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Risk of venous thromboembolism in immune-mediated inflammatory diseases: a UK matched cohort study

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ABSTRACT

Objectives To describe the risk of venous thromboembolism (VTE), and risk factors for VTE, in people with immune-mediated inflammatory diseases (IMID) (ulcerative colitis, Crohn's disease (CD), rheumatoid arthritis (RA) and psoriatic arthritis (PsA)), compared with a matched control population.

Methods A total of 53 378 people with an IMID were identified over 1999–2019 in the UK Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database and were matched to 213 512 people without an IMID. The association between the presence of any IMID, and each IMID separately, and risk of VTE was estimated using unadjusted and multivariable-adjusted Cox proportional hazards models. The prevalence of VTE risk factors, and associations between VTE risk factors and risk of VTE, were estimated in people with and without an IMID.

Results People with an IMID were at increased risk of VTE (adjusted HR [aHR] 1.46, 95% CI 1.36,1.56), compared with matched controls. When assessing individual diseases, risk was increased for CD (aHR 1.74, 95% CI 1.45 to 2.08), ulcerative colitis (aHR 1.27, 95% CI 1.10 to 1.45) and RA (aHR 1.54, 95% CI 1.40 to 1.70) but there was no evidence of an association for PsA (aHR 1.21, 95% CI 0.96 to 1.52). In people with an IMID, independent risk factors for VTE included male sex, overweight/obese body mass index, current smoking, history of fracture, and, across study follow-up, abnormal platelet count.

Conclusions VTE risk is increased in people with IMIDs. Routinely available clinical information may be helpful to identify individuals with an IMID at increased future risk of VTE.

Observational study registration number Clinicaltrials.gov (NCT03835780).

Key messages

What is already known about this subject?

- Risk of venous thromboembolism (VTE) is increased in people with immune-mediated inflammatory diseases (IMIDs; ulcerative colitis, Crohn's disease, rheumatoid arthritis and psoriatic arthritis) compared with the general population, but differences in VTE risk have not been systematically compared across these conditions.
- The magnitude and relevance of VTE risk from traditional VTE risk factors (such as obesity, fractures, and use of specific medications) in IMIDs is unknown.

What does this study add?

- In over 266 890 people, risk of VTE was increased to a similar degree in people with ulcerative colitis, Crohn's disease and rheumatoid arthritis. For psoriatic arthritis, risk was not significantly increased, likely due to lack of statistical power.
- Risk factors identified in people with IMIDs include male sex, overweight/obese BMI, smoking, fractures, use of corticosteroids and oral contraceptives, and abnormal platelet count.

How might this impact on clinical practice?

- Knowledge of specific risk factors in people with immune-mediated inflammatory diseases can help identify those susceptible to developing VTE.

INTRODUCTION

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), is relatively common, with an incidence in the general population of around 3 cases per 1000 patient years.[1] It is associated with significant morbidity and mortality.[2 3]

Inflammation increases the risk of VTE,[4] and observational data demonstrate higher VTE rates in individuals with immune-mediated inflammatory diseases (IMID) including ulcerative colitis (UC), Crohn's disease (CD) and rheumatoid arthritis (RA) compared with the general population.[5–9] Evidence for VTE risk in other inflammatory diseases, including psoriatic arthritis (PsA) is more limited.[6] Risk factors for VTE have been well described in the general population, and include obesity, fractures, surgery, use of oral corticosteroids and hormone therapies.[10 11] and high platelet count which has been reported to be a risk factor for VTE in hospital inpatients,[12] and is recognised as

a marker of inflammation in inflammatory bowel disease and RA.[13 14] There has however been little systematic interrogation of whether VTE risk factors convey the same risk in individuals with and without an IMID.[15]

In this study, we set out to use a large UK primary care database to establish the excess risk of VTE in people with an IMID (UC, CD, RA and PsA) compared with a control population without any of these conditions. We then compared the prevalence of traditional VTE risk factors in people with and without an IMID, and the associations between these features and future risk of VTE.

METHODS

Study design

We performed a cohort study using matched populations to compare VTE risk in adults with an IMID (UC, CD, RA and PsA) and controls between 1999 and 2018 inclusive, using UK population-based primary care data.

Data source

Data were sourced from the Royal College of General Practitioners Research (RCGP) and Surveillance Centre (RSC) database. RCGP RCS derives data from a representative network of general practices distributed across England, currently covering a registered population of 2 million people.[16] RCGP RSC contains information on demographics, clinical features and diagnoses, laboratory tests and prescriptions, and studies using RCGP RSC data have been published across a range of chronic diseases.[17–20]

Study population

Adults (aged ≥18) were eligible for inclusion if registered with a general practice between January 1, 1999 and December 31, 2018, with at least one consultation over that period (to minimise the impact of 'ghost' patients), and no history of VTE.

Definition of the exposed cohort with IMID

The exposed cohort was defined as all individuals with an existing or incident diagnosis of UC, CD, RA or PsA in the RCGP RSC database over the study period. UC, CD and RA were identified using Read diagnostic codes and algorithms previously validated by review of individual patient records or collection of questionnaires from general practitioners in UK primary care studies.[21–25] In the absence of a validated method to identify the presence of PsA from UK primary care data, this was identified using a Read code list generated in accordance with published guidance.[26 27] The index date for start of follow-up for exposed individuals began on the latest of the date of diagnosis indicated by first diagnostic code, January 1, 1999, or 180 days after practice registration.

Definition of the matched unexposed cohort

People with an IMID were matched at their index date with four unexposed individuals at general practice level by current age (per year), sex and years since practice registration (nearest neighbour matching, with replacement). The eligible pool of unexposed individuals at each index date comprised individuals registered at that date with no history of an IMID and at least 1 year of follow-up in RCGP RCS (to minimise the risk they had a non-recorded existing IMID diagnosis). Follow-up for each matched individual started on the index date of their matched case. Individuals with an incident diagnosis of an IMID during the study period were included in the pool of eligible unexposed individuals, but if matched were censored on the date of their diagnosis of an IMID; that is, these individuals were eligible to contribute to unexposed person time before their diagnosis of an IMID. Follow-up for each individual ended at the earliest of the study end-date (December 31, 2018), the date an individual was transferred from an included practice, date of death or the date an individual developed an outcome of interest.

Outcome measures

The primary outcome was a diagnosis of VTE (a composite of PE or DVT). The secondary outcomes were individual diagnoses of PE and DVT. When both PE and DVT occurred on the same date this was classified as PE. Outcomes were identified using updated Read code lists previously validated by review of patient records and provision of general practitioner questionnaires.[28] Risk of each outcome was compared between individuals with an IMID and the matched control population, and between individuals with UC, CD, RA and PsA and their matched counterparts.

Recorded characteristics and VTE risk factors

Baseline features comprised sociodemographic characteristics, clinical VTE risk factors, comorbidities and medication use. VTE risk factors were selected based on existing literature demonstrating an established association with VTE[6 10] and clinical expertise. Clinical VTE risk factors were body mass index (BMI), smoking status, alcohol use, evidence of reduced mobility, thrombophilia, fracture of the lower limb and family history of VTE. Socioeconomic status was defined using index of multiple deprivation (IMD), the official national measure of socioeconomic status in the UK.[29] Ethnicity was extracted from the primary care record and grouped into major UK ethnic groups: white, black, Asian, mixed and others.[30] BMI, smoking status and alcohol use were defined using the most recently recorded data prior to the index date. Diagnostic codes were used to define the following baseline comorbidities: hypertension, hyperlipidaemia, type 2 diabetes, peripheral vascular disease, cardiovascular disease (atrial fibrillation, angina, myocardial infarction, congestive heart failure), stroke, malignancy, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) (stages 3–5), liver disease and thrombophilia. Type 2 diabetes was identified using an algorithm developed for use within RCGP RSC.[31] Read codes used

to describe cardiovascular disease within RCGP RSC have been previously reported.[30 32] Platelet count measures were extracted at baseline (the most recent value up to 2 years prior to the index date) and across study follow-up.

We examined the following medications commonly used for the management of IMIDs: non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, non-biologic immunosuppressant medications and biologic therapies recorded in primary care. We also examined hormone therapy (hormonal contraceptives, hormone replacement therapy (HRT)), antiplatelet agents (aspirin or ADP receptor inhibitors), warfarin, direct oral anticoagulants (DOACs), and statins. Hormonal contraceptives comprised only combined oestrogen and progestogen preparations; progesterone only contraceptives were not included as these preparations are not associated with VTE.[33] HRT comprised systemic oestrogen only preparations. Active prescribing was defined as an issued prescription in the 3 months preceding and/or 1 month after the index date.

Statistical analyses

We estimated the risk of VTE, the primary outcome, using unadjusted Cox proportional hazards models, stratified by matched set (exposed cohort vs unexposed cohort), to provide overall HRs with 95% CI for the association. Models were subsequently adjusted for all sociodemographic, clinical and VTE risk factors, as described above, in multivariable analysis. We then repeated the same analyses for PE and DVT as separate endpoints and each condition (UC, CD, RA and PsA) separately. Proportional hazards assumptions for each model were checked graphically by plotting Schoenfeld residuals.

VTE risk factors

We used multivariable Cox models to examine the influence of baseline-recorded characteristics and VTE risk factors on risk of VTE. Models were run separately in cohorts with and without an IMID. If baseline platelet count was significant in the model, we proposed to explore the impact of changing platelet count over study follow-up on VTE risk in time-updated analysis, by including platelet count as a time-updated exposure in unadjusted and multivariable-adjusted Cox models. Platelet count was both categorised as low ($<150\times10^9$/L), normal ($150–400\times10^9$/L) or high ($>400\times10^9$/L), and analysed continuously using a restricted cubic spline prespecified with 3 knots.

Sensitivity analysis

Sensitivity to the introduction of the Quality and Outcomes Framework (QOF), an incentivised programme to monitor clinical and health improvement indicators for general practice that rewards completeness of electronic coding,[34] was tested by repeating the main analyses with the study follow-up beginning on January 1, 2004. All statistical analyses used R (version 3.4.1).

RESULTS

Study population

A total of 53 378 people with an IMID were included, of whom 14 182 (26%) had a first diagnosis of UC, 9489 (18%) CD, 23 410 (44%) RA and 6297 (12%) PsA (table 1). Matched controls comprised 213 512 people without an IMID of interest. Average study follow-up was 8.2 (SD 6.2) years.

Baseline characteristics

People with an IMID were similar in characteristics to their matched counterparts (table 1). Several comorbidities were more common in the exposed group including type 2 diabetes, COPD and chronic liver disease. BMI was similar although differences were observed between individuals with an IMID; more people with PsA were obese (32.9%) than people with UC (16.7%) or CD (14.6%), and more people with CD were underweight (5.6%) compared with other IMIDs (range 1.0–2.6%). Use of NSAIDs, corticosteroids and immunosuppressive medications were, as expected, considerably higher in the IMID group.

Risk of VTE

Unadjusted VTE event rates were higher in the IMID group (34.9 [95% CI 33.2 to 36.7] per 10 000 person-years) compared with controls (21.7 [95% CI 21.0 to 22.4] per 10 000 person-years, p<0.001) (figure 1); 1532 (2.9%) people with an IMID developed VTE compared with 3804 (1.8%) controls. Table 2 reported study follow-up and outcome events for the primary VTE outcome and the secondary outcomes of PE and DVT.

In the primary outcome analysis, adjusted models demonstrated an association between UC, CD and RA and the development of VTE, with the strength of association greatest for people with CD. Associations were consistent in analyses of separate PE and DVT endpoints (table 2, online supplemental figure 1). For PsA, a significant increase in risk was seen only for the DVT endpoint (table 2). Sensitivity analysis exploring the impact of QOF demonstrated primary results were consistent with follow-up beginning in 2004 (online supplemental table 1).

Table 3 shows associations between record characteristics and risk of developing VTE in people with an IMID and matched controls. Increasing age at entry, being overweight/obese and thrombophilia history were associated with an increased risk of VTE in both groups. Associations between VTE risk factors and risk of VTE differed, with male sex, history of fracture, current smoking and alcohol abstinence associated with an increased VTE risk only in the IMID group. Reduced mobility (increased risk) and Asian ethnicity (decreased risk) were risk factors only in controls. COPD, chronic liver

Table 1 Covariate summary statistics for individuals with and without an immune-mediated inflammatory disease (IMID)

	Without IMID n=213 512	With IMID n=53 378	Ulcerative colitis n=14 182	Crohn's disease n=9489	Psoriatic arthritis n=6297	Rheumatoid arthritis n=23 410
	Sociodemographic characteristics					
Age at study entry (years) Mean (SD)	51.7 (17.8)	51.6 (17.4)	47.2 (17.0)	41.8 (16.6)	49.2 (13.8)	59.0 (15.5)
Male sex (n (%))	85 383 (40.0)	21 291 (39.9)	7126 (50.2)	4296 (45.3)	3093 (49.1)	6776 (28.9)
Time since GP practice registration (years). Mean (SD)	9.1 (12.1)	9.1 (12.3)	7.8 (11.1)	7.5 (10.6)	9.2 (11.6)	10.4 (13.5)
Ethnicity (n (%))						
Asian	9569 (5.8)	2434 (5.7)	724 (6.5)	347 (4.7)	249 (4.9)	1114 (5.9)
Black	4121 (2.5)	643 (1.5)	127 (1.1)	91 (1.2)	22 (0.4)	403 (2.1)
Mixed	1483 (0.9)	346 (0.8)	85 (0.8)	67 (0.9)	44 (0.9)	150 (0.8)
Other	1448 (0.9)	296 (0.7)	93 (0.8)	54 (0.7)	26 (0.5)	123 (0.7)
White	148 832 (90.0)	38 708 (91.2)	10 099 (90.8)	6763 (92.4)	4727 (93.3)	17 119 (90.5)
Missing	48 059 (22.5)	10 951 (20.5)	3054 (21.5)	2167 (22.8)	1229 (19.5)	4501 (19.2)
Index of multiple deprivation quintile (n (%))						
1 (most deprived)	29 144 (13.6)	7293 (13.7)	1689 (11.9)	1324 (14.0)	803 (12.8)	3477 (14.9)
2	32 323 (15.1)	8274 (15.5)	2109 (14.9)	1518 (16.0)	919 (14.6)	3728 (15.9)
3	41 379 (19.4)	10 570 (19.8)	2680 (18.9)	1901 (20.0)	1250 (19.9)	4739 (20.2)
4	50 087 (23.5)	12 439 (23.3)	3475 (24.5)	2186 (23.0)	1452 (23.1)	5326 (22.8)
5 (least deprived)	56 209 (26.3)	13 684 (25.6)	3963(27.9)	2350 (24.8)	1720 (27.3)	5651 (24.1)
IMD not recorded	4370 (2.0)	1118 (2.1)	266 (1.9)	210 (2.2)	153 (2.4)	489 (2.1)
VTE risk factors (n (%))						
BMI (kg/m^2)						
Underweight (≤18.5)	4704 (2.2)	1571 (2.9)	368 (2.6)	536 (5.6)	60 (1.0)	607 (2.6)
Normal weight (18.5–25)	73 675 (34.5)	19 280 (36.1)	5721 (40.3)	4225 (44.5)	1576 (25.0)	7758 (33.1)
Overweight (25–30)	67 076 (31.4)	16 664 (31.2)	4352 (30.7)	2446 (25.8)	2131 (33.8)	7735 (33.0)
Obese (≥30)	44 303 (20.7)	11 611 (21.8)	2367 (16.7)	1386 (14.6)	2071 (32.9)	5787 (24.7)
BMI not recorded	23 754 (11.1)	4252 (8.0)	1374 (9.7)	896 (9.4)	459 (7.3)	1523 (6.5)
Smoking status						
Non-smoker	94 985 (44.5)	21 620 (40.5)	6328 (44.6)	3917 (41.3)	2522 (40.1)	8853 (37.8)
Current smoker	52 035 (24.4)	13 070 (24.5)	2574 (18.1)	2914 (30.7)	1519 (24.1)	6063 (25.9)
Ex-smoker	63 798 (29.9)	18 315 (34.3)	5147 (36.3)	2551 (26.9)	2232 (35.4)	8385 (35.8)
Smoking status not recorded	2694 (1.3)	373 (0.7)	133 (0.9)	107 (1.1)	24 (0.4)	109 (0.5)
Alcohol intake						

Continued

Table 1 Continued

	Without IMID n=213 512	With IMID n=53 378	Ulcerative colitis n=14 182	Crohn's disease n=9489	Psoriatic arthritis n=6297	Rheumatoid arthritis n=23 410
	Sociodemographic characteristics					
Non-drinker	36 623 (17.2)	10 608 (19.9)	2371 (16.7)	1798 (18.9)	1035 (16.4)	5404 (23.1)
Within limits	117 939 (55.2)	29 316 (54.9)	7727 (54.5)	4917 (51.8)	3508 (55.7)	13 164 (56.2)
Over recommended l imits	30 096 (14.1)	7145 (13.4)	2083 (14.7)	1228 (12.9)	1067 (16.9)	2767 (11.8)
Alcoholism	3438 (1.6)	823 (1.5)	217 (1.5)	138 (1.5)	128 (2.0)	340 (1.5)
Alcohol intake not recorded	25 416 (11.9)	5486 (10.3)	1784 (12.6)	1408 (14.8)	559 (8.9)	1735 (7.4)
Reduced mobility	3562 (1.7)	1022 (1.9)	184 (1.3)	117.2 (1.2)	85 (1.3)	636 (2.7)
Thrombophilia	151 (0.1)	49 (0.1)	11 (0.1)	11 (0.1)	7 (0.1)	20 (0.1)
Family history of VTE	403 (0.2)	113 (0.2)	28 (0.2)	27 (0.3)	21 (0.3)	37 (0.2)
History of fracture	14 542 (6.8)	3887 (7.3)	978 (6.9)	593 (6.2)	467 (7.4)	1849 (7.9)
Platelet count category (n (%))						
Low (<150×10^9/L)	2393 (1.1)	635 (1.2)	141 (1.0)	100 (1.1)	85 (1.3)	309 (1.3)
Normal (150–400×10^9/L)	83 707 (39.2)	29 655 (55.6)	7251 (51.1)	4610 (48.6)	3910 (62.1)	13 884 (59.3)
High (>400×10^9/L)	3111 (1.5)	4204 (7.9)	908 (6.4)	1158 (12.2)	293 (4.7)	1845 (7.9)
Missing	124 301 (58.2)	18 884 (35.4)	5882 (41.5)	3621 (38.2)	2009 (31.9)	7372 (31.5)
Comorbidity (n (%))						
Hypertension	43 296 (20.3)	11 298 (21.2)	2206 (15.2)	1043 (10.7)	1334 (21.2)	6809 (29.1)
Hyperlipidaemia	51 377 (24.1)	12 241 (22.9)	2606 (18.4)	1243 (13.1)	1542 (24.5)	6850 (29.3)
Type 2 diabetes	12 423 (5.8)	3466 (6.5)	714 (5.0)	307 (3.2)	452 (7.2)	1993 (8.5)
Peripheral vascular disease	1948 (0.9)	530 (1.0)	98 (0.7)	61 (0.6)	59 (0.9)	312 (1.3)
Atrial fibrillation	4569 (2.1)	1227 (2.3)	251 (1.8)	118 (1.2)	79 (1.3)	779 (3.3)
Myocardial infarction	4325 (2.0)	1280 (2.4)	286 (2.0)	125 (1.3)	102 (1.6)	767 (3.3)
Stroke	3344 (1.6)	818 (1.5)	164 (1.2)	99 (1.0)	66 (1.0)	489 (2.1)
Heart failure	2276 (1.1)	654 (1.2)	129 (0.9)	57 (0.6)	39 (0.6)	429 (1.8)
Chronic kidney disease stages 3–5	6936 (3.2)	1819 (3.4)	294 (2.1)	168 (1.8)	131 (2.1)	1226 (5.2)
Chronic obstructive pulmonary disease	5628 (2.6)	2039 (3.8)	359 (2.5)	225 (2.4)	130 (2.1)	1325 (5.7)
Chronic liver disease	992 (0.5)	559 (1.0)	208 (1.5)	87 (0.9)	61 (1.0)	203 (0.9)
Malignancy	8703 (4.1)	2169 (4.1)	455 (3.2)	238 (2.5)	211 (3.4)	1265 (5.4)
Medication use (n (%))						
NSAID use	49 829 (23.3)	20 385 (38.2)	2621 (18.5)	1754 (18.5)	3509 (55.7)	12 501 (53.4)
Corticosteroid use	10 438 (4.9)	13 166 (24.7)	3283 (23.1)	2734 (28.8)	893 (14.2)	6256 (26.7)

Continued

Table 1 Continued

	Without IMID n=213 512	With IMID n=53 378	Ulcerative colitis n=14 182	Crohn's disease n=9489	Psoriatic arthritis n=6297	Rheumatoid arthritis n=23 410
	Sociodemographic characteristics					
Immunosuppressive medication (in primary care)	1654 (0.8)	18 248 (34.2)	1830 (12.9)	2338 (24.6)	2801 (44.5)	11 279 (48.2)
Statin use	29 735 (13.9)	7655 (14.3)	1378 (9.7)	674 (7.1)	839 (13.3)	4764 (20.4)
Antiplatelet therapy	17 620 (8.3)	4484 (8.4)	871 (6.1)	413 (4.4)	416 (6.6)	2784 (11.9)
Warfarin	2842 (1.3)	760 (1.4)	150 (1.1)	72 (0.8)	49 (0.8)	489 (2.1)
Direct oral anticoagulants	939 (0.4)	288 (0.5)	49 (0.3)	25 (0.3)	21 (0.3)	193 (0.8)
Hormone replacement therapy	4283 (2.0)	1359 (2.5)	204 (1.4)	196 (2.1)	206 (3.3)	753 (3.2)
Oral contraceptive use	9681 (4.5)	2434 (4.6)	856 (6.0)	817 (8.6)	215 (3.4)	546 (2.3)

BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; VTE, venous thromboembolism.

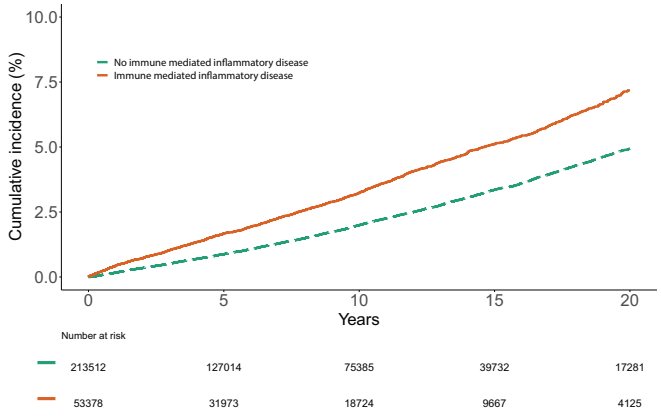

Figure 1 Cumulative incidence of VTE in individuals with an immune-mediated inflammatory diseases compared with matched controls. Individuals with both DVT and PE on the same day (n=180) classified as having had a PE. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

disease, peripheral vascular disease and family history of VTE were all associated with an increased risk of VTE only in controls. CKD was associated with increased risk of VTE only in people with an IMID. For medication, warfarin, DOACs, corticosteroids, and, in females, use of oral contraceptives, were associated with an increased risk of VTE in both groups. Statins (decreased risk) and NSAIDs (increased risk) were risk factors only in the IMID group. Risk of VTE was increased in people with an IMID and low number of platelets ($<150\times10^9$/L), and in people without an IMID and high number of platelets ($>400\times10^9$/L). In the IMID group, relative to people with UC, risk of VTE was increased in CD only.

Association of platelet count across study follow-up with risk of VTE

To further interrogate the relationship between baseline platelets and VTE in each group, a time-updated analysis was undertaken. Individuals with at least one platelet count were included in the analysis (96% of those with an IMID and 75% of those without an IMID). Platelet count across study follow-up was initially categorised as low, normal or high (table 4). High and low platelet counts were more common in individuals with an IMID (proportion of individuals with 1+ one high platelet count 29.2%, low count 10.9%) compared with those without an IMID (high count 11.5%, low count 7.4%).

Higher time-varying platelet counts were associated with an increased risk of VTE in individuals with and without an IMID (table 4, figure 1). Figure 2 confirms the association between time-updated lower and higher platelet count and higher risk of VTE in both groups when modelling platelet count as a non-linear continuous variable; a positive association was also seen for platelet counts $<200\times10^9$/L.

DISCUSSION

Our study shows that VTE is more common in people with UC, CD, RA, and PsA compared with people without these IMIDs. UC, CD and RA were independently associated to a similar degree with increased risk of VTE, while the wide CI for PSA suggests we lacked statistical power to detect a difference in this group. Established risk factors for VTE had a similar prevalence in people with an IMID compared with the wider population, and similar strengths of association were observed in people with and without an IMID for higher age, being overweight or obese, thrombophilia, malignancy, and corticosteroid use. Notable differences were also observed; only in people with an IMID did we find evidence that

Table 2 Associations between immune-mediated inflammatory diseases (IMID) and risk of VTE in unadjusted and multivariable analysis

	No.	Patient years at risk	Events	HR (95% CI) Unadjusted	HR (95% CI) Adjusted
Primary outcome: risk of VTE					
All immune mediated inflammatory diseases					
Controls	213 512	1 756 381	3804	1.00 (ref)	1.00 (ref)
Immune mediated inflammatory disease	53 378	438 743	1532	**1.62 (1.52, 1.71)**	**1.46 (1.36, 1.56)**
Ulcerative colitis					
Controls	56 728	476 506	956	1.00 (ref)	1.00 (ref)
Ulcerative colitis	14 182	119 635	335	**1.40 (1.23, 1.58)**	**1.27 (1.10, 1.45)**
Crohn's disease					
Controls	37 956	307 373	460	1.00 (ref)	1.00 (ref)
Crohn's disease	9489	76 685	220	**1.92 (1.63, 2.25)**	**1.74 (1.45, 2.08)**
Rheumatoid arthritis					
Controls	93 640	770 424	2020	1.00 (ref)	1.00 (ref)
Rheumatoid arthritis	23 410	19 022	845	**1.69 (1.56, 1.83)**	**1.54 (1.40, 1.69)**
Psoriatic arthritis					
Controls	25 188	202 078	368	1.00 (ref)	1.00 (ref)
All Immune mediated inflammatory diseases	6297	51 400	132	**1.41 (1.16, 1.72)**	**1.20 (0.96, 1.52)**
Secondary outcome: risk of PE					
All Immune mediated inflammatory diseases					
Controls	213 509	1 777 837	1737	1.00 (ref)	1.00 (ref)
Immune mediated inflammatory disease	53 370	443 470	672	**1.57 (1.44, 1.72)**	**1.43 (1.29, 1.58)**
Ulcerative colitis					
Controls	56 728	482 186	452	1.00 (ref)	1.00 (ref)
Ulcerative colitis	14 182	120 710	149	**1.35 (1.12, 1.62)**	**1.23 (1.01, 1.49)**
Crohn's disease					
Controls	37 956	310 470	207	1.00 (ref)	1.00 (ref)
Crohn's disease	9489	77 393	98	**1.96 (1.55, 2.49)**	**1.69 (1.29, 2.20)**
Rheumatoid arthritis					
Controls	93 639	780 883	916	1.00 (ref)	1.00 (ref)
Rheumatoid arthritis	23 408	193 534	373	**1.66 (1.47, 1.87)**	**1.57 (1.36, 1.80)**
Psoriatic arthritis					
Controls	25 186	204 299	161	1.00 (ref)	1.00 (ref)
Psoriatic arthritis	6297	51 833	52	**1.27 (0.93, 1.73)**	**1.08 (0.75, 1.55)**
Secondary outcome: risk of DVT					
All Immune mediated inflammatory diseases					
Controls	213 510	1 773 186	2335	1.00 (ref)	1.00 (ref)
Immune mediated inflammatory disease	53 372	441 330	978	**1.70 (1.58, 1.83)**	**1.57 (1.45, 1.71)**
Ulcerative colitis					
Controls	56 728	480 944	583	1.00 (ref)	1.00 (ref)
Ulcerative colitis	14 182	120 309	207	**1.43 (1.22, 1.68)**	**1.33 (1.13, 1.57)**
Crohn's disease					
Controls	37 956	309 769	279	1.00 (ref)	1.00 (ref)
Crohn's disease	9489	77 115	140	**2.05 (1.67, 2.50)**	**1.96 (1.57, 2.45)**
Rheumatoid arthritis				RA	
Controls	93 640	778 523	1242	1.00 (ref)	1.00 (ref)
Rheumatoid arthritis	23 408	192 276	542	**1.78 (1.61, 1.97)**	**1.64 (1.45, 1.84)**
Psoriatic arthritis					
Controls	25 817	203 949	231	1.00 (ref)	1.00 (ref)
Psoriatic arthritis	6297	51 630	89	**1.52 (1.21, 1.97)**	**1.34 (1.01, 1.77)**

Adjusted for age, sex, IMD quintile, ethnicity, BMI category, smoking status, alcohol use category, hypertension, hyperlipidaemia, type 2 diabetes, peripheral arterial disease, atrial fibrillation, myocardial infarction, stroke, heart failure, CKD stage 3–5, COPD, chronic liver disease, malignancy, reduced mobility, use of NSAIDs, antiplatelets, warfarin, DOACs, hormone replacement therapy, oestrogen contraceptives, immunotherapy, corticosteroids, statins and baseline platelet category.
BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; DOAC, direct oral anticoagulants; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; RA, rheumatoid arthritis

Table 3 Association of baseline recorded characteristics and VTE risk factors with risk of VTE among individuals with and without immune-mediated inflammatory diseases (IMID) in multivariable analysis

	Without IMID (n=213 512)	With IMID (n=53 378)
Type of IMID		
Ulcerative colitis	NA	1.00 (ref)
Crohn's disease	NA	1.20 (1.01, 1.42)
Psoriatic arthritis	NA	0.87 (0.71, 1.07)
Rheumatoid arthritis	NA	1.11 (0.97, 1.28)
Sociodemographic characteristics		
Age at study entry (years)	1.04 (1.04, 1.05)	1.03 (1.03, 1.04)
Male sex	1.02 (0.95, 1.10)	1.13 (1.01, 1.26)
Ethnicity		
Asian	0.46 (0.34, 0.63)	0.96 (0.70, 1.31)
Black	1.19 (0.90, 1.56)	1.08 (0.62, 1.87)
Mixed	1.40 (0.87, 2.27)	1.01 (0.45, 2.27)
Other	0.96 (0.51, 1.78)	0.45 (0.11, 1.80)
Missing	1.04 (0.96, 1.12)	0.96 (0.84, 1.09)
White	1.00 (ref)	1.00 (ref)
Index of multiple deprivation quintile (IMD)		
1 (most deprived)	1.00 (ref)	1.00 (ref)
2	1.05 (0.94, 1.19)	1.02 (0.84, 1.22)
3	0.97 (0.86, 1.09)	0.95 (0.79, 1.13)
4	0.93 (0.83, 1.03)	0.94 (0.79, 1.12)
5 (least deprived)	0.94 (0.84, 1.04)	0.86 (0.72, 1.02)
IMD not recorded	0.87 (0.67, 1.12)	1.00 (0.69, 1.45)
VTE risk factors		
BMI (kg/m^2)		
Underweight (≤18.5)	1.06 (0.80, 1.41)	0.99 (0.68, 1.44)
Normal weight (18.5–25)	1.00 (ref)	1.00 (ref)
Overweight (25–30)	1.24 (1.14, 1.35)	1.23 (1.08, 1.39)
Obese (≥30)	1.91 (1.75, 2.08)	1.66 (1.45, 1.91)
BMI not recorded	1.14 (0.98, 1.32)	1.31 (1.03, 1.65)
Smoking status		
Non-smoker	1.00 (ref)	1.00 (ref)
Current smoker	1.08 (0.99, 1.17)	1.22 (1.07, 1.39)
Ex-smoker	1.06 (0.98, 1.15)	1.07 (0.95, 1.21)
Smoking status not recorded	0.32 (0.12, 0.87)	0.37 (0.05, 2.62)
Alcohol intake		
Non-drinker	1.07 (0.98, 1.16)	1.17 (1.03, 1.32)
Within limits	1.00 (ref)	1.00 (ref)
Over recommended limits	1.01 (0.91, 1.11)	0.90 (0.77, 1.06)
Alcoholism	1.19 (0.92, 1.54)	1.44 (0.99, 2.08)
Alcohol intake not recorded	1.07 (0.93, 1.23)	1.17 (0.94, 1.46)
Reduced mobility	1.39 (1.12, 1.72)	0.96 (0.67, 1.37)
Family history of VTE	3.10 (1.60, 6.01)	1.29 (0.32, 5.19)
Thrombophilia	4.66 (2.31, 9.40)	4.13 (1.53, 11.11)
History of fracture	1.11 (0.98, 1.25)	1.29 (1.08, 1.55)
Platelet count	1.16 (0.90, 1.50)	1.23 (1.01, 1.50)
Normal (150–400×10^9/L)	1.00 (ref)	1.00 (ref)
High (>400×10^9/L)	1.37 (1.02, 1.84)	1.07 (0.67, 1.72)
Missing	0.55 (0.51, 0.59)	1.07 (0.94, 1.22)
Comorbidity		
Hypertension	1.02 (0.94, 1.10)	1.02 (0.90, 1.15)
Hyperlipidaemia	1.03 (0.94, 1.15)	1.08 (0.91, 1.28)
Type 2 diabetes	1.03 (0.90, 1.17)	0.90 (0.72, 1.11)
Peripheral vascular disease	1.30 (1.02, 1.65)	0.73 (0.44, 1.20)
Atrial fibrillation	0.44 (0.34, 0.57)	0.32 (0.21, 0.48)
Myocardial infarction	0.97 (0.80, 1.17)	1.11 (0.84, 1.48)
Stroke	1.15 (0.93, 1.43)	0.91 (0.62, 1.34)
Heart failure	0.99 (0.76, 1.29)	1.10 (0.76, 1.61)
Chronic kidney disease stages 3 to 5	1.16 (0.98, 1.37)	1.29 (1.00, 1.67)
Chronic obstructive pulmonary disease	1.35 (1.14, 1.59)	1.21 (0.96,1.53)
Chronic liver disease	1.79 (1.24,2.59)	1.29 (0.81, 2.07)
Malignancy	1.30 (1.14, 1.48)	1.27 (1.02, 1.57)
Medication use		
NSAID use	1.26 (1.15, 1.38)	1.05 (0.92, 1.21)
Corticosteroid use	1.33 (1.16, 1.54)	1.22 (1.06, 1.40)
Immunosuppressive medication use	1.55 (1.15, 2.10)	1.14 (0.99, 1.30)
Statin use	0.85 (0.74, 0.98)	0.87 (0.68, 1.10)
Antiplatelet therapy	0.94 (0.83, 1.07)	0.94 (0.76, 1.16)
Warfarin use	2.37 (1.88, 3.00)	4.20 (2.96, 5.96)
Direct oral anticoagulants	2.68 (1.84, 3.91)	8.36 (5.40, 12.94)
Hormone replacement therapy*	0.77 (0.59, 1.00)	1.12 (0.80, 1.56)
Combined oral contraceptive use†	1.20 (0.87, 1.66)	1.63 (1.10, 2.40)

*For females only, HRs were 1.15 (95% CI 0.83 to 1.48) in people without an IMID and 1.11 (95% CI 0.78 to 1.44) in people with an IMID.
†For females only, HRs were 1.85 (95% CI 1.45 to 2.45) in people without an IMID and 1.64 (95% CI 1.24 to 2.04) in people with an IMID.
Values are HRs with 95% CIs.
BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug.

male sex, current smoking, CKD, and history of fracture were independent risk factors for VTE. Across study follow-up, abnormal platelet counts were found to be independently associated with risk of VTE in both groups but were substantially more common in people with an IMID.

Our study for the first time assesses the risk of developing VTE across four common IMIDs using the same study design. VTE incidence in this study was similar to that

Table 4 Association of time-varying platelet count with time to VTE in individuals with and without immune-mediated inflammatory diseases (IMID) in adjusted and multivariable analysis

	Without IMID n=160 969, VTE events=3250		With IMID n=51 389, VTE events=1417	
Platelets	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Low (<150×10^9/L)	1.88 (1.60–2.20)	1.06 (0.98–1.14)	1.62 (1.23–2.12)	1.24 (0.94–1.62)
Normal (150–400×109/L)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
High (>400×10^9/L)*	2.13 (1.83–2.43)	1.98 (1.73–2.26)	1.59 (1.35–1.87)	1.72 (1.46–2.03)

*Adjusted for age, sex, index of multiple deprivation quintile, ethnicity, body mass index category, smoking status, alcohol category, hypertension, hyperlipidaemia, type 2 diabetes, peripheral arterial disease, atrial fibrillation, myocardial infarction, stroke, heart failure, Chronic kidney disease stage 3–5, Chronic obstructive pulmonary disease, chronic liver disease, malignancy, reduced mobility, use of medication (NSAIDs, antiplatelets, warfarin, DOACs, hormone replacement therapy, oestrogen contraceptives, immunotherapy, corticosteroids and statins).
Individuals with at least one valid platelet measure over the study period included.
DOAC, direct oral anticoagulants; ,NSAID non-steroidal anti-inflammatory drug.

previously reported in the UK,[1] and a similar difference in incidence rates between people with PsA, RA and psoriasis and matched controls was recently reported using UK primary care data.[6] Results are in keeping with previous studies that have consistently found people with RA to be at increased risk of VTE.[5 6 9 35] Ogdie *et al* conducted the first observational study of VTE risk in people with PsA and similar to our study, likely lacked power to detect a difference for overall VTE risk,[6] suggesting further evaluation of VTE risk in patients with PsA in even larger cohorts is an important area for future research.

We also demonstrate an interesting u-shaped association between platelet count and VTE risk, with both high and low platelet count demonstrated to be markers of increased risk compared with normal platelet count in people with IMIDs managed in primary care. Given initial positive associations with baseline platelet count, and the recognised interaction between inflammatory cytokines and platelet function,[36] we explored this association in depth using time-updated platelet counts across study follow-up to further delineate thresholds of risk/association with time to VTE. Time-updated high and low platelets were independently associated with risk of VTE in both people with and without an IMID; however, high and low platelet counts were much more common in people with an IMID, suggesting particular clinical utility in this group. Although the direction of effects was the same for the baseline and time-varying platelet analysis, differences in statistical significance and effect size may relate to the increased power and greater predictive ability gained from incorporating time-updated platelet measures. Our findings for high platelet count are in keeping with previous studies that have demonstrated thrombocytosis to be both a risk factor for VTE in inpatient populations,[12] and to be associated with increased mortality risk in population-based cohorts.[37] To our knowledge, the association between low platelet count and increased VTE risk is novel, with one possible explanation that clumping of platelets occurs with platelet activation and could cause an artificially low platelet count.

Our evaluation of VTE risk factors is in keeping with other less comprehensive previous studies, which have demonstrated the influence of obesity, fractures, smoking, BMI and medications including oral corticosteroids and oral contraceptives.[10 38] We were able to explore these and other risk factors with adjustment for other patient characteristics. Results highlight an interesting absence of association with VTE for traditional cardiovascular disease risk factors including hypertension and hyperlipidaemia.

Strengths of our large, long-term population-based study include the comprehensive capture of VTE risk factors and patient characteristics, allowing interrogation not only of VTE risk across multiple diseases in adjusted analysis but also assessment of independent risk factors for VTE. Exposures and outcomes were defined using algorithms previously validated in primary care. Interpretation of coefficients for individual risk factors may be limited by the potential of confounding, and these estimates do not provide a causal interpretation.[39] A further limitation of the study, similar to all studies using routine data, include the potential of unmeasured confounding and selection bias. Findings may not be generalisable to more ethnically diverse populations than the UK. Despite the use of validated algorithms to classify CD, UC, RA and the use of published guidance to define PsA, the lack of medical record review and use of clinical criteria to classify these IMIDs is a further limitation of the study, since diagnoses were recorded in primary care and may not have been made by specialists. When evaluating VTE risk factors, chance findings offer a potential explanation for differences in the groups with and without an IMID due to the number of associations tested. Family history of VTE is poorly captured in primary care data, and a resultant lack of power offers the most likely explanation for the observation that family history of VTE was not a significant risk factor in the IMID cohort. Similarly, this study will have systematically under captured biologic

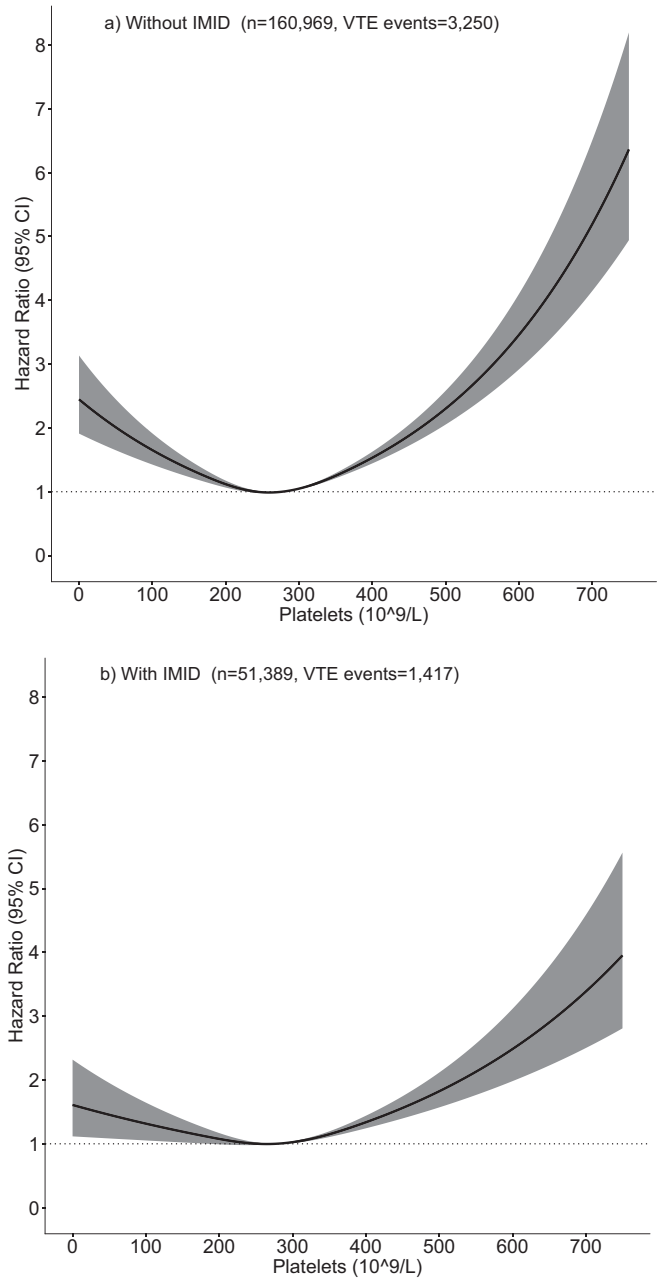

Figure 2 Association of continuous time-varying platelet count with time to venous thromboem bolism (VTE) in individuals with and without immune-mediated inflammatory diseases (IMID). Platelet count modelled using a restricted cubic spline with 3 knots in multivariable models adjusted for the same covariates as listed in Table 4, relative to the mean platelet count in individuals with an IMID (277×10^9/L).

medication prescribing as, in the UK, these are prescribed by specialists and not captured in primary care. Secondary care data were not available to evaluate risk associated with surgery, an established major VTE risk factor. For analysis of time-updated platelet count, we used a complete-case approach, and for other missing information including BMI and ethnicity, we used the missing indicator variable method, as data are likely to be missing not at random meaning multiple imputation may lack validity.[40]

Our study is timely and of particular relevance in the context of the clinical interest in VTE in people with IMID. Our data provide an understanding of the contextual risk in IMID populations, and suggests considerable potential to update or augment existing VTE risk stratification decision aids such as the Wells Score with more refined multivariable prediction models incorporating routinely measured clinical patient characteristics. Another interesting direction for future research would be to use time-updated risk models to evaluate the temporal association between measures of IMID disease extent and severity, and by use of medication, in particular immunosuppressive treatment, and risk of VTE. This would provide further important information for clinicians responsible for monitoring patients with IMIDs in primary care.

In summary, VTE is more common in people with UC, CD, RA, and PsA compared with those without these diseases, highlighting the need for increased awareness among clinicians. Although associations do not have a causal interpretation, this study refines our understanding of classical VTE risk factors in people with an IMID compared with the wider population. Our data provide an initial platform for the risk assessment of individual patients with an IMID, and support active monitoring and strategies to mitigate VTE risk in people with an IMID.

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