# Supplementary Online Content

Vallerand IA, Lewinson RT, Parsons LM, et al. Assessment of a bidirectional association between major depressive disorder and alopecia areata. *JAMA Dermatol.* Published online January 16, 2019. doi:10.1001/jamadermatol.2018.4398



This supplementary material has been provided by the authors to give readers additional information about their work.

**eAppendix 1.** Methods

## Data Source

This study used The Health Improvement Network (THIN) as a data source. THIN is an electronic database that contains general practice medical records from over 12,000,000 individuals in the United Kingdom (UK).[1] Approximately 99% of individuals in the UK are registered with a general practice physician, and THIN represents approximately 5% of the UK population.[1] THIN is a longitudinal database, with over 25 years of follow-up in some practices. In the UK, all specialist referrals must originate from patients' general practice physician, and data from specialists' offices and hospitals are provided to general practice physicians and recorded in THIN. In addition, the patients registered in THIN have similar age and sex distributions to the general UK population.[2,3] Therefore, THIN is a large, representative database with longitudinal follow-up and detailed medical history data.

Given that the prevalence of AA is low (approximately 1%),[4] THIN represents an ideal data source for the study of this condition. THIN has been used previously for the study of dermatologic disease and psychiatric disorders.[5,6]

## Study Population, Exposure and Outcomes

***Risk of alopecia areata study.*** THIN was used to identify all individuals between the ages of 10-90 years who were registered in THIN for at least one year. Two cohorts were defined: a MDD cohort, and a general population cohort. The MDD cohort represents those who have had a MDD diagnosis, which was defined by presence of a Read code for MDD, as done previously.[5] To be included in the MDD cohort of the study, the patient must have been enrolled in THIN for at least one year prior to diagnosis of MDD to ensure only incident cases were included. Additionally, diagnosis of MDD was required to precede diagnosis of AA (if applicable). Any patients with diagnoses of AA prior to MDD were excluded from the MDD cohort. Moreover, patients with any records corresponding to bipolar disorder were excluded. The general population cohort comprised all other individuals in THIN with at least one year of registration who did not have any Read codes for MDD recorded in THIN. To minimize the threat of survival bias, a time-dependent exposure approach was used whereby the person-time for the MDD cohort was partitioned into unexposed time from the start date in THIN until their MDD diagnosis date, and their exposure time commenced at the time of their MDD diagnosis until the end of the study period.[7] Patients in the referent cohort were followed from their start date in THIN until the end of the study period. Within the MDD cohort and general population referent cohort, individuals who developed incident AA (primary outcome measure) were identified.

As we are not aware of established case definitions for diagnosis of AA in THIN, we sought to develop a case definition in a similar manner to what has been done for MDD as well as other autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis and psoriasis.[5,8-10] Therefore, we established a list of Read codes corresponding to AA which were agreed upon by consensus among a panel of 3 dermatologists (LMP, JH, RMH), and subsequently compared its performance in terms of face validity to known prevalence of AA in the general population, sex differences, and age of onset distributions. Based on this analysis, we found that the prevalence of AA in our study was 0.11%, the sex distribution was relatively equivalent (AA patients comprised 56.1% females) and we also found that males developed AA at a slightly earlier age (Mean= 31.1, SD=12.6 years) compared to females (Mean age=35.7, SD=15.2 years). Recently, the descriptive epidemiology of AA was reviewed and the prevalence was reported as being between 0.1-0.2% in the general population, equal between males and females and males were reported to develop AA at an earlier age (Mean=31.5 vs. Mean=36.2 years in females).[11] Therefore, our case definition performed extremely well from a face validity perspective when being compared to existing and recent estimates reported in the literature.

To be eligible for study inclusion, if a diagnostic code for AA was present, it had to be an incident case. This established the temporality of the conditions under question, where MDD was required to occur first, followed by AA. Patients who were not observed to develop AA during the follow-up period were censored.

***Risk of major depressive disorder study*.** THIN was used to identify all individuals between the ages of 10-90 years who were registered in THIN for at least one year. Two cohorts were defined: an AA

cohort, and a general population cohort. The AA cohort comprised those who had an incident AA diagnosis. Diagnosis of AA was made using case definitions from Read codes, as described above. To be included in the AA cohort of the study, the patient must have been enrolled in THIN for at least one year prior to diagnosis of AA to ensure only incident cases were included. Additionally, diagnosis of AA was required to precede diagnosis of MDD (if applicable). Any patients with diagnoses of MDD prior to AA were excluded from the AA cohort. The general population cohort comprised all other individuals in THIN with at least one year of registration who did not have any Read codes for MDD recorded in THIN. As was done with the risk of AA study, a time-dependent exposure approach was used to minimize the threat of survival bias.[7] Therefore, the person-time for the AA cohort was split into unexposed (from the start date in THIN until AA diagnosis) and exposed (from AA diagnosis until the end of the study) periods. Patients in the referent cohort were followed from their start date in THIN until the end of the study period.

Within the AA cohort and general population referent cohort, individuals who developed incident MDD (primary outcome measure) were identified. Diagnosis of MDD was made using case definitions from Read codes for MDD, excluding any patients with records for bipolar disorder, as done previously.[5] To be eligible for study inclusion, if a diagnosis of MDD was present, it had to be an incident case. Again, this established the temporality of the conditions under question, where AA was required to occur first, followed by MDD. Patients who were not observed to develop the outcome of MDD during the follow-up period were censored.

**Covariates**

***Risk of alopecia areata study.*** Age was dichotomized by age <40 or ≥40 years.[12] Categorization of age may have reduced the ability of the model to control for confounding effects, but when age was also assessed as a continuous variable, it made no difference to the adjusted effects. Thus, results were reported based on dichotomized age, in keeping with previous literature.[12] Sex was dichotomized by male or female. Alcohol was dichotomized as either an alcohol user or non-user. Smoking was categorized as either current smoker, ex-smoker or never smoker. Socioeconomic status was determined using the Townsend Deprivation Index.[13] These variables were all determined by the values closest to the start of follow-up in THIN. Medical comorbidity status was determined using the Charlson Comorbidity Index within three years of each patient's start date in THIN,[14] as done previously.[5] To assess the impact of MDD treatment, use of any antidepressant medication was documented during the study period (including selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), tricyclics (TCA), monoamine oxidase inhibitors (MAOI), and atypical antidepressants).

***Risk of major depressive disorder study*.** Age was dichotomized by age <40 or ≥40 years and was also assessed as a continuous variable. Again, the estimated effects were the same using both approaches, thus the results were reported based on the dichotomized age variable. Sex was dichotomized by male or female. These variables were all determined at the start of follow-up in THIN. Medical comorbidity status was determined using the Charlson Comorbidity Index within three years of each patient's start date in THIN,[14] as done previously.[5] To assess the impact of treatment for AA, intralesional steroid injections and potent topical steroid use were documented during the study period, as per the British Association of Dermatology treatment guidelines for AA.[15] Socioeconomic status, alcohol use and smoking were not considered in this study, as it is not clear that these factors would be associated with exposure to alopecia areata, and since total sample size in this analysis was low, restricting broad implementation of covariates without rationale.

**Data Analysis**

***Risk of alopecia areata study.*** Baseline covariates were compared between the MDD and referent cohort using Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Cox proportional hazard regression models were used to first assess for the presence of effect modification, comparing a model with interaction terms for each covariate to a model without, using a Likelihood Ratio test. Next, models were constructed using a backward elimination approach to assess for the presence of confounding, with removal of one covariate at a time. Covariates that differed across cohorts at baseline and elicited a >10% change to the estimated HR with removal from the fully adjusted model were deemed as confounding variables. A model adjusting for all covariates including age, sex, socioeconomic status (according to the Townsend deprivation index), medical comorbidities (using the

Charlson comorbidity index), smoking, alcohol use and antidepressants was constructed and compared against a crude, unadjusted model (Table 2). The proportional hazards assumption was verified statistically using Shoenfeld residuals. Although data on obesity were missing at baseline in 53.1% of the MDD and 50.7% of the referent cohort, the impact of obesity on the estimated risk of developing AA, was assessed in a sensitivity analysis (Supplementary file). A sensitivity analysis was also performed whereby all individuals with codes for telogen effluvium were excluded to help minimize misclassification of another form of hair loss that may be related to stress. All statistical analyses were performed using Stata MP v.13.1 with $\alpha$=0.05.

***Risk of major depressive disorder study*.** A comparison of covariates at baseline between each cohort was done using Chi-squared tests for categorical data and Wilcoxon rank-sum tests comparing median age. Cox proportional hazard regression was used to first assess for the presence of effect modification by creating interaction terms for age and sex only, as data were underpowered to assess other covariates. A model including these interaction terms was compared against a model without, using an omnibus Likelihood Ratio test. An assessment of confounding was performed next by using a backward elimination approach to determine the impact of all covariates including age, sex, medical comorbidities (Charlson Comorbidity Index), and steroid therapy on the estimated HR, by removing each covariate, one at a time. Any covariate that produced a >10% change to the estimated HR with its removal, and was significantly different between cohorts at baseline was considered a confounding variable. A model adjusting for all covariates was constructed as well as a crude, unadjusted model (Table 2). The proportional hazards assumption was tested using Shoenfeld residuals. All statistical analyses were performed using Stata MP v13.1, with $\alpha$=0.05.

**eAppendix 2.** Results

In the risk of AA study, a sensitivity analysis was conducted to further investigate the impact of antidepressant use on the risk of developing AA, since antidepressants were identified as producing a confounding effect in the model. As such, incidence rates were determined for patients using antidepressants vs. those not using antidepressants among each cohort. The results revealed that while patients in the MDD cohort had a higher incidence of developing AA compared to the referent cohort (Supplementary table), the patients with MDD who used antidepressants had a lower incidence of AA (IR=24.8, 95%CI: 22.9 to 27.0, per 100,000 person-years) than patients with MDD who did not use antidepressants (IR=32.0, 95%CI: 26.1 to 39.1, per 100,000 person-years). Furthermore, patients using antidepressants in the referent cohort (for various indications other than MDD), had a lower incidence of AA (IR=8.6, 95%CI: 8.1 to 9.1, per 100,000 person-years) compared to those who did not use antidepressants (IR=14.8, 95%CI: 14.4 to 15.2, per 100,000 person-years).

A second sensitivity analysis examined the inclusion of BMI as a covariate using multiple imputation since BMI had >50% missing data in each cohort. Ultimately, the imputation of BMI data did not change the main result (HR=1.90, 95%CI 1.67 to 2.15, p<0.0001). In addition, exclusion of 1,543 patients with a code for telogen effluvium (a condition also responsible for hair loss) did not change the main result (HR 1.90, 95%CI 1.67 to 2.16, p<0.0001).

**eReferences**


1. IMS Health U. Statistics. 2016; http://www.csdmruk.imshealth.com/our-data/statistics.shtml. Accessed February 6, 2016.
2. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet.*352:1970-1973.
3. Bhayat F, Das-Gupta E, Smith C, McKeever T, Hubbard R. The incidence of and mortality from leukaemias in the UK: a general population-based study. *BMC cancer.* 2009;9:252.
4. Gilhar A, Etzioni A, Paus R. Alopecia areata. *N Engl J Med.* 2012;366(16):1515-1525.
5. 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.
6. Wan J, Wang S, Haynes K, Denburg MR, Shin DB, Gelfand JM. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ.* 2013;347:f5961.
7. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol.* 2005;162(10):1016-1023.
8. 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.
9. Ogdie A, Alehashemi S, Love TJ, et al. Validity of psoriatic arthritis and capture of disease modifying antirheumatic drugs in the health improvement network. *Pharmacoepidemiol Drug Saf.* 2014;23(9):918-922.
10. Seminara NM, Abuabara K, Shin DB, et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. *Br J Dermatol.* 2011;164(3):602-609.
11. Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. *J Am Acad Dermatol.* 2018;78(1):1-12.
12. Korten NC, Comijs HC, Lamers F, Penninx BW. Early and late onset depression in young and middle aged adults: differential symptomatology, characteristics and risk factors? *J Affect Disord.* 2012;138(3):259-267.
13. Townsend P, Phillimore P, A. B. Inequalities in health in the Northern region: an interim report. Published jointly by the Northern Regional Health Authority and the University of Bristol. 1986.
14. St Germaine-Smith C, Liu M, Quan H, Wiebe S, Jette N. Development of an epilepsy-specific risk adjustment comorbidity index. *Epilepsia.* 2011;52(12):2161-2167.
15. Messenger AG, McKillop J, Farrant P, McDonagh AJ, Sladden M. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. *Br J Dermatol.* 2012;166(5):916-926.

**eTable.** Incidence Rates for the Development of Alopecia Areata Among Patients Prescribed an Antidepressant, Stratified by Cohort

| | **Major Depressive Disorder Cohort (n =405,339)** | | | **Referent Cohort (n =5,738,596)** | | |
|---|---|---|---|---|---|---|
| | Treated with Antidepressants (n=357,844) | Not Treated with Antidepressants (n=47,495) | *P* Value | Treated with Antidepressants (n=1,064,658) | Not Treated with Antidepressants (n=4,673,938) | *P* Value |
| Risk of Alopecia Areata per 100,000 person-years (95%CI) | 24.8 (22.9 to 27.0) | 32.0 (26.1 to 39.1) | .0227 | 8.6 (8.1 to 9.1) | 14.8 (14.4 to 15.2) | <.0001 |