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**Burden of illness in adults with atopic dermatitis (AD):
analysis of National Health and Wellness Survey data from
France, Germany, Italy, Spain and the U.K.**

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Pharmaceuticals, Inc. A.G. is an employee of and stockholder in Regeneron Pharmaceuticals, Inc. J.M.G. is an employee of the University of Pennsylvania Perelman School of Medicine which has received research funding from Sanofi/Regeneron Pharmaceuticals, Inc. In the previous 12 months, J.M.G. served as a consultant for AbbVie, AstraZeneca, Celgene Corp, Coherus, Eli Lilly, Janssen Biologics (formerly Centocor), Sanofi, Merck, Novartis Corp, Regeneron Pharmaceuticals, Inc., Valeant, and Pfizer Inc., receiving honoraria; and received research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Eli Lilly, Janssen, Novartis Corp, Regeneron, Sanofi, and Pfizer Inc.; and has received payment for continuing medical education work related to psoriasis. He is also a co-patent holder of Resiquimod for the treatment of cutaneous T cell lymphoma.

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Abstract

Background: The disease burden of AD in European populations is not well-known.

Objective: To establish disease burden in European adult AD patients.

Methods: Data were from 2016 National Health and Wellness Survey (NHWS) conducted in France, Germany, Italy, Spain and U.K.. Bivariate analyses were conducted on outcomes between matched non-AD controls versus AD self-reports (both n=1860).

Results: AD and a subset of inadequately-controlled AD (IC-AD) patients, respectively, versus non-AD controls reported significantly higher ($P < .001$) Short-form 36 physical and mental component summaries (PCS, MCS), and anxiety (31.9%, 51.7% vs 14.4%), depression (25.8%, 36.2% vs 12.9%) and sleep disorder (22.7%, 39.7% vs 12.6%) prevalences. IC-AD patients versus non-AD controls reported significantly greater ($P < .001$) overall work (57.1% vs 23.7%) and activity impairment (51.7% vs 26.5%). 21.6% of AD and 37.9% of IC-AD patients reported previous-6-month emergency room visit ≥ 1 versus 16.5% non-AD; 93.1% AD versus 84.2% non-AD had ≥ 1 clinician visit (both $P < .001$). Of these, IC-AD versus controlled AD patients showed greater burden on most outcomes.

Limitations: Low response rate, possible selection bias due to survey technology availability; patient-reported data susceptible to recall bias.

Conclusion: AD patients reported significant burden on health, health-related-quality-of-life, productivity, activities and healthcare.

Capsule summary

- 23 • Limited data exists on the burden of illness associated with atopic dermatitis
24 (AD) in Europe.
- 25 • In this study, adult AD patients, especially those with uncontrolled disease,
26 reported a significant burden on health, health-related quality of life,
27 productivity, activities and healthcare.

Introduction

Atopic dermatitis (AD) is a TH2 immune disease characterized by a chronic inflammatory skin condition and intense pruritus.¹⁻³ AD usually first presents in early infancy and childhood.^{4,5} However, for about half of pediatric patients, AD persists into adulthood,^{6,7} becoming a chronic, lifelong condition^{4,5} especially for those with later onset disease and/or presenting with greater severity.⁸ AD can also initially present at adulthood.^{7,9-11}

AD prevalence in adults varies according to severity, assessment method and region. Limited AD prevalence data in European adults indicate prevalence rates between 4.4%–7.1% (with a range between countries of 2.2%–17.6%)^{12,13} and trends of increasing prevalence.¹⁴ Self-reported disease severity prevalence in European adults with AD is 54%, 43% and 3% for mild, moderate and severe disease (2.4%, 1.9% and 0.13% of the European population), respectively.¹³

Moderate-to-severe AD carries a substantial patient burden^{13,15} due to itch, sleep disturbances, functional impairment, depression, anxiety and reduced overall health-related quality of life (HRQoL).^{1,16-19} Additionally, AD in adults impairs work productivity and activity.^{1,18} Real-world data on the burden of illness among adult AD patients in Europe is limited.

This study aimed to establish the real-world burden of illness in adult AD patients in five European countries (France, Germany, Italy, Spain and the United Kingdom [U.K.]). We further characterized the burden in AD patients with inadequate disease control.

METHODS

Study design

This study evaluated the burden of AD in adult patients using a cross-sectional study design. Patient-level data were obtained from the 2016 National Health and Wellness Survey (NHWS), a large general population survey administered to individuals aged ≥ 18 years using a self-administered, internet-based questionnaire. A random, stratified sampling framework on which the NHWS is designed ensures that the survey is representative of the demographic composition of the general population.

The 2016 NHWS was approved by the centralized Pearl Institutional Review Board (Indianapolis, IN, U.S.A.). Individuals who completed the survey gave informed consent online for their anonymized data to be used for research purposes. The present cross-sectional study was a pooled analysis of February 2016 to May 2016 NHWS datasets from France, Germany, Italy, Spain and the U.K.

Subjects

AD patients were identified by self-reported presence of AD and self-reported presence of a physician diagnosis by answering 'yes' to the questions whether "they had ever experienced atopic dermatitis" or "had experienced atopic dermatitis in the past 12 months" and whether "their atopic dermatitis had been diagnosed by a physician". These questions, which required affirmative answers, ensured the sample provided a true representative population of patients with self-reported AD. Adults who did not meet the criteria above were allocated to the non-AD control group.

Outcomes

AD burden was measured across patient-reported outcomes: comorbidities, HRQoL, work and productivity impairment, and healthcare resource utilization (HCRU).

Self-reported comorbidities such as mood disorders, including anxiety, depression, and sleep disorders, were also recorded. The survey asked patients “Which of the following conditions have you experienced in the past 12 months?” or “Which of the following conditions have you ever experienced”. For each condition identified, respondents also had to answer ‘Yes’ to the question, “Has your condition been diagnosed by a physician?”.

HRQoL was assessed using the 36-item Short Form Health Survey (SF-36v2)²⁰ and the dermatology-specific 10-question Dermatology Life Quality Index (DLQI)²¹; both the questionnaires have been linguistically validated for the languages across the study countries^{22,23}. Patient responses to SF-36v2 Mental Component Summary (MCS) and Physical Component Summary (PCS) covered period for the previous 4 weeks; higher scores indicating better health status. For the DLQI, patients provided information on their HRQoL regarding the previous week; higher scores indicate increased impairment in HRQoL.

A subset of subjects with self-reported AD who provided a DLQI score were also examined between those who reported DLQI >10 (indicating a “very large effect on patient’s life”²⁴) and categorized as patients with “inadequately controlled AD (IC-AD)” versus those who reported DLQI ≤ 10 categorized as “controlled AD (C-AD)”

The Work and Productivity Impairment questionnaire (WPAI) was used to evaluate work productivity and activity impairment, during the past 7 days, across four

domains:²⁵ absenteeism (percentage of work time missed due to a health problem); presenteeism (percentage of work time impaired); overall work impairment (percentage of overall work impairment; absenteeism + presenteeism); activity impairment (percentage of activity impairment).

HCRU over the previous 6 months was determined using responses to the following survey questions: “How many visits did you make to the following traditional healthcare provider(s) in the past 6 months?”; “How many times have you been to the ER for your own medical condition in the past 6 months?”; “How many times have you been hospitalized for your own medical condition in the past 6 months?”.

Statistical methods

AD patients were propensity-score-matched 1:1 with non-AD controls using the following variables: country, age, gender, education, income, employment status, body mass index (BMI), smoking status and Charlson Comorbidity Index (CCI). IC-AD patients were analyzed as a separate subgroup. Propensity score matching was conducted using variables that were statistically different between the AD and non-AD groups at baseline and during iterations of the propensity matching process. Relevant variables were entered into a logistic regression model using the SAS/STAT[®] LOGISTIC procedure to generate the propensity score. Matching was completed using the ‘greedy matching’ technique.²⁶ This approach ensures that the algorithm makes the ‘best’ matches first (highest digital match on propensity score; 5 decimal points), followed by the ‘next-best’ matches, continuing in a hierarchical sequence until no further matches are possible (0 decimal points). The best matches have the least absolute difference in matched propensity score.

119 Between-group comparisons of categorical and continuous variables were
120 conducted using Chi-square and *t* tests, respectively, with the two-tailed significance
121 level (α) set at 0.05. Analyses were performed using SAS version 9.3 (SAS Institute,
122 Cary, NC, U.S.A.).

RESULTS

Demographic and clinical characteristics

Of 971,854 adults contacted, 80,600 adults completed the survey (**Table I**); another 21,168 respondents either left the survey during the screener, refused informed consent, or didn't meet the inclusion criteria.

Subsequently, 1860 adults with a self-reported diagnosis of AD (including 441 who reported a DLQI score, of which 58 [3.1%] were IC-AD and 383 were C-AD) were propensity-score-matched to 1860 subjects with no diagnosis of AD (**Table I**). Most subjects, with or without a diagnosis of AD, were from Spain (37.0%), followed by Italy (24.6%), France (19.0%), Germany (10.6%) and the U.K. (8.9%). Most subjects (69.3%) were female and mean age was 44 years. The matching process resulted in good comparability between the AD and non-AD groups at baseline ($P > .10$) (**Table I**).

Comorbidities

Self-reported comorbidities were significantly more prevalent in patients with AD versus non-AD controls, and in IC-AD patients versus non-AD controls (**Fig 1**).

Depression was more prevalent in AD patients, affecting 25.8% and 36.2% of those with AD and IC-AD, respectively, compared with 12.9% of non-AD controls ($P < 0.001$ for both comparisons) (**Fig 1**).

The rate of anxiety was also higher in AD patients versus non-AD controls (31.9% vs 14.4%, respectively; $P < .001$), particularly in those with IC-AD (51.7%; $P < .001$ vs. non-AD controls and vs C-AD patients which was 31.6%; $P = .003$) (**Fig 1**). The pattern was similar for sleep disorders, which were reported by 22.7% and 39.7% of

AD and IC-AD patients, respectively, versus 12.6% of non-AD controls ($P < .001$ for both comparisons) and 21.7% versus C-AD patients ($P = .003$) (**Fig 1**).

Health-related quality of life

Both AD and IC-AD patients had significantly reduced HRQoL, indicated by lower mean SF-36v2 MCS scores, 41.96 and 34.78, respectively, versus 44.23 in non-AD controls (both $P < .001$) and mean PCS scores 49.41 and 43.87, respectively, versus 51.15 compared with non-AD controls (both $P < .001$) (**Fig 2A**). In addition, IC-AD patients had significantly reduced MCS (42.52) and PCS (49.52) scores (both $P < .001$) versus C-AD patients.

Fig 2B shows a comparison of mean MCS and PCS scores between AD patients and IC-AD patients versus normative populations in each study country^{20,27}. AD, IC-AD and C-AD patients reported MCS and PCS scores that were lower than the normative scores in each of the study countries.

Activity and work impairment

The presence of AD and IC-AD had a significant ($P < .001$) impact on work productivity (i.e. presenteeism and overall work impairment) and the ability to undertake activities. Presenteeism rates were 24.7% for AD and 53.5% for IC-AD patients, versus 21.2% in non-AD controls ($P = .002$ and $P < .001$, respectively), and overall work impairment rates of 27.0% for AD and 57.1% for IC-AD patients, versus 23.7% in non-AD controls ($P = .009$ and $P < .001$, respectively) (**Fig 3**). Significant activity impairment was also reported by AD and IC-AD patients, 31.8% and 51.7% respectively versus 26.5% of non-AD controls (both $P < .001$) (**Fig 3**). In contrast, rates of absenteeism did not differ significantly between those with and without AD, but was numerically higher for patients with IC-AD (**Fig 3**).

For C-AD versus IC-AD patients, absenteeism (10.2%) was not significant but differences in the rates of presenteeism (21.8%), overall work impairment (23.6%) and activity impairment (31.2%) were significant (all $P < .001$) (**Fig 3**).

Healthcare resource utilization

The proportion of patients with ≥ 1 traditional provider visit in the previous 6 months was higher in patients with AD (93.1%; mean number of visits 7.4 ± 11.2) and IC-AD (94.8%; mean number of visits 13.9 ± 17.8) compared with non-AD controls (84.2%, $P < .001$ and $P = .027$, respectively; mean number of visits 4.5 ± 7.2 , $P < .001$ for both comparisons) (**Fig 4**).

Similarly, the proportion of patients with ≥ 1 emergency room (ER) visit (21.6% in AD patients, 37.9% for IC-AD patients vs 16.5% for non-AD controls; both $P < .001$). The proportion of patients with ≥ 1 hospitalization was similar in AD patients and non-AD controls (9.0% and 8.7%, respectively), but significantly higher in those with IC-AD (19.0%; $P = .007$) (**Fig 4**). The mean number of healthcare provider visits, ER visits and hospitalizations for patients with IC-AD (13.9 ± 17.8 , 0.9 ± 1.7 , 0.4 ± 1.4 , respectively) compared with non-AD controls (4.5 ± 7.2 , 0.3 ± 1.5 , 0.1 ± 0.6 , respectively) were all significantly higher ($P < .001$, $P < .001$, $P = .003$).

There were also significant differences in HCRU between patients with IC-AD versus C-AD for at least one ER visit (37.9% versus 20.9%; $P = .004$) and at least one hospitalization (19.0% vs 9.1%; $P = .022$), respectively (**Fig 4**). The mean number of healthcare provider visits (13.9 ± 17.8 versus 7.6 ± 9.3), ER visits (0.9 ± 1.7 versus 0.4 ± 0.9) and hospitalizations (0.4 ± 1.4 versus 0.1 ± 0.5) were also greater for patients with IC-AD versus C-AD (all $P < .001$).

DISCUSSION

This study of adult AD patients from France, Germany, Italy, Spain and the U.K. indicates that AD is associated with significant disease burden in terms of higher prevalence of atopic and psychological comorbidities, impaired HRQoL, lower work productivity, increased activity impairment and increased healthcare utilization. The burden is even higher among patients with IC-AD.

The importance of disease burden in AD, and the limitation of European data in this field, has been recognized by the European Federation for Allergy and Airways Diseases Patients' Associations, which has initiated a survey in nine member states to obtain better information about the impact of AD in Europe.²⁸ Our findings highlight the burden of AD in Europe, consistent with the patient-reported burden of AD in the U.S.,^{19,29,30} and Japan,³¹ and another study based on DLQI data in Spain.³² These studies support conclusions by the World Health Organization, based on the 2010 Global Burden of Disease survey, that AD is associated with the highest number of disability-adjusted life-years of all skin disorders.^{33,34} Our results are also consistent with global epidemiologic studies highlighting the public health importance and burden of skin diseases, including AD.^{35,36}

Furthermore, our results are in line with an analysis of participants in a multinational clinical trial, including patients from four European countries, which revealed the multifactorial impact of AD on patients.¹⁷ The results also support the known link between AD and other conditions.

In this study, depression and anxiety were common in AD patients versus non-AD controls. Higher rates of depression in European AD patients have been reported previously,¹⁶ and are confirmed by our findings. In terms of HRQoL, all AD patients

had substantially lower SF-36v2 MCS scores than scores for normative populations in each study country,²⁰ highlighting the negative psychological impact of AD. For patients with IC-AD, PCS scores were also substantially lower than scores of the normative populations. The minimal clinically important difference (MCID) in SF-36v2 MCS and PCS scores is not known for AD, but values of 3–5 points have been reported for other chronic diseases.⁴¹⁻⁴⁵ Compared with this reference marker of MCID, the 6 to 9-point differences in these scores between non-AD and IC-AD suggest important decrements in HRQoL related to AD. Impaired HRQoL in adults with AD compared with the general population has previously been reported.⁴⁶⁻⁴⁸

Consistent with U.S.^{29,30} and Japanese³¹ NHWS data, work productivity and activities of European AD patients were negatively impacted by the presence of AD, in particular for IC-AD patients. Given the deleterious impact of AD on society in terms of reduced national levels of productivity, effective AD treatment is important not just for individual patients but for society as a whole." As one of the variables used in the propensity-score matching was employment status, it is possible that the impact of AD on work life may have been underestimated in this study.

We observed an additional burden; compared with non-AD controls, patients with objectively-defined markers of poor disease control also revealed increased HCRU, including significantly higher rates of ER and traditional healthcare visits. The survey questions relating to HCRU were not specific for AD in order to allow a full comparison of resource use by AD and non-AD subjects. These results were in line with a U.S.-based study of AD-related HCRU, with severity defined on clinical parameters.⁴⁹ While a previous comparison of healthcare utilization in AD patients based on the U.S. NHWS did not find any significant difference between those with

self-reported moderate/severe versus mild disease, but small numbers of patients reporting the higher level of disease severity might have limited the power of the analysis.²⁹ Regional differences in healthcare systems and clinical practice are another possible contributor to the differences in study findings.

The key strength of this study lies on the NHWS sampling approach, which was defined to ensure that the sample was representative of the general adult populations of the study countries. The use of propensity score matching of the AD and non-AD groups reduced the chances of confounding differences in baseline demographic characteristics between the groups. However, while the frequency of self-reported AD in this study was 2.3% (1860/80600), which is on the low side of point prevalence of AD in adults reported in the literature which ranges from 4.4–7.1%,^{12,50} this may be attributable to the case definition as AD is a more specific term than eczema which is more commonly recognized by the general population.

Study limitations include technology limitations which may have biased the sample to favor younger, healthier adults, hence under-representing AD patients, particularly those with more severe AD. In addition, the sample of patients reporting a DLQI score was limited to 441 patients only. Although a random, stratified sampling framework was used, ensures those without access to a computer or internet were likely not to have been contacted or participated in the study. In addition, those hospitalized or extremely ill may have not been healthy enough to complete a 30-minute survey. Finally, only 6% of patients offered the survey completed it; they may not be representative of the entire population; particularly for those in the middle part of life, busy with their jobs and family life, such patients may not have had the time to participate in the study. The socio-demographic data for the full population of

contacted individuals indicate the most prevalent age groups across countries to be 18-29 years.

Another potential limitation of the study is that the presence of AD was largely based on patient reporting. While previous research has reported discrepancies in physician and patient assessments of AD at up to 30%⁵¹, patient-reported data is imperative for obtaining the patient perspective in the evaluation of disease outcomes.⁵² Diagnoses and other clinical variables were not confirmed by review of patient medical charts due to the self-reported nature of the data; therefore, the present data may have been susceptible to recall bias.⁵³ Furthermore, patients with AD were matched to controls by country rather than geographical region; as region can impact access to healthcare and therefore use of healthcare resources, this may have affected our findings.

As a representation of the populations in five European countries, this study has provided evidence on the impact of disease severity and overall burden in adult patients with AD in Europe, for which data are currently sparse.

280 **CONCLUSION**

281 This study highlights the significant disease burden associated with IC-AD in a
282 European adult population, suggesting the need for more effective AD management
283 strategies.

ABBREVIATIONS

AD: atopic dermatitis

BMI: body mass index

CCI: Charlson Comorbidity Index

DLQI: Dermatology Life Quality Index

ER: emergency room

HCRU: healthcare resource utilization

HRQoL: health-related quality of life

IC-AD: inadequately controlled AD

IL: interleukin

MCS: Mental Component Summary

NHWS: National Health and Wellness Survey

PCS: Physical Component Summary

SF-36v2: 36-item Short Form Health Survey

WPAI: Work and Productivity Impairment questionnaire

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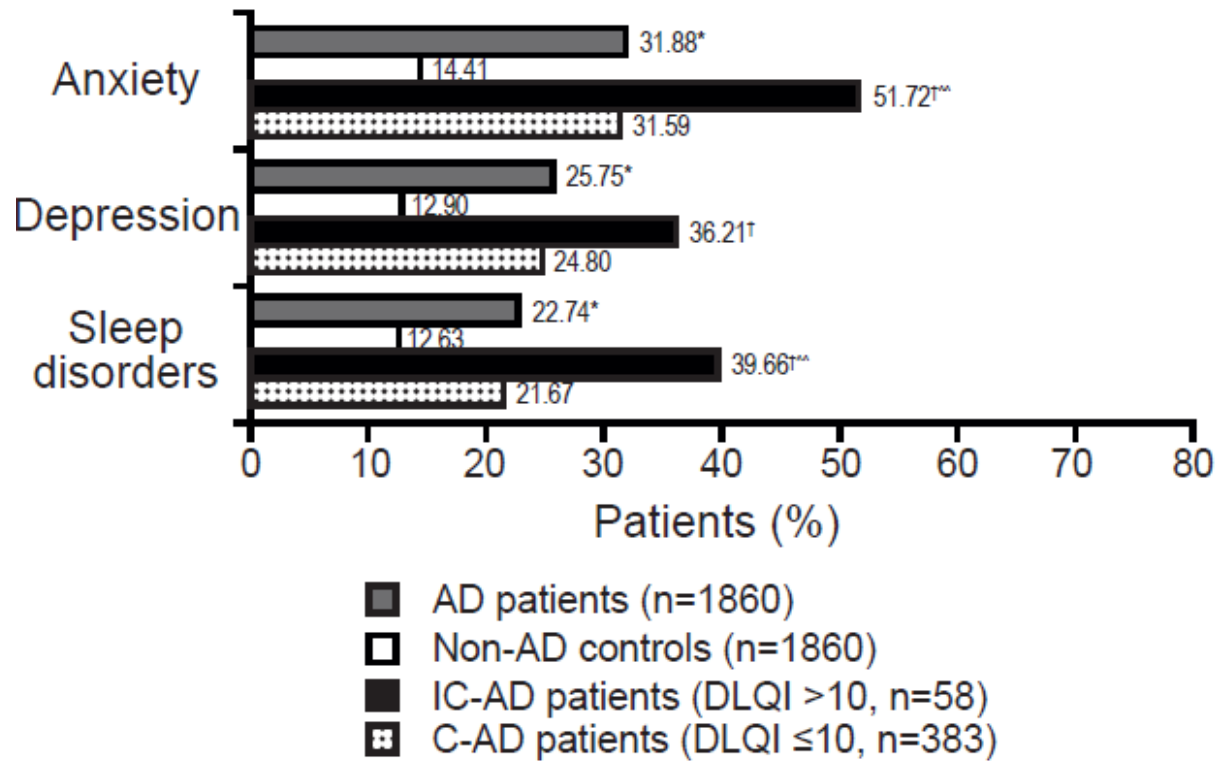
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Table I. Patient characteristics at baseline in atopic dermatitis (AD) and inadequately controlled AD (IC-AD) patients versus non-AD controls

	Non-AD controls (n = 1860)	AD patients (n = 1860)	P-value vs non-AD controls	IC-AD patients (n = 58)	P-value vs non-AD controls
Age, years	43.6 (15.0)	43.9 (14.5)	0.44	37.9 ± 14.6	0.004
Female, n (%)	1266 (68.1)	1312 (70.5)	0.10	35 (60.3)	0.22
Body mass index, kg/m ²	25.3 (5.5)	25.3 (5.5)	0.75	25.3 ± 5.8	0.95
Employed, n (%)	1172 (63.0)	1140 (61.3)	0.28	38 (65.5)	0.70
College educated, n (%)	1017 (54.7)	1014 (54.5)	1.00	25 (43.1)	0.19
Married/living with partner, n (%)	1152 (61.9)	1119 (60.2)	0.45	34 (58.6)	0.76
Annual household income of €50,000/pounds or greater, n (%)	282 (15.2)	292 (15.7)	0.72	9 (15.5)	0.48
Charlson Comorbidity Index	0.4 (1.1)	0.4 (0.9)	0.12	1.3 ± 4.5	< 0.001
Dermatology Life Quality Index >10, n (%)	–	58 (13.2)	–	58 (100)	

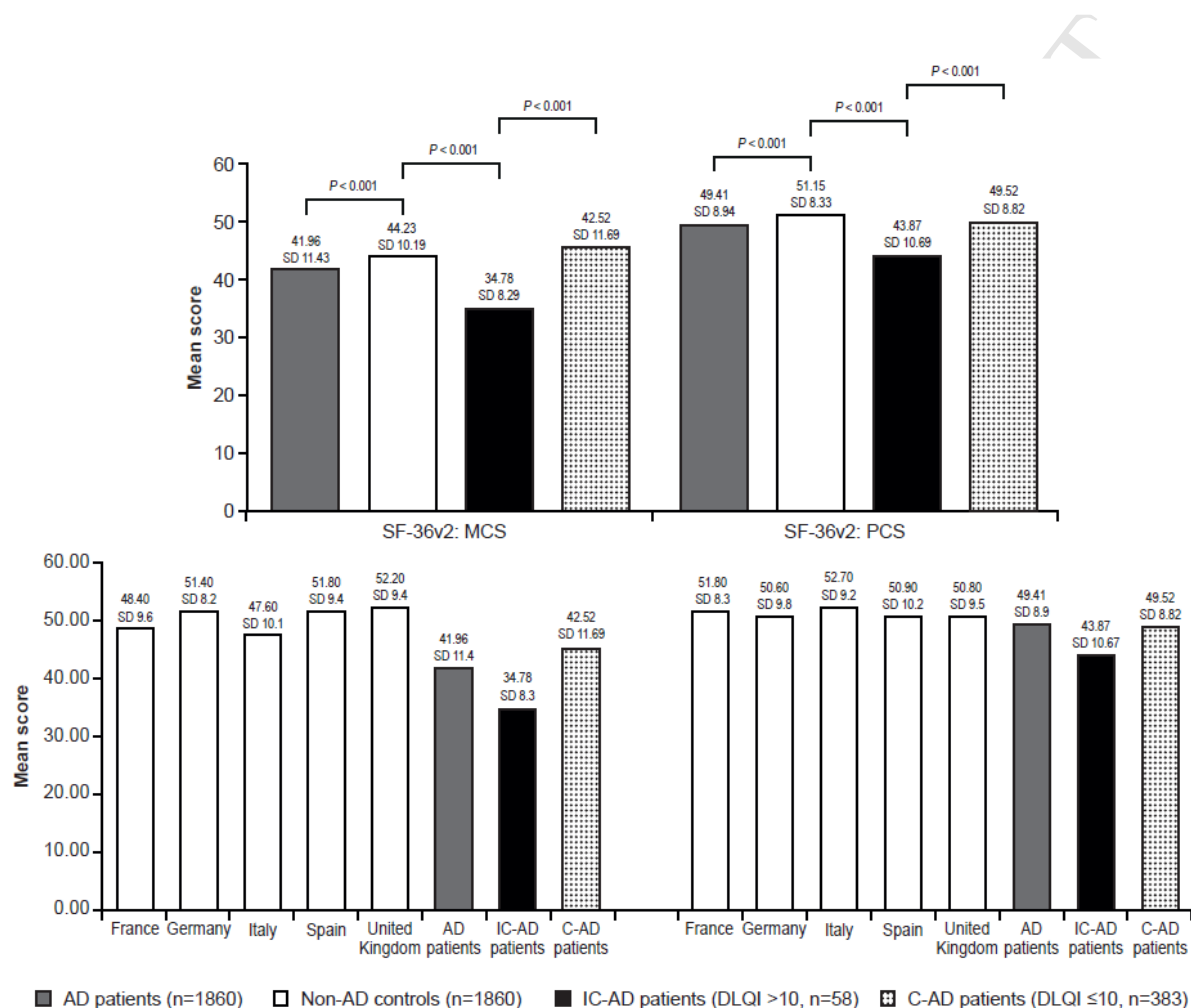
Values are mean (standard deviation) or number of patients (%)

Fig 1. Self-reported prevalence of comorbidities in atopic dermatitis (AD) and inadequately controlled AD (IC-AD) patients versus non-AD controls.



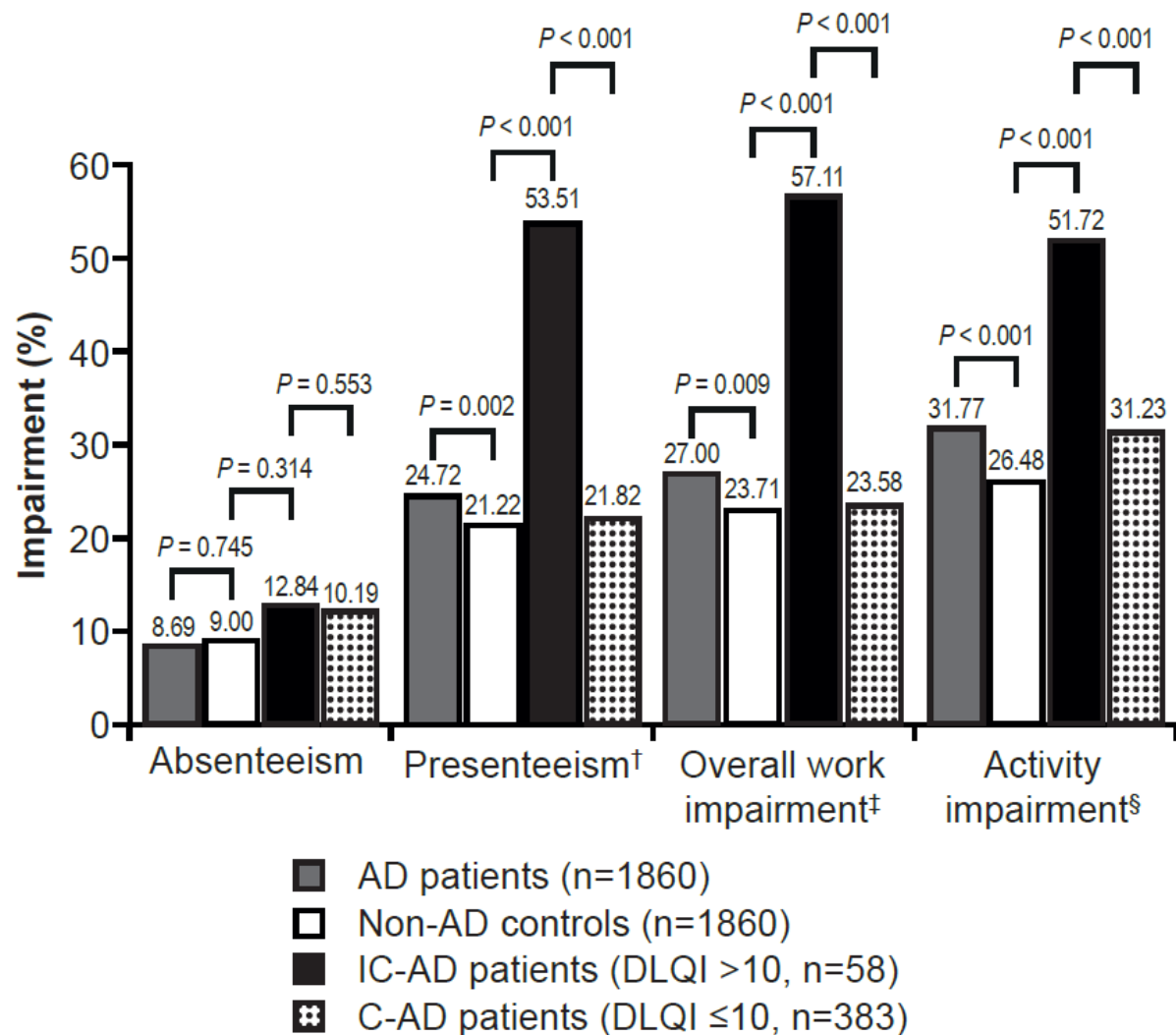
*All *P*-values between AD versus non-AD cohort: $P < .001$; [†]All *P*-values between non-AD cohort versus AD patients with IC-AD (DLQI > 10): $P < .001$; ^{**}*P*-values between C-AD patients versus patients with IC-AD (DLQI > 10): $P = 0.003$.

Fig 2. Health-related quality of life* in A) atopic dermatitis (AD) and inadequately controlled AD (IC-AD) patients versus non-AD controls and B) AD and IC-AD patients versus normative populations in France, Germany, Italy, Spain and the U.K., respectively.



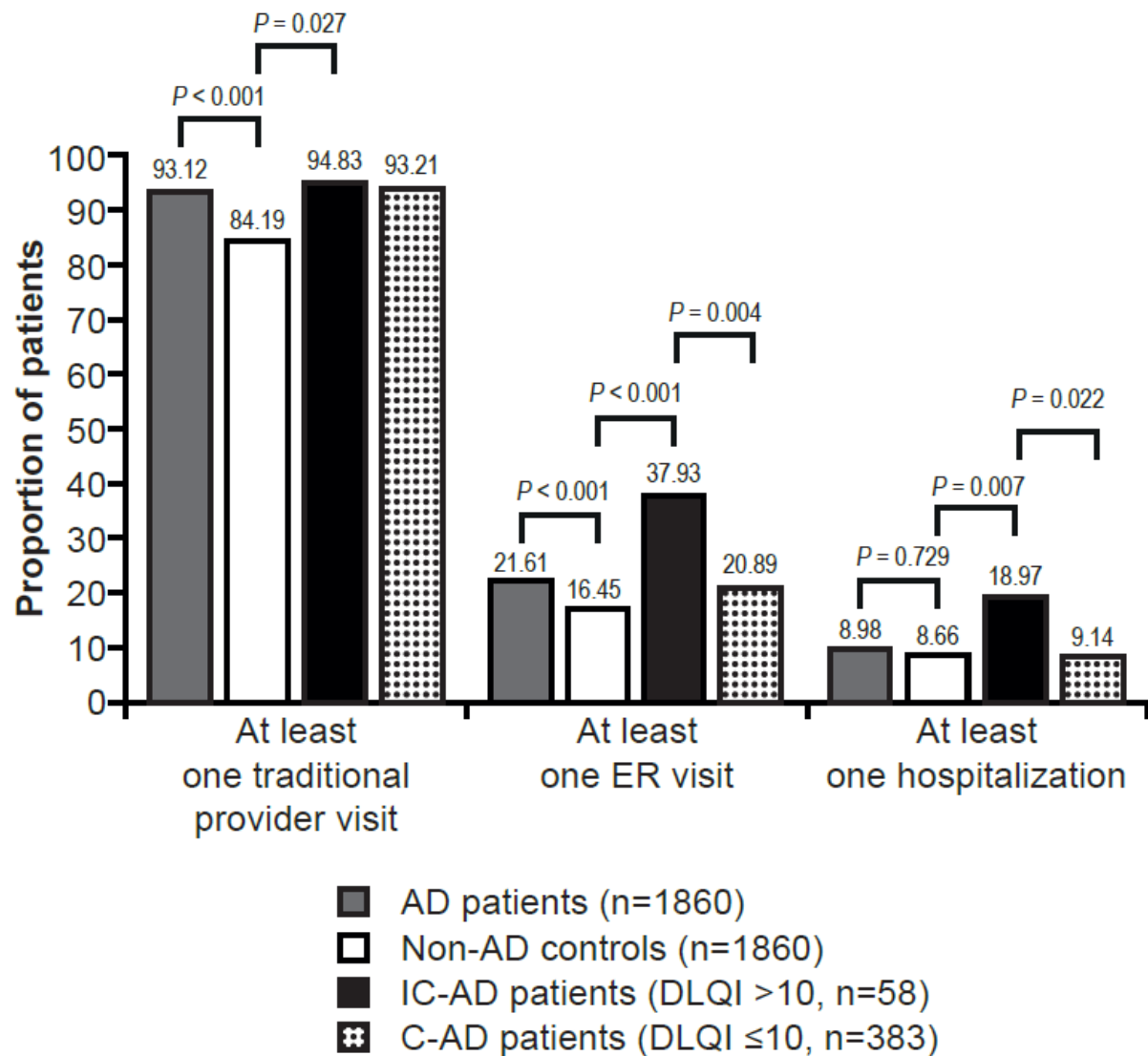
* Lower scores imply more impairment in health-related quality of life

Fig 3. Work and Productivity Impairment questionnaire (WPAI) scores in atopic dermatitis (AD) and inadequately controlled AD (IC-AD) patients versus non-AD controls.



[†]Presenteeism: percentage reduced productivity while at work; [‡]Overall work impairment: percentage of overall work impairment; absenteeism + presenteeism; [§]Activity impairment: Percentage reduced everyday activity.

Fig 4. Healthcare resource utilization over the previous 6 months in atopic dermatitis (AD) and inadequately controlled AD (IC-AD) patients versus non-AD controls.



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