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A Nationwide Cohort Study

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Risk of Myocardial Infarction in Patients with Psoriasis and Psoriatic Arthritis: A Nationwide Cohort Study

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Psoriasis has been associated with increased risk of myocardial infarction (MI) in some, but not all, studies. This study investigated the risk of MI in patients with psoriasis and psoriatic arthritis in Denmark. All residents aged ≥18 years from 1 January 2008 through 31 December 2012 were included. Adjusted hazard ratios (HRs) did not show an increased risk of MI in patients with mild psoriasis (HR 1.02; 95% confidence interval (95% CI) 0.96–1.09), whereas the risk was slightly increased in patients with severe psoriasis (HR 1.21; 1.07–1.37). Stratified by age, there was no increased risk of MI in any specific age group, regardless of severity. Limited to first-time MI, the risk was increased only in patients with severe psoriasis aged <50 years (HR 1.52; 1.03–2.25). The same applied to patients without psoriatic arthritis (severe psoriasis aged <50 years; HR 1.74; 1.11–2.72). In analyses restricted to patients with psoriatic arthritis, age-specific strata did not show any association between psoriatic arthritis and MI risk.

Psoriasis is one of the most common immune-mediated inflammatory diseases, with an estimated prevalence of 2–3% in Europe (1). Approximately 70–80% of patients are mildly affected and can be managed with topical treatment (2, 3). Psoriatic arthritis is the most common comorbidity, affecting approximately 30% of patients, and as much as 42% in a Danish study (4). Risk factors for cardiovascular disease, such as hypertension, dyslipidaemia, diabetes, obesity, smoking, and excessive alcohol intake, occur more frequently in patients with psoriasis compared with healthy controls (5, 6). In 1973, small studies (7, 8) indicated an increased risk of cardiovascular disease (CVD) in patients with psoriasis. In 2004, Mallbris et al. (9) reported an increased cardiovascular mortality in hospitalized younger patients with severe psoriasis compared with the general population. In contrast, there was no excessive risk in outpatients with psoriasis.

The most consistent association between psoriasis and CVD is the risk of myocardial infarction (MI), which could be increased up to 2-fold in severe psoriasis and particularly increased in young individuals according to a meta-analysis (10). However, this association has been extensively debated due to conflicting data. For example, based on data from the United Kingdom General Practice Research Datalink between 1987 and 2002, Gelfand et al. (11) found a significantly increased risk of MI in patients with psoriasis. Interestingly however, another study with overlapping cohorts (1994–2009) found somewhat opposing results and recent meta-analyses have failed to determine whether psoriasis imposes an increased risk of CVD independent of the traditional risk factors (12–15).

In an inception cohort design between 1997 and 2006, Ahlehoff et al. (16) reported an increased risk of MI in Danish patients with both mild and severe psoriasis. However, in that study, the number of hospital visits was used to ascertain disease severity, and lack of adjustment for important confounding factors may have biased the results. While data suggest that the heightened CVD risk in psoriasis cannot be explained by the classical cardiovascular risk factors alone, the so-called "independent" impact of psoriasis on CVD is a topic of ongoing debate (17). The aim of the current study was to examine the risk of MI in patients with psoriasis and psoriatic arthritis, using a more restrictive design, in a nationwide cohort of the Danish population between 2008 and 2012.

MATERIALS AND METHODS

Data sources and study population

Study approval was obtained from the Danish Data Protection Agency (reference 2007-58-0015, international reference GEH-2014-018, I-Suite 02736). Approval from an ethics committee is not required for register studies in Denmark (Danish law: Lov om videnskabelig behandling af sundhedsvidenskabelige forskningsprojekter, § 14, stk. 2). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (18).

In brief, the Danish Civil Registration System assigns a permanent and unique 10-digit personal identification number to all citizens at birth or immigration, which allows for unambiguous linkage across nationwide registers (19). Moreover, the Danish Civil Registration System contains information, such as date of birth, sex, and vital status, and Statistics Denmark records information on tax-reported household income (20). The Danish National Patient Register contains information on all inpatient and outpatient (ambulatory) hospital contacts since 1978 according to

the International Classification of Diseases (ICD) (prior to 1994 according to the 8th revision (ICD-8) and thereafter the 10th revision (ICD-10); for administrative reasons ICD-9 was never used in Denmark), and hospital treatment interventions, surgeries, and hospital administered pharmacotherapy are coded as treatment procedure (SKS) codes (21). All pharmacy dispensed prescriptions in Denmark are recorded accurately in the Register of Medicinal Product Statistics since 1994, and all drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification (22). Within 14 days of death, all deaths as causes of deaths are recorded in the National Causes of Death Registry (23).

All Danish adults (≥18 years) alive and resident in Denmark on 1 January 2008 (i.e. the date of study start for all individuals in the cohort) were identified. Subjects were followed from study start until 31 December 2012, death, migration, or diagnosis of MI, whichever came first. Patients were classified as having psoriasis if, prior to study start, they had received either a diagnosis of psoriasis (ICD-8, 696.10, 696.19 and ICD-10, L40) recorded in the DNPR, or if they had been dispensed at least 2 prescriptions of topical vitamin D derivatives (ATC code D05AX), which is the preferred first-line treatment and is used exclusively for psoriasis in Denmark. At least 2 prescriptions were required to ensure persistent medical therapy. Patients were classified as having severe psoriasis if they received systemic therapy for the condition (biological drugs, ciclosporin, psoralen plus ultraviolet A (PUVA), retinoids, or methotrexate). Patients with psoriasis who had not received systemic therapy were classified as having mild psoriasis. This method for identification of psoriasis and classification of severity has been described and validated elsewhere (24). Patients were classified as having psoriatic arthritis if, prior to study start, they had received a diagnosis of psoriatic arthritis (ICD-8 696.09 and ICD-10 M07.0-M07.3, M09.0). The primary endpoint was a diagnosis of MI (ICD-10 I21–I22). The identification of MI has been validated previously in the National Patient Register with a positive predictive value of 93.6% (25). Fatal MIs were collected from the National Causes of Death Registry based on death certificates.

Statistical analysis

Baseline characteristics were described, with means and standard deviations for continuous variables and frequencies and percentages for categorical variables. SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA) and STATA software version 13.0 (StataCorp, College Station, TX, USA) were used to summarize incidence rates per 1,000 person-years, and Cox regression

models were performed to obtain HRs for the risk of MI. These HRs were calculated as age- and sex-adjusted, and fully adjusted (in which age, sex, socioeconomic status, smoking, alcohol abuse, previous CVD, diabetes, hypertension, statin use, and healthcare consumption were considered). Included covariates were assessed at baseline and up to 5 years prior to study start for comorbidity, and up to 6 months prior to study start for medication use. The definition of CVD included acute coronary syndrome comprising both MI and unstable angina pectoris, angina pectoris, cerebrovascular event or stroke, transient ischaemic attack, peripheral artery disease and revascularization procedures, including coronary artery bypass surgery, percutaneous coronary intervention and percutaneous transluminal coronary angioplasty. Diabetes was defined by either a hospital diagnosis (in- or outpatient), or use of glucose-lowering drugs. Collection of proxy data on hypertension, smoking, and alcohol abuse has been described elsewhere (24, 26, 27). An index of socioeconomic status (standardized by age) between 0 (lowest group) and 4 (highest group) was calculated based on the mean gross annual income during a 5-year period before study inclusion. Sensitivity analyses were performed in which patients with a history of MI prior to study start were excluded, in order to assess the risk of first-time MI. In addition, the primary analysis was repeated with stratification based on age (<50, 50–<60, 60–<70, ≥70 years). Sensitivity analyses were performed, in which comorbidity and medication use were included as time-dependent variables that were updated during follow-up. Model assumptions, including linearity of continuous variables and the proportional hazards assumption, were tested and found to be valid. Two-tailed p-values <0.05 were considered statistically significant, and results were reported with 95% confidence intervals (CIs), where applicable. Throughout this paper the term "increased risk" refers to a statistically significant increased risk, unless explicitly stated otherwise.

RESULTS

The study comprised a total of 4,361,688 Danish residents, aged ≥18 years on 1 January 2008. Of these, 49,646 and 11,957 patients were classified as having mild and severe psoriasis, respectively, including 8,149 patients with psoriatic arthritis. Consistently across the study groups, there was a slight female predominance, and the mean age ranged between 48.6 and 56.7 years (**Table I**).

Table I. Baseline characteristics of the study population

	General population (n = 4,300,085)	With or without psoriatic arthritis		Cutaneous psoriasis only		Psoriatic arthritis (n = 8,149)
		Mild psoriasis (n = 49,646)	Severe psoriasis (n = 11,957)	Mild psoriasis (n = 46,085)	Severe psoriasis (n = 7,369)	
Age, years, mean (standard deviation)	48.6 (18.0)	54.6 (16.3)	55.7 (14.9)	54.5 (16.4)	56.7 (15.5)	54.6 (14.1)
Sex, n (%)						
Women	2,184,102 (50.8)	25,563 (51.5)	6,256 (52.3)	23,522 (51.0)	3,747 (50.9)	4,550 (55.8)
Men	2,115,983 (49.2)	24,083 (48.5)	5,701 (47.7)	22,563 (49.0)	3,622 (49.1)	3,599 (44.2)
Socioeconomic status, n (%)						
Lowest	864,785 (20.1)	6,304 (12.7)	1,247 (10.4)	5,904 (12.8)	878 (11.9)	769 (9.4)
Below average	857,899 (20.0)	11,300 (22.8)	3,139 (26.3)	10,391 (22.6)	1,977 (26.8)	2,071 (25.4)
Average	858,842 (20.0)	10,582 (21.3)	2,912 (24.4)	9,705 (21.1)	1,706 (23.2)	2,083 (25.6)
Above average	859,895 (20.0)	10,010 (20.2)	2,436 (20.4)	9,326 (20.2)	1,441 (19.6)	1,679 (20.6)
Highest	858,664 (20.0)	11,450 (23.1)	2,223 (18.6)	10,759 (23.4)	1,367 (18.6)	1,547 (19.0)
Smoking, n (%)	423,021 (9.8)	7,670 (15.5)	2,246 (18.8)	7,090 (15.4)	1,501 (20.4)	1,325 (16.3)
Alcohol abuse, n (%)	180,662 (4.2)	3,084 (6.2)	788 (6.6)	2,866 (6.2)	542 (7.4)	464 (5.7)
Cardiovascular disease, n (%)	370,831 (8.6)	7,019 (14.1)	1,949 (16.3)	6,476 (14.1)	1,233 (16.7)	1,259 (15.5)
Diabetes, n (%)	153,969 (3.6)	3,278 (6.6)	947 (7.9)	3,053 (6.6)	588 (8.0)	584 (7.2)
Hypertension, n (%)	516,585 (12.0)	9,649 (19.4)	2,485 (20.8)	8,884 (19.3)	1,525 (20.7)	1,725 (21.2)
Cholesterol-lowering drugs, n (%)	392,237 (9.1)	7,534 (15.2)	1,881 (15.7)	6,862 (15.1)	1,154 (15.7)	1,299 (15.9)

Table II. Summary of number of events, follow-up time, and incidence rates per 1,000 person-years (PY)

	General population	Including psoriatic arthritis		Cutaneous psoriasis only		Psoriatic arthritis
		Mild psoriasis	Severe psoriasis	Mild psoriasis	Severe psoriasis	
Any myocardial infarction						
Follow-up time, years	20,539,481	233,806	56,212	216,917	34,269	38,832
Number of events	53,272	896	263	826	175	158
Incidence rate/1,000 PY	2.59	3.83	4.68	3.81	5.11	4.07
95% confidence interval	2.57–2.62	3.59–4.09	4.15–5.28	3.56–4.08	4.40–5.92	3.49–4.76
First-time myocardial infarction						
Follow-up time, years	20,193,191	227,119	54,467	210,726	33,185	37,675
Number of events	44,129	723	213	670	138	128
Incidence rate/1,000 PY	2.19	3.18	3.91	3.18	4.16	3.40
95% confidence interval	2.17–2.21	2.96–3.42	3.42–4.47	2.95–3.43	3.52–4.91	2.86–4.04

During follow-up, a total of 53,272 subjects from the general population were diagnosed with an MI, of which 44,129 were first-time MIs. Among patients with mild and severe psoriasis, there were 896 (first-time MI, $n=723$) and 263 (first-time MI, $n=213$) cases of MI, of which 158 (first-time MI, $n=128$) occurred in patients with psoriatic arthritis. The corresponding incidence rates par 1,000 person-years of exposure are shown in **Table II**.

Risk of myocardial infarction in patients with either psoriasis or psoriatic arthritis

Adjusted analyses (i.e. adjusted for age, sex, socioeconomic status, smoking, alcohol abuse, previous CVD, diabetes, hypertension, statin use, and healthcare consumption) did not show an increased risk of MI in patients with mild psoriasis (hazard ratio (HR) 1.02; 95% confidence interval (95% CI) 0.96–1.09), whereas the risk was slightly increased in patients with severe psoriasis (HR 1.21; 95% CI 1.07–1.37) (**Table III**). Stratified by age, there was no increased risk of MI in any specific age group, for either mild or severe psoriasis (**Table IV**). When analyses were limited to patients with first-time MI, the overall adjusted HRs were 1.03 (95% CI 0.96–1.11) and 1.21 (95% CI 1.05–1.39) for mild and severe psoriasis, respectively. When the analyses for first-time MI risk were stratified by age, the risk was only

Table III. Risk of myocardial infarction in patients with psoriasis and psoriatic arthritis

	Any myocardial infarction		First-time myocardial infarction	
	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Any psoriasis				
Mild psoriasis	1.02 (0.96–1.09)	0.5209	1.03 (0.96–1.11)	0.3646
Severe psoriasis	1.21 (1.07–1.37)	0.0023	1.21 (1.05–1.39)	0.0065
Cutaneous psoriasis only				
Mild psoriasis	1.01 (0.94–1.08)	0.7881	1.03 (0.95–1.11)	0.4790
Severe psoriasis	1.19 (1.03–1.39)	0.0221	1.15 (0.97–1.37)	0.1028
Joint disease				
Psoriatic arthritis	1.22 (1.05–1.43)	0.0116	1.23 (1.04–1.47)	0.0177

CI: confidence interval; HR: hazard ratio: adjusted for age, sex socioeconomic status, previous cardiovascular disease (CVD), diabetes, alcohol, smoking, hypertension, cholesterol-lowering drug use, and healthcare consumption.

significantly increased in patients with severe psoriasis aged <50 years (HR 1.52; 95% CI 1.03–2.25).

Risk of myocardial infarction in patients with cutaneous psoriasis only

In analysis limited to patients without psoriatic arthritis, the overall HR of MI was 1.01 (95% CI 0.94–1.08) for mild, and 1.19 (95% CI 1.03–1.39) for severe psoriasis. In age-specific strata, the risk was only significantly increased among patients aged <50 years with severe psoriasis (HR 1.74; 95% CI 1.11–2.72). For first-time MI, there was no increased risk associated with either mild or severe psoriasis. However, in patients aged <50

Table IV. Risk of myocardial infarction in patients with psoriasis and psoriatic arthritis, age stratified
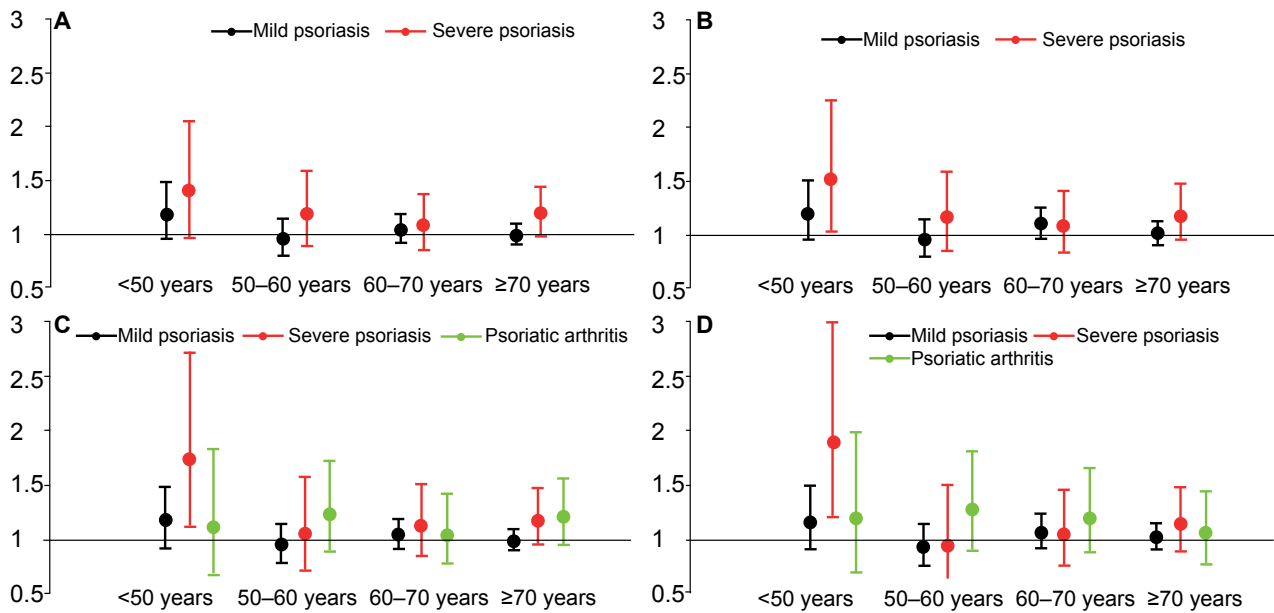
	Any myocardial infarction		First-time myocardial infarction	
	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Any psoriasis				
Mild psoriasis				
<50 years	1.19 (0.96–1.49)	0.1133	1.19 (0.95–1.50)	0.1344
50–<60 years	0.96 (0.81–1.14)	0.6514	0.95 (0.79–1.14)	0.5908
60–<70 years	1.05 (0.93–1.19)	0.4213	1.09 (0.95–1.25)	0.2287
≥70 years	1.00 (0.91–1.10)	0.9486	1.01 (0.90–1.12)	0.9020
Severe psoriasis				
<50 years	1.41 (0.97–2.06)	0.0712	1.52 (1.03–2.25)	0.0346
50–<60 years	1.20 (0.90–1.59)	0.2264	1.16 (0.85–1.59)	0.3454
60–70 years	1.09 (0.86–1.37)	0.4891	1.08 (0.83–1.40)	0.5779
≥70 years	1.20 (0.99–1.44)	0.0602	1.18 (0.95–1.47)	0.1247
Cutaneous psoriasis only				
Mild psoriasis				
<50 years	1.18 (0.93–1.48)	0.1665	1.16 (0.91–1.49)	0.2203
50–<60 years	0.95 (0.79–1.14)	0.5778	0.94 (0.77–1.14)	0.5189
60–<70 years	1.05 (0.92–1.19)	0.5075	1.07 (0.93–1.23)	0.3572
≥70 years	1.00 (0.90–1.10)	0.8989	1.02 (0.91–1.14)	0.7480
Severe psoriasis				
<50 years	1.74 (1.11–2.72)	0.0160	1.90 (1.20–3.02)	0.0064
50–<60 years	1.06 (0.71–1.58)	0.7764	0.96 (0.62–1.50)	0.8709
60–<70 years	1.14 (0.85–1.51)	0.3710	1.05 (0.76–1.45)	0.7693
≥70 years	1.18 (0.95–1.47)	0.1439	1.15 (0.89–1.48)	0.2781
Joint disease				
Psoriatic arthritis				
<50 years	1.11 (0.68–1.83)	0.6706	1.19 (0.71–1.99)	0.5014
50–<60 years	1.24 (0.89–1.72)	0.2011	1.28 (0.90–1.81)	0.1705
60–<70 years	1.05 (0.78–1.42)	0.7381	1.21 (0.88–1.65)	0.2447
≥70 years	1.22 (0.95–1.56)	0.1243	1.06 (0.78–1.44)	0.6993

CI: confidence interval; HR: hazard ratio: adjusted for age, sex socioeconomic status, previous cardiovascular disease (CVD), diabetes, alcohol, smoking, hypertension, cholesterol-lowering drug use, and healthcare consumption.

Fig. 1. Risk of myocardial infarction in patients with psoriasis and psoriatic arthritis, age stratified. (A) Risk of any myocardial infarction in patients with mild and severe psoriasis, regardless of presence or absence of psoriatic arthritis. (B) Risk of first-time myocardial infarction in patients with mild and severe psoriasis, regardless of presence or absence of psoriatic arthritis. (C) Risk of any myocardial infarction in patients with mild and severe psoriasis (cutaneous only), and psoriatic arthritis, respectively. (D) Risk of first-time myocardial infarction in patients with mild and severe psoriasis (cutaneous only), and psoriatic arthritis, respectively.

years with severe psoriasis we did find an increased risk (HR 1.90; 95% CI 1.20–3.02), as shown in Table IV and **Fig. 1**.

Risk of myocardial infarction in patients with psoriatic arthritis

When analyses were limited to patients with psoriatic arthritis, the overall risk of MI was slightly increased (HR 1.22; 95% CI 1.05–1.43), as was the risk of first-time MI (HR 1.23; 95% CI 1.04–1.47). However, in age-specific strata, there was no association between psoriatic arthritis and risk of MI, including first-time MI (Table IV and Fig. 1).

In sensitivity analyses, where covariates were adjusted during follow-up, there were no significant differences compared with our primary analyses (data not shown). Detailed data on model coefficients are available in the supplementary materials.

DISCUSSION

In this nationwide cohort study of the Danish population between 2008 and 2012, we found a slightly (yet statistically significant) increased risk of MI in patients with psoriasis and psoriatic arthritis. Notably, however, the risk was increased only among patients <50 years of age, and predominantly present in patients without psoriatic arthritis.

Previously, using data from the UK, Gelfand et al. (11) demonstrated an age- and psoriasis severity-dependent increased risk of MI where the adjusted relative risk (RR) in young patients (aged 30 years) was 1.29 (95% CI 1.14–1.46) for mild, and 3.10 (95% CI 1.98–4.86) for severe psoriasis, respectively. Conversely, for older patients (aged 60 years), the adjusted RR was 1.08 (95% CI 1.03–1.13) for mild, and 1.36 (95% CI 1.13–1.64) for severe psoriasis, respectively. On the other hand, using the same data source Parisi and colleagues (12) did not show a significantly increased risk of major adverse cardiovascular events (MACE) in patients with severe psoriasis (adjusted HR 1.28; 95% CI 0.96–1.69). However, in a subanalysis excluding patients with psoriatic arthritis, the risk of MACE was significantly increased (adjusted HR 1.46; 95% CI 1.11–1.92) in patients with severe psoriasis. One previous Danish study using the same register data as here (16) found an increased risk of first-time MI associated with mild psoriasis (adjusted RR 1.22; 95% CI 1.12–1.33), and severe psoriasis (adjusted RR 1.45, 95% CI 1.10–1.90), respectively. Notably, when stratified by age, the risk of MI in patients with mild disease was increased only in patients > 70 years of age (adjusted RR 1.30; 95% CI 1.16–1.45), whereas the risk in patients with severe psoriasis was significantly increased only in patients ≤50 years of age (adjusted RR 2.32; 95% CI 1.19–4.50). The apparent discrepancy between the results here and the previous findings may be due to the applied definition of disease severity. As in the studies by Gelfand et al. (11) and Parisi et al. (12), we used systemic anti-psoriatic therapy to ascertain disease severity; a method which we have previously validated (24). Conversely, in the previous study from the Danish

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databases (16), patients were considered to have mild disease until the time of their third hospital visit due to psoriasis, whereby patients in private dermatology clinics were automatically considered to have mild disease, as were patients who were seen only twice in a hospital setting at the time of their MI. We believe that this strategy may introduce bias in the analyses, since patients with severe psoriasis are treated in secondary clinics in rural parts of Denmark.

The link between psoriasis and atherosclerosis has been highlighted by the fact that both conditions are characterized by T-helper (Th)1 and Th17 activation and reduced T-regulatory cell function, with striking similarities in their immunoinflammatory mechanisms (28). Indeed, inflammation is important in atherogenesis and atherosclerosis (29, 30), and systemic inflammation has been put forward as a potential explanation for the observed increased prevalence and risk of CVD in patients with psoriasis. However, patients with psoriasis also tend to exercise less (31) and smoke more than the general population (32), and the level of alcohol consumption is correlated with the extent of psoriasis (33). In addition, presence of depression also appears to significantly affect the CVD risk in patients with psoriasis (34). While our models were adjusted for factors such as smoking and alcohol abuse, these potential confounders were unaccounted for in the previous study from Denmark (16). Nevertheless, important limitations apply to the interpretation of the present results. The algorithm for identification of smoking history may lead to an underestimation of smoking in this cohort, whereby the increased MI risk in our study may partly be explained by residual confounding. We identified patients with psoriasis either by a diagnosis of psoriasis or by claimed prescriptions for topical vitamin D analogues (Tables SI–SIV[1], Fig. S1[1]). While the National Patient Register contains inpatient and outpatient diagnoses for all individuals seen in hospital clinics, patients seen, for example, by dermatologists in private clinics would not be captured by such diagnostic codes. However, use of topical vitamin D analogues allowed identification of patients seen outside a hospital setting. Indeed, in Denmark, these agents are the preferred anti-psoriatic therapy by general practitioners and dermatologists (35). Moreover, use of the above-mentioned method allowed for direct comparison between our study and the study by Ahlehoff et al. (16), since the both studies used the same definition of psoriasis. Due to the observational nature of our study, we cannot claim a causal link. Also, the apparent increased prevalence of CVD in psoriasis may be partially attributed to the high prevalence of metabolic abnormalities, for which obesity, lifestyle, and genetics may provide the link (36, 37). Indeed, patients

with psoriasis tend to be heavier than non-psoriatic individuals, and a causal link between obesity and psoriasis has been discussed (36). In addition, data suggest that the "independent" effect of psoriasis on the risk of CVD is virtually eliminated when the results are adjusted for a family history of CVD (37). We lacked information on body weight and family history, and it is likely that at least some of the observed MI risk in our study was due to residual confounding owing to obesity and other lifestyle factors. The present study applied a prevalent rather than incident disease design. This approach was chosen because the exact onset of disease may by imprecise, since patients may have had psoriasis for many years before seeking medical attention. The strengths of a prevalent vs. an incident disease design for psoriasis research has been described in detail elsewhere (17). Lastly, certain anti-psoriatic pharmacotherapies may also increase the risk of MI (38).

In conclusion, we found a slightly increased risk of MI in patients with psoriasis and psoriatic arthritis. Notably, however, the risk was increased only among patients <50 years of age, and predominantly present in patients without psoriatic arthritis. Therefore, it remains unclear if psoriasis is an independent risk factor for MI.

ACKNOWLEDGEMENTS

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