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ORIGINAL ARTICLE

Risk of Adverse Cardiovascular Outcomes in Postmenopausal Women with Inflammatory Bowel Disease

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Abstract

Background Individuals with inflammatory bowel disease (IBD) who lack traditional cardiovascular disease (CVD) risk factors, such as young females, are observed to experience adverse CVD outcomes. Whether women with IBD have increased CVD risk after the menopause transition is unclear.

Methods We conducted a survival analysis of Women's Health Initiative (WHI) participants and excluded those with missing IBD diagnosis, model covariate data, follow-up data, or a baseline history of the following CVD outcomes: coronary heart disease (CHD), ischemic stroke, venous thromboembolism (VTE), peripheral arterial disease (PAD). Risk of outcomes between IBD and non-IBD women was performed using Cox proportional hazard models, stratified by WHI trial and follow-up. Models were adjusted for age, socio-demographics, comorbidities (e.g., hypertension, diabetes, hypercholesterolemia, etc.), family history, and lifestyle factors (e.g., smoking, alcohol, physical activity, body mass index, etc.).

Results Of 134,022 WHI participants meeting inclusion criteria, 1367 (1.0%) reported IBD at baseline. Mean baseline age was 63.4 years. After adjusting for age and other confounders, no significant difference was observed between IBD and non-IBD women for the risk of CHD (HR 0.96, 95% CI 0.73–1.24), VTE (HR 1.11, 95% CI 0.81–1.52) or PAD (HR 0.64, 95% CI 0.28–1.42). After adjusting for age, risk of ischemic stroke was significantly higher (HR 1.41, 95% CI 1.06–1.88) in IBD than non-IBD women. With further adjustment, the excess risk of ischemic stroke among IBD women was attenuated and no longer statistically significant (HR 1.31, 95% CI 0.98–1.76).

Conclusions Among postmenopausal women with IBD, risk of ischemic stroke may be higher than in non-IBD women.

Keywords Cardiovascular disease · Stroke · Inflammatory bowel disease · Postmenopausal

Abbreviations

BMI	Body mass index
CV	Cardiovascular
CVD	Cardiovascular disease
CHD	Coronary heart disease
CRP	C-reactive protein
DM	Diabetes
HLD	Hypercholesterolemia
HTN	Hypertension
IBD	Inflammatory bowel disease

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MI	Myocardial infarction
PE/DVT	Pulmonary embolism or deep vein thrombosis
PAD	Peripheral arterial disease
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
VTE	Venous thromboembolism
WHI	Women's Health Initiative
JAK	Janus kinase

Introduction

Inflammatory bowel disease (IBD), namely Crohn's disease and ulcerative colitis, are conditions of chronic immune-mediated inflammation affecting the gastrointestinal tract. Individuals with IBD may also experience systemic inflammatory activity beyond the GI tract presenting as extra-intestinal manifestations or co-morbid immune mediated conditions. Although data are mixed, many studies indicate individuals with IBD have an increased risk of adverse cardiovascular (CV) outcomes not fully explained by traditional CV risk factors [1–9]. For instance, female and younger individuals with IBD may have higher risk of coronary heart disease (CHD) and stroke, in contrast to the traditional CV risk factors of male sex and older age [7, 10–15]. Endothelial dysfunction with accelerated atherosclerosis is proposed as a potential mechanism of adverse CV events in IBD [16–18] and is observed in other conditions of chronic inflammation, such as rheumatoid arthritis and systemic lupus erythematosus [19–24]. In addition, proinflammatory cytokines, such as C-reactive protein (CRP), tumor necrosis factor-alpha, and homocysteine are associated not only with IBD activity but also play a central role in the inflammatory cascade leading to atherosclerosis and thrombogenesis [25, 26].

Sex difference in the risk of coronary heart disease and stroke in IBD may be due to higher systemic inflammation in females [11, 27]. While endogenous estrogen is thought to be cardioprotective, decline in estrogen levels during the menopause transition is linked to decline in endothelial function [28, 29]. The menopause transition is also associated with increases in blood pressure, atherogenic lipids, visceral adiposity, and insulin resistance [28, 30–32]. It has been suggested that CV risk from a chronic inflammatory condition, such as IBD, may be less apparent in older populations due to the increasing prevalence of traditional CV risk factors with age. However, the risk of adverse CV outcomes among older women with IBD is unclear. Particularly in the setting of increased CV events observed with newer agents, such as Janus kinase (JAK) inhibitors, used in the treatment of IBD, identifying factors that elevate the CV risk for patients with IBD is increasingly important. Thus, this study aimed to assess the risk of incident cardiovascular disease (CVD) among postmenopausal women with IBD.

Methods

Study Population

The Women's Health Initiative (WHI) is a long-term cohort study investigating clinical outcomes among postmenopausal women. Originally initiated in the early 1990s with the recruitment of women ages 50–79 years from 40 clinical centers nationwide, WHI has continued with extension studies that collect annual health updates and outcomes of participants. A total of 161,808 women were recruited and enrolled into the initial study to participate in either the clinical trials or the parallel observational study. The clinical trial component randomized women into four trials, which were overlapping for some participants: two hormone therapy (estrogen + progesterone vs. placebo and estrogen alone vs. placebo), dietary modification (low-fat diet vs. self-selected dietary behavior), and calcium with vitamin D supplementation (vs. placebo).

Extensive data from participants in both the clinical trials and observational study were collected by self-administered questionnaire, interview, and physical exam at the baseline visit and scheduled follow-ups. Further details of the study design have been previously described [33]. WHI data was analyzed at the WHI Clinical Coordinating Center. As secondary data analysis, this study was exempt from IRB review.

Exposure and Outcomes

All WHI participants completed a baseline questionnaire with information on medical history. In this study, IBD was defined as self-reported diagnosis by affirmative response to the question "Has a doctor told you that you have any of the following conditions? Ulcerative colitis or Crohn's disease." Details regarding IBD age of diagnosis and disease duration were not collected.

A major WHI clinical outcome of interest was CVD morbidity and mortality. The CVD outcomes of interest were coronary heart disease (CHD), ischemic stroke, pulmonary embolism or deep vein thrombosis (PE/DVT), or peripheral arterial disease (PAD). The outcomes of CHD, ischemic stroke, and PAD were adjudicated throughout the WHI study period. PE/DVT outcomes were by self-report [34].

Statistical Analysis

We performed a survival analysis of participants who were enrolled during the period 1993–1998 for the initial WHI cohort and were followed through Extension 1 of the study in 2010. Participants in both the WHI clinical trial and

observational study were included. We excluded participants with missing data on self-reported IBD diagnosis at enrollment, missing model covariate data, no follow-up data, or a previous history of one of the CVD outcomes of interest.

We compared baseline characteristics of women with and without IBD as well as baseline characteristics between women who did and did not have a CVD outcome event, using t-test for continuous variables and chi-square test for categorical variables. We then assessed the risk of each CVD outcome between women with and without IBD using Cox proportional hazard models, stratified within the model by WHI component (clinical trial / observational study), hormone use (never, past, current; incorporating WHI hormone therapy trial component), WHI dietary modification trial arm (intervention, usual diet comparison group), and time-dependent WHI follow-up period (WHI, extension 1, extension 2). The proportional hazard assumption was assessed and confirmed by graphical methods and by fitting a model of the interaction between IBD and follow-up. Models were adjusted a priori for the following potential confounders: age; socio-demographics (ethnicity, race, education); comorbidities (treated hypertension, HTN; treated diabetes, DM; treated hypercholesterolemia, HLD; rheumatoid arthritis, RA; systemic lupus erythematosus, SLE; corticosteroids; body mass index, BMI); family history MI or stroke; and lifestyle factors (e.g. smoking status, alcohol use, physical activity, visit to a regular doctor in the past year, any health insurance). We performed a subgroup analysis to separately assess for interaction between IBD and age group (<65 years vs. ≥ 65), RA/SLE, hormone therapy use, and smoking.

Statistical significance for all analyses was defined as $p<0.05$. All statistical analyses were performed using SAS for Windows 9.4.

Results

Of the total 161,808 women enrolled in WHI, there were 134,022 who met inclusion criteria, of whom 1367 (1.0%) had self-reported IBD at baseline. As seen in Table 1, the mean age among women with and without IBD was similar (63.4 vs. 63.5 years). The majority of women in both groups were of non-Hispanic ethnicity (95.1% vs. 94.9%) and White race (87.9% vs. 85.6%). Overall hormone therapy use, defined by either self-report at enrollment or assignment into the hormone therapy trial, was not significantly different among women with and without IBD ($p=0.21$). With respect to co-morbid CVD risk factors, there were no significant differences in HTN (28.4% vs. 27.8%) or DM (3.4 vs. 3.7%), whereas more women with than without IBD had HLD (17.0% vs. 12.5%), RA (8.3% vs. 4.7%), and SLE (SLE, 6.5% vs. 0.4%); $p<0.001$ for all comparisons. More women with than without IBD also had a family history of MI (52.5% vs. 48.9%, $p=0.02$) and stroke (38.0% vs. 35.9%, $p=0.04$) and were either past or current smokers (never smokers: 43.7% vs. 51.0%, $p<0.001$). Of note, less women with IBD were on regular aspirin, defined as ≥ 80mg for thirty days or more, than those without IBD (15.0% vs. 18.8%, $p<0.001$) (Table 1). From baseline (1993–1998) through the end of the study period (2010), very few women reported use of IBD biologics that were just coming to market (i.e. infliximab, adalimumab, certolizumab).

In the overall study population, traditional CV risk factors were more common among women who had an adverse CVD event compared to women who did not have an event (HTN—no event 26.4% vs. event 36.6–49.7%; DM—no event 3.3% vs. event 5.3–12.3%, $p<0.001$ for all comparisons). In addition, RA and SLE were more common in women who experienced CHD, ischemic stroke, and PE/DVT (no event—RA 4.5%, SLE 0.4% vs. event RA 6.5–7.3%, SLE 0.7–0.8%, $p<0.001$ for all comparisons). Finally, smoking and less physical activity were also more common among women who had an event compared to those who did not (never smokers—no event 51.3% vs. event 25.4–50.8%; mean metabolic equivalent hours—no event 12.8 vs. event 9.6–11.3%, $p<0.05$).

The annual rate of CVD events was approximately 0.36% for CHD, 0.25% for PE/DVT, and 0.04% for PAD among all women regardless of IBD status. The annual rate of ischemic stroke, however, was 0.09% higher for women with IBD than women without IBD (Table 2). On survival analysis, women with IBD had overall lower stroke-free survival than those without IBD during the study period (Fig. 1).

After adjusting for age and other potential confounders (ethnicity, race, education, HTN, DM, HLD, family history of MI or stroke, RA, SLE, corticosteroids, BMI, smoking, alcohol, physical activity, visit to doctor in the past year, any insurance), no significant difference was observed between women with IBD compared to those without IBD for risk of CHD (HR 0.96, 95% CI 0.73–1.24), PE/DVT (HR 1.11, 95% CI 0.81–1.52), or PAD (HR 0.64, 95% CI 0.28–1.42) (Table 2). After adjusting for age, the risk of ischemic stroke was significantly higher (HR 1.41, 95% CI 1.06–1.88) in women with IBD compared to those without IBD. On further adjustment for the abovementioned socio-demographic characteristics, comorbidity, family history, and lifestyle factors, the higher risk of ischemic stroke among women with IBD was attenuated and no longer statistically significant (HR 1.31, 95% CI 0.98–1.76) (Table 2).

In a subgroup analysis among women who had ischemic stroke, no significant interaction was observed between IBD and age (<65 vs. ≥ 65 years), comorbid RA/SLE, hormone therapy use, or smoking on the risk of ischemic stroke. (Table 3).

Table 1 Baseline characteristics of women with and without IBD, defined as self-report of colitis at enrollment ($n = 134,022$)

Characteristic	Self-report IBD			
	No ($n = 132,655$)		Yes ($n = 1367$)	
	n	%	*n*	%
Demographics				
Age at screening, mean (SD)	63.5	(7.2)	63.4	(7.3)
< 60	42,543	32.1	446	32.6
60–69	59,899	45.2	605	44.3
≥ 70	30,213	22.8	316	23.1
Ethnicity				
Not Hispanic	125,870	94.9	1345	95.1
Hispanic	5660	4.3	60	4.2
Unknown/not reported	1078	0.8	9	0.6
Race				
American Indian/Alaska Native	389	0.3	2	0.1
Asian	3635	2.7	21	1.5
Native Hawaiian/Pacific Islander	114	0.1	2	0.1
Black	11,078	8.4	95	6.9
White	113,545	85.6	1202	87.9
More than one race	1564	1.2	18	1.3
Unknown/not reported	2330	1.8	27	2.0
Education				
≤ High school / GED	28,765	21.7	312	22.8
School after high school	49,739	37.5	514	37.6
≥ College degree	54,151	40.8	541	39.6
Income				
< $20,000	19,092	14.4	245	17.9
$20,000–$49,999	55,400	41.8	534	39.1
$50,000–$74,999	25,375	19.1	266	19.5
≥ $75,000	24,265	18.3	235	17.2
Any insurance	126,748	95.5	1292	94.5
Women's Health				
WHI Component				
Clinical Trial	54,104	40.8	466	34.1
Observational Study	78,551	59.2	901	65.9
Hormone therapy use[2]				
Never	49,881	37.6	500	36.6
Past	18,842	14.2	178	13.0
Current	63,932	48.2	689	50.4
Lifetime HT use, y				
0	57,157	43.1	575	42.1
< 2.5	18,411	13.9	171	12.5
2.5–8	21,756	16.4	217	15.9
≥ 8	35,331	26.6	404	29.6
WHI Dietary Modification Trial				
Intervention	15,309	11.5	122	8.9
Comparison	22,930	17.3	179	13.1
Not randomized	94,416	71.2	1066	78.0
Visit to regular doctor in past year				
No	21,183	16.0	188	13.8
Yes	99,219	74.8	1062	77.7
No regular care provider	8202	6.2	80	5.9

Table 1 (continued)

Characteristic	Self-report IBD			
	No ($n=132,655$)		Yes ($n=1367$)	
	n	%	*n*	%
Comorbidities				
Treated hypertension	36,848	27.8	388	28.4
Treated diabetes	4970	3.7	46	3.4
Treated hypercholesterolemia	16,549	12.5	233	17.0
Rheumatoid arthritis	6208	4.7	114	8.3
Systemic lupus erythematosus	502	0.4	89	6.5
Cardiovascular risk factors				
Body mass index, kg/m^2, mean (SD)	27.8	(5.9)	27.5	(5.9)
< 25	48,270	36.4	519	38.0
25–< 30	46,025	34.7	496	36.3
≥ 30	38,360	28.9	352	25.7
Family history of MI	64,833	48.9	717	52.5
Family History of stroke	47,581	35.9	520	38.0
Lifestyle				
Smoking				
Never	67,714	51.0	597	43.7
Past	54,793	41.3	663	48.5
Current	8816	6.6	94	6.9
Alcohol drinks/wk				
0	54,734	41.3	579	42.4
> 0–< 7	62,004	46.7	629	46.0
≥ 7	15,917	12.0	159	11.6
Physical activity, MET-h/week, mean (SD)	12.6	(13.8)	11.8	(14.4)
< 2.5	33,127	25.0	388	28.4
2.5–< 18.25	66,552	50.2	668	48.9
≥ 18.25	32,976	24.9	311	22.8
Medications				
Corticosteroid	1041	0.8	44	3.2
Anticoagulant	684	0.5	6	0.4
Aspirin[3]	24,900	18.8	205	15.0
IBD medications[4]	565	0.4	237	17.3
Anti-metabolite	479	0.4	16	1.2
Inflammatory bowel agent	92	0.1	229	16.8

Missing Data: income, $n=8610$; visit to regular doctor in past year, $n=4088$; treated hypertension, $n=1053$; treated hypercholesterolemia, $n=354$; rheumatoid arthritis, $n=1221$; family history of MI, $n=6801$; family history of stroke, $n=7279$; smoking, $n=1345$; medications, $n=2$

[1]p value comparing demographics by IBD at baseline from t-test for continuous characteristics and chi-square test for categorical characteristics

[2]Hormone therapy use incorporates self-report of use at enrollment as well as WHI Hormone Trial intervention assignment

[3]Regular aspirin use defined as ≥ 80 mg for ≥ 30 days

[4]Anti-metabolites: azathioprine, mercaptopurine, methotrexate, thioguanine; inflammatory bowel agents: balsalazide, certolizumab, infliximab, adalimumab, mesalamine, olsalazine, sulfasalazine

Discussion

In this large cohort study of postmenopausal women, those with IBD had a 41% age-adjusted increased risk of ischemic stroke compared to women without IBD. After adjusting for socio-economic factors as well as co-morbid rheumatologic disorders (RA, SLE) and traditional CV risk factors, the excess risk of ischemic stroke among women with IBD was no longer statistically significant. Importantly, this higher risk of ischemic stroke among women with IBD did

Table 2 Hazard ratios of self-report IBD on outcome events

Outcome		No IBD	IBD	
CHD	Events (Ann%)	5385 (0.35)	57 (0.36)	
		HR (95% CI)	*HR (95% CI)*	*p value*
	Model 1	1.00 (ref)	1.05 (0.81, 1.37)	0.69
	Model 2	1.00 (ref)	0.97 (0.74, 1.26)	0.79
	Model 3	1.00 (ref)	0.96 (0.73, 1.24)	0.74
Ischemic stroke	Events (Ann%)	3332 (0.21)	47 (0.30)	
		HR (95% CI)	*HR (95% CI)*	*p value*
	Model 1	1.00 (ref)	1.41 (1.06, 1.88)	0.02
	Model 2	1.00 (ref)	1.32 (0.99, 1.77)	0.06
	Model 3	1.00 (ref)	1.31 (0.98, 1.76)	0.07
PE/DVT	Events (Ann%)	3251 (0.21)	40 (0.25)	
		HR (95% CI)	*HR (95% CI)*	*p value*
	Model 1	1.00 (ref)	1.23 (0.90, 1.68)	0.20
	Model 2	1.00 (ref)	1.12 (0.82, 1.54)	0.48
	Model 3	1.00 (ref)	1.11 (0.81, 1.52)	0.51
PAD	Events (Ann%)	871 (0.06)	6 (0.04)	
		HR (95% CI)	*HR (95% CI)*	*p value*
	Model 1	1.00 (ref)	0.68 (0.31, 1.52)	0.35
	Model 2	1.00 (ref)	0.66 (0.29, 1.47)	0.31
	Model 3	1.00 (ref)	0.64 (0.28, 1.42)	0.27
CHD/ Ischemic stroke/ PAD	Events (Ann%)	8944 (0.58)	98 (0.62)	
		HR (95% CI)	*HR (95% CI)*	*p value*
	Model 1	1.00 (ref)	1.09 (0.89, 1.33)	0.41
	Model 2	1.00 (ref)	1.02 (0.83, 1.25)	0.85
	Model 3	1.00 (ref)	1.01 (0.82, 1.23)	0.95

Hazard ratios and *p* values form proportional hazards models with the outcome of interest as a function of IBD status at enrollment. All models are stratified within the model by WHI component (clinical trial / observational study, hormone use (never, past, current; incorporating WHI HT trial component), WHI Dietary Modification Trial arm (intervention, comparison, not randomized), and time-dependent WHI follow-up period (WHI, extension 1, extension 2)

Model 1: Adjusted for age

Model 2: Model 1 + ethnicity, race, education, treated hypertension, treated diabetes, treated hypercholesterolemia, family hx of MI, family hx of stroke, rheumatoid arthritis, lupus, BMI, corticosteroid use

Model 3: Model 2 + smoking, alcohol, physical activity, visit to regular doctor in the past year, any insurance

not differ based on age (< 65 years vs. ≥ 65 years), comorbid RA/SLE, hormone therapy use, or smoking status. We found no significant difference in the risk of the CVD outcomes of CHD, PE/DVT, or PAD between women with IBD compared to those without IBD.

In a previous meta-analysis of observational studies that reported incident cases of stroke and ischemic heart disease among an adult IBD and non-IBD population, those with IBD had an approximately 20% increased risk of stroke (28% for women) [5]. Both ischemic and hemorrhagic stroke as well as transient ischemic attack were included in the meta-analysis, which may account for difference in estimated risk compared to the current study in which only ischemic stroke was included. The results of the meta-analysis suggested a 26% increased risk of ischemic heart disease (inclusive of acute coronary syndrome, history of MI, and/or angina) among women of all ages with IBD, while we did not find a significant difference in risk of CHD in our population. Reasons for this difference in findings are unclear but may be due to the specific focus on postmenopausal women in the current study.

The landmark WHI hormone therapy clinical trial was designed to assess the safety and efficacy of hormone therapy for the primary prevention of CHD in postmenopausal women. Data from the trial, however, demonstrated excess risk of CHD, stroke, VTE, and breast cancer among hormone therapy use participants. As a result of these findings, the use of hormone therapy among postmenopausal women has declined substantially [35] so that the prevalence of hormone therapy use in our study population is likely greater than that of the present day IBD population. However, there was no significant difference in hormone therapy use among women with and without IBD in our analysis. In addition, there was no interaction between IBD and hormone therapy use for the risk of stroke, suggesting the excess age-adjusted risk of stroke observed among IBD women was not associated with exposure to hormone therapy.

Notably, women with IBD in our study had higher rates of HLD but no difference in other traditional CVD risk factors, such as DM and HTN, compared to women without IBD. It is also interesting to note that most women regardless of IBD status did not report regular aspirin use, but even less so among women with IBD. One of the largest trials examining aspirin primary prevention in women showed a reduction in ischemic stroke among those receiving aspirin on alternate days compared to those receiving placebo [36]. However, the role of aspirin as primary prophylaxis against CVD is controversial [37] and currently is only recommended by the US Preventive Services Task Force for individuals 40–59 years with increased CVD risk factors [38]. In IBD, there has been concern for precipitating flares of disease activity with use of non-steroidal anti-inflammatory drugs (NSAIDs) [39], although recent data suggest lack of adverse effect from

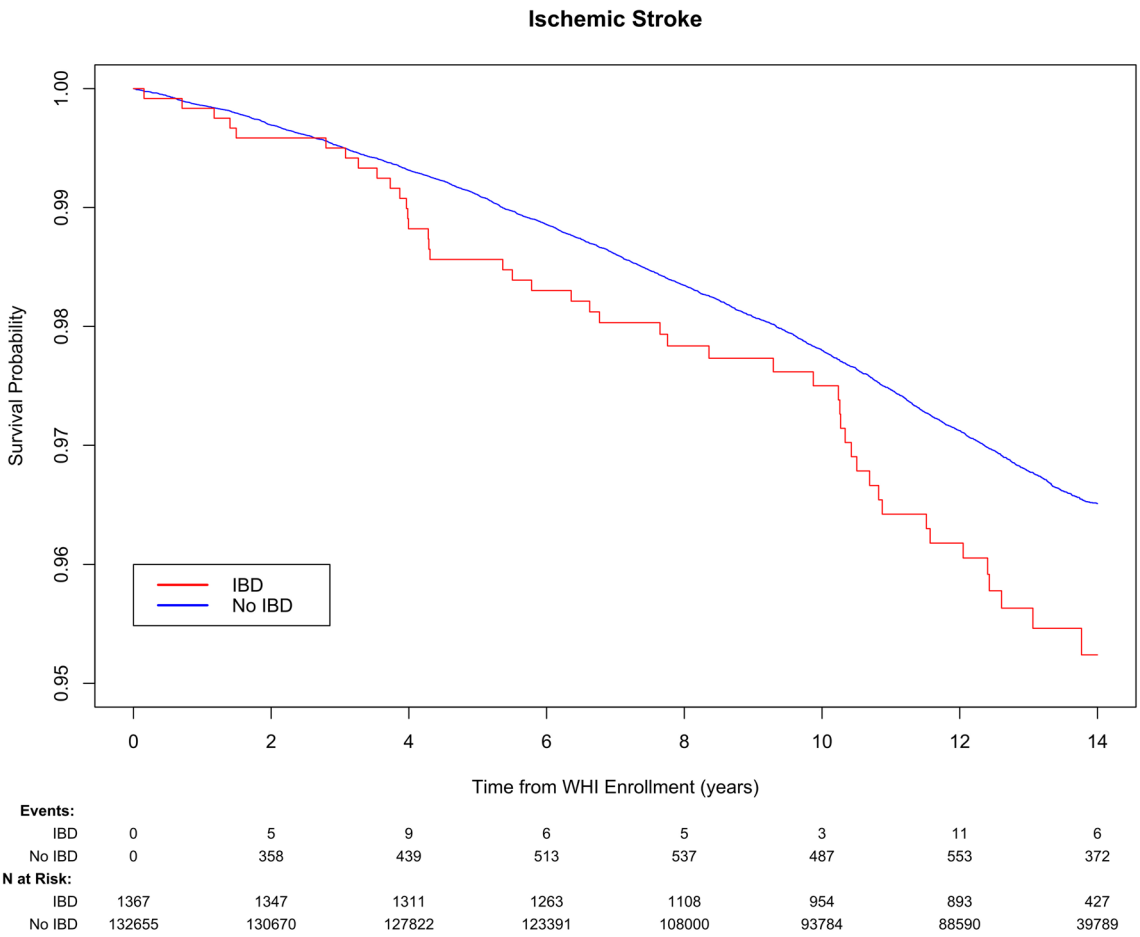

Fig. 1 Survival-free of ischemic stroke between women with and without IBD, Women's Health Initiative, 1993–2010

aspirin on IBD outcomes [40, 41]. Specific data on the role of aspirin for CVD risk factor reduction in IBD are lacking.

This study has several strengths including a well-characterized cohort of women in the WHI studies with data on socio-economic and traditional CV risk factors, a robust process of adjudication of CVD events, and a substantial follow-up period. Our study is also one of the first to specifically examine adverse CVD outcomes among IBD women after the menopause transition, a period of known increased CVD risk for women. We do acknowledge there are some limitations. The majority of women included in the study were of non-Hispanic White race and ethnicity, limiting the generalizability of study findings among an increasingly racial and ethnically diverse IBD population. IBD diagnosis was self-reported at baseline, so misclassification bias is a potential limitation. We assessed for diagnosis of IBD after baseline enrollment (1993–1998) by expanding the definition of IBD to include use of IBD medications during follow-up in 2010. However, this did not alter the results. Of note, very few women in the study reported taking an IBD biologic medication, which is unsurprising since initial WHI enrollment occurred in the pre-biologic era. Infliximab was only first approved for use in Crohn's disease in 1998, which is when initial WHI enrollment closed. While WHI data included the rheumatologic conditions RA and SLE, data on psoriasis was not available. Given that psoriasis is also more common in IBD and a known CVD risk factor, absence of this data is a limitation. Data on IBD activity and subtype (Crohn's disease vs. ulcerative colitis) were also not available in the data set, and the CVD outcomes reported here may differ based on level of underlying inflammation [3, 7, 13]. Measurement of CRP as a biomarker of IBD activity and a marker of atherosclerotic disease was missing for the majority of women. Future studies should examine the influence of IBD activity on adverse CVD outcomes in postmenopausal women, particularly now in the biologic era.

In summary, we found that IBD is associated with an age-adjusted excess risk of ischemic stroke among postmenopausal women that is no longer statistically significant after accounting for traditional CVD risk factors. Future studies should investigate underlying mechanisms and potential interventions for this increased risk. As newer medications used in the treatment of IBD, such as JAK inhibitors, are associated with increased CV events, understanding other

Table 3 Hazard ratios of self-report IBD on ischemic stroke, stratified by baseline subgroups

Subgroup	Annualized rates		Hazard ratios	Interaction
	IBD	No IBD	IBD vs. No IBD (ref)	
	Events (Ann%)	Events (Ann%)	HR (95% CI)	*p* value[1]
All participants	*47 (0.30)*	*3332 (0.21)*	*1.31 (0.98, 1.76)*	
Age				0.35
<65	11 (0.12)	938 (0.10)	1.03 (0.57, 1.86)	
≥65	36 (0.55)	2394 (0.36)	1.43 (1.05, 1.99)	
RA/SLE				0.64
No	37 (0.27)	3059 (0.21)	1.31 (0.95, 1.81)	
Yes	10 (0.46)	230 (0.32)	1.55 (0.82, 2.92)	
HT use				0.27
Never/past	29 (0.38)	1845 (0.23)	1.52 (1.05, 2.20)	
Current	18 (0.22)	1487 (0.19)	1.09 (0.68, 1.73)	
Smoking				0.55
Never/past	42 (0.28)	3033 (0.21)	1.29 (0.95, 1.76)	
Current	5 (0.50)	264 (0.27)	1.72 (0.71, 4.18)	

Hazard ratios and *p* values form proportional hazards models with the outcome of interest as a function of IBD status at enrollment, the subgroup of interest, and their interaction. All models are stratified within the model by WHI component (clinical trial/observational study, hormone use (never, past, current; incorporating WHI HT trial component), WHI Dietary Modification Trial arm (intervention, comparison, not randomized), and time-dependent WHI follow-up period (WHI, extension 1, extension 2)

Models are adjusted for age, ethnicity, race, education, treated hypertension, treated diabetes, treated hypercholesterolemia, family hx of MI, family hx of stroke, rheumatoid arthritis, lupus, BMI, corticosteroid use, smoking, alcohol, physical activity, visit to regular doctor in the past year, any insurance

Individual subgroup models are not stratified nor adjusted for the variable of interest. For example, the categorical age subgroup is not adjusted for continuous age

[1]*p* value from the interaction term between IBD and the subgroup of interest

factors that may elevate the CV risk for patients with IBD is increasingly important. Additionally, with an aging population, the number of postmenopausal women with IBD will almost certainly continue to rise, and findings from this study highlight the importance of pursuing modifiable risk factor reduction among women with IBD.

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Declarations

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