Vitiligo and major depressive disorder: A bidirectional population-based cohort study

Isabelle A. Vallerand, PhD,[a] Ryan T. Lewinson, MD, PhD,[b] Laurie M. Parsons, MD,[b] Jori Hardin, MD, MSc,[b] Richard M. Haber, MD,[b] Mark W. Lowerison, MSc,[a,c] Cheryl Barnabe, MD, MSc,[a,d] and Scott B. Patten, MD, PhD[a,e]
Calgary, Canada

Background: Vitiligo patients often report their mental health has an effect on their skin. However, it is unknown as to whether a common mental disorder, such as major depressive disorder (MDD), can also precipitate the onset of vitiligo.

Objective: Evaluate a bidirectional relationship between MDD and vitiligo using The Health Improvement Network database.

Methods: Incident MDD and referent cohorts were followed until the development of vitiligo. Also, incident vitiligo and referent cohorts were followed until the development of MDD. Cox proportional hazards models were used, and numerous covariates were adjusted for.

Results: In adjusted models, MDD patients (n = 405,397) were at a 64% increased risk for vitiligo (hazard ratio 1.64, 95% confidence interval [CI] 1.43-1.87, $P < .0001$) compared with the referent cohort (n = 5,739,048). This risk was decreased in patients using antidepressants. Compared with the referent cohort (n = 6,137,696), patients with vitiligo (n = 7104) that were <30 years of age at diagnosis had a higher risk of developing MDD than patients ≥30 years of age (hazard ratio 1.31, 95% CI 1.14-1.50, $P < .0001$ vs 1.22, 95% CI 1.08-1.37, $P = .001$, respectively).

Limitations: This study did not evaluate the severity of MDD or vitiligo on outcome development.

Conclusion: These results highlight the burden of depression in patients with vitiligo and support the possible existence of pathophysiological connections between these 2 conditions. (J Am Acad Dermatol 2019;80:1371-9.)

Key words: depression; epidemiology; inflammation; mental health; psychodermatology; vitiligo.

Vitiligo is an autoimmune disease characterized by skin depigmentation.[1] It is well known that autoimmune diseases, including vitiligo, can have psychologic effects on patients[2]; however, few studies have assessed these relationships longitudinally. Given the highly visible nature of vitiligo, it is not surprising that patients with vitiligo might be at greater risk for major depressive disorder (MDD)[3]—a clinical diagnosis of depression (not just symptoms) that has a high degree of morbidity and mortality.[4,5]

The question of whether vitiligo onset can be precipitated by MDD has received less attention, despite the notion that patients often ask their dermatologist if stress or depression might have contributed to their disease.[6] Interestingly, MDD

From the Department of Community Health Sciences,[a] Division of Dermatology,[b] Clinical Research Unit,[c] Department of Medicine,[d] and Department of Psychiatry,[e] Cumming School of Medicine, University of Calgary.

Funding sources: Supported by Alberta Innovates (to Dr Vallerand).
Conflicts of interest: None disclosed.
Accepted for publication November 21, 2018.

Reprints not available from the authors.
Correspondence to: Isabelle A. Vallerand, PhD, Cumming School of Medicine, University of Calgary, 3330 Hospital Dr NW, Calgary, Alberta, Canada T2N 4N1. E-mail: ivall@ucalgary.ca.

Published online December 5, 2018.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.11.047

might share similar human leukocyte antigen signatures with vitiligo,[7,8] and MDD was found to contribute to systemic inflammation independent of underlying autoimmune disease.[9] The diathesis stress model of MDD suggests that a susceptible individual exposed to stressors might develop MDD, and this finding has been supported by animal models,[10] simulations,[11] and human studies.[12,13] By extension, if MDD shares similar genetic and inflammatory patterns to established autoimmune diseases such as vitiligo, MDD could potentially increase the risk of subsequently developing vitiligo. This relationship would offer support to a possible brain-inflammation-skin axis, and provide novel insights to vitiligo pathogenesis. The lack of studies to examine an effect of MDD on vitiligo incidence might relate to sample size requirements of such research, a problem best addressed through access to large databases.

CAPSULE SUMMARY

- It is known that patients with vitiligo are at risk for depression; however, this study demonstrated an increased risk for vitiligo in patients with depression, which might be due to immune dysregulation.
- Clinicians treating vitiligo patients should be aware of this bidirectional relationship and refer these patients for mental health services accordingly.

In this study, we used The Health Improvement Network (THIN), a large medical records database in the United Kingdom, to conduct 2 population-based cohort studies whereby the bidirectional relationship between MDD and vitiligo was assessed. Given that vitiligo can be socially stigmatizing and the diathesis-stress model, along with similar genetic and inflammatory underpinnings for vitiligo and MDD, we hypothesized that MDD would have a significant bidirectional relationship with vitiligo.

METHODS

Data source

We used the THIN database, which contains records for about 12 million patients with up to 26 years of follow-up (1986-2012).

Study population, exposure, and outcomes

Any patient aged 10-90 years registered in THIN for ≥1 year was included in cohort determination. Exposed cohorts and outcomes were defined on the basis of the presence of ≥1 diagnostic code called Read codes in THIN, which correspond closely to the International Classification of Disease, Ninth Revision, classification. Read codes for MDD have been utilized in previous studies,[14-17] and Read codes for vitiligo were identified and agreed upon by a consensus panel of dermatologists (Dr Parsons, Dr Hardin, and Dr Haber).

Analysis 1: MDD as a risk factor for vitiligo. Patients were considered in the exposed MDD cohort if they had an incident diagnostic code for MDD at any time in THIN (Fig 1, *A*). The remainder of patients without a diagnostic code for MDD comprised the referent general population cohort. All included patients were followed up through THIN until diagnosis of vitiligo (outcome) or were censored. Patients with a diagnosis of vitiligo that preceded their MDD diagnosis were excluded.

Analysis 2: vitiligo as a risk factor for MDD. Patients were considered in the vitiligo (exposure) cohort if they had an incident diagnostic Read code for vitiligo (Fig 1, *B*). All other patients without a diagnostic code for vitiligo were considered in the referent cohort. Included patients were followed up until they developed MDD (outcome) or were censored. Patients with MDD diagnosed before their vitiligo diagnosis were excluded.

Covariates

In our analysis of the risk for vitiligo, we investigated the effects of covariates, such as age (continuous and dichotomized by age [<30 or ≥30 years]), sex, alcohol use (user or nonuser), smoking (current smoker, exsmoker, never smoker), socioeconomic status (on the basis of the Townsend Deprivation Index using postcode indicators in the United Kingdom, categorized into quintiles), medical comorbidities (using Charlson Comorbidity Index as an ordinal variable), and antidepressant medication (user or nonuser).

When analyzing the risk for MDD among those with vitiligo, we considered the effects of the following covariates: age (dichotomized by earlier age of onset <30 years or later age of onset ≥30 years),[18] sex, medical comorbidities (using Charlson Comorbidity Index as an ordinal variable), and vitiligo treatment (including users or nonusers of topical steroids, calcineurin inhibitors, or phototherapy).

Data analysis and manuscript preparation

In both analyses, we first compared baseline demographics between the exposed and referent cohorts, using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for median

Abbreviations used:

CI: confidence interval
HR: hazard ratio
IR: incidence rate
MDD: major depressive disorder
THIN: The Health Improvement Network

values with continuous variables. Any covariate that differed between cohorts at baseline was adjusted for in regression modeling. Incidence rates (IRs) were determined by using the number of outcome diagnoses and person-time of each cohort. For the main analyses, we used Cox proportional-hazard regression to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). We assessed effect modification using an omnibus likelihood ratio test comparing a model with all covariates by exposure interaction terms and a model without interactions. In the case of a significant likelihood ratio test result, a Wald test was used to identify specific effect modifiers to then stratify models accordingly. Next, we assessed for confounding by using a backward elimination approach, whereby covariates were removed 1 at a time while identifying any substantial (≥10%) change to the HR. We also constructed an unadjusted model and a model adjusting for all covariates.

In the analysis investigating the risk for vitiligo, we performed a sensitivity analysis assessing the incidence of vitiligo diagnosis among users and nonusers of antidepressants, stratified by MDD status. To ensure results were not biased relating to wait times for dermatology services, a sensitivity analysis was performed imposing a minimum of 6 months between the exposure of MDD and outcome of vitiligo, as <6 months is the typical time from general practitioner referral to treatment by a dermatologist in the United Kingdom.[19] We used STATA/MP version 13.1 (StataCorp LLC, College Station, Texas' $\alpha = 0.05$) for all analyses. This manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[20]

RESULTS

Analysis 1: MDD as a risk factor for vitiligo

The MDD cohort (n = 405,397) was slightly older, included more female patients, had a lower socioeconomic status, had more medical comorbidities, and drank less alcohol but included more current smokers and used more antidepressants than the referent cohort (n = 5,739,048) (Table I, all $P < .0001$).

Overall, 532 patients in the MDD cohort received vitiligo diagnoses, with an IR of 20.6 (95% CI 18.9-22.4)/100,000 person-years, higher than the referent cohort, with 6644 new diagnoses of vitiligo and an IR of 13.7 (95% CI 13.4-14.0)/100,000 person-years.

There was no evidence of effect modification by any covariate ($P = .8896$) or any violation of the proportional hazards assumption using Shoenfeld residuals ($P = .9886$). The unadjusted model demonstrated that MDD increases the risk for vitiligo diagnosis by 36% (HR 1.36, 95% CI 1.24-1.49, $P < .0001$). After adjusting for all covariates, the risk for vitiligo among those with MDD was 64% higher than those without MDD (HR 1.64, 95% CI 1.43-1.87, $P < .0001$; Table II). The use of antidepressants produced a strong confounding effect (>10% change in the HR) that strengthened the association between MDD and vitiligo with adjustment. Adjusting by continuous age demonstrated similar results, though with less precision (HR 1.57, 95% CI 1.37-1.79, $P < .0001$).

A sensitivity analysis comparing the incidence of vitiligo diagnosis among users and nonusers of antidepressants by MDD status revealed an overall protective effect of antidepressants among both cohorts (Table III). Specifically, patients with MDD who used antidepressants had a lower incidence of vitiligo diagnosis (IR 19.7 [95% CI 18.0-21.6]/100,000 person-years) than those with MDD who did not use antidepressants (IR 27.5 [95% CI 22.2-34.3]/100,000 person-years; $P = .0053$). Likewise, those in the referent cohort who used antidepressants had about half the risk of vitiligo (IR 8.3 [95% CI 7.8-8.8]/100,000 person-years) compared with those who did not use antidepressants (IR 15.7 [95% CI 15.3-16.10]/100,000 person-years; $P < .0001$), although the incidence of vitiligo diagnosis was lower in the referent cohort than the MDD cohort, regardless of antidepressant use. An additional sensitivity analysis imposing a minimum of 6 months between MDD diagnosis and vitiligo demonstrated similar results (adjusted HR 1.52, 95% CI 1.32-1.75, $P < .0001$).

Analysis 2: vitiligo as a risk factor for MDD

The vitiligo cohort (n = 7104) was slightly younger, consisted of more female patients, contained more vitiligo treatment users, and had more medical comorbidities than the referent cohort (n = 6,137,696) (all $P < .0001$; Table I).

A total of 463 patients with vitiligo developed MDD, with an IR of 1114.8 [95% CI 1014.0-1216.0]/100,000 person-years, higher than the rate in the referent cohort, with 405,292 new MDD diagnoses and an IR of 835.6 [95% CI 833.1-838.2]/100,000 person-years.

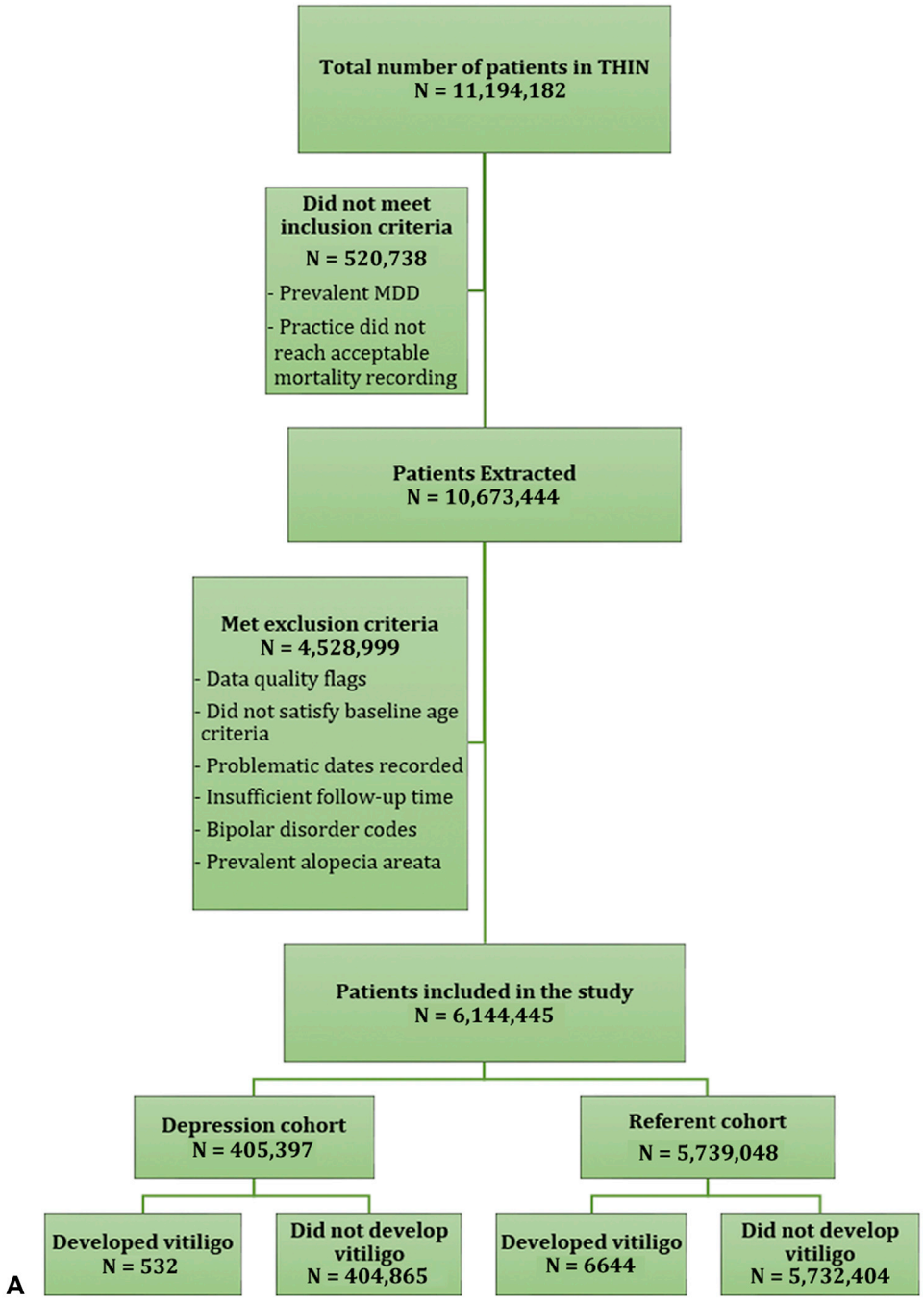

Fig 1. **A**, Study flow diagram of the risk for vitiligo study. **B**, Study flow diagram for the risk for MDD study. *MDD*, Major depressive disorder; *THIN*, The Health Improvement Network.

There was no evidence of a violation of the proportional hazards assumption using Shoenfeld residuals (P = .0675). The unadjusted Cox proportional hazards model demonstrated that patients with vitiligo diagnoses had a 27% increased risk for MDD than those without vitiligo (HR 1.27, 95% CI 1.16-1.40, $P < .0001$). Effect modification was detected using an omnibus likelihood ratio test (P = .0403), and a Wald test corresponding to the age by vitiligo exposure interaction term was significant (P = .0040). Therefore, models were stratified by age ≥30 years and adjusted for all other covariates. Younger patients with vitiligo had a higher risk of developing MDD than those who were older at diagnosis (age <30 years [HR 1.31, 95% CI 1.14-1.50, $P < .0001$] vs age ≥30 years [HR 1.22, 95% CI 1.08-

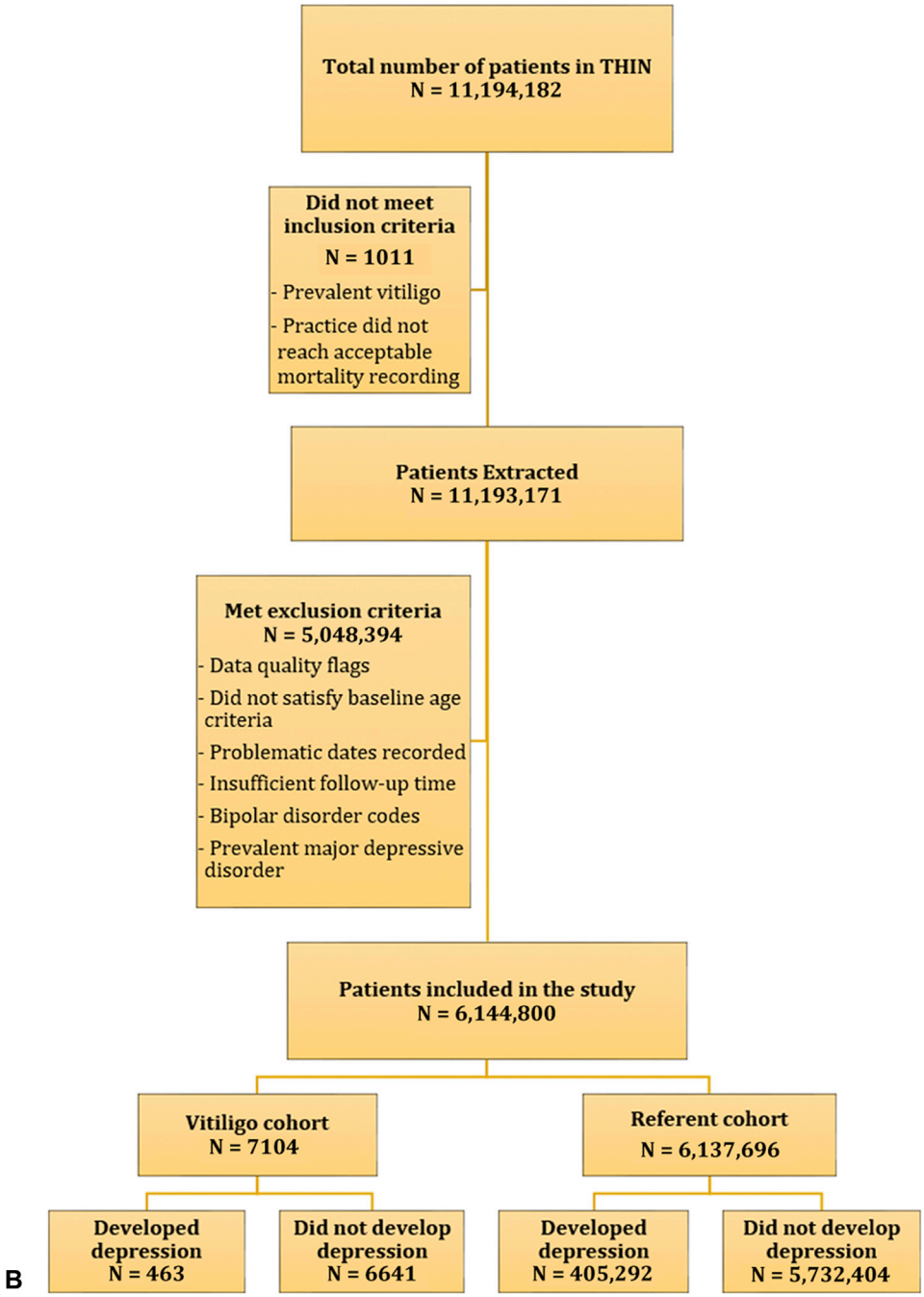

Fig 1. Continued.

1.37, P = .0010]). There was no evidence of confounding associations.

DISCUSSION

Using a longitudinal population-based data registry, we found that patients with MDD had a 64% increased risk for vitiligo diagnosis compared with people without MDD. We also demonstrated that younger vitiligo patients (with vitiligo diagnoses at <30 years of age) had a 31% increased risk of developing MDD and those ≥30 years of age had a 22% increased risk for MDD compared with the referent population. To date, existing literature has focused on mental health conditions occurring more frequently in people with existing dermatologic conditions like vitiligo,[3] and our results support this previous literature showing vitiligo patients are at increased risk for MDD. Unexpectedly, the magnitude of the reciprocal association was highest, with MDD being a risk factor for vitiligo. This highlights

Table I. Baseline characteristics of MDD patients, vitiligo patients, and the general population

Variable	MDD cohort, n = 405,397	General population, n = 5,739,048	*P* value
Age, y			<.0001
Median (IQR)	36.7 (23.9)	35.8 (27.3)	
Sex			<.0001
Female	263,954 (65.1)	2,912,535 (50.7)	
Smoking status			<.0001
Current	105,645 (26.1)	1,141,500 (19.9)	
Exsmoker	32,568 (8.0)	528,914 (9.2)	
Never	188,565 (46.5)	2,882,642 (50.2)	
Missing	78,619 (19.4)	1,185,992 (20.7)	
Alcohol use			<.0001
Users	162,811 (40.2)	2,550,029 (44.4)	
Nonusers	87,155 (21.5)	978,303 (17.0)	
Missing	155,431 (38.3)	2,210,716 (38.5)	
Socioeconomic status*			<.0001
1	83,655 (20.6)	1,242,438 (21.6)	
2	76,755 (18.9)	1,102,613 (19.2)	
3	80,019 (19.7)	1,110,074 (19.3)	
4	80,464 (19.8)	1,051,840 (18.3)	
5	62,836 (15.5)	760,342 (13.2)	
Missing	21,668 (5.3)	470,741 (8.2)	
Charlson Comorbidity Index†			<.0001
0	315,546 (77.8)	4,627,022 (80.6)	
1	65,459 (16.1)	714,045 (12.4)	
2	12,022 (3.0)	158,952 (2.8)	
3	4305 (1.1)	60,697 (1.1)	
≥4	8065 (2.0)	178,332 (3.1)	
Antidepressant use			<.0001
Users	357,906 (88.3)	1,064,911 (18.6)	
Variable	**Vitiligo cohort, n = 7104**	**General population, n = 6,137,696**	***P* value**
Age			<.0001
Median (IQR)	37.7 (15.8)	40.0 (18.7)	
Sex			<.0001
Female	3903 (54.9)	3,172,762 (51.7)	
Charlson Comorbidity Index†			<.0001
0	5842 (82.2)	4,936,993 (80.4)	
1	944 (13.3)	778,598 (12.7)	
2	151 (2.1)	170,837 (2.8)	
3	70 (1.0)	64,945 (1.1)	
≥4	97 (1.4)	186,323 (3.0)	
Vitiligo treatment‡			<.0001
Users	1096 (15.4)	218,081 (3.6)	

Values are the number (percentage) of patients with a given characteristic, except where indicated.
*Higher numbers indicate increased socioeconomic deprivation.
†Higher numbers indicate greater severity or higher number of medical comorbidities.
‡Vitiligo treatment includes potent and very potent topical steroids, calcineurin inhibitors, and phototherapy.

the notion that mental health might have a greater impact on the body, specifically with dermatologic manifestations, than previously thought.[21]

MDD has also been identified as a risk factor for other autoimmune diseases, including psoriatic arthritis, and rheumatoid arthritis.[15,16] Recently, MDD has been shown to have increased levels of pro-inflammatory cytokines, including tumor necrosis factor α and interleukin 6.[22] Given that vitiligo is considered an autoimmune disease[1] and that MDD might share similar human leukocyte antigen patterns with vitiligo,[7,8] our results could represent

overlap of diseases that commonly cluster together, either due to reciprocal causation or shared underlying determinants.

Our study also revealed that antidepressant use had a confounding effect that was protective regarding the risk for vitiligo. As expected, patients with MDD were more likely to utilize antidepressants than the general population. Although patients with MDD were at higher risk for vitiligo diagnosis than the general population, our sensitivity analysis revealed that patients with MDD who used antidepressants had a lower risk than patients with MDD who did not use antidepressants. Interestingly, we also observed this relationship in the referent cohort, where antidepressant users had approximately half the incidence of vitiligo than patients who did not use antidepressants. Therefore, it is possible that treating depression could help reduce circulating pro-inflammatory cytokines and, in turn, reduce the risk for an autoimmune response. Alternatively, it also seems possible that antidepressants might act as immunomodulators in the skin. For example, antidepressants might influence the T helper 1 and 2 cell balance,[22] which has also been associated with vitiligo.[23] In addition, serotonin availability could have a role in our findings. Serotonin availability in the neuronal synapse is implicated in MDD, and stemming from the concept that both neurons and melanocytes have an ectodermal origin, it has been proposed that melanocytes might also produce serotonin in the skin that has a cellular modularity role.[24] Further, experimental data has suggested that skin serotonin levels might be reduced in patients with vitiligo,[25] and high levels of skin serotonin might contribute to hair repigmentation in northern animals during summer months.[26] Thus, there appears to be a link between serotonin and melanocytes, and it might be possible that antidepressants have an influence on this relationship, although the exact mechanism leading to this reduced risk for vitiligo requires further investigation.

In our investigation of the risk for MDD, we found a significant interaction with age, such that patients with vitiligo diagnosed before the age of 30 years had a higher risk for MDD than those with a later age of vitiligo onset. Although vitiligo might have a variable presentation, it can often occur on the face—an area of high visibility like acne, which has also been linked to depression recently.[17] As such, it is possible that youths or young adults who develop vitiligo are more vulnerable to MDD given these differences in their appearance relative to their peers. A recent meta-analysis on the prevalence of depression among vitiligo patients found a slight decrease in the prevalence of symptoms of depression for every 10-year increase in age[3]; thus, our results are consistent with this finding, demonstrating a slightly lower incidence of depression in older vitiligo patients.

Table II. Risk for vitiligo associated with MDD and risk for MDD associated with vitiligo

Model	HR (95% CI)	*P* value
Risk for vitiligo model*		
Unadjusted model		
Depression	1.36 (1.24-1.49)	<.0001
Multivariable adjusted model*		
Depression	1.64 (1.43-1.87)	<.0001
Age	0.87 (0.81-0.93)	<.0001
Male sex	0.82 (0.77-0.88)	<.0001
Socioeconomic status		
2	0.94 (0.86-1.03)	.196
3	0.97 (0.89-1.07)	.538
4	0.99 (0.90-1.09)	.861
5	1.05 (0.95-1.17)	.326
Charlson comorbidity index	1.11 (1.03-1.20)	.009
Alcohol use	1.00 (0.93-1.07)	.972
Smoking		
Current	0.84 (0.78-0.91)	<.0001
Exsmoker	1.02 (0.92-1.12)	.748
Antidepressant use	0.58 (0.54-0.63)	<.0001
Risk for MDD model†		
Unadjusted model		
Vitiligo	1.27 (1.16-1.40)	<.0001
Age stratified multivariable adjusted models‡		
Age <30 y		
Vitiligo	1.31 (1.14-1.50)	<.0001
Male sex	0.44 (0.43-0.44)	<.0001
Charlson Comorbidity Index	1.21 (1.20-1.23)	<.0001
Vitiligo treatment	0.68 (0.66-0.70)	<.0001
Age ≥30 y		
Vitiligo	1.22 (1.08-1.37)	.001
Male sex	0.58 (0.57-0.58)	<.0001
Charlson Comorbidity Index	1.26 (1.25-1.27)	<.0001
Vitiligo treatment	0.58 (0.57-0.59)	<.0001

CI, Confidence interval; *HR*, hazard ratio; *MDD*, major depressive disorder.

*Cox proportional hazards models were used to estimate the HR of developing vitiligo on the basis of whether patients had MDD or not (ie, MDD vs general population). MDD significantly increases the risk of developing vitiligo when using unadjusted models as well as models accounting for numerous covariates.

†Cox proportional hazards models were used to estimate the HR of developing MDD on the basis of whether patients had vitiligo or not (ie, vitiligo vs general population). Vitiligo significantly increases the risk of developing MDD when using unadjusted models, as well as models accounting for numerous covariates.

‡Age interaction term Wald test $P = .0040$. Observations with missing data were omitted from the models.

Table III. Incidence rates for the development of vitiligo among patients prescribed antidepressants, stratified by cohort

	Major depressive disorder cohort, n = 405,339			Referent cohort, n = 5,738,596		
	Treated with antidepressants, n = 357,906	Not treated with antidepressants, n = 47,491	*P* value	Treated with antidepressants, n = 1,064,911	Not treated with antidepressants, n = 4,674,137	*P* value
Risk for vitiligo per 100,000 person-years (95% CI)	19.7 (18.0-21.6)	27.5 (22.2-34.3)	.0053	8.3 (7.8-8.8)	15.7 (15.3-16.1)	<.0001

CI, Confidence interval.

There are some limitations to acknowledge with this study, including a risk for misclassification of MDD or vitiligo, although this likely occurred nondifferentially across both exposure and outcome groups equally and, therefore, would have contributed to a dilution of the effect. Moreover, because we did not have data on treatment response, it remains unknown whether subclinical depression or even stress also contributes to the risk for vitiligo, although stress is thought to play an important role in the pathogenesis of MDD according to the diathesis stress model.[11] Last, we did not have data on the severity or extent of MDD or vitiligo involvement, which might have affected outcomes.

The current study had methodologic strengths that might have enabled our identification of the reported effects. The use of big data, with >6 million patients in each analysis and up to 26 years of follow-up, renders this study one of the largest on psychodermatology to date. As THIN contains data on numerous covariates, this enabled a thorough assessment of effect modification and confounding factors. Moreover, an important consideration toward identifying a causal link between depression and vitiligo is temporality, which was carefully identified in our bidirectional analyses with the use of washout periods to identify only incident exposures and outcomes. As such, a possible causal relationship between MDD and vitiligo is supported by these results.

In conclusion, our study demonstrated a significant bidirectional relationship between MDD and vitiligo. Ultimately, our finding suggests that mental health appears to play a large role in the pathogenesis of autoimmune diseases like vitiligo, which in turn can increase the risk for MDD, especially in younger patients. Clinicians involved in the care of patients with vitiligo and other dermatologic conditions should be aware of the strong link with MDD and initiate treatment with mental health professionals when needed. Future research should be done to determine the impact that mental health treatments, such as antidepressants, have on remission and recurrences of autoimmune dermatologic conditions and identify the underlying mechanism of action.

REFERENCES

1. Taieb A, Picardo M. Clinical practice. Vitiligo. *N Engl J Med*. 2009;360(2):160-169.
2. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56.
3. Lai YC, Yew YW, Kennedy C, Schwartz RA. Vitiligo and depression: a systematic review and meta-analysis of observational studies. *Br J Dermatol*. 2017;177(3):708-718.
4. Patten SB, Williams JV, Lavorato D, Li Wang J, Khaled S, Bulloch AG. Mortality associated with major depression in a Canadian community cohort. *Can J Psychiatry*. 2011;56(11):658-666.
5. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med*. 2013;10(11):e1001547.
6. Thompson AR, Montgomery K. Stress and more stress: the importance in skin disease of worrying about what others think. *Br J Dermatol*. 2018;178(4):821-822.
7. Jin Y, Andersen G, Yorgov D, et al. Genome-wide association studies of autoimmune vitiligo identify 23 new risk loci and highlight key pathways and regulatory variants. *Nat Genet*. 2016;48(11):1418-1424.
8. Weitkamp LR, Stancer HC, Persad E, Flood C, Guttormsen S. Depressive disorders and HLA: a gene on chromosome 6 that can affect behavior. *N Engl J Med*. 1981;305(22):1301-1306.
9. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.
10. Cohen S, Janicki-Deverts D, Doyle WJ, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci U S A*. 2012;109(16):5995-5999.
11. Patten SB. Major depression epidemiology from a diathesis-stress conceptualization. *BMC Psychiatry*. 2013;13:19.
12. Colodro-Conde L, Couvy-Duchesne B, Zhu G, et al. A direct test of the diathesis-stress model for depression. *Mol Psychiatry*. 2018;23(7):1590-1596.
13. Goshen I, Kreisel T, Ben-Menachem-Zidon O, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. *Mol Psychiatry*. 2008;13(7):717-728.
14. Josephson CB, Lowerison M, Vallerand I, et al. Association of depression and treated depression with epilepsy and seizure

outcomes: a multicohort analysis. *JAMA Neurol*. 2017;74(5):533-539.
15. Lewinson RT, Vallerand IA, Lowerison MW, et al. Depression is associated with an increased risk of psoriatic arthritis among patients with psoriasis: a population-based study. *J Invest Dermatol*. 2017;137(4):828-835.
16. Vallerand IA, Lewinson RT, Frolkis AD, et al. Depression as a risk factor for the development of rheumatoid arthritis: a population-based cohort study. *RMD Open*. 2018;4(2):e000670.
17. Vallerand IA, Lewinson RT, Parsons LM, et al. Risk of depression among patients with acne in the U.K.: a population-based cohort study. *Br J Dermatol*. 2018;178(3):e194-e195.
18. Kanwar AJ, Mahajan R, Parsad D. Effect of age at onset on disease characteristics in vitiligo. *J Cutan Med Surg*. 2013;17(4):253-258.
19. UK National Health Service. Results for dermatology services in E1 1BB. 2018; https://www.nhs.uk/service-search/Dermatology/E1-1BB/Results/41/-0.058118622750043 9/51.5190162658691/680/0?distance=25. Accessed October 6, 2018.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.
21. Bewley A. The neglected psychological aspects of skin disease. *BMJ*. 2017;358:j3208.
22. Komori T. The significance of proinflammatory cytokines and Th1/Th2 balance in depression and action of antidepressants. *Neuropsychiatry*. 2017;07(01).
23. Zhen Y, Yao L, Zhong S, Song Y, Cui Y, Li S. Enhanced Th1 and Th17 responses in peripheral blood in active non-segmental vitiligo. *Arch Dermatol Res*. 2016;308(10):703-710.
24. Johansson O, Liu PY, Bondesson L, et al. A serotonin-like immunoreactivity is present in human cutaneous melanocytes. *J Invest Dermatol*. 1998;111(6):1010-1014.
25. Schallreuter KU, Salem MA, Gibbons NC, et al. Blunted epidermal L-tryptophan metabolism in vitiligo affects immune response and ROS scavenging by Fenton chemistry, part 1: epidermal H2O2/ONOO(-)-mediated stress abrogates tryptophan hydroxylase and dopa decarboxylase activities, leading to low serotonin and melatonin levels. *FASEB J*. 2012;26(6):2457-2470.
26. Iyengar B. Indoleamines and the UV-light-sensitive photoperiodic responses of the melanocyte network: a biological calendar? *Experientia*. 1994;50(8):733-736.