PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The epidemiology, management, and the associated burden of mental health illness, atopic and autoimmune conditions, and common infections in alopecia areata: Protocol for an observational study series
AUTHORS	Harries, Matthew; Macbeth, Abby; Holmes, Susan; Thompson, Andrew; Chiu, Wing; Gallardo, William; Messenger, Andrew; Tziotzios, Christos; de Lusignan, Simon

VERSION 1 – REVIEW

REVIEWER	Agre, KAtherine Mayo Clinic
REVIEW RETURNED	04-Dec-2020

GENERAL COMMENTS	I applaud you on a substantial undertaking with this study. I agree with the strengths and limitations of this study, specifically that understanding ongoing treatment and management of AA may be challenging if most patients are referred and cared for my specialists. Regardless, these data will be important to continue clarifying the incidence of AA and associated comorbid conditions.

REVIEWER	Castelo-Soccio, Leslie National Institutes of Health, Dermatology
REVIEW RETURNED	18-Dec-2020

GENERAL COMMENTS	This is a excellent protocol with an important area of focus. The true incidence and prevalence is not really known. Studies vary widely and the ones you mention are 20 years old and likely biased. This is a well defined population with extensive coding through primary care. Focus on infections and mental health is compelling. Data for triggering AA flares by infections or AA making one more prone to infections is lacking. I have a few concerns about your approach to mental health and this is why a revision is requested. I have smaller concerns about how robust the data will be on self-describe race/ethnicity and whether this data would be generalizable outside of the UK. For mental health: You propose to look at 2 years after diagnosis which I think is a loaded time period especially with a new diagnosis. You will likely find changes and more referrals but are these relevant long term. I think it would be important to match control patients to other with a

	new diagnosis of a visible chronic disease since this alone may increase burden. Here I suspect you will get your statistical significance but is it more than someone else with a visible chronic disease rather than another autoimmune.The first year of AA as you know is a great period of adjustment and it might be relevant to look beyond the first 2 years. It would also be important to look for previous mental health disorders/familial mental health disorders. I appreciate that you adjust for socioeconomic status for mental health- there may be different levels of support with different economic backgrounds and more acceptance of mental health disorders among certain patient populations who might seek more care. Thank you for doing this important work. It appears that there are very specific codes for types of alopecia. It would be nice to see that as part of your protocol you pulled 100 cases and had one of the dermatology authors review the chart to see if you are including true cases of alopecia areata and that those excluded because they have a second hair loss condition really do not have alopecia areata. I often seen concomitant trichotillosis or in children kids who have aa but then develop later tinea capitis. Sensitivity analysis of algorithm is stated as such: "For sensitivity analyses we will also extract alopecia recorded where the type has not been specified (Supplementary Table S1.1, Additional file 2) and alopecia extent if recorded (Supplementary Table S1.2, Additional file 2). " but I am still not clear on this. .

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Katherine Agre, Mayo Clinic

>> We thank the reviewer for taking the time to review our protocol. We are glad you found our planned series of studies in AA to be of clinical importance, and that the strengths and limitations of the study have been appropriately highlighted.

Reviewer: 2
Dr. Leslie Castelo-Soccio, CHOP, University of Pennsylvania

Comments to the Author:

This is a excellent protocol with an important area of focus. The true incidence and prevalence is not really known. Studies vary widely and the ones you mention are 20 years old and likely biased. This is a well defined population with extensive coding through primary care. Focus on infections and mental health is compelling. Data for triggering AA flares by infections or AA making one more prone to infections is lacking.

I have a few concerns about your approach to mental health and this is why a revision is requested. I have smaller concerns about how robust the data will be on self-describe race/ethnicity and whether this data would be generalizable outside of the UK.

>> Thank you for reviewing our protocol. We are glad the reviewer found our planned study set to be of importance, and the topics of study to be compelling. We have endeavoured to respond in detail to the specific concerns raised below.

The point on race/ethnicity and generalisability is a very interesting one of particular relevance in AA. Ethnicity recording across the UK healthcare system has improved dramatically over the last decade – and is 78.3% complete for patients registered since 2006. Previous studies have shown the ethnic breakdown in primary care data is similar to the UK census, in which 86% of people are from white ethnic groups, supporting the use of this information for research. We will, where sample size allows, stratify key results by major UK census defined ethnic groups (White, Asian, Black, Mixed, Other). Whilst we hope this contrast will provide useful information for clinicians, we acknowledge the results will not necessarily be generalizable to other countries with a substantially different ethnic mix than the UK. We have added this point to the study limitations, as follows:

Discussion, page 24: "Whilst a previous study has shown the ethnic breakdown in primary care data is similar to the UK census and suitable for research,(70) 86% of people in the UK are from white ethnic groups, limiting power to evaluate people of non-white ethnicity despite the large sample size. Findings may not be generalisable to countries with a substantially different ethnicity mix to the UK. "

For mental health:

You propose to look at 2 years after diagnosis which I think is a loaded time period especially with a new diagnosis. You will likely find changes and more referrals but are these relevant long term. I think it would be important to match control patients to other with a new diagnosis of a visible chronic disease since this alone may increase burden. Here I suspect you will get your statistical significance but is it more than someone else with a visible chronic disease rather than another autoimmune.The first year of AA as you know is a great period of adjustment and it might be relevant to look beyond the first 2 years. It would also be important to look for previous mental health disorders/familial mental health disorders.

>> Thank you for raising this interesting point. Our approach is designed to both examine the prevalence of pre-existing mental health conditions at AA diagnosis, and the incidence of new onset mental health conditions after diagnosis. For the new onset analysis, we appreciate the point regarding time period however our specific aim is to evaluate mental health conditions developing just after the time of AA onset. Examining this co-occurrence will provide important real-world evidence on the possible bidirectional causal association between AA and common mental health disorders. In our view, extending the time period would decrease the likelihood that mental health conditions identified related to AA co-occurrence, and potentially limits the inferences we can draw. Whilst we appreciate the point about the comparator group, we are attempting to answer the question of whether people with AA have a higher incidence of mental health problems than people who are not affected by the conditions. We feel the most robust way to evaluate this is with the proposed propensity matching (controlling for age, sex, GP practice) with subsequent adjustment for major comorbidities in multivariable analysis. We believe that this approach should be sufficient to provide insight into the specificity of our findings; in partcular comparison of unadjusted and comorbidity adjusted estimates will demonstrate the extent to which other comorbidities underlie any differences in risk we observe.

I appreciate that you adjust for socioeconomic status for mental health- there may be different levels of support with different economic backgrounds and more acceptance of mental health disorders among certain patient populations who might seek more care.

>> Thank you - we agree this is a key consideration. We plan not only to adjust for SES when evaluating mental health outcomes but also to stratify key estimates (e.g. baseline prevalence of mental health disorders, and incidence of new onset mental health conditions) by quintile of index of multiple

deprivation, the UK official measure of SES. We hope this will provide important insight into any variation in mental health disorders by SES in this population. We will adopt a similar approach to evaluate other key outcomes (health care utilisation, infection risk, autoimmune disease) across the study series.

Thank you for doing this important work.

It appears that there are very specific codes for types of alopecia. It would be nice to see that as part of your protocol you pulled 100 cases and had one of the dermatology authors review the chart to see if you are including true cases of alopecia areata and that those excluded because they have a second hair loss condition really do not have alopecia areata. I often seen concomitant trichotillosis or in children kids who have aa but then develop later tinea capitis. Sensitivity analysis of algorithm is stated as such: "For sensitivity analyses we will also extract alopecia recorded where the type has not been specified (Supplementary Table S1.1, Additional file 2) and alopecia extent if recorded (Supplementary Table S1.2, Additional file 2).

" but I am still not clear on this. .

>> Validation of our diagnostic code list for AA would be ideal but unfortunately it is beyond the scope of this work. We have access only to anonymised healthcare record data for these studies and as such are unable to access detailed case records and clinical notes to validate the AA diagnoses for any of the patients in the dataset. However, as reported in the Discussion, “our ontological approach to detecting cases of AA and associated comorbidities will improve accuracy compared to the use of diagnostic codes alone. This is a 3-step approach that involves first defining the relevant concepts (aetiology, diagnosis, clinical features of a condition), then creating a code list from the ontology, and then developing a logical data extraction model based on when is well-captured in the primary care record. Further details of the approach are provided in: *de Lusignan S. In this issue: Ontologies a key concept in informatics and key for open definition of cases, exposures and outcome measures. BMJ Health & Care Informatics. 2015;22(2):*i-*v,* which we have now referenced in the manuscript. In this study, a key element of the AA ontological approach is the exclusion of individuals with potentially confounding conditions (i.e. other causes of hair loss) which is likely to improve the accuracy of our estimates. We have added to the study limitations to highlight the lack of a validated case definition, as well as our aforementioned strategy to mitigate this:

Discussion, page 23: “A limitation of the study is the lack of a validated AA case definition using primary care data. We are unable to develop one as we have access only to coded anonymised healthcare record data for this study.”

We appreciate the point around appropriate clarifying the sensitivity analysis – these are reported in detail in the Supplementary statistical analysis plan. In particular we will 1) ascertain the clinical characteristics of those with non-specified alopecia and compare these with our AA cohort; 2) where appropriate, repeat the primary analysis for each study in the patients with non-specific alopecia codes only (to ascertain specificity of reported associations). We agree that such careful sensitivity analysis will be paramount given the potential for misclassification as highlighted by the reviewer. We have moved the AA case detection section (previously P.14) to the sensitivity analysis section to clarify in the main article the reason for defining the non-specific AA cohort and running the sensitivity analysis:

Sensitivity analysis, P.20: “To evaluate the specificity of any identified associations to our AA case definition, in sensitivity analysis we will extract alopecia recorded where the type has not been specified (Supplementary Table S1.1, Additional file 2). We will then assess the characteristics of people with non-specific alopecia codes only (i.e. no prior or subsequent codes specifying alopecia type) compared to the primary AA cohort. If the characteristics are not markedly different, which would indicate the groups are clinically different and not comparable, we will evaluate major study outcomes in this non-specific AA cohort and compare results to those obtained for the primary AA cohort. We will also evaluate whether stratifying analyses by alopecia extent is possible, dependent on how well this is recorded in primary care data (Supplementary Table S1.2, Additional file 2).

Reviewer: 1

Competing interests of Reviewer: None declared

Reviewer: 2

Competing interests of Reviewer: I am currently studying epidemiology of AA in children in the USA but not at mental health or infections.

VERSION 2 – REVIEW

REVIEWER	Castelo-Soccio, Leslie National Institutes of Health, Dermatology
REVIEW RETURNED	13-Aug-2021

GENERAL COMMENTS	Thank you for clarifying your work and addressing previous concern about methods in each of the 4 sections of your study.