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The risk of depression, anxiety and suicidality in patients with psoriasis: A population-based cohort study

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Abstract

Objective—The purpose of this study is to determine the incidence of depression, anxiety and suicidality in patients with psoriasis compared to the general population.

Design—A population-based cohort study using data collected as part of patient's electronic medical record from 1987 to 2002.

Setting—General Practice Research Database

Patients—Up to 5 controls without psoriasis were selected from the same practices and cohort entry dates as psoriasis patients.

Main Outcome Measures—Clinical diagnosis of depression, anxiety and suicidality were compared among 146,042 mild psoriasis, 3,956 severe psoriasis, and 766,950 control patients.

Results—The adjusted hazard ratios for receiving a diagnosis of depression, anxiety and suicidality in patients with psoriasis compared to controls, were 1.39 (95% CI 1.37, 1.41), 1.31 (95% CI 1.29, 1.34) and 1.44 (95% CI 1.32, 1.57), respectively. The adjusted relative risk of depression was higher in severe (HR 1.72, 95% CI 1.57, 1.88), compared to mild psoriasis (HR

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1.38, 95% CI 1.35, 1.40). Younger psoriasis patients had elevated relative risks of outcomes compared to older psoriasis patients.

Conclusions—Psoriasis patients have an increased risk of depression, anxiety, and suicidality. We estimate that in the UK, in excess of 10,400 diagnoses of depression, 7,100 diagnoses of anxiety, and 350 diagnoses of suicidality are attributable to psoriasis annually. It is important for clinicians to evaluate patients with psoriasis for these conditions in order to improve outcomes. Future investigation should determine the mechanisms by which psoriasis is associated with psychiatric outcomes as well as approaches for prevention.

Introduction

Psoriasis is a common chronic condition that affects 1-3% of the general population and estimates suggest that 0.4-2.3% of the adult population have psoriasis but remain undiagnosed[1]. Psoriasis is associated with impairments in health-related quality of life even in mild cases and is associated with excess cardiovascular risk and mortality in patients with more severe disease[2-4]. Psoriasis is caused by a complex interaction of multiple genes and environmental factors and results in chronic T helper (Th)1 and Th17 inflammation in the skin, blood, and in some patients, the joints[5, 6].

Psoriasis has long been recognized to be associated with potentially adverse effects on mental health. In the 1960's a popular ad campaign labeled the emotional burden of this skin disease as the “heartbreak of psoriasis.” However, there have been relatively few studies evaluating psychological outcomes in patients with psoriasis. Published studies have been primarily from tertiary care referral centers, are cross-sectional in nature, have suffered from small sample sizes, often lacked a control group, and have measured psychological symptomatology using a variety of research questionnaires rather than clinical diagnoses[7-13].

Quantifying the relationship between psoriasis and major psychological outcomes is important in order to identify to which mental health disorders psoriasis patients may be particularly susceptible. Therefore, we conducted a large, broadly representative, population-based cohort study in order to investigate the hypothesis that patients with psoriasis have an increased risk of clinical diagnoses of depression, anxiety, and suicidality compared to the general population.

Methods

Study design

Source Population—A population-based cohort study was conducted using data collected as part of patients' electronic medical record between 1987 and 2002, maintained in the General Practice Research Database (GPRD). More than 1500 practitioners in the United Kingdom (UK), who are unaware of research hypotheses to be tested, participate in the GPRD. The GPRD contains data on more than 8 million persons with more than 35 million years of follow-up time and is broadly representative of the UK population[14]. General practitioners (GPs) receive specific training and are subject to financial inducements and penalties to ensure data accuracy. The data are audited for completeness and practices receive an up-to-standard (UTS) designation when at least 95% of relevant prescriptions and diagnoses are captured electronically. The ability of the GPRD to capture data from specialists and validly identify psoriasis has been demonstrated previously[14, 15]. The GPRD has been used extensively to study depression[15-19], anxiety[16] and suicidality[14, 17, 18, 20].

Exposures—Diseases are classified in the GPRD using Oxford Medical Information System (OXMIS) and Read codes. The dataset was created by selecting all patients with a diagnostic code for psoriasis and up to 5 random controls who had at least one day of observation time. Controls were seen in the same practice and had a date of observation in the practice within 60 days of cohort entry for the corresponding psoriasis patient. Control subjects did not have a diagnostic code for psoriasis at any time.

Severe psoriasis was defined by both a diagnostic code for psoriasis and a code indicating a systemic treatment modality. Systemic therapies include psoralen or phototherapy, methotrexate, azathioprine, cyclosporine, etretinate, acitretin, hydroxyurea or mycophenolate. Psoriasis patients who did not receive systemic therapy were classified as mild. This method for classification of psoriasis has been previously validated and used in several peer-reviewed publications[2-4, 21, 22].

Definition of Study Period—Cohort entry was defined as the latest date of when the patient was registered in the practice, the practice was UTS, the patient first received a diagnostic code for psoriasis (psoriasis patients only), and the date corresponding to the first code for systemic treatment (severe psoriasis patients only). Follow-up time ended for both psoriasis patients and controls at the earliest date of when the patient developed the outcome of interest, transferred out of the practice, died, or the practice was no longer UTS.

Outcomes—Patients were defined has having incident depression, anxiety or suicidality by a corresponding diagnostic code occurring after the start of follow-up time. A database of Read and OXMIS diagnostic codes was queried to generate the coding algorithm used. Depression included all clinician diagnoses of depressive symptomology including bipolar disorder. Anxiety included clinician diagnosis of anxiety and related disorders in which anxiety symptoms are common. Suicidality was defined as diagnosis of suicidal ideation, suicide attempt or suicide. This list included all diagnostic codes used in previously published GPRD studies of depression, anxiety and suicidality[15-20].

Covariates—Information on age, sex and follow-up time was obtained as well as history of depression, anxiety and suicidality (defined as a corresponding diagnostic code occurring prior to cohort entry).

Statistical Analysis—Calculations made prior to data analysis suggested that with a fixed sample size of 150,000 psoriasis patients and approximately 765,000 controls, we would have greater than 0.95 power to detect an effect size (hazard ratio) as small as 1.1, assuming baseline rates of 20-, 15- and 5 per 1000 person years for depression, anxiety, and suicidality, respectively.

Comparisons of age, sex, follow-up time, history of depression, anxiety and suicidality and reason for censorship from the dataset between groups were tested using Fisher's exact test for categorical variables and the t-test for continuous variables. All p values reported are two-sided.

Incidence was calculated using the number of subjects who received a diagnostic code for the outcome, divided by the cumulative years of observation. Adjusted attributable risk (AR) was calculated using incidence rates in the exposed and unexposed groups, multiplied by hazard ratios adjusted for age and sex. Number of cases of depression, anxiety and suicidality each year in the UK attributable to psoriasis was calculated by multiplying the AR by the estimated number of patients with psoriasis in the UK based on GPRD statistics.

Cox proportional hazard regression was used to determine the hazard ratio (HR, relative risk) of receiving a clinical diagnosis of depression/anxiety/suicidality after cohort entry in patients with psoriasis compared to controls. The appropriateness of this model was tested using diagnostic log-log survival plots which demonstrated adequate proportionality. The primary analysis incorporated adjustment for age and sex. Interaction terms for age and sex were tested *a priori* and if significant, the analysis was stratified and presented accordingly. Numerous sensitivity analyses were conducted: Analysis excluding patients seen less than once per year on average was done to assess the impact of observation bias. Another excluded patients with a diagnosis of the outcome measured prior to or within six months of cohort entry to ensure capture of incident rather than prevalent psychiatric disease. An analysis was performed excluding patients treated with retinoids (etretinate, acitretin) as these therapies may be associated with depression or suicidality; another excluded patients with a diagnosis of psoriatic arthropathy to ensure the capture of severe skin phenotype. Analysis of only those patients treated with psoralen or phototherapy (treatments highly specific for psoriasis) and analysis controlling for comorbid conditions such as diabetes, hypertension, hyperlipidemia, cancer and body mass index were performed. All statistical analyses were performed using Intercooled Stata 10 (Stata Corp, College Station, TX).

This study was conducted in accordance with cohort study guidelines outlined in the STROBE statement (http://www.strobe-statement.org/) and with the Declaration of Helsinki. This study was approved by the Independent Scientific Advisory Committee for research involving the GPRD and granted exempt status by the Institutional Review Board at the University of Pennsylvania.

Results

A total of 146,042 patients with mild psoriasis, 3,956 patients with severe psoriasis, and 766,950 patients without psoriasis were included in the analyses. Overall, psoriasis patients were older, contributed greater person-time, and had higher rates of depression, anxiety and suicidality occurring prior to cohort entry than patients without psoriasis (Table 1). Over half (57.74%) of severe psoriasis patients were treated with methotrexate (Table 2).

The unadjusted (crude) incidence of clinical diagnosis of depression, anxiety and suicidality in patients with psoriasis was 25.9, 20.9 and 0.9 per 1000 person years, respectively (data for mild and severe psoriasis groups shown separately in Table 1). The hazard ratios (relative risks) for receiving a clinical diagnosis of depression, anxiety and suicidality after cohort entry in patients with psoriasis compared to controls, after adjusting for age and sex, were 1.39 (95% confidence interval [CI] 1.37, 1.41), 1.31 (95% CI 1.29, 1.34) and 1.44 (95% CI 1.32, 1.57), respectively. The adjusted relative risk of diagnosis of depression was higher in patients with severe psoriasis (HR 1.72, 95% CI 1.57, 1.88) than mild psoriasis (HR 1.38, 95% CI 1.35, 1.40) (Table 3). The adjusted relative risk of anxiety was similar in both mild and severe psoriasis groups compared to controls (Table 3). The adjusted HR of suicidality was higher in patients with severe psoriasis (HR 1.51, 95% CI 0.92, 2.49) than mild psoriasis (HR 1.44 95% CI 1.32, 1.57); the confidence interval for the severe psoriasis group, however, spanned a relative risk of 1.0 (Table 3).

A statistically significant interaction between psoriasis and sex was found only for depression comparing severe psoriasis patients to controls (interaction term HR 1.21, 95% CI 1.00, 1.46) (Table 3). These results suggest that the relative risk of receiving a clinical diagnosis of depression is significantly higher in men compared to women with severe psoriasis. An interaction of psoriasis and age was seen in mild and severe psoriasis groups for all three outcomes with the exception of suicidality in the severe psoriasis cohort, suggesting that the relative risk of these outcomes is greatest in younger patients.

The absolute risk of diagnosis of depression, anxiety, and suicidality attributable to psoriasis (adjusted for age and sex) was 11.8, 8.1, and 0.4 per 1000 person years, respectively (Table 4). Attributable risks for these outcomes were similar between mild and severe psoriasis except for depression (11.5 and 25.5 per 1000 person years, respectively). Stated another way, the excess risk attributable to psoriasis is one case of depression for every 39 severe psoriasis patients per year (or per 87 patients per year with mild psoriasis). The excess risks associated with psoriasis for anxiety and suicidality correspond to one case per 123 and 2500 psoriasis patients per year, respectively.

Sensitivity analyses were conducted to ensure capture of incident rather than prevalent depression, anxiety, and suicidality, as well as to test for several types of observation and misclassification. The hazard ratios for the risk of incident depression, anxiety and suicidality remained robust to these sensitivity analyses with the exception of suicidality in the severe psoriasis cohort when patients with prior history of suicidality were excluded from the analysis; these data are included in Appendix A.

Discussion

Our results suggest that patients with psoriasis are at increased risk for the development of depression, anxiety and suicidality. Based on these data and the prevalence of psoriasis in the UK[22], we estimate that in the UK there are over 10,400 diagnoses of depression, 7,100 diagnoses of anxiety, and 350 diagnoses of suicidality attributable to psoriasis each year. The relative risk of these psychiatric outcomes is particularly elevated in younger patients with psoriasis with the greatest relative risk being for depression in patients with severe psoriasis (especially if young and male).

To our knowledge a higher relative risk of depression in men has not been previously described and this novel finding warrants attention. Interestingly, excess alcohol consumption in male psoriasis patients has been demonstrated by several studies, suggesting the possibility of self-medication with alcohol for depression and other psychological problems in men with psoriasis[23, 24].

This study significantly advances the literature of psoriasis and psychiatric outcomes in that it examines the incidence of *clinical diagnosis* of depression, anxiety and suicidality in patients with psoriasis. Particular strengths of this study include its population-based design, which minimizes bias while maximizing generalizability of the results. Furthermore, the results remained robust to multiple sensitivity analyses, further ensuring the validity of the findings. The large sample size also allowed for the identification of sub-populations of patients with psoriasis who are particularly susceptible to these psychiatric disorders as well as the study of rarer outcomes such as suicidality. As with all epidemiological studies, there are important limitations to consider. By using systemic psoriasis treatment as a construct to measure severe psoriasis, it is likely that there is misclassification with regard to psoriasis severity. Although patients with mild psoriasis are unlikely to receive systemic therapies, severe patients may not receive systemic treatment and therefore may be misclassified into the mild psoriasis cohort. In addition there may be confounding by indication in the severe psoriasis cohort whereby the systemic treatment, rather than severe psoriasis itself is associated with the outcome. Oral retinoids (etretinate and acitretin) have been associated with depression and suicidality, although sensitivity analyses excluding subjects treated with retinoids showed consistent results. The majority of severe psoriasis patients were treated with methotrexate and the authors are unaware of any evidence that shows methotrexate can cause depression, anxiety or suicidality. In database studies, it is possible that there may be miscoding of the outcome leading to misclassification. As the data were collected by GPs unaware of hypotheses to be tested, it is unlikely that misclassification would occur

preferentially in either the psoriasis or control cohorts and therefore such misclassification will bias findings towards the null[25]. It is also possible that the relationship between psoriasis and these psychiatric outcomes could be indirect (e.g., due to confounding by unmeasured factors) and not a direct consequence of having psoriasis. Finally, the outcomes measured are general practitioner clinical diagnosis of depression, anxiety and suicidaltiy. Formal validation of these codes with psychiatrist diagnosis using Diagnostic and Statistical Manual (DSM) of mental disorders criteria has not been conducted. It is important to recognize that clinical diagnosis may not predictably correlate with the gold standard of diagnosis (i.e., DSM criteria applied by a psychiatrist or psychologist). Moreover, based on study design, we cannot comment on the degree of severity nor the duration of outcomes measured.

In conclusion, patients with psoriasis are at increased risk for depression, anxiety and suicidality compared to the general population. It is important to identify these psychiatric disorders as they represent substantial morbidity that can be improved with a variety of pharmacological and non-pharmacological approaches. Furthermore, recent data suggest that psychiatric comorbidity may negatively affect response to certain psoriasis treatments (e.g., photochemotherapy)[10], while other studies suggest that control of psoriasis is associated with improvements in psychological symptoms[26]. Future studies are necessary to determine the mechanisms by which psoriasis is associated with depression, anxiety, and suicidality as well as approaches to prevent such adverse outcomes in patients with psoriasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary Statistics

	Controls (Mild) N=746,930 (81.44%)	Mild PSO N=146,042 (15.94%)	Controls (Severe) N=20,020 (2.19%)	Severe PSO N=3,956 (0.43%)
Male Sex (%)	356,669 (47.82%)	69,231 (47.40%)	9,569 (47.80%)	1,920 (48.53%)
	P=0.004		P=0.403	
Median Age (IQR)	33 (18, 53)	40 (26, 57)	34 (18, 54)	48 (35, 62)
	P<0.001		P<0.001	
History of Depression (%)	31,984 (4.29%)	14,327 (9.81%)	938 (4.69%)	493 (12.46%)
	P<0.001		P<0.001	
History of Anxiety (%)	24,152 (3.24%)	10,890 (7.46%)	651 (3.25%)	291 (7.36%)
	P<0.001		P<0.001	
History of Suicidality (%)	2,946 (0.39%)	1,041 (0.71%)	76 (0.38%)	40 (1.01%)
	P<0.001		P<0.001	
Median Person Time (IQR)	5.24 (2.18, 9.12)	6.18 (2.97, 9.55)	5.62 (2.45, 9.49)	7.59 (3.86, 9.90)
	P<0.001		P<0.001	
Reason for Censorship				
Death (%)	39,206 (5.26%)	7,334 (5.02%)	1,095 (5.47%)	309 (7.81%)
End UTS (%)	493,810 (66.20%)	108,377 (74.21%)	13,143 (65.65%)	3,179 (80.36%)
Transfer (%)	212,914 (28.54%)	30,331 (20.77%)	5,782 (28.88%)	468 (11.83%)
	P<0.001		P<0.001	
Unadjusted incidence rate per 1000 person y, (95% CI)				
Depression	17.4 (17.3, 17.6)	25.7 (25.3, 26.1)	17.0 (16.2, 17.7)	31.8 (29.5, 34.3)
Anxiety	14.7 (14.6, 14.9)	20.9 (20.6, 21.3)	14.5 (13.8, 15.2)	20.8 (18.9, 22.8)
Suicidality	0.66 (0.63, 0.68)	0.93 (0.85, 1.00)	0.66 (0.52, 0.82)	0.92 (0.57, 1.41)

IQR= interquartile range

Table 2

Systemic Psoriasis Therapy*

Systemic psoriasis Therapy	N (%) of severe psoriasis patients
Methotrexate	2284 (57.74%)
Psoralen or Phototherapy	680 (17.19%)
Azathioprine	625 (16.48%)
Cyclosporice	412 (10.14%)
Etretinate or Acitretin	351 (8.87%)
Hydroxyurea	222 (5.61%)
Mycophenolate mofetil	12 (0.30%)

*Percentages add up to >100 because some subjects received multiple treatments.

Table 3

Hazard ratios

	Mild Psoriasis Hazard Ratio (95% CI)	Severe Psoriasis Hazard Ratio (95% CI)		All Psoriasis Hazard Ratio (95% CI)
Depression				
Adjusted for age and sex	1.38 (1.35, 1.40) P<0.001	1.72 (1.57, 1.88) P<0.001		1.39 (1.37, 1.41) P<0.001
Sex interaction term	NS P=0.806	1.21 (1.00, 1.46) P=0.050		NS P=0.512
Age interaction term	0.99 (0.99, 0.99) P<0.001	0.98 (0.98, 0.99) <0.001		0.99 (0.99, 0.99) p<0.001
		Women	Men	
Age=20 years	1.81 (1.59, 1.65)	2.51 (2.11, 2.98)	2.91 (2.39, 3.54)	1.83 (1.78, 1.87)
Age=40 years	1.45 (1.42, 1.47)	1.85 (1.65, 2.08)	2.15 (1.84, 2.51)	1.46 (1.44, 1.49)
Age=60 years	1.16 (1.13, 1.19)	1.37 (1.21, 1.55)	1.59 (1.34, 1.88)	1.17 (1.14, 1.20)
Anxiety				
Adjusted for age and sex	1.31 (1.29, 1.34) P<0.001	1.29 (1.15, 1.43) P<0.001		1.31 (1.29, 1.34) P<0.001
Sex interaction term	NS P=0.907	NS P=0.161		NS P=0.725
Age interaction term	0.99 (0.99, 0.99) P<0.001	0.98 (0.98, 0.99) P<0.001		0.99 (0.99, 0.99) P<0.001
Age=20 years	1.61 (1.56, 1.65)	2.11 (1.75, 2.55)		1.61 (1.57, 1.66)
Age=40 years	1.37 (1.34, 1.40)	1.49 (1.33, 1.67)		1.37 (1.34, 1.40)
Age=60 years	1.17 (1.14, 1.19)	1.06 (0.93, 1.20)		1.16 (1.13, 1.19)
Suicidality				
Adjusted for age and sex	1.44 (1.32, 1.57) P<0.001	1.51 (0.92, 2.49) P=0.103		1.44 (1.32, 1.57) P<0.001
Sex interaction term	NS P=0.955	NS P=0.765		NS P=0.914
Age interaction term	0.99 (0.98, 0.99) P<0.001	NS P=0.432		0.99 (0.98, 0.99) P<0.001
Age=20 years	1.83 (1.64, 2.05)	---		1.83 (1.64, 2.05)
Age=40 years	1.38 (1.26, 1.51)			1.38 (1.27, 1.51)
Age=60 years	1.04 (0.90, 1.19)			1.04 (0.91, 1.20)

NS= non significant HRs not reported

Table 4

Attributable Risk

	Mild Psoriasis	Severe Psoriasis	All Psoriasis
Depression			
Attributable Risk[1] per 1000 person y	11.5	25.5	11.8
Anxiety			
Attributable Risk[1] per 1000 person y	8.0	8.1	8.1
Suicidality			
Attributable Risk[1] per 1000 person y	0.4	0.4	0.4

[1] Adjusted for age and sex