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WHAT YOU NEED TO KNOW:

Background and Context: There are insufficient population-level data on the effects of primary sclerosing cholangitis (PSC) in patients with inflammatory bowel disease (IBD).

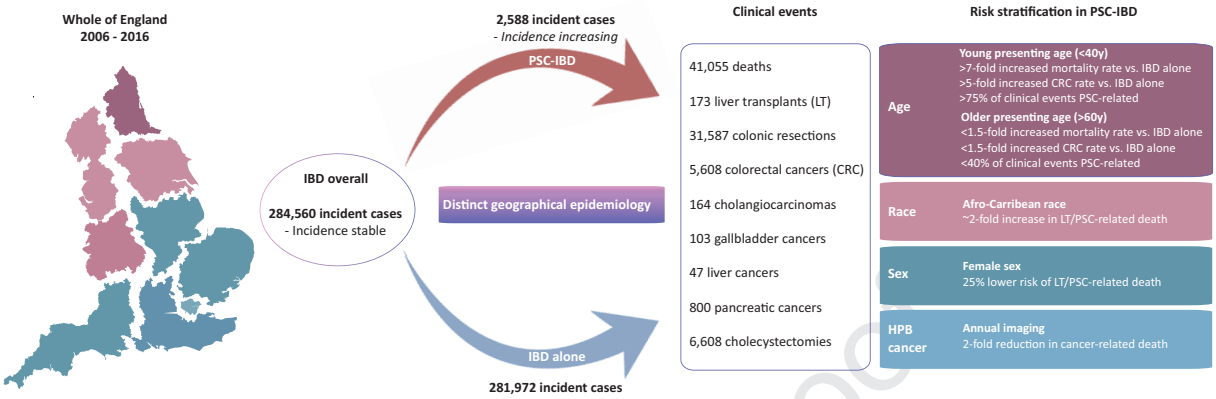
New findings: In a 10-year study of 284,560 patients with IBD, onset of PSC increased risks of cancers and death. The incidence of liver transplantation or PSC-related death was increased in patients who received a diagnosis of PSC younger than 40 years, patients of Afro-Caribbean heritage, and men.

Limitations: This analysis of the population of England, based on medical databases, is restricted to patients with PSC and concomitant IBD.

Impact: Age at diagnosis, sex, and race should be considered in design of clinical trials, disease prediction models, and prognostic biomarkers of PSC.

LAY SUMMARY:

In an analysis of patients with inflammatory bowel diseases in England, the study shows that development of primary sclerosing cholangitis affects risk of needing surgery, development of cancer, and death; rates differ according to age at diagnosis, sex, and race.



Effects of Primary Sclerosing Cholangitis on Risks of Cancer and Death in People With Inflammatory Bowel Diseases, Based on Sex, Race, and Age

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PT and GMH: Conceived the study idea and study design. PT, HC and JM: Case finding, clinical data acquisition and event capture, statistical analysis. PT and SB: Quality control and validation of clinical coding. TI and JF: Critical revision of the manuscript for important intellectual content. PT: Wrote the first draft of the manuscript, and incorporated subsequent revisions before finalising the draft through to submission. PT, HC and GMH: Critical revision of the manuscript for important intellectual content, including writing contribution to first and subsequent versions of the manuscript. GMH also provided overall study supervision.

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ABSTRACT

Background & Aims: There are insufficient population-level data on effects of primary sclerosing cholangitis (PSC) in patients with inflammatory bowel disease (IBD).

Methods: We identified incident cases of IBD, with PSC (PSC-IBD) and without, from April 2006 through to April 2016 and collected data on outcomes through April 2019. We linked data from national healthcare registries maintained for all adults in England on hospital attendances, imaging and endoscopic evaluations, surgical procedures, cancer, and deaths. Our primary aim was to quantify the effects of developing PSC in patients with all subtypes of IBD and evaluate its effects on hepatopancreatobiliary disease, IBD-related outcomes, and all-cause mortality, according to sex, race, and age.

Results: Over 10 years, we identified 284,560 incident cases of IBD nationwide; of these 2588 developed PSC. In all, we captured 31,587 colectomies, 5608 colorectal cancers (CRCs), 173 first liver transplants, 6608 cholecystectomies and 41,055 patient deaths. Development of PSC was associated with increased risk of death and CRC (hazard ratios [HRs], 3.20 and 2.43, respectively; $P<.001$), and a lower median age at CRC diagnosis (59 years vs 69 years without PSC; $P<.001$). Compared to patients with IBD alone, patients with PSC-IBD had a 4-fold higher risk of CRC if they received a diagnosis of IBD at an age younger than 40 years; there was no difference between groups for patients diagnosed with IBD at an age older than 60 years. Development of PSC also increased risks of cholangiocarcinoma (HR, 28.46), hepatocellular carcinoma (HR, 21.00), pancreatic cancer (HR, 5.26), and gallbladder cancer (HR, 9.19) ($P<.001$ for all). Risk of hepatopancreatobiliary cancer-related death was lower among patients with PSC-IBD who received annual imaging evaluations before their cancer diagnosis, compared to those who did not undergo imaging

(HR, 0.43; *P*=.037). The greatest difference in mortality between the PSC-IBD alone group vs the IBD alone group was for patients younger than 40 years of age (incidence rate ratio >7), in contrast to those who received a diagnosis of IBD older than 60 years (incidence rate ratio <1.5). Among patients with PSC-IBD, liver transplantation and PSC-related events accounted for approximately 75% of clinical events when patients received a diagnosis of PSC at an age younger than 40 years, vs 31% of patients who received a diagnosis older than 60 years (*P*<.001). Afro-Caribbean heritage associated with increased risks of liver transplantation or PSC-related death compared with Caucasian race (HR, 2.05; *P*<.001), whereas female sex associated with reduced risk (HR, 0.74; *P*=.025).

Conclusions: In a 10-year, nationwide study, we confirmed that patients with PSC-IBD have increased risks of CRC, hepatopancreatobiliary cancers, and death compared to patients with IBD alone. In the PSC-IBD group, diagnosis of IBD at age younger than 40 years was associated with greater risks of CRC and all-cause mortality compared with diagnosis of IBD at older ages. Patients who receive a diagnosis of PSC at an age younger than 40 years, men, and patients of Afro-Caribbean heritage have an increased incidence of PSC-related events.

KEY WORDS: epidemiology, malignancy, population-based, survival

.

INTRODUCTION

The dominant clinical presentation of primary sclerosing cholangitis (PSC) is in association with inflammatory bowel disease (IBD).[1,2] However, despite improvements in managing IBD, interventions that benefit patients with PSC remain limited, and clinical outcomes are determined by development of recurrent cholangitis, cirrhosis and end-stage liver disease. This is alongside a heightened but variable risk for malignancies of the biliary tree[1] and colon.[3–5] Disease heterogeneity compounds challenges to 'risk-predict' for patients in routine care; and importantly, to best design and deliver effective clinical trials based on carefully considered eligibility criteria.

Representative data from high-volume programmes indicate a median transplant-free survival approximating 15 years,[1,6] with population-based cohorts, largely from Scandinavia and the Netherlands, providing further insight,[2,3,7] However, significantly greater survival time is reported for patients diagnosed in non-transplant units,[2] underscoring the need for nationally-representative epidemiological data.

PSC affects all age groups, with older age at diagnosis reportedly associated with worse transplant-free survival.[1,6,8] However, causal mortality analysis according to age at PSC diagnosis has not been determined. Such findings have critical implications for interventional trial design, as 40 to 50% of all deaths may not be attributable to liver disease.[2,6] Nevertheless, currently proposed surrogates which are applied to clinical trials derive from studies that incorporate transplantation and all-cause mortality as a composite endpoint.[9,10] Phenotypic diversity according to sex and age may also influence the clinical course that patients experience.[8,11] Whilst the majority of datasets derive from Caucasian populations, a recent

study indicates that PSC may be as common in patients of Afro-Caribbean descent.[12] However, it is unknown whether heritage-specific differences in disease risk exist in PSC.

In this study we evaluate patients with PSC and concomitant IBD, as reflective of the dominant pattern of PSC, using a large population-based dataset from across the whole of England. In so doing, we seek to better understand key features of disease including incidence, as well as natural history. Our analyses quantify the additive risk of developing PSC for patients with IBD across all its subtypes, and show critical differences in event rates according to sex, race and age, as relate to hepatobiliary disease, IBD-specific outcomes, and all-cause mortality.

METHODS

Study population

This was a nationwide population-based study conducted throughout England, performed via evaluating patient medical records held by the Hospital Episode Statistics (HES) registry, and linkage to the Office of Population Censuses and Surveys Classification of Interventions and Procedures Classification version 4 (OPCS-4), and the Office of National Statistics (ONS) database. HES data encompasses all National Health Service (NHS) Clinical Commissioning Groups in England, detailing every adult (>18y of age) hospital admission, attendance, and investigative and therapeutic procedure undertaken in the National Health Service (NHS).[13] Notably, NHS free healthcare constitutes 98-99% of all hospital activity in England,[14] being available to every British citizen. Individual HES records have been longitudinally linked to the same patient since 1997/98, with outpatient data captured prospectively from 2004/5 onwards. Patient identification is reliant on the unique 10-digit NHS number ascribed to all registered users of health services in England. Each HES record contains a broad range of data about a patient attending healthcare services, including information about diagnoses and operations; demographics; and administrative and geographical data such as the dates and route of admission and discharge, patient residential address, location of treatment, and hospital type. No laboratory parameters or medication data are captured. OPCS-4 classification relates to all surgical procedures performed throughout the NHS; whereas ONS captures dates, location, and causes of death of all individuals across the UK.

Case ascertainment

Extraction of NHS registry data yields fully anonymised records, with no traceable patient identifiable information provided to the researcher. Case finding was through detailed review of all hospital attendances and admissions, out-patient visits, imaging logs (transabdominal

ultrasound scans, magnetic resonance cholangiopancreatograms (MRCP) and/or MRI liver scans, ultrasound-guided and transjugular liver biopsies, endoscopic retrograde cholangiopancreatograms (ERCP), and endoscopic ultrasound scans), endoscopy reports, theatre reports (bowel resections, liver resections and liver transplantations), cancer records (colorectal, bile duct, hepatocellular, gallbladder and pancreatic), and deaths across the aforementioned time period. The level of accuracy and completeness of NHS registry data is presented elsewhere.[15–19]

First, data was collected prospectively from all incident cases of IBD from the 1st of April 2006 to 1st of April 2016 throughout England, with a minimum observation period of three years thereafter (study end date 1st April 2019). Patients having an IBD diagnosis recorded prior to April 2006 were excluded, in order to reduce the possible impact of prevalent out-patient cases on our findings.[4,20] Case finding strategy was extrapolated from the studies by Jess, Olén and Lindqvist.[3,4,7,21–23] Briefly, we applied the International Statistical Classification of Diseases and Related Health Problems (ICD) version 10 codes for ulcerative colitis (UC, K51), Crohn's disease (CD, K52) or IBD-unclassified (IBD-U, K52.3) before identifying patients having PSC-IBD more specifically.[3,4,7,21–23] Given that the ICD10 code for IBD-unclassified was only introduced in 2012, patients with IBD-U were also identified by the methods introduced by Everhov and Olén,[23,24] wherein patients having a UC diagnosis who later went on to have a code for CD attributed (or vice versa) were reclassified as IBD-U.

To avoid diagnostic ambiguity, and in order to maximise the legitimacy and accuracy of PSC diagnosis, we excluded those with alternative aetiologies of liver disease (**Supp. Table 1A**), and only patients having a documented PSC-related investigation or intervention approved for diagnosis (either an MRCP, ERCP, or liver biopsy performed by any route), together with a documented PSC diagnosis code, were classified as having PSC. Additional validation and

quality control was performed, via manual cross-referencing of selected medical records held within the host institution against their recorded codes including the accuracy of dates (**Supp. Table 1B and C**).

Data collection and clinical events

Individual patient characteristics were captured, relating to patient sex, age at IBD diagnosis, subtype of IBD diagnosis, age at PSC diagnosis, index of multiple deprivation, Charlson Comorbidity Index, race, residential location, and hospital at which IBD diagnosis and PSC diagnosis were first recorded. Follow-up continued until the point of death, or censoring at the end of the study (31st March 2019).

Clinical events were classified according to all-cause mortality, liver transplantation, PSC-related death, colorectal cancer (CRC) and colonic resection. Incidents of cholangiocarcinoma (CCA), pancreatic cancer, gallbladder cancer, hepatocellular carcinoma (HCC) and cholecystectomy were evaluated as additional endpoints. These were analysed separately from liver transplantation and PSC-related death, given that the majority of hepatopancreatobiliary (HPB) cancers, particularly CCA, develop within the first 12 months of PSC diagnosis,[1] and factors contributing to progressive liver disease are likely distinct to those leading to malignancy.

Surveillance practice and post-cancer survivorship

National administrative healthcare registries do not capture the indication for endoscopic procedures. However we evaluated the impact of periodic colonoscopy performed at 1-2 yearly intervals, and its potential impact on CRC-related death, as per methodology by Claessen and Boonstra.[2,25] To account for competing risks, and in order to classify patients' surveillance status prior to CRC diagnosis, patients who underwent colectomy, developed

CRC, or who died/reached the end of follow-up within 2 years of PSC diagnosis were excluded from this analysis (given that they would not have had an opportunity to undergo at least 2 surveillance examinations a year apart).

Routine surveillance for HPB malignancies is more contentious, and not standard of care in the UK given paucity of evidence and the fact that the vast majority of CCA occur in the first year after PSC diagnosis.[1] However, annual imaging is performed by some centres; consisting of a transabdominal ultrasound, and/or MRCP, and/or computed tomography (CT). To this effect, we determined the impact of annual imaging on post-cancer survivorship, akin to methodology presented by the Mayo clinic.[26] Liver transplantation and non-HPB cancer events were handled as competing risks.

Data interpretation and statistical analysis

Categorical variables are expressed as raw numbers (percentages in parenthesis), and continuous data as medians (and interquartile ranges, IQR). Differences between individual groups of continuous and categorical data were assessed using the Mann Whitney U test and Chi-squared test, respectively. Clinical event rates (with 95% confidence intervals, CI) are presented from both the point of IBD diagnosis and PSC diagnosis. Patients failing to meet a clinical event were censored at the end of the study, taking into account competing risks as indicated. In line with the principal aims of this study, incidence rates per 1,000-patient-years (IR) were stratified according to patient age at presentation of IBD diagnosis and PSC diagnosis as indicated, before determining the incidence rate ratio (IRR) between PSC-IBD vs IBD alone.

To calculate years of life lost (YLL), the numbers of deaths occurring at each age were counted, split according to cohort group and sex. These counts were multiplied by the period

expectation of life 2016-2018 estimates from the Office for National Statistics,[27] summed to obtain the total YLL and then divided by the death count for that group, to obtain average YLL. Cox proportional hazards models were fit to assess the impact of individual covariates on the instantaneous rate of clinical events, and hazard ratios (HR) with respective 95% CIs shown in parenthesis. Covariates yielding a P-value of 0.1 on univariate analysis were fed into respective multivariable models.[28–32] P-values <0.05 were deemed statistically significant. Given that development of IBD does not parallel that of PSC, the prognostic impact of PSC onset was assessed as a time-dependent covariate.

Statistical analyses were performed using R, including the packages 'ggplot2' and 'sf' (plotting choropleth maps), 'epiR' and 'epitools' (estimation of incidence rates and incidence rate ratios), 'survival' and 'survminer' (survival analyses and plotting), and 'cmprsk' (for competing risk models; **Supp. Table 2).** Regulatory board approval was obtained prior to study initiation and database/chart review (UHB CAB-04186-12 and CARMS-02246).

RESULTS

Cohort overview

Over a ten-year period, 50,168,647 adult patients had contact with healthcare services in England. Of this group, 284,560 incident cases of IBD were identified (**Fig. 1, Supp. Table 3**). From the overall IBD cohort, 2,588 individuals were diagnosed with PSC >12 months prior to (n=393), within 12 months of (n=1,306), or >12 months of IBD diagnosis (n=889) (**Supp. Fig. 1**). A male predominance was observed in PSC-IBD and PSC-UC groups when PSC presented at an age <40 years (~70%), which became less apparent in older age (~50%, **Supp. Fig. 2**).

From 2006 to 2016, the incidence of IBD remained relatively constant, but appeared to increase for PSC-IBD (0.58 per-100,000-population in 2016). Notably, regions of heightened PSC-IBD incidence did not parallel that of IBD**,** neither was there tendency for PSC diagnosis to cluster around liver transplant units (**Fig. 2, Fig. 3** and **Supp. Figs. 3-5**). Overall, we captured 31,587 colonic resections, 5,608 incidents of colorectal cancer (CRC), 173 first liver transplants and 41,055 patient deaths (**Fig. 4**). Cumulative follow-up till death or censor was 1,994,441-person-years for the IBD alone group, and 18,823-person-years for those with PSC-IBD.

Patients with PSC-IBD exhibit a heightened mortality rate

Relative to the background population, the YLL following IBD diagnosis was 12.7 and 12.6 years vs 17.1 and 16.4 years for men and women with IBD alone vs PSC-IBD, respectively. A greater all-cause mortality rate was observed with PSC-IBD vs IBD **(Fig. 5),** with PSC onset conferring a time-dependent HR of 3.20, 3.01-3.40, P<.001), independently of sex, race, deprivation index, comorbidities and advancing age, and on PSC-IBD sub-group analysis

(Supp. Fig. 6). In both groups, all-cause mortality was approximately 2-fold greater in Caucasian vs non-Caucasian patients, and also increased with advancing age at IBD diagnosis (**Supp. Tables 4-6)**. In PSC-IBD specifically, the negative prognostic impact of age was retained on multivariable analysis (but not for race); however, the greatest most discrepant mortality ratio compared to IBD alone was for those diagnosed <40 years old (**Fig. 6; Supp. Tables 7-8**).

Patients with IBD had a greater comorbidity index compared to PSC-IBD, although differences for any single comorbidity were not significant upon age-adjustment **(Supp. Table 9).** The single leading cause of death in the IBD alone group related to ischaemic heart disease, although the majority died from other, miscellaneous causes. In turn, 50.1% of deaths in the PSC-IBD group were not related to liver or biliary disease (**Supp. Table 10**); however, this varied by age at PSC diagnosis (**Fig. 5** and **Fig. 6**).

Afro-Caribbean heritage and male sex confer heightened risk of liver transplantation and PSC-related clinical events

Compared to Caucasians, PSC-IBD patients of Afro-Caribbean heritage were at greater risk of transplantation/PSC-related death, whilst women were at a 25% lower risk than men **(Supp. Table 11-13)**. These findings were retained on multivariable testing (adj. HR: 2.05, 1.14-3.70, P=.016; and HR: 0.74, 0.57-0.97, P=.026; respectively). Notably, adult-onset PSC manifest at a younger age amongst patients of non-Caucasian vs Caucasian heritage (median diagnosis age in patients of Afro-Caribbean, Asian and Caucasian descent: 40 (IQR 29-48) years, 38 (29-52) years, and 58 years (38-71) years, respectively). Advancing age at PSC diagnosis was not a risk factor for transplantation/PSC-related death (HR: 1.02; 0.96-1.09, P=.543).

Incidence of liver transplantation/PSC-related death is greatest in patients of young presenting age, those diagnosed at transplant centres, and who have PSC-UC.

According to age, we found the highest incidence rate for liver transplantation/PSC-related death amongst PSC-IBD patients diagnosed between 31 to 40 years (**Fig. 5** and **Fig. 6**). Moreover, the proportional contribution of PSC-related clinical events approximated 75% for patients diagnosed <40 years vs ~30% for the over 60s (**Fig. 5**). The median age at transplantation was 43 years (33-57) and 46 years (35-60) for men and women with PSC-IBD, respectively.

The incidence of liver transplantation/PSC-related death was significantly lower for patients diagnosed with PSC at non-transplant (IR 17.6, 15.4-20.1) vs liver transplant centres (IR 33.1, 22.1-48.1); IRR 0.5, 0.4-0.8, P<.001. This contrasted to all-cause mortality rates, which were greater amongst patients first presenting to non-transplant sites **(Supp. Table 14).** Of note, adults diagnosed with PSC at a transplant centre were of a lower median age than those in non-transplant units (47 years, IQR 29-62; vs 57 years, 32-66; P<.01). In turn, a greater proportion of patients diagnosed at non-transplant sites had a comorbidity index >5 (18% vs 15%; P<.001).

When examining primary clinical event rates by PSC-IBD sub-group, we found that PSC-CD conferred heightened risks of all-cause mortality vs PSC-UC, albeit a lower risk of transplantation / PSC-related death (**Supp. Fig. 7 and 8**). Non-hepatic deaths in the PSC-CD group were attributable to miscellaneous causes, with extra-colonic / extra-hepatic malignancy also being prevalent (**Supp. Table 15**).

PSC onset confers heightened risks of HPB cancer

164 patients with PSC-IBD developed cholangiocarcinoma **(Supp. Table 16)**, with a numerically lower median age at CCA onset amongst men than women (64 years, IQR 48-71 years; vs 67 years, 56-79 years; respectively, P<.001). Incidence rates of CCA were 2.4 (1.0-4.7), 8.1 (4.5-13.3), 11.3 (7.6-16.1), 11.9 (7.6-76.6) and 20.2 (16.5-25.0) per 1,000 patient-years, for individuals diagnosed with PSC aged 18-30 (n=13), 31-40 (n=11), 41-50 (n=24), 51-60 (n=38) and >60 years (n=78), respectively. 138 patients died from CCA during the study period (median time till death of 0.45 years; IQR 0.15-1.30). Only advancing age at PSC diagnosis was identified as a risk factor for CCA amongst PSC-IBD patients (HR per 10-year increase: 1.26, 1.16-1.37, P<.001). The number of CCA amongst PSC-CD and IBD-U was too small to permit sub-group analyses.

Additionally, 1.8% patients with PSC-IBD (n=47/2,588) developed HCC **(Supp. Table 16, Supp. Fig. 9)**. Within this group specifically, the only factor conferring increased HCC risk was advancing age at PSC diagnosis (HR: 1.33, 1.13-1.57, P<.001). We also observed 800 incidents of pancreatic cancer; *n*=717 (<1%) in the IBD alone group and 83 (3%) amongst those with PSC-IBD. PSC onset associated with heightened pancreatic cancer risk, even after adjustment for age, sex, race, deprivation, IBD phenotype and comorbidities (time-dependent adj. HR 5.26, CI 2.81-9.84, P<.001; **Supp. Fig. 9)**. Within the PSC-IBD group, advancing age at PSC diagnosis was a risk factor for pancreatic cancer (HR: 1.76, 1.52-2.03; P<.001), but no effect was seen for other covariates.

Overall, 33 patients with PSC-IBD developed gallbladder cancer **(Supp. Table 16)**. The risk of cancer was heightened for PSC-IBD patients, even after adjusting for age, sex, race, deprivation, comorbidities and IBD-subgroup (adj. HR: 9.19, 2.91-29.05; **Supp. Fig. 9).**

Advancing age at PSC diagnosis was the only identifiable risk factor for gallbladder cancer within the PSC-IBD group (HR 1.44, 1.18-1.75, P>0.001).

In entirety, 6608 patients with IBD underwent cholecystectomy; 6304 with IBD alone and 304 with PSC-IBD (including 18/33 PSC-IBD patients with a gallbladder cancer diagnosis). All but 2 of the PSC-IBD patients with gallbladder cancer who did not undergo cholecystectomy died before the end of follow up. Development of PSC associated with greater risk of cholecystectomy vs IBD alone **(Supp. Fig. 9)**, with the onset of gallbladder cancer conferring even greater risk (HR: 11.42, 5.06-25.76). Advancing age at PSC diagnosis (HR: 1.16, 1.10-1.23; P<.001) and female sex (HR: 1.37, 1.11-1.71; P=.004) were identified as additional risk factors for cholecystectomy.

Annual imaging is associated with a lower risk of cancer-related death

Of all patients who developed HPB cancer >12 months following PSC diagnosis (*n*=117/334), 64/117 died before the end of follow-up. Post-cancer survivorship analysis showed that annual imaging (minimum of 2 interval scans) prior to cancer diagnosis was associated with >2-fold risk reduction in HPB cancer-related death (HR 0.43, 0.23-0.80, P=.037; **Supp. Fig. 10a)**. In all, 66% of CCA (n=111/164) were identified within the first year of PSC diagnosis, and 84% (n=138/164) died prior to the end of the study period. After exclusion of all CCA cases from the first year there was no difference in post-CCA survivorship, specifically, between surveillance vs no surveillance groups **(Supp. Fig. 10b).**

PSC onset confers heightened risks of colectomy in UC, IBD-U but not CD

Amongst patients with IBD alone, the incidence **(Supp. Table 17** and **18)** and risks of colonic resection **(Supp. Table 19)** were greatest in the CD group, even following adjustment for other covariates (adj. HR: 2.21, 2.15-2.27, P<.001).

Development of PSC conferred >40% added risk for colonic resection amongst IBD patients (time-dependent adj. HR: 1.65, 1.45-1.85, P<.001); a finding retained on sub-analyses of PSC-UC vs UC and PSC-IBD-U vs IBD-U. However, colectomy rates were no different between PSC-CD vs CD alone **(Supp. Fig. 11).**

The incidence of colectomy is similar for older age PSC-IBD versus IBD alone

In patients with IBD alone, the risk of colonic resection was lower for women vs men (adj. HR: 0.85, 0.83-0.88; P<.001) and amongst non-Caucasian patients (pooled adj. HR <0.7; P<.001), but decreased with advancing age (adj. HR: 0.89, CI:0.89-0.90, P<.001) (**Supp. Table 19)**. With regards PSC-IBD, a lower risk of colonic resection was also observed for women (adj. HR: 0.74, 0.60-0.93, P=.009), but there was no effect of race **(Supp. Table 20**). The incidence of colonic resection was greatest amongst PSC-IBD patients diagnosed <50 years, with a gradual decline observed in advancing age. Reciprocally, no difference in colectomy rate was observed in the PSC-IBD vs IBD only groups diagnosed >50 years (IRR<**1; Fig. 6**).

We found a greater proportion of patients undergoing colonic resection had CRC as an indication in the PSC-IBD group vs IBD alone (22% vs 12%, respectively, P<.001; **Supp. Fig. 12)**. Of the 30 PSC-IBD patients who did not undergo resection within 12 months of CRC diagnosis, 21 died during the study period.

Colorectal cancer develops at a younger age in PSC-IBD versus IBD alone

In IBD alone, the incidence of CRC increased with advancing age (**Fig. 6**), and was greater amongst patients of Caucasian vs non-Caucasian race, men vs women, and patients with UC compared to other IBD subtypes (**Supp. Tables 21-23**). This differed to our PSC-IBD group;

whilst the risk of CRC was significantly lower amongst women vs men (adj. HR: 0.46, 0.29-0.72, P<.001), the incidence peaked when IBD was diagnosed between the ages of 40 and 50 years, particularly amongst those with PSC-UC (**Fig. 6, Supp. Table 21**). Notably, the median age at CRC diagnosis was significantly lower for patients with PSC-IBD vs IBD alone (59 years, IQR 47-72 years; versus 69 years, IQR 58-78; P<.001). In turn, the incidence of CRC was 5-fold greater for the PSC-IBD group vs those with IBD alone amongst those diagnosed <50 years, but <2-fold for older individuals (**Fig. 6**). No difference in the incidence of CRC was found between PSC-IBD vs IBD alone for patients diagnosed above the age of 60 years (**Fig. 6)**. CRC cases amongst non-Caucasians with PSC-IBD numbered too few to permit robust statistical analysis according to race (**Supp. Table 24)**.

Observing the study population in its entirety, the onset of PSC associated with >3-fold increased risk of developing CRC **(Fig. 7A)**, independently of sex, age, race, deprivation and comorbidities, and in sub-analysis of patients with UC and IBD-U **(Fig. 7B)**. CRC risk was also increased for PSC-CD vs CD alone, but of borderline significance.

Across our PSC-IBD cohort, 363/2,588 patients (14%) underwent colonic resection and 105/2,588 (4%) developed CRC at some point. Of this group 162 and 43 patients underwent resection or developed CRC, respectively, after IBD diagnosis (but prior to PSC), with an additional 83 and 32 patients experiencing these clinical events within the first 2 years of PSC onset. Of the remaining 30 patients who developed CRC thereafter, 6 experienced a CRC-related death. Lower rates of CRC-related death were observed in the group undergoing annual colonoscopy vs the non-surveyed group (18% vs 21%), although numbers were underpowered to detect statistical significance.

DISCUSSION

In recognition of the barriers involved in developing effective new therapy for rare disease, it is critical that robust descriptors of clinical course exist, in a way that is least biased, most representative of the patient population, and inclusive of the target demographic. Herein, we report that the incidence of PSC-IBD, whilst numerically low (consistent with the rarity of disease), appear to be rising across England, but does not follow that of IBD overall, geographically or temporally. This supports distinctions in epidemiology between the two entities, and argues against the fact that 'more IBD begets more PSC.' Whilst all-cause mortality rates increase with age in all patients, the magnitude of risk between PSC-IBD vs IBD alone exceeds seven-fold if PSC is diagnosed below the age of 40, but lower than two-fold in the over 60s.

Perhaps most striking is the fact that the proportional representation of clinical events differs according to age at diagnosis. Liver transplants/PSC-related deaths predominate across younger age groups, whereas non-PSC-related deaths are the majority case-contributor in older individuals. Taken together with data indicating a more inflammatory biochemical phenotype in young- versus older-age onset PSC,[8] we propose that existing and future clinical prediction tools and surrogate markers be modified to account for young presenting age as a risk stratifier, and be calibrated to PSC-related events specifically, rather than transplantation and all-cause mortality.

Historically, there has been little data to suggest an increased risk of pancreatic cancer in PSC, although one previous study reported a standardised incidence rate greater than that of the general population;[33] data which is supported by our findings herein. We were also able to validate findings presented by the Mayo clinic, in that the probability of all-cause HPB

cancer-related death is lower in patients undergoing annual imaging prior to cancer diagnosis. Whilst national administrative healthcare registries do not capture tumour stage, our findings suggest that surveillance may be associated with better clinical outcomes for patients. Unfortunately, as the incidence of cholangiocarcinoma is greatest nearer the time of PSC diagnosis, we were unable to demonstrate survival benefit for this group specifically. Further efforts, potentially looking at prevalent PSC cases and the future, longer-term incidence of cholangiocarcinoma are urgently needed.

Availability of an unselected nationwide cohort also showed that Afro-Caribbean race and male sex are associated with heightened risks of transplantation and PSC-related death – the latter mirroring our experience as part of the International PSC Study Group.[1,34] Additionally, we confirm a lower incidence of transplantation/PSC-related death, and of CRC, in those with PSC and Crohn's disease compared to PSC-UC.[34,35] The reasons for these differences are unknown, but highlight a need to better understand IBD classification in PSC. Whilst national registries do not capture details pertaining to the distribution of intestinal inflammation, evidence suggests that the CD of PSC is invariably localised to the colon (isolated small bowel disease being rare), yet genetic signals appear distinct to PSC-UC.[34,36,37]

The long-held view that IBD follows a quiescent clinical course in PSC also appears to be challenged. Our data, together with that from others, show a greater incidence of colonic resection in PSC-IBD compared to IBD alone.[3,38] Whilst CRC is more commonly an indication, most often colectomies were performed for non-CRC-related reasons, presumably persistent active colitis. Whilst the number of CRC-related deaths was low and our observation period too short to determine the protective impact of CRC surveillance, a number of studies are supportive. Notably, Boonstra et al. showed a lower number of CRC-related deaths amongst PSC-IBD patients who participated in colonoscopic surveillance over

the long-term, presumably due to cancer diagnosis at an earlier more curable stage.[2] Notably, to detect any beneficial effect of CRC surveillance requires longer terms studies, particularly as the incidence of CRC is greatest nearer the time of PSC diagnosis.[4,39] Moreover, 40-45% of all colonic resections take place prior to PSC diagnosis;[40] a statistic which we validate herein. Auditing and addressing the reasons for non-adherence to surveillance practice is important, given that PSC patients more often present with advanced colonic lesions than those with IBD alone, together with persistence of sub-clinical inflammation.[41]

Our study represents a large population-based cohort in terms of patient number, clinical events captured and cumulative follow-up. Notwithstanding, there are recognised limitations. Firstly, the observation period was restricted to 10(+3) years, and prolonged follow-up is needed to determine validity of findings over the longer-term. The proportion of individuals who developed CRC is similar to that of other populations,[2,4] although differences in follow-up time may account for the lower frequency of PSC amongst IBD patients compared to some studies.[42] Nonetheless, the proportion of IBD patients who developed PSC in our cohort is within the expected range quoted by contemporary population-based estimates from Spain (0.6%)[43] and Denmark (2.6%).[3] Moreover, the incidence of PSC-IBD in England mirrors that of the Netherlands (0.5 per 100,000),[2] albeit slightly lower than in Finland, Norway and Sweden.[23,44,45] The reason for these differences are unclear, but potentially explained by variations in follow-up, methodology, and distinct burden of genetic and/or environmental contributors between regions.[46] The median age at transplantation is similar to that presented elsewhere,[47] although we do find an older median age at PSC diagnosis in England compared to certain other countries. This is likely because of our enrolment criteria, which excludes patients diagnosed <18 years of age, and hence those with paediatric age onset PSC. Regardless, data from several independent sources confirm an older age at PSC diagnosis in the UK compared to other European and North American centres.[20,35,48,49] Importantly, we

find that patients diagnosed at non-transplant centres are older at PSC diagnosis compared to those from liver transplant units. Whilst this could indicate a more aggressive disease course for younger patients, it is equally possible that the difference in transplant rates is because of referral bias, whereby patients of older age having a greater comorbidity index are perceived as 'not ideal' transplant candidates, and thus less likely to be referred to transplant centres.

Of importance to highlight is the fact that NHS registry data does not capture laboratory parameters, extent of disease involvement, high-level phenotypic classification (for instance; small duct versus large duct PSC, dominant stenoses), histopathology or prescription level data. This highlights a caveat when interpreting the risks of HPB cancer in PSC. For instance, the proportion of patients who developed HCC is within the expected range quoted for PSC-IBD; whilst greater than that reported from studies in Germany,[50] it is lower than the 2.8% rate quoted in North America.[26] However, studies identifying a higher rate of HCC are almost exclusively of cirrhotic PSC patients.[26] Whilst we suspect the same to be true of HCC patients in our cohort, the absence of data relating to liver fibrosis stage or disease severity highlights a relevant limitation to our study. Similarly, our data suggests that an added risk of pancreatic cancer also exists, but it is possible that a proportion of these are in fact cholangiocarcinomas originating in the distal common bile duct that have infiltrated the pancreatic head. As data relating to the location and histology of pancreatic cancers is limited in most (if not all) published PSC series, our understanding of risk would benefit by linking administrative healthcare and national cancer registries in future studies.[51]

Moreover, as our approach to case finding is reliant on the correctness of clinical coding, we sought the most homogeneous PSC patient cohort to test a hypothesis – namely PSC associated with IBD. We maximised the legitimacy of diagnosis by excluding those with other concomitant liver disorders, and including only those patients who had undergone a

relevant investigation (or intervention) from which a PSC diagnosis can be inferred. Whilst we validate the accuracy of case finding methodology through the host institution, it is plausible that estimates may have still undercut the true incidence of disease in England. As the principled intent was to determine the additive burden of developing PSC amongst individuals with IBD, detailing the clinical course of PSC-non-IBD cases was outside study remit. Indeed, a major limitation is the fact that it was not possible to identify PSC patients without IBD, as the accuracy of coding could not be validated in this context. Future epidemiological studies using this dataset may therefore benefit from the recently introduced ICD11 code for PSC (K83.01) in order to overcome these limitations.

In conclusion, we present prospectively collected epidemiological data across one of the largest nationwide population-based PSC-IBD cohorts. Our study indicates that whilst PSC-IBD is rare, the incidence is rising compared to IBD alone. The onset of PSC confers heightened risks of all HPB malignancies, although annual imaging surveillance may associate with a reduced risk of cancer-related death. Whilst all-cause mortality rates increase with age, younger patients show a disproportionately increased incidence of liver transplantation, PSC-related death and colorectal cancer. Consideration of age at diagnosis should therefore be applied in the stratification of patients for future clinical trials, disease prediction models and prognostic biomarker discovery.

Fig. 1: Study cohort

(**A**) At time of analysis, data were available for n=50,168,647 individuals in England, who had registered contact with healthcare services at any point during the indicated time frame (including obstetric care, day case attendances, clinic appointments, radiological investigations, hospital admissions, investigative / therapeutic procedures, or operations). Following identification of incident IBD cases, and application of indicated exclusions, resulted in 284,560 patients with IBD overall, of which 2,588 developed PSC. (**B**) The IBD patient group (adjusted) was categorised into those receiving a first diagnosis of UC, CD or IBD-U. Notably, an ICD10 code for IBD-U was only introduced in 2012, therefore patients coded as having concomitant CD and UC during follow-up, either concurrently or sequentially, were reclassified as having IBD-U.

Fig. 2: Incidence of IBD and PSC-IBD across England

The incidence per 100,000 population are presented for (**A**) and (**B**) IBD alone, and (**C**) and (**D**) PSC-IBD. Data shown at the start of the study in 2006 in (**A**) and (**C**), and at the end of the study recruitment period in 2016 (**B**) and (**D**). Choropleth maps indicate the rates by geographical region, and hierarchical colour coding indicates the regions of greatest (dark) to lowest incidence (light). Red squares indicate liver transplant units in England.

Fig. 3: Changes in the incidence rate of IBD and PSC-IBD in England

Changes in incidence over the course of our study period are summarised for the whole population of England between 2006 and 2016, for IBD (**A**) and PSC-IBD (**B**).

Fig. 4: Landscape of clinical event rates across our study cohort

The observed clinical event rates are shown for our study cohort per 1,000-patient-years, specifically for those with IBD alone in (**A**); and from the point of IBD and PSC diagnosis in **(B**). *PSC-related deaths do not include HPB cancer (presented separately); **Colonic resections occurring after IBD diagnosis but prior to PSC diagnosis excluded respectively. ***CRC occurring after IBD diagnosis but prior to PSC diagnosis excluded respectively.

Figure 5: All-cause mortality and transplantation / PSC-related clinical events

Kaplan-Meier estimates shown for all-cause mortality in panel (**A**), stratified according to IBD alone versus PSC-IBD groups; adjusted time-dependent hazard ratio of PSC-onset independent of age, sex, race, deprivation, IBD subtype and comorbidities on multivariable analysis: 3.20 (95% CI 3.01-3.40) P<.001. All-cause mortality rates from the point of IBD diagnosis: 20.2 (20.0-20.4) and 39.2 (36.5-42.2) per-1,000-person-years for IBD alone and PSC-IBD, respectively (IRR: 1.9 (CI 1.8-2.1)). All-cause mortality rate from the point of PSC diagnosis in PSC-IBD: 49.8 (46.3-53.5) per-1,000-person-years. Cumulative incidence estimates are shown for liver transplantation or PSC-related death in (**B**), with non-PSC-related deaths handled as competing risk. IBD study groups are stratified according to the presence or absence of PSC. The incidence rate of clinical events in the PSC-IBD group from the point of IBD diagnosis and PSC diagnosis are 15.8 (13.5-18.3) and 20.3 (17.5-23.5), respectively, per-1,000-person-years. The proportion of first clinical events attributable to liver transplantation, PSC-related death, cholangiocarcinoma and non-PSC-related death is shown for the PSC-IBD group specifically in (**C**), stratified by age at PSC diagnosis.

Figure 6: Stratified clinical event rates by age at diagnosis

Clinical event rates are shown for all-cause mortality (**A**), liver transplantation/PSC-related deaths (**B**), colonic resection (**C**), and CRC (**D**); all stratified according to age at diagnosis. Blue circles indicate the patient group with IBD alone and red those with PSC-IBD. Solid circles indicate onset stratified by age at IBD diagnosis, and clear circles indicate onset stratified by age at PSC diagnosis. Incidence rate ratios calculated for PSC-IBD versus IBD alone groups, matched according to age at IBD diagnosis.

Figure 7: Incidence of colorectal cancer

Cumulative incidence estimates are shown for developing CRC, after colectomy events have been taken into account by competing risk analysis in (**A**). Event rates stratified according to the presence or absence of PSC. Incidence rates from the point of IBD diagnosis: 2.9 (95% CI 2.8-3.0) and 6.1 (5.0-7.4) for the IBD alone and PSC-IBD groups, respectively; IRR: 2.1 (1.7-2.6); and from the point of PSC diagnosis: 5.9 (4.7-7.4) per-1,000-patient-years. In (**B**), hazard ratios are presented, illustrating the impact of PSC onset (as a time-dependent covariate) on the development of CRC amongst patients with IBD, independently of age, sex, race, deprivation and comorbidity.

REFERENCES

1 **Weismüller* T, Trivedi* PJ**, Bergquist A, *et al.* Patient Age, Sex, and Inflammatory Bowel Disease Phenotype Associate With Course of Primary Sclerosing Cholangitis. *Gastroenterology* 2017;**152**:1975–84.

2 Boonstra K, Weersma RK, van Erpecum KJ, *et al.* Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013;**58**:2045–2055.

3 **Sørensen JØ, Nielsen OH,** Andersson M, *et al.* Inflammatory bowel disease with primary sclerosing cholangitis: A Danish population-based cohort study 1977-2011. *Liver Int* 2018;**38**:532–41.

4 Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing Risk of Colorectal Cancer in Patients With Inflammatory Bowel Disease Over 30 Years. *Gastroenterology* 2012;**143**:375-381.e1.

5 Olén O, Askling J, Sachs MC, *et al.* Mortality in adult-onset and elderly-onset IBD: a nationwide register-based cohort study 1964–2014. *Gut* 2020;**69**:453–61.

6 Goode EC, Clark AB, Mells GM, *et al.* Factors Associated With Outcomes of Patients With Primary Sclerosing Cholangitis and Development and Validation of a Risk Scoring System. *Hepatology* 2019;**69**:2120–35.

7 de Valle MB, Björnsson E, Lindkvist B. Mortality and cancer risk related to primary sclerosing cholangitis in a Swedish population-based cohort. *Liver Int* 2012;**32**:441–8.

8 Rupp C, Rössler A, Zhou T, *et al.* Impact of age at diagnosis on disease progression in patients with primary sclerosing cholangitis. *United Eur Gastroenterol J* 2018;**6**:255–62.

9 Lindström L, Hultcrantz R, Boberg KM, Friis–Liby I, Bergquist A. Association Between Reduced Levels of Alkaline Phosphatase and Survival Times of Patients With Primary Sclerosing Cholangitis. *Clin Gastroenterol Hepatol* 2013;**11**:841–6.

10 Rupp C, Rössler A, Halibasic E, *et al.* Reduction in alkaline phosphatase is associated with longer survival in primary sclerosing cholangitis, independent of dominant stenosis. *Aliment Pharmacol Ther* 2014;**40**:1292–301.

11 Gregorio GV, Portmann B, Karani J, *et al.* Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. *Hepatology* 2001;**33**:544–53.

12 Goldberg D, Levy C, Yimam K, *et al.* Primary Sclerosing Cholangitis is not Rare Among Blacks in a Multi-Center North American Consortium. *Clin Gastroenterol Hepatol* 2018;**16**:591–3.

13 England population mid-year estimate - Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/enpop

14 Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017;**46**:1093–1093i.

15 Holt PJE, Poloniecki JD, Thompson MM. Multicentre study of the quality of a large administrative data set and implications for comparing death rates. *BJS* 2012;**99**:58–65.

16 Burns EM, Rigby E, Mamidanna R, *et al.* Systematic review of discharge coding accuracy. *J Public Health* 2012;**34**:138–48.

17 Britton A, Milne B, Butler T, *et al.* Validating self-reported strokes in a longitudinal UK cohort study (Whitehall II): Extracting information from hospital medical records versus the Hospital Episode Statistics database. *BMC Med Res Methodol* 2012;**12**:83.

18 Vallance AE, vanderMeulen J, Kuryba A, *et al.* Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases. *Br J Surg* 2017;**104**:918–25.

19 Parisi R, Webb RT, Carr MJ, *et al.* Alcohol-Related Mortality in Patients With Psoriasis: A Population-Based Cohort Study. *JAMA Dermatol* 2017;**153**:1256–62.

20 Card TR, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: A population-based cohort study. *J Hepatol* 2008;**48**:939–44.

21 Lindkvist B, Benito de Valle M, Gullberg B, Björnsson E. Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden. *Hepatology* 2010;**52**:571–7.

22 Olén O, Erichsen R, Sachs MC, *et al.* Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study. *Lancet Gastroenterol Hepatol* 2020;

23 Olén O, Erichsen R, Sachs MC, *et al.* Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. *Lancet* 2020;**395**:123–31.

24 Everhov ÅH, Sachs MC, Malmborg P, *et al.* Changes in inflammatory bowel disease subtype during follow-up and over time in 44,302 patients. *Scand J Gastroenterol* 2019;**54**:55–63.

25 Claessen MMH, Vleggaar FP, Tytgat KMAJ, Siersema PD, van Buuren HR. High lifetime risk of cancer in primary sclerosing cholangitis. *J Hepatol* 2009;**50**:158–64.

26 **Ali AH, Tabibian JH,** Nasser-Ghodsi N, *et al.* Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. *Hepatology* 2018;**67**:2338–51.

27 National life tables: England - Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables

28 Jeong H-W, Jung K-W, Kim S-O, *et al.* Early postoperative weight gain is associated with increased risk of graft failure in living donor liver transplant recipients. *Sci Rep* 2019;**9**.

29 Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med* 2008;**3**:17.

30 Lang T. Documenting research in scientific articles: Guidelines for authors:3. Reporting multivariate analyses. *Chest* 2007;**131**:628–32.

31 Newcombe PJ, Connolly S, Seaman S, Richardson S, Sharp SJ. A two-step method for variable selection in the analysis of a case-cohort study. *Int J Epidemiol* 2018;**47**:597–604.

32 Mah JM, DeWit Y, Djerboua M, Menard A, Booth CM, Flemming JA. Association Between Institutional Factors and Long-Term Survival Following Transjugular Intrahepatic Portosystemic Shunt. *Hepatol Commun* 2019;**3**:838–46.

33 Bergquist A, Ekbom A, Olsson R, *et al.* Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002;**36**:321–7.

34 Halliday JS, Djordjevic J, Lust M, *et al.* A unique clinical phenotype of primary sclerosing cholangitis associated with Crohn's disease. *J Crohns Colitis* 2012;**6**:174–81.

35 Braden B, Halliday J, Aryasingha S, *et al.* Risk for colorectal neoplasia in patients with colonic Crohn's disease and concomitant primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2012;**10**:303–8.

36 Boonstra K, van Erpecum KJ, van Nieuwkerk KMJ, *et al.* Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:2270–6.

37 **Ji S-G, Juran BD,** Mucha S, *et al.* Genome-wide association study of primary sclerosing cholangitis identifies new risk loci and quantifies the genetic relationship with inflammatory bowel disease. *Nat Genet* 2017;**49**:269–73.

38 Khan N, Trivedi C, Shah Y, Cole E, Lewis J, Yang Y-X. The Natural History of Newly Diagnosed Ulcerative Colitis in Patients with Concomitant Primary Sclerosing Cholangitis. *Inflamm Bowel Dis* 2018;**24**:2062–7.

39 Navaneethan U, Kochhar G, Venkatesh PGK, *et al.* Duration and severity of primary sclerosing cholangitis is not associated with risk of neoplastic changes in the colon in patients with ulcerative colitis. *Gastrointest Endosc* 2012;**75**:1045-1054.e1.

40 Nordenvall C, Olén O, Nilsson PJ, *et al.* Colectomy prior to diagnosis of primary sclerosing cholangitis is associated with improved prognosis in a nationwide cohort study of 2594 PSC-IBD patients. *Aliment Pharmacol Ther* 2018;**47**:238–45.

41 **Shah SC, Ten Hove JR,** Castaneda D, *et al.* High Risk of Advanced Colorectal Neoplasia in Patients With Primary Sclerosing Cholangitis Associated With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2018;**16**:1106-1113.e3.

42 Lunder AK, Hov JR, Borthne A, *et al.* Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in Patients With Long-term Inflammatory Bowel Disease. *Gastroenterology* 2016;**151**:660-669.e4.

43 Guerra I, Bujanda L, Castro J, *et al.* Clinical Characteristics, Associated Malignancies and Management of Primary Sclerosing Cholangitis in Inflammatory Bowel Disease Patients: A Multicentre Retrospective Cohort Study. *J Crohns Colitis* 2019;**13**:1492–500.

44 Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: A systematic review. *J Hepatol* 2012;**56**:1181–8.

45 Barner-Rasmussen N, Pukkala E, Jussila A, Färkkilä M. Epidemiology, risk of malignancy and patient survival in primary sclerosing cholangitis: a population-based study in Finland. *Scand J Gastroenterol* 2020;**55**:74–81.

46 Invernizzi P. Geoepidemiology of autoimmune liver diseases. *J Autoimmun* 2010;**34**:J300-306.

47 Trivedi PJ, Scalera I, Slaney E, *et al.* Clinical outcomes of donation after circulatory death liver transplantation in primary sclerosing cholangitis. *J Hepatol* 2017;**67**:957–65.

48 Kingham JGC, Kochar N, Gravenor MB. Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. *Gastroenterology* 2004;**126**:1929–30.

49 Liang H, Manne S, Shick J, Lissoos T, Dolin P. Incidence, prevalence, and natural history of primary sclerosing cholangitis in the United Kingdom. *Medicine (Baltimore)* 2017;**96**.

50 **Zenouzi R, Weismüller TJ,** Hübener P, *et al.* Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis. *Clin Gastroenterol Hepatol* 2014;**12**:1733–8.

51 Luchini C, Brosens LAA, Wood LD, *et al.* Comprehensive characterisation of pancreatic ductal adenocarcinoma with microsatellite instability: histology, molecular pathology and clinical implications. *Gut* 2020;

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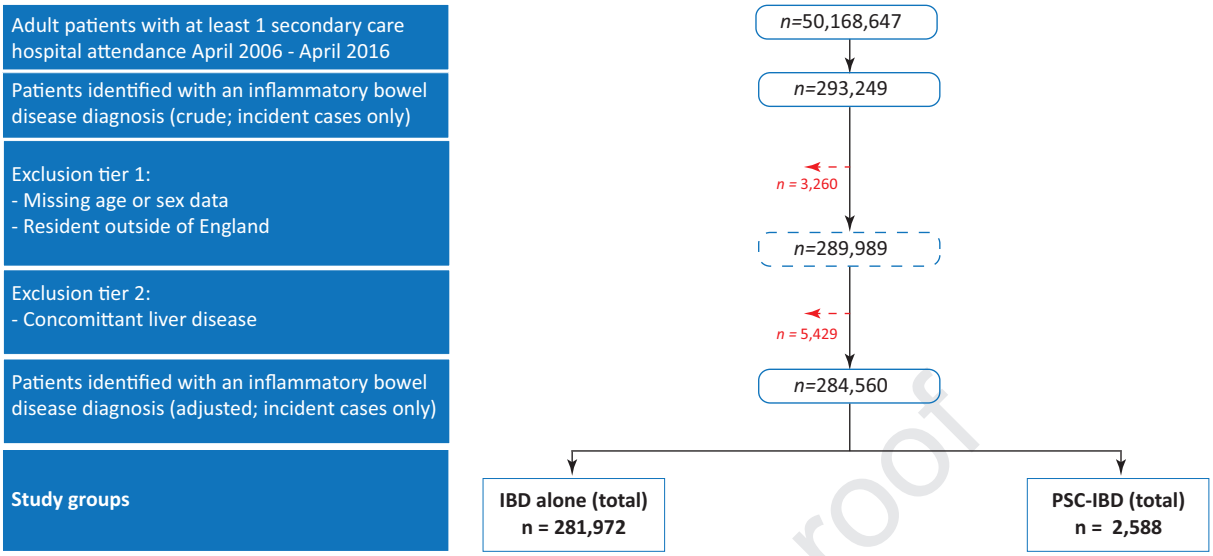

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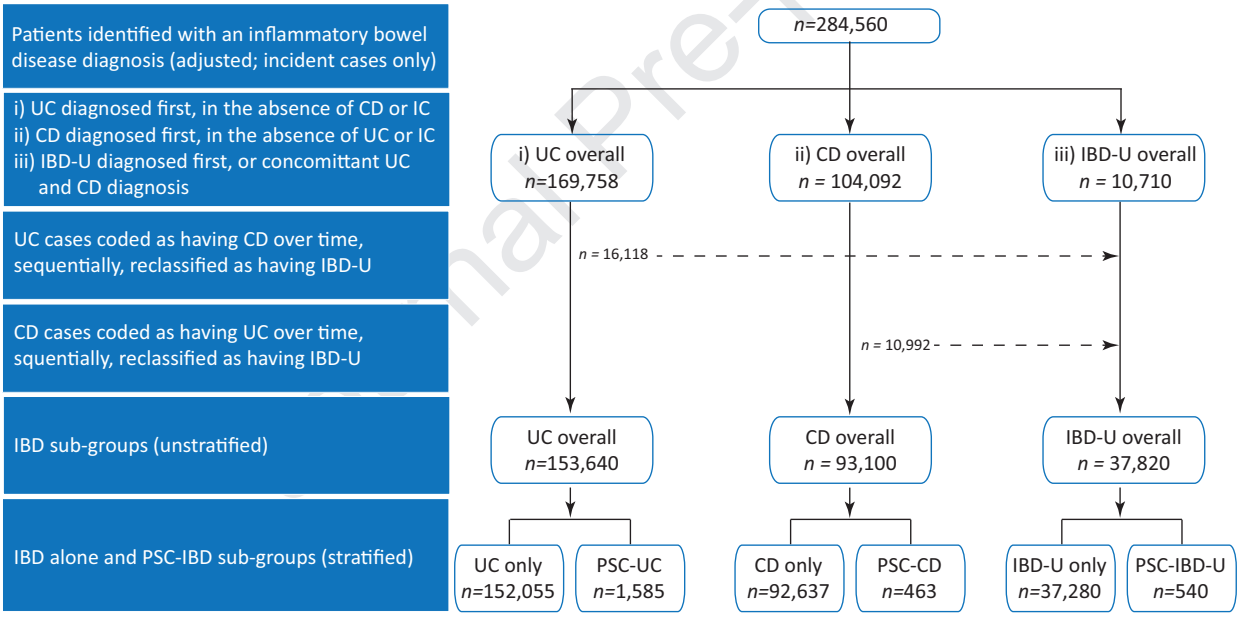

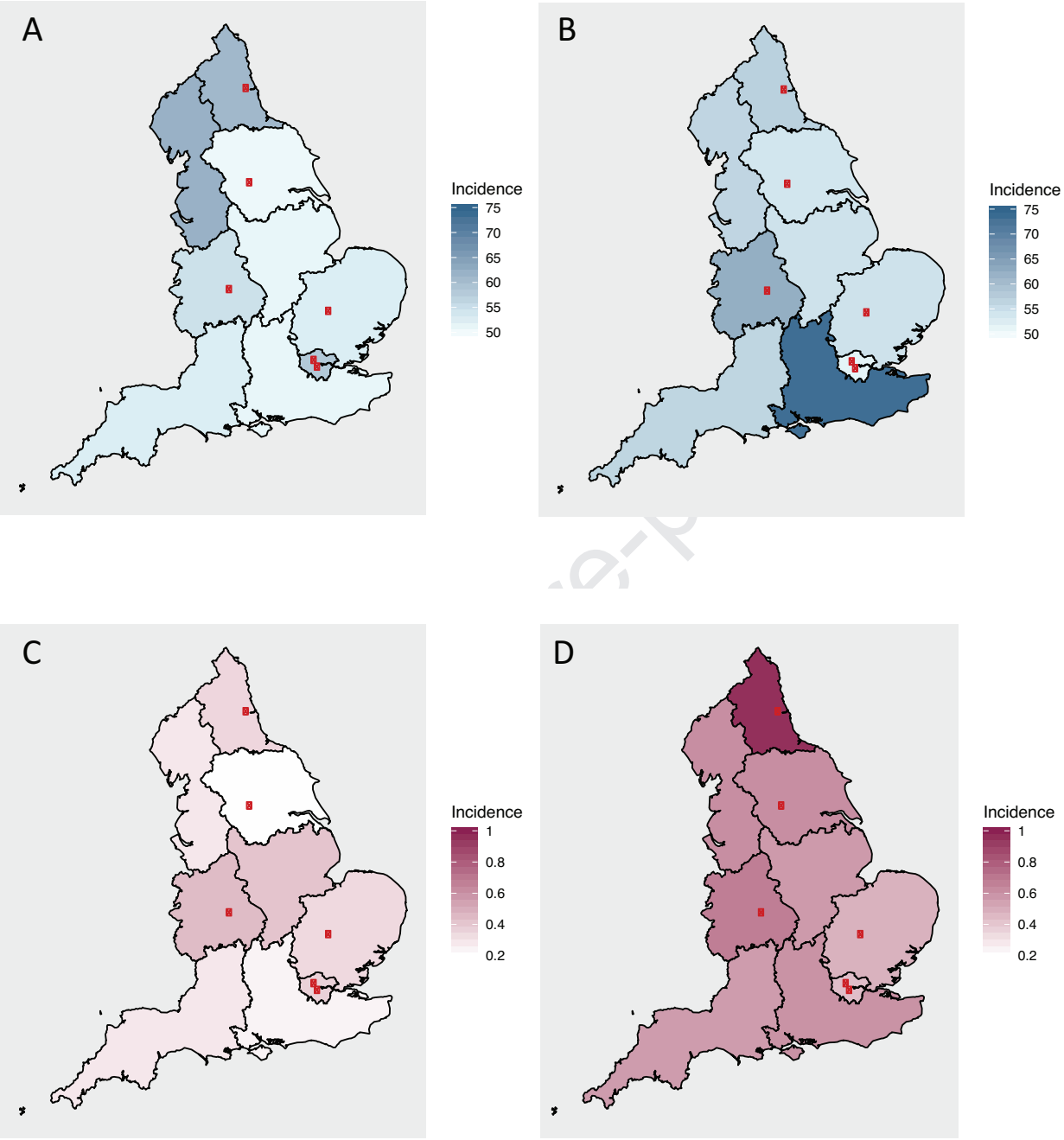
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