



GERMANY

Disease Burden

Prevalence, Diagnosis, and Comorbidities

The prevalence of AD in German children was estimated at 15.6% in a nationally representative sample of patients; AD was most prevalent in children less than one year of age (22%), followed by adolescents (8%) and then adults (2–4%).¹²³

Other studies have found similar results: a lifetime prevalence of 13.2% in German children and adolescents¹²⁴ and a lifetime prevalence of 4.3% in German adults aged 50–75, much lower than the estimates in younger individuals.¹²⁵ A survey-based study found that the prevalence of AD in German school-aged children increased during a 5-year period between 1994/1995 and 1999/2000, a trend that was observed in other developed nations around the same time.^{126,2}

Recent epidemiologic studies have captured disease associations with AD in the German population. A study analyzing data from the German National Health Insurance beneficiaries found that patients with (vs. without) AD were at increased risk for incident rheumatoid arthritis and inflammatory bowel disease.¹²⁷ In a cohort of German adults sampled from the LIFE-Adult-Study, AD was significantly associated with autoimmune disease.¹²⁸ Children with AD had an increased relative risk of impetigo and vitiligo.¹²⁹

Physical and Psychosocial Consequences

The Atopic Health study, a nationally representative sample of 1,678 AD patients with a mean SCORAD of 42.3 (indicating moderate disease), reported a mean DLQI of 8.5 (indicating a moderate effect on the patient's QoL),¹³⁰ and up to a third of patients felt that their quality of life could be improved.¹³¹ By contrast, the ADIA study of US patients found a much lower (better

¹²³Schmitt, J., Schmitt, N. M., Kirch, W. & Meurer, M. [Significance of atopic dermatitis in outpatient medical care. Analysis of health care data from Saxony]. *Hautarzt* 60, 320–327 (2009).

¹²⁴Schmitz, R., Atzpodien, K. & Schlaud, M. Prevalence and risk factors of atopic diseases in German children and adolescents. *Pediatr Allergy Immunol* 23, 716–723 (2012).

¹²⁵Wolkewitz, M. et al. Lifetime prevalence of self-reported atopic diseases in a population-based sample of elderly subjects: results of the ESTHER study. *Br J Dermatol* 156, 693–697 (2007).

¹²⁶Maziak, W. et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Münster, Germany. *Allergy* 58, 572–579 (2003).

¹²⁷Schmitt, J. et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. *J Allergy Clin Immunol* 137, 130–136 (2016).

¹²⁸Treudler, R., Zeynalova, S., Walther, F., Engel, C. & Simon, J. C. Atopic dermatitis is associated with autoimmune but not with cardiovascular comorbidities in a random sample of the general population in Leipzig, Germany. *Journal of the European Academy of Dermatology and Venereology* 32, e44–e46 (2018).

¹²⁹Augustin, M. et al. Epidemiology and Comorbidity in Children with Psoriasis and Atopic Eczema. *DRM* 231, 35–40 (2015).

¹³⁰Langenbruch, A. et al. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. *J Eur Acad Dermatol Venereol* 28, 719–726 (2014).

¹³¹Steinke, S., Langenbruch, A., Ständer, S., Franke, N. & Augustin, M. Therapeutic benefits in atopic dermatitis care from the patients' perspective: results of the German national health care study 'Atopic Health'. *Dermatology* 228, 350–359 (2014).

DLQI of 4.71, though a majority of those patients (60.1%) had mild disease as classified by POEM; only 28.9% had moderate disease.⁴ This discrepancy highlights the importance of accounting for disease severity. Comorbidities matter as well; AD and hay fever were found to contribute to worse health-related quality of life (HRQoL) in German adolescents.¹³² As these data were collected at intervals of four weeks and 12 months, the authors posit that it is important to consider more immediate relief for symptoms of AD and hay fever when considering treatment for this population.¹³³

Several studies have focused on the burden associated with pruritus (itch), specifically. In the German Atopic Dermatitis Intervention Study (GADIS), itch and sleeplessness were found to be significantly correlated;¹³⁴ another study found that 26.6% of patients reported suffering “often” or “every night” as a result of pruritus.¹³⁰ As pruritus worsened, QoL worsened in both German children and adolescents.¹³⁴ 24.3% of German-language google searches on the topic of pruritus included AD, indicating that there may be an unmet need for patients specifically with symptoms of pruritus.¹³⁵ A nationwide survey of patients’ needs revealed that a top priority was “to be free of itching” (96.0% rated this as “quite important” or “very important”), followed by “to get better skin quickly” (87.7%) and “to be healed of all skin defects” (85.7%).¹³⁶

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German children who were diagnosed with AD at infancy and followed until age 10 were found to be at significantly increased risk for mental health problems and emotional symptoms at age 10; the association between these variables strengthened if AD was persistent the entire time.¹³⁷ An additional study found that infants with AD were at increased risk for developing hyperactivity/inattention at 10 years; the odds of developing emotional and/or behavioral problems were the highest with an infant diagnosis of AD,¹³⁸ onset before age four,¹³⁹ and comorbid sleep problems.¹³⁸ Romanos et al. found that AD and ADHD were independently associated with sleep difficulties but not with each other, and the authors posited that the observed association between AD and ADHD could be influenced by a lack of sleep.¹⁴⁰ A study that analyzed the effect of chronic conditions (of which AD made up a significant portion) on school performance in German first-graders found that children with chronic conditions and special healthcare needs performed worse than both healthy children and children with chronic conditions but no special healthcare needs.¹⁴¹

The Girolomoni et al study analyzing the psychosocial and economic burden attributable to moderate-to-severe AD examined a cohort of German patients as well. 16.4%, 19.5%, and 24.6% of patients had a moderate effect, very large effect, and extremely large effect of AD on reported DLQI, respectively.³⁴ 29.0%, 30.1%, and 9.8% of patients reported mild, moderate, and severe sleep difficulties, respectively. 29.5% of German patients reported anxiety, which was lower than other countries surveyed in the report including France (57.4%), Italy (51.3%), and the UK (61.5%), as well as across the EU5 (52.7%).³⁴ As measured by the PHQ-9, mild, moderate, moderately severe, and severe depression was experienced by 31.7%, 26.2%, 14.8%, and 8.2% of German patients, similar to other countries surveyed in the report.³⁴

This discrepancy highlights the importance of accounting for disease severity.

¹³²Beikert, F. C. et al. Willingness to pay and quality of life in patients with atopic dermatitis. *Arch Dermatol Res* 306, 279–286 (2014).

¹³³Matterne, U., Schmitt, J., Diepgen, T. L. & Apfelbacher, C. Children and adolescents’ health-related quality of life in relation to eczema, asthma and hay fever: results from a population-based cross-sectional study. *Qual Life Res* 20, 1295–1305 (2011).

¹³⁴Weisshaar, E. et al. Itch intensity evaluated in the German Atopic Dermatitis Intervention Study (GADIS): correlations with quality of life, coping behaviour and SCORAD severity in 823 children. *Acta Derm Venereol* 88, 234–239 (2008).

¹³⁵Zink, A. et al. Medical needs and major complaints related to pruritus in Germany: a 4-year retrospective analysis using Google AdWords Keyword Planner. *J Eur Acad Dermatol Venereol* 33, 151–156 (2019).

¹³⁶Augustin, M. et al. Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. *J Eur Acad Dermatol Venereol* 34, 142–152 (2020).

¹³⁷Schmitt, J. et al. Infant-onset eczema in relation to mental health problems at age 10 years: results from a prospective birth cohort study (German Infant Nutrition Intervention plus). *J Allergy Clin Immunol* 125, 404–410 (2010).

¹³⁸Schmitt, J. et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISApplus. *Allergy* 66, 404–411 (2011).

¹³⁹Genuneit, J. et al. Infant atopic eczema and subsequent attention-deficit/hyperactivity disorder—a prospective birth cohort study. *Pediatr Allergy Immunol* 25, 51–56 (2014).

¹⁴⁰Romanos, M., Gerlach, M., Warnke, A. & Schmitt, J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health* 64, 269–273 (2010).

¹⁴¹Hoffmann, I. et al. Chronic health conditions and school performance in first graders: A prospective cohort study. *PLOS ONE* 13, e0194846 (2018).

In adults, Schmitt et al. found that the risk for developing psychiatric comorbidities increased with AD severity.¹⁴² Compared to German adults without AD, German adults with AD were at increased risk for suicidal ideation, anxiety, and depression; the odds of experiencing suicidal ideation were 11 times higher in adults with AD compared to adults without.¹⁴³ Another study estimated the prevalence of suicidal ideation in German adults with AD to be 21.3%, with 3.9% of patients above the cutoff for acute suicidality. Again, severe AD was positively associated with suicidality in this population, indicating a possible unmet need for psychiatric screening.¹⁴⁴ A study comparing the happiness of patients with various chronic diseases found that patients with AD experienced significantly lower heuristic happiness and positive affect than the healthy control group, greater positive affect than patients with chronic IBD, and lower positive affect than patients with HIV.¹⁴⁵

An association was observed between German mothers with asthma, AD, or hay fever and a reduced numbers of children independent of reproductive ability; this may be because mothers with atopy, including AD, are reluctant to pass their condition on to their children.¹⁴⁶

The profound impacts of AD may be best illustrated by two studies that posed hypothetical scenarios in which patients could be cured of their AD for a price. In one study, patients with uncontrolled AD were willing to accept a 40% shorter life expectancy as a hypothetical tradeoff for curing their AD, on par with conditions such as severe angina pectoris, rheumatoid arthritis, multiple sclerosis, chronic anxiety, regional esophageal cancer, and interferon therapy for melanoma.¹⁴⁷ In contrast, a study examining willingness to pay (WTP) in German adults with AD found that patients would be willing to pay a median of €1,000 to cure their AD.¹³²



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Caregiver Burden

Among mothers of children with AD, single mothers (vs. mothers living with a partner) scored higher on measures of helplessness, aggression, and experiencing stress within the family; they scored lower on general life satisfaction.¹⁴⁸ This highlights a particularly vulnerable caregiver population that may benefit from targeted intervention. An analysis by Schut et al. found a significant association between parent-caregiver interest in educational interventions and dissatisfaction with medical care, low social support, and high active problem-solving behavior. I.e. parents and caregivers who scored highly in these areas were more likely to be interested in education interventions. The authors suggest that additional educational interventions may be more successful in this population.¹⁴⁹ Indeed, several interventions have focused on the German caregiver population and are discussed in the Interventions section.

Financial Burden

The financial burden for German patients with AD is comparable to other developed countries except for the US (which has higher costs). German patients had average annual costs ranging from €956 for mild AD to €1425 for severe AD; the direct cost of one flare was an average of €123.¹⁵⁰

The Girolomoni et al study examined work absenteeism, presenteeism, and overall work impairment in a German cohort of patients as well. Work absenteeism rates ranged from 22.4% to 38.3% in patients with moderate and extremely large effect to DLQI, respectively; work presenteeism rates ranged from 34.8% to 41.0%; and overall work impairment rates ranged from 40.4% to 64.4%.³⁴

¹⁴²Schmitt, J., Romanos, M., Pfennig, A., Leopold, K. & Meurer, M. Psychiatric comorbidity in adult eczema. *Br J Dermatol* 161, 878–883 (2009).

¹⁴³Dieris-Hirche, J., Gieler, U., Kupfer, J. P. & Milch, W. E. [Suicidal ideation, anxiety and depression in adult patients with atopic dermatitis]. *Hautarzt* 60, 641–646 (2009).

¹⁴⁴Dieris-Hirche, J. et al. Suicidal Ideation in Adult Patients with Atopic Dermatitis: A German Cross-sectional Study. *Acta Derm Venereol* 97, 1189–1195 (2017).

¹⁴⁵Schuster, B. et al. Happiness in dermatology: a holistic evaluation of the mental burden of skin diseases. *Journal of the European Academy of Dermatology and Venereology* 34, 1331–1339 (2020).

¹⁴⁶Karmaus, W. & Eneli, I. Maternal atopy and the number of offspring: is there an association? *Pediatr Allergy Immunol* 14, 470–474 (2003).

¹⁴⁷Schmitt, J., Meurer, M., Klon, M. & Frick, K. D. Assessment of health state utilities of controlled and uncontrolled psoriasis and atopic eczema: a population-based study. *British Journal of Dermatology* 158, 351–359 (2008).

¹⁴⁸Gieler, U. et al. Atopic Eczema and Stress among Single Parents and Families: An Empirical Study of 96 Mothers. *Acta Derm Venereol* 97, 42–46 (2017).

¹⁴⁹Schut, C., Mahmutovic, V., Gieler, U. & Kupfer, J. Patient education programs for childhood atopic dermatitis: who is interested? *J Dtsch Dermatol Ges* 10, 657–661 (2012).

¹⁵⁰Ehlsen, B. et al. [Cost-of-illness study in patients suffering from atopic eczema in Germany]. *Hautarzt* 56, 1144–1151 (2005).

Interestingly, there are published inpatient rehabilitation guidelines for patients whose AD severely limits their capacity to work and/or impairs everyday life. These comprehensive guidelines cover areas such as the need for and suitability of rehabilitation, prognosis, diagnosis, therapy goals and elements, and objective symptom evaluation.¹⁵¹

Treatment

Schmitt et al. found that AD patients were much more likely to be prescribed high-potency TCS than TCI and systemic corticosteroids than other systemic immunosuppressants. Systemic corticosteroids were prescribed at higher rates than cyclosporine (over 10% and less than 0.1%, respectively, in a sample of 11,555 patients with AD) despite the more favorable tolerability profile of cyclosporine compared to systemic corticosteroids.¹⁰ AD patients with concomitant atopic comorbidities were found to be prescribed TCS and systemic corticosteroids more often than AD patients without other atopic comorbidities; this may suggest that the AD phenotype may be more severe in patients with atopic comorbidities, or that the comorbid conditions themselves warranted additional steroid therapy. In either case, patients with AD and atopic comorbidities incur a greater treatment burden and potential side effects associated with systemic therapy.¹⁵²



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Concerns about the overuse of corticosteroids notwithstanding, several studies have found German AD patients to be relatively satisfied with their treatments—unlike in most other COI. In the Atopic Health study, 82.1% of patients reported high satisfaction with treatment, and 88.4% of patients reported a therapeutic benefit.¹³¹ Also, 75.8% of patients in the Atopic Health study felt as though their treatment regimens were not bothersome or were only moderately so.¹³⁰ Topical TCIs were well-liked by patients; 76.5% of patients rated the efficacy as “good,” and 83.1% of patients rated the tolerability as “good.”¹⁵³ Topical therapy was associated with a significant improvement in QoL scores in both adults and children with AD.¹⁵³

As in other COI, some caregivers choose to pursue homeopathic/CAM therapies, but this approach is usually not supported by empirical evidence. Parents of children with mild-to-moderate AD did not find any therapeutic benefit to homeopathic therapy relative to conventional therapy. Furthermore, adjusted costs in the homeopathic group were €935.02 at 6 months and €1524.23 at 12 months compared to €514.44 at 6 months and €721.21 at 12 months in the control group.¹⁵⁴ A study of the long-term outcomes of homeopathic therapy vs. conventional therapy found once again that homeopathic therapy did not outperform conventional therapy in the long-term and was associated with increased costs.¹⁵⁵

¹⁵¹Buhles, N., Wehrmann, J., Hinsch, K.-D. & Nürnberg, W. S1 Guideline: Dermatological inpatient rehabilitation in adult atopic dermatitis*. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 9, 558–561 (2011).

¹⁵²Werner-Busse, A., Kostev, K., Heine, G. & Worm, M. Impact of comorbidities on the treatment of atopic dermatitis in clinical practice. Int J Clin Pharmacol Ther 52, 726–731 (2014).

¹⁵³Sunderkötter, C., Weiss, J. M., Bextermöller, R., Löffler, H. & Schneider, D. [Post-marketing surveillance on treatment of 5,665 patients with atopic dermatitis using the calcineurin inhibitor pimecrolimus: positive effects on major symptoms of atopic dermatitis and on quality of life]. J Dtsch Dermatol Ges 4, 301–306 (2006).

¹⁵⁴Witt, C. M. et al. Homeopathic versus conventional therapy for atopic eczema in children: medical and economic results. Dermatology 219, 329–340 (2009).

¹⁵⁵Roll, S. et al. Comparative effectiveness of homeopathic vs. conventional therapy in usual care of atopic eczema in children: long-term medical and economic outcomes. PLoS One 8, e54973 (2013).

Healthcare

Utilization

The Girolomoni et al study analyzing the psychosocial and economic burden experienced by patients with moderate-to-severe AD examined healthcare provider visit rates, emergency room visit rates, and hospitalization rates within a 6-month period preceding the survey in a German cohort of patients as well. These rates were reported among patients with moderate, very large, and extremely large effects to DLQI; statistically significant differences were observed among the DLQI groups within emergency room visit rates (0.28%, 0.34%, and 0.88% of patients, respectively) and hospitalization rates (0.28%, 0.34%, and 1.12%, respectively).³⁴ Additionally, a study by Schmitt et al found that adult AD patients accounted for 60% of all outpatient visits for AD.¹²³

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Satisfaction with Care

In the Atopic Health survey, 49.4% of patients reported their health care as either “good” or “very good,” 37.3% of patients assessed their healthcare as “moderate,” and 13.3% of patients felt that the care they received was either “bad” or “deficient.”¹³¹ A cross-sectional study performed on two years of survey data from an AD outpatient unit in Dresden found that important determinants of treatment satisfaction included the professional competence of the physician (most important), the physician’s sensitivity, disease severity, education about the condition, and the patient’s ability to adjust treatment with disease activity.¹⁵⁶

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Two studies have characterized the treatment goals of AD patients. In the first study, important treatment goals included complete skin clearing and minimizing itch and burning; a reduction in disease severity accounted for only 20% of the entirety of treatment satisfaction.¹⁵⁷ Similarly, in the second study, patients cared most about the healing of all skin changes (88.3%), decreasing itch and burning (73.3%), reducing healthcare visits, avoiding severe side effects, improving psychological well-being, and reducing the time spent administering treatment. Interestingly, a large majority of physicians agreed that a treatment priority was the reduction of itch and burning (93.9%).¹⁵⁸

Patient-Centered Interventions

The German Atopic Dermatitis Intervention Study (GADIS) sought to determine whether educational interventions could improve QoL parameters in caregivers.¹⁵⁹ In parents of children aged 3 months to 7 years, the intervention (relative to an untreated control group) significantly increased caregivers’ psychosomatic wellbeing, confidence in medical treatment, emotional coping, and acceptance of disease, and the intervention significantly decreased the effects of the child’s AD on the caregiver’s social life. Parents of children aged 8–12 years experienced significant improvements in their confidence in medical treatment, emotional coping, and acceptance of disease.¹⁵⁹

¹⁵⁶Schmitt, J., Csötönyi, F., Bauer, A. & Meurer, M. Determinants of treatment goals and satisfaction of patients with atopic eczema. *J Dtsch Dermatol Ges* 6, 458–465 (2008).

¹⁵⁷Breuer, K. et al. Predictors of benefit from an atopic dermatitis education programme. *Pediatric Allergy and Immunology* 25, 489–495 (2014).

¹⁵⁸Zschocke, I., Hammelmann, U. & Augustin, M. [Therapeutic benefits in dermatological therapy. Evaluation of therapy from the physician’s and patient’s perspective in psoriasis and atopic dermatitis]. *Hautarzt* 56, 839–842, 844–846 (2005).

¹⁵⁹Staab, D. et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ* 332, 933–938 (2006).

Caregivers have been the primary focus of two other interventional studies. In an evaluation of individually tailored nursing consultations for the caregivers of children with AD, 90% of caregivers found the intervention to be highly supportive 14 days after the original consultation. Areas of significant improvement included increased self-efficacy regarding treatment recommendations, the frequency of moderate and severe symptoms, and scores for sleep disruption and pruritus.¹⁶⁰ Breuer et al. sought to determine factors that predict the long-term success of parent-oriented educational interventions; “success” was defined by improvements in the parent’s QoL, the child’s SCORAD, TCS use, and knowledge of AD. Parents with poor past treatment experiences who scored worse on measures of coping skills benefited most from the intervention; the association was even stronger for these parameters than for the child’s SCORAD at baseline.¹⁵⁷

Kupfer et al. expanded on these findings to determine if educational interventions could bolster the psychological coping abilities of both caregivers *and* the children themselves.¹⁶¹ Children in the intervention group scored significantly better on both measures: anxious or depressive mood and itching/scratching behavior. Parents in the intervention group improved in three out of the four domains: anger toward the child’s scratching, seeking to control their child’s scratching, and poor experience with treatment; they did not significantly improve on overprotective behavior. The authors also sought to determine whether the improvements were attributable to or independent from a reduction in disease severity (quantified via SCORAD); interestingly, the children’s improvement was independent of the change in disease severity, while the parents’ improvement was not.¹⁶¹



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¹⁶⁰Rolinck-Werninghaus, C., Trentmann, M., Reich, A., Lehmann, C. & Staab, D. Improved management of childhood atopic dermatitis after individually tailored nurse consultations: A pilot study. *Pediatr Allergy Immunol* 26, 805–810 (2015).

¹⁶¹Kupfer, J. et al. Structured education program improves the coping with atopic dermatitis in children and their parents—a multicenter, randomized controlled trial. *Journal of Psychosomatic Research* 68, 353–358 (2010).

KEY FINDINGS

While studies in the US have identified a wide range of comorbid associations, comorbidity studies in Germany have focused on inflammatory disorders, indicating a potential need for broader population-wide studies. However, the German literature comprehensively describes comorbid mental health associations in children with AD. The in-depth investigations into sleep and ADHD are particularly interesting, especially the finding that sleep disturbances may confound the observed association between AD and ADHD.¹⁴⁰

Although German AD patients appeared to have worse DLQI scores than US AD patients, the difference seems attributable to the focus on moderate disease severity in the Germany study.^{4,130} Studies with comparable patient populations would be more useful for drawing country-wide comparisons. In lieu of studies with common, reproducible methodologies, it may be possible to draw comparisons with hypothetical negotiations for disease clearance (e.g., adults with uncontrolled AD would be willing to accept a 40% shorter life expectancy¹⁴⁷ and to pay €1,000,132 in exchange for disease clearance).

Compared to patients in other COI, German patients seem more satisfied with their care, more satisfied with treatment options, and more amenable to using TCS, though it is hard to draw robust cross-national comparisons in the absence of standardized satisfaction measures. A major development in Germany has been the successful implementation of educational interventions, with improvements in the QoL parameters of both children with AD and their caregivers as well as a reduction in disease severity. The GADIS trial and subsequent studies of the effectiveness of educational interventions make Germany a leader in this regard and may provide a model with which other countries may begin to address unmet needs.

