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ORIGINAL ARTICLE

History of Diverticulitis and Risk of Incident Cardiovascular Disease in Men: A Cohort Study

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Abstract

Background Diverticulitis and cardiovascular disease (CVD) are two highly prevalent disorders sharing common risk factors which are hypothesized to have an inflammatory basis.

Aims To examine the association between history of diverticulitis and risk of incident CVD.

Methods We conducted a prospective cohort study of 43,904 men aged 40 to 75 years without a history of CVD (fatal or nonfatal myocardial infarction and stroke) at enrollment who were followed up from 1986 to 2012 in the Health Professionals Follow-Up Study. Lifestyle factors, dietary intake, and disease information were self-reported biennially or quadrennially. Incident diverticulitis and CVD were confirmed by review of medical records. We used Cox proportional hazard models to calculate age- and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) of incident CVD. We conducted a stratified analysis according to the presence or absence of CVD risk factors (smoking, hypertension, hyperlipidemia, and diabetes).

Results We identified 3848 incident cases of CVD during 856,319 person-years of follow-up. Men with diverticulitis had higher incidence of CVD (727 cases per 100,000 person-years) compared to men without diverticulitis [446 cases per 100,000 person-years, multivariate HR of 1.35 (95% CI 1.07–1.70)]. The association of diverticulitis and subsequent CVD appeared more evident among men without known CVD risk factors (HR 4.06, 95% CI 2.04–8.08) compared to those with one or more CVD risk factors (HR 1.27, 95% CI 0.98–1.63).

Conclusions Diverticulitis may be an independent risk factor of incident CVD, suggesting possible common etiopathogenic mechanisms. Diagnosis of diverticulitis underscores the importance of preventive measures to reduce future CVD.

Keywords Diverticulitis · Cardiovascular disease prevention · Cardiovascular disease risk factors

Idy Tam and Po-Hong Liu have contributed equally to this work as joint first authors. Lisa L. Strate, Edward L. Giovannucci and Andrew T. Chan have contributed equally to this work as joint senior authors.

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Introduction

Diverticular disease is a highly prevalent disease in developed countries. It is the third most common gastrointestinal diagnosis on hospital discharge in the USA, accounting for $3.6 billion in health care costs each year [1, 2]. The prevalence of diverticulosis increases with age, affecting approximately 60% of individuals 70 years of age [3]. Among patients with diverticulosis, an estimated 4% will develop acute diverticulitis [4]. Diverticulitis is inflammation and micro-perforation of one or more diverticula in the colon that may progress to complications including abscess, fistula, or peritonitis. Risk factors for diverticulitis include low fiber intake, obesity, hypertension, smoking, and physical inactivity [5]. These risk factors also increase the risk of cardiovascular disease (CVD) contributing to the hypothesis of shared or exacerbated risk between these two diseases [6–11]. In addition, diverticulitis may arise in a background of low-grade, chronic inflammation potentially mediated by changes in the microbiota composition which could predispose to the development of CVD [12–15].

Several studies have demonstrated an association between diverticular disease and risk of CVD [16–18]. One large retrospective cohort study reported a 25% increased risk for acute coronary syndrome in patients with a history of diverticulitis [18]. However, existing studies are based on medical or insurance registries which utilize ICD codes for identification of exposures and outcomes, and therefore, were not able to differentiate diverticulitis, diverticular bleeding, and uncomplicated diverticulosis or account for important potential risk factors such as lifestyle and dietary factors. Therefore, we performed this study to analyze the association between a history of diverticulitis and risk of incident CVD in a large prospective cohort of US men in the Health Professional Follow-up Study (HPFS) in which we collected detailed information on risk factors for both CVD and diverticulitis and confirmed incident cases of CVD and diverticulitis through medical record review.

Methods

Study Population

The HPFS is a large ongoing prospective cohort study of 51,529 US male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists aged 40–75 years at baseline in 1986. The cohort members report on demographics, lifestyle and medical history biennially and dietary information every 4 years via self-administered questionnaires by mail. The questionnaires for each cycle can be found in the following website: https://sites.sph.harvard.edu/hpfs/hpfs-questionnaires/. The biennial follow-up rate averages 94% [19]. This study was approved by the institutional review board at the Harvard T.H. Chan School of Public Health.

We excluded participants who reported CVD, malignancy (except for non-melanoma skin cancer), or non-plausible calorie intake (less than 800 or greater than 4200 kcal daily) at baseline. The final analysis included 43,904 men.

Assessment of Diverticulitis

History of diverticulitis was based on responses from supplemental diverticular disease questionnaires, which were sent to men who reported newly diagnosed diverticulitis or diverticulosis on biennial questionnaires since 1990. Diverticulitis was defined as abdominal pain attributed to diverticular disease and one of the following criteria: (1) complicated by perforation, abscess, fistula, or obstruction; (2) requiring hospitalization, antibiotics, or surgery; or (3) pain categorized as severe or acute or abdominal pain presenting with fever, requiring antibiotics, or confirmed using abdominal CT. In 2006, supplemental questionnaires were updated to further assess diverticular complications including diverticular bleeding; uncomplicated diverticulitis; diverticular abscess, obstruction, perforation, and fistula. We have previously validated these methods and used these case definitions in prior analyses [6, 10].

Assessment of Cardiovascular Disease

The primary endpoint of this study was incident CVD, defined as fatal myocardial infarction, nonfatal myocardial infarction, and stroke. For participants who reported newly diagnosed CVD or stroke, permission was requested for medical records. All medical records were reviewed by physicians who were blind to the questionnaire data to confirm the diagnosis. Nonfatal myocardial infarction is defined according to World Health Organization criteria, which required typical symptoms plus either diagnostic electrocardiographic findings or elevated cardiac enzyme concentrations. We also considered myocardial infarctions requiring hospital admission and corroborated by phone interview or letter only as probable cases. Stroke was confirmed by use of the National Survey of Stroke criteria, requiring a constellation of neurological deficits, sudden or rapid onset, and duration of $\geq$ 24 h or until death. When medical records were not available, interviews or letters confirmed coronary and stroke events, which were designated as probable cases. Deaths were identified from the state vital statistics records and the National Death Index or were reported by families

and the postal system [20–24]. The cause listed on the death certificate was not considered sufficient to confirm a coronary or stroke death. Underlying and contributing causes of deaths were confirmed by study physicians via review of medical records or autopsy reports with permission of family members.

Assessment of Covariables

Medical history and lifestyle factors were assessed biennially. Covariables that were considered included age, body mass index (BMI), smoking status, alcohol intake, physical activity, and regular use of aspirin, non-steroidal anti-inflammatory drugs (NSAID), acetaminophen, cholesterol-lowering medication, and anti-hypertensive medication (e.g., thiazide diuretics, calcium-channel blockers, beta-blockers, other antihypertensives). Self-reported hypertension, hypercholesterolemia, diabetes mellitus, family history of myocardial infarction and diabetes mellitus were also assessed biennially. Dietary factors including dietary fiber, total energy intake, unprocessed and processed red meat intake, and the Alternate Healthy Eating Index (AHEI) were derived from validated food frequency questionnaires administered every four years [25].

Statistical Analysis

In our primary analysis, we examined the association between history of diverticulitis and risk of incident CVD. We used biennially updated reports of diverticulitis to define the exposure. We also defined recent history of diverticulitis as having diverticulitis within 4 years of incident CVD disease. Participants with diverticulitis at least 4 years prior to questionnaire cycle were defined as having remote histories of diverticulitis. Person-years were calculated from baseline (1986) until the development of CVD disease, death, or end of follow-up (January 2012), whichever came first. Participants who developed CVD and cancer during the follow-up were censored. Age-stratified cox proportional hazard models with time-varying covariables were used to estimate age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of incident CVD. The following were included in multivariable models: age, BMI (6 categories, <18.5, 18.5–22.9, 23–24.9, 25–29.9, 30–34.9, and ≥ 35 kg/m^2), physical activity (metabolic equivalents per week in quintiles), smoking status (pack-years in categories: never smokers, 1–4.9, 5–19.9, 20–39.9, ≥ 40), alcohol intake (nondrinker, 0.1–4.9, 5–14.9, 15–29.9, ≥ 30 g/d), total energy intake (in quintiles), AHEI (in quintiles), total red meat (in quintiles), dietary fiber (in quintiles), history of hypertension, hypercholesterolemia, and diabetes (all yes or no), family history of myocardial infarction and diabetes (both yes or no), and regular use of aspirin, NSAIDs, acetaminophen, lipid-lowering medication, and anti-hypertensive medication (yes or no). We updated history of diverticulitis and other covariables at 2- or 4-year intervals.

We also considered the possibility that participants who did not report history of diverticulitis and CVD or who reported fewer cardiovascular risk factors may have less interaction with health care. We therefore conducted a sensitivity analysis restricting to participants who had routine physical examinations for health screening in the same questionnaire cycle. In addition, we conducted stratified analyses in patients with history of diverticulitis according to the presence or absence of the following CVD risk factors: hypertension, hypercholesterolemia, diabetes, or smoking. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.). Two-sided p values less than 0.05 were considered statistically significant.

Participants Involvement

Participants were not involved in the design of research questions or outcome measures. They were not involved in the design and implantation of the study. There are no plans to involve participants in the dissemination of results.

Results

The mean ages at baseline were 53.8 in men without diverticulitis and 52.4 in men with diverticulitis. During 856,319 person-years of follow-up, we documented 3848 incident cases of CVD. Compared to men without a history of diverticulitis, men with history of diverticulitis tended to have CVD risk factors, such as higher total red meat intake, greater pack-years of smoking, less physical activity, and a higher prevalence of hypercholesterolemia. In addition, men with a history of diverticulitis used aspirin, NSAID, and acetaminophen more often (Table 1).

Participants with a history of diverticulitis had higher incidence of CVD (727 cases per 100,000 person-years) compared to men without diverticulitis (446 cases per 100,000 person-years). The multivariate HR after adjustment for age, BMI, smoking status, alcohol intake, physical activity, red meat intake, dietary fiber, and AHEI was 1.40 (95% CI 1.11–1.76). Further adjustment for personal history of hypertension, hyperlipidemia, diabetes, family history of myocardial infarction and diabetes, and use of aspirin, non-aspirin NSAIDs, acetaminophen, lipid-lowering medication, and anti-hypertensive medication showed similar results (HR 1.35, 95% CI 1.07–1.70, Tables 2, 3, 4).

As an exploratory analysis, we evaluated the influence of a recent (within 4 years) or remote (greater than 4 years) history of diverticulitis and risk of incident CVD. We observed trends toward increases in risk of CVD with both recent

Table 1 Characteristics of men in the Health Professionals Follow-Up Study at baseline (1986) and midpoint (1998) according to presence or absence of diverticulitis

Characteristics*	Baseline 1986		Midpoint 1998	
	No Diverticulitis n = 42,744	Diverticulitis n = 1160	No Diverticulitis n = 33,545	Diverticulitis n = 1013
Age, years	53.8 (9.6)	52.4 (8.7)	63.9 (8.9)	63.4 (8.5)
Total red meat intake, g/day	76.2 (55.0)	81.7 (54.5)	70.3 (53.2)	74.9 (52.8)
Dietary fiber, g/day	20.9 (7.0)	19.8 (6.4)	23.6 (7.5)	22.7 (6.9)
All physical activity, MET-hours/week	19.0 (26.3)	16.7 (22.1)	29.1 (29.2)	28.2 (28.2)
Vigorous physical activity, MET-hours/week	13.2 (26.3)	10.5 (21.1)	13.6 (25.4)	11.7 (25.8)
Body mass index, kg/m^2	25.5 (3.3)	25.6 (3.0)	26.2 (3.7)	26.5 (3.6)
Ever smokers, %	51.2	56.1	48.8	55.0
Pack-years among ever smokers	24.3 (18.6)	25.9 (18.8)	23.2 (18.3)	25.8 (19.3)
Alcohol intake, g/day	11.3 (15.4)	11.4 (14.6)	11.1 (14.2)	10.6 (13.2)
Regular aspirin use, %	27.0	28.9	51.9	56.1
Regular NSAID use, %	5.4	7.2	17.5	22.9
Regular acetaminophen use, %	5.7	8.4	7.7	9.9
Hypertension, %	20.3	19.9	34.8	38.3
Hyperlipidemia, %	10.7	11.9	45.2	50.2
Diabetes, %	0.4	0.4	4.3	4.7
Any hypertension, hyperlipidemia, or diabetes, %	27.3	27.9	61.3	67.0
Any hypertension, hyperlipidemia, diabetes, or ever smoker, %	61.4	64.1	77.8	81.8

MET metabolic equivalent of tasks, *NSAID* non-steroid anti-inflammatory drugs

*Mean (standard deviation) is presented for continuous variables

Table 2 History of diverticulitis and risk of incident cardiovascular disease among all participants

	Any history of diverticulitis		Recent history of diverticulitis within past 4 years		Remote history of diverticulitis beyond 4 years	
	No	Yes	No	Yes	No	Yes
Number of CVD events	3772	76	3772	27	3772	49
Person-years	845,861	10,458	845,861	3432	845,861	7036
Age-adjusted	1 (Ref)	1.49 (1.18–1.88)	1 (Ref)	1.61 (1.09–2.36)	1 (Ref)	1.43 (1.07–1.90)
Multivariable-adjusted[a]	1 (Ref)	1.40 (1.11–1.76)	1 (Ref)	1.52 (1.03–2.23)	1 (Ref)	1.34 (1.00–1.79)
Full model[b]	1 (Ref)	1.35 (1.07–1.70)	1 (Ref)	1.45 (0.98–2.14)	1 (Ref)	1.30 (0.97–1.73)

Table 3 History of diverticulitis and risk of incident cardiovascular disease among participants below age of 65 years

	Any history of diverticulitis		Recent history of diverticulitis within past 4 years		Remote history of diverticulitis beyond 4 years	
	No	Yes	No	Yes	No	Yes
Number of CVD events	1466	21	1466	8	3772	13
Person-years	512,650	4392	512,650	1829	845,861	2563
Age-adjusted	1 (Ref)	1.50 (0.97–2.32)	1 (Ref)	1.34 (0.67–2.71)	1 (Ref)	1.62 (0.93–2.81)
Multivariable-adjusted[a]	1 (Ref)	1.36 (0.88–2.11)	1 (Ref)	1.27 (0.63–2.56)	1 (Ref)	1.43 (0.82–2.48)
Full model[b]	1 (Ref)	1.28 (0.83–1.98)	1 (Ref)	1.20 (0.59–2.44)	1 (Ref)	1.33 (0.76–2.32)

Table 4 History of diverticulitis and risk of incident cardiovascular disease among participants above age of 65 years

	Any history of diverticulitis		Recent history of diverticulitis within past 4 years		Remote history of diverticulitis beyond 4 years	
	No	Yes	No	Yes	No	Yes
Number of CVD events	2306	55	2306	19	2306	36
Person-years	333,211	6066	333,211	1603	333,211	4463
Age-adjusted	1 (Ref)	1.48 (1.12–1.94)	1 (Ref)	1.75 (1.11–2.78)	1 (Ref)	1.36 (0.97–1.90)
Multivariable-adjusted[a]	1 (Ref)	1.41 (1.07–1.85)	1 (Ref)	1.67 (1.05–2.65)	1 (Ref)	1.30 (0.93–1.81)
Full model[b]	1 (Ref)	1.36 (1.04–1.80)	1 (Ref)	1.60 (1.01–2.54)	1 (Ref)	1.27 (0.90–1.77)

Note: Hazard ratio and 95% confidence interval are shown

[a]Adjusted for lifestyle factors (red meat intake, fiber intake, body mass index, calorie intake, smoking, Alternate Healthy Eating Index, alcohol consumption, and physical activity)

[b]Additionally adjusted for family history (myocardial infarction or diabetes), medication (aspirin, NSAID, acetaminophen, lipid-lowering, and anti-hypertensive), hypertension, diabetes, and hyperlipidemia

(HR 1.45, 95% CI 0.98–2.14) and remote (HR 1.30, 95% CI 0.97–1.73) history of diverticulitis, even though these did not reach statistical significance. Our main results remained unchanged in a sensitivity analysis limiting to participants who had received screening physical examinations (Table 5).

In the stratified analyses, we found that history of diverticulitis was associated with higher risk of incident CVD (HR 4.06, 95% CI 2.04–8.08) among participants without CVD risk factors (hypertension, hypercholesterolemia, diabetes, and smoking, Table 6), but not in those with CVD risk factors (HR 1.27, 95% CI 0.98–1.63, p for interaction = 0.12).

Discussion

In this large prospective cohort of men, we found that a history of diverticulitis was associated with a significant 34% increased risk of incident CVD, independent of conventional lifestyle and dietary risk factors. The trend toward an increased risk of incident CVD was observed with both recent history and remote history of diverticulitis, although this association did not reach statistical significance. Results were similar when we limited the exposure to those with regular contact with the health care system through regular physical examinations. In addition, the association between diverticulitis and risk of CVD was more evident in participants without traditional CVD risk factors.

Our findings are consistent with evidence from previous limited studies [14–18]. In particular, a large prospective cohort study of more than 77 thousand patients with incident diverticular disease identified in the Danish medical registries found that patients with diverticular disease had a modestly increased risk of acute myocardial infarction and venous thromboembolic events when compared to matched controls, with adjusted incidence rate ratios 1.11 (95% CI 1.07–1.14) and 1.35 (95% CI 1.30–1.43), respectively. These studies were limited by the use of diagnostic coding from medical and insurance registries, and therefore, were unable

Table 5 History of diverticulitis and risk of incident cardiovascular disease among participants with regular screening practices

	Any history of diverticulitis		Recent history of diverticulitis within past 4 years		Remote history of diverticulitis beyond 4 years	
	No	Yes	No	Yes	No	Yes
Number of CVD events	2001	49	2001	14	2001	35
Person-years	445,383	6294	445,383	1792	445,383	4502
Age-adjusted	1 (Ref)	1.69 (1.26–2.27)	1 (Ref)	1.53 (0.89–2.62)	1 (Ref)	1.77 (1.25–2.49)
Multivariable-adjusted[a]	1 (Ref)	1.56 (1.17–2.09)	1 (Ref)	1.40 (0.82–2.41)	1 (Ref)	1.64 (1.16–2.32)
Full model[b]	1 (Ref)	1.51 (1.13–2.03)	1 (Ref)	1.40 (0.82–2.41)	1 (Ref)	1.56 (1.10–2.20)

Hazard ratio and 95% confidence interval are shown

[a]Adjusted for lifestyle factors (red meat intake, fiber intake, body mass index, calorie intake, smoking, Alternate Healthy Eating Index, alcohol consumption, and physical activity)

[b]Additionally adjusted for family history (myocardial infarction or diabetes), medication (aspirin, NSAID, acetaminophen, lipid-lowering, and anti-hypertensive), hypertension, diabetes, and hyperlipidemia

Table 6 History of diverticulitis and risk of incident cardiovascular disease in participants with and without cardiovascular risk factors

	Without hypertension, diabetes, hyperlipidemia, and smoking		With either hypertension, diabetes, hyperlipidemia, or smoking	
	History Diverticulitis		History Diverticulitis	
	No	Yes	No	Yes
Number of CVD events	466	11	3306	65
Person-years	207,933	1601	637,928	8857
Age-adjusted	1 (Ref)	3.72 (1.88–7.35)	1 (Ref)	1.39 (1.08–1.79)
Multivariable-adjusted[a]	1 (Ref)	3.89 (1.96–7.73)	1 (Ref)	1.32 (1.03–1.70)
Full model[b]	1 (Ref)	4.06 (2.04–8.08)	1 (Ref)	1.27 (0.98–1.63)

Hazard ratio and 95% confidence interval are shown

[a]Adjusted for lifestyle factors (red meat intake, fiber intake, body mass index, calorie intake, smoking, Alternate Healthy Eating Index, alcohol consumption, and physical activity)

[b]Additionally adjusted for family history (myocardial infarction or diabetes), medication (aspirin, NSAID, acetaminophen, lipid-lowering, and anti-hypertensive), hypertension, diabetes, and hyperlipidemia

to identify and differentiate among diverticulitis, diverticular bleeding, and uncomplicated diverticulosis. In addition, previous studies could not adjust for important covariables such as lifestyle factors and dietary intake. In contrast, in our study, we utilized a prospective cohort-based design with updated assessments of lifestyle and dietary factors for over 26 years of follow-up, which minimized the probability of selection and recall bias. In addition, we provided validated assessments of diverticulitis and CVD cases in comparison with existing studies and comprehensively controlled for multiple potential confounding factors.

Our results have biological plausibility. Chronic low-grade systemic inflammation due to gut microbiome dysbiosis may play a role in explaining the association between cardiovascular and diverticular disease. Studies have postulated that gut microbiota is a contributor to atherosclerosis, a precursor of CVD through modulation of host metabolism and inflammation, as well as various CVD risk factors such as metabolic syndrome, obesity, and diabetes [13, 14, 26–29]. Previous studies have shown that gut microbiota metabolizes choline, phosphatidylcholine, and L-carnitine to trimethylamine which is oxidized to trimethylamine-N-oxide, a proatherogenic metabolite [30, 31]. Gut microbiota composition of patients with atherosclerotic CVD has an abundance of species that have been also associated with inflammatory bowel disease [32]. Interestingly, studies that have examined gut microbiota composition in patients with diverticular disease found changes, such as abundance of *Enterobacteriaceae* and depletion of *Faecalibacterium prausnitzii,* that are similar to those in patients with atherosclerotic CVD [12]. Initial data suggest that patients with diverticular disease could harbor changes in gut microbiota composition which alter host immune defenses and cause dysfunction of mucosal barrier, leading to cross-reactivity and release of proinflammatory cytokines leading to systemic inflammation [13, 33, 34]. These changes contribute to the development of chronic low-grade systemic inflammation which can then contribute to atherosclerotic plaque formation [13, 31, 32]. Hence, dysbiosis in gut microbiota and an attendant chronic inflammatory state may be the link for the increased risk of CVD in patients with history of diverticulitis observed in this study. Indeed, a recent prospective analysis found that patients with a history of diverticulitis had a higher inflammatory potential of diet as well as higher circulating levels of C-reactive protein (CRP), interleukin 6 (IL6), markers of chronic inflammation [35, 36]. Therefore, patients with a history of diverticulitis appear to be in a state of chronic low-grade inflammation and may harbor an increased risk of CVD through this mechanism. The observed increased risk of CVD in men with either a recent or remote history of diverticulitis may be explained by this chronic inflammatory state rather than any acute events occurring at the time of a diverticulitis episode.

In addition, we found that stratification by several main components of the Framingham Risk Score [37] CVD risk factors modified the association between diverticulitis and CVD, although formal testing was not statistically significant (p for interaction = 0.12). Remarkably, risks of CVD associated with history of diverticulitis appeared to be more prominent in presumably healthier men, *i.e.*, those without hypertension, hypercholesterolemia, diabetes, and smoking history. Since CVD risk factors such as hypertension, hypercholesterolemia, and diabetes are often asymptomatic and may go undiagnosed, it is possible we did not fully account for their potential confounding in our multivariate models. However, our results were largely unchanged when we limited our analysis to those participants with routine physical examinations in which these conditions are likely to be diagnosed through asymptomatic screening. An alternative explanation is that men with hypertension, hypercholesterolemia, diabetes, and smoking history had a higher absolute risk to CVD;

therefore, the increased risk attributable to diverticulitis might be less evident compared to those men without CVD risk factors. A history of diverticulitis may be associated with gut microbial changes that also predispose to the development of obesity, diabetes, and hypertension, which in turn is associated with CVD. Thus, adjusting for these factors may attenuate a potential association. Finally, it is possible that patients who are diagnosed with hypertension, hypercholesterolemia, and diabetes might make healthier lifestyle modifications compared to men without these diagnoses, which could mitigate an association between diverticulitis and risk of CVD among patients with CVD risk factors. Further studies are warranted to explore these underlying mechanisms.

The main strengths of this study include large sample size and a prospective population-based design with update assessment of lifestyle and dietary factors for over 26 years of follow-up. The comprehensive lifestyle information available allowed us to finely adjust for potential confounders, anti-hypertensive, and lipid-lowering medications, and risk factors shared between diverticulitis and CVD. In addition, we were able to demonstrate a similar effect among participants with regular contact with health care, minimizing possible under-reporting of CVD risk factors. Finally, we were also able to differentiate diagnoses of diverticulitis from uncomplicated diverticulosis and diverticular bleeding as these diseases have distinct clinical manifestations and risk factors.

Nevertheless, our study has some potential limitations that need to be considered. First, it is possible that the association between history of diverticulitis and incident CVD can be confounded by a higher prevalence of CVD risk factors, such as low fiber intake, hypertension, smoking, and physical inactivity [6–11]. However, even after adjusting for these risk factors, the risk of developing CVD remained higher in individuals with history of diverticulitis, which suggests that shared risk factors may not fully account for the association that we observed. In addition, although we considered a comprehensive list of potential confounders, there is possibility of residual, unmeasured confounding. However, in our secondary analysis, we limited the analysis to those who have routine health physicals to minimize unmeasured confounding of asymptomatic diseases. Second, diagnoses of diverticulitis were self-reported and could potentially be misclassified. However, the validity of self-reported diverticulitis has been confirmed in this cohort and health professionals are more likely to provide an accurate account of medical information [6, 10]. Third, our study may lack generalizability due to the homogeneity of our population, particularly for women and other racial or ethnic groups. Finally, due to the observational nature of this study, a causal relationship between diverticulitis and CVD could not be proven.

Conclusion

Our results indicate that a history of diverticulitis is associated with an increased risk of incident CVD. These findings highlight the possibility that there are biological pathways which underlie both conditions. Clinically, this suggests that a diagnosis of diverticulitis may be an early marker of an underlying predisposition to CVD and underscores the importance of frequent monitoring of lifestyle factors that could influence not only risk of recurrent diverticulitis but also other health conditions associated with chronic inflammation.

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Declarations

Conflict of interest A.T.C. previously served as a consultant for Bayer Pharma AG, Janssen Pharmaceuticals and Pfizer Inc. for work unrelated to the topic of this manuscript. This study was not funded by Bayer Pharma AG, Janssen Pharmaceuticals or Pfizer Inc.

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