

Table 1. Quality Assessment of Selected Studies Included in the Review

Study	Study Design	Appraisal Tool Used	Quality Rating	Main Strengths	Main Limitations
Cipriani et al., 2018	Systematic review and network meta-analysis	AMSTAR 2	High	Large comparative review of antidepressant efficacy and acceptability; strong relevance to SSRI treatment limitations	Adult depression focus; not specific to adolescents or microbiome
Lu et al., 2024	Systematic review and meta-analysis	AMSTAR 2	High	Large synthesis of global depression/depressive symptoms in children and adolescents	Heterogeneity across countries, definitions, and screening tools
Kerr et al., 2025	Systematic review	AMSTAR 2	Moderate–High	Directly relevant to adolescent social media use and anxiety	Associations do not prove causation; study designs vary
Khalaf et al., 2023	Systematic review	AMSTAR 2	Moderate	Relevant background on social media and adolescent mental health	Heterogeneous included studies; limited causal inference
Vidal et al., 2020	Scoping review	AMSTAR 2/scoping review appraisal	Moderate	Useful overview of adolescent social media and depression literature	Scoping design summarizes evidence but does not provide strong causal conclusions
García-Ríos et al., 2025	Systematic review	AMSTAR 2	Moderate–High	Directly relevant to oral dysbiosis and depression	Included studies likely heterogeneous; oral microbiome field remains early
Cerroni et al., 2018	Systematic review	AMSTAR 2	Moderate	Relevant to orthodontic appliances and periodontal status	Orthodontic oral-health outcomes, not mental-health outcomes
Meade et al., 2023	Scoping review	AMSTAR 2/scoping review appraisal	Moderate	Useful for orthodontic patient experiences on social media	Does not establish biological or mental-health causation

Zeng et al., 2025	Human case-control study	NIH/JBI case-control tool	Moderate–High	Directly studies oral microbiota in treatment-naïve adolescents with depression; clinically relevant age group	Case-control design cannot prove causality; sample and population may limit generalizability
Wingfield et al., 2021	Human case-control study	NIH/JBI case-control tool	Moderate	Direct salivary microbiome comparison between depressed and healthy young adults	Small sample size; association only
Zheng et al., 2025	Population-based observational study	NIH observational/cross-sectional tool	Moderate–High	Large population-based data set; directly examines oral microbiome and depression	Cross-sectional design; residual confounding possible
Qiu et al., 2025	Cross-sectional NHANES analysis	NIH observational/cross-sectional tool	Moderate–High	Large U.S. population sample; examines oral microbial diversity and depression scores	Cross-sectional; cannot determine direction of effect
Liu et al., 2020	Human observational study	NIH observational tool	Moderate	Connects gut bacteria and depression in young adults	Observational association; limited causal inference
Zhong et al., 2022	Human observational study	NIH observational tool	Moderate	Relates gut microbiota composition to severity of major depressive disorder	Possible confounding by diet, medication, disease severity, and lifestyle
Lu R. et al., 2014	Human longitudinal periodontal treatment study	NIH cohort/longitudinal tool	Moderate–High	Repeated SCFA measurements in gingival crevicular fluid after periodontal treatment	Periodontal population only; does not evaluate mood outcomes
Qiqiang et al., 2012	Human longitudinal periodontal study	NIH cohort/longitudinal tool	Moderate	Measures changes in volatile fatty acids before and after therapy	Small clinical sample; no mental-health outcomes
Marincak Vrankova et al., 2022	Pilot human orthodontic/oral microbiota study	NIH observational tool	Moderate	Direct relevance to orthodontic appliances and oral microbiota	Pilot design; small sample; not linked to depression outcomes
Vanhatalo et al., 2018	Human interventional/physiologic study	NIH controlled intervention tool	Moderate–High	Demonstrates functional oral microbiome role in nitric oxide physiology	Not primarily designed around mood or depression

Human Microbiome Project Consortium, 2012	Large descriptive human microbiome study	NIH observational/descriptive tool	High	Foundational large-scale microbiome characterization	Background relevance; not specific to mood or SCFAs
Aas et al., 2005	Human descriptive oral microbiome study	NIH observational/descriptive tool	Moderate–High	Foundational description of normal oral bacterial flora	Descriptive design; not linked to mood outcomes
Dewhirst et al., 2010	Human oral microbiome catalogue/descriptive study	NIH observational/descriptive tool	Moderate–High	Strong foundational relevance to oral microbiome composition	Descriptive; not causal or mood-focused
Zhang et al., 2021	Cross-sectional oral microbiome study in children	NIH cross-sectional tool	Moderate	Relevant to tongue microbiota and oral health in children	Oral-health focus rather than mood; cross-sectional
Chen B.-J. et al., 2023	Human association plus ex vivo experiment	NIH observational + adapted in vitro tool	Moderate–High	Combines human oral rinse data with experimental butyrate exposure	Male-only or limited sample features may reduce generalizability; not mood-focused
Takigawa et al., 2008	In vitro gingival epithelial cell study	Adapted SciRAP/Tox RTool	Moderate	Mechanistic evidence that butyric acid affects epithelial adhesion/inflammation	Cell-line model; dose and tissue-context translation limitations
Lu X. et al., 2025	In vitro periodontal ligament cell study	Adapted SciRAP/Tox RTool	Moderate	Mechanistic evidence for butyrate/propionate inflammatory signaling via GPR41	Laboratory model; no direct human behavioral outcome
Hoyles et al., 2018	Mechanistic microbiome-host/BBB study	Adapted experimental appraisal	Moderate–High	Strong mechanistic relevance to propionate and blood-brain barrier protection	Translational relevance to adolescents and depression remains indirect
Wang et al., 2021	Mechanistic experimental study	Adapted in vitro/in vivo appraisal	Moderate–High	Supports butyrate as a regulator of HIF/prolyl hydroxylase signaling	Mechanistic rather than clinical; not mood-specific

Braniste et al., 2014	Animal experimental study	SYRCLE risk-of-bias tool	Moderate–High	Strong mechanistic evidence linking microbiota to blood-brain barrier permeability	Mouse model; translation to humans uncertain
Erny et al., 2015	Animal experimental study	SYRCLE risk-of-bias tool	Moderate–High	Important evidence linking microbiota to microglial maturation/function	Animal model; behavioral relevance indirect
Wu W.-L. et al., 2021	Animal experimental study	SYRCLE risk-of-bias tool	Moderate–High	Mechanistic link between microbiota, stress-response neurons, and social behavior	Animal behavior tests may not fully represent human mood disorders
Agranyoni et al., 2021	Animal experimental/fecal transfer study	SYRCLE risk-of-bias tool	Moderate	Connects microbiota, social behavior, metabolism, and inflammation	Mouse model; complex behavior translation limited
Wu J.-T. et al., 2022	Animal experimental study	SYRCLE risk-of-bias tool	Moderate–High	Tests SCFA replacement after microbiome depletion and anxiety-like behavior	Antibiotic-depletion model may not reflect natural human dysbiosis
Needham et al., 2022	Animal experimental study	SYRCLE risk-of-bias tool	High	Strong mechanistic evidence that a gut-derived metabolite alters anxiety behavior	Mouse model; direct human relevance still uncertain
MacFabe et al., 2007	Animal experimental study	SYRCLE risk-of-bias tool	Moderate	Demonstrates behavioral effects of propionic acid exposure	Direct brain infusion and high-dose exposure limit real-world translation
Meeking et al., 2020	Animal behavioral study	SYRCLE risk-of-bias tool	Moderate	Supports propionic-acid-related behavioral effects	Animal behavior model and dose relevance limitations
Colombo et al., 2021	Animal experimental study	SYRCLE risk-of-bias tool	Moderate–High	Shows SCFA effects on microglia and amyloid- β plaque deposition	Alzheimer's model; relevance to adolescent depression is indirect
Zhou et al., 2021	Animal experimental study	SYRCLE risk-of-bias tool	Moderate	Links SCFAs to microglial activation and pain-related outcomes	Pain model; indirect relevance to mood/depression

Fonseca et al., 2014	Human perception study	NIH observational tool	Moderate	Relevant to orthodontic appliance appearance and social perception	Not microbiome-focused; indirect mental-health relevance
Doğrugören et al., 2023	Social media observational/content analysis	NIH observational/adapted appraisal	Moderate	Relevant to orthodontic patient experiences on Instagram	Social media data may be biased and nonrepresentative
Arumugam et al., 2011	Human microbiome observational/metagenomic study	NIH observational/descriptive tool	High	Major foundational study on gut microbiome composition	Not focused on depression or oral microbiome
Rinninella et al., 2019	Narrative review	Narrative review/context appraisal	Moderate	Useful background on healthy gut microbiota	Review article; not primary evidence
Magne et al., 2020	Narrative/review article	Narrative review/context appraisal	Moderate	Useful dysbiosis background	Not primary evidence; not mood-specific
Loh et al., 2024	Narrative/mechanistic review	Narrative review/context appraisal	Moderate	Strong mechanistic background on microbiota-gut-brain axis	Not primary evidence
Tan et al., 2022	Narrative/mechanistic review	Narrative review/context appraisal	Moderate	Useful explanation of vagus nerve and depression mechanisms	Mechanistic review; not primary evidence
Singhal and Shah, 2020	Narrative/mechanistic review	Narrative review/context appraisal	Moderate–High	Strong background on hypoxia and HIF signaling in the gut	Not directly tested in adolescent mood outcomes
Fock and Parnova, 2023	Narrative/mechanistic review	Narrative review/context appraisal	Moderate	Helpful synthesis of SCFAs and blood-brain barrier protection	Review evidence; not primary causal evidence
NICE, 2022	Clinical guideline	Guideline appraisal/context assessment	High	Authoritative clinical guidance for depression treatment	Adult treatment guideline; not microbiome-specific

Bowland and Weyrich, 2022	Narrative/perspective review	Narrative review/context appraisal	Moderate	Useful conceptual framework for oral-microbiome-brain axis	Anthropological/perspective design; not primary clinical evidence
Nireeksha et al., 2025	Narrative review	Narrative review/context appraisal	Moderate	Relevant overview of SCFAs in gut and oral microbiome	Review article; should not be treated as causal evidence
Kilian et al., 2016	Narrative review/update	Narrative review/context appraisal	Moderate–High	Strong oral microbiome background for dental professionals	Background review; not mental-health-focused
Marsh, 1994	Narrative review	Narrative review/context appraisal	Moderate	Foundational oral biofilm ecology	Older background source; not mood-specific
Holt and Ebersole, 2005	Narrative review	Narrative review/context appraisal	Moderate	Important background on periodontal pathogens	Not direct evidence on SCFAs or depression
Shi and Gilkes, 2025	Narrative/mechanistic review	Narrative review/context appraisal	Moderate	Useful background on HIF biology	Cancer/HIF focus; indirect relevance
Chen Y. et al., 2022	Narrative review	Narrative review/context appraisal	Moderate	Useful background on <i>Fusobacterium nucleatum</i>	Not directly mood-focused
Zhang and An, 2007	Narrative review	Narrative review/context appraisal	Moderate	Useful background on cytokines and inflammation	