Journal of Crohn's and Colitis, 2021, 757–765
doi:10.1093/ecco-jcc/jjaa235
Advance Access publication November 20, 2020
Original Article

Original Article

Association Between Statin Use and Inflammatory Bowel Diseases: Results from a Swedish, Nationwide, Population-based Case-control Study

Paul Lochhead,[a,b] Hamed Khalili,[a,b] Michael C. Sachs,[c] Andrew T. Chan,[a,b] Ola Olén,[c,d,e] Jonas F. Ludvigsson[f,g]

[a]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA [b]Division of Gastroenterology, Massachusetts General Hospital, Boston, MA, USA [c]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden [d]Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden [e]Sachs' Children and Youth Hospital, Stockholm South General Hospital, Stockholm, Sweden [f]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden [g]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden

Corresponding author: Jonas F. Ludvigsson, MD, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, SE-17177 Stockholm, Sweden. Tel.: +46-19-6021000; fax: +46-19-187915; email: jonasludvigsson@yahoo.com

Abstract

Background: In addition to their potent lipid-lowering action, statins may modulate inflammation. However, data on statin use and the risk of inflammatory bowel diseases [IBD] have been inconsistent.

Methods: We searched the Nationwide Swedish Patient Register [inpatient and non-primary outpatient care] to identify adults diagnosed with Crohn's disease [CD, $n = 7637$] or ulcerative colitis [UC, $n = 15\ 652$] from 2006 to 2014. Each case was matched to 10 general population controls [$n = 232\ 890$]. Data on dispensed statin prescriptions were extracted from the Prescribed Drug Register. Conditional logistic regression models estimated odds ratios [ORs] for risk of IBD according to statin exposure while controlling for potential confounders, including indications for statin therapy.

Results: In multivariable adjusted models, compared with no statin use, any statin use was associated with a lower risk of CD (OR = 0.71; 95% confidence interval [CI], 0.63–0.79), but not UC [OR = 1.03; 95% CI, 0.96–1.11]. The lowest OR for CD was seen for current statin use [OR = 0.67; 95% CI, 0.60–0.75]. For CD, the lowest category of cumulative statin dose [31–325 defined daily dose, DDD] was associated with an OR of 0.73 [95% CI, 0.61–0.88] and the highest category [>1500 DDD] with an OR of 0.66 [95% CI, 0.55–0.80], $p_{trend} = 0.10$. For UC, the lowest and highest dose categories yielded ORs of 1.12 [95% CI, 1.00–1.25] and 0.99 [95% CI, 0.88–1.13], respectively, $p_{trend} = 0.13$.

Conclusions: Statin use was associated with a lower risk of CD, but not of UC. The association with CD risk appeared strongest for current statin use. Our findings suggest that statin use may influence the development of CD.

Key Words: Crohn's disease; ulcerative colitis; inflammatory bowel diseases; statin; registry; prescription; adult; medication; drug; pharmacoepidemiology; Sweden

1. Introduction

Inflammatory bowel diseases [IBD], comprising Crohn's disease [CD] and ulcerative colitis [UC], are chronic inflammatory conditions of the gastrointestinal tract that are estimated to affect 6.8 million individuals globally, constituting an important source of morbidity and economic burden on health care systems.[1,2] Despite the increasing number of genetic loci that have been associated with IBD risk, it is clear from twin studies and temporal and geographical patterns of disease incidence that environmental factors must contribute substantially to the aetiopathogenesis of IBD.[3–5] In addition to dietary and lifestyle exposures, several medications, including non-steroidal anti-inflammatory drugs [NSAIDs] and oral contraceptives, have been identified as putative risk factors for IBD development, flares, or progression.[6,7]

Statins are potent lipid-lowering agents prescribed on a global scale for the primary and secondary prevention of cardiovascular disease and treatment of dyslipidmia.[8] Statins reduce endogenous cholesterol synthesis through inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA], but also appear to have pleiotropic effects independent of their lipid-lowering action, including modulation of inflammation, cellular proliferation, and apoptosis.[9] In vitro, simvastatin inhibits TNF-alpha induced IL-8 expression in intestinal epithelial cells and ameliorates disease severity in a dextran sulphate sodium murine model of UC.[10] Simvastatin has also been shown to exhibit dose-dependent intestinal antifibrotic effects in the trinitrobenzenesulphonic acid [TNBS]-induced colitis model.[11] A limited number of epidemiological studies have evaluated the association between statin use and IBD risk, with inconsistent results.[12,13] We therefore sought to examine the association between statin use and risk of IBD in a population-based case-control study based on Swedish health and population registry data.

2. Methods

2.1. Ascertainment of cases and controls

Sweden provides all citizens with universal access to publicly funded health care, including coverage of prescription medications. Individual-level data on hospital admissions have been collected by the Swedish National Board of Health and Welfare at county level since 1964 and at national level since 1987.[14] Entries in the National Patient Register are organised according to a unique personal identity number [PIN] and contain details of the dates of admission, discharge, and diagnoses, coded using the International Classification of Diseases [ICD] system.[15] From 2001, the register has also collected data on attendances for specialised outpatient care.[14]

We identified individuals with adult-onset IBD [≥18 years] from the Swedish Patient Register. A diagnosis of CD or UC was defined by having at least two relevant ICD codes [ICD-10: K50 and K51 for CD and UC, respectively] from January 2006 through December 2014. The accuracy of using ≥2 diagnostic entries for IBD from in patient and non-primary care outpatient encounters has been validated by chart review with a positive predictive value of 93%.[16] For each IBD case, Statistics Sweden identified up to 10 controls from the whole Swedish population, using the Total Population Register.[17] Matching was performed based on sex, age, year of birth, and place of residence. Controls had to be alive, living in Sweden, and free of IBD at their index date, but theoretically could be diagnosed with IBD at a later date. It was also possible that, by chance, a control could be sampled more than once and matched to more than one case with different indexing dates. The study was approved by the Stockholm regional ethics committee.

2.2. Exposure definition and covariates

The Swedish Prescribed Drug Register was established on July 1, 2005, and is maintained by the Swedish National Board of Health and Welfare.[18] The register gathers information on dispensed prescriptions for the entire Swedish population, including redemption date, drug name, and amount dispensed. Information is transferred each month from the National Corporation of Swedish Pharmacies and organised by unique PIN. The register is virtually complete, with only 0.3% of items lacking patient identity data.[18] Drugs are classified by the Anatomical Therapeutic Chemical [ATC] classification system and dose information is recorded in WHO Defined Daily Doses [DDDs], which represent the assumed average adult maintenance dose for the main product indication.[19] Statin use was identified using ATC codes C10AA [HMG CoA reductase inhibitors], which encompasses all statin medications available in Sweden during the study period, and C10BA, which includes combination formulations with other lipid-lowering agents such as fibrates and ezetimibe [less than 0.05% of prescriptions in the current analysis]. Any statin use before IBD diagnosis was defined as having at least two dispensed prescriptions with a combined cumulative DDD >30. To account for diagnostic delay, minimise potential bias from more frequent contact with health care providers preceding IBD diagnosis, and to recognise the timing of a biologically plausible association between statin use and IBD evolution, we classified those with a first statin prescription within 6 months of first IBD diagnostic code entry as unexposed. This is consistent with previous analyses.[12] We further defined current statin use as a prescription for a statin within the 12 months preceding IBD diagnosis. We calculated cumulative dose of statin in DDD from date of first prescription through to the date of the prescription most proximate to diagnosis. A small proportion of statin users [4%] had implausibly high cumulative doses, considering their duration of exposure and recommended doses for each drug. We therefore truncated cumulative dose by limiting the average daily dose to the highest clinically recommended [eg. 80 mg or 2.7 DDD for simvastatin]. These cutoffs fell between the 95th and 97th percentiles for average daily dose among all statin users. We also classified statins according to type, as lipophilic [simvastatin, atorvastatin, and fluvastatin] and hydrophilic [pravastatin and rosuvastatin], based on the statin prescribed closest to the date of IBD diagnosis/indexing.

Information on educational status was obtained through Statistics Sweden [total years of compulsory education, upper secondary school education, and university education].[20] The Patient Register was searched for primary or secondary diagnoses for several chronic medical conditions that may be indications for statin use, including type 1 and type 2 diabetes mellitus, hypertension, ischaemic heart disease, cerebrovascular disease, heart failure, and other atherosclerotic diseases [including carotid stenosis, transient ischaemic attack, and peripheral vascular disease][ICD codes listed in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online]. For hypertension and diabetes, ascertainment through Patient Register entries was complemented by searching the Prescribed Drug Register for antihypertensive and antidiabetic medications, given that hypertension and type 2 diabetes are managed predominantly in primary care.[21–23] Data on any previous use of prescribed non-steroidal anti-inflammatory medications [NSAIDs] and of oral contraceptives [OC] use among women were also extracted from the Prescribed Drug Register. We searched the Swedish Patient Register for diagnostic codes for disorders of lipid metabolism [ICD-9272 and ICD-10 E78; Supplementary Table 1]. However, since statin use itself could be considered a surrogate for ascertaining dyslipidaemia in

primary care, we considered ascertainment of dyslipidaemia incomplete. Indeed, only 24% of those with any previous statin use had a secondary care diagnostic code for a lipid disorder. Given that data on smoking status were not available from the patient registers, we extracted information on any secondary care entry for chronic obstructive pulmonary disease [COPD; Supplementary Table 1] for use as a proxy. Consistent with our primary exposure definition, all covariate exposures were defined based on status 6 months preceding to IBD diagnosis or indexing as a control. To capture health care use, we recorded the total number of outpatient and inpatient encounters for each individual over a 1-year period, from 18 to 6 months before diagnosis/indexing.

2.3. Statistical analysis

To test for differences in characteristics between cases and controls, we used the chi square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. We used conditional logistic regression models, stratified on match, to estimate odds ratios [ORs] and 95% confidence intervals [95% CI] for the association between statin use and diagnosis of CD or UC. Basic models controlled for the matching factors, age at diagnosis/indexing, sex, and region of residence. Multivariable models adjusted for additional potential confounders including years in full-time education [≤9, 10–12, and >12 years] and the presence or absence of chronic medical conditions before diagnosis/indexing [all binary]. We considered any statin use our primary exposure of interest. Secondary exposures were current statin use [defined as above] and cumulative statin dose in DDD. We generated a categorical variable by dividing cumulative dose into >30-325, 326-750, 751–1500, and >1500 DDD categories. These cut points were approximately equivalent to the 25th, 50th, and 75th percentiles for cumulative dose among all statin users. The distribution of cumulative dose was similar between IBD types and by case/control status. To test for linear trend, we used the continuous variable for cumulative DDD in the models. In exploratory analyses, we assessed for effect modification in models stratified by age [above and below the approximate overall median of 42 years], sex, and presence or absence of one or more chronic medical diagnoses we considered as covariates. Statistical evidence for interaction was based on the Wald test for multiplicative interaction terms for any statin use and the factor of interest. We additionally investigated associations for age in finer strata of ≤40, >40–50, >50–60, >60–70, and >70 years. We also performed an exploratory analysis of duration of statin use in categories of 31–500, 501–1000, 1001–2000, and >2000 days from the first dispensed statin prescription to the prescription date preceding diagnosis/indexing. We performed sensitivity analyses additionally adjusting for dyslipidaemia [based on Patient Register entries only], COPD, and total secondary care encounter number. For cumulative dose, we ran sensitivity analyses restricted to incident statin users [those with no statin prescriptions during the first 6 months after introduction of the Prescribed Drug Register] and excluding individuals where cumulative dose had been truncated. We also repeated our main analysis without the requirement for a 6-month interval between first statin prescription and diagnosis/indexing. All analyses were conducted using SAS version 9.4 [SAS Institute Inc., Cary, NC]. All *P*-values were two-sided and the threshold for statistical significance was set at 0.05.

3. Results

We identified 7637 cases of CD, matched to 76 370 population controls, and 15 652 cases of UC, matched to 156 520 controls. The clinical and demographic characteristics of cases and controls are shown in Table 1. As expected, there were no differences between cases and controls in the matching factors of age [matched on year of birth and age], sex, or region of residence. The average age at diagnosis was 44.3 years for CD cases and 46.0 years for UC cases. The distribution of years in full-time education was statistically significantly different between CD cases and controls, with a slightly lower proportion of cases having spent more than 12 years in full-time education [32%] compared with controls [35%]. The proportion of CD and UC cases with hypertension, ischaemic heart disease, other arterial diseases, heart failure, dyslipidaemia, and previous OC or NSAID use was statistically significantly greater than controls, although, in most cases, the numerical differences were modest [Table 1]. Additionally, compared with controls, a greater proportion of CD cases had a history of stroke and type 2 diabetes. Any statin use preceding IBD diagnosis did not differ significantly between CD cases and controls [8.1% and 8.4%, respectively], but was statistically significantly more common among UC cases [9.9%] compared with controls [9.0%].

3.1. Any statin and current statin use

In logistic models controlling only for matching factors, compared with no statin use, any statin use was not statistically significantly associated with the risk of CD [Table 2; OR = 0.95; 95% CI, 0.87–1.05] and was associated with a slightly higher risk of UC [Table 3; OR = 1.15; 95% CI, 1.08–1.22]. However, in the multivariable adjusted model, any statin use was associated with a statistically significantly lower risk of CD [OR = 0.71; 95% CI, 0.63–0.79] but not of UC [OR = 1.03; 95% CI, 0.96–1.11]. The magnitude of the association between statin use and risk of CD was stronger for current statin use, where a statin had been dispensed within the 12 months before diagnosis or indexing [Table 2; multivariable OR = 0.67; 95% CI, 0.60–0.75].

Compared with no statin use, all categories of cumulative statin dose were statistically significantly associated with lower risk of CD in the full model [Table 2]. The OR for the lowest dose category [31–325 DDD] was 0.73 [95% CI, 0.61–0.88] and for the highest dose category was 0.66 [95% CI, 0.55–0.80]. A test of linear trend did not, however, meet statistical significance [$p = 0.10$]. For UC [Table 3], compared with no statin use, the lowest category of cumulative dose [31–325 DDD] was associated with a slightly higher risk of borderline statistical significance [OR = 1.12; 95% CI, 1.00–1.25], whereas the highest category was null [0.99; 95% CI, 0.88–1.13]. No trend was observed for UC risk with increasing DDD [$p = 0.13$]. Since cumulative statin dose may not have been reliably estimated for individuals who were prevalent statin users at the initiation of the Prescribed Drug Register, we performed a sensitivity analysis restricted to incident statin users [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online]. The results were overall similar to our main cumulative dose analysis for CD and UC. However, for CD, the numerical trend toward lower estimates with increasing cumulative DDD category was more pronounced, with the highest category [>1500 DDD] yielding a multivariable OR of 0.57 [95% CI, 0.41–0.79]. We additionally ran analyses for cumulative statin dose excluding the small number of statin users where total DDD was truncated [Supplementary Table 3, available as Supplementary data at *ECCO-JCC* online]. The results were similar to those of our main analysis although, for CD, the test of linear trend was borderline significant [$p = 0.045$].

Table 1. Characteristics of IBD cases and matched population controls at date of diagnosis or indexing.

Clinical or demographic feature	CD cases [*n* = 7637]	CD-matched controls [*n* = 76 370]	$p_{difference}$	UC cases [*n* = 15 652]	UC-matched Controls [n = 156 520]	$p_{difference}$
Average age at diagnosis/indexing,[a] years [SD]	44.3 [18.8]	44.3 [18.8]	>0.99	46.0 [18.6]	46.0 [18.6]	0.99
Median month and year of diagnosis/indexing [range]	8/2010 [1/2006 - 12/2014]		-	4/2010 [1/2006 - 12/2014]		-
Sex[a] [%]						>0.99
Male	3685 [48]	36850 [48]	>0.99	8129 [52]	81290 [52]	
Female	3952 [52]	39520 [52]		7523 [48]	75230 [48]	
Region[a] [%]						>0.99
Stockholm-Gotland	1856 [24]	18560 [24]		2944 [19]	29440 [19]	
Uppsala-Örebro	1524 [20]	15240 [20]		3512 [22]	35120 [22]	
Södra [south]	1683 [22]	16830 [22]	>0.99	3135 [20]	31350 [20]	
Sydöstra [south-east]	1015 [13]	10150 [13]		1771 [11]	17710 [11]	
Västra [west]	963 [13]	9630 [13]		2996 [19]	29960 [19]	
Norra [north]	596 [7.8]	5960 [7.8]		1294 [8.3]	12940 [8.3]	
Years in full-time education [%]						0.15
≤9	1540 [20]	14155 [19]	<0.001	2912 [19]	29896 [19]	
10–12	3647 [48]	35512 [47]		7280 [47]	71645 [46]	
>12	2450 [32]	26703 [35]		5460 [35]	54979 [35]	
Dyslipidaemia[b] [%]	208 [2.7]	1789 [2.3]	0.037	463 [3.0]	3751 [2.3]	<0.001
Hypertension [%]	1767 [23]	14390 [19]	<0.001	3490 [22]	31364 [20]	<0.001
Ischaemic heart disease [%]	352 [4.6]	2831 [3.7]	<0.001	768 [4.9]	6657 [4.3]	<0.001
Stroke [%]	196 [2.6]	1581 [2.1]	0.004	367 [2.3]	3526 [2.3]	0.46
Other arterial diseases [%]	217 [2.3]	1671 [2.2]	<0.001	438 [2.8]	3578 [2.3]	<0.001
Heart failure [%]	157 [2.1]	1009 [1.3]	<0.001	301 [1.9]	2552 [1.6]	0.006
Type 2 diabetes [%]	328 [4.3]	2913 [3.8]	0.038	669 [4.3]	6320 [4.0]	0.15
Chronic obstructive pulmonary disease [%]	182 [2.4]	907 [1.2]	<0.001	296 [1.8]	1881 [1.2]	<0.001
Type 1 diabetes [%]	27 [0.4]	359 [0.5]	0.15	73 [0.5]	772 [0.5]	0.65
Any previous use of prescribed NSAIDs [%]	1687 [22]	11617 [15]	<0.001	2861 [18]	23129 [15]	<0.001
Any previous oral contraceptive use among women [%]	1038 [26]	8869 [22]	<0.001	1829 [24]	15718 [21]	<0.001
Average number of outpatient and inpatient encounters over previous year [SD][c]	2.4 [5.4]	1.1 [2.7]	<0.001	1.6 [4.0]	1.1 [3.1]	<0.001
Any statin use before diagnosis/indexing [%]	620 [8.1]	6421 [8.4]	0.38	1552 [9.9]	14042 [9.0]	<0.001
Statin use in 12 months before diagnosis/indexing [%]	519 [6.8]	5642 [7.4]	0.059	1344 [8.6]	12376 [7.9]	0.003
Average cumulative statin dose among statin users, DDD[d] [SD]	1135 [1184]	1163 [1257]	0.039	1078 [1155]	1112 [1205]	0.09

Percentages for categorical variables may not sum to 100 due to rounding.
SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug.
[a]Matching factor.
[b]Ascertained using diagnostic entries in outpatient and inpatient registers only.
[‡c]Total encounters between 18 and 6 months before diagnosis as case or indexing as a control.
[d]WHO Defined Daily Dose

3.3. Remote and non-current statin use

Our definition of statin exposure ignored prescriptions within the 6 months preceding diagnosis/indexing. To further explore the potential for bias from events leading up to IBD diagnosis, we examined statin use status 3 years before diagnosis/indexing. For CD and UC, the 3-year exposure lag yielded estimates similar to our main analysis [any statin use multivariable OR = 0.74; 95% CI, 0.65–0.83 for CD and OR = 0.99; 95% CI, 0.92–1.08 for UC]. Given that CD risk appeared most strongly associated with current statin use, we also explored associations for non-current statin use. Overall, only 12% of ever statin users [1.1% of the total study population] were not current users by our definition of having a dispensed prescription in the 12 months before diagnosis/indexing. Accepting this limitation in power, non-current statin use did not appear to be associated with risk of CD [multivariable OR = 0.98; 95% CI, 0.79–1.22]. For UC, non-current use was associated with a modestly higher risk [multivariable OR = 1.18; 95% CI, 1.01–1.37].

3.4. Statin type

The vast majority of statin users [94%] were prescribed the lipophilic statins simvastatin [79%], atorvastatin [14%], or fluvastatin [0.4%]. Only a small proportion of statin users were prescribed the hydrophilic statins pravastatin [2.8%], or rosuvastatin [3.5%]. For the association with CD, effect estimates were similar for any use of a lipophilic statin [multivariable OR = 0.71; 95% CI, 0.63–0.79] or hydrophilic statin [multivariable OR = 0.73; 95% CI, 0.53–1.02] [$p_{heterogeneity}$ for statin type = 0.85]. Similarly, for UC, the null association did not vary by statin type [multivariable OR = 1.04; 95% CI, 0.96–1.11 for lipophilic statins and multivariable OR = 0.99; 95% CI, 0.79–1.23 for hydrophilic statins; $p_{heterogeneity}$ = 0.65].

3.5. Stratified analyses

We conducted exploratory analyses stratified by age, sex, and presence or absence of one or more of the chronic medical diagnoses we included as covariates. For CD [Table 4], multivariable estimates were generally

Table 2. Association between statin use and odds of Crohn's disease.

Statin use status	Cases/ controls [*n*]	Basic model[a] OR [95% CI]	*p*-value	Full model[b] OR [95% CI]	*p*-value
No statin use	7017/69949	Referent		Referent	
Any statin use	620 /6421	0.95 [0.87–1.05]	0.34	0.71 [0.63–0.79]	<0.001
Current statin use[c]	519/5642	0.90 [0.81–1.00]	0.039	0.67 [0.60–0.75]	<0.001
Cumulative statin dose, DDD[d]					
31–325	138/1476	0.93 [0.77–1.11]	0.41	0.73 [0.61–0.88]	0.001
326–750	169/1616	1.04 [0.88–1.22]	0.68	0.78 [0.66–0.93]	0.005
751–1500	151/1680	0.89 [0.75–1.06]	0.18	0.64 [0.53–0.77]	<0.001
>1500	162/1649	0.97 [0.81–1.15]	0.72	0.66 [0.55–0.80]	<0.001
P_{trend}[e]		0.56		0.10	

NSAID, non-steroidal anti-inflammatory drug.

[a]The basic model controlled for the matching factors sex, age, and area or residence through conditional logistic regression.

[b]The full model was a conditional logistic model additionally adjusted for education, previous use of NSAIDs or oral contraceptives, and previous history of hypertension, ischaemic heart disease, stroke, other arterial diseases, heart failure, and type 1 and type 2 diabetes.

[c]Current use required a dispensed statin prescription in the 12 months preceding diagnosis/indexing.

[d]Cumulative dose among those with any statin use in WHO Defined Daily Dose [DDD].

[e]*p* for linear trend was calculated for statin users only, using the continuous variable for cumulative DDD.

Table 3. Association between statin use and odds of ulcerative colitis.

Statin use status	Cases/ controls [*n*]	Basic model[a] OR [95% CI]	*p* -value	Full model[b] OR [95% CI]	*p*-value
No statin use	14100/142478	Referent		Referent	
Any statin use	1552 /14042	1.15 [1.08–1.22]	<0.001	1.03 [0.96–1.11]	0.38
Current statin use[c]	1344/12376	1.11 [1.04–1.19]	0.001	1.00 [0.93–1.07]	0.92
Cumulative statin dose, DDD[d]					
31–325	387/3282	1.22 [1.09–1.36]	<0.001	1.12 [1.00–1.25]	0.059
326–750	424/3852	1.15 [1.03–1.28]	0.01	1.04 [0.93–1.16]	0.55
751–1500	371/3547	1.09 [0.97–1.21]	0.16	0.97 [0.86–1.09]	0.56
>1500	367/3361	1.14 [1.01–1.28]	0.031	0.99 [0.88–1.13]	0.93
p_{trend}[e]		0.33		0.13	

OR, odds ratio; CI, confidence interval.

[a]The basic model controlled for the matching factors sex, age, and area or residence through conditional logistic regression.

[b]The full model was a conditional logistic model additionally adjusted for education, previous use of non-steroidal anti-inflammatory drugs [NSAIDs] or oral contraceptives, and previous history of hypertension, ischaemic heart disease, stroke, other arterial diseases, heart failure, and type 1 and type 2 diabetes.

[c]Current use required a dispensed statin prescription in the 12 months preceding diagnosis/indexing.

[d]Cumulative dose among those with any statin use in WHO Defined Daily Dose [DDD].

[e]*p* for linear trend was calculated for statin users only using the continuous variable for cumulative DDD.

Table 4. Stratified analyses for statin use and odds of Crohn's disease.

Stratifying variable	Cases/ controls [*n*]	Any statin use[a] OR [95% CI]	*P*-value	$p_{interaction}$
Sex				0.067
Men	3685/36850	0.71 [0.61–0.84]	<0.001	
Women	3952/39520	0.72 [0.62–0.83]	<0.001	
Chronic medical conditions				0.60
Absent	5707/60326	0.76 [0.57–1.01]	0.058	
Present	1930/16044	0.70 [0.62–0.79]	<0.001	
Age				0.24
<42 years	3851/38492	0.64 [0.31–1.33]	0.23	
≥42 years	3786/37878	0.71 [0.63–0.79]	<0.001	

OR, odds ratio; CI, confidence interval.

[a]Estimates derived from full multivariable logistic models.

similar between strata and we did not detect statistical evidence of effect modification by any of the stratifying variables [all $P_{interaction} \geq 0.067$]. The precision of the estimate for those <42 years of age was lower than for those 42 aged years or older, likely as a result of the low frequency of statin use in younger individuals [ever statin use was observed in only 0.3% of individuals under 42 years]. For UC [Table 5], compared with no statin use, any statin use was associated with a higher risk [OR = 1.24; 95%, 1.07–1.45] among those with a chronic medical condition, but not among

Table 5. Stratified analyses for statin use and odds of ulcerative colitis.

Stratifying variable	Cases/ controls [*n*]	Any statin use[a] OR [95% CI]	*P*-value	$p_{interaction}$
Sex				0.65
Men	8129/81290	1.04 [0.94–1.15]	0.41	
Women	7523/75230	1.04 [0.93–1.15]	0.51	
Chronic medical conditions				0.008
Absent	11805/121679	1.24 [1.07–1.45]	0.005	
Present	3847 /34841	0.99 [0.91–1.07]	0.75	
Age				0.94
<42 years	7518/75140	1.22 [0.83–1.80]	0.32	
≥42 years	8134/81380	1.03 [0.96–1.11]	0.46	

OR, odds ratio; CI, confidence interval.
[a]Estimates derived from full multivariable logistic models

those without [OR = 0.99; 95%, 0.91–1.07; $p_{interaction}$ = 0.008]. No interaction was observed for statin use and UC risk according to age or sex [both $p_{interaction}$ ≥0.65]. As exploratory analyses, we examined the association between statin use and IBD among finer strata of age [Supplementary Table 4, available as Supplementary data at *ECCO-JCC* online]. Allowing for lower precision due to reduced power, the results were consistent with our primary interaction analysis and there was no obvious pattern in the estimates across strata to suggest effect modification by age.

3.6. Duration of statin use

We explored time exposed to statin use and found this to be highly correlated with cumulative statin dose [Pearson $r = 0.82$; $p < 0.001$]. In multivariable models, compared with no statin use, all durations of use were associated with a lower risk of CD, but not UC [Supplementary Table 5, available as Supplementary data at *ECCO-JCC* online]. The OR for CD associated with the lowest duration category [31–500 days] was 0.81 [95% CI, 0.68–0.97] and the OR for the highest duration category [>2000 days] was 0.60 [95% CI, 0.49–0.74; p_{trend} = 0.08]. For UC, similar to cumulative dose, we observed a slightly higher risk for the shortest duration of use category [multivariable OR = 1.15; 95% CI, 1.03–1.29]. Estimates for all other duration categories for UC were close to unity [p_{trend} = 0.98]. Restriction to incident statin users did not meaningfully alter the results [data not shown].

3.7. Additional sensitivity analyses

We used multivariable models to further control for the presence of a secondary care diagnostic entry for dyslipidaemia; however, this did not meaningfully alter any of the estimates for UC or CD [any statin use OR = 0.70; 95% CI, 0.62–0.78 for CD and OR = 1.01; 95% CI, 0.94–1.09 for UC]. Given the lack of information on smoking status, we ran multivariable models additionally controlling for any secondary care diagnostic entry for COPD as a proxy. Again, estimates were unchanged [OR = 0.71; 95% CI, 0.64–0.80 for CD and OR = 1.03; 95% CI, 0.96–1.11 for UC]. Additional adjustment for number of outpatient and inpatient encounters did not substantially influence the results either [data not shown]. Finally, we ran our main analyses without the requirement for a 6-month interval between first dispensed statin prescription and date of diagnosis/ indexing. If anything, the association between statin use and CD was stronger, with a multivariable OR of 0.68 [95% CI, 0.61–0.76] for any statin use and 0.65 [95% CI, 0.58–0.73] for current statin use. For UC, multivariable estimates for any and current statin use remained null [OR = 1.01; 95% CI, 0.94–1.09, and OR = 0.98; 95%CI, 0.91–1.06, respectively].

4. Discussion

In our population-based case control analysis using Swedish national registry data, we found that any previous use of statins was associated with a lower risk of CD, but not UC. The magnitude of this inverse association appeared strongest among individuals who were likely to be current statin users. Indeed, we did not detect an association between past statin use and CD risk, although statistical power was limited. We observed a non-significant trend towards lower CD risk with increasing statin cumulative dose in our main analysis, which reached borderline statistical significance [$P = 0.045$] when those with implausible cumulative statin dose were excluded. The lower risk of CD associated with statin use appeared consistent regardless of age, sex, comorbidities, and statin type. These data suggest that statin use may influence the development of CD.

Our findings for CD are in keeping with a previous published study conducted using a US national claims and pharmacy database[12] [key studies of statin use and IBD are summarised in Supplementary Table 6, available as Supplementary data at *ECCO-JCC* online]. In a case-control analysis comprising 9617 cases of IBD matched to 46 665 controls, any statin use was associated with a lower risk of CD [OR = 0.64; 95% CI, 0.59–0.71].[12] In contrast to our analysis, the authors observed a similar association for UC [OR = 0.70; 95% CI, 0.65–0.76]. Overall, our analysis for UC was null. It is possible that differences between study populations could have contributed to this discordant result. Cases in the US study were, on average, around 10 years older than in our analysis and, in age-stratified analyses, risk estimates were null or greater than 1 for age groups 30–40 and 18–30 years [OR = 1.01 and OR = 1.22 respectively]. Whereas we did not observe evidence of effect modification by age in our analysis, the low frequency of statin exposure among younger individuals may have limited our ability to detect a statistically significant interaction for age. An additional previous epidemiological study used data from a US military health care system to examine the frequency of incident IBD and non-infectious gastroenteritis in a retrospective cohort of 6342 statin users matched 1:1 with non-users.[13] This analysis found no association between statin use and the risk of IBD. Although the cohort for this analysis comprised a large number of statin users, incident IBD cases numbers were quite small [$n = 93$], which may have limited the power to detect an association. Moreover, risks for incident CD and UC were not examined separately, which may have resulted in a biased estimate if the individual associations were heterogeneous.

We did not hypothesise, a priori, that the association between statin use and IBD would differ according to disease type. Although it is unclear, mechanistically, why such a difference might exist, it is

incontrovertible that CD and UC are biologically heterogeneous conditions and differential associations have been reported for a wide variety of other environmental exposures, most notably smoking,[24] but also for certain dietary components and patterns, measures of adiposity, and oral contraceptive use.[7,24–27] We do not believe that the finding of an association for CD, but not UC, precludes the possibility that the observed association may be causal.

Compared with studies of IBD risk, a larger number of studies have examined statin use among patients with established IBD. In uncontrolled clinical studies of patients with CD, atorvastatin has been reported to reduce circulating levels of inflammatory markers, cytokines, and chemokines.[28,29] In a retrospective cohort analysis that included 1986 IBD patients exposed to statins and 9871 unexposed individuals with IBD, statin use was associated with a statistically significant reduction in the risk of steroid prescription in UC [HR =0.75; 95% CI, 0.62-0.91], IBD overall [HR = 0.82; 95% CI, 0.71-0.94], but not CD [HR = 0.91; 95% CI, 0.74-1.12].[30] Stratification by disease type revealed that dose and duration-dependent associations were apparent only for UC and not CD.[30] In a small, randomised, controlled trial of patients with recently diagnosed UC [*N* = 36], atorvastatin 40 mg daily was associated with a non-statistically significant reduction in clinical disease activity score at 24 weeks.[31] However, in a small, randomised trial conducted in India [*N* = 64], atorvastatin 20 mg daily did not result in clinical improvement in patients with established UC experiencing a mild to moderate disease exacerbation.[32] Statin use has also been associated with risk of colorectal cancer [CRC] among patients with IBD. In an analysis including 11 001 IBD patients from the greater Boston area, statin use over follow-up of 9 years was associated with an 58% reduction in risk of CRC.[33] An analysis of data from IBD patients at Mount Sinai Hospital, New York, found no association between statin use and risk of colorectal neoplasia; however, the study included only 57 statin-exposed patients.[34]

Several anti-inflammatory and immunomodulatory mechanisms have been proposed through which statins may influence the development or progression of IBD [reviewed by Cote-Daigneault *et al.*[35]]. These mechanisms include reduced prenylation of proteins critical to antigen processing and presentation, and leukocyte activation and migration,[36] effecting anti-inflammatory shifts in Th1/Th2 cell balance[36] and Treg/Th7 balance,[37] and preventing intestinal fibrosis.[11] Recent data also suggest that statin use alters the composition of the gut microbiome.[38] In an animal model of high-fat diet-induced obesity, atorvastatin and rosuvastatin increased the abundance of genera including *Bacteroides*, *Butyricimonas*, and *Mucispirillum*, and microbial community alterations correlated with increased ileal expression of the anti-inflammatory mediator, TFGβ-1.[39] Among patients with hypercholesterolaemia, treatment with atorvastatin is associated with higher abundance of anti-inflammatory bacterial species including the butyrate-producing commensal, *Faecalibacterium prausnitzii*.[40] Depletion of *F. prausnitzii* is a feature of the dysbiosis associated with CD.[41] Given that several microbial species have been found to be differentially abundant in the dysbiosis of CD compared with that of UC,[41] an effect of statins on IBD risk through modulation of gut microbial communities is one plausible mechanism that might account for a selective association with CD risk.

Our study has several strengths. First, our cases and controls were drawn from the general population across the whole of Sweden, minimising selection biases. We used a validated method for IBD case ascertainment, which has been shown to have a high positive predictive value.[16] The requirement for two diagnostic entries for IBD has also previously been shown to yield stable estimates for IBD prevalence in Sweden, comparable to other European countries.[42] Allowing for our age inclusion criterion [≥18 years], average age at diagnosis for CD and UC was similar to estimates from other Nordic countries.[43] We therefore expect our study sample to be representative of other Western populations. Use of the Prescribed Drug Register likely resulted in near complete capture of statin prescriptions.[18] We were able to control for multiple potential confounding factors, including indications for statin use, and NSAID and OC use. Finally, our case and control numbers were relatively large, which allowed us to generate precise estimates and permitted subgroup analyses.

Our analysis also has some limitations. In common with all observational studies, it is possible that unmeasured or residual confounding influenced our results. COPD is an imperfect proxy for smoking status and data were not available for other possible confounding exposures, such as body mass index, physical activity, and diet. We cannot exclude the possibility of a healthy user bias associated with statin use. Nonetheless, we estimate that for the association observed for any statin use and CD to be completely explained by an unmeasured binary confounder, the confounder would need to be present in 7% of statin-exposed individuals compared with 30% of un-exposed individuals and be associated with CD with an OR of 3.0.[44] Our exposure was based on dispensed prescriptions, which are a proxy for actual medication use. We were not able to completely adjust for dyslipidaemia as a source of confounding. However, additional adjustment based on secondary care diagnostic codes for lipid disorders did not change our estimates. Furthermore, for CD, risk estimates were similar between those who had other chronic medical diagnoses that are indications for statin use and those who did not.

Despite random population sampling, IBD cases in our study had a slightly higher frequency of vascular disease diagnoses compared with controls. Only after controlling for this in multivariable models did we detect an inverse association between statin use and CD. Several studies have suggested an increased rate of cardiovascular and thromboembolic events among patients with established IBD.[45] It is interesting that, in our analysis, cardiovascular diagnoses must have occurred more than 6 months before IBD diagnosis. Shared risk factors such as smoking, obesity, and physical inactivity may be implicated[25,46]; however, the association between vascular disease and IBD risk deserves further scrutiny.

In conclusion, statin use was associated with a lower risk of CD, consistent with one previous observational analysis. Notwithstanding their inherent limitations, additional adequately-powered observational studies examining statin use and IBD risk would be of value. Although there is evidence to suggest the existence of a preclinical phase in CD,[47,48] our ability to identify those at risk of IBD, in whom statin use could avert disease progression, remains limited. Further studies focusing on the role of statins in IBD progression are also therefore warranted.

The data underlying this article cannot be shared publicly due to Swedish regulations. Researchers may request access to these data from the Swedish National Board of Health and Welfare.

Funding

PL is supported by a Career Development Award from the Crohn's and Colitis Foundation. HK is supported by a Senior Research Award from the Crohn's and Colitis Foundation.

Conflict of Interest

JFL coordinates a study on behalf of the Swedish IBD quality register [SWIBREG], which has received funding from Janssen. ATC has consulted for Pfizer Inc., Boeringher Ingleheim, and Bayer Pharma AG. OO has served as PI

on projects partly financed by investigator-initiated grants from Janssen and Ferring, and reports a grant from Pfizer in the context of a national safety monitoring programme. These studies are unrelated to the present study. Karolinska Institutet has received fees from Janssen, Ferring, Takeda, and Pfizer for lectures given by OO and for participation on advisory boards regarding topics unrelated to the present study. HK has received funding from Pfizer Inc. and Takeda Inc. for projects unrelated to the present study, and has consulted for Takeda Inc. and AbbVie Inc. None of the other authors declare any conflicts of interest.

Author Contributions

Study concept and design: PL, OO, HK, ATC, MCS JFL. Acquisition of data: OO. Data analysis and interpretation: PL, HK, MCS, ATC, JFL. Drafting the manuscript: PL, JFL. Critical revision of manuscript: all authors.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Global Burden of Disease; Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: A systematic analysis for the global burden of disease study 2017. *Lancet Gastroenterol Hepatol* 2020;**5**:17–30.
2. Ananthakrishnan AN, Kaplan GG, Ng SC. Changing global epidemiology of inflammatory bowel diseases: Sustaining health care delivery into the 21st century. *Clin Gastroenterol Hepatol* 2020;**18**:1252-60.
3. Halfvarson J, Bodin L, Tysk C, Lindberg E, Järnerot G. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. *Gastroenterology* 2003;**124**:1767–73.
4. Ng SC, Shi HY, Hamidi N, *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;**390**:2769–78.
5. Ananthakrishnan AN, Bernstein CN, Iliopoulos D, *et al*. Environmental triggers in IBD: a review of progress and evidence. *Nat Rev Gastroenterol Hepatol* 2018;**15**:39–49.
6. Moninuola OO, Milligan W, Lochhead P, Khalili H. Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDs] and risk of Crohn's disease and ulcerative colitis exacerbation. *Aliment Pharmacol Ther* 2018;**47**:1428–39.
7. Khalili H, Higuchi LM, Ananthakrishnan AN, *et al*. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut* 2013;**62**:1153–9.
8. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2016;**316**:2008–24.
9. Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol Med* 2008;**14**:37–44.
10. Lee JY, Kim JS, Kim JM, Kim N, Jung HC, Song IS. Simvastatin inhibits NF-kappaB signaling in intestinal epithelial cells and ameliorates acute murine colitis. *Int Immunopharmacol* 2007;**7**:241–8.
11. Abe Y, Murano M, Murano N, *et al*. Simvastatin attenuates intestinal fibrosis independent of the anti-inflammatory effect by promoting fibroblast/myofibroblast apoptosis in the regeneration/healing process from TNBS-induced colitis. *Dig Dis Sci* 2012;**57**:335–44.
12. Ungaro R, Chang HL, Côté-Daigneault J, Mehandru S, Atreja A, Colombel JF. Statins associated with decreased risk of new onset inflammatory bowel disease. *Am J Gastroenterol* 2016;**111**:1416–23.
13. Khalil D, Boktor M, Mortensen EM, Frei CR, Mansi I. Comparison of frequency of inflammatory bowel disease and noninfectious gastroenteritis among statin users versus nonusers. *Am J Cardiol* 2015;**115**:1396–401.
14. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**:659–67.
16. Jakobsson GL, Sternegård E, Olén O, *et al*. Validating inflammatory bowel disease [IBD] in the Swedish National Patient Register and the Swedish Quality Register for IBD [SWIBREG]. *Scand J Gastroenterol* 2017;**52**:216–21.
17. Ludvigsson JF, Almqvist C, Bonamy AK, *et al*. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016;**31**:125–36.
18. Wettermark B, Hammar N, Fored CM, *et al*. The new Swedish Prescribed Drug Register – opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;**16**:726–35.
19. Cosentino M, Leoni O, Banfi F, Lecchini S, Frigo G. An approach for the estimation of drug prescribing using the defined daily dose methodology and drug dispensation data. Theoretical considerations and practical applications. *Eur J Clin Pharmacol* 2000;**56**:513–7.
20. Olén O, Bihagen E, Rasmussen F, Ludvigsson JF. Socioeconomic position and education in patients with coeliac disease. *Dig Liver Dis* 2012;**44**:471–6.
21. Ekstrom N, Schioler L, Svensson AM, *et al*. Effectiveness and safety of metformin in 51,675 patients with type 2 diabetes and different levels of renal function: A cohort study from the Swedish national diabetes register. *BMJ Open* 2012;**2**:e001076.
22. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B; Steering Committee of the Swedish National Diabetes Register. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. *Diabetes Care* 2003;**26**:1270–6.
23. Wallentin F, Wettermark B, Kahan T. Drug treatment of hypertension in Sweden in relation to sex, age, and comorbidity. *J Clin Hypertens [Greenwich]* 2018;**20**:106–14.
24. Vedamurthy A, Ananthakrishnan AN. Influence of environmental factors in the development and outcomes of inflammatory bowel disease. *Gastroenterol Hepatol [N Y]* 2019;**15**:72–82.
25. Khalili H, Ananthakrishnan AN, Konijeti GG, *et al*. Measures of obesity and risk of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2015;**21**:361–8.
26. Khalili H, Chan SSM, Lochhead P, Ananthakrishnan AN, Hart AR, Chan AT. The role of diet in the aetiopathogenesis of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2018;**15**:525–35.
27. Khalili H, Håkansson N, Chan SS, *et al*. Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies. *Gut* 2020;**69**:1637–44.
28. Grip O, Janciauskiene S. Atorvastatin reduces plasma levels of chemokine [CXCL10] in patients with Crohn's disease. *PLoS One* 2009;**4**:e5263.
29. Grip O, Janciauskiene S, Bredberg A. Use of atorvastatin as an anti-inflammatory treatment in Crohn's disease. *Br J Pharmacol* 2008;**155**:1085–92.
30. Crockett SD, Hansen RA, Stürmer T, *et al*. Statins are associated with reduced use of steroids in inflammatory bowel disease: a retrospective cohort study. *Inflamm Bowel Dis* 2012;**18**:1048–56.
31. Higgins P, Kahn T, Mapili J, Zimmermann E. Atorvastatin decreases SEO index in patients with short duration of disease in ulcerative colitis: A randomized placebo-controlled clinical trial. *Gastroenterology* 2006;**130**:A120.
32. Dhamija P, Hota D, Kochhar R, Sachdev A, Chakrabarti A. Randomized clinical trial: atorvastatin versus placebo in patients with acute exacerbation of mild to moderate ulcerative colitis. *Indian J Gastroenterol* 2014;**33**:151–6.
33. Ananthakrishnan AN, Cagan A, Cai T, *et al*. Statin use is associated with reduced risk of colorectal cancer in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2016;**14**:973–9.
34. Shah SC, Glass J, Giustino G, *et al*. Statin exposure is not associated with reduced prevalence of colorectal neoplasia in patients with inflammatory bowel disease. *Gut Liver* 2019;**13**:54–61.

35. Côté-Daigneault J, Mehandru S, Ungaro R, Atreja A, Colombel JF. Potential immunomodulatory effects of statins in inflammatory bowel disease. *Inflamm Bowel Dis* 2016;**22**:724–32.
36. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol* 2006;**6**:358–70.
37. Shahbaz SK, Sadeghi M, Koushki K, Penson PE, Sahebkar A. Regulatory T cells: Possible mediators for the anti-inflammatory action of statins. *Pharmacol Res* 2019;**149**:104469.
38. Liu Y, Song X, Zhou H, *et al*. Gut microbiome associates with lipid-lowering effect of rosuvastatin in vivo. *Front Microbiol* 2018;**9**:530.
39. Kim J, Lee H, An J, *et al*. Alterations in gut microbiota by statin therapy and possible intermediate effects on hyperglycemia and hyperlipidemia. *Front Microbiol* 2019;**10**:1947.
40. Khan TJ, Ahmed YM, Zamzami MA, *et al*. Atorvastatin treatment modulates the gut microbiota of the hypercholesterolemic patients. *OMICS* 2018;**22**:154–63.
41. Lloyd-Price J, Arze C, Ananthakrishnan AN, *et al*.; IBDMDB Investigators. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019;**569**:655–62.
42. Büsch K, Ludvigsson JF, Ekström-Smedby K, Ekbom A, Askling J, Neovius M. Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. *Aliment Pharmacol Ther* 2014;**39**:57–68.
43. Lophaven SN, Lynge E, Burisch J. The incidence of inflammatory bowel disease in Denmark 1980-2013: a nationwide cohort study. *Aliment Pharmacol Ther* 2017;**45**:961–72.
44. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;**15**:291–303.
45. Fumery M, Xiaocang C, Dauchet L, Gower-Rousseau C, Peyrin-Biroulet L, Colombel JF. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis* 2014;**8**:469–79.
46. Khalili H, Ananthakrishnan AN, Konijeti GG, *et al*. Physical activity and risk of inflammatory bowel disease: prospective study from the Nurses' Health Study cohorts. *BMJ* 2013;**347**:f6633.
47. Lochhead P, Khalili H, Ananthakrishnan AN, Richter JM, Chan AT. Association between circulating levels of C-reactive protein and interleukin-6 and risk of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2016;**14**:818–24.e6.
48. Torres J, Petralia F, Sato T, *et al*. Serum biomarkers identify patients who will develop inflammatory bowel diseases up to 5 years before diagnosis. *Gastroenterology* 2020;**159**:96-104.