National Institute for Health and Care Excellence

Draft for consultation

Acne vulgaris: management

[L] Evidence review for risk factors for scarring due to acne vulgaris

NICE guideline number tbc

Evidence review underpinning recommendations 1.2.4 and 1.4.4 and a research recommendation in the NICE guideline

December 2020

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Risk factors for scarring due to acne vulgaris 6
Review question 6
Introduction 6
Summary of the protocol 6
Methods and process 6
Clinical evidence 7
Summary of clinical studies included in the evidence review 7
Quality assessment of included studies in the evidence review 8
Economic evidence 8
Economic model 8
Evidence statements 8
The committee's discussion of the evidence 9
Recommendations supported by this evidence review 10
References 10
Appendices 11
Appendix A – Review protocol 11
Review protocol for review question: What are the risk factors for scarring resulting from acne vulgaris? 11
Appendix B – Literature search strategies 16
Literature search strategy for review question: What are the risk factors for scarring resulting from acne vulgaris? 16
Appendix C – Clinical evidence study selection 20
Clinical study selection for review question: What are the risk factors for scarring resulting from acne vulgaris? 20
Appendix D - Evidence tables 21
Evidence tables for review question: What are the risk factors for scarring resulting from acne vulgaris? 21
Appendix E – Forest plots 24
Forest plots for review question: What are the risk factors for scarring resulting from acne vulgaris? 24
Appendix F – GRADE tables 25
GRADE tables for review question: What are the risk factors for scarring resulting from acne vulgaris? 25
Appendix G - Economic evidence study selection 26
Economic evidence study selection for review question: What are the risk factors for scarring resulting from acne vulgaris? 26
Appendix H – Economic evidence tables 27
Economic evidence tables for review question: What are the risk factors for scarring resulting from acne vulgaris?' 27
Appendix I – Economic evidence profiles 28
Economic evidence profiles for review question: What are the risk factors for

scarring resulting from acne vulgaris? 28
Appendix J – Economic analysis 29
Economic analysis for review question: What are the risk factors for scarring resulting from acne vulgaris? 29
Appendix K – Excluded studies 30
Excluded clinical and economic studies for review question: What are the risk factors for scarring resulting from acne vulgaris? 30
Appendix L – Research recommendations 32
Research recommendations for review question: What are the risk factors for scarring resulting from acne vulgaris? 32

Risk factors for scarring due to acne vulgaris

Review question

What are the risk factors for scarring resulting from acne vulgaris?

Introduction

Scarring as a result of acne can be severe and permanent, not only affecting the individual physically but also overall well-being. Recognising risk factors associated with scarring may help to prompt treatment and reduce frequency of the outcome.

Summary of the protocol

Please see Table 1 for a summary of the Population, Risk Factors and Outcome characteristics of this review.

Table 1: Summary of the protocol

Population	People with acne vulgaris
Risk factors	Risk factors associated with scarring might include: • Acne relapse • Acne severity • Acne type (e.g. conglobate, fulminans) • Delaying treatment • Distribution of acne • Duration of acne • Ethnicity • Family history of acne scarring • Gender • Severe picking of squeezing behaviours (aka: acne excoriée; 'pickers acne')
Outcomes	**Critical** • Risk of scarring due to acne

For further details, see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Overall two articles (Tan 2010, Tan 2017) reporting results from the Canadian Acne Epidemiological Survey were included in this review. The included studies are summarised in Table 2.

One article reported on the development of an acne scar scale (including the trunk and the face) and examined whether there is a correlation between the duration of acne and severity of acne scarring (Tan 2010). The other included article described the frequency of acne scars in people consulting a dermatologist as well as their clinical profile and examined whether there is an association between potential risk factors (acne severity, time to effective treatment, relapsing acne and gender), and scarring due to acne (Tan 2017).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Risk factors	Diagnostic criteria for scarring	Outcomes
Tan 2010 Cross-sectional Canada	N=973 Participants with acne scars • Participant-reported: n=710/973 (73%) • Dermatologist-reported: - Facial acne scars n=846/973 (87%) - Acne scarring at the chest n=369/973 (38%) - Acne scarring at the back n=496/973 (51%) Participants with no acne scars n=263/973 (27%)	• Duration of acne	• Participants reporting of acne scarring; • Acne severity evaluation by a dermatologist using a 6-category global system based on a global evaluation scale modified for acne scarring (SCAR-S)[a]	Severity of acne scarring (reported as Spearman rank correlation coefficient, *r*): • Participant reported • Dermatologist reported
Tan 2017 Prospective cohort Canada	N=1960 Participants with atrophic acne scars, n=843 Acne severity: • Almost clear/mild n=276/843 (33%) • Moderate n=310/843	• Acne severity (severe/very severe vs other severities) • Time to effective	• Census completed by participating office-based dermatologists for all potential participants over a 5-day period	• Risk of scarring due to acne reported as odds ratio

Study	Population	Risk factors	Diagnostic criteria for scarring	Outcomes
	(37%) • Severe/very severe n=216/843 (26%) • No facial acne n=41/843 (5%) Participants with no acne scars, n=1117 Acne severity: • Almost clear/mild n=712/1117 (64%) • Moderate n=302/1117 (27%) • Severe/very severe n=66/1117 (6%) • No facial acne n=37/1117 (3%)	treatment (≥3 years; <3 years) • Relapsing acne (yes; no) • Gender (male; female)		

[a]*SCAR-S: Global Scale for Acne Scar Severity; scale ranges from score of 0 (Clear - No visible scars from acne) to 5 (Very severe - Entire area covered with prominent atrophic or hypertrophic scars).*

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of included studies in the evidence review

Since data from both papers are correlational or univariate, no grading of outcomes based on GRADE was undertaken. For reviews where GRADE is not used evidence statements are produced (see section below) which include a description of the overall risk of bias for each study (see also supplementary material 2 – methods). The detailed risk of bias analysis using the Quality in Prognostic Studies (QUIPS) checklist for all domains of each study is provided in the final column of the clinical evidence tables in appendix D.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No economic modelling was conducted for this review question, because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Due to the study designs no GRADE assessment was carried out and therefore evidence statements are included:

- One study (N=973, moderate risk of bias) reported a weak correlation (Spearman rank correlation coefficient r=0.244) between the duration of acne and self-reported severity of acne scarring. The same study reported a very weak correlation (r=0.152) between the duration of acne and dermatologist-assessed severity of acne scarring.
- One study (N=1960, moderate risk of bias) reported a clinically important difference between severe or very severe acne (OR=6.5 [95% CI 5.1-8.1]), time to effective treatment of 3 or more years (OR=2.8 [95% CI 2.4-3.2]), experiencing a relapse in acne vulgaris (OR=1.4 [95% CI 1.2-1.5]) and the male gender (OR=1.8 [95% CI 1.6-2]) and acne scarring.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee chose the risk of scarring due to acne vulgaris as the critical outcome because it is a known and frequent complication and it can substantially negatively affect a person's physical and overall psychological well-being. Mitigation of risk factors may reduce the occurrence of acne scarring and therefore these negative effects. Due to the paucity of evidence, the committee decided to consider the outcome of severity of acne scarring as reported in Tan 2010 as a proxy measure of the association between the duration of acne vulgaris and risk of acne-related scarring.

The quality of the evidence

The quality of the studies relative to outcome was not assessed using an adaption of GRADE for prognostic reviews as the included studies only reported correlational or univariate estimates. Risk of bias was therefore assessed by study using the Quality in Prognostic Studies (QUIPS) checklist. Risk of bias of the studies was moderate. Biases were mainly related to studies not reporting the measures for risk factors and it was not clear from the latter study whether the reported effect estimates were adjusted for confounding by potential factors (that is it was unclear whether multivariable regression analysis was conducted or not).

Benefits and harms

The committee agreed that the evidence was very limited and not sufficient to make strong recommendations about the risk factors for scarring due to acne vulgaris. However, they agreed that it is important to provide some guidance to people with acne vulgaris and healthcare professionals as scarring can have a substantial and long-lasting physical and psychological impact.

The committee discussed the various actions that people with acne vulgaris can subject their acne lesions to such as picking, scratching, squeezing and scooping, which may lead to scarring. However, the committee noted the absence of evidence for these actions, and the lack of certainty about whether or not squeezing or scooping a lesion to release pus could be beneficial or harmful with regard to scarring. They agreed, using their knowledge and experience, to focus on persistent picking or scratching (which would cause greater damage to the skin), and recommended that people with acne vulgaris should be advised that persistent picking or scratching of acne lesions can increase the risk of scarring.

Although the evidence suggests that the severity of acne vulgaris and delaying treatment for it may be risk factors for scarring, there is substantial uncertainty as the studies did not control for the influence of other factors. Despite this, the committee agreed that the identification of these as risk factors for scarring due to acne vulgaris was consistent with their knowledge and experience and therefore agreed that people with acne vulgaris should

be advised of these potential links. They noted that these two factors are not mutually exclusive and interpreted the delay in treatment may not necessarily lead to scarring in mild to moderate acne but would be a more of a risk when severe acne is not treated quickly enough. They therefore specified this in the recommendation.

Due to the limited evidence and the impact that scarring can have on people's self-esteem and mood the committee decided to prioritise this topic for a research recommendation (see appendix L).

Cost effectiveness and resource use

No relevant economic evidence was identified. The committee agreed that identifying risk factors for scaring and offering relevant advice to people with acne vulgaris may potentially prevent scarring and/or help identify and manage scarring at earlier stages. Prevention and early management of scarring can lead to improved outcomes and potential cost-savings, as it may reduce the need for more costly interventions further down the care pathway.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.4 and 1.4.4 and a research recommendation on risk factors for scarring in the guideline.

References

Tan 2010

Tan JKL, Tang J, Fung K et al. Development and validation of a scale for acne scar severity (SCAR-S) of the face and trunk. Journal of Cutaneous Medicine and Surgery 2010, 14:156-160

Tan 2017

Tan J, Kang S, Leyden J. Prevalence and risk factors of acne scarring among patients consulting dermatologists in the USA. Journal of Drugs in Dermatology 2017, 16:97-102

Appendices

Appendix A – Review protocol

Review protocol for review question: What are the risk factors for scarring resulting from acne vulgaris?

Table 3: Review protocol for the risk factors for scarring resulting from acne vulgaris

Field	Content
PROSPERO registration number	CRD42019137762
Review title	Risk factors for scarring
Review question	What are the risk factors for scarring resulting from acne vulgaris?
Objective	The aim of this review is to identify the major risk factors for scarring due to acne
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date: No restriction • Language of publication: English language only • Publication status: Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias • Standard exclusions filter (animal studies/low level publication types) will be applied • For each search (including economic searches), the principal database search strategy is quality assured by a second information specialist using an adaption of the PRESS 2015 Guideline Evidence-Based Checklist
Condition or domain being studied	Acne vulgaris
Population	Inclusion: People with acne vulgaris Exclusion: Neonatal acne
Risk factors	Risk factors associated with scarring due to acne will be identified through the literature review but might include: • Acne relapse • Acne severity • Acne type (for exampleconglobate, fulminans) • Delay in treatment (that is time between acne onset and first effective treatment) • Distribution of acne • Duration of acne • Ethnicity • Family history of acne scarring

	• Gender • Severe picking or squeezing behaviours (aka: acne excoriée; 'pickers acne')
Confounders	• Not applicable for studies using simple correlational; or univariate analysis • Studies that identify 'independent' risk factors should adjust for confounding factors using appropriate type of regression to conduct multivariable analysis. Data on the factors adjusted for will be extracted.
Types of study to be included	• Systematic reviews of observational studies examining factors associated with scarring due to acne The following types of study design will be considered for this review: • Cohort studies • Nested case-control studies within a cohort of known size If no studies of the above types are identified, the following study designs will be considered: • Non-nested case control studies • Cross-sectional studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	Studies with indirect population: where studies with a mixed population [that is including people with acne vulgaris and another condition different to acne vulgaris] are identified, those with <66% of the relevant population will be excluded, unless subgroup analysis for acne vulgaris has been reported.
Context	Recommendations will apply to those receiving care in all healthcare settings (for examplecommunity, primary, secondary care).
Primary outcomes (critical outcomes)	**Critical outcomes** • Risk of scarring due to acne Note: Measure used to assess scarring due to acne must be investigator-rated. Only studies that use validated, objective, investigator-rated scales of scarring due to acne will be included. Definition used in studies will be extracted. Participant-rated assessment of scarring due to acne will be excluded.
Secondary outcomes (important outcomes)	Not applicable
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardized form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). All data extraction will be quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual.

Strategy for data synthesis	**Synthesis of data**: • Meta-analysis for an identified independent prognostic factor will be conducted only if there is a sufficient number of studies, a consistent measure to assess this factor is used, and each study has adjusted for same set of confounders. Otherwise a narrative summary of the available results for each factor will be provided. • Odds or risk ratios for the association of a potential prognostic factor with scarring due to acne will be analysed separately. • If studies report adjusted data from multivariable analysis and unadjusted data from univariate analysis, the former will be preferred. • If there are no studies that conduct multivariable analysis, results from correlational/univariate analyses will be tabulated indicating the direction of association for each factor (that is increased risk, reduced risk, no association) and whether it was statistically significant. **Heterogeneity:** • Heterogeneity will be assessed by visual examination of the forest plots to examine the magnitude and direction of effect and the I2 statistic (where I2 ≥50% indicates serious heterogeneity and I2≥80 indicates very serious heterogeneity). **Appraisal of methodological quality:** • GRADE will not be applied to risk factors identified in studies that use simple correlational/univariate analysis. Evidence statements summarising the potential risk factors will be presented. • The quality of the evidence for each independent prognostic factor identified from studies that use multivariable regression analysis will be evaluated for each outcome using an adapted version of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/. For further details as to how GRADE will be adapted, see Huguet, A., Hayden, J. A., Stinson, J., McGrath, P. J., Chambers, C. T., Tougas, M. E., & Wozney, L. (2013). Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Systematic reviews, 2(1), 71	
Analysis of sub-groups	Subgroup analysis will be conducted for the following group if there is available data: • Type of scarring (that is atrophic, hypertrophic)	
Type and method of review	☐	Intervention
	☐	Diagnostic
	☒	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or	30 May 2019	

actual start date			
Anticipated completion date	13 January 2021		
Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
	Preliminary searches	☐	☑
	Piloting of the study selection process	☐	☐
	Formal screening of search results against eligibility criteria	☐	☑
	Data extraction	☐	☑
	Risk of bias (quality) assessment	☐	☑
	Data analysis	☐	☑
Named contact	**5a. Named contact** National Guideline Alliance **5b Named contact e-mail** AcneManagement@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be		

	documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/gid-ng10109/documents/committee-member-list.	
Other registration details		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=137762	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Acne; atrophic; boxcar; hypertrophic; icepick; keloid; risk factors; rolling; scarring; scar.	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information		
Details of final publication	www.nice.org.uk	

GRADE: Grading of Recommendations Assessment, Development and Evaluation; NHS: National health service; NICE: National Institute for Health and Care Excellence

Appendix B – Literature search strategies

Literature search strategy for review question: What are the risk factors for scarring resulting from acne vulgaris?

Clinical search

Date of initial search: 11/06/2019

Database(s): Embase Classic+Embase 1947 to 2019 June 03, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to June 03, 2019

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	(exp scar formation/ or exp skin scar/ or exp scar/) use emczd
6	exp Cicatrix/ use ppez
7	(cicatri* or scar*1 or scarred or scarring or scarification).tw.
8	or/5-7
9	4 and 8
10	risk factor/ use emczd
11	Risk Factors/ use ppez
12	risk factor*.tw.
13	(therapy delay/ or time to treatment/) use emczd
14	Time-to-Treatment/ use ppez
15	((therap* or treatment* or intervention* or medicat*) adj2 (delay* or time)).tw.
16	(atrophic skin disease/ or density/ or disease severity/ or hypertrophic skin disease/ or hypertrophy/ or skin atrophy/ or virulence/) use emczd
17	(Atrophy/ or Hypertrophy/ or Virulence/) use ppez
18	(atroph* or chronic or dens* or distribut* or hyperproliferat* or hypertroph* or locali* or proliferat* or sever* or spread* or virulen*).tw.
19	(disease course/ or disease duration/ or disease exacerbation/) use emczd
20	duration.tw.
21	(exp ethnic group/ or exp "ethnic or racial aspects"/) use emczd
22	exp Ethnic Groups/ use ppez
23	(ethnic* or african* or black* or arab* or asian* or bangladesh* or bengali* or caribbean* or caucasian* or chinese or ethno* or gujurati* or hindu* or hispanic* or indian* or jew* or latino* or muslim* or pacific islander* or pakistan* or punjabi or race or races or racial or roma or romany or romanies or gyps*).tw.
24	(family history/ or genetic association/ or heredity/ or inheritance/) use emczd
25	(Medical History Taking/ or Heredity/ or exp Genetic Background/) use ppez
26	(family histor* or family medical histor* or heredi* or inherit* or genetic*).tw.
27	(exp gender/ or exp "groups by sex"/) use emczd
28	exp Gender Identity/ use ppez
29	(gender* or female* or feminin* or male* or masculin* or sex or sexes).tw.
30	scratching/ use emczd
31	(dermatillomani* or excoriat* or excoriee or pick* or scratch* or squeez*).tw.
32	or/10-31
33	9 and 32
34	limit 33 to english language
35	Letter/ use ppez
36	letter.pt. or letter/ use emczd
37	note.pt.
38	editorial.pt.
39	Editorial/ use ppez
40	News/ use ppez
41	exp Historical Article/ use ppez
42	Anecdotes as Topic/ use ppez
43	Comment/ use ppez
44	Case Report/ use ppez
45	case report/ or case study/ use emczd
46	(letter or comment*).ti.
47	or/35-46
48	randomized controlled trial/ use ppez

#	Searches
49	randomized controlled trial/ use emczd
50	random*.ti,ab.
51	or/48-50
52	47 not 51
53	animals/ not humans/ use ppez
54	animal/ not human/ use emczd
55	nonhuman/ use emczd
56	exp Animals, Laboratory/ use ppez
57	exp Animal Experimentation/ use ppez
58	exp Animal Experiment/ use emczd
59	exp Experimental Animal/ use emczd
60	exp Models, Animal/ use ppez
61	animal model/ use emczd
62	exp Rodentia/ use ppez
63	exp Rodent/ use emczd
64	(rat or rats or mouse or mice).ti.
65	or/52-64
66	34 not 65

Date of initial search: 11/06/2019

Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 6 of 12, June 2019; Cochrane Central Register of Controlled Trials, Issue 6 of 12, June 2019

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Cicatrix] explode all trees
#5	(cicatri* or scar or scars or scarred or scarring or scarification):ti,ab
#6	#4 or #5
#7	#3 and #6
#8	MeSH descriptor: [Risk Factors] explode all trees
#9	risk factor*:ti,ab
#10	MeSH descriptor: [Time-to-Treatment] explode all trees
#11	((therap* or treatment* or intervention* or medicat*) near/2 (delay* or time)):ti,ab
#12	MeSH descriptor: [Atrophy] explode all trees
#13	MeSH descriptor: [Hypertrophy] explode all trees
#14	MeSH descriptor: [Virulence] explode all trees
#15	(atroph* or chronic or dens* or distribut* or hyperproliferat* or hypertroph* or locali* or proliferat* or sever* or spread* or virulen*):ti,ab
#16	duration:ti,ab
#17	MeSH descriptor: [Ethnic Groups] explode all trees
#18	(ethnic* or african* or black* or arab* or asian* or bangladesh* or bengali* or caribbean* or caucasian* or chinese or ethno* or gujurati* or hindu* or hispanic* or indian* or jew* or latino* or muslim* or pacific islander* or pakistan* or punjabi or race or races or racial or roma or romany or romanies or gyps*):ti,ab
#19	MeSH descriptor: [Medical History Taking] explode all trees
#20	MeSH descriptor: [Heredity] explode all trees
#21	MeSH descriptor: [Genetic Background] explode all trees
#22	(family histor* or family medical histor* or heredi* or inherit* or genetic*):ti,ab
#23	MeSH descriptor: [Gender Identity] explode all trees
#24	(gender* or female* or feminin* or male* or masculin* or sex or sexes):ti,ab
#25	(dermatillomani* or excoriat* or excoriee or pick* or scratch* or squeez*):ti,ab
#26	{or #8-#25}
#27	#7 and #26 in Cochrane Reviews, Cochrane Protocols, Trials

Health Economics search

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Economics/
6	Value of life/
7	exp "Costs and Cost Analysis"/
8	exp Economics, Hospital/
9	exp Economics, Medical/
10	Economics, Nursing/
11	Economics, Pharmaceutical/
12	exp "Fees and Charges"/
13	exp Budgets/
14	(or/5-13) use ppez
15	health economics/
16	exp economic evaluation/
17	exp health care cost/
18	exp fee/
19	budget/
20	funding/
21	(or/15-20) use emez
22	budget*.ti,ab.
23	cost*.ti.
24	(economic* or pharmaco?economic*).ti.
25	(price* or pricing*).ti,ab.
26	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
27	(financ* or fee or fees).ti,ab.
28	(value adj2 (money or monetary)).ti,ab.
29	or/22-27
30	14 or 21 or 29
31	4 and 30
32	limit 31 to english language
33	limit 32 to yr="2004 -Current"
34	remove duplicates from 33

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Databases(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHS EED)

#	Searches
1	MeSH DESCRIPTOR Acne Vulgaris EXPLODE ALL TREES
2	(acne) IN NHSEED, HTA FROM 2004 TO 2018
3	#1 OR #2

Search for health utility values

Date of initial search: 29/01/2019

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

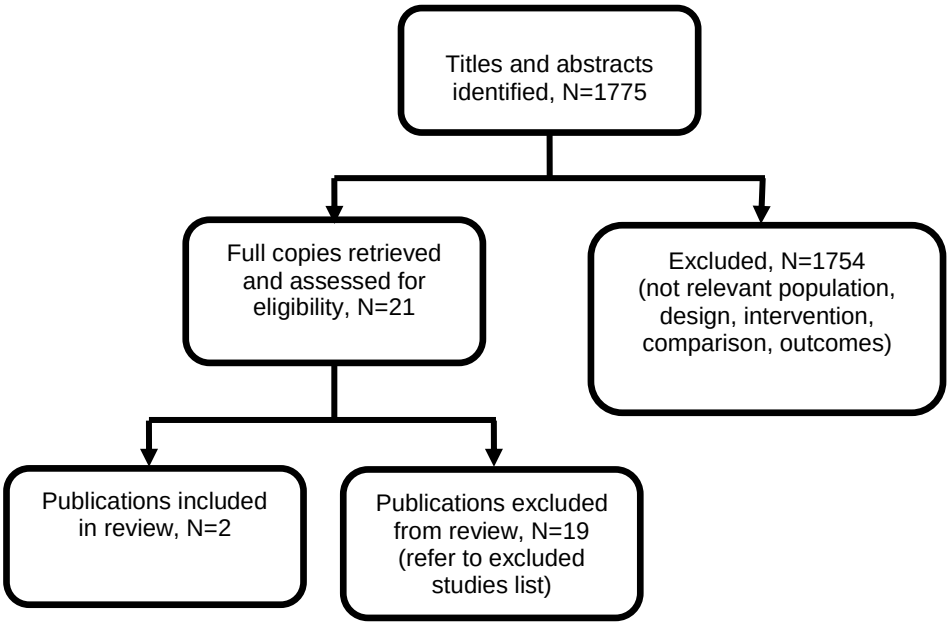
#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Quality-Adjusted Life Years/ use ppez
6	Sickness Impact Profile/
7	quality adjusted life year/ use emez
8	"quality of life index"/ use emez
9	(quality adjusted or quality adjusted life year*).tw.

#	Searches
10	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
11	(illness state* or health state*).tw.
12	(hui or hui2 or hui3).tw.
13	(multiattibute* or multi attribute*).tw.
14	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
15	utilities.tw.
16	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
17	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
18	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
19	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
20	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
21	Quality of Life/ and ec.fs.
22	Quality of Life/ and (health adj3 status).tw.
23	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
24	(quality of life or qol).tw. and cost benefit analysis/ use emez
25	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
26	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
27	cost benefit analysis/ use emez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
28	*quality of life/ and (quality of life or qol).ti.
29	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
30	quality of life/ and health-related quality of life.tw.
31	Models, Economic/ use ppez
32	economic model/ use emez
33	or/5-32
34	4 and 33
35	limit 34 to english language
36	limit 35 to yr="2004 -Current"
37	remove duplicates from 36

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What are the risk factors for scarring resulting from acne vulgaris?

Figure 1: Study selection flow chart



Appendix D - Evidence tables

Evidence tables for review question: What are the risk factors for scarring resulting from acne vulgaris?

Table 4: Evidence table

Study details	Population	Factors and results	Limitations
Full citation Tan, J. K. L., Tang, J., Fung, K., Gupta, A. K., Thomas, D. R., Sapra, S., Lynde, C., Poulin, Y., Gulliver, W., Sebaldt, R. J., Development and validation of a scale for acne scar severity (SCAR-S) of the face and trunk, Journal of Cutaneous Medicine and Surgery, 14, 156-160, 2010 **Ref Id** 1048671 **Country/ies where the study was carried out** Canada **Study type** Cross-sectional **Study dates** Not reported **Consecutive recruitment** Not reported (data for the study were obtained from the Canadian Acne Epidemiological Survey). **Source of funding** This study was supported by unrestricted educational grants from Hoffman-	**Cases** Participant-reported: n=710/973 (73%) reported the presence of acne scars. Of those, approximately 2/3 reported scarring as mild, 1/3 as moderate or greater severity Dermatologist-reported*: 1) Facial acne scars n= 846/973 (87%), of those 32% graded as almost clear, 31% mild, 19% moderate, 5% severe; SCAR-S grade mild or greater 55% 2) Acne scarring at the chest n=369/973 (38%), of those 24% graded as almost clear, 11% mild; SCAR-S grade mild or greater 14% 3) Acne scarring at the back n=496/973 (51%), of those 27% graded as almost clear, 16% mild; SCAR-S grade mild or greater 24% *using a 6-category global system based on global evaluation scale modified for acne scarring - Global Scale for Acne Scar Severity (SCAR-S) Socio-demographic characteristic for the whole population: Age (mean (SD)): 25.4 (7.9); Female: 58% Caucasian: 79% **Diagnostic criteria**	**Factor** Duration of acne **Relative risk estimates** Spearman rank correlation coefficient (r) for the correlation between the duration of acne and: 1) participant-reported severity of acne scarring: 0.244 2) overall SCAR-S scores (investigator measured): 0.152	**Methodological limitations assessed using QUIPS checklist** **Study participation** Moderate risk of bias as not described how the participants were chosen **Study attrition** Low risk of bias **Prognostic factor measurement** Moderate risk of bias as not reported how the risk factor was measured **Outcome measurement** Low risk of bias **Study confounding** Not relevant as the study's primary aim was to develop a global scale for acne scar severity inclusive of the trunk and the face. **Statistical analysis and reporting** Low risk of bias **Other information** The primary aim of the study was to develop a global scale for acne scar severity inclusive of the trunk and the face.

Study details	Population	Factors and results	Limitations
La Roche Ltd, Berlex, Stiefel, and Dermik Laboratories	Participants reporting of acne scarring; acne severity evaluation by participating dermatologists using a 6-category global system based on a global evaluation scale modified for acne scarring – SCAR-S: • Clear 0 - No visible scars from acne • Almost clear 1 - Hardly visible scars from 2.5 m away • Mild 2 - Easily recognisable; less than half the affected area (e.g., face, back, or chest) involved • Moderate 3 - More than half the affected area (e.g., face, back, or chest) involved • Severe 4 - Entire area involved • Very severe 5 - Entire area with prominent atrophic or hypertrophic scars **Controls** Participants with no acne scars, n=263/973 (27%) **Inclusion criteria** People with acne referred from community-based primary care physicians to participating dermatologists for standard care. **Exclusion criteria** Postinflammatory dyspigmentation from acne		
Full citation Tan, J., Kang, S., Leyden, J., Prevalence and risk factors of acne scarring among patients consulting dermatologists in the USA, Journal of Drugs in Dermatology, 16, 97-102, 2017	**Cases** Participants with anthropic acne scars, n=843 Acne severity: • Almost clear/mild = 276 (33%); • Moderate = 310 (37%); • Severe/very severe = 216 (26%);	**Factors** • Acne severity (severe/very severe vs other severities) • Time to effective treatment (>=3 years vs <3 years) • Relapsing acne (yes vs no) • Gender (male vs female)	**Methodological limitations assessed using QUIPS checklist** **Study participation** Low risk of bias **Study attrition** Low risk of bias

Study details	Population	Factors and results	Limitations
Ref Id 969169 **Country/ies where the study was carried out** Canada **Study type** Prospective cohort **Study dates** May 2012 to Mach 2013 **Consecutive recruitment** A short census completed by office-based dermatologists for all those who were seen by a dermatologist over a 5-day period (the same study sample as in Tan 2010, that is from the Canadian Acne Epidemiological Survey). **Source of funding** Funding for editorial assistance was provided by Galderma Laboratories L.P., Fort Worth, TX	• No facial acne = 41 (5%) Mean age for the whole group: 22.9 (range: 9-72) **Diagnostic criteria** A census completed by office-based dermatologists for all potential participants over a 5-day period **Controls** Participants with no acne scars, n=1117 Acne severity: • Almost clear/mild = 712 (64%); • Moderate = 302 (27%); • Severe/very severe = 66 (6%); • No facial acne = 37 (3%) **Inclusion criteria** People consulting a dermatologist for acne vulgaris **Exclusion criteria** Participants with macular pigmentary changes including post-inflammatory erythema (persistent redness) or post-inflammatory hyperpigmentation (residual brown or black discoloration in the location of previous acne or other inflammatory reaction) and those with beards	• Smoking (no data presented, only stated that it was not significantly associated with scarring) • BMI (no data presented, only stated that it was not significantly associated with scarring) **Relative risk estimates** Risk factors associated with acne scarring (reported as odds ratios (OR) with 95% confidence interval (CI))*: • Acne severity (severe/very severe vs other severities): 6.5 (5.1-8.1) • Time to effective treatment (>=3 years vs <3 years): 2.8 (2.4-3.2) • Relapsing acne (yes vs no): 1.4 (1.2-1.5) • Gender (male vs female): 1.8 (1.6-2.0) *No raw data presented; not clear from the paper whether the analysis accounted for any confounders	**Prognostic factor measurement** Moderate risk of bias as not reported how the risk factors were measured **Outcome measurement** Low risk of bias **Study confounding** Moderate risk of bias as it is not clear from the paper whether the analysis accounted for any confounders **Statistical analysis and reporting** Moderate risk of bias as it is not clear from the paper whether regression analysis was multivariable; selective reporting as no data presented for the non-significant results, that is smoking and BMI

Appendix E – Forest plots

Forest plots for review question: What are the risk factors for scarring resulting from acne vulgaris?

This section includes forest plots only for outcomes that are meta-analysed. No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F – GRADE tables

GRADE tables for review question: What are the risk factors for scarring resulting from acne vulgaris?

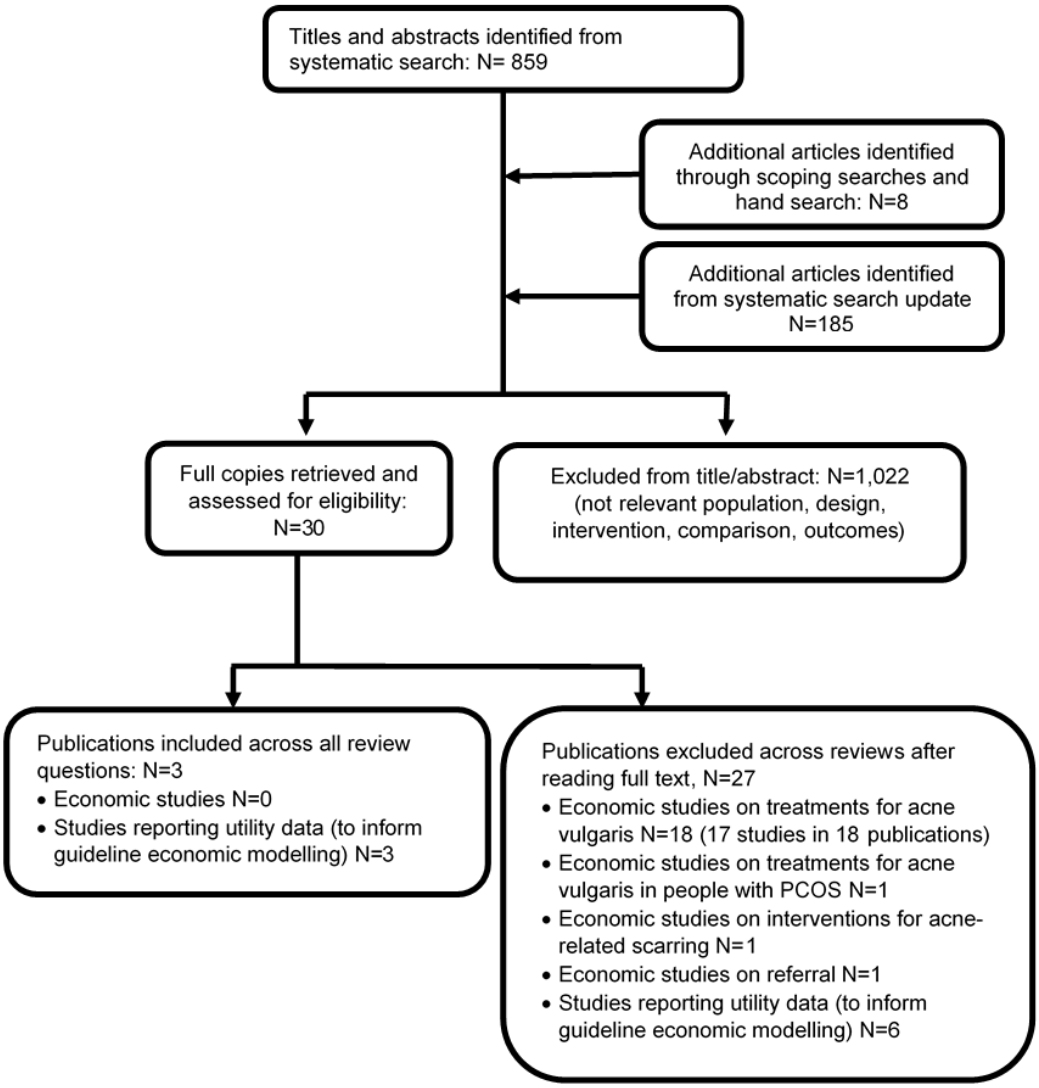
Since data from the included studies are correlational or univariate, no grading of outcomes with GRADE was undertaken.

Appendix G - Economic evidence study selection

Economic evidence study selection for review question: What are the risk factors for scarring resulting from acne vulgaris?

A global health economics search was undertaken for all areas covered in the guideline. Figure 2 shows the flow diagram of the selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data.

Figure 2. Flow diagram of selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data



Appendix H – Economic evidence tables

Economic evidence tables for review question: What are the risk factors for scarring resulting from acne vulgaris?'

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the risk factors for scarring resulting from acne vulgaris?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: What are the risk factors for scarring resulting from acne vulgaris?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What are the risk factors for scarring resulting from acne vulgaris?

Clinical studies

Table 5: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Abo El-Fetoh, N. M., Alenezi, N. G., Alshamari, N. G., Alenezi, O. G. Epidemiology of acne vulgaris in adolescent male students in Arar, Kingdom of Saudi Arabia. The Journal of the Egyptian Public Health Association, 91, 144-149, 2016	Article not available
Akoglu, G., Tan, C., Ayvaz, D. C., Tezcan, I., Tumor necrosis factor alpha-308 G/A and interleukin 1 beta-511 C/T gene polymorphisms in patients with scarring acne, Journal of Cosmetic Dermatology, 18, 395-400, 2019	No relevant data reported
Chan, H. H. L., Manstein, D., Yu, C. S., Shek, S., Kono, T., Wei, W. I., The prevalence and risk factors of post-inflammatory hyperpigmentation after fractional resurfacing in Asians, Lasers in Surgery and Medicine, 39, 381-385, 2007	Study examines the risk and prevalence of post-inflammatory hyperpigmentation after treatment with fractional resurfacing
Dessinioti, C., Zisimou, C., Platsidaki, E., Katsambas, A., Antoniou, C., A cross-sectional study of clinical factors associated with acne facial scarring in patients with active acne, Journal of the European Academy of Dermatology and Venereology, 32, e212-e214, 2018	Letter to the Editor
Faraji Zonooz, M., Sabbagh-Kermani, F., Fattahi, Z., Fadaee, M., Akbari, M. R., Amiri, R., Vahidnezhad, H., Uitto, J., Najmabadi, H., Kariminejad, A., Whole Genome Linkage Analysis Followed by Whole Exome Sequencing Identifies Nicastrin (NCSTN) as a Causative Gene in a Multiplex Family with gamma-Secretase Spectrum of Autoinflammatory Skin Phenotypes, Journal of Investigative Dermatology, 136, 1283-1286, 2016	Letter to the Editor
Hazarika, N., Rajaprabha, R., Assessment of life quality index among patients with acne vulgaris in a suburban population, Indian Journal of Dermatology, 61, 163-168, 2016	No relevant data reported
Hello, M., Prey, S., Leaute-Labreze, C., Khammari, A., Dreno, B., Stalder, J. F., Barbarot, S., Infantile acne: A retrospective study of 16 cases, Pediatric Dermatology, 25, 434-438, 2008	Case series describing epidemiological data concerning infantile acne and evaluating its natural history
Holland, D. B., Jeremy, A. H., Roberts, S. G., Seukeran, D. C., Layton, A. M., Cunliffe, W. J., Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar, British Journal of Dermatology, 150, 72-81, 2004	No relevant outcomes reported
J. Goodman G, Post-acne scarring: A short review of its pathophysiology, Australasian Journal of Dermatology, 42, 84-90, 2001	Review about post-acne scarring and its pathophysiology
Kilkenny, M., Merlin, K., Plunkett, A., Marks, R., The prevalence of common skin conditions in Australian school students: 3. acne vulgaris, British Journal of	Study describes the prevalence and severity of facial acne; no risk factors

DermatologyBr J Dermatol, 139, 840-5, 1998	
Kubba, R., Bajaj, A., Thappa, D., Sharma, R., Vedamurthy, M., Dhar, S., Criton, S., Fernandez, R., Kanwar, A., Khopkar, U., Kohli, M., Kuriyipe, V., Lahiri, K., Madnani, N., Parikh, D., Pujara, S., Rajababu, K., Sacchidanand, S., Sharma, V., Thomas, J., Acne scars, Indian Journal of Dermatology, Venereology and Leprology, 75, S52-S53, 2009	Consensus document on acne management
Lauermann, F. T., De Almeida, H. L., Duquia, R. P., Martins de Souza, P. R., Breunig, J. A., Acne scars in 18-year-old male adolescents: A population-based study of prevalence and associated factors, Anais brasileiros de dermatologia, 91, 291-295, 2016	No relevant data reported
Layton, A. M., Henderson, C. A., Cunliffe, W. J., A clinical evaluation of acne scarring and its incidence, Clinical and Experimental Dermatology, 19, 303-308, 1994	No relevant data reported
Layton, A. M., Seukeran, D., Cunliffe, W. J., Scarred for life?, Dermatology, 195, 15-21, 1997	Study examines the effectiveness of oral isotretinoin therapy on acne scarring
Muthupalaniappen, L., Tan, H. C., Puah, J. W., Apipi, M., Sohaimi, A. E., Mahat, N. F., Rafee, N. M., Acne prevalence, severity and risk factors among medical students in Malaysia, Clinica Terapeutica, 165, 187-92, 2014	Study examines risk factors for acne and not for post-acne scarring
Park, S. Y., Park, M. Y., Suh, D. H., Kwon, H. H., Min, S., Lee, S. J., Lee, W. J., Lee, M. W., Ahn, H. H., Kang, H., Lee, J. B., Ro, Y. S., Ahn, K. J., Kim, M. N., Kim, K. J., Kim, N. I., Cross-sectional survey of awareness and behavioral pattern regarding acne and acne scar based on smartphone application, International Journal of Dermatology, 55, 645-652, 2016	No relevant data reported
Rajar, U. D. M., Majeed, R., Sheikh, F., Sheikh, I., Siddique, A. A., Kumar, S., Scarring in acne patients - A study done at Isra University Hyderabad, Journal of the Pakistan Medical Association, 59, 525-527, 2009	Study describes the clinical presentation of acne in an outpatients clinic
Tan, J., Acne and Scarring: Facing the Issue to Optimize Outcomes, Journal of drugs in dermatology, 17, s43, 2018	Short introduction on acne and scarring
Tan, J., Tanghetti, E., Baldwin, H., Stein Gold, L., Lain, E., The Role of Topical Retinoids in Prevention and Treatment of Atrophic Acne Scarring: Understanding the Importance of Early Effective Treatment, Journal of drugs in dermatology, 18, 255-260, 2019	Article discusses topical retinoids in treatment of acne and acne scars

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What are the risk factors for scarring resulting from acne vulgaris?

Research question

What are the risk factors for scarring resulting from acne vulgaris?

Why this is important

Scarring is a common complication of acne vulgaris. Both acne and scarring can lead to impaired quality of life and both are associated with low self-esteem and mental health problems including depression and anxiety. Prevention of acne related scarring is a concern for both patients and clinicians and is often an important factor when considering treatment options and providing advice to patients.

Table 6: research recommendation rationale

Research question	What are the risk factors for acne vulgaris related scarring?
Why is this needed	
Importance to 'patients' or the population	Scarring is a common complication of acne and is associated with impaired quality of life. Therefore, finding risk factors could help prevent scarring because treatment of scarring may be expensive, painful and may have limited benefit. Prevention would be better for the person with acne as well as decrease downstream costs.
Relevance to NICE guidance	This is important for NICE guidance because risk factors could be an important consideration in the choice of relevant treatment options. Knowledge of risk factors may reveal targets for intervention.
Relevance to the NHS	Prevention of scarring in those at risk is likely to be more cost effective than treatment of scarring once established.
National priorities	• Improving the mental health of young people is a national priority. Acne related scarring affects people's self-esteem, mood and social interactions. Rates of depression and suicide are increasing in the under 25 year old age group, especially amongst men 20-25 years old. (suicides in the UK 2019 ons.gov.uk). In 2018 the government produced a paper 'Transforming children's and young people's mental health provision', including improving services for those 16-25 years old. This aligns with a need to understand support required for young people with acne vulgaris https://www.gov.uk/government/consultations/transforming-children-and-young-peoples-mental-health-provision-a-green-paper/quick-read-transforming-children-and-young-peoples-mental-health-provision

Research question	What are the risk factors for acne vulgaris related scarring?
Current evidence base	Only two studies were identified by the evidence review. One prospective and one cross sectional study with moderate risk of bias.
Equality	There may be a number of equality issues such as age, gender, race or socioeconomic status that impact the differences in risk of scarring and therefore may impact on equality of care.
Feasibility	Well-designed prospective studies with sufficient numbers of participants which take into account potential confounding factors and minimise risk of bias are feasible.
Other comments	Not applicable.

Table 7: Research recommendation characteristics

Criterion	Explanation
Population	• People with acne vulgaris
Risk factor(s)	The following factors will be considered: • epidemiological (e.g. age, gender,race, socioeconomic status), • genetic, • ethnographic, • lifestyle, • acne related (for example, type, duration, location, relapsing) • acne treatments (type of treatment, time to treatment) • practices (for example, picking)
Outcomes	• Type, location, severity, extent of scarring • Impact on quality of life • Psychological well-being
Study design	Prospective cohort studies accounting for a variety of possible confounding factors which would include also the risk factors listed above.
Timeframe	• Minimum of 12 months or longer
Additional information	For an 80% powered study the following rule of thumb (see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6640316/) could be applied: 100 participants plus another 100 per predictor variable (that is for 1 predictor 200 participants, for 2 predictors 300 participants, and so on).