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The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017*

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Summary

Background The Global Burden of Disease (GBD) Study provides an annually updated resource to study disease-related morbidity and mortality worldwide.
Objectives Here we present the burden estimates for atopic dermatitis (AD), including data from inception of the GBD project in 1990 until 2017.
Methods Data on the burden of AD were obtained from the GBD Study.
Results Atopic dermatitis (AD) ranks 15th among all nonfatal diseases and has the highest disease burden among skin diseases as measured by disability-adjusted life-years (DALYs). Overall, the global DALY rate for AD in 1990 was 121 [95% uncertainty interval (UI) 65·4–201] and remained similar in 2017 at 123 (95% UI 66·8–205). The three countries with the highest DALY rates of AD were Sweden (327, 95% UI 178–547), the UK (284, 95% UI 155–478) and Iceland (277, 95% UI 149–465), whereas Uzbekistan (85·1, 95% UI 45·2–144), Armenia (85·1, 95% UI 45·8–143) and Tajikistan (85·1, 95% UI 46·1–143) ranked lowest.
Conclusions The global prevalence rate of AD has remained stable from 1990 to 2017. However, the distribution of AD by age groups shows a bimodal curve with the highest peak in early childhood, decreasing in prevalence among young adults, and a second peak in middle-aged and older populations. We also found a moderate positive correlation between a country's gross domestic product and disease burden. GBD data confirm the substantial worldwide burden of AD, which has remained stable since 1990 but shows significant geographical variation. Lifestyle factors, partially linked to affluence, are likely important disease drivers. However, the GBD methodology needs to be developed further to incorporate environmental risk factors, such as ultraviolet exposure, to understand better the geographical and age-related variations in disease burden.

What is already known about this topic?

- Atopic dermatitis (AD) is a common skin condition affecting around 20% of children and up to 10% of adults in high-income countries.
- There is a sparsity of studies that have taken a truly global approach, in particular among adult populations.

What does this study add?

- We provide the first global map of the burden of AD across age groups, including disability-adjusted life-years.
- This ranks AD 15th among nonfatal diseases overall and top among skin diseases.
- The burden of AD has remained stable between 1990 and 2017, with the highest prevalence rate seen during early childhood and a second rise from middle age.

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Conflicts of interest
C.F. is chief investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials, as well as the UK–Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918). C.F. and S.M.L. are principal investigators in the European Union Horizon 2020 IMI2-funded BIOMAP Consortium (grant number 821511). The department of C.F. has also received funding from Sanofi Genzyme for skin microbiome work. R.P.D. served as a medical consultant to Altus Labs from July 2018 to July 2020, and he directs a big data dermatology research fellowship with independently awarded and administrated competitive grant funds provided to his department by Pfizer Pharmaceuticals (grant numbers 41064185 and 58858477).

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Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition affecting around 20% of children[1,2] and up to 10% of adults in high-income countries.[3–6] The pathogenesis is complex, involving genetic susceptibility, impaired skin barrier function, dysfunctional cell-mediated immunity, and environmental and lifestyle factors.[7,8] AD is also associated with sleep disruption (mainly due to pruritus), decreased work productivity,[9] and depression and anxiety, which all carry additional health and economic burdens for patients and their families.[10]

Assessing the economic burden of AD is complex as it consists of costs for medical care and nonmedical care and indirect costs (e.g. loss of education and workdays). The degree to which medical costs are an individual (out-of-pocket) burden or a collective one depends largely on the healthcare system. This diversity is reflected in the studies on this subject. Firstly, two studies from the USA reported direct and indirect costs totalling about USD 3300 per person per year (pppy) for children[11] and adults in 2013·[12] Three European studies reported out-of-pocket costs for medical care as USD 1500 pppy for Italian children (2016),[13] €351 for French adults (2018)[14] and €927 for adults with moderate-to-severe AD in nine European countries (2018).[15] In the latter study, for German patients costs were higher for AD than for psoriasis and rheumatoid arthritis (€941, €224 and €628, respectively).[15] Similar cost estimates have been published for AD in Singapore,[16] the Asia Pacific region, Thailand, South Korea and Vietnam.[17] Understandably, cost increases with disease severity.[12,14,16]

Burden of disease can also be expressed in terms of disability-adjusted life-years (DALYs), a measure for the difference between living a life in perfect health and living with a disease. DALYs are calculated as years lost due to disability plus the years of life lost. In other words, one DALY equals 1 year lost to illness, disability or premature death within a given population. In nonfatal diseases such as AD, DALYs are measured predominantly by years lost due to disability. The Global Burden of Disease (GBD) Institute for Health Metrics and Evaluation measures, compares and reports health loss from disease through the use of DALYs. This study presents data from the GBD on AD by geographical location from 1990 to 2017 to understand better the global burden of this common skin disease.

Material and methods

A comprehensive description of the methodology used by GBD can be found in previous studies.[18,19] In this publication, we report the burden of AD by prevalence rates and DALYs (the sum of years lost to disability and years of life lost). These results are estimated for 21 age groups, with no sex restrictions, and in 195 countries and territories from 1990 to 2017. We report rates as age-standardized rates as per the World Health Organization world population age structure. All values are presented with 95% uncertainty intervals (UIs), which estimate the distribution based on all data and input parameters including all sources. Values presented as rates indicate the value per 100 000 persons and for all individuals, unless otherwise specified, as per GBD standard approaches.

Disability weights measure the relative valuations of health states, defined as an individual level of functioning within a set of health domains. For skin diseases weights encompass physical disfigurement, itch and pain. The descriptions for disfigurement assessed in the disability weight surveys include the psychological morbidity attributable to each skin disease. The values range between 0 (full health) and 1 (states equivalent to death) and were generated through expert consensus.[20] The severity associated with AD is split into three levels: mild, moderate and severe (Table S1; see Supporting Information).

Data sources were obtained from a systematic search of the global scientific literature using PubMed and Google Scholar, as well as through claims submitted to US commercial health insurance companies. The prevalence estimates from these epidemiological studies were input into DisMod-MR 2·1 (https://pypi.org/project/dismod-mr), a Bayesian metaregression tool, to estimate prevalence by age, sex, year and geography (subnational, country, region and super-region) for AD.

For electronic health record data, AD was defined by International Classification of Diseases 10th Revision code L20. Prevalence data for AD were derived from 195 countries and territories grouped into 21 regions and GBD super-regions. A complete list of data sources used for estimation can be found using the Global Health Data Exchange online interactive tool (https://vizhub.healthdata.org/gbd-compare). Inpatient data were not included. Study-level covariates were used to adjust prevalence estimates from the Medical Expenditure Panel Survey,[21] including claims data from the USA for 2000, 2010 and 2012, along with self-reported and administrative data based on clinical examination. In order to improve regional and global estimates, the minimum coefficient of variation was set at 0·4 and location random effects for Paraguay, Sweden and England were restricted to (−0·25, 0·25), (−0·25, 0·25) and (−0·5, 0·5), respectively. A time window of 10 years was used to determine which data points were used for a particular year of fit.[19]

The gross domestic product (GDP) for each country was obtained through The Word Bank national account data (http://data.worldbank.org). The linear correlation between GDP and either DALY rate or prevalence rate was calculated using Pearson's correlation coefficient. A P-value $< 0·05$ was considered statistically significant. The analyses were performed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA).

Results

Out of 359 diseases and injuries analysed by the GBD 2017, AD was responsible for 0·36% of the total DALYs. This ranked AD 59th among all GBD diseases and injuries in age-standardized global DALY rate, below measles and above cirrhosis/other chronic liver diseases due to alcohol use. Among all nonfatal diseases, AD had the 15th highest age-standardized

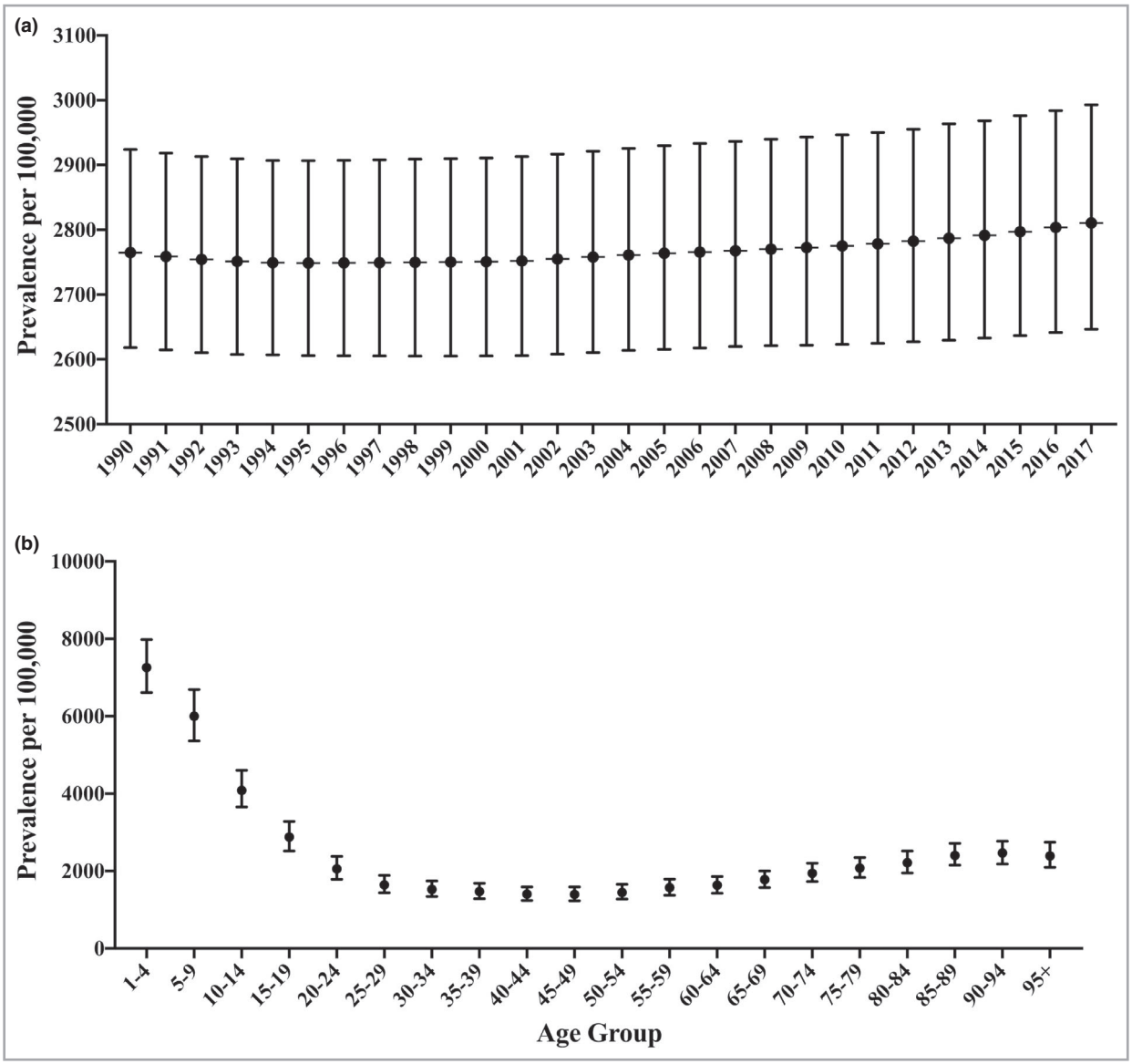

Figure 1 The global prevalence of atopic dermatitis per 100 000 in all individuals (a) by year and (b) by age group (in years). Bars indicate the 95% uncertainty interval.

global DALY rate. Furthermore, AD represented the highest age-standardized DALY rate out of all skin diseases in 2017 (123, 95% UI 66·8–205), followed by psoriasis (70·0, 49·7–92·5), urticaria (67·5, 44·8–95·4), scabies (60, 33·2–97·8) and fungal skin diseases (54·9, 21·8–114). In 2017, the global prevalence rate of AD was 2690 per 100 000 persons (95% UI 2535–2861). The global DALY rates for AD were stable between 1990 and 2017 (121, 65·4–201 vs. 123, 66·8–205, respectively). The global age-standardized prevalence rates of AD have also remained stable between 1990 and 2017 (Figure 1a; and Table S2; see Supporting Information). The prevalence of AD is highest in the paediatric population and decreases in prevalence among young adults, only to increase again within the middle-aged and older adult populations (Figure 1b).

There were notable differences in prevalence between countries, with moderate positive correlations between GDP and both DALY rates and prevalence rates: Pearson's $r = 0{\cdot}46$, $P < 0{\cdot}001$ and Pearson's $r = 0{\cdot}45$, $P < 0{\cdot}001$, respectively (Figure 2; and Figure S1; see Supporting Information).

Of the 195 countries, the five with the highest age-standardized DALY rates per 100 000 persons related to AD in 2017 were Sweden (327, 95% UI 178–547), the UK (284, 155–478), Iceland (277, 149–465), Finland (264, 144–443) and Denmark (255, 137–424). The five countries with the lowest age-standardized DALY rates due to AD in 2017 were Uzbekistan (85·1, 95% UI 45·2–144), Armenia (85·1, 45·8–143), Tajikistan (85·1, 46·1–143), China (82·1, 44·2–138) and Kazakhstan (80·9, 43·6–136) (Figure 3).

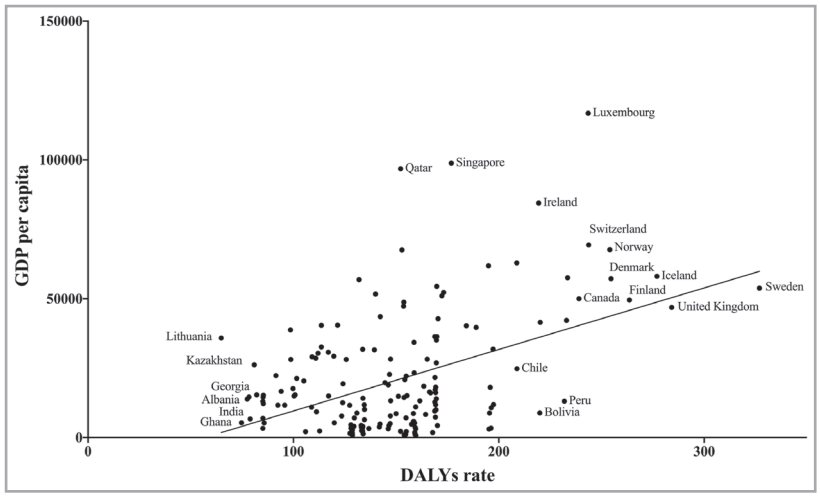

Figure 2 Scatterplot showing disability-adjusted life-years (DALYs) vs. gross domestic product (GDP) per capita per country. Correlation measured by Pearson's r = 0·46, P < 0·001.

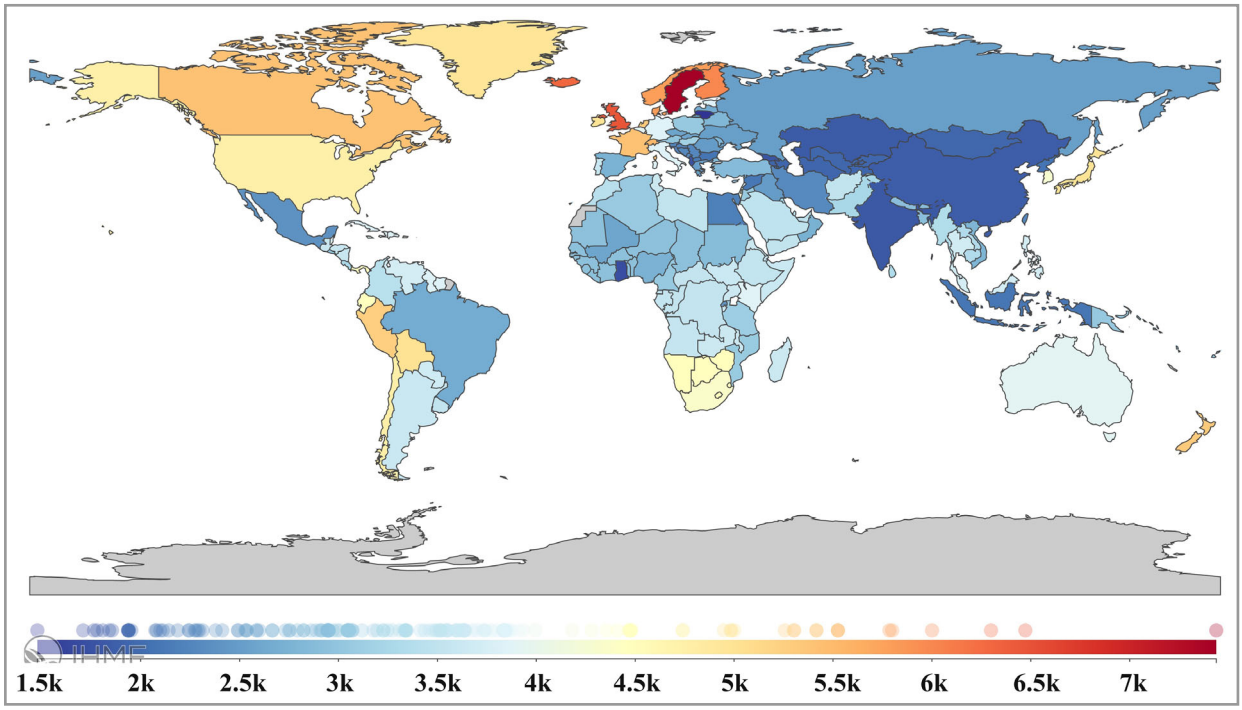

Figure 3 The global age-standardized prevalence of atopic dermatitis in all individuals per 100 000 persons. Blue areas indicate low prevalence and red areas indicate high prevalence. Source: Global Burden of Disease project 2017 data, Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA.

In 2017, the five world regions with the highest age-standardized DALY rates of AD were Andean Latin American (220, 95% UI 121–372), high-income North America (212, 113–372), high-income Asia Pacific (209, 113–352), Western Europe (205, 111–345) and Southern sub-Saharan Africa (193, 105–322). In 2017, the five world regions with the lowest age-standardized DALY rates were Central Europe (117, 95% UI 63–194), Eastern Europe (112, 61–186), South Asia (92, 50–153), Central Asia (84, 45–142) and East Asia (83, 44–139) (Table 1).

Discussion

AD has the highest DALY burden of all skin diseases and ranks 15th among all nonfatal diseases globally, with five European countries ranking top in age-standardized DALYs: Sweden, the

Table 1 Age-standardized disability-adjusted life-year (DALY) rate and prevalence rate (per 100 000 persons) of atopic dermatitis in 2017 by region, arranged in descending order of DALYs

Region	Age-standardized DALYs (95% UI)	Age-standardized prevalence (95% UI)
Andean Latin America	220·3 (120·5–372·0)	4994 (4644–5398)
High-income North America	211·7 (112·8–372·0)	4804 (4679–4940)
High-income Asia Pacific	209·2 (113·4–352·2)	4737 (4499–4991)
Western Europe	205·0 (111·0–345·1)	4653 (4442–4876)
Southern sub-Saharan Africa	192·9 (104·6–322·2)	4394 (4098–4694)
Australasia	182·0 (98·8–304·3)	4134 (3935–4342)
Southern Latin America	171·5 (93·2–287·4)	3894 (3693–4094)
Caribbean	168·9 (90·5–283·3)	3839 (3522–4144)
Central sub-Saharan Africa	154·6 (82·2–254·8)	3549 (3229–3857)
Eastern sub-Saharan Africa	152·6 (82·4–256·6)	3485 (3174–3821)
Oceania	133·2 (71·0–220·2)	3047 (2787–3318)
Central Latin America	131·3 (71·1–220·9)	2972 (2799–3172)
South East Asia	127·6 (68·9–213·4)	2896 (2698–3112)
North Africa and Middle East	124·4 (68·0–206·9)	2845 (2593–3142)
Western sub-Saharan Africa	120·3 (65·5–200·7)	2762 (2498–3344)
Tropical Latin America	118·8 (63·7–199·3)	2702 (2597–2817)
Central Europe	116·6 (63·3–194·2)	2656 (2462–2869)
Eastern Europe	111·6 (60·7–186·4)	2543 (2413–2691)
South Asia	92·3 (49·8–153·4)	2110 (1989–2244)
Central Asia	84·2 (45·1–141·5)	1915 (1738–2095)
East Asia	82·6 (44·4–138·9)	1866 (1786–1948)

UI, uncertainty interval.

UK, Iceland, Finland and Denmark. The global burden of AD expressed in DALYs remained stable during the data collection period from 1990 to 2017. While the disease prevalence rate is highest during early childhood, there was a second rise from middle age. In addition, we found a moderate positive correlation between a country's GDP and AD burden.

Key strengths of the GBD dataset include its global reach, annually updated systematic data collection and disease burden estimates. However, the use of many different data sources invariably leads to pooling of data from studies that have used different methodologies and may have used different definitions of AD. The environmental factors that drive differences in disease burden between populations are difficult to determine with the GBD methodology. Furthermore, large prevalence studies commonly use questionnaire tools, which tend to overestimate the true disease burden, compared with standardized skin examination by a trained investigator (which may underestimate AD as it relies on the presence of AD at the time of examination).[22] There is also a risk of disease misclassification using questionnaires, partly because there are a number of pruritic skin conditions, including scabies, that might be reported as AD instead or vice versa.

Misclassification might also have contributed to the high regional AD burden seen in Andean Latin America and some African settings, as well as the high burden in European countries. However, high disease prevalence for AD has previously been noted in paediatric and adult populations for South America and Africa.[2,23]

We report that the highest AD prevalence is in children, with a subsequent decline in prevalence and a later increase in prevalence in middle-aged and older adults, which may be due to a gradual decline in the water-holding properties of the skin barrier in older age. These observations are consistent with reports from UK primary care data, a UK birth cohort and a survey of US adults.[6,24,25] Interpretations discussed in the recent literature are that adult AD may be more common than previously believed, and likely includes both persisting or recurring disease from childhood and new-onset adult AD; further research is required to characterize adult AD better.

There is limited research on the association between disease burden and GDP. Previous reports are consistent with our estimates, although these associations were not as strong as we had expected.[26] However, GDP is only a crude surrogate measure of lifestyle and other environmental factors linked with per capita income and AD development, such as air pollution, antibiotic prescribing, hygiene measures, dietary factors and obesity.[27] We are only starting to understand how such environmental factors interact with the skin and gut microbiomes, as well as host cell interactions at the level of the skin barrier.[28]

Where do we go from here? It will be important to develop the GBD methodology further, for instance by providing better estimates of prevalence and harmonized definitions, and efforts to map ultraviolet and air pollution exposure against burden of disease. These efforts will be particularly important to interpret effects of climate change. It is important to note that the burden of AD does not include commonly seen comorbidities such as food and respiratory allergies, or psychiatric diseases (anxiety and depression).[29] Combining these associated diseases with AD burden estimates would help reflect the patient burden more closely. Further large population-based studies are needed to fill the remaining gaps on the burden of AD outside of Europe and North America, in particular in adult populations.

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References

1 Odhiambo JA, Williams HC, Clayton TO *et al.* Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009; **124**:1251–8.

2 Deckers IAG, McLean S, Linssen S *et al*. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. *PLoS One* 2012; **7**:e39803.
3 Abuabara K, Yu AM, Okhovat JP *et al*. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. *Allergy* 2018; **73**:696–704.
4 Lee HH, Patel KR, Singam V *et al*. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. *J Am Acad Dermatol* 2019; **80**:1526–32.
5 Barbarot S, Auziere S, Gadkari A *et al*. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy* 2018; **73**:1284–93.
6 Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol* 2013; **132**: 1132–8.
7 Malik K, Heitmiller KD, Czarnowicki T. An update on the pathophysiology of atopic dermatitis. *Dermatol Clin* 2017; **35**:317–26.
8 Rutter CE, Silverwood RJ, Williams HC *et al*. Are environmental factors for atopic eczema in ISAAC Phase Three due to reverse causation? *J Invest Dermatol* 2019; **139**:1023–36.
9 Ismail N, Bray N. Atopic dermatitis: economic burden and strategies for high-quality care. *Br J Dermatol* 2020; **182**:1087–8.
10 Drucker AM, Wang AR, Li WQ *et al*. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol* 2017; **137**:26–30.
11 Filanovsky MG, Pootongkam S, Tamburro JE *et al*. The financial and emotional impact of atopic dermatitis on children and their families. *J Pediatr* 2016; **169**:284–90.
12 Drucker AM, Qureshi AA, Amand C *et al*. Health care resource utilization and costs among adults with atopic dermatitis in the United States: a claims-based analysis. *J Allergy Clin Immunol Pract* 2018; **6**:1342–8.
13 Ricci G, Bendandi B, Pagliara L *et al*. Atopic dermatitis in Italian children: evaluation of its economic impact. *J Pediatr Heal Care* 2006; **20**:311–5.
14 Launois R, Ezzedine K, Cabout E *et al*. Importance of out-of-pocket costs for adult patients with atopic dermatitis in France. *J Eur Acad Dermatol Venereol* 2019; **33**:1921–7.
15 Zink A, Arents B, Fink-Wagner A *et al*. Out-of-pocket costs for individuals with atopic eczema: a cross-sectional study in nine European countries. *Acta Derm Venereol* 2019; **99**:263–7.
16 Olsson M, Bajpai R, Wee LWY *et al*. The cost of childhood atopic dermatitis in a multi-ethnic Asian population: a cost-of-illness study. *Br J Dermatol* 2020; **182**:1245–52.
17 Tsai TF, Rajagopalan M, Chu CY *et al*. Burden of atopic dermatitis in Asia. *J Dermatol* 2019; **46**:825–34.
18 Roth GA, Abate D, Abate KH *et al*. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**:1736–88.
19 Karimkhani C, Dellavalle RP, Coffeng LE *et al*. Global skin disease morbidity and mortality: an update from the Global Burden of Disease Study 2013. *JAMA Dermatol* 2017; **153**:406–12.
20 Lopez AD, Mathers CD, Ezzati M *et al*. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**:1747–57.
21 Boslaugh SE. Medical expenditure panel survey (MEPS). In: *The SAGE Encyclopedia of Pharmacology and Society* (Boslaugh S, ed.). Thousand Oaks, CA: Sage Publications Inc., 2016; 870–2.
22 Flohr C, Weinmayr G, Weiland SK *et al*. How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. *Br J Dermatol* 2009; **161**:846–53.
23 Beasley R, Keil U, Von Mutius E, Pearce N. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; **35**:1225–32.
24 Abuabara K, Magyari A, McCulloch CE *et al*. Prevalence of atopic eczema among patients seen in primary care: data from the health improvement network. *Ann Intern Med* 2019; **170**:354–6.
25 Abuabara K, Ye M, McCulloch CE *et al*. Clinical onset of atopic eczema: results from 2 nationally representative British birth cohorts followed through midlife. *J Allergy Clin Immunol* 2019; **144**:710–9.
26 Flohr C, Weiland SK, Weinmayr G *et al*. The role of atopic sensitization in flexural eczema: findings from the International Study of Asthma and Allergies in Childhood Phase Two. *J Allergy Clin Immunol* 2008; **121**:141–7.
27 Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014; **69**:3–16.
28 Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. *Allergy* 2020; **75**:63–74.
29 Schonmann Y, Mansfield KE, Hayes JF *et al*. Atopic eczema in adulthood and risk of depression and anxiety: a population-based cohort study. *J Allergy Clin Immunol Pract* 2020; **8**:248–57.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 A scatterplot showing the prevalence rate vs. gross domestic product (GDP) per capita per country. Correlation measured by Pearson's $r = 0.45$, $P < 0.001$.

Figure S2 Age-standardized disability-adjusted life-year (DALY) rates for atopic dermatitis per 100 000 by sex and region (in descending order of DALY rate). Bars indicate the 95% uncertainty interval.

Table S1 Disability weighting of atopic dermatitis.

Table S2 Atopic dermatitis age-standardized rate of disability-adjusted life-years (DALYs), percentage change of DALY rate from 1990 to 2017, prevalence rate and percentage change of prevalence rate from 1990 to 2017, by country.