Incidence of cardiovascular events in a population-based Danish cohort with atopic dermatitis

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Background: The risk of cardiovascular disease in atopic dermatitis (AD) is not well established.
Objectives: Our aims were to evaluate the incidence rate (IR) of venous thromboembolism (VTE) in patients with AD in a population-based cohort study and to assess atherosclerotic cardiovascular disease (ASCVD) risk factors and incidence of malignancies, major adverse cardiovascular events (MACE), and VTE in patients with AD and rheumatoid arthritis (RA) in a nested cohort analysis.
Methods: Data from individuals age 12 years or older (nested cohort age ≥ 18 years) from January 1, 2000, to December 31, 2018, were extracted from the Danish National Patient Registry. Patients with AD were age- and sex-matched with 10 healthy controls. ASCVD risk factors included age 65 years or older and history of smoking, coronary artery disease, stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and malignancy.
Results: The population-based cohort comprised 190,751 patients (17,341 patients with AD and 173,410 healthy controls). The IRs per 100 patient-years were comparable between the AD cohort and healthy controls for VTE (0.14 [95% CI = 0.12-0.16] vs 0.11 [95% CI = 0.11-0.12]), DVT (0.08 [95% CI = 0.06-0.09] vs 0.06 [95% CI = 0.06-0.07]), and PE (0.06 [95% CI = 0.05-0.08] vs 0.05 [95% CI = 0.05-0.05]). The IR for VTE was higher in the AD cohort age 65 years or older (0.71 [95% CI = 0.56-0.90]) than in the age-matched controls (0.50 [95% CI = 0.46-0.54]). ASCVD risk factors were more frequent in the patients with RA than in the patients with AD. The IRs for malignancies and MACE were higher with specific ASCVD risk factors.
Conclusions: The IRs of cardiovascular events were comparable between the AD cohort and general population. The risk of VTE, malignancy, or MACE was higher with specific ASCVD risk factors, underscoring the need for patient monitoring. (J Allergy Clin Immunol Global 2024;3:100338.)

Key words: *Atherosclerotic cardiovascular disease, atopic dermatitis, deep vein thrombosis, Denmark, Janus kinase inhibitor, major adverse cardiovascular event, malignancies, pulmonary embolism, rheumatoid arthritis, venous thromboembolism*

Cardiovascular disease (CVD) is a major cause of mortality and morbidity globally. It has been linked to various chronic inflammatory conditions, including psoriasis and rheumatoid arthritis (RA).[1-3] Atopic dermatitis (AD) is a common inflammatory skin disorder defined by itch, eczematous lesions, and a chronic relapsing/remitting disease course.[4] The 1-year prevalence rates of AD in adults range from 2.2% to 17.6% worldwide; between-country variation may be driven by environmental and genetic heterogeneity.[5] Prevalence estimates are often higher in North European countries (14.3% in Denmark, 9.0% in Sweden, and 8.1% in the United Kingdom) than in other European countries (5.1% in Germany and 4.2% in Spain).[6,7]

AD is associated with sleep disturbances, anxiety, and depression, which result in impaired quality of life and an increased risk of CVD.[8-11] Previous population-based studies have identified an association between AD and cardiovascular risk factors, including smoking, diabetes, and high serum cholesterol levels.[12,13] However, another study reported no increase in the risk of myocardial infarction (MI) in patients with AD after adjusting for diagnosis severity and cardiovascular risk factors.[14] Furthermore, most studies reporting CVD risk in patients with AD have focused on MI and stroke, with limited evidence on the incidence of venous thromboembolic embolisms (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).[15]

Chronic inflammation, a hallmark of AD pathophysiology, has also been shown to increase the risk of malignancy and promote metastatic growth and spread.[16-19] Several insurance claims database analyses of population-based cohorts have shown an increased risk of lymphoma, nonmelanoma skin cancer (NMSC), breast cancer, and colorectal cancer in patients with AD versus in the general population.[15,20-22]

The management of AD requires regular maintenance therapy, the potency of which differs depending on disease severity.[23] Although mild AD is typically managed using topical medicated therapy (eg, topical corticosteroids), patients with moderate or severe AD and those whose disease is refractory to topical treatment may require systemic therapies[23]; the options currently approved in Europe for the treatment of moderate-to-severe AD include Janus kinase inhibitors (JAKIs; ie, abrocitinib, baricitinib, and upadacitinib),[24-26] and mAbs (ie, dupilumab, lebrikizumab, and

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Received for publication March 22, 2024; revised July 3, 2024; accepted for publication August 6, 2024.

Available online September 1, 2024.

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2772-8293

https://doi.org/10.1016/j.jacig.2024.100338

Abbreviations used

AD: Atopic dermatitis
ASCVD: Atherosclerotic cardiovascular disease
CAD: Coronary artery disease
CVD: Cardiovascular disease
DVT: Deep vein thrombosis
ICD: International Classification of Diseases
IR: Incidence rate
JAKI: Janus kinase inhibitor
MACE: Major adverse cardiovascular event
MI: Myocardial infarction
NMSC: Nonmelanoma skin cancer
PE: Pulmonary embolism
PY: Patient-years
RA: Rheumatoid arthritis
VTE: Venous thromboembolism

tralokinumab).[27-29] The decision to switch to systemic agents must consider patient attitudes toward treatment, disease severity, impact on quality of life, and any underlying risk factors, such as patient age and underlying comorbid health conditions.[30-32]

To facilitate proper patient selection and management of cardiovascular risk factors, we evaluated incidence rates (IRs) of VTE, DVT, and PE in patients with and without AD in a population-based cohort study in Denmark. We also assessed the IRs of malignancies, major adverse cardiovascular events (MACE), and VTE and the distribution of atherosclerotic CVD (ASCVD) risk factors in patients with AD in a nested cohort analysis. To understand whether the distribution of risk factors differs among inflammatory diseases, patients with RA were included as a comparison cohort.

METHODS

Study participants

Data were extracted from the Danish National Patient Register, a nationwide longitudinal registry of hospital admissions since 1977 and outpatient contacts since 1995. All individuals age 12 years or older (≥18 years in the nested cohort) between January 1, 2000, and December 31, 2018, with at least 1 day of follow-up were eligible for inclusion in the population-based cohort study.

Both the population-based cohort study and nested cohort analysis included patients with at least 1 diagnosis of AD (using the International Classification of Diseases [ICD], 10th Revision, diagnostic code ICD-L20) during the study period. Incidence density sampling was used to match (on the basis of sex and date of birth) each patient with AD with 10 individuals from those members of the general population in Denmark with no recorded history of a diagnosis of AD. The nested cohort analysis included patients with a diagnosis of RA (ICD, 10th Revision, diagnostic codes M05-M06) during the study period as an additional comparison population. Patients were eligible for inclusion in the RA cohort only if they were not already included in the AD cohort or the general population.

Assessments

In the population-based cohort study, patients were grouped by age (12 to <18 years, 18 to <65 years, and ≥65 years), and incidence of VTE was assessed (primary outcome). VTE was stratified into PE and DVT and examined as separate outcomes. The nested cohort analysis assessed the distribution of ASCVD risk factors in patients with AD, patients with RA, and the general population. The rates of malignancies, MACE, and VTE were assessed in patients with AD with and without selected ASCVD risk factors (age ≥ 65 years; former/current smoker; and history of coronary artery disease [CAD], stroke, DVT, PE, and malignancy). The follow-up period for both analyses was from the first recorded diagnosis during the study period until the occurrence of death or an end point, the first instance of migration, or December 31, 2018.

Data analysis

In the nested cohort analysis, ASCVD was defined in 2 ways: (1) by using a broader definition, which included patients with at least 1 of the following: history of CAD (defined as the presence of a history of stable angina pectoris, artery procedure, coronary heart disease, or MI), cerebrovascular disease (stroke or carotid atherosclerosis), peripheral artery disease, or undefined ASCVD and (2) by using the same criteria as in the first definition except that CAD was defined as presence of a history of coronary heart disease or MI only. History of CVD, peripheral artery disease, and undefined ASCVD was determined on the basis of the preferred terms listed in Table E1 (available in this article's Online Repository at www.jaci-global.org).

Summary statistics were descriptive and expressed as means and SDs for normally distributed variables, medians and interquartile ranges for nonnormally distributed continuous variables, and frequencies for categorical variables. IRs are shown per 100 patient-years (PY) of exposure with 95% CIs.

RESULTS

Population-based cohort study: Patient characteristics

Of the 190,751 patients in the population-based cohort study, 17,341 were diagnosed with AD and 173,410 were age- and sex-matched controls from the general population. Baseline characteristics are shown in Table I. Most of the patients with AD (71.6%) were 18 to <65 years of age. History of VTE was comparable between the AD cohort and the general population (1.0% vs 0.6%), including DVT (0.7% vs 0.4%) and PE (0.3% vs 0.2%). Medication use was comparable between the AD cohort and the general population, except for use of oral glucocorticoids (34.3% vs 11.2%), methotrexate (8.0% vs 1.1%), and azathioprine (10.5% vs 0.5%).

Population-based cohort study: IRs of VTE, DVT, and PE

VTE. The IR of a VTE per 100 PY was largely comparable between the AD cohort (IR = 0.14 [95% CI = 0.12-0.16]) and the age- and sex-matched general population (IR = 0.11 [95% CI = 0.11-0.12] [Fig 1]). VTE incidence was higher (with nonoverlapping CIs) in patients with AD age 65 years or older (IR = 0.71 [95% CI = 0.56-0.90]) than in the younger cohorts (age 18 to <65 years, IR = 0.11 [95% CI = 0.09-0.13]; age 12 to <18 years, IR = 0.02 [95% CI = 0.00-0.08]) and the general population age 65 years or older (IR = 0.50 [95% CI = 0.46-0.54] [Fig 1]).

TABLE I. Baseline patient demographics and disease characteristics in the population-based cohort study

Characteristic	General population (n = 173,410)	AD cohort (n = 17,341)
Age (y)		
Mean (SD)	32.7 (17.2)	32.7 (17.2)
Median (IQR)	27.9 (18.8-43.1)	27.9 (18.8-43.1)
12 to <18, no. (%)	39,017 (22.5)	3,909 (22.5)
18 to <65, no. (%)	124,162 (71.6)	12,408 (71.6)
≥65, no. (%)	10,231 (5.9)	1,024 (5.9)
Sex, no. (%)		
Female	104,910 (60.5)	10,491 (60.5)
Male	68,500 (39.5)	6,850 (39.5)
Socioeconomic status, no. (%)		
Lowest group	34,794 (20.1)	3,356 (19.4)
Below average	34,584 (19.9)	3,566 (20.6)
Average	34,698 (20.0)	3,453 (19.9)
Above average	34,802 (20.1)	3,348 (19.3)
Highest group	34,532 (19.9)	3,618 (20.9)
Charlson comorbidity index		
None	168,137 (97.0)	16,399 (94.6)
1	2,643 (1.5)	432 (2.5)
2	1,701 (1.0)	311 (1.8)
3 or more	929 (0.5)	199 (1.1)
Diabetes history, no. (%)	8,308 (4.8)	867 (5.0)
Previous VTE, no. (%)	1,021 (0.6)	166 (1.0)
Previous DVT	749 (0.4)	123 (0.7)
Previous PE	356 (0.2)	56 (0.3)
Medication use, no. (%)		
Cholesterol-lowering drugs	16,283 (9.4)	1,666 (9.6)
Platelet inhibitors	11,803 (6.8)	1,260 (7.3)
Oral glucocorticoids	19,484 (11.2)	5,947 (34.3)
β-blockers	15,516 (9.0)	1,627 (9.4)
Thiazide diuretics	294 (0.2)	34 (0.2)
ACE inhibitors/ARB	18,969 (10.9)	1,962 (11.3)
Vitamin K antagonists	2,602 (1.5)	317 (1.8)
Loop diuretics	7,402 (4.3)	1,013 (5.8)
Spironolactone	2,573 (1.5)	333 (1.9)
Methotrexate	1,890 (1.1)	1,393 (8.0)
Azathioprine	895 (0.5)	1,823 (10.5)
Mycophenolate	159 (0.1)	204 (1.2)
Cyclosporine	187 (0.1)	493 (2.8)

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *IQR*, interquartile range.

Similar trends for VTE incidence were observed in the AD cohort without a history of VTE ([Fig 1]).

DVT. The IR of DVT was comparable between the AD cohort (IR = 0.08 [95% CI = 0.06-0.09]) and the age- and sex-matched general population (IR = 0.06 [95% CI = 0.06-0.07] [Fig 2]). DVT incidence was higher (with nonoverlapping CIs) in patients with AD age 65 years or older (IR = 0.23 [95% CI = 0.15-0.34]) than in the younger cohorts (age 18 to <65 years, IR = 0.07 [95% CI = 0.06-0.09]; 12 to <18 years, IR = 0.01 [95% CI = 0.00-0.07]) and numerically higher (with overlapping CIs) than in the general population age 65 years or older (IR = 0.21 [95% CI = 0.19-0.24] [Fig 2]). Similar trends for DVT incidence were observed in the AD cohort without a history of VTE (Fig 2).

PE. The IR of PE was comparable between the AD cohort (IR = 0.06 [95% CI = 0.05-0.08]) and the age- and sex-matched general population (OR = 0.05 [95% CI = 0.05-0.05] [Fig 3]). PE incidence was higher (with nonoverlapping CIs) in patients with AD age 65 years or older (0.47 [0.35-0.63]) than in the younger cohorts (age 18 to <65 years, IR = 0.04 [95% CI = 0.03-0.05]; age 12 to <18 years, IR = 0.01 [95% CI = 0.00-0.07]) and the general population age 65 years or older (IR = 0.28 [95% CI = 0.25-0.32] [Fig 3]). Similar trends for PE were observed in the AD cohort without a history of VTE (Fig 3).

Nested cohort analysis: Patient characteristics

Of the 195,807 patients in the nested cohort, 13,432 were diagnosed with AD and 134,320 were age- and sex-matched controls from the general population; 48,055 patients were included in the RA cohort (Table II). The mean age was 37.8 years in the AD cohort and 60.3 years in the RA cohort. The mean body mass index was 25.1 kg/m^2, 24.9 kg/m^2, and 25.7 kg/m^2 in the AD cohort, the general population, and the RA cohort, respectively. In the AD cohort, 6.6% of patients had comorbidities versus 3.8% in the general population and 30.3% in the RA cohort. Current medication use (ie, a prescription filled within the past 180 days) was lower for most medications in the AD cohort and the general population compared with the RA cohort.

Nested cohort analysis: Distribution of risk factors and IRs of malignancies, MACE, and VTE

Malignancies. Risk factors for malignancies (excluding NMSC) were observed in comparable proportions of patients in the AD cohort and general population but were more frequent in the RA cohort (Table III). A similar trend was observed in the distribution of additional risk factors for malignancy (see Table E2 in this article's Online Repository at www.jaci-global.org). The IRs for any malignancy (excluding NMSC) were higher in the AD cohort with at least 1 risk factor for malignancy than in those patients without any risk factors (Table III); this was consistent across all assessed risk factors except for smoking, in which case the 95% CIs overlapped. The IR of malignancies was higher in patients with a history of malignancies than in those without such a history (IR = 11.41 [95% CI = 9.83-13.25] vs IR = 0.44 [95% CI = 0.40-0.48]), and in older (age ≥ 65 years) versus younger (age < 65 years) patients (IR = 3.09 [95% CI = 2.75-3.48] vs IR = 0.36 [95% CI = 0.33-0.40] [Table III]). The IRs of malignancies (excluding NMSC) were higher in the AD cohort whose members had additional risk factors than among those patients who did not have these risk factors (see Table E2).

MACE. The frequency of major risk factors for MACE was comparable between the AD cohort and general population but higher in the RA cohort (Table IV). Hypertension and dyslipidemia occurred more frequently in the RA cohort than in the AD cohort and general population. The frequency of risk factors for MACE, including a history of smoking, was higher in the RA cohort than in the AD cohort and the general population (Table IV). Similarly, the frequency of additional risk factors for MACE was higher in the RA cohort than in the AD cohort and general population (see Table E3 in the Online Repository at www.jaci-global.org).

The IR for MACE in the AD cohort was higher in patients with risk factors for MACE than in those without risk factors for MACE, in older (age ≥ 65 years) versus younger (age < 65 years) patients, and in current or former smokers than in never smokers (albeit with overlapping 95% CIs [Table IV]). Patients with a history of ASCVD had a higher IR of MACE than those without a

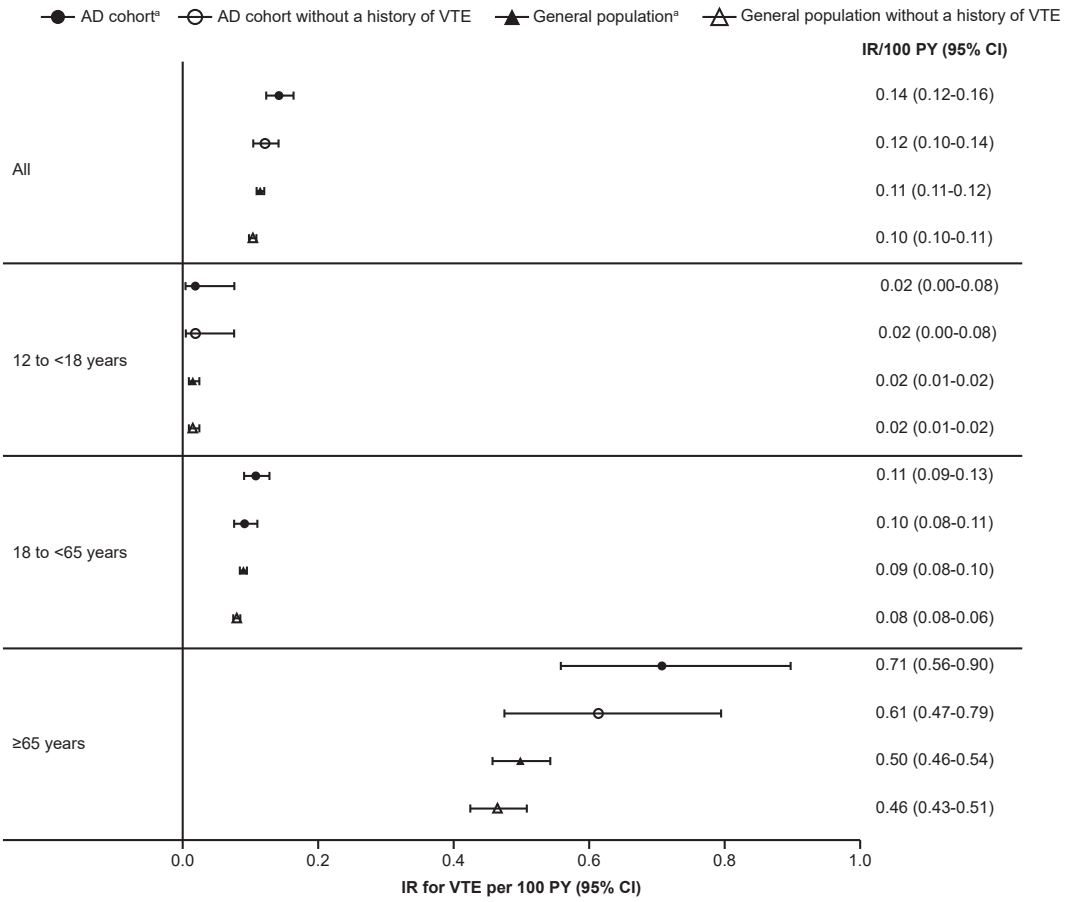

FIG 1. IR of VTE events per 100 PY among patients with AD and age- and sex-matched controls from the general population (population-based cohort study). [a]Includes patients with and without a history of VTE.

history of ASCVD. The IRs for MACE were higher among patients with a history of hypertension and dyslipidemia than in those without such a history. Similarly, the IRs for MACE were higher in patients in the AD cohort who had additional risk factors for MACE compared with patients without such risk factors (see Table E3).

VTE. Risk factors for VTE were generally comparable between the AD cohort and the general population and more prevalent in the RA cohort (Table V); a similar trend was observed in the distribution of additional risk factors for VTE (see Table E4 in the Online Repository at www.jaci-global.org). Patients in the AD cohort with a history of VTE, DVT, or PE or inherited thrombophilia carried a substantially greater risk of VTE events than did patients without these risk factors (Table V). The IR of VTE per 100 PY was higher in older (age ≥ 65 years) than younger (age < 65 years) patients (IR = 0.71 [95% CI = 0.56-0.90] vs IR = 0.12 [95% CI = 0.10-0.15]). The rate of VTE increased as the number of risk factors increased, albeit with overlapping 95% CIs (Table V). Similarly, the IRs for VTE per 100 PY were higher in the AD cohort with additional risk factors for VTE than in the AD cohort without these risk factors (see Table E4).

DISCUSSION

Our large population-based cohort study demonstrated that the IRs of VTE, DVT, and PE in 17,341 patients with AD were comparable with those in the general population. An increased risk of VTE, DVT, and PE was observed in patients who had a history of these events. An increased risk of VTE, DVT, and PE was also seen in patients with AD age 65 years or older. In the nested cohort analysis, the frequency of risk factors was generally higher in patients with RA than in the AD cohort and general population. In the AD cohort, the incidence of MACE was higher in those patients age 65 years or older who had a history of ASCVD, CAD, and stroke. The risk of malignancies was also higher in patients with a history of previous malignancies.

Other population-based cohort studies have reported higher rates of VTE, DVT, and PE in patients with AD than in healthy controls. In a Taiwan population-based cohort study by Chen et al, the IRs of VTE, DVT, and PE per 1000 PY were 1.05, 0.85, and 0.25, respectively, in the AD cohort, compared with 0.82, 0.68, and 0.19 in the non-AD cohort; similar to our study, an increased risk of VTE was reported in older patients (age ≥ 45 years) than in younger patients with AD.[33] A retrospective claims-based cohort study in the United States by Hedderson et al reported IRs per 1000 PY of 2.0, 1.6, and 0.7 for VTE, DVT, and PE, respectively, in patients with AD versus 1.1, 0.66, and 0.41, respectively, in the general population.[34] Another retrospective US claims-based cohort study by Meyers et al showed higher IRs per 100 PY for VTE and DVT (0.31 for VTE and 0.25 for DVT) in patients with moderate-to-severe AD than in the overall AD population (IRs of 0.24 and 0.19, respectively) and controls without AD

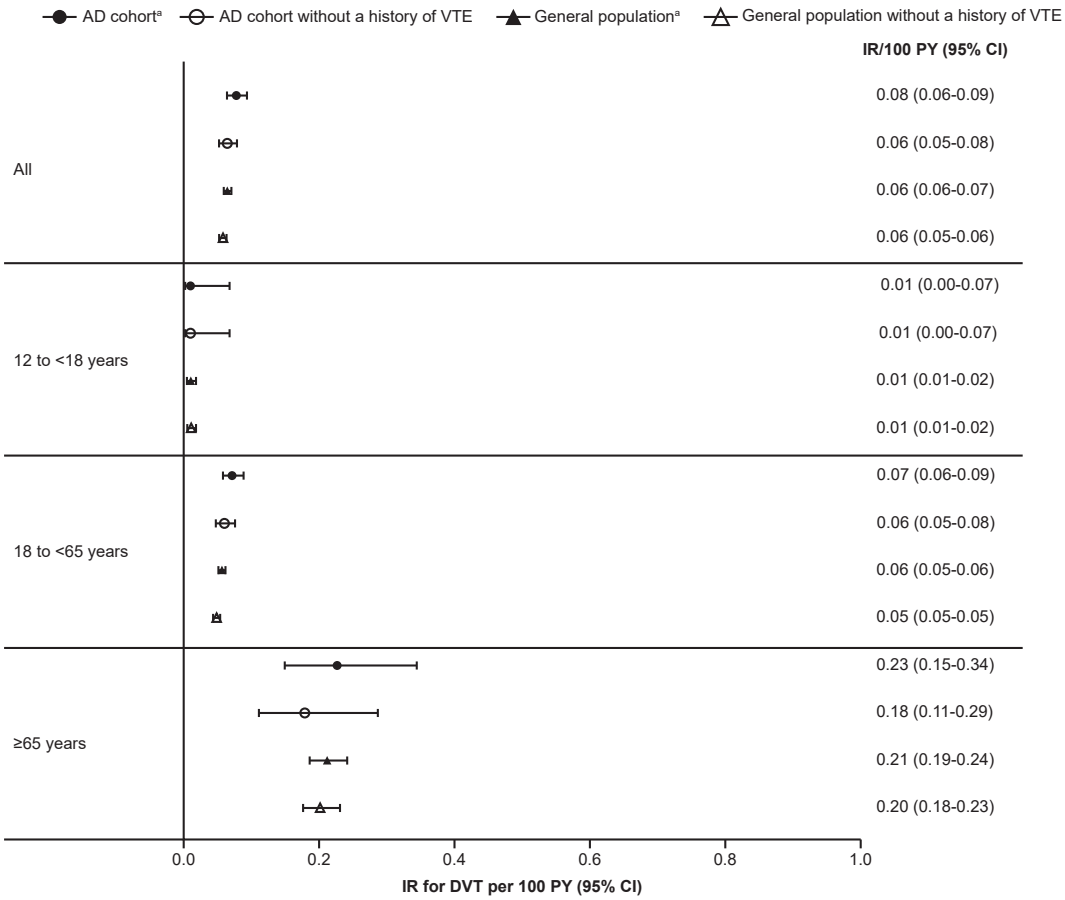

FIG 2. IR of DVT per 100 PY among patients with AD and age- and sex-matched controls from the general population (population-based cohort study). [a]Includes patients with and without a history of VTE.

(IRs of 0.25 and 0.19, respectively).[35] These rates are higher than the rates observed in our study and may be attributable to the differences in AD severity; both the aforementioned study by Hedderson et al and subgroup analysis from Meyers et al excluded patients with mild disease,[34,35] whereas our study included all patients with AD irrespective of disease severity.

In our study, the IR of overall malignancy in the AD cohort with ASCVD risk factors was 0.59 per 100 PY. In a UK population-based cohort study by Wan et al, the IRs of various malignancies ranged from 97.4 to 125.3 per 10,000 PY.[15] In another US claims database analysis by Hedderson et al,[22] the IRs of malignancies (lung cancer, breast cancer, melanoma, and lymphoma) in patients with moderate-to-severe AD ranged from 0.4 to 2.1 per 1000 PY. The differences between these IRs and those in our study may be attributable to the exclusion criteria; patients with any history of malignancy were excluded from the US study.

Similar to the findings in our study, a pooled safety analysis of clinical trials with baricitinib demonstrated a higher risk of VTE, MACE, and malignancy in patients with AD with ASCVD risk factors (IRs of 0.12, 0.25, and 0.45, respectively) than in those patients with AD without ASCVD risk factors (IRs of 0.04, 0.04, and 0.13, respectively).[36] In baricitinib-treated patients with RA with risk factors for ASCVD, the IRs per 100 PY for VTE, MACE, and malignancy were 0.66, 0.70, and 1.23, respectively, versus 0.09, 0.05, and 0.20 in patients with RA without the ASCVD risk factors.[36] The differences in the IRs of VTE, MACE, and malignancy between the clinical trials with baricitinib and our study may be attributable to the differences in the study populations. The baricitinib clinical trials excluded patients with a history of previous VTE, MI, stroke, serious infection, or malignancy and thus likely included a healthier group of patients than in our population-based AD cohort.

The selection of patients with RA as a comparator population in the current study was based on the recent reassessment by the European Medicines Agency of all oral JAKIs currently approved for the treatment of chronic inflammatory disorders such as AD, RA, psoriatic arthritis, juvenile idiopathic arthritis, axial spondylarthritis, ulcerative colitis, and alopecia areata.[37] This reassessment was implemented in response to findings from a postauthorization safety trial that highlighted an increased risk of MACE and malignancies in patients with RA who were age 50 years or older, with at least 1 additional cardiovascular risk factor, and who had received treatment with the JAKI tofacitinib versus with a tumor necrosis factor-α (TNF-α) inhibitor.[38] Additionally, in a pooled (Europe, the United States, and Japan) claims database and disease registry-based analysis of patients with RA, Salinas et al reported a higher risk of VTE and MACE in patients with RA treated with baricitinib than in patients treated with a TNF-α inhibitor.[39] The European Medicines Agency ruled in favor of including an advisory on all JAKI labels cautioning the

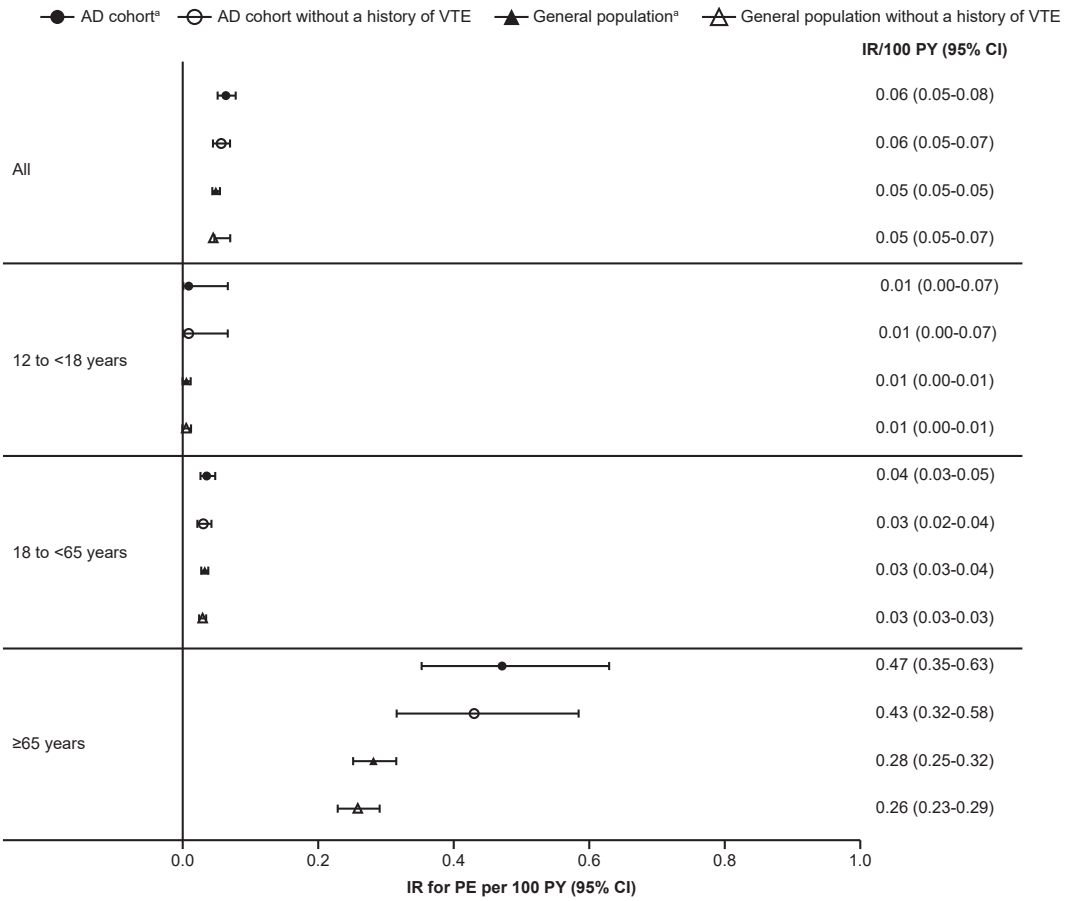

FIG 3. IR of PE per 100 PY among patients with AD and age- and sex-matched controls from the general population (population-based cohort study). [a]Includes patients with and without a history of VTE.

prescription of JAKIs to at-risk populations (patients age ≥ 65 years with a history of ASCVD, smoking, and malignancies or patients at risk of VTE, PE, or DVT).[31,40]

It is important to note the general differences between the patients with AD and those with RA in our study. In our study, the patients with AD were much younger than those with RA (mean age 37.8 years vs 60.3 years), and the prevalence of most assessed risk factors for malignancy, MACE, and VTE was lower in patients with AD than in patients with RA, trends that have been noted previously.[31] However, compared with earlier Danish nationwide cohort studies of patients with psoriasis (mean age 26.3-48.4 years across studies),[41,42] the frequency of many risk factors for VTE and MACE was higher in patients with AD in the current study. Together, these findings emphasize the importance of monitoring patients with systemic inflammatory conditions: product labels for systemic therapies for AD, including JAKIs, describe the risk factors associated with these therapies, including the risk factors analyzed in the current study, and recommend patient selection and monitoring.[31]

A key strength of our study is its large sample size derived from a universal health care system, which allowed for assessment of adverse events in various subgroups of patients with AD. Additionally, the use of claims data from a universal health care system minimized the potential selection bias that is likely to occur in smaller data sets from privately insured health care systems. Our study has several limitations. Comorbidities were diagnosed solely on the basis of presence of the corresponding code in the Danish National Patient Register; the severity of each comorbidity is not known. Additionally, diagnoses were defined on the basis of a predominantly hospital-based population and may not be representative of all patients with AD. Our analysis is representative mainly of a northern European (predominantly White) population and hence may not be generalizable to other populations, particularly in terms of health indices, which might differ between countries (eg, body mass index tends to be higher in the US general population).[43]

Conclusions

In conclusion, our analysis of 2 large cohorts of adults and adolescents with AD showed that the incidence of VTE, DVT, and PE was comparable to that in the general population. The risk of VTE and PE increased in patients with AD who were older (ie, age ≥ 65 years) and in patients who had a history of VTE, DVT, PE, or inherited thrombophilia. The rates of MACE were higher in patients age 65 years or older with AD and a history of smoking, ASCVD, CAD, and stroke, and the risk of malignancies was higher in those with a history of previous malignancies. The proportions of patients with risk factors for malignancies

TABLE II. Baseline patient demographics and disease characteristics in the nested cohort analysis

Characteristic	General population (n = 134,320)	AD cohort (n = 13,432)	RA cohort (n = 48,055)
Age (y)			
Mean (SD)	37.8 (16.2)	37.8 (16.2)	60.3 (15.1)
Median (IQR)	34.2 (24.4-47.7)	34.2 (24.4-47.7)	61.7 (50.6-71.7)
≥65, no. (%)	10,240 (7.6)	1,024 (7.6)	20,174 (42.0)
Sex, no. (%)			
Female	83,500 (62.2)	8,350 (62.2)	33,567 (69.9)
Male	50,820 (37.8)	5,082 (37.8)	14,488 (30.2)
Ethnicity, no. (%)			
Danish	125,541 (93.5)	12,789 (95.2)	45,906 (95.5)
European, excluding Danish	4,402 (3.3)	290 (2.2)	1,319 (2.7)
Asian	3,176 (2.4)	274 (2.0)	600 (1.3)
African	927 (0.7)	56 (0.4)	123 (0.3)
Other	274 (0.2)	23 (0.2)	107 (0.2)
BMI			
Patients with BMI data available, no. (%)	16,806 (12.5)	4,039 (30.1)	3,766 (7.8)
Mean (SD)	24.9 (6.1)	25.1 (5.5)	25.7 (5.8)
Median (IQR)	23.7 (21.2-27.3)	24.1 (21.6-27.3)	25.0 (22.0-28.5)
≥30 kg/m^2, no. (%)	2,522 (15.0)	567 (14.0)	714 (19.0)
General comorbidity, no. (%)			
Congestive heart failure	462 (0.3)	99 (0.7)	1,018 (2.1)
RA	677 (0.5)	107 (0.8)	48,055 (100.0)
Diabetes	1,611 (1.2)	170 (1.3)	1,448 (3.0)
IBD	1,228 (0.9)	281 (2.1)	683 (1.4)
Moderate/severe chronic renal disease	263 (0.2)	83 (0.6)	393 (0.8)
Malignancy (excluding NMSC)	3,105 (2.3)	396 (3.0)	3,306 (6.9)
Coronary artery disease (definition 1)	2,775 (2.1)	353 (2.6)	4,291 (8.9)
Coronary artery disease (definition 2)	1,881 (1.4)	246 (1.8)	3,401 (6.3)
Stroke/TIA	1,879 (1.4)	248 (1.9)	1,985 (4.1)
Atrial fibrillation	1,386 (1.0)	197 (1.5)	2,213 (4.6)
COPD	567 (0.4)	168 (1.3)	1,354 (2.8)
Charlson comorbidity index, no. (%)			
None	129,256 (96.2)	12,541 (93.4)	33,472 (69.7)
1	2,529 (1.9)	410 (3.1)	9,943 (20.7)
2	1,641 (1.2)	289 (2.2)	2,821 (5.9)
3 or more	894 (0.7)	192 (1.4)	1,891 (3.8)
Medication use,* no. (%)			
Cholesterol-lowering drugs	387 (0.3)	64 (0.5)	495 (1.0)
Platelet inhibitors	295 (0.2)	46 (0.3)	523 (1.1)
Oral glucocorticoids	634 (0.5)	751 (6.0)	2,782 (5.8)
β-blockers	491 (0.4)	60 (0.5)	499 (1.0)
Thiazide diuretics	10 (0.0)	3 (0.0)	41 (0.1)
ACE inhibitors/ARB	444 (0.3)	53 (0.4)	633 (1.3)
Vitamin K antagonists	93 (0.1)	10 (0.1)	201 (0.4)
Loop diuretics	197 (0.2)	68 (0.5)	814 (1.7)
Spironolactone	92 (0.1)	17 (0.1)	221 (0.5)
Methotrexate	53 (0.0)	94 (0.7)	1,847 (3.8)
Azathioprine	33 (0.0)	166 (1.2)	140 (0.3)
Mycophenolate	<3 (NS)	8 (0.1)	4 (0.0)
Cyclosporine	6 (0.0)	29 (0.2)	37 (0.1)
Hormone replacement therapy	51 (0.0)	6 (0.0)	10 (0.0)
Antipsychotics	280 (0.2)	32 (0.2)	122 (0.3)
Oral contraceptives	640 (0.5)	62 (0.5)	53 (0.1)
Tamoxifen	12 (0.0)	5 (0.0)	11 (0.0)

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *COPD*, chronic obstructive pulmonary disease; *IBD*, inflammatory bowel disease; *IQR*, interquartile range; *NS*, not shown; *TIA*, transient ischemic attack.
*Filled prescription within 180 or fewer days.

(excluding NMSC), MACE, and VTE were comparable in the AD cohort and general population, but higher in patients with RA. This analysis underscores the need for appropriate monitoring and reporting of cardiovascular events in patients with AD and active management of risk factors with early and effective therapeutic intervention.

TABLE III. Distribution of risk factors for malignancy excluding NMSC and IR per 100 PY of malignancies excluding NMSC (nested cohort analysis)

	Study population			IR per 100 PY (95% CI)	
Risk factor, no. (%)	General population n = 134,320	AD cohort n = 13,432	RA cohort n = 48,055	AD cohort with risk factor(s)	AD cohort without risk factor(s)
Overall	134,320 (100.0)	13,432 (100.0)	48,055 (100.0)	0.59 (0.54-0.64)	Not applicable
Risk factor					
Age ≥ 65 y	10,240 (7.6)	1,024 (7.6)	20,174 (42.0)	**3.09 (2.75-3.48)**	**0.36 (0.33-0.40)**
Ever smoked	124/221 (56.1)	1,304/2,568 (50.8)	162/227 (71.4)	0.50 (0.40-0.64)	0.34 (0.25-0.46)
History of malignancy (excl. NMSC/cervical cancer)	2,976 (2.2)	382 (2.8)	3,215 (6.7)	**11.41 (9.83-13.25)**	**0.44 (0.40-0.48)**
Any of the aforementioned risk factors	133/221 (60.2)	1,374/2,568 (53.5)	172/227 (75.8)	**0.59 (0.47-0.73)**	**0.24 (0.17-0.35)**
Any of the aforementioned risk factors (excl. smoking)	12,007 (8.9)	1,243 (9.3)	21,193 (44.1)	**4.69 (4.18-5.27)**	**0.34 (0.31-0.38)**
History of ASCVD (definition 1)	5,398 (4.0)	689 (5.1)	8,292 (17.3)	**2.12 (1.73-2.59)**	**0.52 (0.48-0.57)**
History of ASCVD (definition 2)	4,663 (3.5)	603 (4.5)	7,338 (15.3)	**2.00 (1.61-2.49)**	**0.53 (0.49-0.58)**

IRs with nonoverlapping 95% CIs are shown in bold.
CHD, Coronary heart disease.

TABLE IV. Distribution of risk factors for MACE and IR of MACE per 100 PY (nested cohort analysis)

	Study population			IR per 100 PY (95% CI)	
Risk factor, no. (%)	General population (n = 134,320)	AD cohort (n = 13,432)	RA cohort (n = 48,055)	AD cohort with risk factor(s)	AD cohort without risk factor(s)
Overall	134,320 (100.0)	13,432 (100.0)	48,055 (100.0)	0.33 (0.29-0.36)	Not applicable
Major risk factor (definition 1)					
Age ≥ 65 y	1,024 (7.6)	1,024 (7.6)	20,174 (42.0)	**2.30 (2.01-2.63)**	**0.15 (0.13-0.17)**
Ever smoker	124/221 (56.1)	1,304/2,568 (50.8)	162/227 (71.4)	0.17 (0.11-0.26)	0.07 (0.03-0.13)
History of ASCVD (definition 1)	5,398 (4.0)	689 (5.1)	8,292 (17.3)	**5.02 (4.37-5.76)**	**0.15 (0.13-0.18)**
Any major risk factor (definition 1)	133/221 (60.2)	1,377/2,568 (53.6)	171/227 (75.3)	**0.18 (0.12-0.27)**	**0.04 (0.02-0.10)**
Any major risk factor (definition 1; excl. smoking)	13,200 (9.8)	1,387 (10.3)	22,959 (47.8)	**3.45 (3.07-3.89)**	**0.09 (0.07-0.11)**
Major risk factor (definition 2)					
Age ≥ 65 y	10,240 (7.6)	1,024 (7.6)	20,174 (42.0)	**2.30 (2.01-2.63)**	**0.15 (0.13-0.17)**
Ever smoker	124/221 (56.1)	1,304/2,568 (50.8)	162/227 (71.4)	0.17 (0.11-0.26)	0.07 (0.03-0.13)
History of ASCVD (definition 2)	4,663 (3.5)	603 (4.5)	7,338 (15.3)	**5.55 (4.83-6.39)**	**0.16 (0.13-0.18)**
Any major risk factor (definition 2)	133/221 (60.2)	1,374/2,568 (53.5)	171/227 (75.3)	**0.18 (0.12-1.27)**	**0.04 (0.02-0.10)**
Any major risk factor (definition 2; excl. smoking)	12,737 (9.5)	1,337 (10.0)	22,603 (47.0)	**3.56 (3.16-4.01)**	**0.09 (0.07-0.11)**
Other risk factor					
Hypertension	7,601 (5.7)	856 (6.4)	9,968 (20.7)	**2.93 (2.48-3.47)**	**0.21 (0.19-0.24)**
Dyslipidemia	3,899 (2.9)	429 (3.2)	4,214 (8.8)	**2.23 (1.72-2.90)**	**0.28 (0.25-0.32)**
No major and 0 other risk factors	86/221 (38.9)	1,152/2,568 (44.9)	46/227 (20.3)	**0.04 (0.02-0.11)**	**0.18 (0.12-0.26)**
No major and 1 other risk factor	NS	34/2,568 (1.3)	8/227 (3.5)	NS	0.12 (0.08-0.17)
No major and 2 other risk factors	NS	5/2,568 (0.2)	NS	NS	0.12 (0.08-0.17)
No major and 0 other risk factors (excl. smoking)	116,512 (86.7)	11,555 (86.0)	21,789 (45.3)	**0.08 (0.06-0.09)**	**2.55 (2.27-2.86)**
No major and 1 other risk factor (excl. smoking)	4,035 (3.0)	431 (3.2)	2,916 (6.1)	**0.37 (0.21-0.67)**	**0.12 (0.09-0.17)**
No major and 2 other risk factors (excl. smoking)	573 (0.4)	59 (0.4)	391 (0.8)	0.53 (0.13-2.11)	0.12 (0.08-0.17)

No or too few MACE prevented estimation of risk factor distribution in some groups. IRs with nonoverlapping 95% CIs are shown in bold.
CHD, Coronary heart disease; *excl.*, excluding; *NS*, not shown.

DISCLOSURE STATEMENT

This study was funded by Pfizer Inc.

Disclosure of potential conflicts of interest: A. Egeberg has received research funding from Pfizer Inc, AbbVie, Almirall, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly and Company, Novartis, Janssen, the Danish National Psoriasis Foundation, the Simon Spies Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, as well as honoraria for serving as a consultant and/or speaker from Pfizer, AbbVie, Amgen, Almirall, Bristol-Myers Squibb, Boehringer Ingelheim, Dermavant, Eli Lilly and Company, Galápagos NV, Galderma, Horizon Therapeutics, Janssen, LEO Pharma, McNeil Consumer Healthcare, Mylan, Novartis, Samsung Bioepis Co, Ltd, Sun Pharmaceuticals, UCB, Union Therapeutics, and Zuellig Pharma, Ltd. A.

TABLE V. Distribution of risk factors for VTE and IR of VTE per 100 PY (nested cohort analysis)

	Study population			IR per 100 PY (95% CI)	
Risk factor, no. (%)	General population (n = 134,320)	AD cohort (n = 13,432)	RA cohort (n = 48,055)	AD cohort with risk factor(s)	AD cohort without risk factor(s)
Overall	134,320 (100.0)	13,432 (100.0)	48,055 (100.0)	0.18 (0.15-0.20)	Not applicable
Risk factor					
Age ≥ 65 years	10,240 (7.6)	1,024 (7.6)	20,174 (42.0)	**0.71 (0.56-0.90)**	**0.12 (0.10-0.15)**
Ever smoker	124/221 (56.1)	1,304/2,568 (50.8)	162/227 (71.4)	0.13 (0.08-0.21)	0.11 (0.06-0.18)
History of VTE	1,013 (0.8)	166 (1.2)	1,451 (3.0)	**4.01 (2.80-5.74)**	**0.15 (0.13-0.17)**
Previous DVT	743 (0.6)	123 (0.9)	1,110 (2.3)	**4.17 (2.77-6.27)**	**0.16 (0.13-0.18)**
Previous PE	354 (0.3)	56 (0.4)	447 (0.9)	**4.80 (2.72-8.44)**	**0.16 (0.14-0.19)**
OCP or HRT	691 (0.5)	68 (0.5)	63 (0.1)	0.35 (0.09-1.40)	0.17 (0.15-0.20)
Inherited thrombophilia	149 (0.1)	23 (0.2)	42 (0.1)	**4.26 (1.60-11.34)**	**0.17 (0.15-0.20)**
Recent surgery/immobilization	7,306 (5.4)	2,469 (18.4)	12,752 (26.5)	**0.39 (0.32-0.49)**	**0.13 (0.10-0.15)**
BMI ≥30 kg/m^2	2,552/16,806 (15.2)	567/4,039 (14.0)	714/3,766 (19.0)	0.26 (0.15-0.46)	0.10 (0.07-0.15)
0 risk factors	61/218 (28.0)	883/2,550 (34.6)	33/225 (14.7)	0.06 (0.02-0.14)	0.15 (0.10-0.22)
1 risk factor	103/218 (47.3)	1,175/2,550 (46.1)	100/225 (44.4)	0.08 (0.04-0.15)	0.16 (0.10-0.24)
2 risk factors	48/218 (22.0)	416/2,550 (16.3)	66/225 (29.3)	**0.26 (0.15-0.47)**	**0.09 (0.06-0.14)**
≥3 risk factors	6/218 (2.8)	76/2,505 (3.0)	26/225 (11.6)	**0.79 (0.33-1.91)**	**0.10 (0.07-0.15)**
0 risk factors (excl. smoking)	11,665/16,806 (69.4)	2,742/4,039 (67.9)	1,505/3,766 (40.0)	**0.06 (0.03-0.10)**	**0.27 (0.18-0.39)**
1 risk factor (excl. smoking)	4,324/16,806 (25.7)	1,061/4,039 (26.3)	1,422/3,766 (37.8)	0.17 (0.10-0.29)	0.11 (0.07-0.16)
2 risk factors (excl. smoking)	659/16,806 (3.9)	195/4,039 (4.8)	633/3,766 (16.8)	**0.51 (0.23-1.13)**	**0.11 (0.08-0.15)**
≥3 risk factors (excl. smoking)	168/16,806 (1.0)	41/4,039 (1.0)	206/3,766 (5.5)	**3.69 (1.66-8.22)**	**0.11 (0.08-0.15)**

IRs with nonoverlapping 95% CIs are shown in bold.
BMI, Body mass index; *excl.*, excluding; *HRT*, hormone replacement therapy; *OCP*, oral contraceptive pill.

Wollenberg is an advisor, speaker, or investigator for Pfizer, Aileens, Almirall, Beiersdorf, Bioderma, Bristol-Myers Squibb, Chugai, Eli Lilly and Company, Galápagos, Galderma, GSK, Hans Karrer, Hexal, Janssen, LEO Pharma, L'Oreal, Maruho, MedImmune, Novartis, Pierre Fabre, Regeneron, Sanofi-Genzyme, Santen, and UCB. T. Bieber is a lecturer and/or consultant for Pfizer Inc, AbbVie, Almirall, AnaptysBio, Arena Pharmaceuticals, Asana Biosciences, BioVerSys, Boehringer Ingelheim, Daiichi Sankyo, Dermavant Roivant, Eli Lilly and Company, Galápagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, Kymab, LEO Pharma, L'Oréal/La Roche Posay, Menlo Therapeutics, Novartis, RAPT Therapeutics (FLX Bio), Sanofi Regeneron, UCB, and Vectans Pharma and an investigator for AFYX (DermTreat). A. R. Lemeshow is an employee and shareholder in Pfizer Inc. S. Vyas was an employee and shareholder in Pfizer Inc at the time of the study.

Editorial and medical writing support under the guidance of authors was provided by Megan K. Elder, PhD, at ApotheCom, San Francisco, Calif, and was funded by Pfizer, New York, NY, in accordance with Good Publication Practice (GPP 2022) guidelines (*Ann Intern Med* 2022;10:7326/M22-1460). Data sharing statement: On request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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