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Received: 8 August 2022 | Accepted: 9 November 2022

DOI: 10.1111/jdv.18848

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

SYSTEMATIC REVIEW

Quality of life in children and adolescents with alopecia areata—A systematic review

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Funding information
Deutsche Stiftung Kinderdermatologie, Grant/Award Number: NA

Abstract

Alopecia areata (AA) is an autoimmune-mediated non-scarring hair loss whose stigmatizing effect may have a severe psychosocial impact. AA has been reported to be correlated with bullying, reduced quality of life (QoL) and psychiatric comorbidities. The effect of AA on QoL in adult patients has been systematically reviewed and found to be detrimental. No systematic evaluation of QoL in children with AA has been performed. The aim of this review is to systematically describe QoL in the child and adolescent population affected by AA. A systematic review of multiple databases and grey literature sources was conducted. Search terms included, but were not limited to, alopecia areata and quality of life. Only studies reporting results on health-related QoL in children and adolescents were included. We evaluated the studies regarding the risk of bias, and conceptual rigour concerning the quality of life and performed a descriptive synthesis of findings. Eight studies met the inclusion criteria, encompassing 358 participants with AA and 64 healthy peers. Seven studies were quantitative using four different standardized questionnaires and scores to measure QoL. One study used a qualitative design. All studies described impairment of children and adolescents' QoL by AA. The most consistently affected QoL domain was embarrassment and self-consciousness. Further psychosocial implications of AA included bullying and limiting participation in school or spare time activities. Existing evidence indicates a substantial impact of AA on QoL in children. In daily clinical practice as well as for developing new treatments QoL in paediatric AA plays a critical role. It should be considered a key outcome in clinical research and decision-making.

INTRODUCTION

The WHO defines Quality of Life (QoL) as a broad concept of 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns'.[1] Health-related quality of life (hrQoL) is a more focused, multidimensional concept relevant to a person's health. Definitions differ, but the considered domains usually encompass the 'physical, role functioning, social, and psychological aspects of well-being and functioning'. This includes objective as well as subjective perspectives on all dimensions.[2,3]

Alopecia areata (AA) is an autoimmune-mediated disorder characterized by partial or complete non-scarring hair loss whose stigmatizing effect may have a severe psychosocial impact on the affected. The prevalence of AA in children and adolescents is estimated at 1.83% (95% CI: [1.21–2.58]) which is significantly higher than in adults.[4] AA has been shown to be correlated with bullying, poor QoL and psychiatric comorbidities such as clinical depression and anxiety disorders.[5–8] Whilst the evidence of the effect of AA on QoL in adult patients has been systematically reviewed and found to be detrimental,[6,7,9] to the best of our knowledge until now no summary of the available evidence has been performed in the

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paediatric population. In 40% of patients, the first AA manifestation occurs by the age of 20 years.[10] Moreover, the onset of AA during childhood has been reported to be associated with more severe disease and poorer prognosis.[11] This illustrates the importance of gaining an understanding of how this disease affects young people. Children may handle the social and psychological burden of the disease differently from adults due to the age-dependent development of individual coping mechanisms and social mechanisms in their peer group.[12] Different age or sex groups may experience the impact of AA differently, as shown by Wolf and Baker.[13] They report that girls experience a greater psychological effect and more difficulty with social interactions caused by their AA than boys. Additionally, late-onset, as well as age, were associated with a more negative impact on self-acceptance and confidence.

The main aim of this review is to systematically describe hrQoL in the paediatric population affected by AA. The secondary objectives are to summarize the possible impact of AA on hrQoL on different groups of children and adolescents.

METHODS

Registration

This systematic review was conducted following the PRISMA statement[14] and was registered with PROSPERO (record number CRD42020205503).[15]

Eligibility criteria

The eligibility criteria were primary study reports reporting quantitative or qualitative evidence on QoL of patients with a medically confirmed diagnosis of AA under the age of 18 in otherwise good health. Studies that only included questionnaires for the diagnosis of psychiatric diseases were excluded as these were not considered measurements of QoL. We did not apply language restrictions and excluded literature published before 1975.

Information sources

We performed searches in Web of Science, Medline and Embase via Ovid, the Cochrane Library and CINAHL and PsychINFO via EBSCO. To also include grey literature, we further searched Ethos, Zetoc Conference Search, ClinicalTrials.gov, CenterWatch, CDC Wonder, opengrey.eu, grey literature report, ProQuest Dissertations and Theses, www.worldcat.org for theses and dissertations, the Catalogue of the German National Library and the Charité library's own literature search engine Primo. Additionally, we performed a search on Google Scholar and considered the first 100 results as shown in the order of relevance, since it is difficult to limit the search further and extract the articles. Search string example for Medline and Embase, see Appendix S1.

Search strategy

The search term in all searches consisted of 'alopecia areata' (or synonyms) and ('quality of life' or 'life quality') as keywords and associated mesh terms. For Google Scholar, we added 'and child*' (or synonyms) to the search term narrowing down the search results. For the other searches, we decided to not include 'and child*' (or synonyms) in the search terms, due to the risk of falsely excluding articles. All searches were first performed on the 30th of June 2020 and reperformed to check for new literature on 16 December 2021 by MP. References found in the relevant publications were screened for additional relevant studies. Identified relevant publications were used for a forward search via Web of Science.

Selection process

Two reviewers (MP and VK-S) screened the retrieved titles and abstracts independently for the eligibility criteria. Any disagreements between reviewers were resolved by consensus or a third party (JK, UB-P, AV).

Full articles of all potentially relevant studies were obtained and examined for eligibility independently by two reviewers (MP and VK-S). Discrepancies between the reviewers were again resolved by consensus or by consulting a third author (JK, UB-P). If the study included both children and adults but did not clearly distinguish between the two groups when reporting results, then the study authors were contacted for further information and clarification if the study otherwise met the eligibility criteria and was included in the newly attained information rendered it eligible. If the asked information was not provided or demonstrated that the study is not eligible, it was excluded.

Data collection process

One reviewer (MP), using standardized extraction forms, conducted data extraction from included studies. Another reviewer (RS) cross-checked the extracted data independently. Discrepancies between the reviewers were again resolved by consensus or by consulting a third author (JK, UB-P).

Data items

Authors, years, year and location of data collection, study design, study aims and purposes, funding, sample size and characteristics as well as used methods were extracted. If standardized instruments to measure QoL were used, the name of the instrument and mean and spread estimates per sample were documented. If the study used qualitative methods, general themes, and first- and second-order constructs were extracted.

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Synthesis methods

A descriptive synthesis of the results was conducted. Based on the quality of reporting and risk of bias, we summarized hrQoL across studies for each hrQoL measure. Considering the comparability, hrQoL domains (e.g. physical, social, emotional) were compared across hrQoL measures. Qualitative data was described in a summary.

Certainty assessment

Critical appraisal tools for cross-sectional, case studies, cohort studies and qualitative research by the Joanna Briggs Institute[16–19] were used to describe of risk of bias. To assess the QoL research-specific methodological and conceptual rigour we used the modified criteria by Gill and Feinstein.[20]

RESULTS

Study selection

The search yielded 205 results on the Web of Science, 442 results on Medline and Embase via Ovid, 59 results on CINAHL and PsycINFO via Ebsco, 50 results via the Cochrane Library, and 159 results in total from the grey literature sources. Additionally, we considered the 100 top-rated articles of the 2030 results from the Google Scholar Search. Deduplicating resulted in 690 articles. Evaluation of the title and abstract deemed 144 articles worthy of further consideration. We contacted 41 authors for additional information, of which 4 replied, though none with information that rendered the article eligible for inclusion. Five articles had to be translated because their full text was not available in English or German. Eight articles met the criteria in the full-text screening and were included for data extraction and synthesis (See Figure 1). These articles were used for a forward search on the Web of Science, which produced 82 results. Deduplication resulted in 65 studies which had not yet been considered before. Forty-seven were excluded by abstract, the remaining five after assessing the full text and none were included. Seven articles in the included studies' reference lists were considered potential candidates by title, but all were excluded when screening their abstracts.

Study characteristics

Eight studies with a total number of 358 paediatric AA patients and 64 healthy children in control groups were included. All but one study used quantitative designs: five cross-sectional studies,[21–25] of which one included a comparator group,[21] one case study of two cases[26] and one validation study using a prospective cohort design.[27] One study was qualitative using a semi-structured interview[28] (Table 1). The patients were sampled in the USA (5 studies),[22–24] Turkey (2 studies)[21,26] and Mexico (1 study).[25] Five studies did not give information on the time of data collection.[21,22,26] The other three collected their data between 2016 and 2018.[23–25] There was no overlapping data arising from the primary studies in the included papers. The cross-sectional studies had a

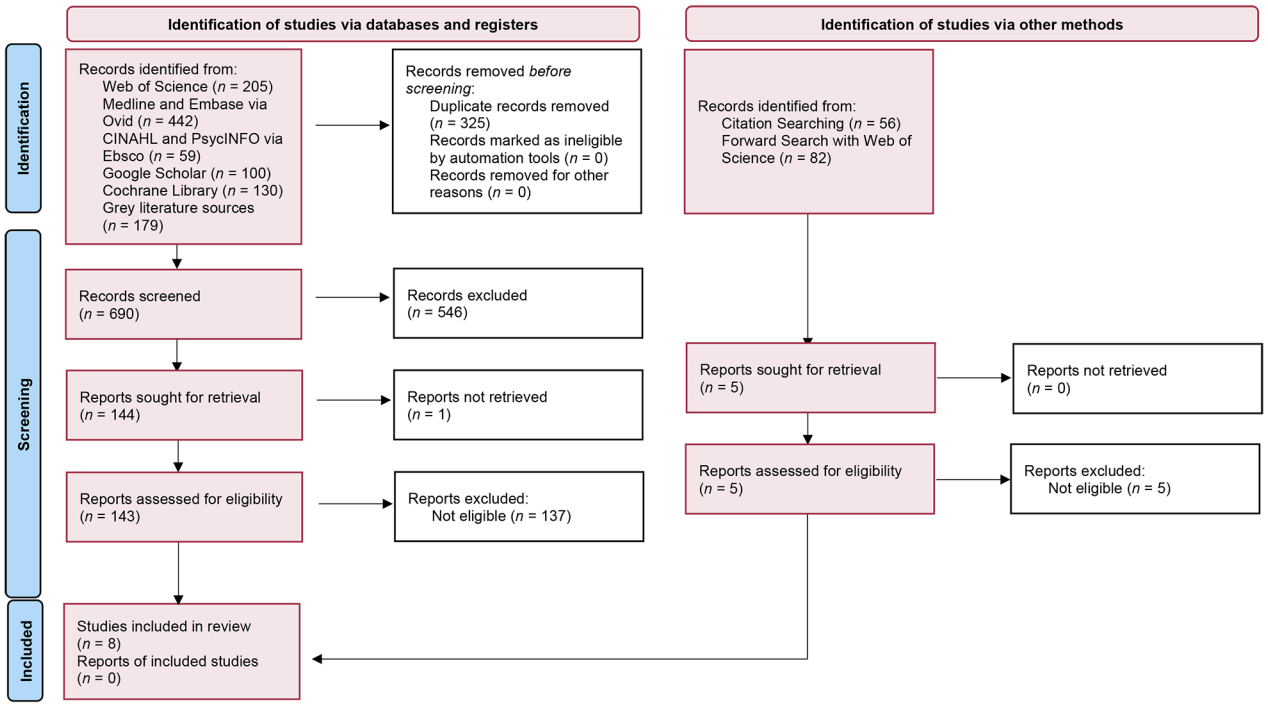

FIGURE 1 PRISMA 2020 flow diagram: Search findings, exclusions and a number of included studies.

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TABLE 1 Studies included in a systematic review.

Reference	Study design	Location, time	Study aims and purposes	Funding
O. Bilgic, A. Bilgic, K. Bahali, A. G. Bahali, A. Gurkan and S. Yilmaz 2014 *Psychiatric symptomatology and health-related quality of life in children and adolescents with alopecia areata*	Cross-sectional with comparison	Turkey, No information on the time of data collection	Assess depression, anxiety and QoL levels of children and adolescents with AA, examine the association between psychological functioning and clinical variables related to AA, test determinants of QoL in these patients	Not described
T. Christensen, J. S. Yang and L. Castelo-Soccio 2017 *Bullying and Quality of Life in Paediatric Alopecia Areata*	Cross-sectional study	USA, No information on the time of data collection	Investigate prevalence of bullying and surrounding emotional impact of AA in paediatric patients	The Children's Hospital of Philadelphia, The University of Pennsylvania Undergraduate Research Mentoring Program
T. Kara and Z. Topkarcı 2018 *Interactions between Posttraumatic Stress Disorder and Alopecia Areata in Child with Trauma Exposure: Two Case Reports*	Case study of 2 cases	Turkey, No information on the time of data collection	Emphasize the need for consideration of consultation-liaison psychiatry in patients with acute hair loss symptoms	Not described
L. Liu, B. King and B. Craiglow 2017 *Alopecia areata is associated with impaired health-related quality of life amongst affected children and their families*	Cross-sectional	USA, 07/2016	Explore the impact of AA on affected children and their families using validated dermatology-specific HRQoL instruments	Not described
E. Putterman, D. P. Patel, G. Andrade, K. L. Harfmann, M. Hogeling, C. E. Cheng, C. Goh, R. S. Rogers and L. Castelo-Soccio 2019 *Severity of disease and quality of life in parents of children with alopecia areata, totalis, and universalis: A prospective, cross-sectional study*	Cross-sectional	USA, 04/2017–07/2018	Describe and evaluate QoL in parents of paediatric patients with all subtypes of alopecia areata, investigate the relationship between QoL and severity of disease, duration of disease, age of patient	Paediatric Dermatologic Research Alliance Grant
R. D. Velez-Muniz, M. Peralta-Pedrero, F. J. S. Cruz and M. A. Morales-Sanchez 2019 *Psychological profile and quality of life of patients with Alopecia areata*	Cross-sectional	Mexico, 03/2017–02/2018	Determine the prevalence of mental disorder symptoms and QoL amongst Mexican patients with mild and severe forms of AA, analyse if there is an association between the severity of AA and their psychological profile	Centro Dermatologico 'Dr. Ladislao de la Pascua'

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TABLE 1 (Continued)

Reference	Study design	Location, time	Study aims and purposes	Funding
K. W. Wyrwich, R. Winnette, R. Bender, K. Gandhi, N. Williams, N. Harris, L. Nelson 2021 *Validation of the Alopecia Areata Patient Priority Outcomes (AAPPO) Questionnaire in adults and adolescents with alopecia areata*	Prospective	USA, No information on the time of data collection	Conduct a noninterventional, quantitative evaluation consistent with the requirements of the FDA's patient-focused guidance to determine the optimal structure and scoring algorithm, to assess the psychometric properties of the AAPPO, including reliability and construct validity	Under contract with RTI Health Solutions and Pfizer, study funded by Pfizer
R. Winnette, S. Martin, N. Harris, L.S. Deal 2020 *Development of the Alopecia Areata Patient Priority Outcomes instrument: a qualitative study*	Qualitative	USA, No information on the time of data collection	Explore the consequences and priority treatment outcomes of adults and adolescents with AA, [...] develop a patient-reported outcome (PRO) measure consistent with current regulatory expectations and representing clinical benefit from the AA patient perspective	Pfizer Inc., RTI Health Solutions

mean number of 62.6 including patients with a range of 32–91 participants. Three studies did not report the proportions of sex.[23–25] The other studies with more than two patients had female-to-male ratios between 0.75 and 1.0.[21,22,27,28] The case study comprised two male patients.[26] Only three studies reported mean age, 12.1, 14 and 15 years.[21,27,28] The case study described the patient's extent of AA clinically; one study rated AA severity as mild, moderate or severe.[22,26] The Alopecia Areata Patient Priority Outcomes (AAPPO) development and validation studies reported severity as ordinal Severity of Alopecia Tool (SALT) score categories.[27,28] Two studies measured the SALT Scores[29] but did not report them separately for the paediatric subgroup[24,25] (Table 2).

QoL-specific conceptual rigour

None of the articles provided definitions of QoL and only three stated the domains they measured as components of QoL.[21,24,26] Three articles gave reasons for choosing the used methods or instruments,[22,24,28] whilst six aggregated multiple items, domains or instruments into a single composite score for QoL.[21,24–27,30] Global ratings of QoL by the patients themselves were not provided. Two articles referred to hrQoL,[21,30] none of the included papers explicitly distinguished overall QoL from hrQoL (Table 3). Therefore, we do not distinguish between the two in the following presentation of results.

Risk of bias

The included case report met all applicable Risk of Bias criteria, except for clearly describing the post-interventional clinical condition[26] (Table 4). The qualitative study fulfilled all Risk of Bias criteria except locating the researcher theoretically and addressing his influence on the research[28] (Table 5). Three of the cross-sectional studies clearly defined the inclusion criteria.[21,24,25] None of the cross-sectional studies described the study subjects and settings in detail for the paediatric study population exclusively considered in this review. All articles used objective, standard criteria for the diagnosis of AA. Three articles reported confounding factors,[21,24,25] but none stated strategies to deal with them. All but one study - which used a self-constructed survey not included in the publication[22]—measured QoL in a valid and reliable way. Three cross-sectional studies used appropriate statistics,[21,24,25] whilst this is unclear for the other two[22,23] (Table 6). The cohort study met all but two applicable Risk of Bias criteria: It did not state strategies to deal with confounding factors and it is unclear if the participants were free of the outcome at the beginning of the study[27] (Table 7).

Measurement of QoL

To evaluate QoL, one study applied the Paediatric Quality of Life Inventory (PedsQL), an instrument with a self- and

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TABLE 2 Health-related quality of life in the included literature

Reference	Sample size	Sample characteristics	Method	Instrument	Results
Bilgic et al. (2014)	Total: *n* = 138 Patients with AA: *n* = 74 Comparator group: *n* = 64	Patients with AA: • age: mean 12.1 years (SD 2.8), range 8–18 years • sex: 44.6% female • age of onset: mean 11.0 years (SD 3.1) • duration of illness: mean 13.5 (SD 26.8) months • parents' education level: father mean 7.2 (SD 3.1) years, mother mean 5.5 (SD 3.2) years Comparator group: • age: mean 12.3 years (SD 2.9), range 8–18 years • sex: 53.8% female • parents' education level: father mean 7.9 (SD 3.4) years, mother mean 6.3 (SD 2.5) years	Patients/healthy peers and caregivers filled out a validated QoL instrument as self- and proxy report (resp.)	PedsQL[a] reporting total score with domains physical and psychosocial health	Patients with AA • Proxy mean score 70.3 (SD 13.4) • Proxy mean score 8–12 years 72.1 (SD 13.0) • Proxy mean score 13–18 years 68.2 (SD 75.9[b]) • Self mean score 74.0 (SD 13.4) • Self mean score 8–12 years 72.3 (SD 14.5) • Self mean score 13–18 years 76.1 (SD 11.8) Comparator group: • Proxy mean score 77.6 (SD 11.9) • Proxy mean score 8–12 years 79.1 (SD 10.4) • Proxy mean score 13–18 years 75.9 (SD 13.1) • Self mean score 78.5 (SD 10.0) • Self mean score 8–12 years 76.7 (SD 10.5) • Self mean score 13–18 years 80.1 (SD 9.2)
Christensen et al. (2017)	*n* = 69	Age: 5–11 years: 49.3%, 12–14 years: 21.7%, 15–19: 29% Sex: 50.7% female AA severity is classified as mild (47.8%), moderate (30.4%) or severe (21.7%)	Patients and caregivers filled out a self-developed survey, as self- and proxy-report (resp.)		Experiencing bullying: 23% • by age: 5–11 years: 17.6%, 12–14 years: 13.3%, 15–20 years: 40% • by sex: female: 17.1%, male: 38.2% Others notice or comment on AA: • by age: 5–11 years: 76.5%, 12–14 years: 21.9%, 15–20 years: 23.5% AA effects QoL: • by age: 5–11 years: 53.3%, 12–14 years: 66.7%, 15–20 years: 40% AA limits participation in activities: • by age: 5–11 years: 35%, 12–14 years: 75%, 15–20 years: 50% Embarrassment about AA: 48% Stayed home from school at least once because of AA: 33%
Kara et al. (2018)	*n* = 2	Sex: male Age: 9 and 10 years Alopecia areata circumscripta included. Clinical description of AA severity	Patients filled out a validated QoL instrument as self-report	CDLQI[c]	CDLQI scores: 8 and 15
Liu et al. (2017)	*n* = 91	No information given	Patients filled out a validated QoL instrument as self-report	CDLQI	Mean CDLQI Score: 6.3 (SD 5.9) Range CDLQI: 0–23
Putterman et al. (2019)	Total: *n* = 153 Participants filling out the CDLQI: *n* = 47	Alopecia areata circumscripta, universalis and totalis included	Patients filled out a validated QoL instrument as self-report	CDLQI	Mean CDLQI Score: 4.4 (SD 4.9) Range CDLQI: 0–22

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TABLE 2 (Continued)

Reference	Sample size	Sample characteristics	Method	Instrument	Results
Velez-Muniz et al. (2019)	*n* = 32	No information on the subgroup of children and adolescents given	Patients filled out a validated QoL instrument as self-report	CDLQI	Mean CDLQI score 2.25 (SD 0.96) • by sex: female: 2, male: 2.5 • by AA severity: SALT <25%: 4.36 (SD 3.96), SALT 25%–49%: 6 (SD 4.97), SALT 50–74%: 7, SALT 100%: 3.33 (SD 2.52)
Wyrwich et al. (2021)	*n* = 36	Age: mean 14.0 (SD 1.68) Sex: 44.4% female Occupation: 94.4% of students Alopecia areata circumscripta, totalis and universalis included. AA severity as SALT score distribution: • 25%–49% SALT: 16.7% • 50%–75% SALT: 8.3% • 76%–100% SALT: 75%	Patients filled out a QoL instrument as self-report	AAPPO (Alopecia areata patient priority outcomes)	Emotional symptoms mean score: 1.7 at baseline, 1.6 at 2-week follow-up Activity limitations mean score: 0.53 at baseline and 2-week follow-up
Winnette et al. (2020)	*n* = 7	Age: mean 15 (range 12–17) Sex: 42.9% female Alopecia areata circumscripta (57.1%), totalis (28.6%), universalis (14.3%), of eyebrows/eyelashes and nail changes included	Semi-structured interview by telephone using concept elicitation (for concept exploration) and cognitive debriefing (for concept confirmation) to confirm an AA consequence model developed upon the findings of a review of literature, instruments and FDA meeting materials review, self-report		*First-order constructs* e.g. 'I feel embarrassed because I look different than other people.' *Second-order constructs* • Assumptions and Ideas: Participants stated or agreed to statements aggregated in the following concepts: hard to participate in daily or outdoor activities, sadness, self-image/self-consciousness, frustrated, social interactions, embarrassed, worry, anxiety, anger, bullied, depressed, work or school productivity • Interpretations and Conclusions: Results and feedback consistent across adult and adolescent participants Participants found items comprehensive, easy to understand, simple to answer, did not identify key concepts missing from the items • Opinions: Final item set adequately and appropriately assesses priority consequences of AA to adolescents and adults

[a]Interpretation of PedsQL: score in percent between 0 and 100.

[b]No explanation for this conspicuously high standard deviation could be obtained from the authors.

[c]Interpretation of CDLQI: 0–1 = no effect on child's life, 2–6 = small effect, 7–12 = moderate effect, 13–18 = very large effect, 19–30 = extremely large effect.

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TABLE 3 Methodological and conceptual rigour in quality of life research (modified criteria by Gill and Feinstein 1994)

Reference	Definition of QoL given	Domains measured as components of QoL were stated	Reasons for choosing the used methods or instruments were given	Multiple items, domains or instruments were aggregated into a single composite score for QoL	Patients were asked to give their own global rating for QoL	Overall QoL was distinguished from hrQoL
Bilgic et al. (2014)	No	Yes	No	Yes	No	Not explicitly, but only refers to hrQoL
Christensen et al. (2017)	No	No	Yes	No	No	No
Kara et al. (2018)	No	No	No	Yes	No, but interview about general well-being by psychiatrist	No
Liu et al. (2017)	No	No	No	Yes	No	Not explicitly, but only refers to hrQoL
Putterman et al. (2019)	No	Yes, but only in proxy-report by caregiver	Yes	Yes	No	No
Velez-Muniz et al. (2019)	No	No	No	Yes	No	No
Wyrwich et al. (2021)	No	Yes	Not applicable	Yes	No	No
Winnette et al. (2020)	No	No	Yes	No	No	No

TABLE 4 Risk of bias of case studies

Reference	Patient's demographic characteristics clearly described	Patient's history clearly described and presented as timeline	Current clinical condition of patient at presentation clearly described	Diagnostic tests or assessment methods and the results clearly described	Intervention(s) or treatment procedure(s) clearly described	Post-intervention clinical condition clearly described	Adverse events (harms) or unanticipated events identified and described	Takeaway lessons described
Kara et al. (2018)	Yes	Yes	Yes	Yes	Yes	No	Not applicable	Yes

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TABLE 5 Risk of bias of qualitative studies

Reference	Congruity between stated philosophical perspective and research methodology	Congruity between research methodology and research question or objectives	Congruity between research methodology and methods used to collect data	Congruity between research methodology and representation and analysis of data	Congruity between research methodology interpretation of results	Statement locating researcher culturally or theoretically	Influence of researcher on research, and vice versa, is addressed	Adequate representation of participants, and their voices	Evidence of ethical approval by an appropriate body	Drawn conclusions flow from the analysis/ interpretation of the data
Winnette et al. (2021)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes

TABLE 6 Risk of bias of cross-sectional studies

Reference	Criteria for inclusion clearly defined	Study subjects and settings described in detail	Exposure measured in a valid and reliable way	Objective, standard criteria used for measurement of condition	Confounding factors identified	Strategies to deal with confounding factors stated	Outcomes (here: QoL) measured in a valid and reliable way	Appropriate statistical analysis used
Bilgic et al. (2014)	Yes	No	Not applicable	Yes	Yes	No	Yes	Yes
Christensen et al. (2017)	No	No	Not applicable	Yes	No	No	No	Unclear
Liu et al. (2017)	No	No	Not applicable	Yes	No	No	Yes	Unclear
Putterman et al. (2019)	Yes	No, overall study population described in detail, but not subpopulation that filled out CDLQI.	Not applicable	Yes	Yes	No	Yes	Yes
Velez-Muniz et al. (2019)	Yes	Unclear, no info on age and gender distribution of the subpopulation of children.	Not applicable	Yes	Yes	No	Yes	Yes

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TABLE 7 Risk of bias of cohort studies

Reference	Groups similar and recruited from the same population	Exposures measured similarly to assign people to both groups	Exposure measured in valid and reliable way	Confounding factors identified	Strategies to deal with confounding factors stated	Participants free of outcome at start of study or moment of exposure	Outcomes (here: QoL) measured in a valid and reliable way	Follow-up time reported and of sufficient length	Complete follow-up or reasons of loss to follow-up were explored	Strategies to address incomplete follow-up	Appropriate statistical analysis used
Wyrwich et al. (2021)	Not applicable	Not applicable	Yes	Yes	No	Unclear	Yes	Yes	Yes	Not applicable	Yes

proxy-report measuring physical and psychosocial disease-related health in the paediatric population.[21,31] The PedsQL Score is given as a percentage between 0 and 100 with higher values indicating a better QoL. One study used a non-validated self-constructed questionnaire.[22] The remaining three cross-sectional studies and the case study measured QoL with the Children's Dermatology Life Quality Index (cDLQI), a dermatology-specific self-report instrument.[22–26,32] The cDLQI score ranges between 0 and 30, with 0–1 indicating no effect on the child's life, 2–6 a small effect, 7–12 a moderate effect, 13–18 a very large effect and over 18 an extremely large effect. The qualitative study employed a semi-structured interview by telephone using concept elicitation (for concept exploration) and cognitive debriefing (for concept confirmation) to confirm an AA consequence model developed upon the findings of a review of literature, HrQoL instruments and FDA meeting materials review.[28] The resulting AAPPO questionnaire was tested by Wyrwich et al.[27] AAPPO scores vary between 0 (low QoL) and 4 (high QoL) and are given for physical items as well as two psychosocial domains (Table 2).

Results of individual studies

Bilgic et al. reported significantly worse psychosocial and total QoL in patients with AA as compared to healthy peers (e.g. parent-rated psychosocial: 70 vs. 79). Age of disease onset was positively correlated with parent-rated physical and total QoL ($r = 0.46$ and $r = 0.55$). Age of disease onset, location and severity of AA were not associated with QoL. In the structural equation modelling, the length of the disease predicted better self-rated physical QoL, whilst the severity of the disease predicted worse QoL. Age at disease onset predicted a better QoL score.[21]

Velez-Muniz et al.'s study reported a mean cDLQI of 2.25 (SD 0.96). In their study, 76.7% of children and adolescents had a QoL impairment by AA. Boys' QoL was worse than girls' (mean score 2.0 vs. 2.5 resp.). QoL did not differ in subgroups by family history, education level, SALT score, and disease duration.[25]

Putterman et al. measured a mean cDLQI of 4.4 (SD 4.9) with a range of 0 to 22. Physical symptoms and embarrassment or self-consciousness most prominently indicated impaired QoL in their study.[24]

Liu et al. reported a mean cDLQI of 6.3 (SD 5.9) with a range of 0%–23.78.1% of the patients had an effect of AA on their QoL. AA most frequently impacted the domains feelings of self-consciousness and skin symptoms. Clothing decisions and feelings of self-consciousness had the highest impact on QoL. Poor QoL in the child or adolescent was correlated with poor QoL in their family members ($r = 0.584$).[30]

In Christensen et al.'s study, 21.9%–75% of the patients reported that their AA had a negative impact on their QoL, increasing with age. Boys were bullied significantly more often than girls. Being bullied was significantly

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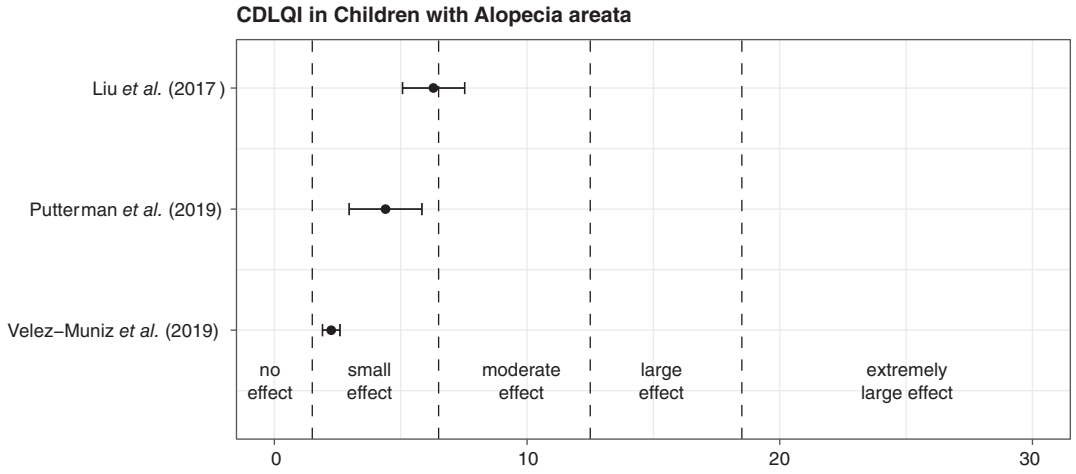

FIGURE 2 Arithmetic mean, 95% CI of CDLQI and its interpretation as disease's effect on HRQOL collected from paediatric AA patients as referenced in the literature.

less frequent in milder as compared to more severe AA. Having been bullied ranged from 13% (middle school) to 40% (high school) depending on age group. 23% of the entire patients had been bullied because of their AA. Further impairment of QoL was described in the form of others noticing or commenting, embarrassment about AA, staying home from school or AA limiting the participation in activities.[22]

Kara et al.'s case report captured cDLQIs of 8 and 15. In the psychological evaluation, the two patients reported 'a state of uneasiness, being easily startled, anxious appearance, wanting to sleep with the mother, not wanting to be alone at home, reluctance [or fear] to go to school, sleeping disorder, […] decline in school success', 'feeling tense, […] appetite and sleep deprivation [and] distress after reminders'.[26]

Winnette et al.'s qualitative study aggregated the interview contents to the psychosocial items of 'hard to participate in daily or outdoor activities, sadness, self-image/self-consciousness, frustrated, social interactions, embarrassed, worry, anxiety, anger, bullied, depressed and work [or] school productivity'. These items formed a priority outcomes questionnaire (AAPPO) found comprehensive and not missing key concepts by participants.[28]

Wyrwich et al. performed a validation study of the AAPPO. They reported activity limitations mean score of 0.53 and 0.53 as well as emotional symptoms mean score of 1.7 and 1.6 at baseline and 2-week follow-up, respectively. QoL tended to be worse for adolescents with lower SALT scores (25%–49%) than for those with more severe hair loss.[27]

DISCUSSION

This systematic review summarizes current evidence available on QoL in children and adolescents with AA.

General interpretation

All included studies reported an impairment of children and adolescents' QoL by AA. The cross-sectional studies using the cDLQI reported small to moderate negative effects of AA on QoL (see Figure 2) with ca. three-quarters of the included patients having their QoL negatively impacted by AA. The case study, on the other hand, estimated a higher impact on QoL. Additionally, paediatric patients with AA reported significantly worse QoL when compared to healthy peers via the PedsQL.

Across all included studies, the most consistently affected QoL domain was embarrassment and self-consciousness. Further prominent psychosocial implications of AA were being bullied, influencing clothing decisions and limiting participation in school or spare time activities. Physical implications such as skin symptoms were also reported frequently across studies. However, the one study explicitly investigating psychosocial and physical QoL separately with the PedsQL presents a higher degree of evidence for AA's negative impact on the psychosocial as compared to the physical QoL domain.[21]

Results on the influence of sex on QoL were limited in the included studies: In one study, boys were found to have significantly worse hrQoL in comparison to girls.[25] Boys were also reported to be more often subjected to bullying in another study.[22] QoL, in general, seems to aggravate puberty,[33] but the evidence of AA's negative impact on QoL of affected children or adolescents depending on age was contradictory in the included studies. In different studies, adolescents reported a higher rate of bullying,[22] increasing age of disease onset correlated with better hrQoL,[21] or QoL did not differ in subgroups by duration of disease.[25] Similarly, results regarding the influence of the severity of AA on QoL were contradictory: There was either no effect,[25] higher AA severity was associated with better hrQoL,[27] predictive of decreased hrQoL,[21] or associated with an increased incidence of bullying.[22] This is mirrored in

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the literature by evidence that QoL is not correlated with physician's assessment of severity of hair loss in adults.[34]

Limitations of included studies

The total number of studies covering QoL in paediatric AA is surprisingly low, comprising a total number of 358 included participants. In contrast, according to the estimated world child population of over 2 billion in 2021 with an AA prevalence of 1.92%, more than 38.4 million children worldwide are currently experiencing AA.[4,35] The data collection of all the identified studies were done in only three countries, none of them European.

The risk of bias assessment reveals that some of the studies' results have limited credibility. Moreover, the heterogeneity of the employed instruments for the survey of QoL renders the results only conditionally comparable. Thus, available data must be interpreted with caution due to possible reporting bias, and conclusions must be drawn cautiously.

The reported CDLQI values indicating only a small effect of AA on QoL raise the question of the instrument's suitability to depict QoL in AA. Studies investigating CDLQI in children and adolescents with other dermatological diseases such as atopic dermatitis, vitiligo, leprosy and psoriasis in a medical setting report mean values of 1.5–12.2 with maximum mean values in patient groups with severe acute dermatitis, congenital ichthyosis and scabies.[36–40] The mean CDLQI values in these studies do not occupy the full instrument scale up to 30. This may indicate that the CDLQI's higher end of the scale might be reached by individual patients but usually not by the mean of a study population. Additionally, the only small effect measured by the CDLQI might be traced back to the instrument having been designed specifically for skin-related and not hair-related diseases. A disease-specific instrument—as developed by Wyrwich et al. for adolescents—may be more suitable to accurately depict QoL in AA. Moreover, CDLQI inquires exclusively about symptoms of the previous week. A chronic disease that impacts appearance, such as AA, especially leads to problems during a change in the social environment. Thus, in AA it may be more appropriate to measure symptoms over a longer time period.

Limitations of review

Although multiple databases as well as grey literature sources were used for the identification of potentially eligible studies, this review might still not have found all existing literature. Since not enough studies using the same QOL instrument could be included to conduct a meta-analysis, the synthesis is only descriptive.

Implications

The included studies in this review reveal a clear overall impact of AA on Qol in the child and adolescent population whilst data do not allow to draw clear associations with individual characteristics such as age or severity of AA. Comparing the global estimate of more than 38.4 million children with AA to the 358 considered for QoL research in the retrieved literature highlights a lack of adequate investigation in current research activities. As can be seen in Figure 3, the QoL of paediatric patients with AA seems to have only been of interest to the scientific research community within the last 12 years with fluctuating numbers of investigated children with AA in the identified literature. Considering children and adolescents as an especially vulnerable population whilst looking at their mental development, there is an immediate need to raise awareness for the psychological burden of AA in the paediatric population. With the existing data demonstrating a negative effect of AA on children's QoL, further research

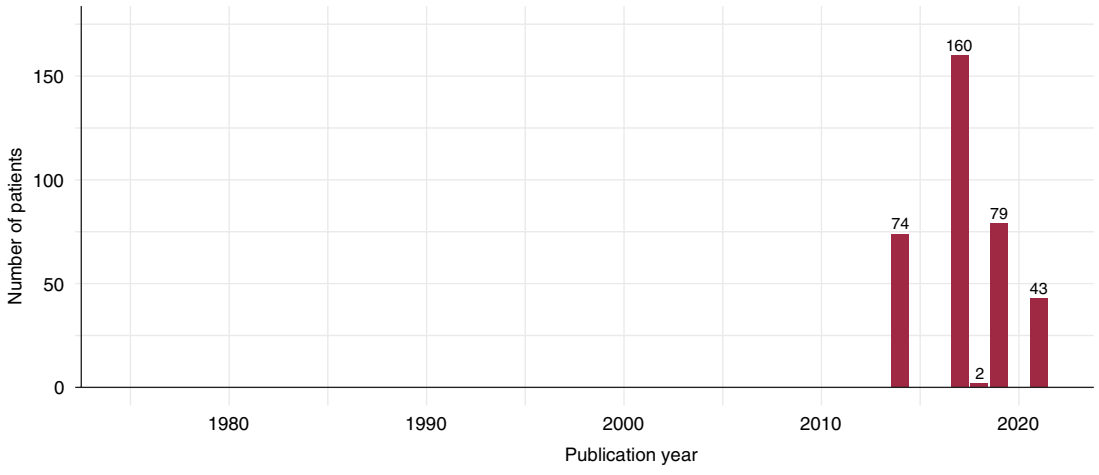

FIGURE 3 Number of paediatric AA patients whose hrQoL was referenced in the scientific literature by year from 1975 to 2021.

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on this topic is needed to gather more evidence and increase recognition. Moreover, due to cultural reasons, the results may not be generalizable to other countries as cultural factors influence the way dermatologic conditions affect QoL.[41] Therefore, to gain a more comprehensive understanding of the effect AA has on children's and adolescents' QoL, studies from a multitude of countries are especially desirable. The discrepancies between clinical assessment of hair loss severity and its influence on the patient's QoL must be taken under consideration in clinical decision-making and clinical trial design. QoL should be considered a key outcome in future studies.

AUTHOR CONTRIBUTIONS

Idea and conception: UB-P. Review protocol and search strategy: MP, VK-S, JK, UB-P and AV. Literature search and manuscript retrieval: MP. Evaluation of literature eligibility: MP, VK-S, AV, UB-P, JK, DW and KH. Data extraction, analysis, and interpretation: MP, DW, KH, RS and UB-P. Writing of original manuscript: MP. Revision of manuscript: MP, VK-S, AV, UB-P, JK, DW, KH and RS.

ACKNOWLEDGEMENTS

Our sincere thanks to Dr. Sayedmohammad Hasheminasab and Prof. Özlem Dicle for their support in screening the Iranian and Turkish articles. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

MP's work was partly financed by Deutsche Stiftung Kinderdermatologie.

CONFLICT OF INTEREST

MP, VK-S, DW, KH, RS and JK have no conflict to declare, AV has received honoraria for lectures on hair diseases from Bayer, Galderma, Johnson&Johnson, Pierre Fabre, and UB-P has been an advisor to AbbVie, Galderma, Leo, Lilly, Neuroderm, Sanofi Regeneron, Novartis, Pfizer and Pierre Fabre.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Prendke M, Kanti-Schmidt V, Wilborn D, Hillmann K, Singh R, Vogt A, et al. Quality of life in children and adolescents with alopecia areata—A systematic review. J Eur Acad Dermatol Venereol. 2023;37:1521–1534. https://doi.org/10.1111/jdv.18848

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