The only known potential precursor of EA/EGJA is Barrett's esophagus (BE), which is associated with a 10-times

**Corresponding author:** Jessica L. Petrick, PhD, MPH, Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6E-334 Bethesda, MD 20892-9774; jessica.petrick@nih.gov

<sup>1</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; <sup>2</sup>Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island; <sup>3</sup>Center for Public Health, School of Medicine, Dentistry, and Biomedical Sciences, Queens University Belfast, Belfast, Northern Ireland; <sup>4</sup>Division of Biomarkers of Early Detection and Prevention, Department of Population Sciences, City of Hope Comprehensive Cancer Center, Duarte, California; <sup>5</sup>Division of Research, Kaiser Permanente, Northern California, Oakland, California; <sup>6</sup>Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas; <sup>7</sup>Department of Population Health Sciences, University of Utah, Salt Lake City, Utah; <sup>8</sup>Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, Washington; <sup>9</sup>Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada; <sup>10</sup>Ann Arbor Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan; <sup>11</sup>Barrett's Esophagus Program, Division of Gastroenterology, University of Michigan, Ann Arbor, Michigan; <sup>12</sup>Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina; <sup>13</sup>Section of Epidemiology and Population Sciences, Department of Medicine, Baylor College of Medicine, Houston, Texas; <sup>14</sup>Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas; <sup>15</sup>Department of Epidemiology, GROW School for Oncology and Biology, Maastricht University Medical Center, Maastricht, Netherlands; <sup>16</sup>Program in Cancer Epidemiology, Fred Hutchinson Cancer Center, Seattle, Washington; <sup>17</sup>Cancer Control, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; <sup>18</sup>Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California; <sup>19</sup>Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina

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to 40-times increased risk of EA/EGJA.<sup>6-8</sup> Among individuals older than 50 years with gastroesophageal reflux disease (GERD), an estimated 10% also have BE.<sup>9</sup> In the last 30 years, BE diagnosis increased 200% to 300%, independent of the number of gastrointestinal endoscopies performed.<sup>10-12</sup>

Obesity has previously been associated with BE<sup>13</sup> and EA/EGJA.<sup>14</sup> Two hypotheses have been proposed for the association between obesity and these tumors: 1) mechanical effects on the integrity of the esophago-gastric junction, including both direct somatic pathways, whereby central adiposity promotes the development of GERD, which may then promote BE development,<sup>15</sup> and indirect pathways, whereby diabetes induces mechanophysiological changes in the esophagus, which may then promote the development of tumors<sup>16</sup>; or 2) systemic metabolic alterations because of obesity increasing the levels of various hormones, including insulin, which may promote the development of BE or the progression of BE to cancer.<sup>17</sup>

Type 2 diabetes, which accounts for 95% of diabetes diagnoses,<sup>18</sup> is often characterized by hyperinsulinemia and has been associated with a higher risk of various cancers, including malignancies of the liver, pancreas, endometrium, colorectum, breast, and bladder.<sup>19,20</sup> Diabetes has been increasing in prevalence, and 12% of adults in the United States<sup>18,19</sup> and 9% worldwide<sup>21</sup> have prevalent diabetes. However, the association between diabetes and EA/EGJA remains understudied,<sup>22</sup> with several studies suggesting an increased risk<sup>23-28</sup> and others showing no association.<sup>29-31</sup> In addition, few studies have assessed the association between diabetes and BE, with inconsistent results.<sup>31-35</sup> Thus, we used studies from the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON; <http://beacon.tlvnet.net/>) to examine the associations of diabetes with risk of BE and EA/EGJA.

## MATERIALS AND METHODS

### *Study Design and Population*

This study draws on the resources of BEACON, which, as previously described,<sup>36</sup> was formed to facilitate pooling of epidemiologic studies focused on the BE/EA continuum. In brief, this consortium was formed in 2005 by an international group of investigators to provide an open epidemiologic research forum for all completed or ongoing, population-based studies of EA or BE.<sup>36</sup> Thus, this consortium allows for pooled analyses of individual-level data and avoids reliance on only published data. The current study pools information

from 13 BEACON studies that included assessment of diabetes: 3 cohort studies and six case-control studies examining EA or EGJA (see Supporting Table 1) and 1 cohort study and 5 case-control studies examining BE (see Supporting Table 2). Two studies included examination of both BE and EA/EGJA.<sup>37,38</sup> Of the 9 EA and EGJA studies, 6 were conducted in North America, 2 were conducted in Europe, and 1 was conducted in Australia. Of the 6 BE studies, 3 were conducted in North America, 2 were conducted in Europe, and 1 was conducted in Australia. Detailed descriptions of recruitment procedures can be found in study-specific publications.<sup>32,37-48</sup> Institutional review board or research ethics committee approval was obtained by each sponsoring institution.

Cases were categorized as EA, EGJA, or BE. We also combined EA and EGJA cases (EA/EGJA). Case eligibility was determined by the parent studies based on endoscopy, pathology, and/or medical records. Histology and site determination were based on radiology, surgery, pathology, and/or endoscopy reports or linkage with a cancer registry.

For the cohort studies, a nested case-control approach was used. The case-to-control ratio used was 1:2 in the Netherlands Cohort Study (NLCS), 1:4 in the National Institutes of Health-AARP Diet and Health Study (NIH-AARP), and 1:8 in the Kaiser-Permanente Multiphasic Health Checkup Study (MHC). The EA/EGJA case-control studies recruited population-based controls, whereas the BE case-control studies recruited population-based and/or endoscopy controls.

The analytic study population was restricted to non-Hispanic whites because there were few cases from nonwhite ethnic groups (EA/EGJA: 60 black, 127 Hispanic, 77 other race or ethnic group; BE: 54 black, 23 Hispanic, 10 other race or ethnic group). Our pooled study population included 2309 EA cases, 1938 EGJA cases, 1728 BE cases, and 16,354 controls. Participants had a mean age of 60 years and were more likely to be men (73.5%).

### *Exposure*

To provide comparable data from the parent studies, we harmonized responses from the 9 EA/EGJA and 6 BE parent studies for diabetes and potential covariates. To assess diabetes, most studies used a variation of the question, "Did a doctor ever tell you that you had diabetes?" Prior studies have shown that the agreement between self-reported diabetes compared with medical record review ranges from 83% to 98%.<sup>49-51</sup> In addition, the Newly

Diagnosed Barrett's Esophagus Study (NDB) also measured fasting glucose to determine undiagnosed diabetes, which resulted in 11 additional participants classified with diabetes (7.6% of total participants with diabetes in the NDB study).<sup>33</sup> Only 1 study, Factors Influencing the Barrett's/Adenocarcinoma Relationship Study (FINBAR),<sup>37</sup> specifically asked about type 1 versus type 2 diabetes. For the studies that had age at diabetes diagnosis available (5 EA/EGJA studies and 2 BE studies), a diagnosis after age 30 years was assumed to be type 2 diabetes because most type 1 diabetes is diagnosed peripuberty. In addition, 95% of diabetes is type 2.<sup>18</sup> Duration of type 2 diabetes in years was examined as a continuous variable for tests of linear trends and categorized as from 0.5 to 3, from >3 to 5, from >5 to 10, and >10 years.<sup>23,24</sup> BEACON study responses for other covariates were harmonized and have been previously described for cigarette smoking,<sup>52,53</sup> alcohol consumption,<sup>54,55</sup> body mass index (BMI),<sup>13,14</sup> waist circumference,<sup>13,14</sup> nonsteroidal anti-inflammatory drug use,<sup>56,57</sup> and reflux symptoms.<sup>58</sup>

### Statistical Analyses

For our pooled study, we conducted a 2-step analytic approach. First, we used multivariable unconditional (for case-control studies) or conditional (for matched case-control studies nested within cohorts) logistic regression to estimate study-specific odds ratios (ORs) and 95% CIs for the association between diabetes and EA, EGJA, combined EA/EGJA, or BE. Then, the study-specific estimates were pooled using meta-analytic techniques.<sup>59</sup> Estimates generated with fixed-effects and random-effects models were similar. Given that the latter are more robust to study heterogeneity,<sup>60</sup> we only present random-effects models. Between-study heterogeneity was assessed using a chi-square test based on the Q statistic and the I<sup>2</sup> statistic (where 0% indicates no heterogeneity and larger values indicate increasing heterogeneity between studies).<sup>61</sup> Although investigating differences across studies includes quantification of heterogeneity, the most critical aspects are ensuring that the studies are comparable in clinical and methodologic aspects,<sup>61</sup> as BEACON was designed. To demonstrate that there was no selection bias (ie, "publication bias"), funnel plots were visually inspected for asymmetry and quantitatively assessed using the Begg and Mazumdar rank correlation test<sup>62</sup> and the Egger linear regression test.<sup>63</sup> To determine the influence of individual studies, we conducted a meta-influence analysis, whereby we excluded 1 study at a time and re-estimated the summary effect estimates.

Potential confounders<sup>64</sup> included age (at diagnosis for cases and at interview for controls), sex, education (<high school, high school graduate/vocational school, college graduate for BE studies; study-specific education categories for EA and EGJA studies), cigarette smoking (ever, never; current, former, never; duration in years; and pack-years), alcohol consumption (drinks per day), BMI (kg/m<sup>2</sup>), waist circumference (cm), nonsteroidal anti-inflammatory drug use (ever, never), and fruit and vegetable consumption (servings per day). Age, sex, and BMI were included a priori as confounders. For the other potential confounders, if the log OR changed by ≥10% because of variable elimination in any parent study, the variable was considered a confounder and was retained in all models.<sup>64</sup> Final models included age (continuous), sex, smoking status (ever, never), and BMI (continuous).

We considered effect measure modification by sex, BMI (<25/≥25 kg/m<sup>2</sup>), smoking (ever/never), and age (<60/≥60 years). In addition, reports of heartburn (retrosternal burning), regurgitation, and any reflux symptoms (ie, heartburn or regurgitation) were assessed as potential modifiers (ever/never). Heartburn symptoms were defined as burning or aching pain behind the breastbone/sternum, and regurgitation symptoms were defined as a sour taste in the mouth resulting from regurgitation of acid, bile, or other stomach contents. In the NLCS, reflux symptoms were defined as any report of heartburn, hiatal hernia, esophagitis, gastritis, or an esophageal or stomach/duodenal condition treated with antacids or H<sub>2</sub> antagonists. For analyses of effect measure modification, we used a pooled data set of individual-level data with additional adjustment for parent study instead of the 2-step meta-analytic approach. Departures from the multiplicative null were evaluated through stratification and by using likelihood ratio tests from nested logistic regression models.<sup>64</sup> Departures from the additive null were approximated by calculating the relative excess risk due to interaction (RERI) ( $RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1$ ; null hypothesis = 0), the synergy index (S) ( $S_{OR} = [OR_{11} - 1]/[(OR_{10} - 1) + (OR_{01} - 1)]$ ; null hypothesis = 1), and the attributable proportion (AP) because of interaction, which assumes a causal relationship ( $AP_{OR} = RERI_{OR}/OR_{11}$ ; null hypothesis = 0).<sup>65,66</sup>

### Sensitivity Analysis

Because not all studies assessed heartburn and regurgitation symptoms, we conducted additional effect measure modification models that were restricted to studies that ascertained both of these exposures. For EA/EGJA, this included the Australian Cancer Study

**TABLE 1.** Descriptive Characteristics of the Pooled Study Population: Barrett's and Esophageal Adenocarcinoma Consortium

Characteristic	BE Population, No. (%)			Adenocarcinoma Population, No. (%)		
	BE Cases, n = 1728	Controls		Adenocarcinoma Cases		Controls, n = 11,841
		Population-Based, n = 2830	GERD/Endoscopy, n = 1683	EA, n = 2309	EGJA, n = 1938	
Age: Mean ± SD, y	60.5 ± 9.0	60.5 ± 7.9	57.5 ± 11.8	62.3 ± 8.8	62.0 ± 8.7	60.1 ± 9.4
Sex						
Men	1256 (72.7)	2073 (73.2)	1231 (73.1)	2059 (89.2)	1666 (86.0)	8127 (68.6)
Women	472 (27.3)	757 (26.8)	452 (26.9)	250 (10.8)	272 (14.0)	3713 (31.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
Cigarette smoking						
Never	547 (32.3)	1103 (39.3)	624 (38.5)	471 (20.8)	383 (20.3)	4187 (36.4)
Ever	1147 (67.7)	1700 (60.7)	995 (61.5)	1792 (79.2)	1505 (79.7)	7324 (63.6)
Missing	34	27	64	46	50	330
BMI: Mean ± SD, kg/m <sup>2</sup>	27.8 ± 4.8	27.4 ± 5.1	29.1 ± 5.8	28.0 ± 4.9	27.4 ± 4.7	26.4 ± 4.4
Missing	41	60	31	52	47	298

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; EA, esophageal adenocarcinoma; EGJA, esophagogastric junction adenocarcinoma; GERD, gastroesophageal reflux disease.

(ACS), FINBAR, and the Los Angeles County Multi-Ethnic Case-Control Study (LAS). For BE, this included FINBAR, NDB, the Study of Digestive Health (SDH), and the Epidemiologic Case-Control Study of Barrett's Esophagus (UNC). We also examined heartburn and regurgitation symptoms categorized as "none," "<weekly," and "≥weekly," the latter of which we term "recurrent" symptoms. Analyses were conducted using SAS version 9.4 (SAS Institute Inc) and Stata version 14.0 (StataCorp LP).

## RESULTS

Descriptive characteristics of cases and controls are shown in Table 1. Both EA and EGJA cases were more likely than the population-based controls to be smokers (79.2% and 79.7% vs 63.6%, respectively) and had a slightly higher BMI (28.0 and 27.4 vs 26.4 kg/m<sup>2</sup>, respectively). In the 6 studies with symptoms available, EA and EGJA cases were more likely to have reported reflux symptoms than controls (58.1% and 58.8% vs 45.2%, respectively). In the BE studies, the mean BMI was comparable between BE cases and population-based controls (27.8 vs 27.4 kg/m<sup>2</sup>, respectively) but lower than the endoscopy-based controls (29.1 kg/m<sup>2</sup>). However, BE cases had a higher proportion of smokers (67.7%) compared with both control groups (60.7% and 61.5%, respectively). The prevalence of reflux symptoms was similar between BE cases and endoscopy controls (56.3% vs 66.5%, respectively) but lower in population-based controls (24.6%).

The associations between diabetes and risk of EA/EGJA are shown in Table 2 and Figure 1. In multivariable

analyses, a diabetes diagnosis was associated with a 34% increased risk of EA (OR, 1.34; 95% CI, 1.00-1.80; I<sup>2</sup> = 48.8%), a 27% increased risk of EGJA (OR, 1.27; 95% CI, 1.05-1.55; I<sup>2</sup> = 0.0%), and a 30% increased risk of EA/EGJA (OR, 1.30; 95% CI, 1.06-1.58; I<sup>2</sup> = 34.9%). Results were robust in the meta-influence analysis, dropping 1 study at a time (see Supporting Fig. 1). Selection bias of studies included in BEACON was unlikely as assessed by examination of the funnel plots and with the Begg and Mazumdar ( $P > .05$ ) and Egger ( $P > .05$ ) tests (see Supporting Fig. 2). When the analysis was restricted to individuals with self-reported or suspected type 2 diabetes (ie, classifying individuals with a self-report of diabetes after age 30 years as type 2), compared with individuals without a diabetes diagnosis, diabetes was associated with a nonsignificant 17% increased risk of EA, EGJA, and EA/EGJA (Table 2). There was no trend between duration of type 2 diabetes and EA ( $P$  for trend = .3), EGJA ( $P$  for trend = .5), or EA/EGJA ( $P$  for trend = .3).

As shown in Table 3, the association between diabetes and risk of EA/EGJA was modified by regurgitation symptoms ( $P$  for interaction = .04). Diabetes was associated with a 63% increased risk of EA/EGJA among individuals with regurgitation symptoms (OR, 1.63; 95% CI, 1.19-2.22), but there was no association between diabetes and EA/EGJA among individuals without regurgitation symptoms (OR, 1.03; 95% CI, 0.74-1.43). When cross-classified, the group with diabetes but without regurgitation symptoms was not at an increased risk of EA/EGJA (OR, 1.03; 95% CI, 0.74-1.43), the group with regurgitation but without diabetes was at a 2-times increased risk of EA/EGJA (OR, 2.10;

**TABLE 2.** Adjusted Odds Ratios and 95% CIs for Associations Between Diabetes and Esophageal and Esophagogastric Junction Adenocarcinomas<sup>a</sup>

Case Type	No. of Cases	No. of Controls	OR (95% CI)	I <sup>2</sup> , % <sup>b</sup>	P for Heterogeneity
<b>EA</b>					
Diabetes					
No	1942	7577	Referent		
Yes	238	554	1.34 (1.00-1.80)	48.8	.05
Type 2 diabetes <sup>c</sup>					
No	928	5444	Referent		
Yes	147	544	1.17 (0.90-1.51)	0.0	.8
Duration of type 2 diabetes, y					
0.5-3	38	174	1.01 (0.67-1.52)	0.0	.8
>3 to 5	14	39	1.31 (0.67-2.56)	0.0	.7
>5 to 10	47	148	1.33 (0.89-1.97)	0.0	.9
>10	45	183	1.22 (0.78-1.90)	19.6	.3
<b>EGJA<sup>d</sup></b>					
Diabetes					
No	1622	6584	Referent		
Yes	184	463	1.27 (1.05-1.55)	0.0	.6
Type 2 diabetes <sup>c</sup>					
No	972	4918	Referent		
Yes	123	459	1.17 (0.91-1.51)	0.0	.6
Duration of type 2 diabetes, y					
0.5-3	35	138	1.29 (0.84-1.99)	0.0	.7
>3 to 5	11	39	1.12 (0.45-2.74)	27.2	.2
>5 to 10	32	119	1.31 (0.68-2.54)	43.7	.1
>10	42	163	1.12 (0.66-1.92)	40.7	.1
<b>All EA and EGJA</b>					
Diabetes					
No	3564	10,498	Referent		
Yes	422	735	1.30 (1.06-1.58)	34.9	.1
Type 2 diabetes <sup>c</sup>					
No	1900	6699	Referent		
Yes	270	734	1.17 (0.96-1.42)	0.0	.7
Duration of type 2 diabetes, y					
0.5-3	73	250	1.12 (0.82-1.54)	0.0	.6
>3 to 5	25	39	1.08 (0.60-1.93)	4.2	.4
>5 to 10	79	202	1.37 (1.00-1.88)	0.0	.7
>10	87	243	1.09 (0.67-1.76)	56.0	.04

Abbreviations: BMI, body mass index; EA, esophageal adenocarcinoma; EGJA, esophagogastric junction adenocarcinoma; OR, odds ratio.

<sup>a</sup>Analyses were adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous).

<sup>b</sup>The I<sup>2</sup> statistic indicates the percentage of variation across studies that is due to heterogeneity rather than chance; 0% indicates no heterogeneity, and larger values indicate increasing heterogeneity between studies.

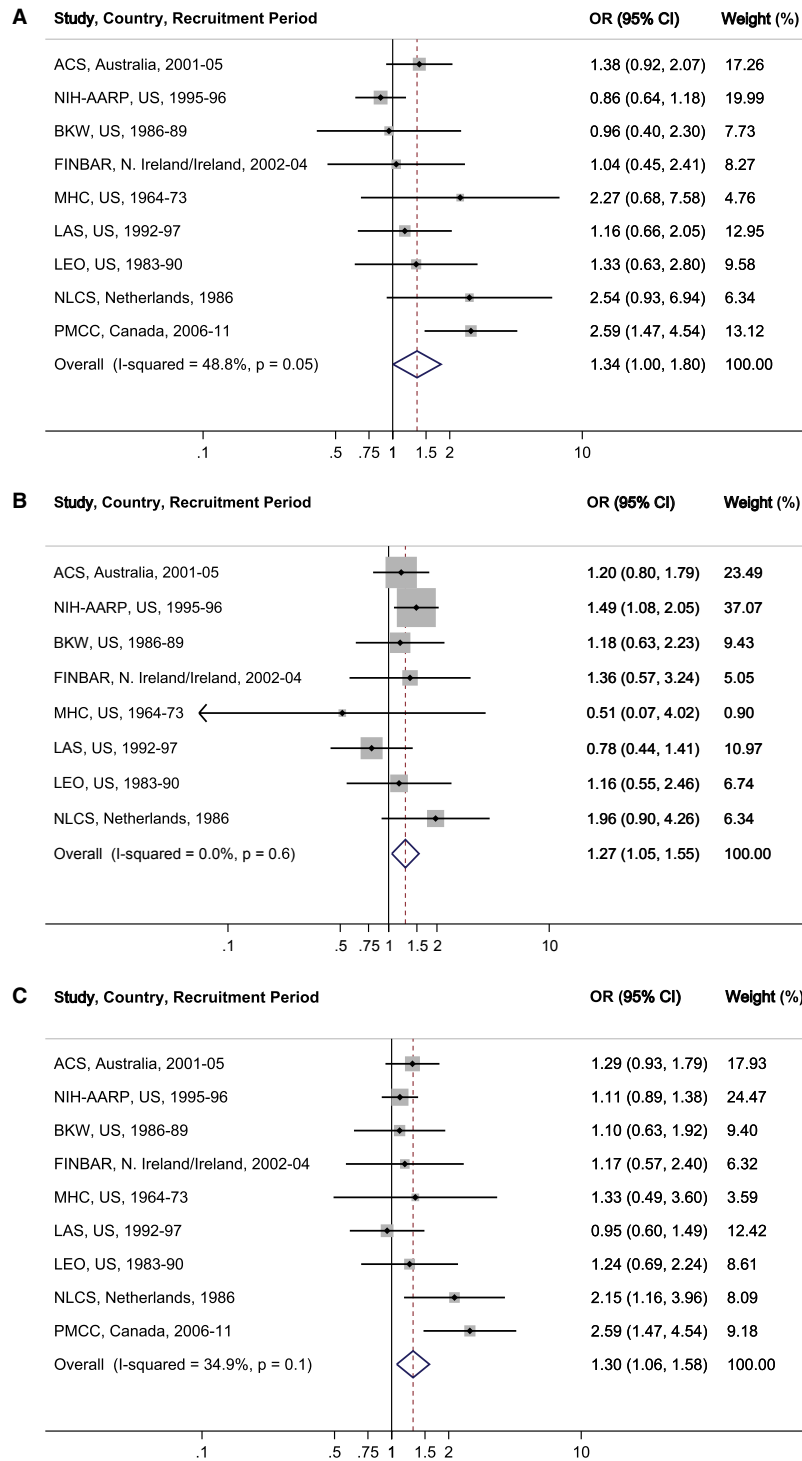
<sup>c</sup>Data were available for the Australian Cancer Study (ACS); the US Population Health Study (BKW); the Factors Influencing the Barrett's/Adenocarcinoma Relationship Study (FINBAR); the Los Angeles County Multi-Ethnic Case-Control Study (LAS); the Larynx, Esophagus, and Oral Cavity Study (LEO); and a subset of the National Institutes of Health-AARP Diet and Health Study (NIH-AARP).

<sup>d</sup>The Princess Margaret Cancer Center Esophageal Cancer Study does not include information on EGJA.

95% CI, 1.81-2.45), and the group with both regurgitation and diabetes was at a 3.4-times increased risk of EA/EGJA (OR, 3.42; 95% CI, 2.49-4.69), each compared with the referent group of individuals without diabetes or regurgitation (data not tabulated). Regurgitation and diabetes provided a RERI of 1.29 (95% CI, 0.22-2.36;  $P = .02$ ), a synergy index of 2.14 (95% CI, 1.23-3.72;  $P = .007$ ), and an attributable proportion because of interaction of 0.38 (95% CI, 0.16-0.59;  $P = .001$ ) in relation to the risk of EA/EGJA. Results were similar when we restricted the analyses to only those studies with information on both symptoms of heartburn and regurgitation (see Supporting Table 3). When we examined

regurgitation and heartburn symptoms categorized as “none,” “<weekly” (nonrecurrent), and “≥weekly” (recurrent), there was also evidence of effect modification in relation to EA/EGJA ( $P$  for interaction = .009) (see Supporting Table 4), with the increased risk observed among individuals reporting nonrecurrent (<weekly) regurgitation symptoms (OR, 1.77; 95% CI, 1.17-2.70) and no associations among individuals reporting recurrent (≥weekly) regurgitation symptoms (OR, 1.10; 95% CI, 0.64-1.90) or reporting no symptoms (OR, 0.84; 95% CI, 0.57-1.24). There was little evidence of effect modification of the diabetes-adenocarcinoma association by BMI, smoking, or sex (Table 3).





**Figure 1.** This is a forest plot of the relationship between diabetes and (A) esophageal adenocarcinoma, (B) esophagogastric junction adenocarcinoma, and (C) all esophageal and esophagogastric junction adenocarcinomas from a random effects model that was adjusted for age, sex, smoking (never, ever), and body mass index (continuous). The I-square ( $I^2$ ) statistic indicates the percentage of variation across studies that is due to heterogeneity rather than chance. ACS indicates the Australian Cancer Study; BKW, the US Population Health Study; FINBAR, the Factors Influencing the Barrett’s/Adenocarcinoma Relationship Study; LOS, the Los Angeles County Multi-Ethnic Case-Control Study; LEO, the Larynx, Esophagus, and Oral Cavity Study; MHC, the Kaiser-Permanente Multiphasic Health Checkup Study; NIH-AARP, the National Institutes of Health-AARP Diet and Health Study; NLCS, the Netherlands Cohort Study; OR, odds ratio; PMCC, the Princess Margaret Cancer Center Esophageal Cancer Study.

**TABLE 3.** Adjusted Odds Ratios and 95% CIs for Interactions Between Diabetes and Other Risk Factors and Esophageal and Esophagogastric Junction Adenocarcinomas<sup>a</sup>

Case Type	Nondiabetes			Diabetes			<i>P</i> for Interaction
	No. of Cases	No. of Controls	OR (95% CI)	No. of Cases	No. of Controls	OR (95% CI)	
<b>EA</b>							
Reflux symptoms <sup>b</sup>							
No	374	3202	Referent	40	157	1.51 (1.01-2.25)	
Yes	625	2082	Referent	99	130	1.56 (1.14-2.12)	.9
Regurgitation <sup>c</sup>							
No	313	1409	Referent	47	118	1.26 (0.84-1.88)	
Yes	429	1186	Referent	76	84	1.67 (1.16-2.41)	.3
Heartburn <sup>b</sup>							
No	438	3553	Referent	54	183	1.61 (1.13-2.29)	
Yes	554	1717	Referent	83	104	1.51 (1.07-2.12)	.8
Sex							
Men	1730	5323	Referent	215	427	1.17 (0.97-1.41)	
Women	212	2254	Referent	23	127	1.44 (0.89-2.34)	.4
BMI, kg/m <sup>2</sup>							
<25	549	33,237	Referent	37	124	1.39 (0.93-2.07)	
≥25	1393	4341	Referent	201	430	1.16 (0.96-1.41)	.4
Smoking							
Never	404	2780	Referent	49	176	1.36 (0.95-1.94)	
Ever	1538	4798	Referent	189	378	1.15 (0.95-1.41)	.4
Age, y							
<60	668	3333	Referent	53	151	1.31 (0.93-1.87)	
≥60	1274	4245	Referent	185	403	1.16 (0.95-1.41)	.5
<b>EGJA<sup>d</sup></b>							
Reflux symptoms <sup>b</sup>							
No	392	2985	Referent	26	139	0.99 (0.63-1.56)	
Yes	469	2047	Referent	56	127	1.32 (0.93-1.86)	.3
Regurgitation <sup>c</sup>							
No	249	1169	Referent	22	98	0.73 (0.44-1.20)	
Yes	338	1174	Referent	45	83	1.47 (0.99-2.20)	.03
Heartburn <sup>b</sup>							
No	493	3345	Referent	40	165	1.12 (0.77-1.63)	
Yes	362	1685	Referent	42	101	1.28 (0.86-1.90)	.6
Sex							
Men	1383	4857	Referent	165	378	1.32 (1.08-1.62)	
Women	239	1978	Referent	19	106	1.21 (0.72-2.03)	.8
BMI, kg/m <sup>2</sup>							
<25	561	2914	Referent	29	127	0.98 (0.64-1.49)	
≥25	1061	3922	Referent	155	357	1.41 (1.14-1.74)	.1
Smoking							
Never	333	2541	Referent	31	159	1.26 (0.84-1.91)	
Ever	1289	4295	Referent	153	325	1.32 (1.07-1.63)	.9
Age, y							
<60	574	2969	Referent	45	135	1.31 (0.91-1.89)	
≥60	1048	3867	Referent	139	349	1.30 (1.05-1.62)	1.0
<b>All EA and EGJA</b>							
Reflux symptoms <sup>b</sup>							
No	766	3202	Referent	66	157	1.24 (0.91-1.72)	
Yes	1094	2082	Referent	155	130	1.49 (1.15-1.94)	.4
Regurgitation <sup>c</sup>							
No	562	1409	Referent	69	118	1.03 (0.74-1.43)	
Yes	767	1186	Referent	121	84	1.63 (1.19-2.22)	.04
Heartburn <sup>b</sup>							
No	931	3553	Referent	94	183	1.35 (1.02-1.78)	
Yes	916	1717	Referent	125	104	1.46 (1.09-1.95)	.7
Sex							
Men	3128	7135	Referent	380	552	1.25 (1.08-1.44)	
Women	452	3321	Referent	42	182	1.31 (0.91-1.88)	.8
BMI, kg/m <sup>2</sup>							
<25	1110	4445	Referent	66	174	1.17 (0.86-1.58)	
≥25	2470	6012	Referent	356	560	1.28 (1.10-1.49)	.6

TABLE 3. Continued

Case Type	Nondiabetes			Diabetes			P for Interaction
	No. of Cases	No. of Controls	OR (95% CI)	No. of Cases	No. of Controls	OR (95% CI)	
Smoking							
Never	740	3818	Referent	80	240	1.34 (1.01-1.77)	
Ever	2840	6639	Referent	342	494	1.23 (1.05-1.43)	.6
Age, y							
<60	925	2966	Referent	71	134	1.32 (1.02-1.72)	
≥60	1650	3859	Referent	257	349	1.23 (1.05-1.43)	.6

Abbreviations: BMI, body mass index; EA, esophageal adenocarcinoma; EGJA, esophagogastric junction adenocarcinoma; OR, odds ratio.

<sup>a</sup>Analyses were adjusted for age (continuous), sex, smoking (never, ever), and BMI (continuous).

<sup>b</sup>Data were available for the Australian Cancer Study (ACS), the Factors Influencing the Barrett's/Adenocarcinoma Relationship Study (FINBAR), the Kaiser-Permanente Multiphasic Health Checkup Study (MHC), the Los Angeles County Multi-Ethnic Case-Control Study (LAS), the Netherlands Cohort Study (NLCS), and Princess Margaret Cancer Center-Esophageal Cancer Study US (PMCC).

<sup>c</sup>Data were available for ACS, FINBAR, LAS, and PMCC.

<sup>d</sup>PMCC does not include information on EGJA.

TABLE 4. Adjusted Odds Ratios and 95% CIs for the Association Between Diabetes and Barrett's Esophagus Compared With Population-Based and Endoscopy Controls, Respectively<sup>a</sup>

Control Type	No. of BE Cases	No. of Controls	OR (95% CI)	I <sup>2</sup> , % <sup>b</sup>	P for Heterogeneity
Population-based controls					
Diabetes					
No	1325	2438	Referent		
Yes	158	301	0.87 (0.67-1.13)	18.3	.3
Type 2 diabetes <sup>c</sup>					
No	709	913	Referent		
Yes	116	144	1.00 (0.64-1.56)	49.3	.1
Duration of type 2 diabetes, y					
0.5-3	35	27	1.74 (0.73-4.15)	48.3	.1
>3 to 5	19	25	0.85 (0.46-1.60)	0.0	.5
>5 to 10	25	31	0.98 (0.44-2.20)	42.4	.2
>10	21	42	0.58 (0.33-1.01)	0.0	.6
Endoscopy controls					
Diabetes					
No	816	1195	Referent		
Yes	130	268	0.93 (0.71-1.20)	0.0	1.0
Type 2 diabetes <sup>c</sup>					
No	709	1006	Referent		
Yes	116	239	0.97 (0.73-1.28)	0.0	1.0
Duration of type 2 diabetes, y					
0.5-3	35	55	1.11 (0.52-2.36)	48.3	.1
>3 to 5	19	34	1.05 (0.55-2.00)	0.0	.5
>5 to 10	25	58	0.77 (0.45-1.31)	0.0	.5
>10	21	44	0.90 (0.51-1.57)	0.0	.5

Abbreviations: BE, Barrett's esophagus; OR, odds ratio.

<sup>a</sup>Analyses were adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous).

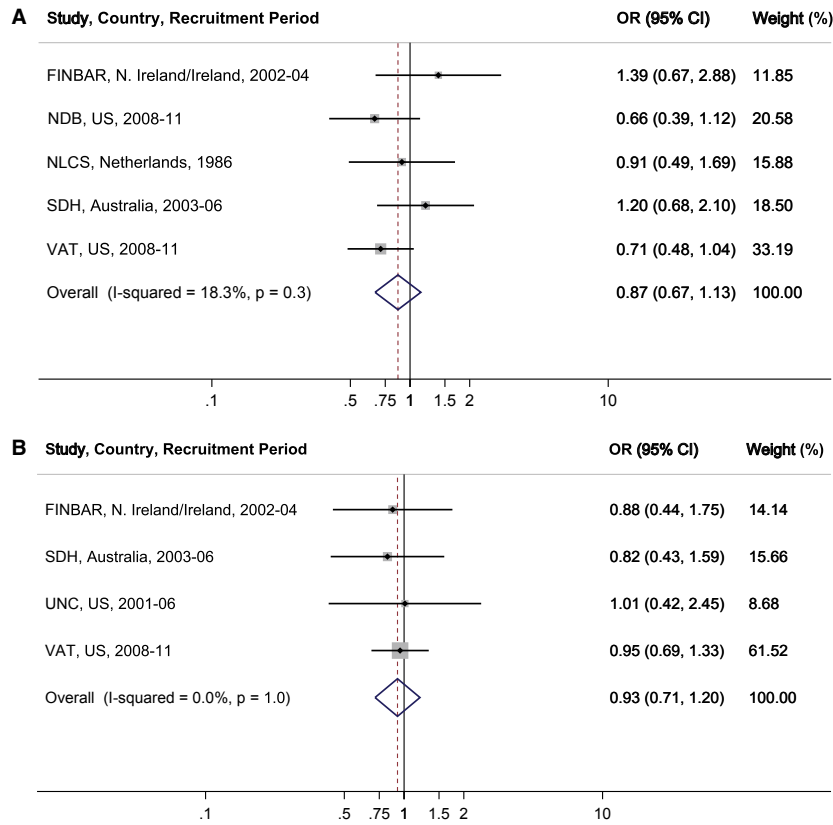
<sup>b</sup>The I<sup>2</sup> statistic indicates the percentage of variation across studies that is due to heterogeneity rather than chance; 0% indicates no heterogeneity, and larger values indicate increasing heterogeneity between studies.

<sup>c</sup>Data were available for the Factors Influencing the Barrett's/Adenocarcinoma Relationship Study (FINBAR), the Newly Diagnosed Barrett's Esophagus Study (NDB), and the Houston Barrett's Esophagus Study (VAT).

The association between diabetes and BE is shown in Table 4 and Figure 2. There was no consistent association between diabetes and BE compared with population-based controls (OR, 0.87; 95% CI, 0.67-1.13; I<sup>2</sup> = 18.3%) or endoscopy controls (OR, 0.93; 95%

CI, 0.71-1.20; I<sup>2</sup> = 0%). Results were robust in the meta-influence analysis, dropping 1 study at a time (see Supporting Fig. 3). Selection bias of studies included in BEACON was unlikely as assessed by examination of the funnel plots and with the Begg and Mazumdar





**Figure 2.** This is a forest plot of the relationship between diabetes and Barrett’s esophagus versus (A) population controls and (B) gastroesophageal reflux disease/endoscopy controls by random effects model adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous). The I-square ( $I^2$ ) statistic indicates the percentage of variation across studies that is due to heterogeneity rather than chance. FINBAR indicates the Factors Influencing the Barrett’s/Adenocarcinoma Relationship Study; NDB, the Newly Diagnosed Barrett’s Esophagus Study; NLCS, the Netherlands Cohort Study; OR, odds ratio; SDH, the Study of Digestive Health; VAT, the Houston Barrett’s Esophagus Study.

( $P > .05$ ) and Egger ( $P > .05$ ) tests (see Supporting Fig. 4). Similarly, when results were restricted to individuals with self-reported or suspected type 2 diabetes, there was no association between diabetes and BE (Table 4). No trend was found between duration of type 2 diabetes and BE compared with population-based ( $P$  for trend = .7) or endoscopy controls ( $P$  for trend = .8). There was no evidence of effect measure modification between diabetes and reflux symptoms, sex, BMI, smoking, or age in relation to BE (Table 5; see Supporting Table 5).

**DISCUSSION**

In this pooled analysis of 13 studies from BEACON, diabetes was associated with a 27% to 34% increased risk of EA/EGJA, but not BE. In the studies of EA/EGJA, we also report a synergistic interaction between diabetes and regurgitation symptoms. Compared with individuals who

did not have diabetes or regurgitation, individuals with diabetes and regurgitation had a 3.4-times increased risk of EA/EGJA. Finally, we did not find that a longer duration of type 2 diabetes was associated with an increased risk of EA/EGJA or BE. The increased risk of EA/EGJA, but not BE, associated with diabetes suggests that diabetes may be acting later in the carcinogenesis pathway.

The current study is the largest study of EA or EGJA reported to date with information on the diabetes status of study participants. One prior meta-analysis examined the association between diabetes and esophageal cancer (all histologic types), but only 3 of the studies included in the meta-analysis were specific for EA.<sup>22</sup> The other studies included were either esophageal squamous cell carcinoma, the other primary type of esophageal cancer which has a different etiology,<sup>67</sup> or a mixture of histological subtypes. Several previous studies have suggested that diabetes increases the risk of EA,<sup>23-28</sup> whereas others showed

**TABLE 5.** Adjusted Odds Ratios and 95% CIs for Interaction Between Diabetes and Other Risk Factors and Barrett's Esophagus Compared With Population-Based and Endoscopy Controls, Respectively<sup>a</sup>

Control Type	Nondiabetes			Diabetes			P for Interaction
	No. of BE Cases	No. of Controls	OR (95% CI)	No. of BE Cases	No. of Controls	OR (95% CI)	
Population-based controls							
Reflux symptoms							
No	622	1844	Referent	60	215	0.91 (0.66-1.27)	
Yes	703	594	Referent	98	86	0.73 (0.52-1.02)	.3
Regurgitation <sup>b</sup>							
No	201	925	Referent	27	134	1.00 (0.63-1.59)	
Yes	434	342	Referent	40	31	0.98 (0.59-1.64)	1.0
Heartburn							
No	708	1962	Referent	62	227	0.85 (0.62-1.18)	
Yes	617	476	Referent	96	74	0.77 (0.54-1.10)	.9
Sex							
Men	945	1730	Referent	140	272	0.79 (0.62-1.02)	
Women	380	708	Referent	18	29	1.01 (0.55-1.86)	.5
BMI, kg/m <sup>2</sup>							
<25	446	955	Referent	21	33	1.21 (0.68-2.15)	
≥25	879	1483	Referent	137	268	0.78 (0.61-1.00)	.2
Smoking							
Never	425	981	Referent	42	101	0.87 (0.59-1.30)	
Ever	900	1457	Referent	116	200	0.80 (0.61-1.05)	.7
Age, y							
<60	523	1088	Referent	41	86	0.93 (0.61-1.41)	
≥60	802	1350	Referent	117	215	0.78 (0.60-1.02)	.5
Endoscopy controls							
Reflux symptoms							
No	149	383	Referent	35	108	1.05 (0.67-1.65)	
Yes	662	802	Referent	95	160	0.87 (0.64-1.17)	.5
Regurgitation <sup>c</sup>							
No	170	264	Referent	14	14	1.14 (0.52-2.49)	
Yes	429	359	Referent	39	38	0.76 (0.46-1.25)	.9
Heartburn							
No	191	429	Referent	36	111	1.01 (0.65-1.56)	
Yes	603	737	Referent	93	156	0.87 (0.64-1.18)	1.0
Sex							
Men	633	842	Referent	114	233	0.92 (0.70-1.21)	
Women	183	353	Referent	16	35	0.98 (0.51-1.90)	.8
BMI, kg/m <sup>2</sup>							
<25	225	305	Referent	17	23	1.03 (0.52-2.06)	
≥25	591	890	Referent	113	245	0.91 (0.69-1.19)	.7
Smoking							
Never	264	489	Referent	35	77	1.11 (0.70-1.76)	
Ever	552	706	Referent	95	191	0.85 (0.64-1.15)	.3
Age, y							
<60	366	655	Referent	36	77	1.17 (0.74-1.84)	
≥60	450	540	Referent	94	191	0.84 (0.62-1.13)	.2

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; OR, odds ratio.

<sup>a</sup>Analyses were adjusted for age (continuous), sex, smoking (never, ever), BMI (continuous), and parent study.

<sup>b</sup>Data were available for the Factors Influencing the Barrett's/Adenocarcinoma Relationship Study (FINBAR), the Newly Diagnosed Barrett's Esophagus Study (NDB), and the Study of Digestive Health (SDH).

<sup>c</sup>Available for the Factors Influencing the Barrett's/Adenocarcinoma Relationship Study (FINBAR), the Newly Diagnosed Barrett's Esophagus Study (NDB), and the Epidemiologic Case-Control Study of Barrett's Esophagus Study (UNC).

no association.<sup>29-31</sup> Of the 3 prior studies showing no association between diabetes and EA, 1 is included in the current pooled analysis.<sup>30</sup> Another was conducted in the UK Clinical Practice Research Datalink, which is a large electronic medical record database.<sup>31</sup> It is unclear why our results would be discrepant, but a further study included herein from Northern Ireland and Ireland (FINBAR) also found little to no association between diabetes and

EA, suggesting potential geographic heterogeneity. The third and final previously published study that reported no association between diabetes and EA/EGJA included fewer cases (with GERD, n = 311) than we report herein (n = 1249).<sup>29</sup> Moreover, it was conducted in a population of US veterans with GERD, which provided an unusually high prevalence of diabetes (36% in EA/EGJA cases, 32% in controls) compared with our study (12% in EA/EGJA

cases, 6% in controls), as well as other factors, including male sex (90%),<sup>68</sup> overweight or obesity (78%),<sup>69</sup> and ever smoking (60%),<sup>70</sup> which reduces the generalizability of its findings.

In the current study, we report a synergistic interaction between diabetes and symptomatic regurgitation, but not overall reflux symptoms (defined as heartburn or regurgitation symptoms). Three prior studies that assessed this interaction reported that reflux did not modify the diabetes-EA/EGJA association.<sup>23,28,31</sup> However, 2 of these studies defined GERD as coded in medical records and were not able to stratify by heartburn or regurgitation symptoms.<sup>28,31</sup>

Few studies have assessed the association between diabetes and BE, and the results have been inconsistent.<sup>31-35</sup> Two of the previous studies, which are included in the current analysis, found little to no association between diabetes and BE.<sup>32,33</sup> Similarly, 2 studies conducted within the UK Clinical Practice Research Datalink offer little evidence for any association between diabetes and BE.<sup>31,34</sup> However, after further adjustment for BMI, smoking, and GERD, Iyer et al reported a 50% increased risk of BE associated with diabetes.<sup>34</sup> Another study using Surveillance, Epidemiology, and End Results (SEER)-Medicare data reported that diabetes was associated with an increased risk of BE compared with population controls, but not endoscopy-negative controls.<sup>35</sup> In the current study, we report no association between diabetes and BE regardless of the control group. If diabetes conferred no increased risk of progression from BE to adenocarcinoma, then the diabetes-EA/EGJA association would be approximately equal to that observed for diabetes-BE. However, as we observed an association between diabetes and EA/EGJA, but not BE, this suggests that diabetes may influence the risk of progression of BE to cancer. The synergistic interaction observed between diabetes and regurgitation symptoms also indicates that diabetes may be promoting progression from reflux or BE to EA/EGJA.

Our pooled study is the first to indicate that the association between diabetes and EA/EGJA may be strongest among those with regurgitation symptoms. Reasons for diabetes and regurgitation synergistically increasing the risk of EA/EGJA are not completely understood. However, putative mechanisms of diabetes-induced mechanophysiological changes may explain our observation,<sup>16</sup> including impaired lower esophageal sphincter relaxation<sup>71,72</sup> and dysfunction of the esophageal body (eg, dysfunctional peristalsis), which may result in decreased motility,<sup>73,74</sup> antral spasms, and gastroparesis,<sup>75</sup> providing

more opportunities for reflux. Diabetes and hyperglycemia may also be associated with gastroparesis through diabetic (vagal) neuropathy,<sup>76</sup> which is thought to result from modification of proteins by advanced glycation end products, leading to development of atrophy and degeneration of nerve fibers.<sup>16</sup>

The interaction between diabetes and regurgitation, but not heartburn symptoms, may be explained by diabetic neuropathy; patients who have GERD with diabetes report less frequent acid regurgitation symptoms than those who have GERD without diabetes,<sup>77,78</sup> whereas prior research indicates little to no decline in the frequency of heartburn symptoms in patients who have GERD with diabetes.<sup>77,78</sup> Symptomatic regurgitation compared with heartburn is associated with a higher proximal extent of the liquid reflux component,<sup>79</sup> which has been used as a proxy measure of increased contact time between the esophageal mucosa and gastric refluxate.<sup>80</sup> Assuming asymptomatic regurgitation is also more severe than heartburn, individuals with diabetes may be experiencing regurgitation symptoms less frequently because of diabetic neuropathy, but they may still be exposed to high levels of gastric refluxate if they are experiencing asymptomatic regurgitation. When we stratified on frequency of reflux symptoms, we found that the association between diabetes and EA/EGJA was primarily confined to individuals with nonrecurrent regurgitation symptoms, suggesting that they may be experiencing asymptomatic reflux. These putative mechanisms aptly explain why we may observe a synergistic interaction between diabetes and regurgitation in relation to EA/EGJA without an independent association between diabetes and cancer risk.

This study has several limitations. First, few BEACON studies assessed age at diabetes diagnosis or differentiated between type 1 and type 2 diabetes. Thus, to improve our assessment of type 2 diabetes, we restricted our analysis to diabetes diagnosed after age 30 years as a proxy for type 2 diabetes. Therefore, some degree of misclassification is likely because type 1 diabetes can be diagnosed at any age. However, type 1 diabetes is most commonly diagnosed in individuals younger than 20 years and only accounts for 5% of all diabetes diagnoses<sup>18</sup>; thus, misclassification of exposure is likely to be minimal. In addition, the little information on diabetes medication use collected in the parent BEACON studies was of insufficient detail to examine. For example, 1 questionnaire asked participants whether they had diabetes treated with insulin injections or diabetes treated with tablets and/or diet.<sup>40,41</sup> Thus, it was not possible to

accurately discern whether individuals were treated with tablets (and if so, what type), dietary changes, or did not receive treatment for diagnosed diabetes. Moreover, different antidiabetic drugs are heterogeneous with respect to their cancer effects, hence detailed information would be needed to assess effects on EA/EGJA. We also did not have information on degree of diabetes control, such as hemoglobin A1c. The majority of participants in BEACON were men of European descent; therefore, the results may not be generalizable to women or non-Europeans. That said, the overwhelming majority of individuals that develop EA and EGJA are white males;<sup>81</sup> thus, these findings are still likely relevant to those at highest risk of developing these cancers. Finally, the current study included populations with both high and low prevalence of diabetes; in the controls, this ranged from 2.7% in the Kaiser-Permanente Multiphasic Health Checkup Study (MHC)<sup>43</sup> to 39.8% in the Houston Barrett's Esophagus Study (VAT).<sup>32</sup> However, we did not observe substantial between-study heterogeneity in the risk estimates, and results were robust in the meta-influence analysis. In addition, this study included case-control and cohort studies. The diabetes diagnoses in case-control studies may be subject to differential misclassification of exposure, whereby cases could be diagnosed incidentally when undergoing testing for a cancer diagnosis and controls would not be diagnosed. However, stratifying the results by case-control versus cohort studies resulted in nearly identical estimates for junctional adenocarcinomas (data not shown).

The large sample size of our pooled study improved the precision of our effect estimates and allowed us to investigate potential effect modification by reflux symptoms, sex, BMI, smoking, and age. However, the number of cases for the stratified analyses was still relatively small. In addition, using BEACON resources, we were able to examine the precursor lesion of BE and invasive cancer, allowing us to speculate about the possible timing of when diabetes may have an effect in the BE-adenocarcinoma continuum. Finally, our study used the pooled meta-analytic approach, which yields less biased effect estimates because we were able to use individual-level, uniform definitions for the exposure and the covariates across all parent studies (in contrast to the standard meta-analytic approach, which must rely on published group information only).

In summary, our large pooled study provides evidence that diabetes is associated with an increased risk of EA/EGJA, but not BE, suggesting that diabetes may influence the risk of progression of BE to cancer. The

increased risk for EA/EGJA was primarily confined to individuals with regurgitation symptoms, which acted synergistically with diabetes. Future studies should evaluate whether the synergistic association between diabetes and regurgitation symptoms persists in individuals with well controlled diabetes and elucidate mechanisms that underlie these observations.

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## CONFLICT OF INTEREST DISCLOSURES

Joel H. Rubenstein reports personal fees from the American Gastroenterological Association outside the submitted work. The remaining authors made no disclosures.

## AUTHOR CONTRIBUTIONS

**Jessica L. Petrick:** Guarantor of the article, study conception, study design, data analysis, data interpretation, and critical review of the article. **Nan Li, Marilie D. Gammon, and Michael B. Cook:** Study conception, study design, data interpretation, and critical review of the article. **Lesley A. Anderson, Leslie Bernstein, Douglas A. Corley, Hashem B. El Serag, Sheetal Hardikar, Linda M. Liao, Geoffrey Liu, Liam J. Murray, Joel H. Rubenstein, Jennifer L. Schneider, Nicholas J. Shaheen, Aaron P. Thrift, Piet A. van den Brandt, Thomas L. Vaughan, David C. Whiteman, Anna H. Wu, and Wei K. Zhao:** Study design, data interpretation, and critical review of the article.

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