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# The risk of venous thromboembolism in atopic dermatitis: a matched cohort analysis in UK primary care

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## Abstract

**Background** Atopic dermatitis (AD) is a common chronic inflammatory skin condition. While other chronic inflammatory conditions are associated with increased risk of venous thromboembolism (VTE), associations between AD and VTE have not been established.

**Objectives** We examined whether AD is associated with an increased risk of VTE in a population-based study.

**Methods** Electronic health records were extracted from UK general practices contributing to the Optimum Patient Care Research Database (1 January 2010 to 1 January 2020). All adults with AD were identified ($n=150\,975$) and age- and sex-matched with unaffected controls ($n=603\,770$). The risk of VTE, consisting of pulmonary embolism (PE) or deep-vein thrombosis (DVT), was compared in people with AD vs. controls using Cox proportional hazard models. PE and DVT were examined separately as secondary outcomes.

**Results** We identified 150 975 adults with active AD and matched them with 603 770 unaffected controls. During the study, 2576 of those with active AD and 7563 of the matched controls developed VTE. Individuals with AD had a higher risk of VTE than controls [adjusted hazard ratio (aHR) 1.17, 95% confidence interval (CI) 1.12–1.22]. When assessing VTE components, AD was associated with a higher risk of DVT (aHR 1.30, 95% CI 1.23–1.37) but not PE (aHR 0.94, 95% CI 0.87–1.02). The VTE risk was greater in older people with AD (≥ 65 years: aHR 1.22, 95% CI 1.15–1.29; 45–65 years: aHR 1.15, 95% CI 1.05–1.26; < 45 years: aHR 1.07, 95% CI 0.97–1.19) and those with obesity [body mass index (BMI) ≥ 30: aHR 1.25, 95% CI 1.12–1.39; BMI < 30: aHR 1.08, 95% CI 1.01–1.15). Risk was broadly consistent across mild, moderate or severe AD.

**Conclusions** AD is associated with a small increase in risk of VTE and DVT, with no increase in risk of PE. The magnitude of this risk increase is modest in younger people, and those without obesity.

**What is already known about this topic?**

- Inflammation and immunity are known to contribute to pro-thrombotic pathways and risk of venous thromboembolism (VTE), and people with chronic inflammatory conditions, including psoriasis, inflammatory bowel disease and rheumatoid arthritis, have an increased risk of VTE.
- Few population-based studies have assessed whether adults with atopic dermatitis (AD) are also at increased risk of VTE, or evaluated heterogeneity in VTE risk in adults with AD with different clinical characteristics.

**What does this study add?**

- In a UK population-based cohort study of 150 975 adults with AD and 603 770 matched unaffected controls, people with AD had a 17% higher risk of VTE and a 30% higher risk of deep-vein thrombosis.
- There was no risk increase for pulmonary embolism.
- AD-associated VTE risk was low in younger people and those without obesity.
- Identification of people with AD at increased VTE risk could inform clinical decision-making.

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Atopic dermatitis (AD) is an inflammatory skin condition affecting around 10% of individuals[1–3] in high-income countries and approximately 200 million people worldwide.[4,5] AD most commonly begins in childhood, although onset can occur at any age.[6,7] There is often a chronic relapsing–remitting course with flare-ups occurring even after long periods of remission,[7,8] and requiring ongoing treatment.[9]

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a relatively common circulatory disease, with an estimated incidence in developed countries of between one and three cases per 1000 patient years[10] and is associated with significant levels of morbidity and mortality.[11] An individual's risk of VTE will depend on multiple risk factors including genetics, age, sex, obesity, smoking history, hormone and oral corticosteroid therapy, and comorbidities including cancer, surgery, fracture history and conditions associated with immobility.[12] There is increasing evidence that both inflammation and immunity contribute to pro-thrombotic pathways and risk of VTE,[13] and recent studies have suggested that people with immune-mediated inflammatory conditions have a 46% higher VTE risk[14] and 49% higher risk of thrombotic events[15] compared with the general population, a finding supported by individual studies of psoriasis,[16] inflammatory bowel disease (IBD)[17–19] and rheumatoid arthritis.[20] In contrast, the potential association between AD and VTE has not been clearly established. A cross-sectional analysis of US hospital inpatients reported a significant AD-associated VTE risk increase of 22%,[21] but this finding is likely to be generalizable only to patients with more severe AD potentially with reduced mobility, given that they are hospitalized, and therefore unlikely to be representative of the wider population with AD. US insurance claim-based cohort studies have not observed a clear association between AD and risk of VTE,[22,23] but may not be representative of those with less severe disease. Furthermore, previous studies have not assessed heterogeneity in VTE risk in adults with AD with different clinical characteristics.

In the UK, most people with AD are managed principally in primary care,[24] meaning electronic health records provide a population-representative sample of those with AD from mild through to more severe disease. We aimed to conduct a large-scale cohort analysis using UK primary care data to establish whether AD is associated with an increased risk of VTE and evaluate heterogeneity in AD-associated VTE risk by AD severity and across pre-specified population subgroups.

## Patients and methods

### Study population

We used routine clinical data from the Optimum Patient Care Research Database (OPCRD).[25] OPCRD incorporates pseudonymized primary care records from over 10 million people registered with 700 general practitioners (GPs) distributed throughout England, Wales and Scotland. All eligible adults $\geq$ 18 years of age (as at date of entry into study) registered with GP practices contributing data to OPCRD between 1 January 2010 and 1 January 2020 were eligible for inclusion either as patients with AD or controls (Figure S1; see Supporting Information). The study protocol was specified *a priori* and registered as an observational study with ClinicalTrials.gov (study identifier: NCT04969653).

### Definition of individuals with active atopic dermatitis

We identified all individuals diagnosed with active AD at any point over the study period. People with a record of AD were identified using a combination of specific diagnosis Read and SNOMED CT codes (Table S1; see Supporting information) and two or more AD treatments prescribed on different dates (Table S2; see Supporting information). Diagnosis codes which are not specific for AD (e.g. hand dermatitis) were not included. To enhance our stringency of case selection, we excluded individuals with conditions that may be misdiagnosed or miscoded as AD in primary care (psoriasis, contact dermatitis, photodermatitis or ichthyosis) (Table S3; see Supporting information). From the records for people with AD, active AD was determined to have started at the latest of two prescriptions of one or more pre-specified treatments (Table S2) in any 1-year period, a definition which has been previously demonstrated to be in good agreement with physician-confirmed active AD.[26]

All adults with an episode of active AD at any point during the study period were included for analysis. The start of the observation period (index date) was the latest of (i) the start of their period of active AD, (ii) the date they turned 18 years of age, or (iii) 1 January 2010 (if their active AD onset predated the study period but their active AD was ongoing at that date).

### Matching strategy: definition of matched controls without active atopic dermatitis

Each adult with active AD was matched at their index date with up to four unaffected controls never diagnosed either with AD or any exclusion skin condition (Table S3) at the date of matching, selected from the pool of eligible adults registered in the same GP practice. Time-dependent propensity score matching was based on age (exact age categories $<$ 45, 45–64, $\geq$ 65 years and then nearest-neighbour continuous age within each age category), sex (exact) and duration of practice registration (nearest neighbour), using a rolling time window so that controls were eligible for matching only if they were actively registered with the same GP practice on the index date of the case in question. After matching, the index date for each control was set to the index date of their matched counterpart.

### Primary outcome

The primary outcome was VTE, identified by the earliest record of PE or DVT using clinical codes validated in UK primary care[27] and updated to include newer clinical codes (Table S4; see Supporting Information). The individual PE and DVT components of the VTE outcome were also examined as separate outcomes; when both PE and DVT were diagnosed on the same day, this was classified as a PE outcome as this is typically the more severe condition of the two.

### Sociodemographic characteristics, clinical features and venous thromboembolism risk factors

Sociodemographic characteristics comprised age, ethnicity (UK census classification: white, Asian, Black, mixed, other) and socioeconomic status as defined by the UK Index of Multiple Deprivation (IMD). Clinical features comprised body mass index (BMI), smoking status and alcohol use (Methods S1; see Supporting Information). Consultation history was included as a binary yes/no to GP contact in the 365 days prior to their index date. VTE risk factors for inclusion in models were selected based on existing literature demonstrating an established association with VTE,[12,16] clinical expertise or their inclusion in the QThrombosis tool[28] and included history of VTE, reduced mobility, thrombophilia, recent hospital admission, major comorbidities, allergic conditions and medications (oral corticosteroids, hormone therapy, warfarin, direct oral anticoagulants, phototherapy and immunosuppressants) (see Methods S1).

### Atopic dermatitis severity

AD severity was defined using the approach used by Silverwood *et al.*[29] in their study of cardiovascular outcomes in AD: AD was considered mild, by default; moderate, following the prescription of a second potent topical corticosteroid treatment within 1 year or a first topical calcineurin inhibitor; and severe, at the first prescription of a systemic immunosuppressant treatment (ciclosporin, azathioprine, mycophenolate, methotrexate and biologics), phototherapy or a dermatology referral. For an individual patient with AD, severity could change during the study follow-up: once fulfilling criteria for moderate AD, cases remained as moderate unless they developed severe AD. When fulfilling criteria for severe AD, cases remained as severe for the remainder of their follow-up.

### Statistical analyses

#### *Primary analysis*

Risk of VTE, and of individual PE and DVT outcomes, was assessed in patients with active AD and matched controls from the index date up to a maximum follow-up of 10 years, with censoring applied prior to this if individuals deregistered from their GP practice or died. Risk of VTE was estimated for each group using the Kaplan–Meier method, with proportional hazards assumptions tested. Unadjusted Cox proportional hazards models, stratified by matched set (patients with active AD vs. matched controls), were used to provide overall hazard ratios (HRs) as summary estimates for the association of the presence of active AD with the time to each outcome. Models were subsequently adjusted for baseline sociodemographic and clinical features in multivariable analysis, with missing categories defined for features with missing data (full analysis set; Methods S1).

#### *Analysis of heterogeneity in venous thromboembolism risk*

Time-dependent adjusted (full analysis set) Cox models were used to evaluate the association between VTE and categories of AD severity, allowing for an individual's AD severity status to change throughout follow-up. Adjusted Cox models were refitted for prespecified subgroups defined by sex, age (18–44, 45–64, 65+ years), obesity (BMI $<30$, BMI $\geq 30$), baseline use of oestrogen-containing contraceptives (hormone treatment) in females aged 18–44 years, and history of allergic conditions (Methods S1). To further explore variations in the association between AD and VTE by baseline BMI and age, we estimated the 10-year cumulative risk of VTE by age category (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80+ years) and BMI category ($<$ 18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, 40+) for cases and controls. We then fitted adjusted (full analysis set) Cox models including interaction terms for continuous BMI by AD case–control status, and continuous age by AD case–control status. To allow for nonlinearity, both continuous BMI and age were fitted using 3-knot restricted cubic splines (knots at 25th, 50th and 75th percentiles).

#### *Sensitivity analysis*

Four sensitivity analyses were performed, as follows: (1) to exclude a risk of selection bias resulting in an uneven distribution of cases with previous VTE in the two groups, we repeated the primary analysis excluding patients with AD with a history of VTE at cohort entry. (2) To mitigate the possibility of misclassification of AD severity caused by a non-AD comorbidity requiring systemic immunosuppressant treatment, we repeated the primary analysis and AD severity analyses in a subgroup of individuals without a diagnosis for a common condition for which these medications are licensed [IBD, comprising ulcerative colitis or Crohn disease, rheumatoid arthritis or psoriasis (already excluded as per the case definition)]. (3) To address the possibility of noncoding of VTE, we also analysed a composite endpoint consisting of the earliest of VTE diagnosis or initiation of anticoagulant prescription without a recorded diagnosis of atrial fibrillation. Anticoagulant prescriptions comprised vitamin K antagonists (warfarin), low-molecular-weight heparins and direct-acting oral anticoagulants. (4) To evaluate the magnitude of potential bias from the inclusion of controls who do not attend their GP practice, we repeated the primary analysis restricting the control set to include only patients with at least one primary care consultation in the year preceding their index date.

All statistical analyses were performed using R version 4.1.3.[30] The study was conducted and reported in line with the RECORD (REporting of studies Conducted using Observational Routinely collected Data) guidelines.[31]

## Results

We matched 150 975 adults with active AD with 603 770 controls (Figure S1). The median follow-up time for patients with AD was 7.16 [interquartile range (IQR) 3.83–9.98] years compared with 6.89 (IQR 3.50–9.93) years for matched controls. Patients with AD had a median age of 40 years (IQR 23–62) and 59% were female (Table 1). Patients with AD and controls were similar in most baseline sociodemographic and clinical features, and VTE risk factors, although patients with AD were more likely to have both asthma and allergic conditions (Table 1). A higher proportion of patients with AD had a GP visit in the 12 months prior to study entry compared with controls (Table 1).

**Table 1** Characteristics of patients and matched controls

| | People with active AD | Matched controls | SMD |
|---|---|---|---|
| *n* | 150 975 | 603 770 | |
| Age years, median (**IQR**) | 40.0 (23.0–62.0) | 41.0 (23.0–62.0) | 0.007 |
| Age group (years), *n* (%) | | | 0.047 |
| 18–29 | 54 634 (36.2) | 213 727 (35.4) | |
| 30–39 | 20 599 (13.6) | 80 118 (13.3) | |
| 40–49 | 17 903 (11.9) | 80 211 (13.3) | |
| 50–59 | 15 765 (10.4) | 61 343 (10.2) | |
| 60–69 | 17 375 (11.5) | 71 571 (11.9) | |
| 70–79 | 15 081 (10.0) | 58 452 (9.7) | |
| 80+ | 9618 (6.4) | 38 348 (6.4) | |
| Sex, *n* (%) | | | |
| Male | 61 882 (41.0) | 247 459 (41.0) | < 0.001 |
| Female | 89 093 (**59**.0) | 356 311 (59.0) | |
| **IMD**, median (**IQR**)[a] | 3.00 (3.0–4.0) | 3.00 (3.0–4.0) | 0.001 |
| Ethnicity, *n* (%)[b] | | | 0.144 |
| White | 87 748 (75.7) | 331 717 (77.0) | |
| Asian or Asian British | 12 635 (10.9) | 38 388 (8.9) | |
| Black or Black British | 2021 (1.7) | 7903 (1.8) | |
| Mixed | 1396 (1.2) | 4281 (1.0) | |
| Not stated | 4638 (4.0) | 21 349 (5.0) | |
| Other | 7503 (6.5) | 26 907 (6.2) | |
| **GP** visit in last 12 months, *n* (%) | 146 440 (97.0) | 536 511 (88.9) | 0.321 |
| **BMI**, median (**IQR**) | 26.00 (23.00–30.00) | 26.00 (22.00–30.00) | 0.040 |
| **BMI** category, *n* (%)[c] | | | 0.191 |
| < 18.5 Underweight | 5931 (4.5) | 24 532 (5.1) | |
| 18.5–24.9 Normal weight | 46 458 (35.3) | 174 953 (36.1) | |
| 25–29.9 Overweight | 43 720 (33.2) | 159 607 (33.0) | |
| 30–34.9 Class I obesity | 21 317 (16.2) | 77 432 (16.0) | |
| 35–39.9 Class II obesity | 8711 (6.6) | 30 258 (6.2) | |
| 40+ Class III obesity | 5353 (4.1) | 17 515 (3.6) | |
| Smoking status, *n* (%)[d] | | | 0.253 |
| Never | 45 152 (30.5) | 189 107 (33.5) | |
| Current | 27 173 (18.4) | 116 895 (20.7) | |
| Ex-smoker | 74 860 (50.6) | 255 950 (45.4) | |
| Passive | 770 (0.5) | 1904 (0.3) | |
| Alcohol status, *n* (%)[e] | | | 0.160 |
| None | 47 083 (37.1) | 170 663 (36.2) | |
| Within limits | 58 905 (46.4) | 226 953 (48.2) | |
| Excess | 18 660 (14.7) | 64 716 (13.7) | |
| Harmful | 2374 (1.9) | 8743 (1.9) | |
| Hospital admission, *n* (%) | 3658 (2.4) | 11 560 (1.9) | 0.035 |
| Comorbidities, *n* (%) | | | |
| Family history VTE | 358 (0.2) | 1150 (0.2) | 0.010 |
| History of PE | 1063 (0.7) | 3521 (0.6) | 0.015 |
| History of DVT | 2126 (1.4) | 6560 (1.1) | 0.029 |
| History of VTE | 3003 (2.0) | 9505 (1.6) | 0.031 |
| Rheumatoid arthritis | 1219 (0.8) | 4194 (0.7) | 0.013 |
| Reduced mobility | 3164 (2.1) | 9955 (1.6) | 0.033 |
| Varicose veins | 11 374 (7.5) | 29 429 (4.9) | 0.110 |
| Chronic kidney disease | 1375 (0.9) | 4693 (0.8) | 0.015 |
| Heart failure | 2303 (1.5) | 7892 (1.3) | 0.018 |
| Inflammatory bowel disease | 5878 (3.9) | 16 132 (2.7) | 0.069 |
| Chronic obstructive pulmonary disease | 5173 (3.4) | 16 012 (2.7) | 0.045 |
| Malignancy | 6546 (4.3) | 23 439 (3.9) | 0.023 |
| Thrombophilia | 318 (0.2) | 1038 (0.2) | 0.009 |
| Asthma | 46 884 (31.1) | 99 277 (16.4) | 0.349 |
| Hypertension | 28 059 (18.6) | 98 370 (16.3) | 0.060 |
| Hyperlipidaemia | 25 359 (16.8) | 89 413 (14.8) | 0.055 |
| Type 2 diabetes | 4822 (3.2) | 16 651 (2.8) | 0.026 |
| Peripheral vascular disease | 2371 (1.6) | 6805 (1.1) | 0.038 |
| Atrial fibrillation | 3696 (2.4) | 13 095 (2.2) | 0.019 |
| Angina | 4576 (3.0) | 14 754 (2.4) | 0.036 |
| Myocardial infarction | 3026 (2.0) | 10 954 (1.8) | 0.014 |
| Stroke | 2419 (1.6) | 8434 (1.4) | 0.017 |
| Dementia | 2354 (1.6) | 9182 (1.5) | 0.003 |
| Chronic liver disease | 2576 (1.7) | 7725 (1.3) | 0.035 |
| Allergic condition | 40 174 (26.6) | 79 164 (13.1) | 0.343 |
| Treatments, *n* (%) | | | |
| Anticoagulant | 5028 (3.3) | 16 469 (2.7) | 0.035 |

**Table 1** (*Continued*)

| | People with active AD | Matched controls | SMD |
|---|---|---|---|
| Oral steroid | 7660 (5.1) | 13 356 (2.2) | 0.153 |
| Warfarin | 2515 (1.7) | 8454 (1.4) | 0.022 |
| Direct oral anticoagulants | 399 (0.3) | 1224 (0.2) | 0.013 |
| Hormone therapy | 12 237 (8.1) | 35 707 (5.9) | 0.086 |
| Phototherapy | 552 (0.4) | 995 (0.2) | 0.039 |
| Systemic immune suppressant | 1092 (0.7) | 2896 (0.5) | 0.032 |

AD, atopic dermatitis; BMI, body mass index; DVT, deep-vein thrombosis; GP, general practitioner; IMD, Index of Multiple Deprivation; IQR, interquartile range; PE, pulmonary embolism; SMD, standard mean difference; VTE, venous thromboembolism. [a]IMD missing for $n=10\,294$ people with active AD and $n=46\,751$ matched controls. [b]Ethnicity missing for $n=35\,034$ people with active AD and $n=173\,225$ matched controls. [c]BMI missing for $n=19\,485$ people with active AD and $n=119\,473$ matched controls. [d]Smoking status missing for $n=3020$ people with active AD and $n=39\,914$ matched controls. [e]Alcohol status missing for $n=23\,953$ people with active AD and $n=132\,695$ matched controls.

## Risk of venous thromboembolism is increased in individuals with active atopic dermatitis

The primary outcome of VTE was higher in patients with AD than in controls [10-year cumulative risk for patients with AD 2.5%, 95% confidence interval (CI) 2.4–2.6; controls 1.9%, 95% CI 1.8–1.9] (Figure 1). Evaluation of the secondary outcomes of PE and DVT showed that this was driven by an increase in DVT only [Figure S2 (see Supporting Information); 10-year PE: patients with AD 0.8%, 95% CI 0.7–0.8; controls 0.8%, 95% CI 0.7–0.8; 10-year DVT: patients with AD 1.8%, 95% CI 1.7–1.9; controls 1.2%, 95% CI 1.2–1.3].

In the adjusted analysis, the relative VTE risk was 17% higher in people with AD than in controls [adjusted hazard ratio (aHR) 1.17 (95% CI 1.12–1.22, $P<0.001$)] (Table 2). This reflected an increased risk of DVT (aHR 1.30, 95% CI 1.23–1.37, $P<0.001$) but not PE (aHR 0.94, 95% CI 0.87–1.02, $P=0.11$) (Table 2).

The risk was broadly consistent across mild, moderate and severe AD, with aHRs vs. controls of 1.32 (95% CI 1.15–1.52, $P<0.001$) for severe AD, 1.12 (95% CI 1.06–1.18, $P<0.001$) for moderate AD and 1.22 (95% CI 1.14–1.31, $P<0.001$) for mild AD (Figure 2).

## Risk of venous thromboembolism is most evident in older individuals and those with obesity

The 10-year risk of VTE was low (≤ 1.5%) in both the AD group and controls aged 18–50 years, and was highest in those over 80 years [cases 6.8% (95% CI 6.1–7.5); controls

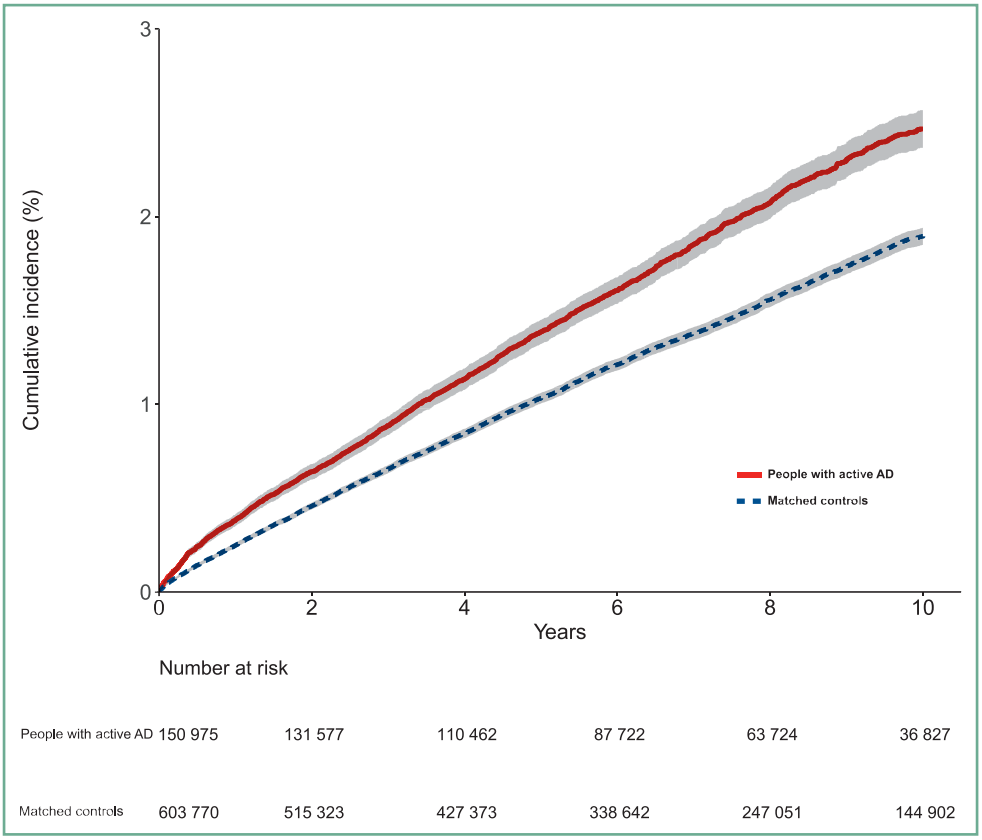


**Figure 1** Cumulative 10-year incidence of venous thromboembolism (VTE) in people with active atopic dermatitis (AD) and matched population controls. Grey shading represents 95% confidence intervals.

**Table 2** Associations between active atopic dermatitis and risk of venous thromboembolism

| | Number of people | Person-years at risk | VTE events | Incidence rate: events/person years at risk (95% CI) | Unadjusted HR | Sex and age adjusted HR | aHR[a] |
|---|---|---|---|---|---|---|---|
| VTE[b] | | | | | | | |
| Matched controls | 603 770 | 3 813 089 | 7563 | 0.198 (0.194–0.203) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| People with active AD | 150 975 | 977 144 | 2576 | 0.264 (0.254–0.274) | 1.33 (1.27–1.39)*** | 1.34 (1.28–1.40)*** | 1.17 (1.12–1.22)*** |
| PE | | | | | | | |
| Matched controls | 603 770 | 3 831 149 | 2942 | 0.077 (0.074–0.080) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| People with active AD | 150 975 | 984 236 | 797 | 0.081 (0.075–0.087) | 1.06 (0.98–1.14) | 1.06 (0.98–1.1) | 0.94 (0.87–1.02) |
| DVT | | | | | | | |
| Matched controls | 603 770 | 3 822 255 | 4934 | 0.129 (0.126–0.133) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| People with active AD | 150 975 | 979 747 | 1887 | 0.193 (0.184–0.201) | 1.49 (1.42–1.58)*** | 1.50 (1.42–1.58)*** | 1.30 (1.23–1.37)*** |

AD, atopic dermatitis; aHR, adjusted HR; BMI, body mass index; CI, confidence interval; DVT, deep-vein thrombosis; HR, hazard ratio; IMD, Index of Multiple Deprivation; PE, pulmonary embolism; VTE, venous thromboembolism. [a]Adjusted for full analysis set of baseline characteristics: age, sex, IMD quintile, ethnicity, BMI, smoking and alcohol use, family history of VTE, evidence of reduced mobility, known thrombophilia, recent hospital admission (prior 6 months), and the presence of comorbidities; varicose veins, chronic kidney disease stages 4 or 5, malignancy, heart failure, chronic obstructive pulmonary disease, inflammatory bowel disease, rheumatoid arthritis, asthma, hypertension, hyperlipidaemia, type 2 diabetes, peripheral vascular disease, atrial fibrillation, angina, myocardial infarction, stroke, dementia, chronic liver disease and history of VTE. Active prescribing at baseline of the following treatments: oral corticosteroids, hormone therapy (oestrogen-containing oral hormonal contraceptives and hormone replacement therapy), warfarin, direct oral anticoagulants, phototherapy and immunosuppressants. Primary care contact history, as a binary yes/no for a GP visit in the 12 months prior to index date. [b]Composite of DVT and PE. ***$P<0.001$.

5.5 (95% CI 5.1–5.8)] (Figure 3a). In relative terms, there was evidence of an interaction between continuous age and case–control status, with an increase in AD-associated VTE risk in cases vs. controls to around age 55 years (Figure 3c). This was supported in subgroup analysis which showed VTE risk was highest in older individuals with AD (≥ 65 years: aHR patients with AD vs. controls 1.22, 95% CI 1.15–1.29, $P<0.001$; 45–64 years: aHR 1.15, 95% CI 1.05–1.26, $P<0.01$; <45 years: aHR 1.07, 95% CI 0.97–1.19, $P>0.05$) (Figure 2; Table S5a, see Supporting Information).

In both the AD group and controls, the absolute 10-year risk of VTE was lowest (< 2.0%) in patients with AD and controls with BMI < 25, and was highest in those with severe obesity [BMI ≥ 40; patients with AD: 4.6% (95% CI 3.9–5.3); controls 3.9% (95% CI 3.6–4.3)] (Figure 3b). When evaluating AD-associated VTE risk using interaction analysis, in relative terms there was evidence of an approximately linear increase in the excess risk of VTE in people with AD as BMI increased up to 30 kg $m^{-2}$ (Figure 3d). Subgroup analysis supported those with obesity having

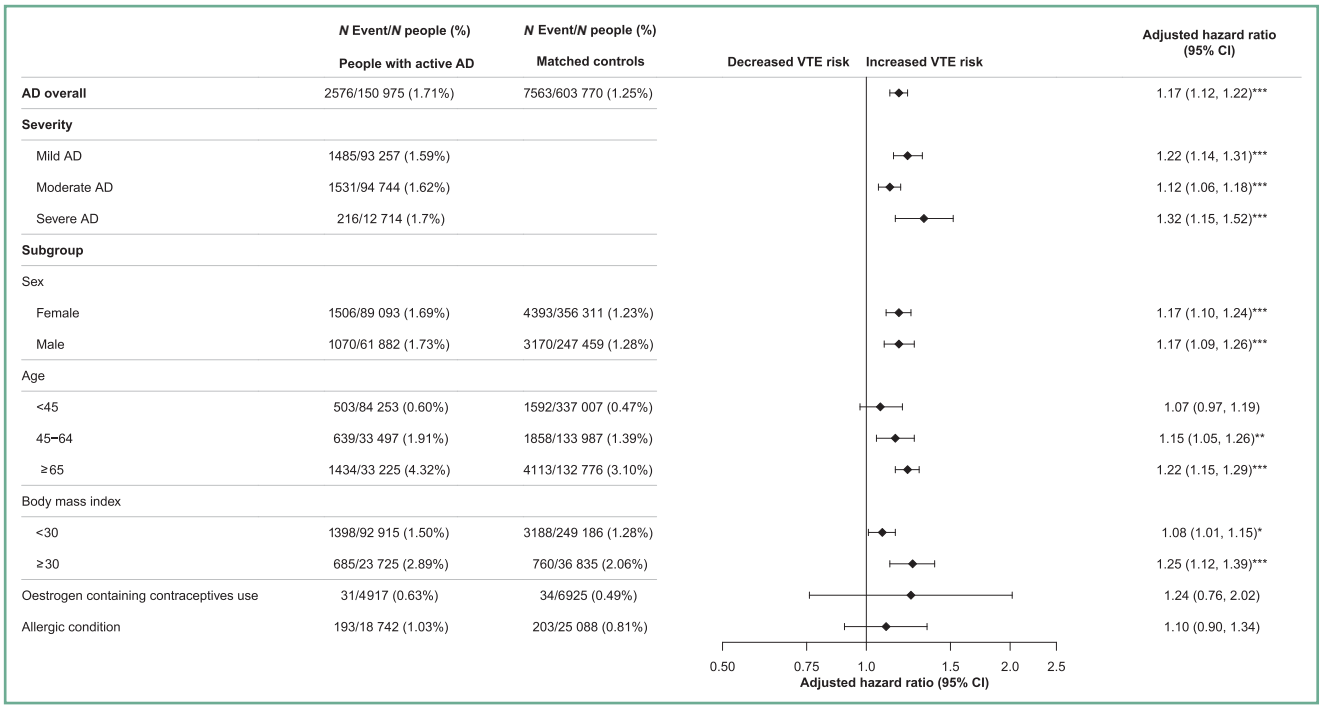


**Figure 2** Associations between active atopic dermatitis (AD) and the primary outcome of venous thromboembolism (VTE). Estimates are adjusted hazard ratios, with 95% confidence intervals (CIs), representing the relative VTE risk in people with AD compared with matched population controls. Adjusted for the full analysis set (see Table 2 legend). ***$P<0.001$ **$P<0.01$ *$P<0.05$.

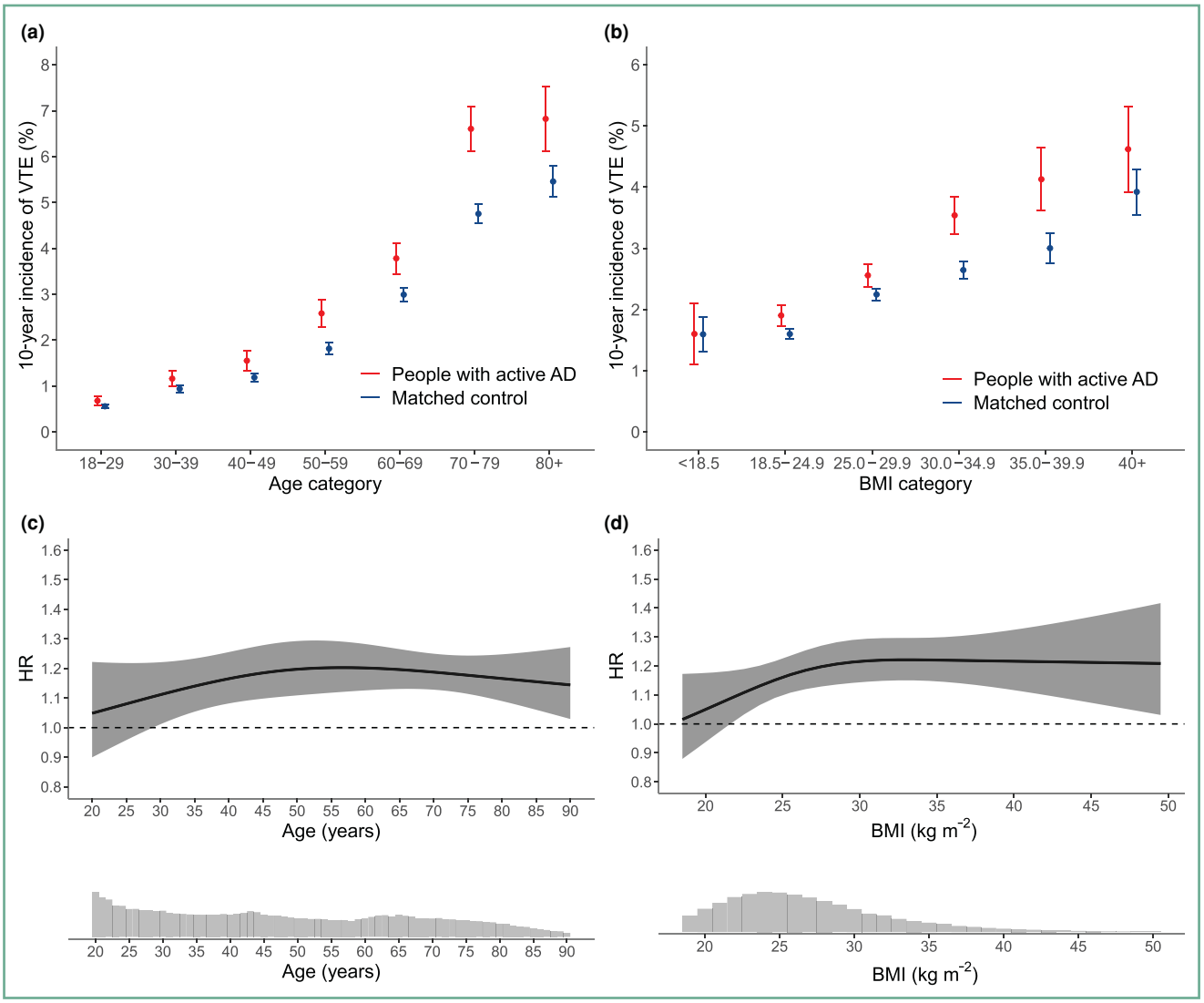


**Figure 3** Associations between active atopic dermatitis (AD) and venous thromboembolism (VTE) by age and body mass index (BMI). The upper panels show 10-year incidence of VTE by (a) age category and (b) BMI category in the AD group compared with matched population controls. Lower panels show the relative risk of VTE in the AD group compared with matched population controls by continuous (c) age and (d) BMI. For (c) and (d), associations are estimated using a 3-knot spline for each of BMI and age (to allow for nonlinearity) and adjusted for the full analysis set (see Table 2 legend). The shaded grey areas show 95% confidence intervals. The histograms below panels (c) and (d) show the relative distribution of participants by age and BMI, respectively. The evaluation of BMI excludes 208 259 patients who did not have a recorded BMI. HR, hazard ratio

the highest AD-associated VTE risk (BMI $\geq$ 30 kg m$^{-2}$: aHR patients with AD vs. controls 1.25, 95% CI 1.12–1.39, $P < 0.001$; BMI < 30 kg m$^{-2}$: aHR 1.08, 95% CI 1.01–1.15, $P < 0.05$) (Figure 2, Table S5a).

For the secondary outcomes, there was no evidence of an association between AD and PE risk across subgroups defined by age, sex, obesity, hormone treatment or history of other allergic conditions (Table S5b). Associations for DVT across the same subgroups were similar to those seen for the primary VTE outcome (Table S5c).

### Sensitivity analysis

Results were consistent in all sensitivity analyses (Table S6; see Supporting Information): excluding patients with AD and controls with any history of VTE prior to cohort entry (aHR 1.18, 95% CI 1.12–1.24); excluding patients with IBD and rheumatoid arthritis (aHR 1.18, 95% CI 1.12–1.24); using a composite definition of VTE based on VTE diagnosis or prescription of anticoagulant therapy (aHR 1.17, 95% CI 1.14–1.21); and excluding controls with no primary care interaction in the year prior to cohort entry (aHR 1.17, 95% CI 1.12–1.23).

## Discussion

Our population-based study of 150 975 adults with AD demonstrates that AD is associated with a modest (17%) increase in relative risk of VTE compared with the general population. The increase in VTE risk reflects a higher risk of DVT and not PE. The precise reason for this selectivity is not clear from these data. Additionally, we observed variation in AD-associated VTE risk by age and BMI. In

absolute terms, the 10-year risk of VTE is low (< 1.5%) in people under 50 years both with and without AD. Above 50 years, the VTE risk increases substantially with age, and the AD-associated risk increases this further in people with active AD. Similarly, in people with BMI < 25 kg $m^{-2}$ the absolute 10-year risk of VTE is low (< 2.0%) in people with and without AD. At higher BMI levels, both absolute VTE risk and AD-associated VTE risk are increased. In contrast to these heterogeneous risks, our results suggest that AD-associated risk does not differ by sex, and we found no evidence of a further VTE risk increase in those with more severe AD compared with mild or moderate AD, or in females with AD receiving oestrogen-based contraceptive treatment.

While our finding of a moderate 17% overall increase in VTE risk for people with AD is comparable with the 22% increased risk for patients with AD observed in hospital inpatients,[21] these findings do not concur with two previous population-based studies.[22,23] The largest of these studies, including 198 685 patients with AD, observed a 24% higher risk in those with moderate-to-severe AD, compared with controls without AD, although only when adjusted for age category, sex and year. In contrast, they noted an overall 23% lower risk of VTE, PE and DVT in people with AD compared with population controls[22] when risk estimates were fully adjusted, which included adjustment for healthcare utilization measures (outpatient visits, number of days hospitalized, and healthcare costs). As healthcare utilization would be part of the expected AD disease course, the observed lower risk may reflect a statistical overadjustment. The second study (30 418 patients with AD) investigated the risk of VTE in patients with a wide range of chronic inflammatory skin diseases, and did not identify associations between AD and VTE.[23] However, in contrast to our careful selection of general population controls from the same GP practice, controls were drawn from dermatology clinics, and so are unlikely to be representative of the general population. Moreover, only 171 VTE events were observed in people with AD, meaning this previous analysis was underpowered to detect the small increase in AD-associated VTE risk we have identified. A further strength of our analysis compared with these previous studies is our use of a stringent AD case identification algorithm and validated definitions for VTE events, whereas previous reports were more exposed to selection bias through less rigorous case definitions.

An association between AD and increased risk of VTE is consistent with growing epidemiological evidence that associations exist between VTE and other immune-mediated chronic inflammatory conditions,[14] especially IBD.[17–19] VTE risk is likely to be modified by a range of different mechanisms, influenced by both inflammation and the immune system, that contribute to pro-thrombotic states including inflammation in blood vessels, cell damage and changes to coagulation.[14] While these shared mechanistic pathways offer a possible explanation for our findings, future in-depth mechanistic studies are needed to elucidate potential causes of both the increase in VTE in people with AD seen in this study and recently reported associations between AD and other cardiovascular outcomes.[29,32]

The significant strengths of our analysis include the contemporary population-representative sample of people with AD, the large sample size and the long duration of follow-up. Our AD case and VTE outcome identification approach was previously validated in UK primary care.[26]

Despite our stringent active AD case definition which meant we excluded those with untreated AD, in common with all studies analysing retrospective data, our definitions may be subject to misdiagnosis or miscoding. We also may have missed some VTE diagnoses recorded in secondary but not primary care. To address this possibility, we undertook a further sensitivity analysis to broaden our capture of VTE cases by also including those who had started anticoagulants without an alternative indication. This did not significantly change our findings.

In keeping with previous UK studies,[29] we used systemic immunosuppressant treatment prescriptions, phototherapy and dermatology referrals as proxy measures for more severe AD. However, in the UK, immune-modulatory treatments are often prescribed by secondary care and therefore there is a risk of under-characterization of severe AD in the analysis of a primary care dataset, which would decrease the power to detect differences in VTE risk associated with disease severity. We were able to identify a clear increased VTE risk in severe AD compared with controls, but this was no greater than that seen in mild and moderate AD. However, in view of these limitations, we expect that the real-world association with severe AD is likely to be stronger.

A final limitation of our analysis is the lack of detailed physical activity and lifestyle information recorded in routine primary care data. While our analysis included comprehensive adjustment for known VTE risk factors (age, sex, deprivation, ethnicity, BMI, smoking and alcohol use, family history of VTE, reduced mobility, thrombophilia, recent hospital admission, comorbidities and prescribing at baseline) we were unable to adjust for other risk factors reported to be associated with both VTE and AD, including physical activity,[33] sleep quality[34] and cardiorespiratory fitness.[35,36] Assessing the potential modifying effects of such VTE risk factors in people with AD is an important area for future work.

In conclusion, this large, population-based analysis found individuals with AD had a small increased risk of VTE and DVT, with no increased risk of PE, compared with population controls. Both the absolute and relative AD-associated risk increase was most evident in older individuals and those with obesity. Absolute VTE risk was low in individuals of healthy body weight and those under 50 years old. In contrast, AD-associated VTE risk did not differ between sexes and was not increased for females on hormone treatment. Understanding why AD associates with an increased risk of VTE is vital for future research. Furthermore, knowledge of this increased VTE risk, as well as identification of subgroups at highest risk, is important for clinicians managing individuals with AD.

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### Conflicts of interest

R.B.W. has received research grants from AbbVie, Almirall, Amgen, Celgene, Janssen, LEO, Lilly, Medac, Novartis, Pfizer and UCB. He receives consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DiCE, GSK, Janssen, LEO, Lilly, Medac, Novartis, Pfizer, Sanofi, Sun Pharma, UCB and UNION. V.B. is an employee and shareholder of Pfizer Ltd. A.L. and C.C. are employees of Momentum Data Ltd, which was a paid consultant to Pfizer in connection with the development of this manuscript. M.R.A.-J. has received funding for consulting/advising/speaking/travel from AbbVie, Almirall, Galderma, Heptares, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, UCB and Unilever in the last 12 months. He has received research grants to his team/hospital to partake in or run studies with AbbVie, Almirall, Amgen, LEO, Pfizer, Sanofi-Genzyme and Unilever.

### Data availability

OPCRD data can be accessed by bona fide researchers for specific research projects, subject to approval by the Anonymized Data Ethics & Protocol Transparency (ADEPT) Committee. The data utilized for this study cannot be made available without such approval.

### Ethics statement

This use of anonymized data from OPCRD for this study was approved by the Anonymized Data Ethics & Protocol Transparency Committee (ADEPT; ADEPT0721) on 15 July 2021.

### Trial Registration

The study protocol was registered with ClinicalTrials.gov (study identifier: NCT04969653.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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