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Association of Skin Psoriasis and Somatic Comorbidity With the Development of Psychiatric Illness in a Nationwide Swedish Study

Kirk Geale, MSc; Martin Henriksson, PhD; Jussi Jokinen, MD, PhD; Marcus Schmitt-Egenolf, MD, PhD

 Supplemental content

IMPORTANCE Psoriasis is a complex systemic disease with skin involvement, somatic comorbidity, and psychiatric illness (PI). Although this view of psoriasis is widely accepted, potential synergies within this triad of symptoms have not been adequately investigated.

OBJECTIVES To investigate the independent association of skin psoriasis and somatic comorbidity with the development of PI and to assess whether skin psoriasis and somatic comorbidity act synergistically to produce a risk of PI that is greater than the additive associations.

DESIGN, SETTING, AND PARTICIPANTS Participants were enrolled between January 2005 and December 2010, in this retrospective matched case-control study using secondary (ie, administrative), population-based registry data from Swedish patients in routine clinical care. The dates of analysis were March 2017 to December 2019. Participants were patients with skin psoriasis and control participants without psoriasis matched on age, sex, and municipality, who were all free of preexisting PI.

EXPOSURES Presence of skin psoriasis and somatic comorbidity (captured through the Charlson Comorbidity Index and the Elixhauser Comorbidity Index).

MAIN OUTCOMES AND MEASURES Risk of PI onset (composite of depression, anxiety, and suicidality) is shown using Kaplan-Meier curves stratified by the presence of skin psoriasis and somatic comorbidity. Adjusted associations of skin psoriasis and somatic comorbidity with the development of PI were analyzed using Cox proportional hazards regression models, including interactions to assess synergistic associations. The 3 components of PI were also assessed individually.

RESULTS A total of 93 239 patients with skin psoriasis (mean [SD] age, 54 [17] years; 47 475 men [51%]) and 1 387 495 control participants (mean [SD] age, 54 [16] years; 702 332 men [51%]) were included in the study. As expected, patients with skin psoriasis were more likely to have somatic comorbidity and PI than control participants. Compared with those without skin psoriasis or somatic comorbidity, patients with psoriasis without somatic comorbidity had a 1.32 times higher risk of PI onset (hazard ratio [HR], 1.32; 95% CI, 1.27-1.36; $P < .001$), whereas patients with psoriasis with somatic comorbidity had a 2.56 times higher risk of PI onset (HR, 2.56; 95% CI, 2.46-2.66; $P < .001$). No synergistic associations of skin psoriasis and somatic comorbidity with the development of PI were found (HR, 0.93; 95% CI, 0.81-1.04; $P = .21$).

CONCLUSIONS AND RELEVANCE This study found that somatic comorbidity appeared to alter PI onset even more than skin psoriasis. The observed association of skin psoriasis and somatic comorbidity with the development of PI reinforces the need for proactive, holistic treatment of patients with psoriasis.

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Author Affiliations: Division of Dermatology, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden (Geale, Schmitt-Egenolf); Quantify Research, Stockholm, Sweden (Geale); Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden (Henriksson); Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Jokinen); Department of Clinical Sciences, Umeå University, Umeå, Sweden (Jokinen).

Corresponding Author: Marcus Schmitt-Egenolf, MD, PhD, Division of Dermatology, Department of Public Health and Clinical Medicine, Umeå University, SE-901 87 Umeå, Sweden (marcus.schmitt-egenolf@umu.se).

Psoriasis occurs among 2% to 4% of the population in Western countries¹ and is associated with many somatic and psychiatric comorbidities.²⁻⁹ Somatic psoriasis comorbidities are also associated with psychiatric illness (PI) in their own right.¹⁰⁻¹⁴ Low-grade chronic systemic inflammation is postulated to be a common pathway underlying psoriasis, somatic comorbidities, and PI.¹⁵⁻¹⁹

These complex associations underscore the need for an in-depth, evidence-based understanding of how skin psoriasis, somatic comorbidity, and PI relate to each other, which to date has not been adequately investigated. Some large-scale studies^{3,20} examining the association of psoriasis with PI have not sufficiently investigated the role of somatic comorbidity. However, the results of a study²¹ that considered somatic comorbidity suggested that PI in patients with psoriasis may be explained by the presence of certain somatic comorbidities. Little is known about the independent risks imparted by skin psoriasis compared with somatic comorbidity on the development of PI or whether they have additive or synergistic associations. Additivity means that each factor acts independently to produce a total association where 1 plus 1 equals 2; in contrast, synergistic associations work together to produce a total association that is larger than the additive associations where 1 plus 1 is greater than 2, which has been studied across disciplines.²² Statistically, an interaction term can be used to test the hypothesis that synergies exist, which is described in the Statistical Analysis subsection of the Methods section.

This study investigated the independent risks of PI onset imparted by skin psoriasis and somatic comorbidity and whether these risks act additively or synergistically. We also assessed whether the findings were consistent across each component of the PI outcome, defined as a composite of depression, anxiety, and suicidality.

Methods

In this retrospective matched case-control study, data were obtained from Swedish population registers, including the National Patient Registry (NPR), Prescribed Drug Register (PDR), Cause of Death Register (CDR), and Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). The NPR began collecting data in 1964 and contains data on patient visits, including *International Classification of Diseases* (ICD) diagnosis codes, in secondary (ie, specialist) patient care. The PDR, established in 2005, records pharmacy-dispensed medication in Sweden, including dates of dispensing and Anatomical Therapeutic Chemical (ATC) codes in both primary and secondary care. The CDR records the date of death for Swedish residents. The LISA contains information about marital status, income, and education level. Individual-level data from each of these registries were linked using a personal identification number unique to each resident of Sweden by the National Board of Health and Welfare. Data collection and research were conducted in accordance with the Declaration of Helsinki²³ and were approved by the regional ethical review board in Umeå, Sweden. According to Swedish law, informed consent is not required for the extrac-

Key Points

Question How are skin psoriasis and somatic comorbidity associated with the development of psychiatric illness?

Findings Among 93 239 patients with skin psoriasis and 1 387 495 control participants in this matched case-control study, skin psoriasis and somatic comorbidity were independently associated with 1.32 and 2.09 times increased risk, respectively, of psychiatric illness onset compared with control participants without psoriasis and without somatic comorbidity. Skin psoriasis and somatic comorbidity acted additively but not synergistically.

Meaning Proactive, holistic treatment of patients with psoriasis is recommended because treating skin symptoms alone cannot remedy the elevated risk for psychiatric comorbidity.

tion and analysis of pseudonymized administrative data and was thus not obtained from study participants.

Patients With Psoriasis and Control Participants

Participants were enrolled between January 2005 and December 2010 in this retrospective matched case-control study using secondary, population-based registry data among Swedish patients in routine clinical care. The dates of analysis were March 2017 to December 2019. Patients with psoriasis in Sweden were identified through ICD codes (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]* code L40, *International Classification of Diseases, Ninth Revision [ICD-9]* codes 696A and 696B, and *International Classification of Diseases, Eighth Revision [ICD-8]* codes 696.0 and 696.1) recorded in the NPR or by an ATC code for a filled calcipotriol prescription (D05AX02 and D05AX52) in the PDR. Psoriasis onset was defined as the date when the patient first met any of these criteria. Patients were included in the study if their first registered psoriasis diagnosis occurred during or after 2005 to coincide with the start of data collection in the PDR. Diagnosis of psoriasis using administrative ICD codes captures patients with skin psoriasis who may also have other somatic or psychiatric comorbidities as indicated by other unique ICD codes. Fifteen control participants from the general population were matched to each patient with psoriasis by Statistics Sweden based on equivalent age, sex, and municipality on the date of psoriasis onset, and all were free of preexisting PI.

The present study focuses on skin symptoms, so psoriatic arthritis was differentiated from skin psoriasis through statistical adjustment, described in the Statistical Analysis subsection of the Methods section. Because it is a type of psoriasis, control participants could not have psoriatic arthritis.

Psychiatric Illness

In this study, we constructed PI as a composite measure consisting of depression, anxiety, and suicidality. Suicidality is composed of suicidal ideation, suicide attempt, and completed suicide. A composite outcome was preferred to capture the holistic concept of PI, provide consistency with previous research,⁹ and improve statistical power. We attempted to address the limitations associated with composite end

points, including various heterogeneities that may exist between the components,²⁴ by also analyzing each PI component separately in a sensitivity analysis.

Clinical diagnoses entered in secondary care were used to identify relevant PI events, including depression (*ICD-10* codes F32x, F33x, and F34.1; *ICD-9* codes 300E, 298A, 311x, and V79A; and *ICD-8* codes 296x, 298x, 300.4, and 790.2), anxiety (*ICD-10* codes F40x, F41x, F42x, and F43x), suicidal ideation (*ICD-10* code R45.8), and suicide attempt (*ICD-10* codes X6x, X7x, X8x, Y1x, Y2x, and Y3x; *ICD-9* codes E95x and E98x; and *ICD-8* codes E95x and E98x). Completed suicide was identified in the CDR using the same *ICD* codes for suicide attempt entered as cause of death.

Somatic Comorbidity

Two common comorbidity profiles, the Elixhauser Comorbidity Index (ECI)²⁵ and the Charlson Comorbidity Index (CCI)²⁶ were calculated for each patient in the year before baseline. Although both indexes were originally derived to predict 1-year mortality, they can effectively be used to control for comorbidity adjustment in survival analyses.²⁷ The ECI was used in the primary analysis because some evidence suggests that it performs better than the CCI, possibly because it contains more comorbidities.^{28,29} However, because there is also evidence indicating that the ECI and the CCI perform similarly in certain contexts,³⁰ the CCI was considered an important sensitivity analysis.

Depression diagnosis codes were included in both PI and the ECI and were thus removed from the ECI. After this modification, drug dependency and certain psychoses remained in the ECI, but most of the index represents somatic comorbidity. There was no such issue for the CCI.

Similar to the composite PI end point, the composite ECI measure was used to broadly capture the concept of somatic comorbidity. To understand the specific contributors to the association of somatic comorbidity with PI, an exploratory analysis was conducted in which each condition included in the ECI was assessed individually.

Statistical Analysis

Summary statistics of patient characteristics and outcomes are presented for patients with psoriasis, control participants, and the overall study population. Patients with psoriasis and control participants were compared using the Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables.

Cox proportional hazards regression models were estimated to measure associations of skin psoriasis, somatic comorbidity, and time to incident PI. Unadjusted models were calculated in which only psoriasis was included as a covariate, in addition to adjusted models that included psoriasis with adjustment for sociodemographics (age, sex, marital status, income, and education level) and somatic comorbidity (ECI/CCI). An interaction term between skin psoriasis and the ECI/CCI was included in the model to evaluate the presence of synergistic associations between the 2. To focus on skin symptoms in the present study rather than on psoriasis-related joint symptoms, the Cox proportional hazards regression models also adjusted for psoriatic arthritis (*ICD-10* code L40.5x).

Patient follow-up began on the date of psoriasis onset, with the same date used for all matched control participants. Those without a PI onset event were censored either at death or at the end of follow-up on the data extraction date of December 31, 2010, whichever occurred first.

Data management, statistical analyses, and graphics production were conducted in SAS version 9.4 (SAS Institute Inc) and R version 3.5.1 (The R Foundation). All *P* values were evaluated as 2-sided tests, with an a priori statistical significance level of $\alpha = .05$.

Results

Analysis Population

A total of 93 239 patients with skin psoriasis (mean [SD] age, 54 [17] years; 47 475 men [51%]) and 1 387 495 control participants (mean [SD] age, 54 [16] years; 702 332 men [51%]) were included in the study. Patients with skin psoriasis were identified according to the inclusion criteria and subsequently matched to control participants from the general population. The analysis excluded those with first psoriasis diagnosis before 2005, age younger than 18 years, or preexisting PI (diagnosis before psoriasis onset) and those with missing values for covariates. Age, marital status, and education level differed statistically significantly between patients with psoriasis and control participants, although the numerical differences were small. Somatic comorbidities and PI were generally more prevalent among patients with psoriasis than among control participants (Table 1).

Although PI events in the present study were defined as the first occurrence of depression, anxiety, or suicidality, many patients ultimately developed more than one of these conditions. The distribution of depression, anxiety, and suicidality in patients with psoriasis and control participants was similar during follow-up (eFigure in the Supplement).

Kaplan-Meier Curves of PI Onset

Kaplan-Meier curves were derived for the composite PI end point and for each component stratified by those with and without psoriasis (Figure 1). At the start of follow-up, there were 1 480 734 individuals at risk of PI onset. A total of 1 513 115, 1 525 166, and 1 557 640 individuals were at risk of depression, anxiety, and suicidality, respectively. In all cases, a log-rank test with a null hypothesis of no difference between the Kaplan-Meier curves was strongly rejected.

Kaplan-Meier curves were also constructed for time to PI onset stratified by the presence of psoriasis and the presence of somatic comorbidity (Figure 2). No important differences in risk of PI onset were observed when somatic comorbidity was measured by the CCI instead of the ECI.

Survival Analysis of Time to PI Onset

Before adjustment, patients with psoriasis had a 34% increased risk of PI onset compared with control participants (hazard ratio [HR], 1.34; 95% CI, 1.30-1.38; $P < .001$) (model A in Table 2). This risk was essentially unchanged after adjustment for sociodemographic covariates and somatic comorbidity

Table 1. Summary of the Analysis Population at Baseline^a

Variable	Control participants (n = 1 387 495)	Psoriasis (n = 93 239)	All (N = 1 480 734)	P value ^b
Age, y				
Mean (SD)	54 (16)	54 (17)	54 (16)	<.001
Median (IQR) [range]	55 (41 to 65) [18 to 98]	55 (41 to 65) [18 to 98]	55 (41 to 65) [18 to 98]	
Sex				
Female	685 163 (49)	45 764 (49)	730 927 (49)	.08
Male	702 332 (51)	47 475 (51)	749 807 (51)	
Education level				
High school	614 182 (44)	43 353 (46)	657 535 (44)	<.001
Less than high school	352 661 (25)	24 437 (26)	377 098 (25)	
More than high school	420 652 (30)	25 449 (27)	446 101 (30)	
Marital status				
Married	699 906 (50)	46 696 (50)	746 602 (50)	.03
Unmarried	687 589 (50)	46 543 (50)	734 132 (50)	
Disposable income, 1000 \$				
Mean (SD)	21 (179)	21 (61)	21 (174)	.08
Median (IQR) [range]	18 (12 to 24) [-7865 to 201 295]	17 (12 to 24) [-968 to 15 842]	18 (12 to 24) [-7865 to 201 295]	
Somatic comorbidity within 1 y of baseline				
ECI				
<0	7968 (1)	902 (1)	8870 (1)	<.001
0	1 289 134 (93)	83 914 (90)	1 373 048 (93)	<.001
1	464 (0)	66 (0)	530 (0)	<.001
2	3483 (0)	361 (0)	3844 (0)	<.001
3	9848 (1)	1111 (1)	10 959 (1)	<.001
4	23 907 (2)	1863 (2)	25 770 (2)	<.001
≥5	52 691 (4)	5022 (5)	57 713 (4)	<.001
CCI				
0	1 275 956 (92)	82 079 (88)	1 358 035 (92)	<.001
1	50 942 (4)	5540 (6)	56 482 (4)	<.001
2	42 555 (3)	3730 (4)	46 285 (3)	<.001
3	9057 (1)	982 (1)	10 039 (1)	<.001
4	3317 (0)	400 (0)	3717 (0)	<.001
≥5	5668 (0)	508 (1)	6176 (0)	<.001
Psoriatic arthritis	0	6589 (7)	6589 (0)	<.001
Associated ICD chapter				
Infection and parasites	21 137 (2)	3312 (4)	24 449 (2)	<.001
Neoplasms	64 467 (5)	5957 (6)	70 424 (5)	<.001
Blood and immune mechanisms	10 009 (1)	1111 (1)	11 120 (1)	<.001
Endocrine, nutritional, and metabolic	51 770 (4)	5612 (6)	57 382 (4)	<.001
Mental and behavioral	16 863 (1)	1729 (2)	18 592 (1)	<.001
Nervous system	31 794 (2)	2991 (3)	34 785 (2)	<.001
Eye and adnexa	69 398 (5)	5933 (6)	75 331 (5)	<.001
Ear and mastoid process	21 113 (2)	2024 (2)	23 137 (2)	<.001
Circulatory system	88 971 (6)	9547 (10)	98 518 (7)	<.001
Respiratory system	34 941 (3)	3774 (4)	38 715 (3)	<.001
Digestive system	52 517 (4)	5232 (6)	57 749 (4)	<.001
Skin and subcutaneous tissue	34 179 (2)	46 017 (49)	80 196 (5)	<.001
Musculoskeletal system and connective tissue	89 306 (6)	12 505 (13)	101 811 (7)	<.001
Genitourinary system	67 809 (5)	5841 (6)	73 650 (5)	<.001
Pregnancy	17 134 (1)	1190 (1)	18 324 (1)	.27
Perinatal	53 (0)	6 (0)	59 (0)	.22
Congenital	3501 (0)	376 (0)	3877 (0)	<.001

(continued)

Table 1. Summary of the Analysis Population at Baseline^a (continued)

Variable	Control participants (n = 1 387 495)	Psoriasis (n = 93 239)	All (N = 1 480 734)	P value ^b
Outcomes				
Composite PI end point	31 007 (2)	2763 (3)	33 770 (2)	<.001
Depression	16 288 (1)	1502 (2)	17 790 (1)	<.001
Anxiety	20 108 (1)	1822 (2)	21 930 (1)	<.001
Suicidality	5633 (0)	472 (1)	6105 (0)	<.001

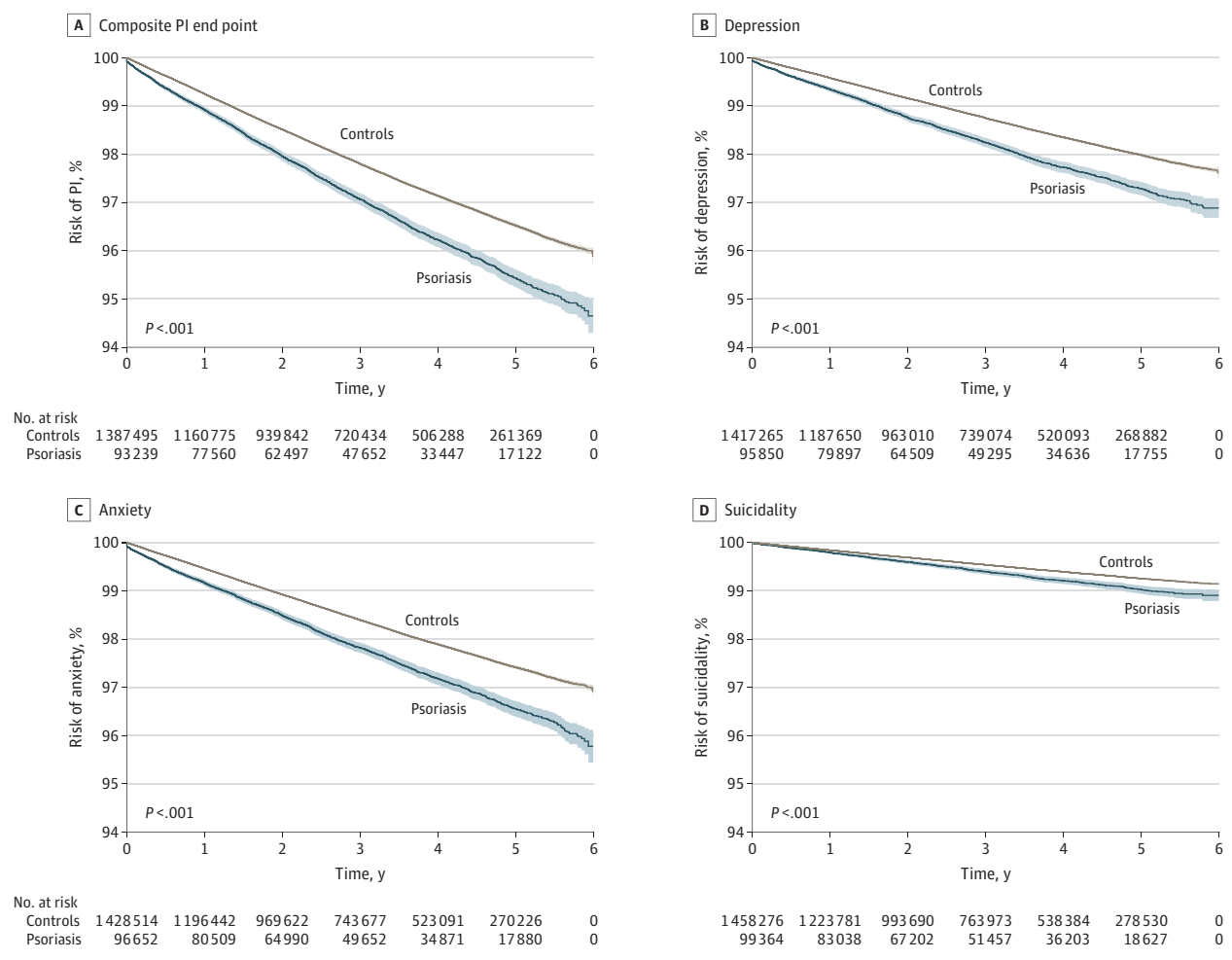
Abbreviations: CCI, Charlson Comorbidity Index; ECI, Elixhauser Comorbidity Index; ICD, *International Classification of Diseases*; IQR, interquartile range; PI, psychiatric illness.

^a Data are presented as No. (%) unless otherwise indicated.

^b P values were calculated based on Kruskal-Wallis test for continuous variables

and χ^2 test for categorical variables, with type I error (statistical significance level) of $\alpha = .05$. Patient characteristics were calculated on the date of psoriasis onset (baseline), except for comorbidities, which were evaluated in the year before baseline.

Figure 1. Kaplan-Meier Curves for Time to Psychiatric Illness (PI) Events



The lines represent the estimated Kaplan-Meier curves, and the shaded areas represent 95% CIs. The reported P values are from a log-rank test of difference between the Kaplan-Meier curves.

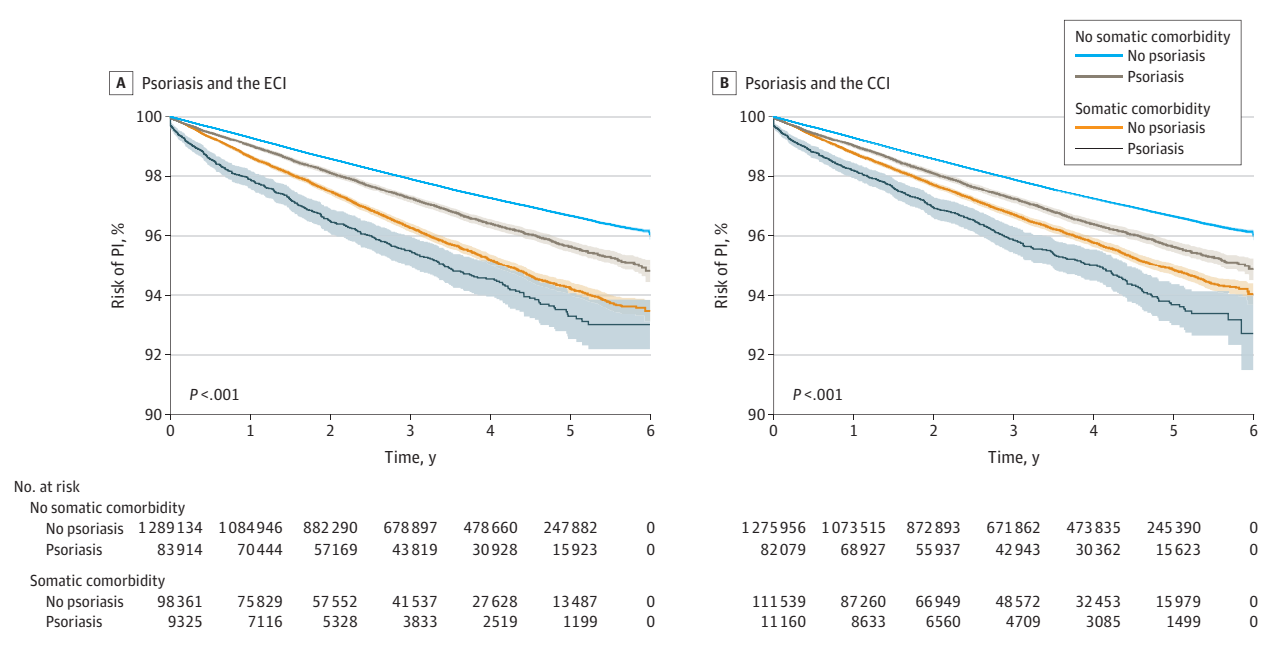
(model C in Table 2). The interaction between skin psoriasis and the ECI was not statistically significant (HR, 0.99; 95% CI, 0.97-1.00; $P = .11$) (model E in Table 2), nor was the interaction between skin psoriasis and the CCI statistically significant (HR, 0.98; 95% CI, 0.94-1.03; $P = .49$) (model F in Table 2). The statistically nonsignificant interaction terms can be in-

terpreted as a lack of evidence for synergistic associations between skin psoriasis and somatic comorbidity.

Simplified Survival Analysis of Time to PI Onset

A simplified analysis was conducted in which somatic comorbidity was classified dichotomously as ECI = 0 and ECI \neq 0

Figure 2. Kaplan-Meier Curves for Time to Composite Psychiatric Illness (PI) Onset



Stratified by individuals with no psoriasis, no somatic comorbidity; psoriasis, no somatic comorbidity; no psoriasis, somatic comorbidity; and psoriasis, somatic comorbidity. The presence of somatic comorbidity was assessed using the Elixhauser Comorbidity Index (ECI) (A) and the Charlson Comorbidity Index

(CCI) (B). The reported P values are from a log-rank test of difference between the Kaplan-Meier curves. The dark lines in each plot represent the Kaplan-Meier estimates, whereas the lighter, shaded areas represent 95% CIs.

(eTable 1 in the Supplement) with adjustment for sociodemographic characteristics. Compared with a reference group of control participants without somatic comorbidity, the HRs of time to PI onset were 1.32 (95% CI, 1.27-1.36; $P < .001$) for patients with psoriasis without somatic comorbidity, 2.09 (95% CI, 2.06-2.13; $P < .001$) for control participants with somatic comorbidity, and 2.56 (95% CI, 2.46-2.66; $P < .001$) for patients with psoriasis with somatic comorbidity. No synergistic associations of skin psoriasis and somatic comorbidity with the development of PI were found in this analysis (HR, 0.93; 95% CI, 0.81-1.04; $P = .21$).

Exploration of the ECI Components and PI Onset

The ECI and CCI represent a wide range of illnesses and are almost exclusively somatic. The ECI items associated with an increased risk of PI onset by a factor of 2 or more include alcohol abuse, drug abuse, and weight loss (Figure 3). Psychoses, one of the few components of the ECI that are not somatic, are also associated with PI onset. As expected, no components of the ECI were statistically significantly associated with a reduced risk of PI onset.

Survival Sensitivity Analysis of Time to Onset of Depression, Anxiety, and Suicidality Individually

The analysis of depression, anxiety, and suicidality individually revealed independent risks associated with psoriasis and somatic comorbidity (eTable 2 in the Supplement) that are consistent with the analysis of the composite PI end point. The interaction terms between skin psoriasis and the ECI were not statistically significant in any of the analyses of depression,

anxiety, or suicidality individually, indicating no risk synergies. For other risk factors, associations with depression, anxiety, or suicidality onset individually were similar to the main composite analysis, with the exception that female sex was associated with shorter time to onset of suicidality than male sex. In contrast, male sex was associated with shorter time to anxiety and depression onset than female sex.

Discussion

The paradigm shift in psoriasis care from management of skin symptoms to holistic patient care is associated with an appreciation of the somatic and psychiatric comorbidity burden of patients with psoriasis. An essential next step to improve care, outlined in the present study, is to investigate how skin psoriasis and somatic comorbidity alter PI. Using population data, we found that both skin psoriasis and somatic comorbidity are independent risk factors for PI onset and its individual components: depression, anxiety, and suicidality. Skin psoriasis and somatic comorbidities act additively on PI onset, not synergistically.

Descriptive Association of Psoriasis and Somatic Comorbidity With PI

The present study supports earlier findings that patients with psoriasis are burdened by a wide spectrum of somatic comorbidities,^{31,32} in particular cardiovascular and metabolic disease,^{5,33} as well as PI.^{3,9} We corroborate previous descriptions of elevated CCI burden in patients with psoriasis

Table 2. Cox Proportional Hazards Regression Models of Time to Onset of Psychiatric Illness

Covariate	Cox proportional hazards regression model (N = 1 480 734) ^a					
	A	B	C	D	E	F
Presence of skin psoriasis ^b						
HR (95% CI)	1.34 (1.30-1.38)	1.33 (1.29-1.37)	1.32 (1.28-1.36)	1.31 (1.27-1.35)	1.33 (1.29-1.37)	1.32 (1.28-1.36)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Age						
HR (95% CI)		0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.99-0.99)
P value		<.001	<.001	<.001	<.001	<.001
Female						
HR (95% CI)		1.35 (1.33-1.37)	1.36 (1.34-1.38)	1.36 (1.34-1.38)	1.36 (1.34-1.38)	1.36 (1.34-1.38)
P value		<.001	<.001	<.001	<.001	<.001
High school education						
HR (95% CI)		0.82 (0.80-0.85)	0.83 (0.80-0.85)	0.83 (0.80-0.85)	0.83 (0.80-0.85)	0.83 (0.80-0.85)
P value		<.001	<.001	<.001	<.001	<.001
More than high school education						
HR (95% CI)		0.69 (0.66-0.72)	0.70 (0.67-0.73)	0.70 (0.67-0.73)	0.70 (0.67-0.73)	0.70 (0.67-0.73)
P value		<.001	<.001	<.001	<.001	<.001
Unmarried						
HR (95% CI)		1.49 (1.46-1.51)	1.48 (1.45-1.50)	1.48 (1.45-1.50)	1.48 (1.45-1.50)	1.48 (1.45-1.50)
P value		<.001	<.001	<.001	<.001	<.001
Disposable income, 10 000 \$						
HR (95% CI)		0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.99-0.99)
P value		<.001	<.001	<.001	<.001	<.001
ECI						
HR (95% CI)			1.07 (1.07-1.07)		1.07 (1.07-1.08)	
P value			<.001		<.001	
CCI						
HR (95% CI)				1.28 (1.27-1.30)		1.28 (1.27-1.30)
P value				<.001		<.001
Psoriatic arthritis						
HR (95% CI)			1.00 (0.85-1.14)	0.98 (0.83-1.12)	1.00 (0.85-1.14)	0.98 (0.83-1.12)
P value			.98	.75	.97	.77
Interaction between skin psoriasis and the ECI						
HR (95% CI)					0.99 (0.97-1.00)	
P value					.11	
Interaction between skin psoriasis and the CCI						
HR (95% CI)						0.98 (0.94-1.03)
P value						.49

Abbreviations: CCI, Charlson Comorbidity Index; ECI, Elixhauser Comorbidity Index; HR, hazard ratio.

^a Model A is unadjusted. Model B is adjusted for sociodemographics. Model C is adjusted for sociodemographics and somatic comorbidity (ECI). Model D is adjusted for sociodemographics and somatic comorbidity (CCI). Model E is

adjusted for sociodemographics and somatic comorbidity (ECI) with interaction between skin psoriasis and the ECI. Model F is adjusted for sociodemographics and somatic comorbidity (CCI) with interaction between skin psoriasis and the CCI.

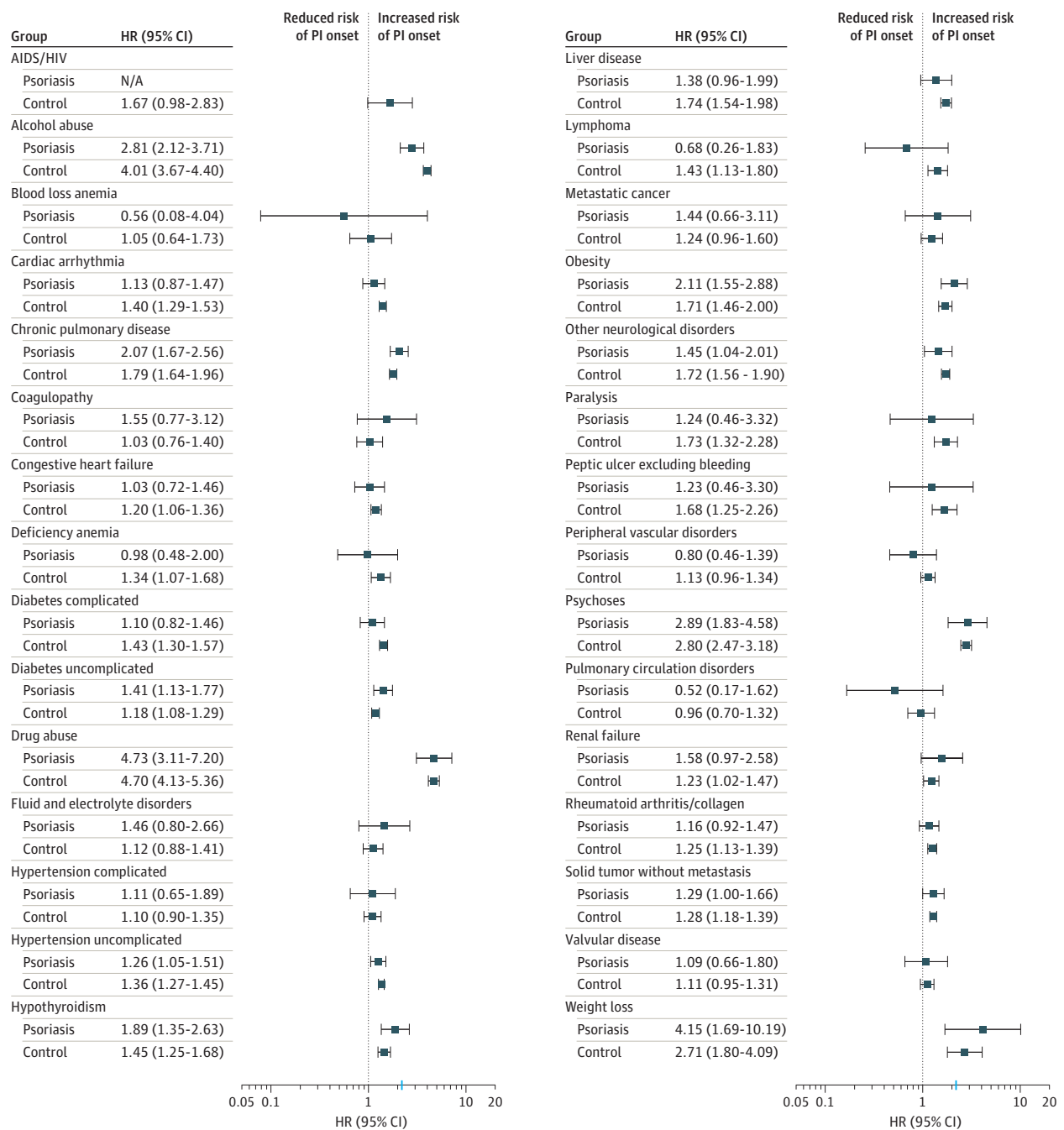
^b Skin psoriasis interpretation applies when adjusting for psoriatic arthritis.

compared with control participants.³² Our comprehensive description of ICD-based diagnoses aligns with a recent literature review describing similar wide-ranging somatic and psychiatric comorbidity profiles in patients with psoriasis.³⁴

As expected, patients with skin psoriasis with somatic comorbidity (the sickest patients) had the highest rate of incident PI (Figure 2). Control participants with somatic comorbidity had higher rates of PI onset than patients with psoriasis without somatic comorbidity. This finding can be

explained in at least 2 ways. First, the somatic comorbidities included in the ECI and CCI may be considered severe (eg, myocardial infarction and cancer) compared with skin psoriasis and thus may contribute more to PI onset than psoriasis. Second, somatic comorbidity was defined broadly using comorbidity indexes, so patients may have had multiple diseases. In contrast, by definition, the patients with skin psoriasis without somatic comorbidity had only one disease recorded (psoriasis).

Figure 3. Forest Plot for Association of Individual Components of the Elixhauser Comorbidity Index With Psychiatric Illness Onset



The forest plot was derived from 2 Cox proportional hazards regression models stratified by patients with psoriasis and control participants. Point estimates and 95% CIs are shown both numerically and in the forest plot. No AIDS/HIV diagnoses were found for patients with psoriasis; therefore, estimates are only available for control participants. Age, sex, education level, marital status,

income, and psoriatic arthritis were included as covariates in the models but are not shown in the forest plot. The hazard ratios (HRs) are plotted on a log scale. For reference, the HR of the composite Elixhauser Comorbidity Index in the simplified results analysis was 2.09 (eTable 1 in the Supplement), marked here by a blue dashed line.

Assessing Synergistic Associations of Psoriasis and Somatic Comorbidity

Despite the large sample size of almost 1.5 million individuals in the present study, the interaction term assessing synergy between skin psoriasis and somatic comorbidity was not statistically significant. Furthermore, the relevant HRs in Table 2 are close to 1,

with 95% CIs that include 1. Together, these findings are most compatible with an additive association, not a synergistic one.

Interpretation of the ECI and CCI Results

This study characterizes somatic comorbidity using the ECI and CCI. Although the main study results (Table 2) seem to show that

the CCI has a greater association with PI onset than the ECI, it is important to note that their respective scales are not comparable. The ECI and CCI include different comorbidities, weighting schemes, and ranges. Therefore, a 1-unit increase in the ECI is not easily compared with a 1-unit increase in the CCI. Similarly, the HR of the skin psoriasis variable (binary) is difficult to compare with the HR of the ECI and CCI (continuous).

However, in the simplified analysis in which somatic comorbidity defined by the ECI is treated as present or not (binary), the hazards are more easily compared. The presence of somatic comorbidity appears to contribute more risk to PI onset (HR, 2.09 [95% CI, 2.06-2.13]; $P < .001$) than skin psoriasis (HR, 1.32 [95% CI, 1.27-1.36]; $P < .001$).

Use of Composite Measures for Somatic Comorbidity and PI

To establish the overarching associations of skin psoriasis, somatic comorbidity, and PI, composite measures were used for somatic comorbidity and PI. We found consistent associations of covariates with onset of each PI component (depression, anxiety, and suicidality) individually. This finding suggests that heterogeneity, which is one of the major disadvantages to using composite end points, is not a large concern in the present study.

To understand how individual components of somatic comorbidity measured by the ECI alter PI onset, we assessed which aspects of somatic comorbidity (via the ECI) contributed most strongly to PI onset (Figure 3). Although the magnitude of the risks varied, it appears that many types of somatic comorbidity are associated with PI onset, meaning that the association of the composite ECI with PI onset is not limited to only a few select somatic comorbidities. This finding highlights the importance of the approach taken in this study of using a wide net to capture the concept of somatic comorbidity. The results also show that most of the ECI components were associated with comparable risks in the psoriasis and control populations.

Findings in the Context of Previous Research

The present study finds that both psoriasis and somatic comorbidity play important independent roles in PI onset. Previous research found that depression in most patients with psoriasis may be solely explained by the presence of certain comorbidities.²¹ However, compared with our analysis, that study was limited by a smaller sample size and a narrower definition of comorbidity. We believe that our results are consistent with the intuitive view that psoriasis skin symptoms independently contribute to PI onset.

A recent systematic review and meta-analysis found an association of psoriasis with suicidality, but it was not statistically significant.³⁵ The authors of that study concluded that the available evidence was insufficient and that more research was needed, which we provide herein. We found a statistically significant association of skin psoriasis with suicidality, with approximately the same risk as that described in the systematic

review and meta-analysis. With this finding, we provide needed evidence for the assessment of suicidality in psoriasis care.³⁶

Strengths, Limitations, and Future Research

The use of Swedish population registries in this study reduced the risk of selection bias because of the mandatory registration of all secondary health care contacts. The wide breadth of data allowed for characterization of baseline somatic comorbidity burden, socioeconomic status, and demographics in the patients with psoriasis, which is beneficial in reducing bias owing to confounding. In addition, the large samples available in Swedish registries ensured that our analyses were well powered, adding confidence to the statistical analyses.

This study had several limitations associated with diagnosis data. Clinical diagnoses from secondary (ie, specialist) care were used to identify psoriasis, somatic comorbidity, and PI. For psoriasis onset, relevant diagnoses recorded in primary care were not captured; therefore, the start of time at risk was underestimated in patients with psoriasis who were first treated in primary care without a calcipotriol prescription. Likewise, this study captured cases of somatic comorbidity recorded in specialist care only. Therefore, the prevalence of each somatic comorbidity may be underestimated, and the comorbidity indexes must be seen as conservative. Similarly, PI onset was underestimated because of the exclusive use of secondary care diagnoses. Finally, the results of this study must be interpreted within the Swedish clinical care environment and may not be directly generalizable to other settings.

Because of the administrative nature of the data used in this study, no clinical information regarding disease severity was available for psoriasis patients or control participants. Therefore, future research should aim to understand how clinical severity interacts with somatic comorbidity and PI in patients with psoriasis. Lifestyle factors associated with both psoriasis and depression⁶ should be studied. Future work should continue to investigate which somatic comorbidities are most important in PI onset using alternative definitions, methods, and data sources.

Conclusions

The somatic and psychiatric consequences in patients with psoriasis are extensive compared with the general population. Skin psoriasis and somatic comorbidity were independently associated with onset of the composite PI end point and with depression, anxiety, and suicidality individually. Skin psoriasis and somatic comorbidity appear to increase the risk of PI additively, not synergistically. This finding means that the total risk of PI onset is equal to the sum of the parts (skin psoriasis and somatic comorbidity). Our findings reinforce the importance of holistic patient management and proactive identification of somatic and psychiatric comorbidity in patients with psoriasis.

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Conflict of Interest Disclosures: Mr Geale reported receiving personal fees from Quantify Research and from Parexel International; he also holds stock options in and is a board member of Quantify Research. Dr Jokinen reported receiving personal fees for serving on a Janssen advisory board concerning esketamine for major depressive disorder with current suicidal ideation with intent. Dr Schmitt-Egenolf reported being responsible for dermatology in project management for the national psoriasis guidelines at the Swedish Board of Health and Welfare. No other disclosures were reported.

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