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Article type   : Original Article

Diabetes in relation to Barrett's esophagus and adenocarcinomas of the esophagus: a pooled study from the International Barrett's and Esophageal Adenocarcinoma Consortium

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Short Title: Diabetes and tumors of the gastroesophageal junction

Word Count: 3,915

Tables: 5

Figures: 2

Supplemental Figures/Tables: 6

Conflict of Interest: The authors declare no potential conflicts of interest.

ABSTRACT

Background: Diabetes is positively associated with various cancers, but its relationship with tumors of the esophagus/esophagogastric junction remains unclear.

Methods: Data were harmonized across 13 studies in the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), comprising 2,311 esophageal adenocarcinoma (EA) cases, 1,943 esophagogastric junction adenocarcinoma (EGJA) cases, 1,728 Barrett's esophagus (BE) cases, and 16,310 controls. Logistic regression was used to estimate study-specific odds ratios (ORs) and 95% confidence intervals (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 35% increased risk of EA (OR=1.35,95%CI:1.00–1.82; I^2=48.8%), 25% for EGJA (OR=1.25, 95%CI:1.03–1.52; I^2=0.0%), and 27% for EA/EGJA combined (OR=1.27,95%CI:1.06–1.53; I^2=34.9%). Regurgitation symptoms modified the diabetes-EA/EGJA association ($p_{interaction}$=0.04) 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.

Keywords: Barrett's esophagus, diabetes, epidemiology, esophageal adenocarcinoma, meta-analysis

Condensed Abstract: The positive association between diabetes and esophageal and esophagogastric junction adenocarcinomas, but not BE, suggests that diabetes may be acting later in the carcinogenesis pathway.

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 (US) and other Western countries.[1-3] The incidence of the anatomically-linked esophagogastric junction adenocarcinoma (EGJA) has also increased but less rapidly than EA.[4] 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.[5] The only known potential precursor of EA/EGJA is Barrett's esophagus (BE), which is associated with 10–40-times increased risk of EA/EGJA.[6-8] Among individuals over the age of 50 years with gastroesophageal reflux disease (GERD), an estimated 10% also have BE.[9] In the last 30 years, BE diagnosis increased 200–300% – independent of the number of gastrointestinal endoscopies performed.[10-12]

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

Type 2 diabetes, which accounts for 95% of diabetes diagnoses,[18] is often characterized by hyperinsulinemia and has been associated with a higher risk of various cancers, including malignancies of the liver, pancreas, endometrium, colorectal, breast and bladder.[19, 20] Diabetes has been increasing in prevalence, and 12% of adults in the US[18, 19] and 9% worldwide[21] have prevalent diabetes. However, the association between diabetes and EA/EGJA remains understudied,[22] with several studies suggesting an increased risk[23-28] and others showing no association.[29-31] Additionally, few studies have assessed the

association between diabetes and BE, with inconsistent results.[31-35] Thus, we utilized 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,[36] was formed to facilitate pooling of resources from epidemiologic studies focused on the Barrett's esophagus/esophageal adenocarcinoma 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.[36] Thusly, this consortium allows for pooled analysis of individual-level data and avoids reliance on only published data. The present study pools information from 13 BEACON studies that included assessment of diabetes: three cohort and six case-control studies examining EA or EGJA (**Supplementary Table S1**); and one cohort and five case-control studies examining BE (**Supplementary Table S2**). Two studies included examination of both BE and EA/EGJA.[37, 38] Of the nine EA and EGJA studies, six were conducted in North America, two in Europe, and one in Australia. Of the six BE studies, three were conducted in North America, two in Europe, and one in Australia. Detailed descriptions of recruitment procedures can be found in study-specific publications.[32, 37-48] 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 employed. A case to control ratio of 1:2 was used 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, as there were few cases from non-white 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 2,311 EA cases,

1,943 EGJA cases, 1,728 BE cases, and 16,310 controls. Participants had a mean age of 60 years and were more likely to be male (73.5%).

Exposure

To provide comparable data from the parent studies, we harmonized responses from the nine EA/EGJA and six BE parent studies for diabetes and potential covariates. To assess diabetes, most 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 to medical record review ranges from 83-98%.[49-51] Additionally, 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).[33] Only one study, Factors Influencing the Barrett's/Adenocarcinoma Relationship Study (FINBAR),[37] specifically asked about type 1 versus type 2 diabetes. For the studies with age at diabetes diagnosis available (five EA/EGJA studies and two BE studies), a diagnosis after age 30 was assumed to be type 2 diabetes, as most type 1 diabetes is diagnosed peri-puberty. Additionally, 95% of diabetes is type 2.[18] Duration of type 2 diabetes in years was examined as a continuous variable for tests of linear trends and categorized as 0.5-3, >3-5, >5-10, and >10 years.[23, 24] BEACON study responses for other covariates were harmonized and have been previously described for cigarette smoking,[52, 53] alcohol consumption,[54, 55] body mass index (BMI),[13, 14] waist circumference,[13, 14] non-steroidal anti-inflammatory drug use,[56, 57] and reflux symptoms.[58]

Statistical Analyses

For our pooled study, we conducted a two-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% confidence intervals (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.[59] Estimates generated with fixed-effects and random-effects models were similar. Given that the latter are more robust to study heterogeneity,[60] we only present random-effects models. Between-study heterogeneity was assessed using a χ^2 test based on the Q statistic and the I^2 statistic (where 0% indicates no heterogeneity and larger values indicate increasing heterogeneity between studies).[61] While investigating differences across studies includes quantification of heterogeneity, the most critical aspects are ensuring that the studies are comparable in clinical and methodologic aspects,[61] as BEACON was designed. To demonstrate that there was no selection bias (i.e., "publication bias"), funnel plots were visually inspected for asymmetry and quantitatively assessed using Begg and Mazumdar's rank correlation test[62] and Egger's linear regression

test.[63] To determine the influence of individual studies, we conducted a meta-influence analysis, whereby we excluded one study at a time and re-estimated the summary effect estimates.

Potential confounders[64] included age (at diagnosis for cases and 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^2), waist circumference (cm), non-steroidal 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% due to variable elimination in any parent study, the variable was considered a confounder and retained in all models.[64] 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^2), smoking (ever/never), and age (<60/≥60 years). Additionally, report of heartburn (retrosternal burning), regurgitation, and any reflux symptoms (i.e., 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_2 antagonists. For analyses of effect measure modification, we used a pooled dataset of individual-level data with additional adjustment for parent study, instead of the two-step meta-analytic approach. Departures from the multiplicative null were evaluated through stratification and by using likelihood ratio tests from nested logistic regression models.[64] Departures from the additive null were approximated by calculating the relative excess risk due to interaction ($RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1$; null hypothesis = 0), synergy index ($S_{OR} = (OR_{11} - 1)/((OR_{10} - 1) + (OR_{01} - 1))$; null hypothesis = 1), and the attributable proportion due to interaction, which assumes a causal relationship ($AP_{OR} = RERI_{OR}/OR_{11}$; null hypothesis = 0).[65, 66]

Sensitivity Analysis

As 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 (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, Cary, NC) and Stata version 14.0 (StataCorp LP, College Station, TX).

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%) and had a slightly higher BMI (28.0 and 27.4 vs. 26.4 kg/m^2). In the six 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%). In the BE studies, mean BMI was comparable between the BE cases and population-based controls (27.8 vs. 27.4 kg/m^2, respectively) but lower than the endoscopy-based controls (29.1 kg/m^2). However, BE cases had a higher proportion of smokers (67.7%) compared with both control groups (60.7 and 61.5%, respectively). Prevalence of reflux symptoms was similar between BE cases and endoscopy controls (56.3 vs. 66.5%), 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^2=48.8%), a 27% increased risk of EGJA (OR=1.27, 95% CI: 1.05–1.55; I^2=0.0%), and a 30% increased risk of EA/EGJA (OR=1.30, 95% CI: 1.06–1.58; I^2=34.9%). Results were robust in the meta-influence analysis, dropping one study at a time (**Supplementary Figure S1**). Selection bias of studies included in BEACON was unlikely as assessed examination of the funnel plots and by the Begg and Mazumdar's (p>0.05) and Egger's tests (p>0.05) (**Supplementary Figure S3**). When the analysis was restricted to individuals with self-reported or suspected type 2 diabetes (i.e., classifying individuals with a self-report of diabetes after age 30 years as type 2), compared to individuals without a diabetes diagnosis, diabetes was associated with a non-significant 17% increased risk of EA, EGJA, and EA/EGJA (**Table 2**). There was no trend between duration of type 2 diabetes and EA (p$_{trend}$=0.3), EGJA (p$_{trend}$=0.5), or EA/EGJA (p$_{trend}$=0.3).

As shown in **Table 3**, the association between diabetes and risk of EA/EGJA was modified by regurgitation symptoms (p$_{interaction}$=0.04). 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, 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 relative excess risk due to interaction (RERI) of 1.29 (95% CI: 0.22–2.36, p=0.02), a synergy index of 2.14 (95% CI: 1.23–3.72, p=0.007), and an attributable proportion due to interaction of 0.38 (95% CI: 0.16–0.59, p=0.001) 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 (**Supplemental Table S3**). When we examined regurgitation and heartburn symptoms categorized as "none", "<weekly" (non-recurrent), and "≥weekly" (recurrent), there was also evidence of effect modification in relation to EA/EGJA ($p_{interaction}$=0.009, **Supplemental Table S4**), with the increased risk observed among individuals reporting non-recurrent (<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, and sex (**Table 3**).

The association between diabetes and BE is shown in **Table 4** and **Figure 2**. There was no consistent association between diabetes and BE when compared to population-based controls (OR=0.87, 95% CI: 0.67–1.13; I^2=18.3%) or endoscopy controls (OR=0.93, 95% CI: 0.71–1.20; I^2=0.0%). Results were robust in the meta-influence analysis, dropping one study at a time (**Supplementary Figure S2**). Selection bias of studies included in BEACON was unlikely as assessed examination of the funnel plots and by the Begg and Mazumdar's (p>0.05) and Egger's tests (p>0.05) (**Supplementary Figure S4**). 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 to population-based (p_{trend}=0.7) or endoscopy controls (p_{trend}=0.8). There was no evidence of effect measure modification between diabetes and reflux symptoms, sex, BMI, smoking, or age in relation to BE (**Table 5 and Supplemental Table S5**).

DISCUSSION

In this pooled analysis of 13 studies from BEACON, diabetes was associated with a 27–34% 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 to those without 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 diabetes status of study participants. One prior meta-analysis examined the association between diabetes and esophageal cancer (all histologic types), but only three of the studies included in the meta-analysis were specific for EA.[22] The other studies included were either esophageal squamous cell carcinoma, the other primary type of esophageal cancer which has a different etiology,[67] or a mixture of histological subtypes. A number of previous studies have suggested that diabetes increases the risk of EA,[23-28] while others showed no association.[29-31] Of the three prior studies showing no association between diabetes and EA, one is included in the current pooled analysis.[30] Another was conducted in the UK Clinical Practice Research Datalink, which is a large electronic medical record database.[31] 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 (n=311) than we report herein (n=1,249).[29] 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%),[68] overweight or obesity (78%),[69] and ever smoking (68%),[70] 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.[23, 28, 31] However, two of these studies defined GERD as coded in medical records and were not able to stratify by heartburn or regurgitation symptoms.[28, 31]

Few studies have assessed the association between diabetes and BE, and the results have been inconsistent.[31-35] Two of the previous studies, which are included in the current analysis, found little to no association between diabetes and BE.[32, 33] Similarly, two studies conducted within the UK Clinical Practice Research Datalink offer little evidence for any association between diabetes and BE.[31, 34] However, after further adjustment for BMI, smoking, and GERD, Iyer *et al*. reported a 50% increased risk of BE associated with diabetes.[34] Another study using SEER-Medicare data reported diabetes was associated with an increased risk of BE when compared with population controls, but not endoscopy negative controls.[35] 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 risk of EA/EGJA are not completely understood. However, putative mechanisms of diabetes-induced mechanophysiological changes may explain our observation,[16] including impaired lower esophageal sphincter relaxation[71, 72] and dysfunction of the esophageal body (e.g., dysfunctional peristalsis) which may result in decreased motility,[73, 74] antral spasms and gastroparesis[75] providing more opportunities for reflux. Diabetes and hyperglycemia may also be associated with gastroparesis via diabetic (vagal) neuropathy,[76] which is thought to result from modification of proteins by advanced glycation end-products leading to development of atrophy and degeneration of nerve fibers.[16]

The interaction between diabetes and regurgitation but not heartburn symptoms may be explained by diabetic neuropathy; GERD patients with diabetes report less frequent acid regurgitation symptoms than GERD patients without diabetes,[77, 78] while prior research indicates little to no decline in frequency of heartburn symptoms in GERD patients with diabetes.[77, 78] Symptomatic regurgitation compared to heartburn is associated with a higher proximal extent of the liquid reflux component,[79] which has been utilized as a proxy measure of increased contact time between the esophageal mucosa and gastric refluxate.[80] Assuming asymptomatic regurgitation is also more severe than heartburn, individuals with diabetes may be experiencing regurgitation symptoms less frequently due to 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 non-recurrent 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, as type 1 diabetes can be diagnosed at any age. However, type 1 diabetes is most commonly diagnosed under age 20 and only accounts for 5% of all diabetes diagnoses;[18] thus, misclassification of exposure is likely to be minimal. In addition, the little information on diabetes medication usage collected in the parent BEACON studies was of insufficient detail to examine. For example, one questionnaire asked participants if they had diabetes treated with insulin injections or if they had diabetes treated with tablets and/or diet.[40, 41] 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 anti-diabetic drugs are heterogeneous with respect to their cancer effects, and 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 males of European descent, and 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;[81] 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 Kaiser-Permanente Multiphasic Health Checkup Study (MHC)[43] to 39.8% in the Houston Barrett's Esophagus Study (VAT).[32] However, we did not observe substantial between-study heterogeneity in the risk estimates, and results were robust in the meta-influence analysis. Additionally, this study included case-control and cohort studies. The diabetes diagnoses 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. Additionally, utilizing 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 utilized 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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Figure Legends.

Figure 1. Forrest plot of the relationship between diabetes and (A) esophageal adenocarcinoma, (B) esophagogastric junction adenocarcinoma, and (C) all esophageal and esophagogastric junction adenocarcinomas, by random effects model adjusted for age, sex, smoking (never, ever), and body mass index (continuous).

Figure 2. Forrest plot of the relationship between diabetes and Barret155t's esophagus, versus (A) population controls and (B) GERD/endoscopy controls, by random effects model adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous).

Table 1. Descriptive characteristics of the pooled study population, Barrett's and Esophageal Adenocarcinoma Consortium.

Study	Barrett's Esophagus Population			Adenocarcinoma Population		
	BE Cases	Controls		Adenocarcinoma Cases		Controls
		Population-based	GERD/Endoscopy	EA	EGJA	
	(n=1,728)	(n=2,830)	(n=1,683)	(n=2,308)	(n=1,938)	(n=11,842)
Age, years (SD)	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, n (%)						
Male	1,256 (72.7)	2,073 (73.2)	1,231 (73.1)	2,059 (89.2)	1,666 (86.0)	8,127 (68.6)
Female	472 (27.3)	757 (26.8)	452 (26.9)	250 (10.8)	272 (14.0)	3,713 (31.4)
Missing	0	0	0	0	0	1
Cigarette Smoking, n (%)						
Never	547 (32.3)	1,103 (39.3)	624 (38.5)	471 (20.8)	383 (20.3)	4,187 (36.4)
Ever	1,147 (67.7)	1,700 (60.7)	995 (61.5)	1,792 (79.2)	1,505 (79.7)	7,324 (63.6)
Missing	34	27	64	46	50	330
Body Mass Index, kg/m² (SD)	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, n	41	60	31	52	47	298

Table 2. Adjusted[a] odds ratios (ORs) and 95% confidence intervals (CIs) for associations between diabetes and esophageal and esophagogastric junction adenocarcinomas.

	Case N	Control N	OR (95% CI)	I^2 (%)	P_{heterogeneity}
Esophageal Adenocarcinoma					
Diabetes					
No	1,942	7,577	Referent		
Yes	238	554	1.34 (1.00–1.80)	48.8	0.05
Type 2 Diabetes[b]					
No	928	5,444	Referent		
Yes	147	544	1.17 (0.90–1.51)	0.0	0.8
Duration of type 2 diabetes					
0.5-3 years	38	174	1.01 (0.67–1.52)	0.0	0.8
>3-5 years	14	39	1.31 (0.67–2.56)	0.0	0.7
>5-10 years	47	148	1.33 (0.89–1.97)	0.0	0.9
>10 years	45	183	1.22 (0.78–1.90)	19.6	0.3
Esophagogastric Junction Adenocarcinoma[c]					
Diabetes					
No	1,622	6,584	Referent		
Yes	184	463	1.27 (1.05–1.55)	0.0	0.6
Type 2 Diabetes[b]					
No	972	4,918	Referent		
Yes	123	459	1.17 (0.91–1.51)	0.0	0.6
Duration of type 2 diabetes					
0.5-3 years	35	138	1.29 (0.84–1.99)	0.0	0.7
>3-5 years	11	39	1.12 (0.45–2.74)	27.2	0.2
>5-10 years	32	119	1.31 (0.68–2.54)	43.7	0.1
>10 years	42	163	1.12 (0.66–1.92)	40.7	0.1
All Esophageal and Esophagogastric Junction Adenocarcinoma					
Diabetes					
No	3,564	10,498	Referent		
Yes	422	735	1.30 (1.06–1.58)	34.9	0.1
Type 2 Diabetes[b]					
No	1,900	6,699	Referent		
Yes	270	734	1.17 (0.96–1.42)	0.0	0.7
Duration of type 2 diabetes					
0.5-3 years	73	250	1.12 (0.82–1.54)	0.0	0.6
>3-5 years	25	39	1.08 (0.60–1.93)	4.2	0.4
>5-10 years	79	202	1.37 (1.00–1.88)	0.0	0.7
>10 years	87	243	1.09 (0.67–1.76)	56.0	0.04

[a]Adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous).

Table 3. Adjusted[a] odds ratios (ORs) and 95% confidence intervals (CIs) for interaction between diabetes and other risk factors and esophageal and esophagogastric junction adenocarcinomas.

		Esophageal Adenocarcinoma					
	Non-Diabetes			Diabetes			
	Case N	Control N	OR (95% CI)	Case N	Control N	OR (95% CI)	P interaction
Reflux Symptoms[b]							
No	374	3,202	Referent	40	157	1.51 (1.01–2.25)	
Yes	625	2,082	Referent	99	130	1.56 (1.14–2.12)	0.9
Regurgitation[c]							
No	313	1,409	Referent	47	118	1.26 (0.84–1.88)	
Yes	429	1,186	Referent	76	84	1.67 (1.16–2.41)	0.3
Heartburn[b]							
No	438	3,553	Referent	54	183	1.61 (1.13–2.29)	
Yes	554	1,717	Referent	83	104	1.51 (1.07–2.12)	0.8
Sex							
Male	1,730	5,323	Referent	215	427	1.17 (0.97–1.41)	
Female	212	2,254	Referent	23	127	1.44 (0.89–2.34)	0.4
BMI							
<25 kg/m^2	549	33,237	Referent	37	124	1.39 (0.93–2.07)	
≥25 kg/m^2	1,393	4,341	Referent	201	430	1.16 (0.96–1.41)	0.4
Smoking							
Never	404	2,780	Referent	49	176	1.36 (0.95–1.94)	
Ever	1,538	4,798	Referent	189	378	1.15 (0.95–1.41)	0.4
Age							
<60 years	668	3,333	Referent	53	151	1.31 (0.93–1.87)	
≥60 years	1,274	4,245	Referent	185	403	1.16 (0.95–1.41)	0.5
		Esophagogastric Junction Adenocarcinoma[d]					
Reflux Symptoms[b]							
No	392	2,985	Referent	26	139	0.99 (0.63–1.56)	
Yes	469	2,047	Referent	56	127	1.32 (0.93–1.86)	0.3
Regurgitation[c]							
No	249	1,169	Referent	22	98	0.73 (0.44–1.20)	
Yes	338	1,174	Referent	45	83	1.47 (0.99–2.20)	0.03
Heartburn[b]							
No	493	3,345	Referent	40	165	1.12 (0.77–1.63)	
Yes	362	1,685	Referent	42	101	1.28 (0.86–1.90)	0.6
Sex							
Male	1,383	4,857	Referent	165	378	1.32 (1.08–1.62)	
Female	239	1,978	Referent	19	106	1.21 (0.72–2.03)	0.8
BMI							
<25 kg/m^2	561	2,914	Referent	29	127	0.98 (0.64–1.49)	
≥25 kg/m^2	1,061	3,922	Referent	155	357	1.41 (1.14–1.74)	0.1
Smoking							
Never	333	2,541	Referent	31	159	1.26 (0.84–1.91)	
Ever	1,289	4,295	Referent	153	325	1.32 (1.07–1.63)	0.9
Age							
<60 years	574	2,969	Referent	45	135	1.31 (0.91–1.89)	
≥60 years	1,048	3,867	Referent	139	349	1.30 (1.05–1.62)	1.0

	All Esophageal and Esophagogastric Junction Adenocarcinoma						
Reflux Symptoms[b]							
No	766	3,202	Referent	66	157	1.24 (0.91–1.72)	
Yes	1,094	2,082	Referent	155	130	1.49 (1.15–1.94)	0.4
Regurgitation[c]							
No	562	1,409	Referent	69	118	1.03 (0.74–1.43)	
Yes	767	1,186	Referent	121	84	1.63 (1.19–2.22)	0.04
Heartburn[b]							
No	931	3,553	Referent	94	183	1.35 (1.02–1.78)	
Yes	916	1,717	Referent	125	104	1.46 (1.09–1.95)	0.7
Sex							
Male	3,128	7,135	Referent	380	552	1.25 (1.08–1.44)	
Female	452	3,321	Referent	42	182	1.31 (0.91–1.88)	0.8
BMI							
<25 kg/m^2	1,110	4,445	Referent	66	174	1.17 (0.86–1.58)	
≥25 kg/m^2	2,470	6,012	Referent	356	560	1.28 (1.10–1.49)	0.6
Smoking							
Never	740	3,818	Referent	80	240	1.34 (1.01–1.77)	
Ever	2,840	6,639	Referent	342	494	1.23 (1.05–1.43)	0.6
Age							
<60 years	925	2,966	Referent	71	134	1.32 (1.02–1.72)	
≥60 years	1,650	3,859	Referent	257	349	1.23 (1.05–1.43)	0.6

[a]Adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous).

[b]Available for ACS, FINBAR, MHC, LAS, NLCS, and PMCC.

[c]Available for ACS, FINBAR, LAS, and PMCC.

[d]PMCC does not include EGJA.

Table 4. Adjusted[a] odds ratios (ORs) and 95% confidence intervals (CIs) for the association between diabetes and Barrett's esophagus, compared to population-based and endoscopy controls, respectively.

	Population-based Controls				
	BE Case N	**Control N**	**OR (95% CI)**	**I^2 (%)**	**P$_{heterogeneity}$**
Diabetes					
No	1,325	2,438	Referent		
Yes	158	301	0.87 (0.67–1.13)	18.3	0.3
Type 2 Diabetes[b]					
No	709	913	Referent		
Yes	116	144	1.00 (0.64–1.56)	49.3	0.1
Duration of type 2 diabetes					
0.5-3 years	35	27	1.74 (0.73–4.15)	48.3	0.1
>3-5 years	19	25	0.85 (0.46–1.60)	0.0	0.5
>5-10 years	25	31	0.98 (0.44–2.20)	42.4	0.2
>10 years	21	42	0.58 (0.33–1.01)	0.0	0.6
	Endoscopy Controls				
Diabetes					
No	816	1,195	Referent		
Yes	130	268	0.93 (0.71–1.20)	0.0	1.0
Type 2 Diabetes[b]					
No	709	1006	Referent		
Yes	116	239	0.97 (0.73–1.28)	0.0	1.0
Duration of type 2 diabetes					
0.5-3 years	35	55	1.11 (0.52–2.36)	48.3	0.1
>3-5 years	19	34	1.05 (0.55–2.00)	0.0	0.5
>5-10 years	25	58	0.77 (0.45–1.31)	0.0	0.5
>10 years	21	44	0.90 (0.51–1.57)	0.0	0.5

[a]Adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous).

[b]Available for FINBAR, SDH, and VAT.

Table 5. Adjusted[a] odds ratios (ORs) and 95% confidence intervals (CIs) for interaction between diabetes and other risk factors and Barrett's esophagus, compared to population-based and endoscopy controls, respectively.

	Population-based Controls						
	Non-Diabetes			Diabetes			
	BE Case N	Control N	OR (95% CI)	BE Case N	Control N	OR (95% CI)	P_interaction
Reflux Symptoms							
No	622	1,844	Referent	60	215	0.91 (0.66–1.27)	
Yes	703	594	Referent	98	86	0.73 (0.52–1.02)	0.3
Regurgitation[b]							
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	1,962	Referent	62	227	0.85 (0.62–1.18)	
Yes	617	476	Referent	96	74	0.77 (0.54–1.10)	0.9
Sex							
Male	945	1,730	Referent	140	272	0.79 (0.62–1.02)	
Female	380	708	Referent	18	29	1.01 (0.55–1.86)	0.5
BMI							
<25 kg/m^2	446	955	Referent	21	33	1.21 (0.68–2.15)	
≥25 kg/m^2	879	1,483	Referent	137	268	0.78 (0.61–1.00)	0.2
Smoking							
Never	425	981	Referent	42	101	0.87 (0.59–1.30)	
Ever	900	1,457	Referent	116	200	0.80 (0.61–1.05)	0.7
Age							
<60 years	523	1,088	Referent	41	86	0.93 (0.61–1.41)	
≥60 years	802	1,350	Referent	117	215	0.78 (0.60–1.02)	0.5
	Endoscopy Controls						
	Non-Diabetes			Diabetes			
	BE Case N	Control N	OR (95% CI)	BE Case N	Control N	OR (95% CI)	P_interaction
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)	0.5
Regurgitation[c]							
No	170	264	Referent	14	14	1.14 (0.52–2.49)	
Yes	429	359	Referent	39	38	0.76 (0.46–1.25)	0.9
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							
Male	633	842	Referent	114	233	0.92 (0.70–1.21)	
Female	183	353	Referent	16	35	0.98 (0.51–1.90)	0.8
BMI							
<25 kg/m^2	225	305	Referent	17	23	1.03 (0.52–2.06)	
≥25 kg/m^2	591	890	Referent	113	245	0.91 (0.69–1.19)	0.7
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)	0.3
Age							
<60 years	366	655	Referent	36	77	1.17 (0.74–1.84)	
≥60 years	450	540	Referent	94	191	0.84 (0.62–1.13)	0.2

[a]Adjusted for age (continuous), sex, smoking (never, ever), body mass index (continuous), and parent study.

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Figure 1. Forrest plot of the relationship between diabetes and (**A**) esophageal adenocarcinoma, (**B**) esophagogastric junction adenocarcinoma, and (**C**) all esophageal and esophagogastric junction adenocarcinomas, by random effects model adjusted for age, sex, smoking (never, ever), and body mass index (continuous).

B

Study, Country, Recruitment Period	OR (95% CI)	Weight (%)
ACS, Australia, 2001-05	1.20 (0.80, 1.79)	23.49
NIH-AARP, US, 1995-96	1.49 (1.08, 2.05)	37.07
BKW, US, 1986-89	1.18 (0.63, 2.23)	9.43
FINBAR, N. Ireland/Ireland, 2002-04	1.36 (0.57, 3.24)	5.05
MHC, US, 1964-73	0.51 (0.07, 4.02)	0.90
LAS, US, 1992-97	0.78 (0.44, 1.41)	10.97
LEO, US, 1983-90	1.16 (0.55, 2.46)	6.74
NLCS, Netherlands, 1986	1.96 (0.90, 4.26)	6.34
Overall (I-squared = 0.0%, p = 0.6)	1.27 (1.05, 1.55)	100.00

C

Study, Country, Recruitment Period	OR (95% CI)	Weight (%)
ACS, Australia, 2001-05	1.29 (0.93, 1.79)	17.93
NIH-AARP, US, 1995-96	1.11 (0.89, 1.38)	24.47
BKW, US, 1986-89	1.10 (0.63, 1.92)	9.40
FINBAR, N. Ireland/Ireland, 2002-04	1.17 (0.57, 2.40)	6.32
MHC, US, 1964-73	1.33 (0.49, 3.60)	3.59
LAS, US, 1992-97	0.95 (0.60, 1.49)	12.42
LEO, US, 1983-90	1.24 (0.69, 2.24)	8.61
NLCS, Netherlands, 1986	2.15 (1.16, 3.96)	8.09
PMCC, Canada, 2006-11	2.59 (1.47, 4.54)	9.18
Overall (I-squared = 34.9%, p = 0.1)	1.30 (1.06, 1.58)	100.00

Figure 2. Forrest plot of the relationship between diabetes and Barret155t's esophagus, versus (**A**) population controls and (**B**) GERD/endoscopy controls, by random effects model adjusted for age (continuous), sex, smoking (never, ever), and body mass index (continuous).

B

Study, Country, Recruitment Period	OR (95% CI)	Weight (%)
FINBAR, N. Ireland/Ireland, 2002-04	0.88 (0.44, 1.75)	14.14
SDH, Australia, 2003-06	0.82 (0.43, 1.59)	15.66
UNC, US, 2001-06	1.01 (0.42, 2.45)	8.68
VAT, US, 2008-11	0.95 (0.69, 1.33)	61.52
Overall (I-squared = 0.0%, p = 1.0)	0.93 (0.71, 1.20)	100.00

.1   .5 .75 1 1.5 2   10

A

Study, Country, Recruitment Period	OR (95% CI)	Weight (%)
ACS, Australia, 2001-05	1.38 (0.92, 2.07)	17.26
NIH-AARP, US, 1995-96	0.86 (0.64, 1.18)	19.99
BKW, US, 1986-89	0.96 (0.40, 2.30)	7.73
FINBAR, N. Ireland/Ireland, 2002-04	1.04 (0.45, 2.41)	8.27
MHC, US, 1964-73	2.27 (0.68, 7.58)	4.76
LAS, US, 1992-97	1.16 (0.66, 2.05)	12.95
LEO, US, 1983-90	1.33 (0.63, 2.80)	9.58
NLCS, Netherlands, 1986	2.54 (0.93, 6.94)	6.34
PMCC, Canada, 2006-11	2.59 (1.47, 4.54)	13.12
Overall (I-squared = 48.8%, p = 0.05)	1.34 (1.00, 1.80)	100.00

.1   .5 .75 1 1.5 2   10

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B

Study, Country, Recruitment Period	OR (95% CI)	Weight (%)
ACS, Australia, 2001-05	1.20 (0.80, 1.79)	23.49
NIH-AARP, US, 1995-96	1.49 (1.08, 2.05)	37.07
BKW, US, 1986-89	1.18 (0.63, 2.23)	9.43
FINBAR, N. Ireland/Ireland, 2002-04	1.36 (0.57, 3.24)	5.05
MHC, US, 1964-73	0.51 (0.07, 4.02)	0.90
LAS, US, 1992-97	0.78 (0.44, 1.41)	10.97
LEO, US, 1983-90	1.16 (0.55, 2.46)	6.74
NLCS, Netherlands, 1986	1.96 (0.90, 4.26)	6.34
Overall (I-squared = 0.0%, p = 0.6)	1.27 (1.05, 1.55)	100.00

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C

Study, Country, Recruitment Period		OR (95% CI)	Weight (%)
ACS, Australia, 2001-05		1.29 (0.93, 1.79)	17.93
NIH-AARP, US, 1995-96		1.11 (0.89, 1.38)	24.47
BKW, US, 1986-89		1.10 (0.63, 1.92)	9.40
FINBAR, N. Ireland/Ireland, 2002-04		1.17 (0.57, 2.40)	6.32
MHC, US, 1964-73		1.33 (0.49, 3.60)	3.59
LAS, US, 1992-97		0.95 (0.60, 1.49)	12.42
LEO, US, 1983-90		1.24 (0.69, 2.24)	8.61
NLCS, Netherlands, 1986		2.15 (1.16, 3.96)	8.09
PMCC, Canada, 2006-11		2.59 (1.47, 4.54)	9.18
Overall (I-squared = 34.9%, p = 0.1)		1.30 (1.06, 1.58)	100.00

.1   .5 .75 1   1.5 2   10
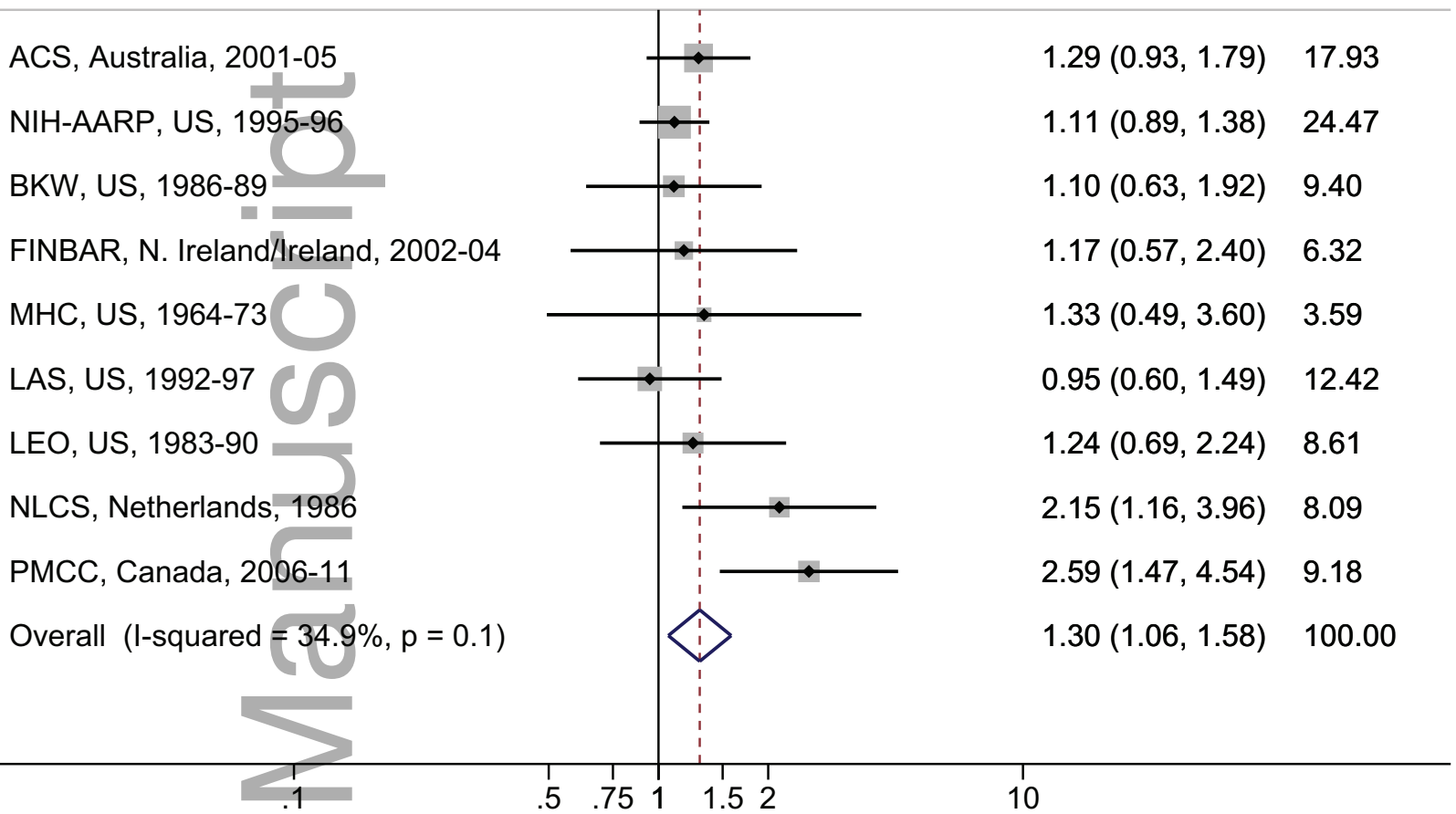
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A

Study, Country, Recruitment Period	OR (95% CI)	Weight (%)
FINBAR, N. Ireland/Ireland, 2002-04	1.39 (0.67, 2.88)	11.85
NDB, US, 2008-11	0.66 (0.39, 1.12)	20.58
NLCS, Netherlands, 1986	0.91 (0.49, 1.69)	15.88
SDH, Australia, 2003-06	1.20 (0.68, 2.10)	18.50
VAT, US, 2008-11	0.71 (0.48, 1.04)	33.19
Overall (I-squared = 18.3%, p = 0.3)	0.87 (0.67, 1.13)	100.00

.1   .5 .75 1 1.5 2   10

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B

Study, Country, Recruitment Period	OR (95% CI)	Weight (%)
FINBAR, N. Ireland/Ireland, 2002-04	0.88 (0.44, 1.75)	14.14
SDH, Australia, 2003-06	0.82 (0.43, 1.59)	15.66
UNC, US, 2001-06	1.01 (0.42, 2.45)	8.68
VAT, US, 2008-11	0.95 (0.69, 1.33)	61.52
Overall (I-squared = 0.0%, p = 1.0)	0.93 (0.71, 1.20)	100.00

.1   .5 .75 1 1.5 2   10

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