Alcohol abuse associated with poor response to systemic therapies for psoriasis: findings from a prospective multicentre cohort study

ISKANDAR, Ireny YK, LUNT, Mark, THORNELOE, Rachael, CORDINGLEY, Lis, GRIFFITHS, Christopher EM and ASHCROFT, Darren M

Published version

ISKANDAR, Ireny YK, LUNT, Mark, THORNELOE, Rachael, CORDINGLEY, Lis, GRIFFITHS, Christopher EM and ASHCROFT, Darren M (2021). Alcohol abuse associated with poor response to systemic therapies for psoriasis: findings from a prospective multicentre cohort study. British Journal of Dermatology.

DR IRENY YOUSSRY KOSTANTIN ISKANDAR (Orcid ID : 0000-0002-8030-1908)
DR RACHAEL JANE THORNELOE (Orcid ID : 0000-0002-7522-221X)
DR CHRISTOPHER ERNEST, MAITLAND GRIFFITHS (Orcid ID : 0000-0001-5371-4427)

Article type : Original Article

Alcohol abuse associated with poor response to systemic therapies for psoriasis: findings from a prospective multicentre cohort study

Ireny Y. K. Iskandar,[1,6] Mark Lunt,[2] Rachael J. Thorneloe,[3] Lis Cordingley,[4] Christopher E. M. Griffiths,[5,6] and Darren M. Ashcroft[1,6,7], on behalf of the British Association of Dermatologists Biologics and Immunomodulators Register and Psoriasis Stratification to Optimise Relevant Therapy Study Groups.

[1]Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester, Manchester, UK.

[2]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK.

[3]Centre for Behavioural Science & Applied Psychology, Department of Psychology, Sociology & Politics, Sheffield Hallam University, Sheffield, UK.

[4]Division of Musculoskeletal and Dermatological Sciences, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK.

[5]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK.

[6]NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK.

[7]NIHR Greater Manchester Patient Safety Translational Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK.

Article type: Original article

Running heading

Alcohol abuse associated with poor response to systemic therapies for psoriasis.

Corresponding author:

Dr Ireny Y.K. Iskandar, PhD

Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, Manchester Academic Health Science Centre, University of Manchester, Oxford Road, Stopford Building, Manchester, M13 9PT, United Kingdom.

Telephone: +447438076738

Email: ireny.iskandar@manchester.ac.uk

Twitter handle: @IrenyIskandar

Author contributions:

Dr Iskandar had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Iskandar, Lunt, Thorneloe, Cordingley, Ashcroft.

Acquisition, analysis, or interpretation of data: Iskandar, Lunt, Thorneloe, Cordingley, Ashcroft.

Drafting of the manuscript: Iskandar.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Iskandar, Lunt.

Obtaining funding: Cordingley, Griffiths, and Ashcroft.

Administrative, technical, or material support: Iskandar.

Study supervision: Ashcroft.

Funding sources:

The Investigating Medication Adherence in Psoriasis (iMAP) study was initially funded by a Medical Research Council (MRC) doctoral fellowship and studentship award by the Psoriasis Association of Great Britain and Ireland awarded to Rachael Thorneloe. Subsequent funding came

from a MRC (MR/1011808/1) award to the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium.

The BADBIR is coordinated by the University of Manchester. The BADBIR is funded by the British Association of Dermatologists. The British Association of Dermatologists has received income from AbbVie, Eli Lilly, Janssen Cilag, Novartis, Pfizer, and Samsung Bioepis for providing pharmacovigilance services. This income finances a separate contract between the British Association of Dermatologists and the University of Manchester, which coordinates the BADBIR. Profs Griffiths and Ashcroft are funded in part by the MRC (MR/L011808/1) and the NIHR Manchester Biomedical Research Centre.

Role of Funders:

The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of Interest Disclosures:

Prof Griffiths has received honoraria and/or research grants from AbbVie, BMS, Almirall, Amgen, Celgene, Eli Lilly Galderma, LEO Pharma, Stiefel GSK, Janssen, MSD, Novartis, Pfizer, Sandoz, Sun Pharmaceuticals, and UCB Pharma. Prof Ashcroft has received grant funding from Abbvie, Almirall, Celgene, Eli Lilly, Novartis, UCB and the Leo Foundation. Dr Cordingley has received honoraria from Janssen, AbbVie, Novatis and Sanofi for educational events and an unrestricted research award as a co-applicant from Pfizer. Dr Thorneloe has received an honorarium from Novartis. None of these awards are associated with the submitted manuscript. The remaining authors state no conflict of interest.

Acknowledgements:

The authors acknowledge the contribution of the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) partners, and the PSORT Executive Committee (in alphabetical order): Jonathan Barker, Michael Barnes, David Burden, Paola DiMeglio, Richard Emsley, Christopher

Griffiths (Chair), Katherine Payne, Nick Reynolds, Catherine Smith, Deborah Stocken, and Richard Warren.

The British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) acknowledges the support of the National Institute for Health Research (NIHR) through the clinical research networks and its contribution in facilitating recruitment into the registry. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the BADBIR, NIHR, the National Health Service or the Department of Health.

The authors are also grateful to the members of the Data Monitoring Committee: Robert Chalmers, Carsten Flohr (Chair), Richard Weller, and David Prieto-Merino and the BADBIR Steering Committee (in alphabetical order): Jonathan Barker, Marilyn Benham (CEO of BAD), David Burden (Chair), Ian Evans, Christopher Griffiths, Sagair Hussain, Brian Kirby, Linda Lawson, Kayleigh Mason, Kathleen McElhone, Ruth Murphy, Anthony Ormerod, Caroline Owen, Nick Reynolds, Catherine Smith, and Richard Warren.

Christopher Griffiths is an NIHR Emeritus Senior Investigator. We acknowledge the enthusiastic collaboration of all of the dermatologists and specialist nurses in the United Kingdom and the Republic of Ireland who provided the data. The principal investigators at the BADBIR participating sites are listed on the following website: http://www.badbir.org.

Finally, we are very grateful to all individuals with psoriasis who took part in this study.

Manuscript word count: 2867 words

Abstract word count: 250 words

Bulleted statements word count: 70 words

References: 40

Figures: 1

Supplementary figures: 1

Tables: 2

Supplementary tables: 2

Attachments: STROBE checklist.

Keywords: psoriasis; conventional systemic therapies; biologic therapies; drug response; alcohol abuse; CAGE.

Abbreviations:

BADBIR, the British Association of Dermatologists Biologics and Immunomodulators Register; CAGE, Cut down, Annoyed, Guilty, Eye opener; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; iMAP, Investigating Medication Adherence in Psoriasis; MARS, Medication Adherence Report Scale; PASI, Psoriasis Area and Severity Index;

What is already known about this topic?

- Factors that might influence response to systemic treatment for moderate-to-severe psoriasis are generally poorly understood, aside from high body weight, suggesting that other unidentified factors may be relevant in determining response to treatment.
- The potential influence of alcohol abuse on response to treatment for psoriasis has not been previously investigated.

What does this study add?

- After adjusting for important factors that could influence response to treatment such as psychological distress and medication non-adherence, alcohol abuse was found to be significantly associated with poor response to treatment.
- Identification of potentially modifiable factors associated with poor treatment response emphasises the need for lifestyle behaviour change support as part of routine clinical care.
- Effective interventions to detect and address high alcohol consumption should form part of routine care for people with psoriasis.

Abstract

Background: Factors that might influence response to systemic treatment for moderate-to-severe psoriasis are varied, and generally, are poorly understood, aside from high body weight, suggesting that other unidentified factors may be relevant in determining response to treatment. The impact of alcohol abuse on treatment response has not been previously investigated.

Objective: To investigate whether alcohol abuse is associated with poor response to treatment for psoriasis.

Methods: Prospective cohort study in which response to systemic therapies was assessed using the Psoriasis Area and Severity Index (PASI). The CAGE questionnaire was used to screen for alcohol abuse. A multivariable factional polynomial linear regression model was used to examine factors associated with change in PASI between baseline and follow-up.

Results: The cohort comprised of 266 patients (biologic cohort, n=134; conventional systemic cohort, n=132). For the entire cohort, the median (interquartile range) PASI improved from 13[10-18.3] at baseline to 3[1-7.5] during follow-up. A higher CAGE score (regression co-efficient: 1.40; 95% CIs: 0.04-2.77); obesity (1.84; 0.48-3.20); and receiving a conventional systemic rather than a biologic therapy (4.39; 2.84-5.95) were significantly associated with poor response to treatment; whereas a higher baseline PASI (-0.83; -0.92,-0.74) was associated with better response to treatment.

Conclusion: The poor response to therapy associated with alcohol abuse and obesity found in people with psoriasis calls for lifestyle behaviour change interventions and support as part of routine clinical care. Targeting interventions to prevent, detect and manage alcohol abuse among people with psoriasis is needed to minimise adverse health consequences and improve treatment response.

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin condition; recognised by the World Health Organization as a serious non-communicable disease that requires effective management.[1] The psychological and social difficulties in combination with the physical discomfort associated with psoriasis may contribute to psychological distress (anxiety and depression) and alcohol abuse.[2-4]

Treatment effectiveness of conventional systemic and biologic therapies used in the management of moderate-to-severe psoriasis is much lower in real-world clinical practice than in clinical trials.[5,6] Factors that might influence response to treatment are varied, and generally, are poorly understood, aside from high body weight, which has consistently been associated with worse outcomes for most therapies.[7-12] This suggests that other unidentified factors may be relevant in

determining response.[13] To date, previous research has focused on demographic, and clinical factors as predictors of response to treatment in psoriasis.[12] However, there are no studies examining the role of alcohol abuse in predicting response to treatment, taking into account other important factors that could also influence treatment response such as psychological distress and medication non-adherence.

The iMAP (Investigating Medication Adherence in Psoriasis) is a multi-centre study collecting biomedical and psychological data from patients with psoriasis prescribed biologic or conventional systemic therapies.[14] All patients in iMAP are also enrolled in the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), a longitudinal pharmacovigilance register representing a "real-world" cohort of patients with psoriasis receiving biologic or conventional systemic therapies.[15,16] This presents an ideal resource to assess the impact of alcohol abuse, alongside patient behavioural and psychological factors on response to conventional systemic and biologic therapies in routine clinical practice. The objectives of this study were to: (i) assess real-world levels of alcohol abuse, psychological distress and medication non-adherence among patients with moderate-to-severe psoriasis and; (ii) investigate whether alcohol abuse is associated with poor response to systemic therapies after controlling for other factors.

Methods

Data source

Patients attending 35 dermatology centers across England were recruited into iMAP between March 2013 and September 2016. Patients aged ≥18 years with a diagnosis of psoriasis under the care of a dermatologist, prescribed a conventional systemic and/or a biologic treatment and enrolled in BADBIR were eligible for inclusion into iMAP.[14]

Data collection

The CAGE (Cut down, Annoyed, Guilty, Eye opener) questionnaire assessed self-perception of alcohol abuse. It consists of 4 questions beginning with the stem "Have you ever": felt the need to *cut* down drinking; felt *annoyed* by criticism of drinking; had *guilty* feeling about drinking; and taken a morning *eye* opener. The items are rated on a scale of 0-1, with a total score ranging from 0 to 4, with a score of ≥2 indicating alcohol abuse.[17,18]

The Medication Adherence Report Scale (MARS) assessed the frequency of non-adherent behaviours on a 5-point Likert scale ranging from very often (1-point) to never (5-points), with scores ranging from 8 to 40, with higher scores indicating higher levels of adherent behaviour.[19] Patients were classified into overall non-adherent category if they scored ≤38/40.[14]

The Hospital Anxiety and Depression Scale (HADS) is a 14-items scale which provided an assessment of symptoms of anxiety (7-items) and depression (7-items). Items are rated on a scale of 0-3, indicating the strength of agreement with that item and are summed to create a HADS anxiety and depression score, both ranging from 0 to 21, with a score of ≥8 indicating a possible caseness of anxiety or depression.[20,21] A score ranging between 8-10, 11-14 and 15-21 indicate mild, moderate and severe symptoms, respectively.[22]

Patients were instructed to independently and anonymously complete an iMAP questionnaire that contained the MARS and the HADS at baseline (upon recruitment) and every 6 months thereafter for up to 18 months. Patients' demographic characteristics (age, sex, height and weight); lifestyle information (smoking status and alcohol abuse [CAGE]); details of type and severity of psoriasis (Psoriasis Area and Severity Index [PASI]) and year of onset; standardised measures of health status using self-reported outcome measures (Dermatology Life Quality Index [DLQI]); detailed information about the patients' current and previous treatments for psoriasis (any change in therapy, concomitant use of systemic therapies, gaps in treatment, start and stop dates, and reasons for discontinuation); and the patients' comorbidities were extracted from BADBIR (with written informed patient consent) at times corresponding to the dates when the patients completed the iMAP questionnaires. Data were extracted from the October 2018 database build.

Study population

Patients were eligible for inclusion in this analysis if they had at least one PASI measurement recorded before and after completing at least one iMAP questionnaire. The PASI recorded closest to the date of completing the iMAP questionnaire were identified and referred to as either “baseline” (recorded prior to completing the questionnaire) or “follow-up” PASI (recorded after completing the questionnaire). Majority of the patients had only one iMAP questionnaire, while few had multiple questionnaires completed between the time the baseline and follow-up PASIs were recorded (Figure S1). Patients were excluded from the analysis if the baseline PASI was measured >12 months prior to or >1 month after the start of therapy; and/or if their follow-up PASI was measured >24 months after the start of their treatment (Figure S1). Patients were

assigned to either the biologic or conventional systemic cohort based on the therapy they were receiving at the time of completing their first iMAP questionnaire, and recorded as either biologic naïve or non-naïve.

Statistical analysis

Multivariable linear regression model, where fractional polynomials were used to model non-linear relationships between the covariates and the outcome, was conducted to investigate factors associated with the change in PASI between baseline and follow-up. An a priori list of covariates was determined to address potential predictors of response. Alcohol abuse (CAGE), medication non-adherence and psychological distress recorded at times corresponding to the dates when the patients completed the iMAP questionnaires were included in the model. In the few patients with more than one valid measurements of the CAGE (19 patients [7%]), patients' medication non-adherence status (28 patients [11%]) and psychological distress (28 patients [11%]) during the study period, an average was taken. An interaction between overall medication non-adherence status and the cohort the patients was assigned to was also included in the model.

Other potential confounders included in the model was body mass index (dated around the start date of the therapy) which was categorised into a binary obese/non-obese variable. The patients' age and disease duration were calculated from the patients' date of birth and year of disease onset recorded at the time of registration into BADBIR and the start date of their therapy, respectively. Baseline DLQI were identified if they were dated within 12 months prior to and 1 month after the start of treatment to be consistent with how baseline PASI were identified (the median [interquartile range] time period between the baseline DLQI measurement and start of therapy was -4 days [-37 days – 0 days]). Comorbidities with inflammatory arthritis and other comorbidities as well as the patients' smoking status were collected at the time of registration into BADBIR. Concomitant use of methotrexate, ciclosporin and/or other conventional systemic therapies was analysed as a binary variable (ever exposed/never exposed) throughout the study. A sensitivity analysis was conducted in which an interaction between alcohol abuse and obesity was also included in the model.

To account for missing data (Table S1), we generated 50 imputed datasets. In each dataset, missing values were replaced by values randomly selected from the expected distribution of that variable conditional on the measured or imputed values of all other variables for that individual. This approach enables all subjects to be used in the analysis, avoiding the selection bias that would

be likely if only subjects with complete data were analyzed.[23] The multivariable linear regression assumptions were assessed by scatterplots and statistical testing. Analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX).

Ethical approval

Ethical approvals for BADBIR and iMAP were obtained from the NHS research Ethics Committee North West England (references 07/MRE08/9 and 12/NW/0619, respectively) in March 2007 and December 2012, respectively, and from research ethics committees local to each recruiting site. All subjects gave written informed patient consent for their participation in the registry prior to data collection.

Results

In total, 266 patients with psoriasis (biologic cohort, n=134; conventional systemic cohort, n=132) followed-up for a median (interquartile range) of 7[6-10] months were included in our analyses (Figure 1). The mean ± standard deviation age of patients and disease duration were 48.2±13.1 and 22.1±14.5 years, respectively, with 45.1% female. At baseline, the median (interquartile range) PASI was 13[10-18.3] and the mean DLQI was 16.2±8.5. Overall, 19.6% reported having inflammatory arthritis, and 67.3% reported having ≥1 comorbidities other than inflammatory arthritis. Patients' demographic and disease characteristics are summarised in Table 1.

The mean CAGE score was 0.3±0.8, with 5.8% of patients scoring ≥2 indicating alcohol abuse (Table 1). The mean HADS anxiety and depression scores were 6.9±4.5 and 5.3±4.1, with 40.5% and 27.6% of patients scoring ≥8 indicating a possible caseness of anxiety and depression, respectively (Table 1). A notable proportion of the study cohort were classified as non-adherent (16.6%; Table 1), with a significantly higher proportion of patients using conventional systemic therapies classified as non-adherent (27.6%) compared to those using biologic therapies (5.9%).

Table 2 presents results from the multivariable linear regression analysis examining factors that affect the change in PASI between baseline and follow-up. Having a higher CAGE score was significantly associated with poor response to treatment as measured by change in PASI (for every 1 point increase in the CAGE score; regression coefficient 1.40; 95% CIs: 0.04, 2.77. Thus a maximum change in CAGE score from 0 to 4 would be associated with a change in PASI of 5.60; 0.16, 11.08). Of the demographic factors, with each 10-year increase in a patient's age there was significantly better response to treatment (-0.63; -1.22, -0.05). Having a higher baseline PASI (for

every 1 point increase in the baseline PASI; -0.83; -0.92, -0.74) was also significantly associated with a better response to treatment, whereas being obese (1.84; 0.48, 3.20); receiving a conventional systemic therapy rather than a biologic therapy (4.39; 2.84, 5.95), and stopping the therapy during the follow-up (4.18; 2.38, 5.97) were significantly associated with poor response to treatment. No significant interaction was found between medication non-adherence and treatment cohort (P=0.336, Table 2) and also between alcohol abuse (CAGE) and obesity (P=0.930, Table S2).

Discussion

Main findings

In this real-world cohort of patients with psoriasis, alcohol abuse, obesity, and receiving a conventional systemic therapy were significantly associated with poor response to treatment as measured by change in PASI between baseline and follow-up. To our knowledge this is the first study to investigate alcohol abuse in a real-world cohort of patients with psoriasis, and explore how it affects response to treatment.

Comparison to other studies

Consistent with other studies, we found that obesity was also associated with poor response to systemic therapies.[7-9] Obesity has also been found to be associated with poor response to therapies in rheumatoid arthritis[24,25] and ankylosing spondylitis.[26] Our findings are also in-line with those reported by Gelfand *et al*.[5], who found biologic therapies to be more effective than conventional systemic therapies. However, by comparison, our study has an important strength: we accounted for important clinical and social factors including smoking status, alcohol abuse, the presence of comorbidities, and medication non-adherence. Although overall non-adherence did not significantly predict response to therapy (P=0.522), the results suggest that it was associated with poor response for those exposed to conventional systemic therapies (2.65; -5.49, 10.79). Clinicians should therefore explore patients' adherence, especially in those who are poor responders to therapy, and provide additional support to improve adherence to treatment regimens.[27] Future studies investigating predictors of response to therapy should ideally include a measure of adherence to reduce potential confounding.

To our knowledge, no previous study has assessed the association of alcohol abuse with poor response to therapies.[7] Our results demonstrate that alcohol abuse is associated with poor response

to treatment. We would be interested to see whether our findings can be replicated independently. The implications of our findings are important. The economic, social and health consequences of alcohol abuse are considerable. Excessive alcohol may worsen the disease, has implications for treatment, and increases the risk of dying in people with psoriasis, on average 3 years younger, compared with peers of the same age and sex in the general population.[28,29]

Strengths and limitations

One of the key strengths of this study is the real-world prospective cohort study design thus ensuring that patients are representative of those receiving treatment in routine clinical practice. Furthermore, the participation of multiple dermatology centers (n=35) across England ensures the external validity of the results. We also performed multiple imputation to account for missing data thus minimising the bias that could have been introduced by only considering a complete case analysis. Self-reported tools of alcohol abuse, medication non-adherence and psychological distress can be criticised for being influenced by poor patient recall or reporting bias and so can underestimate alcohol abuse or overestimate adherence and psychological distress. The CAGE questionnaire can also be criticised for identifying mostly the severe forms of harmful alcohol abuse and dependence, and so can fail to adequately identify those with hazardous use of alcohol. Nevertheless, it is reported that the CAGE has a sensitivity of 93% and a specificity of 76% for the identification of excessive drinking and the use of appropriate theoretical frameworks and validated data collection tools are major strengths.[30,31] An inherent limitation in any observational study is lack of randomisation, which may introduce confounding bias, and although this is partially negated by adjustment for clinically relevant covariates, the presence of other unmeasured confounders, such as the intention behind concomitant medication, cannot be determined. One particular challenge we faced is that some of the patients' demographic characteristics were recorded only at the time of registration with BADBIR. This included data on smoking status and comorbidities. It is possible that some patients may have developed new comorbidities or changed smoking status during the study period. Furthermore, the influence of treatment dose escalation on the PASI response was not assessed. However, we have shown previously that patients in BADBIR routinely receive the recommended dosing regimen but that concomitant treatment with other systemic therapies occurs commonly.[32]

Implications for clinicians

Clinicians should be aware of the considerable psychological distress and psychosocial challenges that are faced by patients with psoriasis which can lead to chronic alcohol abuse and dependence as coping mechanisms.[29] Our findings highlight that at least 40% of our study cohort reported having psychological distress and that alcohol abuse has a negative effect on response to treatment. Psychological and educational interventions for newly diagnosed patients with psoriasis have been developed to minimise distress and to alert patients to the negative impact of alcohol on psoriasis outcomes [e.g. Chisholm *et al.*[33] and Nelson *et al.*[34]]. For those with established disease, the recognition by clinicians of the risks associated with the dual stigma of psoriasis and alcohol abuse on response to treatment is important. Discussions about alcohol use, especially high use, are challenging for both clinicians and patients through fear of stigmatisation, and as a result, are frequently avoided in consultations.[35] Patients may also be unaware of the extent to which they are using alcohol as a coping mechanism. Nevertheless, provision of skilled screening and brief interventions by healthcare teams can enable patients to achieve reduction or abstinence, reduce health harms and improve prognosis without increasing stigma.[36-38]

Our findings also indicate that clinicians need to be aware of, and address, the possibility of medication non-adherence. More than 15% of patients in this study were classified as non-adherent. Patients' beliefs about their medication, including concerns about the potential for adverse events, are key drivers of non-adherence. Concerns about unwanted treatment effects are common in patients with psoriasis, including those who adhere to treatments,[39] and so provision of accessible patient-centred materials (using traditional written or e-health delivery formats) which address these issues may allay some worry in a time efficient way. This can be further supported by all those involved in provision of treatment, medical, nursing and pharmacy staff, all of whom have a role in shaping patients' treatment beliefs. People are more likely to forget to use their medication if they have weak medication-taking habits or routines.[14] Again, very brief messages either delivered directly from relevant clinical staff, or via traditional or electronic media, may enable patients to recognise that habit formation requires an initial period of active engagement in change and could optimise treatment outcomes.[27]

Conclusions

This study provides evidence that alcohol abuse and obesity are associated with poor response to treatment in patients receiving systemic therapies. These are modifiable factors and confirm the important role that clinical teams can play in supporting lifestyle behaviour change in people with

psoriasis. Interventions to prevent or address alcohol abuse and weight gain are important parts of psoriasis health management. Patients may need additional support to recognise the relevance of these lifestyle factors to their skin health;[34,40] and this study highlights how these factors detrimentally affect psoriasis treatment effectiveness. Routine screening, and identification, using simple screening tools, can be used to detect early signs of hazardous, harmful and dependent alcohol consumption which could be implemented in healthcare settings to detect alcohol abuse among people with psoriasis.[38]

References

1 World Health Organisation. Global report on psoriasis. In: World Health Organisation. 2016.

2 Kimball AB, Jacobson C, Weiss S *et al.* The psychosocial burden of psoriasis. *Am J Clin Dermatol.* 2005; **6**: 383-92.

3 Krueger G, Koo J, Lebwohl M *et al.* The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol.* 2001; **137**: 280-4.

4 Hayes J, Koo J. Psoriasis: depression, anxiety, smoking, and drinking habits. *Dermatol Ther.* 2010; **23**: 174-80.

5 Gelfand JM, Wan J, Callis Duffin K *et al.* Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. *Arch Dermatol.* 2012; **148**: 487-94.

6 Iskandar IYK, Ashcroft DM, Warren RB *et al.* Comparative effectiveness of biological therapies on improvements in quality of life in patients with psoriasis. *Br J Dermatol.* 2017; **177**: 1410-21.

7 Edson-Heredia E, Sterling KL, Alatorre CI *et al.* Heterogeneity of response to biologic treatment: perspective for psoriasis. *J Invest Dermatol.* 2014; **134**: 18-23.

8 Di Lernia V, Ricci C, Lallas A *et al.* Clinical predictors of non-response to any tumor necrosis factor (TNF) blockers: a retrospective study. *J Dermatolog Treat* 2014; **25**: 73-4.

9 García-Doval I, Pérez-Zafrilla B, Ferrandiz C *et al.* Development of clinical prediction models for good or bad response to classic systemic drugs, anti-TNFs, and ustekinumab in psoriasis, based on the BIOBADADERM cohort. *J Dermatolog Treat.* 2016; **27**: 203-9.

10 Umezawa Y, Saeki H, Nakagawa H. Some clinical factors affecting quality of the response to ustekinumab for psoriasis. *J Dermatol.* 2014; **41**: 690-6.

11 Zweegers J, Roosenboom B, van de Kerkhof PC *et al.* Frequency and predictors of a high clinical response in patients with psoriasis on biological therapy in daily practice: results from the prospective, multicenter BioCAPTURE cohort. *Br J Dermatol.* 2017; **176**: 786-93.

12 Warren RB, Marsden A, Tomenson B *et al.* Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multicentre longitudinal cohort study. *Br J Dermatol.* 2019; **180**: 1069-76.

13 Foulkes AC, Watson DS, Carr DF *et al.* A framework for multi-omic prediction of treatment response to biologic therapy for psoriasis. *J Invest Dermatol* 2019; **139**: 100-7.

14 Thorneloe RJ, Griffiths CEM, Emsley R *et al.* Intentional and unintentional medication mon-adherence in psoriasis: the role of patients' medication beliefs and habit strength. *J Invest Dermatol.* 2018; **138**: 785-94.

15 Burden AD, Warren RB, Kleyn CE *et al.* The British Association of Dermatologists' Biologic Interventions Register (BADBIR): design, methodology and objectives. *Br J Dermatol.* 2012; **166**: 545-54.

16 Iskandar IYK, Ashcroft DM, Warren RB *et al.* Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. *Br J Dermatol.* 2015; **173**: 510-8.

17 Ewing JA. Detecting alcoholism. The CAGE questionnaire. *Jama* 1984; **252**: 1905-7.

18 Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry.* 1974; **131**: 1121-3.

19 Horne R, Weinman J. Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychology & Health* 2002; **17**: 17-32.

20 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361-70.

21 Bjelland I, Dahl AA, Haug TT *et al.* The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**: 69-77.

22 Stern AF. The Hospital Anxiety and Depression Scale. *Occupational Medicine* 2014; **64**: 393-4.

23 Bodner TE. What improves with increased missing data imputations? *Structural Equation Modeling: A Multidisciplinary Journal* 2008; **15**: 651-75.

24 McWilliams DF, Walsh DA. Factors predicting pain and early discontinuation of tumour necrosis factor-α-inhibitors in people with rheumatoid arthritis: results from the British society for rheumatology biologics register. *BMC Musculoskelet Disord.* 2016; **17**: 337

25 Kleinert S, Tony HP, Krause A *et al.* Impact of patient and disease characteristics on therapeutic success during adalimumab treatment of patients with rheumatoid arthritis: data from a German noninterventional observational study. *Rheumatol Int.* 2012; **32**: 2759-67.

26 Ottaviani S, Allanore Y, Tubach F *et al.* Body mass index influences the response to infliximab in ankylosing spondylitis. *Arthritis Res Ther* 2012; **14**: R115.

27 National Institute for Health and Care Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence 2009. Available at: https://www.nice.org.uk/Guidance/CG76 (last accessed: 03 July 2019)

28 McAleer MA, Mason DL, Cunningham S *et al.* Alcohol misuse in patients with psoriasis: identification and relationship to disease severity and psychological distress. *Br J Dermatol.* 2011; **164**: 1256-61.

29 Parisi R, Webb RT, Carr MJ *et al.* Alcohol-related mortality in patients with psoriasis: a population-based cohort study. *JAMA Dermatol* 2017; **153**: 1256-62.

30 Bernadt MW, Mumford J, Taylor C *et al.* Comparison of questionnaire and laboratory tests in the detection of excessive drinking and alcoholism. *Lancet* 1982; **1**: 325-8.

31 Williams N. The CAGE questionnaire. *Occupational Medicine* 2014; **64**: 473-4.

32 Iskandar IYK, Ashcroft DM, Warren RB *et al.* Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Br J Dermatol.* 2017 **176**: 1297-307.

33 Chisholm A, Nelson PA, Pearce CJ *et al.* Motivational interviewing-based training enhances clinicians' skills and knowledge in psoriasis: findings from the Pso Well® study. *Br J Dermatol.* 2017; **176**: 677-86.

34 Nelson PA, Kane K, Pearce CJ *et al.* 'New to me': changing patient understanding of psoriasis and identifying mechanisms of change. The Pso Well® patient materials mixed-methods feasibility study. *Br J Dermatol.* 2017; **177**: 758-70.

35 Kirby B, Richards HL, Mason DL *et al.* Alcohol consumption and psychological distress in patients with psoriasis. *Br J Dermatol.* 2008; **158**: 138-40.

36 The British Society of Gastroenterology and Bolton NHS Foundation Trust. Alcohol care teams: reducing acute hospital admissions and improving quality of care 2016. Available at: https://www.nice.org.uk/localPractice/collection (last accessed: 03 July 2019)

37 Moriarty KJ, Cassidy P, Dalton D *et al.* Alcohol-Related Disease. Meeting the challenge of improved quality of care and better use of resources 2018. Available at: https://www.bsg.org.uk/resource/alcohol-related-disease-meeting-the-challenge-of-improved-quality-of-care-and-better-use-of-resources.html (last accessed: 03 July 2019)

38 Carvalho AF, Heilig M, Perez A *et al.* Alcohol use disorders. *The Lancet* 2019; **394**: 781-92.

39 Thorneloe RJ, Bundy C, Griffiths CE *et al.* Nonadherence to psoriasis medication as an outcome of limited coping resources and conflicting goals: findings from a qualitative interview study with people with psoriasis. *Br J Dermatol.* 2017; **176**: 667-76.

40 Nelson PA, Kane K, Chisholm A *et al.* 'I should have taken that further' - missed opportunities during cardiovascular risk assessment in patients with psoriasis in UK primary care settings: a mixed-methods study. *Health Expect* 2016; **19**: 1121-37.

Figures

Figure 1: Flow chart showing selection of study participants.

Tables

Table 1: Patients' demographic and disease characteristics.

Table 2: Multivariable linear regression of potential factors associated with changes in PASI between baseline and follow-up.

Table 1: Patient demographic and disease characteristics			
	All patients (n = 266)	Biologic cohort[1] (50.4%, n = 134)	Conventional cohort[2] (49.6%, n = 132)
Age (years), mean ± SD	48.2 ± 13.1	48.1 ± 13.5	48.4 ± 12.8
Female	120 (45.1%)	52 (38.8%)	68 (51.5%)
BMI category, Kg/m^2			
Non-obese (BMI < 30)	145 (54.4%)	63 (46.9%)	82 (62.1%)
Obese (BMI ≥ 30)	121 (45.7%)	71 (53.1%)	50 (38.1%)
Smoking status			
Never smoked	86 (32.5%)	47 (35.0%)	40 (30.0%)
Ex-smoker	98 (36.9%)	52 (39.1%)	46 (34.6%)
Current smoker	82 (30.6%)	35 (25.9%)	47 (35.4%)
Alcohol Use			
CAGE[3], mean ± SD	0.3 ± 0.8	0.3 ± 0.7	0.3 ± 0.8

Alcohol abuse	15 (5.8%)	7 (5.6%)	8 (6.1%)
Inflammatory arthritis/ Other comorbidities			
Inflammatory arthritis	52 (19.6%)	30 (22.4%)	22 (16.7%)
No comorbidities[4]	87 (32.7%)	39 (29.1%)	48 (36.4%)
1-2 comorbidities[4]	122 (45.9%)	63 (47.0%)	59 (44.7%)
3-4 comorbidities[4]	50 (18.8%)	28 (20.9%)	22 (16.7%)
≥ 5 comorbidities[4]	7 (2.6%)	4 (3.0%)	3 (2.3%)
Disease			
Disease duration (years), mean ± SD	22.1 ± 14.5	23.6 ± 14.0	20.5 ± 14.9
Age of onset (years), mean ± SD	26.2 ± 15.9	24.4 ± 15.2	27.9 ± 16.5
PASI at baseline, median[IQR]	13.1 [10 - 18.3]	13.4 [9.2 - 19.4]	12.8 [10.2 - 17.1]
DLQI at baseline, mean ± SD	16.2 ± 8.5	15.8 ± 9.4	16.5 ± 7.6
Unstable psoriasis	37 (13.9%)	17 (12.7%)	20 (15.2%)
Psychological distress (HADS)			
Anxiety score[5], mean ± SD	6.9 ± 4.5	6.7 ± 4.3	7.0 ± 4.6
Anxiety severity[6]			
No anxiety	158 (59.5%)	80 (59.7%)	78 (59.3%)
Mild anxiety	53 (19.9%)	29 (21.3%)	24 (18.5%)
Moderate anxiety	39 (14.5%)	19 (14.3%)	20 (14.6%)
Severe anxiety	16 (6.1%)	6 (4.7%)	10 (7.6%)
Depression Score[5], mean ± SD	5.3 ± 4.1	5.3 ± 4.1	5.3 ± 4.2
Depression severity[6]			
No depression	193 (72.4%)	99 (73.9%)	94 (70.9%)
Mild depression	41 (15.3%)	20 (14.6%)	21 (16.1%)
Moderate depression	27 (10.4%)	13 (10.0%)	14 (10.7%)
Severe depression	5 (1.9%)	2 (1.5%)	3 (2.3%)
Medication non-adherence			
Overall non-adherent, n (%)	44 (16.6%)	8 (5.9 %)	36 (27.6%)
Medication history			
Biologic naïve	238 (89.5%)	106 (79.1%)	132 (100.0%)
Concomitant systemic therapy[7]	28 (10.5%)	17 (12.7%)	11 (8.3%)
Stopped Therapy[8]	42 (15.8%)	16 (11.9%)	26 (19.7%)

Abbreviations: CAGE, Cut down, Annoyed, Guilty and Eye Opener; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile range; PASI, Psoriasis Area and Severity Index; SD, Standard Deviation.

[1] Includes adalimumab (69, 51.5%); etanercept (17, 12.7%); ustekinumab (45, 33.6%); and other biologic therapies [infliximab, golimumab, secukinumab] (3, 2.3%)

[2] Includes acitretin (33, 25.0%); ciclosporin (32, 24.2%); Fumaric acid esters (7, 5.3%); methotrexate (60, 45.5%).

[3] The possible score range for CAGE is 0-4.

[4] Includes any of (excluding inflammatory arthritis) hypertension, angina, ischemic heart disease, stroke, epilepsy, asthma, chronic obstructive pulmonary disease, peptic ulcer, renal disease, hepatic disease, tuberculosis, demyelinating disease, diabetes, impaired glucose tolerance, depression, non-skin cancer, immunodeficiency syndrome, thyroid disease, other.

[5] The possible score range for HADS anxiety and HADS depression is 0-21.

[6] The possible score range for HADS anxiety and HADS depression severity is mild, 8-10; moderate, 11-14; severe, 15-21.

[7] Includes any of acitretin, fumaric acid esters, ciclosporin, methotrexate and mycophenolate mofetil.

[8] Patients stopped therapy received at the time of completing the iMAP questionnaire during the study period.

Table 2: Multivariable linear regression of potential factors associated with changes in PASI between baseline and follow-up.

Variable	**B coefficient (95% CIs)**	**P-value**
Demographics		
Age[a]	**-0.63 (-1.22,-0.05)**	**0.035**
Female	-0.05 (-1.37, 1.27)	0.940
Obesity status[b]		
Obese (BMI 30 kg/m^2)	**1.84 (0.48, 3.20)**	**0.008**
Smoking status[c]		
Ex-smoker	-1.21 (-2.75, 0.33)	0.123
Current smoker	-1.20 (-2.83, 0.44)	0.151

Comorbidities[d]		
Inflammatory arthritis	-0.28 (-1.96, 1.40)	0.745
1-2 comorbidities	-0.40 (-1.88, 1.08)	0.595
3-4 comorbidities	0.30 (-1.75, 2.35)	0.774
≥ 5 comorbidities	-1.31 (-5.62, 2.99)	0.549
Disease		
Disease duration[a]	0.28 (-0.21, 0.77)	0.258
Baseline PASI	**-0.83 (-0.92, -0.74)**	**<0.0001**
Baseline DLQI	-0.06 (-0.17, 0.06)	0.339
CAGE	**1.40 (0.04, 2.77)**	**0.044**
Psychological distress (HADS)		
Anxiety	-0.03 (-0.24, 0.17)	0.74
Depression	0.18(-0.04, 0.39)	0.110
Overall non-adherent	2.65 (-5.49, 10.79)	0.522
Treatment		
Conventional systemic cohort[e]	**4.39 (2.84, 5.95)**	**<0.0001**
Biologic naïve[f]	-1.76 (-4.19, 0.68)	0.156
Concomitantly using conventional systemic therapy[g]	1.78 (-0.36, 3.91)	0.102
Stopped therapy[h]	**4.18 (2.38, 5.97)**	**<0.0001**
Time gap between start of therapy and time the baseline PASI was measured	0.21 (-0.22, 0.65)	0.334
Time gap between start of therapy and time the follow-up PASI was measured	-0.12 (-0.28, 0.04)	0.138
Non-adherence: Conventional systemic cohort[i]	-2.20 (-6.68, 2.29)	0.336

Abbreviation: BMI, body mass index; CAGE, Cut down, Annoyed, Guilty and Eye Opener; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale, PASI, Psoriasis Area Severity Index.

Boldface indicates $P \leq 0.05$. Fractional polynomials were used to determine if any non-linear association between the covariates and the outcome provided a better fit than a simple linear association, but none did.

[a] To evaluate regression coefficients for every 10-year increase in age and disease duration at enrolment into the BADBIR, baseline continuous variables of age and disease duration were transformed to age and disease duration divided by 10. At follow-up, older age at enrolment (by 10 years) was associated with higher improvement in PASI values.

[b] Reference category: non-obese (BMI<30 kg/m^2).

[c] Reference category: never smoked.

[d] Reference category: no comorbidities (excluding inflammatory arthritis); includes any of hypertension, angina, ischemic heart disease, stroke, epilepsy, asthma, chronic obstructive pulmonary disease, peptic ulcer, renal disease, hepatic disease, tuberculosis, demyelinating disease, diabetes, impaired glucose tolerance, depression, non-skin cancer, immunodeficiency syndrome, thyroid disease, other.

[e] Reference category: biologic cohort.

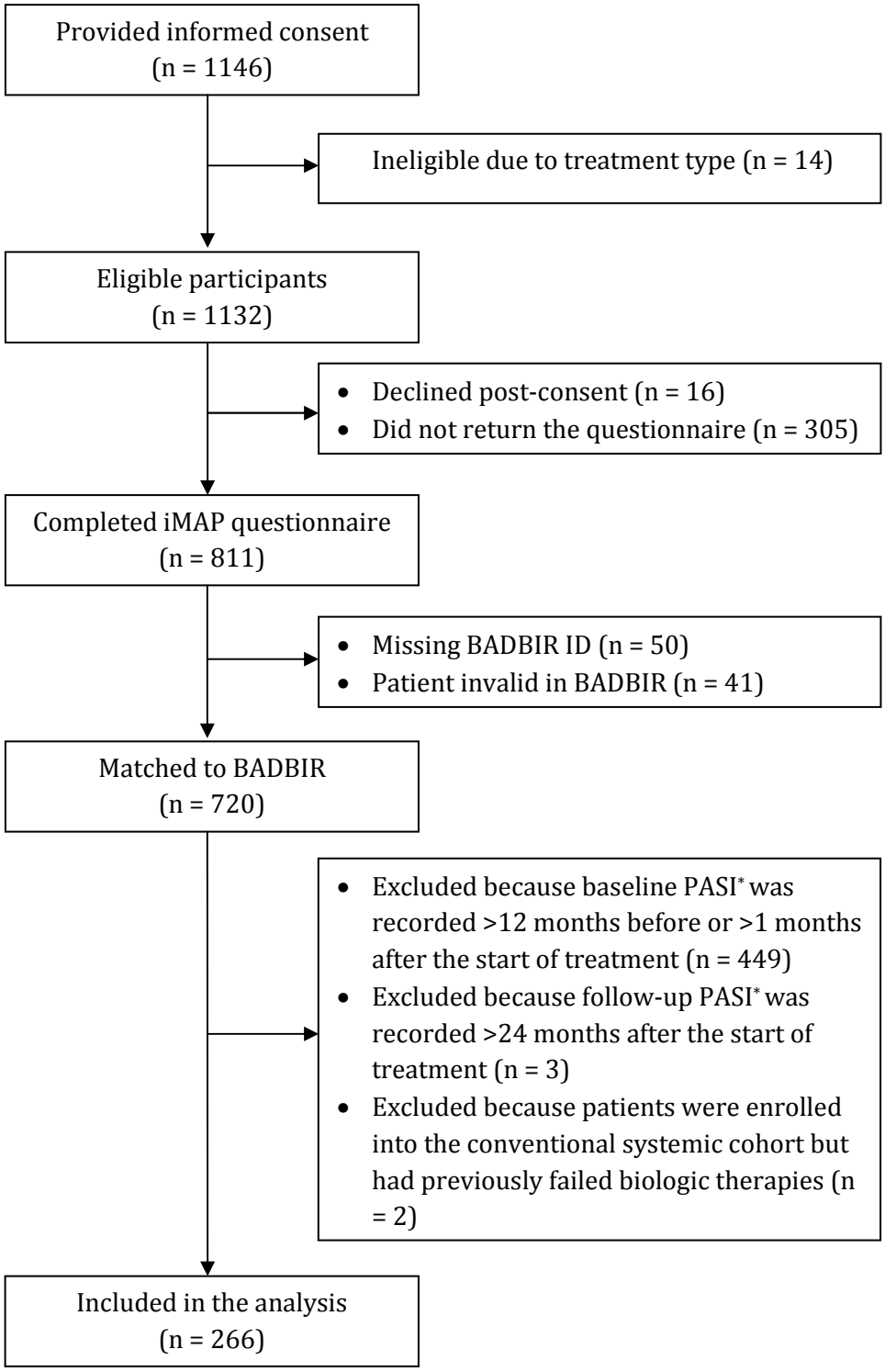
[f] Reference category: biologic non-naïve.

[g] Includes any of acitretin, fumaric acid esters, ciclosporin, methotrexate and mycophenolate mofetil. Included as a binary variable (ever exposed/never exposed). Reference category: never exposed.

[h] Patients stopped therapy received at the time of completing the iMAP questionnaire during the study period. Reference category: continuously used therapy throughout the study period.

[i] An interaction term between cohort and overall non-adherence status.

Figure 1: Flow chart showing selection of study participants.



*The PASI recorded closest to the date of completing the iMAP questionnaire were identified and referred to as either baseline PASI (recorded prior to completing the questionnaire) or follow-up PASI (recorded after completing the questionnaire).