Understanding how interventions for youth depression and anxiety work

Recommendations for mechanistic research

1. Front Matter

1.1 Acknowledgements

This report is authored by Ms Tarisai Bere, University of Zimbabwe (Zimbabwe), Dr Christian Kieling, Universidade Federal do Rio Grande do Sul (Brazil), Dr Katherine Young, Centre for Evidence & Implementation (UK) and science writer Dr Anna McLaughlin, Sci-translate (UK).

All views, interpretations, and perspectives contained herein, including any use of terms such as “we” or “our”, reflect the authors’ own positions and do not necessarily represent the view of Wellcome.

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1.2 Executive Summary

Anxiety and depression are among the leading causes of disability in young people worldwide[1]. Although a wide range of evidence-based interventions are available, many children and adolescents do not experience meaningful symptom improvement, and relapse remains common[2]. These limitations have intensified the urgency to better understand what works, for whom, and why.

To address this, Wellcome aims to strengthen the scientific understanding of how the brain, body, and environment interact in the resolution of anxiety and depression in young people. As part of this effort, Wellcome has commissioned this report to identify the most promising areas for intervention, pinpoint opportunities and gaps in the existing knowledge base, and determine where further mechanistic research is most urgently needed. This report supports that goal by mapping current evidence on the mechanisms of action through which interventions reduce symptoms of anxiety and depression in children and young people under 18. The findings and recommendations will guide future Wellcome funding calls, with a particular focus on investing in mechanistically informed, contextually relevant, and youth-centred research.

The main objectives of this report were to:

- Synthesise evidence from literature reviews and meta-analyses on the mechanisms of youth mental health interventions.
- Identify gaps and opportunities for mechanistic research across different interventions, populations and contexts.
- Incorporate insights from young people with lived experience and international academic stakeholders.

1.2.1 Key Findings

Our review highlights both progress and persistent gaps in youth mental health research. Across interventions, many approaches demonstrated effectiveness in reducing symptoms, yet the underlying mechanisms of how and why they work remain poorly understood. We identified four overarching challenges that cut across the evidence base:

1) Weak Mechanistic Evidence and Theory-Practice Gaps

While theoretical models informed many interventions, these were often untested or lacked rigorous validation in youth populations. Most trials evaluated whole interventions rather than isolating active ingredients, and comparative or dismantling studies remain rare. Few were designed

to test mediation, dose–response, or temporal sequencing, leaving uncertainty about which components drive change. Pre- and post-intervention measures and group-level comparisons dominated, with limited attention to within-person variability or dynamic processes of change. Subgroup differences related to comorbidity, developmental stage, or context were often overlooked, missing opportunities to tailor interventions.

2) Prevention Research Overlooks Mechanistic Risk Factors

A striking gap across the literature was the scarcity of mechanistic evidence on interventions designed to prevent anxiety and depression. Research on primary prevention, which targets underlying risk factors before symptoms emerge, was nearly nonexistent. Most studies focus on secondary prevention, adapting early treatment approaches for subclinical populations. These were often limited by inadequate screening for pre-existing conditions, poor reporting, and insufficient long-term follow-up. Given that early intervention has the potential to alter life-course trajectories and reduce long-term severity, the lack of mechanistic prevention research represents a missed opportunity to reduce the incidence and burden of anxiety and depression at scale.

3) Lack of Research in LMICs and Diverse Contexts

Evidence was heavily concentrated in high-income countries (HICs), Western settings, creating a critical gap in low- and middle-income countries (LMICs). Adaptations for LMICs, displaced populations, or culturally diverse groups remain scarce, despite these being the settings with the greatest unmet needs. Encouragingly, some reviews suggested that validated interventions may lead to even greater benefits in LMIC contexts, highlighting the potential to improve youth mental health where it is most needed. Expanding research and culturally informed adaptations in these settings would also advance our understanding of which intervention components are universally effective versus those that are context-specific.

4) Limited Lived Experience and Real-World Relevance

Research rarely integrates the perspectives of young people with lived experience in defining outcomes and mechanisms. Co-design with young people was even less common, leading to a mismatch between what trials measure and what youth find meaningful, such as agency, hope, or quality of relationships. Young people themselves consistently emphasised the importance of trust, collaboration and therapeutic alliance. However, studies rarely tested these factors in intervention research. Including young people's perspectives in identifying priorities, refining mechanisms, and ensuring real-world relevance is essential for future work.

1.2.2 Recommendations & Priority Areas for Future Research

To address these challenges, we propose 32 recommendations to advance mechanistic understanding of interventions.
These emphasise the need for more precise and theory-driven studies, culturally diverse research, and embedding the perspectives of young people with lived experience to strengthen the scientific and practical value of findings. While all intervention areas would benefit from further investment, the following priority areas highlight key gaps where Wellcome is uniquely positioned to make a significant impact.

Design Studies to Explicitly Test Mechanisms

Future studies should be explicitly designed to test mechanistic hypotheses, using a pragmatic approach with a clear conceptual framework. This requires diverse and mixed-methods approaches combining quantitative, qualitative and co-design work. Examples include qualitative work, including theory of change, N-of-1 trials, moderation, mediation and dose-response analyses, and factorial or adaptive trial designs, among others. Integrating lived experience into study designs will further ensure that mechanistic models reflect real-world contexts and priorities.

Such methodological innovations are essential to move beyond descriptive efficacy towards precision in prevention and treatment. Wellcome is uniquely positioned to catalyse this agenda by encouraging the adoption of frameworks such as Kazdin's criteria, and by promoting pragmatic approaches that specify the types of study designs and evidence needed to advance mechanistic understanding.

Prevention Research to Identify Mechanisms Targeting Risk Factors

Advancing mechanistic understanding of how interventions reduce risk and promote resilience is essential, going beyond symptom reduction alone. Specifically, studies targeting risk factors in a selective prevention framework, especially those testing mechanistic pathways, could provide critical insights into how to reduce incidence and support resilience across developmental stages. Wellcome can help shift the field from understanding how to target underlying risk factors in order to prevent the onset of symptoms and reduce prevalence and burden.

Lifestyle Interventions

Physical activity, sleep and dietary approaches hold strong potential for both prevention and treatment of youth anxiety and depression. Rigorous research should prioritise studies that identify moderators, mediators, and mechanistic pathways. Beyond preventing onset or reducing acute symptoms, it is equally important to understand their role in sustaining recovery and supporting long-term well-being. These approaches can also be particularly suited to low-resource and diverse settings, making them a strategic investment for global impact.

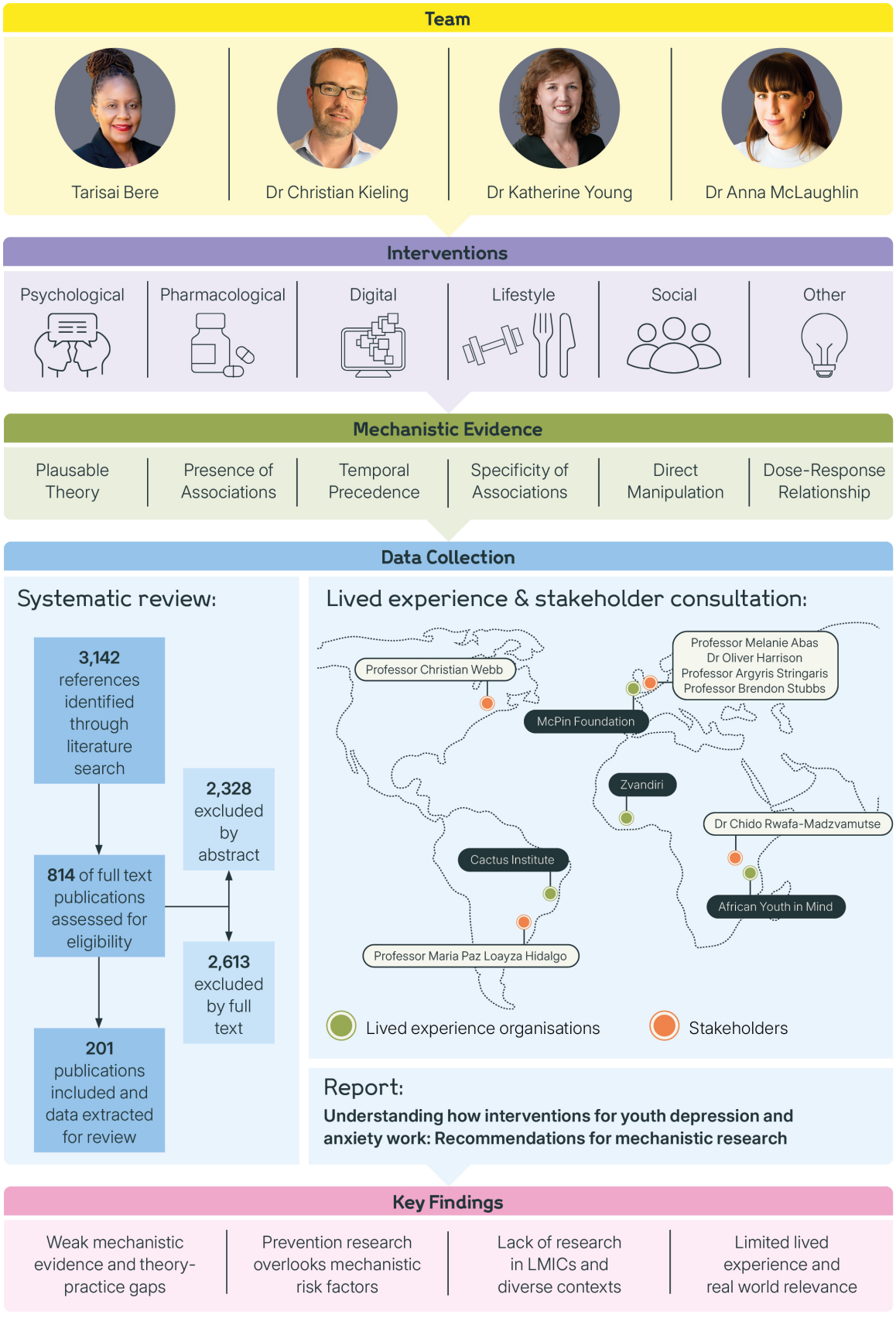
Social & Interpersonal Interventions

Social and interpersonal interventions already demonstrate efficacy and address processes that young people consistently identify as central to their mental health, including relationships, trust, belonging, and peer support. Future research should focus on refining existing theoretical models of change, pay particular attention to cultural adaptation and testing in LMICs, and incorporate lived experience to ensure that interventions align with the social realities of young people.

Creative & Spiritual Interventions

These approaches remain under-researched but have demonstrated early signals of efficacy and are often valued by young people. Rigorous mechanistic testing could clarify whether these interventions act through pathways such as identity formation, social connection, or emotional regulation. Given that such approaches are unlikely to receive support from other funders, Wellcome has a unique opportunity to advance this area.

1.3 Schematic Summary



1.4 Table of Abbreviations

Abbreviation	Definition
AI	Artificial Intelligence
CBT	Cognitive-Behavioural Therapy
EMDR	Eye Movement Desensitisation and Reprocessing
ERP	Exposure Response Prevention
HICs	High-Income Countries
HIV	Human Immunodeficiency Virus
LGBTQ+	Lesbian, Gay, Bisexual, Transgender, Queer or Questioning, Intersex, Asexual, and more
LMICs	Low and Middle-Income Countries
NHS	National Health Service
OCD	Obsessive-Compulsive Disorder
PTSD	Post-Traumatic Stress Disorder
RCT	Randomised Controlled Trial
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TMS	Transcranial Magnetic Stimulation
US	United States
UK	United Kingdom

1.5 Table of Contents

2. Introduction

Globally, one in three children will experience the onset of a mental health condition by age 14, and nearly 50% by age 18[3]. Anxiety disorders are most prevalent in early childhood, while depression peaks in adolescence[1]. Together, they are the leading causes of mental health-related disability among young people[4], negatively affecting academic performance, physical health, quality of life, and increasing the risk of future mental illness[5–7]. The prevalence and severity of youth anxiety and depression have risen steadily over recent decades, with sharp increases observed during the coronavirus pandemic[8,9].

2.1 State of the Field

In recent decades, many evidence-based interventions have been developed to alleviate anxiety and depression in young people. These span psychological, pharmacological, digital, lifestyle, and social or interpersonal interventions, among others.

Psychological therapies are the most widely studied and implemented interventions for youth depression and anxiety, with cognitive-behavioural therapy (CBT) showing the strongest evidence base across ages and settings[10,11]. A recent meta-analysis suggested the effects of validated psychotherapies may be higher in LMICs compared with HICs[12]. However, studies remain disproportionately concentrated in HICs, despite more young people living in LMICs[13].

Pharmacological treatments, primarily Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), have modest effect sizes for treating depression[14]. Evidence for newer antidepressants is limited, with few head-to-head comparisons and uncertainty regarding efficacy and tolerability[15,16]. Exploratory work on novel alternatives, such as omega-3 supplementation and anti-inflammatory agents, remains preliminary[17]. Increasingly, research is investigating how treatments interact with neurodevelopmental processes and identifying biological and psychosocial markers of treatment response[18].

Digital interventions are expanding rapidly, including traditional psychological interventions (such as CBT) delivered via digital platforms, as well as novel interventions ranging from conversational artificial intelligence (AI), gamified apps, and chatbots to wearables that generate continuous behavioural and physiological data, and virtual reality (VR) applications. While these technologies hold promise for monitoring and intervention, most commercial tools lack rigorous evidence, and few have

been tested in real-world settings[19]. Blended approaches, which combine digital tools with face-to-face support, show greater efficacy and adherence[20,21]. Developing a responsible digital ecosystem requires robust, evidence-based design and firm commitments to data privacy standards, security, and regulatory oversight[22].

Lifestyle interventions, including exercise, sleep, and nutrition, offer accessible and lower-risk strategies. Despite their frequent inclusion in clinical guidelines, lifestyle recommendations are often brief, qualitative, and based more on expert opinion than on robust paediatric trials[23]. Family and community-based approaches show promise with growing evidence of efficacy in LMICs[24,25]. Other interventions, such as play therapy, creative arts, and light or brain stimulation techniques, have been trialled but remain at early stages of evidence development in youth populations.

2.2 Challenges & Opportunities

Despite progress, one-third to two-thirds of young people receiving treatment for anxiety or depression do not achieve meaningful symptom reduction[2,26]. This limited effectiveness is attributed to inconsistent treatment fidelity, lack of continuity and personalisation, and slow development of novel approaches[27]. Many interventions are not well-tailored to individual needs, developmental stages, or diverse populations and cultural settings.

Prevention Research to Identify Risk Factors

A fundamental challenge is that few interventions target risk factors or resilience processes. While reviews report small but significant effects of prevention programmes for youth anxiety and depression[26,28–30], findings are inconsistent and constrained by methodological weaknesses, insufficient screening, and short follow-ups[28,29,31]. The majority of prevention programmes focus on secondary rather than primary prevention, adapting treatments for those with subclinical symptoms instead of addressing underlying risk factors. For instance, some physical activity trials include unscreened participants, merging preventive and therapeutic effects[32]. Distinguishing these effects is important, as mechanistically effective prevention should act on vulnerabilities before symptoms emerge.

Mechanistic Research in Diverse Settings

Research is disproportionately concentrated in HICs, even though most of the world's young people live in LMICs[33]. Across LMICs, significant treatment gaps persist, underpinned by limited data, scarce specialist training, and a lack of comprehensive policies. In the African Region, only 11 of 47 countries reported having a dedicated child and adolescent

mental health services plan in 2020[34]. Global mental health research also suffers from limited methodological rigour and reliance on Western measures, with one review finding that over 16% of tools in cross-national studies deemed cultural appropriatene[35]. Such gaps hinder the generalisability of findings and risk misrepresenting culturally specific expressions of distress.

The Value of Lived Experience

There is growing recognition that youth mental health research must be conducted with, not just for, young people. Since 2018, co-design methodologies have gained traction, supported by funders such as Wellcome, the National Institute for Health, and the UK Medical Research Council[36,37]. However, evaluations of co-design in youth mental health show mixed quality as around a third of studies are rated low quality, with limited participation and insufficient attention to issues of power dynamics, ethics, and participant well-being[36]. Poorly implemented approaches risk ethical harm, particularly for young people with depression and suicidality. In contrast, the meaningful inclusion of young people with lived experience improves research relevance, reduces stigma, and fosters mutual expertise and skills[38–40].

2.3 Summary

Despite decades of progress, the field still lacks a clear understanding of how and why interventions work, or which components are most effective[41]. Addressing this requires a shift toward mechanistic, hypothesis-driven research that investigates the psychological, biological, social, and environmental processes through which interventions exert their effects[42]. Mechanistic approaches provide a stronger rationale for investment and implementation by clarifying active ingredients and pathways of change[43]. Research must also be co-designed with young people and embedded within communities and diverse cultural contexts.

These priorities mirror wider shifts in global health policies, such as England's NHS 10-Year Plan that emphasises community-based, digitally-enabled care with a stronger patient voice. Similarly, Finland's "Health in All Policies" integrates mental health into social policy, while South Africa's Higher Health programme embeds health promotion and literacy into educational settings. Such initiatives create a supportive environment for mechanistic research, strengthening the potential to deliver scalable and contextually appropriate interventions. By bringing together mechanistic science and lived experience, future research can identify what works, for whom, and why, while ensuring outcomes are meaningful and relevant to young people's lives.

3. Methodology

We conducted a rapid umbrella scoping review to synthesise peer-reviewed literature reviews and meta-analyses on the mechanisms of interventions for anxiety and depression in children and adolescents under 18 years. We extracted data using the Joanna Briggs Institute framework for systematic reviews and research syntheses. As the authors of this report, we are a multidisciplinary team with expertise in youth mental health, clinical and mechanistic research, and evidence synthesis based in Brazil, the UK, and Zimbabwe.

3.1 Mechanistic Evidence

In this report, we defined mechanisms as the psychological, biological, social, and environmental processes through which interventions exert their effects. Drawing on Kazdin's definition, *"the steps or processes through which therapy (or some independent variable) actually unfolds and produces the change"*[44], we consider mechanisms as the link between the intervention and outcomes. When considering the availability and strength of mechanistic evidence, we sought to identify research that addressed any of the following six key principles, as defined by Kazdin [44]:

1. **Plausible or Coherent Theory:** A coherent and clearly articulated rationale that explains how the mechanism fits within an intervention and leads to outcomes (e.g. face validity).

2. **Presence of Associations:** Significant associations between intervention and mechanism, and between mechanism and outcome.

3. **Temporal Precedence:** Changes in the mechanistic or mediator variable are assessed prior to changes in the outcome.

4. **Specificity of Association:** The mediator accounts for the majority of variance in outcomes, distinguishing it from other plausible mechanisms.

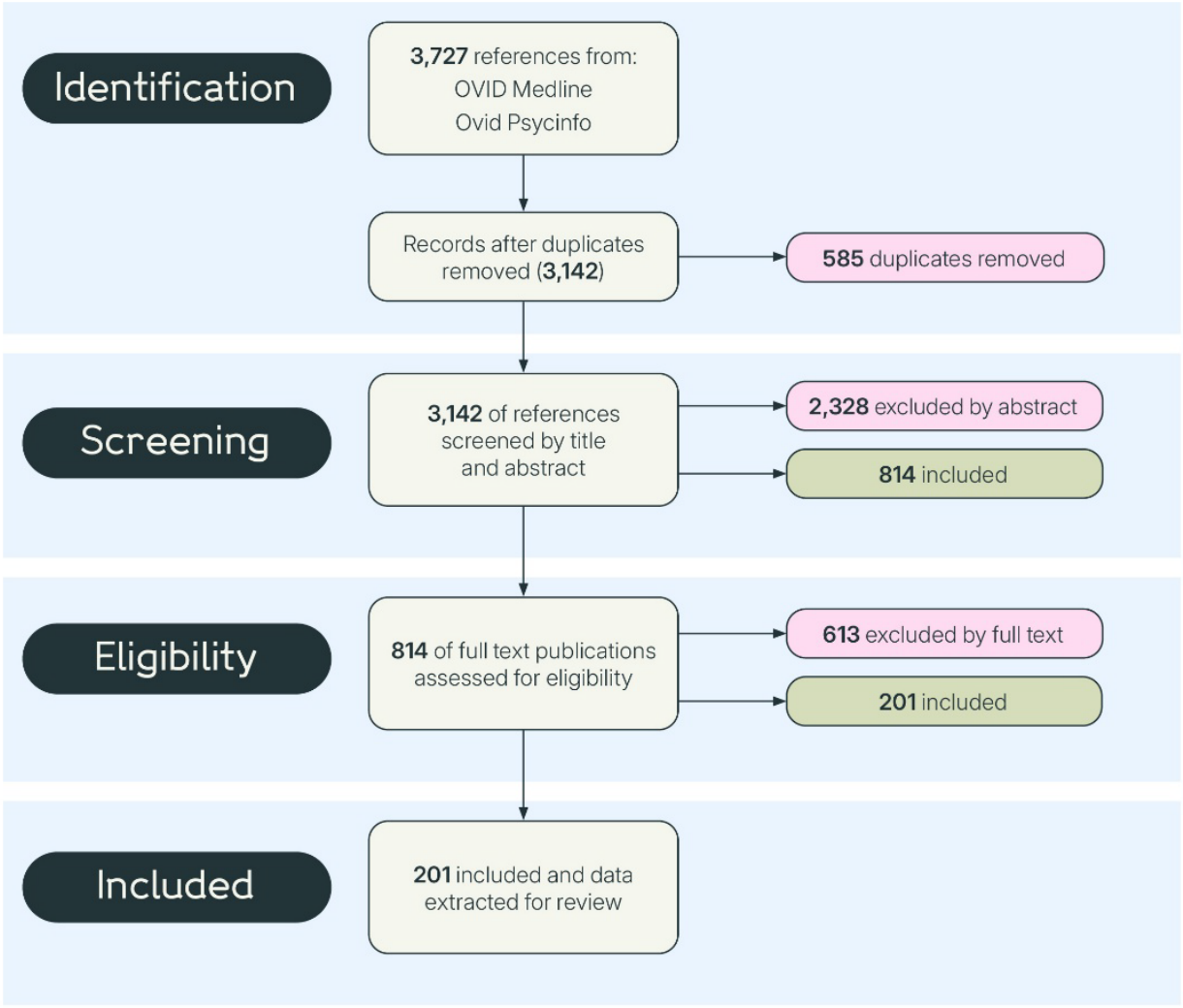
5. **Direct Manipulation:** Targeted studies testing specific 'core components' or 'active ingredients' of an intervention (e.g. behavioural activation alone).

6. **Dose-Response Relationship**: The extent of therapeutic change is related to the 'dose' of the intervention received.

3.2 Lived Experience & Stakeholder Consultation

Young people with lived experience of anxiety and depression from advisory groups across Brazil, Ghana, the UK and Zimbabwe informed the report and recommendations. We also conducted stakeholder interviews with leading researchers and practitioners in mental health.

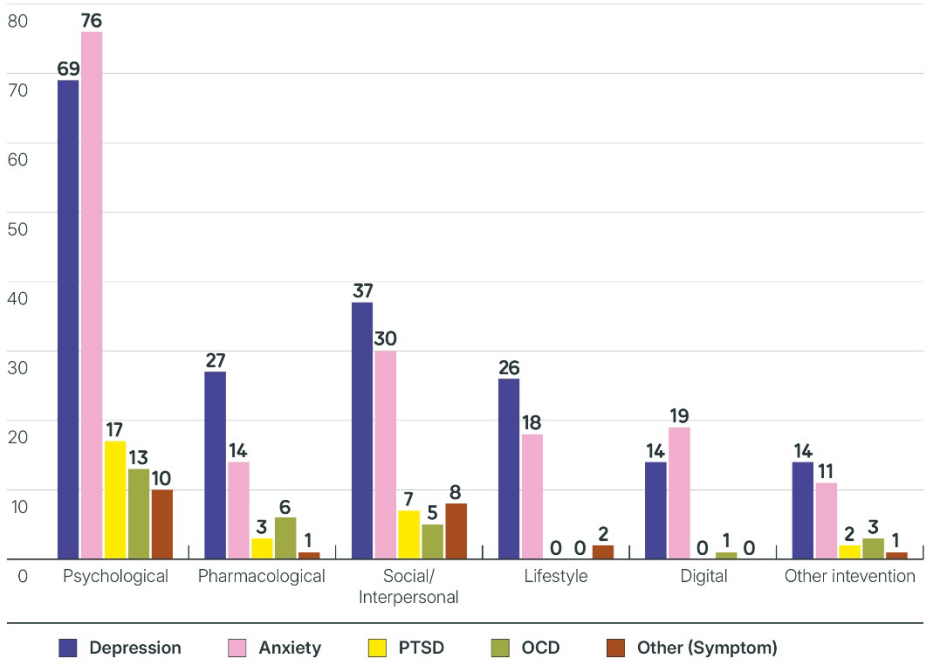
3.3 Methodology Diagram



4. Results & Recommendations

Out of 814 papers screened, 201 (25%) were included for full data extraction. Most exclusions (73%) were due to not meeting the eligibility criteria, primarily because of limited discussion of mechanisms (~60%) or a lack of focus on children and young people (~16%). Only 2% were excluded due to being inaccessible. The reviews were published between 1990 and 2025, with 89% published after 2010. Among the included reviews, 74% used systematic review methodologies.

Chart of Interventions by Condition



Included reviews focused on psychological interventions for depression and anxiety, which were the most frequently discussed conditions among reviews. Some reviews covered multiple conditions or interventions.

When assessing the mechanistic evidence according Kazdin's six key principles [44], we found that while 73% of reviews considered moderators, only 28% assessed mediators, restricting insight into the pathways through which interventions exert their effects. The majority of reviews discussed the theoretical rationale linking interventions to proposed mechanisms, and reported associations between interventions,

mechanisms, and outcomes. Fewer than 25% examined the specificity of these associations or the impact of manipulating core active ingredients. Temporal precedence and dose–response relationships were the least often discussed in the literature[1].

Only one-third of reviews (32%) had registered protocols, raising concerns about transparency and potential bias. Involvement of lived experience was nearly absent, with just 6% of reviews mentioning it in methodologies.

Geographic reporting across reviews was inconsistent, with many papers failing to specify the location of studies included in reviews. Among those that did, research was heavily concentrated in HICs, particularly the United States, the UK, Canada, Australia, and several European nations. Only a small number of reviews (~13%) included studies conducted in LMICs.

The evidence base showed a strong bias toward Western, English-speaking populations, lacking insight into diverse cultural and social factors influencing youth mental health. The underrepresentation of LMICs constrains the generalisability of findings and underscores the need for investment in locally led studies.

4.1 Psychological Interventions

Psychological interventions are the most widely researched and implemented type of intervention for youth mental health conditions. Systematic reviews confirmed the overall efficacy of CBT across developmental stages and settings, making it the current gold standard for treating depression and anxiety[10,11]. Other therapies with good evidence include interpersonal psychotherapy for depression[11] and trauma-focused CBT for post-traumatic stress disorder (PTSD)[45]. Exposure and response prevention (ERP) is particularly effective for obsessive-compulsive disorder (OCD)[46].

Interventions were typically most effective when they targeted specific cognitive and emotional processes, and were tailored to suit the age and specific context of the young people involved[10,11,47,48]. Preschool years were cited as an optimal period for anxiety intervention, with strategies ranging from universal to targeted prevention and treatment using Parent-Child Interaction Therapy[49]. Emerging evidence supported transdiagnostic approaches such as the Unified Protocol for Adolescents, which targets core emotion dysregulation symptoms across depression and anxiety. Trauma-focused CBT, prolonged exposure and Eye-Movement Desensitisation Reprocessing (EMDR) were also effective for PTSD, especially EMDR in conflict settings[50].

Intervention outcomes varied depending on population, developmental stage, and setting. While problem-solving interventions showed effectiveness for clinical populations, their results were mixed in universal or selective prevention settings[51]. Mindfulness, “wise interventions” (including gratitude and self-affirmation exercises), and gamified or school-based programmes showed small, short-term effects on reducing anxiety symptoms, but require more comparative and mechanistic research[52,53]. Evidence in other areas, such as PTSD in displaced populations or brief and unguided OCD interventions, remains weak or inconsistent[54].

Overall, the literature suggested clear benefits of targeting specific psychological processes, including reducing negative thinking, avoidance, and compulsions, and strengthening coping, emotion regulation, and social connection. However, there are gaps in our understanding of which components of interventions are essential and how best to adapt them across diverse groups.

Key Gaps & Challenges

Although psychological interventions are well-established, mechanistic research remains limited. Many interventions were informed by theory but failed to operationalise or measure mechanisms explicitly, and could not demonstrate temporal or causal

relationships. Mechanisms were often assessed concurrently with outcomes, preventing robust conclusions about causality. Moderator analyses were the most common, but still require additional research[55,56]. Formal mediation testing, mid-treatment assessments, and dose–response analyses were uncommon, leaving uncertainty about which components truly drive change[57]. Depression interventions were especially affected by this challenge, as multi-component approaches combine cognitive, behavioural, and interpersonal techniques in ways that obscure which elements are active ingredients. Research on anxiety and OCD interventions was clearer due to reliance on well-defined mechanisms such as ERP.

Other challenges related to the scope and inclusivity of psychological research. Individual variability in response to therapy, shaped by comorbidity, developmental stage, and cultural context, were rarely examined systematically, and most evidence came from high-income, Western populations. Studies testing adaptations for LMICs, displaced populations, or culturally diverse groups remain scarce. Brief or scalable formats, such as Wise interventions or gamified CBT, showed promise but have not been evaluated with sufficient rigour to confirm mechanisms of change. Finally, trials seldom integrated the perspectives of young people or caregivers, meaning research risks overlooking the psychological outcomes and processes that are most meaningful to young people. Future psychological intervention research must move beyond documenting efficacy to directly testing, comparing, and contextualising mechanisms of change and integrating lived experience and adaptations for LMICs.

Insights from young people with lived experience

The young people we interviewed emphasised that psychological interventions are most effective when they are tailored, culturally relevant, and grounded in trust. In the UK, participants valued personalised approaches and preferred practical, behaviour-focused strategies over formulaic CBT. They viewed the therapeutic relationship as critical, but mismatches or a lack of trust could undermine progress. There was frustration that CBT was often the only option offered, leaving little access to trauma-focused, psychodynamic, or systemic therapies.

In Brazil, experiences with CBT were generally positive, but in Zimbabwe and Ghana, challenges of cultural mismatch, access, and parental involvement were more prominent. Zimbabwean youth described how advice from foreign-trained therapists often felt irrelevant to local family dynamics, while costs and reliance on parental approval limited access. Parental participation could be supportive, but was also seen as harmful when parents were the source of distress, with a lack of privacy in school counselling compounding these issues. Ghanaian participants highlighted

poor communication, lack of consent, gender mismatches with therapists, and mistrust in psychiatric services as significant barriers.

These perspectives highlight the need for greater autonomy in therapy choice, culturally adapted delivery, meaningful involvement of young people in shaping interventions, and family dynamics. Where these conditions are absent, therapy risks being ineffective or even harmful.

4.1.1 Recommendations for Psychological Interventions

	Recommendation	Challenge	Strategic Fit
1	Compare efficacy across developmental stages to identify optimal periods for intervention	Lack of age-specific research limits understanding of what works at developmental stages	Robust evidence by age group enables stratified early intervention
2	Invest in diverse study designs, including multiple N-of-1 and qualitative methods, to explore individual-level mechanisms of change	RCTs are not often designed to test mechanisms and miss individual-level responses	Interventions based on individual characteristics and transdiagnostic targeting
3	Integrate contextual adaptations and lived experience to identify mechanisms in real-world settings	Interventions show poor contextual adaptation from adult models and from HICs to LMICs	Scalable, context-sensitive interventions; co-developed with young people with lived experience
4	Prioritise funding for studies that use a clear theory of change to test mechanisms of psychological interventions	Studies lack a theory-driven model of how change occurs, limiting replicability and mechanistic insight	Clearer mechanistic understanding of psychological interventions through hypothesis-driven clinical trials
5	Strengthen research on interventions that equip caregivers to support therapeutic mechanisms	Family context and lack of caregiver training often undermine therapeutic gains in anxiety, depression and OCD	Interventions meeting the needs and priorities of end beneficiaries with lived experience

1) Compare efficacy across developmental stages to identify optimal periods for intervention

Challenge:

There is limited developmental evidence to guide the selection of psychological interventions that are most effective at different ages. Interventions designed for adults are often adapted for younger populations without adequate testing, and effectiveness can vary considerably depending on developmental timing. This lack of age-specific insight limits our ability to tailor support and identify when interventions are most impactful.

Mechanistic Opportunities:

Prioritise mechanistic research that explores how the developmental stage influences the effectiveness and underlying mechanisms of psychological interventions. This includes:

- Comparing treatment response across developmental stages or key phases such as early childhood, middle childhood, and adolescence.
- Testing whether mechanisms such as cognitive restructuring, emotion regulation, problem-solving, or exposure function differently across developmental stages.
- Identifying sensitive periods for intervention, during which symptom improvement is more easily achieved or sustained.

Supporting Evidence:

Preschool years may represent an especially promising period for anxiety intervention, with CBT and parent–child interaction therapy showing utility across universal, targeted, and treatment contexts[54]. Similarly, depression research highlights how interventions targeting cognitive restructuring and social connection can be effective when adapted to developmental needs[11,48]. However, few studies systematically compare effectiveness or mechanisms across developmental periods[2].

2) Invest in diverse study designs, including multiple N-of-1 and qualitative methods, to explore individual-level mechanisms of change

Challenge:

Psychological intervention research in youth is dominated by RCTs, which can lack the sensitivity and specificity to test underlying mechanisms of change. Study designs that focus on averaging group effects lack detailed context on why treatments work for some young people and not others, especially those with comorbid or complex presentations. Diverse study

designs are required for investigating non-responders, comorbid presentations, and complex or non-linear therapeutic pathways.

Mechanistic Opportunities:

Advance person-specific mechanistic research by funding a broader range of study designs. This should include:

- N-of-1 trials and idiographic methods that can capture within-person variation over time, helping identify which mechanisms predict symptom change in individuals.
- Qualitative and mixed-methods designs to uncover emergent or context-dependent mechanisms that are not easily tested in RCTs.
- Research proposals should include clear mechanistic hypotheses and study designs, with explicit targets, validated instruments, and data collection timed to establish temporal precedence.
- Strong attention to treatment fidelity, with requirements for therapist training, supervision, and independent fidelity assessment.

Supporting Evidence:

Existing studies rarely use designs capable of capturing nuanced or individual-level change processes. N-of-1 designs are particularly important for treating complex or comorbid cases, validating person-specific mechanisms, and exploring reasons for therapy non-response[58]. This is especially relevant given the gaps in understanding of how comorbidities influence treatment outcomes.

3) Integrate contextual adaptations and lived experience to identify mechanisms in real-world settings

Challenge:

Most psychological intervention studies in youth are developed and tested in high-resource settings or adapted from adult models with minimal attention to contextual relevance. There is a lack of research into how mechanisms of change operate differently across settings, such as schools, communities, or displaced environments, and limited integration of lived experience input to inform adaptations. This reduces the generalisability and relevance of findings for underserved groups.

Mechanistic Opportunities:

Advance mechanistic research that tests how cultural and contextual factors shape pathways of change. Studies should:

- Include adaptation plans that preserve core processes (e.g. exposure, cognitive restructuring) while ensuring local cultural and developmental relevance.

- Examine how delivery adaptations (e.g. peer-led or school-based formats, culturally grounded framing) influence mechanisms and pathways to symptom change.

- Combine quantitative and qualitative approaches to capture both causal processes and contextual influences that shape how mechanisms operate in real-world settings.

- Use participatory and co-designed methods to identify active mechanisms in diverse real-world contexts, including low-resource and non-clinical settings.

- Integrate lived experience input throughout study design and adaptation, ensuring that mechanistic targets reflect what matters most to young people.

Supporting Evidence:

Interventions demonstrated to be effective in adults may not translate to children in displaced or low-resource settings due to a poor contextual fit[54]. Lived Experience advisory groups also highlighted the importance of contextual fit, noting that advice from foreign-trained therapists often clashed with local customs and family practices.

4) Prioritise funding for studies that use a clear theory of change to test mechanisms of psychological interventions

Challenge:

Many psychological intervention studies in young people lack clearly articulated theories of change, making it challenging to identify how interventions are expected to work or to replicate them in different contexts. There is also a persistent gap between the demonstrated efficacy of mechanism-driven therapies in trials and their effectiveness and accessibility in real-world settings. Implementation is often hindered by insufficient adaptation to local cultural contexts, which limits scalability.

Mechanistic Opportunities:

Require that funded studies define and test hypothesised pathways of change, including:

- A dedicated theory of change section in research proposals that maps the intervention to a Theory of Change framework and highlights causal pathways.

- Clearly articulate the justification for the design of each step, supported by published literature or lived experience input.
- Tracking mediators and symptoms repeatedly across treatment, rather than relying on pre–post assessments, to establish temporal precedence.
- Testing fidelity in adapted delivery models, confirming that changes to format, setting, or providers do not dilute the engagement of active mechanisms and resulting efficacy.

Supporting Evidence:

Certain psychotherapies exhibit different treatment effect sizes in LMICs compared to HICs, which may be due to differences in control conditions, delivery formats, or social and contextual drivers[12]. Incorporating a Theory of Change framework can improve the design and evaluation of complex interventions, ultimately leading to more effective, sustainable and scalable approaches[59].

5) Strengthen research on interventions that equip caregivers to support therapeutic mechanisms

Challenge:

Family involvement has a strong influence on the trajectory of anxiety, depression and OCD in children. Even when young people receive effective individual therapy, their home context may continue to maintain or re-trigger symptoms, reducing the durability and overall impact of treatment. While some interventions involve parents or caregivers, few are explicitly structured to equip caregivers with the skills needed to actively support therapeutic mechanisms.

Mechanistic Opportunities:

Prioritise research on family and systemic interventions that:

- Measure changes in family accommodation, caregiver modelling, and parental support skills across multiple time points, allowing for mediation analyses that test whether caregiver support precedes symptom change.
- Include structured caregiver modules with manuals, training, and independent fidelity checks to ensure consistency in targeting family processes.
- Investigate how cultural and contextual factors shape the expression and impact of accommodation behaviours, with adaptation strategies that preserve core mechanisms.

- Integrate lived experience input to ensure caregiver psychoeducation addresses misconceptions, reduces stigma, and reflects the needs of young people across diverse populations.

Supporting Evidence:

Reductions in family accommodation are associated with greater treatment efficacy and more durable outcomes for OCD[60,61]. Similar effects are observed in anxiety and depression, where caregiver training in adaptive coping, behavioural activation, and supporting gradual exposure enhances children's outcomes [48,52]. Lived experience input also highlighted that caregivers often lack psychoeducation, and that stigma or rigid beliefs, particularly around conditions such as anxiety, human immunodeficiency virus (HIV), and lesbian, gay, bisexual, transgender, queer or questioning, intersex, asexual, and more (LGBTQ+) identities, can worsen distress and undermine therapy[3].

4.2 Pharmacological Interventions

Pharmacological interventions, primarily new generation antidepressants like SSRIs and SNRIs, are key components in the treatment of depression and anxiety in youth[14,62–67]. Some SSRIs, notably fluoxetine, show superiority over placebo for depression and are often considered a first-line option in guidelines[14,15,62]. However, the magnitude of antidepressant effect beyond placebo has been described by some as small and potentially clinically unimportant[14]. The efficacy and tolerability of newer antidepressants beyond SSRIs/SNRIs are under-researched, with limited head-to-head trials and uncertain evidence for many comparisons[15,16,68]. A significant limitation is that clinical trials often exclude key populations who are more typical of those seen in services, such as young people with complex presentations including significant comorbidities or those at high risk of suicide; there is also less data available for preadolescent age groups[69]. Overall, results are often inconsistent, and their generalisability remains limited due to methodological shortcomings, heterogeneity in study designs and populations, small effect sizes, and high placebo response rates[66].

A recent scoping review of RCTs for adolescent depression identified multiple variables associated with treatment outcomes across pharmacological, psychological, and combined interventions. Variables reported as significant in at least three RCTs included age, sex/gender, baseline depression severity, early treatment response, sleep changes, parent–child conflict, overall psychopathology, suicidal ideation, hopelessness, functional impairment, therapy attendance, and trauma history. Despite their potential value for personalising care, few studies tested these factors using a priori hypotheses or adjusted for multiple comparisons, limiting confidence in their predictive power. Incorporating such predictors, moderators, and mediators into rigorously designed pharmacological trials could support precision prescribing and better stratification of youth most likely to benefit, or at risk of harm, from specific treatments[70].

Key Gaps & Challenges

A significant gap exists in understanding the mechanisms by which these pharmacological treatments work, particularly their impact on the developing adolescent brain[66,71,72]. While theories exist involving monoamine systems, neuroplasticity, and changes in brain connectivity or emotional processing, the knowledge of how the acute pharmacological effects translate into clinical benefits is incomplete, and there is a scarcity of relevant mechanistic studies in young people; furthermore, there is a lack of validated biomarkers that could help predict treatment response or inform clinical decision-making for individual patients[66].

Given the profound neural, cognitive, and psychosocial transformations that characterise childhood and adolescence, the effects of SSRIs in youth may differ significantly from those observed in adults. Adding further complexity, clinical trials involving children and adolescents often report elevated placebo response rates, which challenge the interpretation of efficacy outcomes. Although some studies suggest that lower methodological quality may inflate placebo effects, it remains unclear to what extent developmental factors contribute to this phenomenon.

In parallel, regulatory warnings regarding treatment-emergent suicidality in pediatric depression trials raise serious concerns about safety and highlight gaps in our understanding of the risk-benefit profile of antidepressant use in this population. Together, these challenges emphasise the urgent need for rigorous, developmentally informed research to clarify the safety, effectiveness, and underlying mechanisms of SSRIs in young people.

Insights from young people with lived experience

Young people's views on pharmacological interventions reflected both positive experiences and significant concerns. Medication was generally perceived as most helpful when used alongside therapy, particularly for conditions such as depression and PTSD. In these cases, appropriate prescribing could lead to substantial symptom relief and improved day-to-day functioning. Some participants described combining medication with other forms of support as more effective than using medication alone.

Participants also described significant barriers, including delays or restrictions in access to medication for under-18s, lack of informed choice, insufficient discussion of benefits and risks, and side effects that disrupted daily life. In some contexts, there were additional concerns about over-prescription without thorough assessment, over-reliance on medication as a long-term solution, and mistrust in prescribers. Across all contexts, young people consistently called for accessible information in simple formats and for youth-centred research that ensures informed choice, consent, and collaborative discussion are central in the prescribing process.

4.2.1 Recommendations for Pharmacological Interventions

	Recommendation	Challenge	Strategic Fit
1	Clarify how SSRIs exert therapeutic effects in the developing brain	SSRIs are widely prescribed to youth, but their neurobiological mechanisms in the developing brain remain unclear and are largely taken from adult data	Improved interventions grounded in measurable biological characteristics
2	Identify the mechanisms underlying high placebo response rates in youth depression trials	High placebo response rates in youth trials reduce power to detect treatment effects, and underlying biopsychosocial drivers are unknown	More rigorous clinical trials focused on early intervention
3	Investigate mechanisms underlying antidepressant-related suicidality and behavioural activation in youth	Risks of treatment-emergent suicidality and behavioural activation are higher in youth, but mechanisms are poorly understood	Better targeting of pharma interventions to vulnerable subgroups
4	Systematically investigate mechanisms underlying combined pharmacological and psychological interventions in youth	Combined medication and psychotherapy are more effective than either alone, but the mechanisms of synergy are unknown	Integrated and more effective early interventions
5	Investigate the mechanisms of non-SSRI/SNRI treatments and their potential for personalised pharmacological care	Alternatives to SSRIs/SNRIs may work via novel pathways but remain under-researched in youth	New interventions for early-stage treatment, precision pharmacology based on biological characteristics

1) Clarify how SSRIs exert therapeutic effects in the developing brain

Challenge:

SSRIs are the most commonly prescribed antidepressants for children and adolescents, yet the neurobiological mechanisms through which they produce therapeutic effects during development are not well understood. Current use is largely based on adult data, despite fundamental differences in brain maturation.

Mechanistic Opportunities:

Prioritise mechanistic research that investigates how SSRIs influence neurodevelopmental processes relevant to anxiety and depression symptom change in youth. This includes:

- Mapping how SSRIs affect neural circuit maturation, neuroplasticity, neurotrophin expression, synaptic remodelling, and neurotransmitter activity over time.
- Determining whether observed neurobiological changes are causally related to symptom improvement.
- Investigating chronopharmacology approaches, assessing how dosing time interacts with circadian biology in adolescence, given rapid changes in sleep–wake cycles during this period.

Supporting Evidence:

Despite the widespread use of SSRIs in young people, evidence explaining their long-term neurobiological effects in the developing brain remains scarce[66]. A Cochrane network meta-analysis concluded that while SSRIs may provide a small reduction in depression symptoms beyond placebo, the evidence base is limited by methodological shortcomings and lacks robust mechanistic explanations linking drug action to clinical outcomes[14]. Moreover, findings reflected average effects and were insufficient for informing individual-level treatment decisions. Without a clear mechanistic rationale, it is difficult to optimise treatment, stratify by likely responders, or anticipate which patients are more vulnerable to adverse outcomes. Strengthening the mechanistic evidence base would support stratified prescribing guidelines and more targeted early intervention trials.

2) Identify the mechanisms underlying high placebo response rates in youth depression trials

Challenge:

Placebo response rates in pediatric depression trials often exceed 50%, which is substantially higher than in adult populations. This narrows the observable difference between intervention and control groups, reducing the power to detect true treatment effects. Traditional trial designs rarely account for developmental, psychological, and contextual factors that may amplify placebo responsiveness in young people.

Mechanistic Opportunities:

Prioritise research to disentangle the biological, developmental, psychological, and social drivers of placebo response in youth by:

- Identifying biomarkers associated with heightened placebo response
- Studying developmental, psychological and social factors
- Investigating the role of therapeutic alliance, expectations, and context of care in placebo-controlled studies

Supporting Evidence:

Placebo response rates of nearly 50% in pediatric depression trials are higher than what is observed for adults[73,74]. Placebo response was particularly elevated in trials with younger participants, lower baseline severity, and more study sites, but these factors did not fully explain the trend. The phenomenon challenges traditional drug-placebo comparisons and points to the role of developmental and psychosocial influences on treatment outcomes[75]. Improving the understanding of biopsychosocial mechanisms will inform the design of more sensitive trials and improve the interpretation of efficacy results in pharmacological research.

3) Investigate mechanisms underlying antidepressant-related suicidality and behavioural activation in youth

Challenge:

Treatment-emergent suicidality remains a critical concern in the use of antidepressants among children and adolescents, with risks appearing greater than in adults. The mechanisms driving these adverse outcomes, particularly suicidality and behavioural activation syndrome, are poorly understood, limiting the ability to predict and prevent harm.

Mechanistic Opportunities:

Prioritise research to identify why certain young people experience these adverse outcomes by:

- Characterising risk factors such as neurobiological vulnerabilities, pharmacodynamic differences in the developing brain and genetic predisposition.
- Stratifying analyses by antidepressant half-life to assess whether pharmacokinetic profiles predict adverse behavioural outcomes in trials and observational studies.
- Examining psychological pathways that may mediate suicidality risk.
- Investigating mechanisms underlying behavioural activation, which is more common in the pediatric population.

- Using large-scale, long follow-up trials and integrating observational data to address safety, suicidality, and subpopulation responses.

Supporting evidence:

The risks of treatment-emergent suicidality in youth receiving antidepressants have been documented[63,76]. The Food and Drug Authority's 2004 black box warning was based on findings that suicidal ideation and behaviour were approximately twice as likely in children and adolescents treated with SSRIs compared to placebo; a concern later confirmed by a 2021 Cochrane meta-analysis, especially for venlafaxine[14]. Proposed mechanisms include neurodevelopmental vulnerability, serotonergic dysregulation, or early adverse effects like akathisia, leading to agitation and risk. Pharmacokinetic factors, such as shorter half-life agents, may lead to more pronounced withdrawal or fluctuation effects, which could exacerbate risk during initiation or discontinuation[77]. Behavioural activation syndrome, which encompasses side effects such as irritability, agitation, impulsivity, and emotional lability, affects over one in ten youth receiving SSRIs[66,71]. Identifying predictors of risk could enable stratified prescribing and earlier identification of adverse responses

4) Systematically investigate mechanisms underlying combined pharmacological and psychological interventions in youth

Challenge:

Combined treatments such as SSRIs plus CBT are widely used and appear more effective than either treatment alone. However, the mechanisms driving this synergistic effect are not well understood. Without this understanding, it is difficult to optimise or personalise integrated care approaches for young people.

Mechanistic Opportunities:

Conduct mechanistic studies to explore how pharmacological and psychological factors interact in combined treatment approaches for anxiety and depression. Specific areas of focus could include:

- Whether medication-induced neuroplasticity facilitates learning and behavioural change during therapy.
- Whether engagement in psychotherapy influences medication adherence or reduces side effects.
- How treatment sequencing or synchronisation affects outcomes.
- Improve control conditions in both medication and psychotherapy trials (e.g. to address placebo strength and disappointment bias).

Supporting evidence:

Although combined SSRI and CBT treatment has shown efficacy[78], the mechanisms underlying this synergy are poorly understood. For instance, whether pharmacological effects facilitate emotional learning during therapy, or vice versa, remains to be clarified[15,66]. Understanding these interactions could help tailor interventions based on developmental stage, symptom profile, or biological markers.

5) Investigate the mechanisms of non-SSRI/SNRI treatments and their potential for personalised pharmacological care.

Challenge:

The current evidence base for pharmacological treatments in young people is dominated by SSRIs and SNRIs. However, these do not work for all individuals and may have limitations or safety concerns. Alternatives such as agomelatine, ketamine, and anti-inflammatory agents already have initial studies in adolescents, but remain under-researched in this age group compared to adults.

Mechanistic Opportunities:

Expand mechanistic research on how non-SSRI/SNRI agents and other emerging compounds that act via different biological pathways produce therapeutic effects. This includes:

- Investigate how treatments may operate through distinct biological pathways, including circadian rhythm modulation, glutamate transmission, or rapid synaptic plasticity.
- Study anti-inflammatory agents in adolescents with elevated inflammation to evaluate how immune signalling affects neurodevelopment and symptom trajectories.
- Identify biosignatures of treatment response to guide personalised treatment decisions and move beyond monoaminergic-based prescribing.
- Explore the druggable genome (the set of genes encoding proteins that can be modulated by therapeutic compounds, such as receptors, enzymes, and ion channels) and pharmacogenetic approaches to identify novel targets and personalise prescribing in youth mental health.

Supporting evidence:

Non-SSRI treatments such as ketamine, agomelatine, and anti-inflammatory agents have been investigated in adults, but research in youth remains limited. A recent scoping review of omega-3 supplements

found insufficient evidence for efficacy but highlighted potential inflammation-related pathways[17]. There is growing recognition of the need to examine how these alternatives interact with neurodevelopmental processes and to stratify responses using biological markers. A mechanistic approach could move the field beyond trial-and-error prescribing and align with the increasing focus on predictors, moderators, and mediators of treatment response in adolescent depression[70].

4.3 Digital Interventions

Most evidence on digital interventions focuses on internet-delivered psychological therapies, primarily web- or app-based tools that use cognitive–behavioural approaches. Additionally, some digital interventions target specific skills or mechanisms, such as bias modification (attentional or cognitive bias) or mental health monitoring, while others aim to deliver therapeutic content through conversational AI tools, VR, or gamified interventions.

Internet-delivered psychological interventions demonstrate the most consistent evidence of effectiveness for youth anxiety and depression, according to a recent meta-analysis of 34 trials[79]. However, evidence is limited by short follow-up and lack of direct comparisons with other treatment modalities. Other interventions, such as AI chatbots and gamified approaches, show some evidence of efficacy in adults, but research is limited in young people. VR has been shown to reduce anxiety in young people in a small number of studies [80,81]. Bias modification interventions reported mixed results, with limited evidence that changes in attention or interpretation bias led to symptom improvement[82,83].

Key Gaps & Challenges

Mechanistic understanding of digital interventions for youth depression and anxiety is particularly underdeveloped. The quality of studies reported by reviews was medium to poor. Sample sizes were typically small, limiting the statistical power for subgroup or moderator analyses and lacked long-term follow-up. Other challenges include highly varied rates of engagement and significant ethical concerns around balancing privacy and autonomy with the need for appropriate supervision and safety. Some promise lies in integrating digital tools into existing care systems, providing opportunities for clinical oversight, but appropriate escalation pathways and governance are necessary for success.

Reviews examining moderators of digital intervention efficacy failed to identify robust effects for gamified interventions[84,85], VR[81], and psychological interventions[82,83,86]. One review attempted to mechanistically link attentional bias changes with anxiety via moderated mediation analysis, but reported non-significant results and an underpowered sample[87]. In contrast, some interventions were supported by theorised mechanisms of change, such as self-monitoring, rehearsal and social learning in internet-based CBT[88], or emotional validation and reduced disclosure barriers in AI chatbots[89]. However, evidence supporting these theories remains limited.

Insights from young people with lived experience

Young people valued digital interventions for their anonymity, accessibility, and ability to connect with peers. Apps for mindfulness, mood tracking, and moderated peer communities were seen as helpful, particularly for those distrustful of in-person therapy or facing barriers to care. Participants agreed that digital tools should supplement, not replace, human support. AI chatbots and VR raised consistent concerns as they were viewed as potentially depersonalising, unsafe in crisis situations, and lacking practical solutions when used without human oversight.

Differences between regions were related to structural barriers and local context. In Brazil, the focus was on mindfulness and emotion-tracking apps, alongside caution about the real impact of AI tools. In the UK, online peer support was seen as effective for reducing loneliness and stigma. In Zimbabwe, WhatsApp groups were cautiously accepted but raised concerns about privacy and data access. Digital exclusion was a major concern (e.g. access to smartphones, data costs, and lack of privacy at home), leading to calls for the provision of devices and data for app-based support where needed, or the use of hybrid models combining digital and in-person approaches. In Ghana, there was enthusiasm for youth-centred platforms with local content, safe feedback loops, and human moderation, as well as recognition of risks such as misinformation, a lack of regulation, and over-reliance on AI.

Overall, participants supported digital tools that enhance privacy, engagement, and peer connection, but stressed the need for ethical safeguards, cultural adaptation, and integration with human guidance.

4.3.1 Recommendations for Digital Interventions

	Recommendation	Challenge	Strategic Fit
1	Compare specific features with multicomponent interventions and leverage engagement data to identify core components driving outcomes	Unclear which components of multi-component interventions drive change, leading to cumbersome, less engaging tools that may not maximise benefits	Development of digital tools and platforms that advance transformative mental health research and interventions
2	Capture and analyse richer and more diverse datasets to identify what works for whom	Existing moderator and subgroup analyses are underpowered and focus on broad demographics rather than mechanistically informed profiles, limiting progress on personalisation	Better understanding of how to target digital interventions to stratified populations
3	Prioritise ethical considerations in research on standalone anonymous digital tools	Anonymous tools can enhance privacy and autonomy, but raise concerns around safeguarding, crisis support, and appropriate clinical oversight	Collaboration across researchers, ethicists, and communities to ensure that digital mental health research aligns with the needs and priorities of young people
4	Build evidence-based understanding of engagement with digital interventions	Engagement is often variable, and the mechanisms that sustain use and drive outcomes remain poorly defined and under-tested	Interventions developed with, and meeting the needs and priorities of, end beneficiaries

1) Compare specific features with multicomponent interventions and leverage engagement data to identify core components driving outcomes

Challenge

Internet-delivered psychological therapies have demonstrated efficacy, but we have a limited understanding of which components drive these effects. Most interventions are multi-component, and studies rarely isolate the mechanisms responsible for change, despite their standardised structure and real-time metrics that capture engagement.

Mechanistic Opportunities

Digital interventions offer a unique opportunity to test mechanisms of therapeutic change due to their predefined structure, standardised content, and built-in data capture. To pinpoint the most impactful features of digital interventions, research should:

- Test whether core features (e.g. mood monitoring, cognitive restructuring, psychoeducation, interactive exercises) act independently or synergistically to drive symptom change.
- Evaluate the comparative efficacy of single-component and multifaceted digital interventions with other treatment modalities, potentially employing dismantling/additive, SMART or micro-RCT designs.
- Leverage embedded engagement metrics to explore how the use of specific features relates to symptom change and broader outcomes such as quality of life.
- Employ analytic methods such as component network meta-analysis or mediation analysis to identify which features contribute most to outcomes.

Supporting evidence

Early work has begun to identify effective individual intervention components. A recent network meta-analysis showed that including cognitive restructuring techniques improved anxiety compared to interventions lacking this component[79]. Another study found that simply recording daily activities in the control condition reduced depression and anxiety symptoms similarly to mental health monitoring apps[90]. These findings underscore the need to distinguish true mechanistic benefits from general engagement effects, with potential to improve efficiency and inform targeted face-to-face or hybrid approaches. Advanced trial designs can enhance understanding of component efficacy[91].

2) Capture and analyse richer and more diverse datasets to identify what works for whom

Challenge

Most attempts to personalise treatment rely on broad demographic or intervention-specific subgroups, with reviews reporting inconsistent or underpowered findings. Few studies examine relevant individual differences, personality traits, or treatment preferences. For example, neurodivergent youth may engage and benefit from digital interventions differently than neurotypical youth.

Mechanistic Opportunities

Digital interventions generate rich, standardised datasets that combine active self-report and passive objective measures at scale, creating opportunities to inform personalisation with sufficient statistical power. Studies should:

- Capture large, standardised datasets reflecting behaviour, engagement, and outcomes to test moderators and mediators of treatment effects.
- Perform moderator analysis using individual differences (e.g. personality traits, treatment preferences, symptom profiles) instead of broad characteristics (e.g. age, gender, diagnosis, treatment duration, delivery type).
- Identify and examine theoretically informed mechanisms through qualitative research and lived experience consultation, including neurodivergent youth.
- Leverage passive data (e.g. activity levels, mobility, social contexts) alongside active data capture (e.g. ecological momentary assessment, just-in-time data collection) to identify alternative predictors, moderators and mediators of outcomes.
- Apply advanced statistical methods to model the interplay between symptom profiles, intervention components, and treatment response (e.g. network meta-analysis, Markov chain analysis, machine learning/personalised advantage index modelling).

Supporting evidence

Most reviews find no robust moderators of treatment outcomes in youth. Effects of age, gender, symptom severity, and intervention duration are inconsistent across studies, and analyses are often underpowered[87]. Evidence highlights the promise of integrating passive data and objective behavioural measures[92], prioritising theory-driven moderators, and leveraging advanced statistical techniques (e.g. machine learning and network analysis) to advance understanding of personalisation and derive data-driven relationships in the absence of a strong theoretical model[91]. Qualitative research and consultations with young people can help validate these mechanisms[93] and expand generalisability to underserved groups, such as neurodivergent youth[94].

3) Prioritise ethical considerations in research on standalone anonymous digital tools

Challenge

Standalone digital tools such as apps or conversational AI raise pressing ethical questions around data privacy, informed consent, and

safeguarding when used outside of traditional healthcare settings. While anonymity can promote engagement and may enhance self-efficacy and perceived safety, it also creates challenges in crisis support, monitoring at-risk users, and ensuring appropriate pathways to care. Studies often overlook these issues, leaving gaps in our understanding of safe and ethical implementation.

Mechanistic Opportunities

To ensure that digital interventions are not only effective but also ethically sound, research should:

- Develop and validate best-practice frameworks for the ethical implementation of digital tools in real-world settings that protect the privacy and safety of young people.
- Investigate how the anonymity inherent in digital tools affects self-efficacy, engagement, and outcomes, and how these effects can be balanced with the need for safeguarding.
- Integrate perspectives from young people and other stakeholders to address ethical concerns and co-design features to ensure interventions are both protective and effective for youth.

Supporting evidence

While conversational AI chatbots have been shown to be feasible, acceptable, and perceived as helpful[89], there is a limited understanding of the ethical and privacy risks associated with these tools in youth populations. Other review articles identified a limited understanding of the safety of novel interventions, with minimal reporting of adverse effects a particular concern[84,95]. Young people highlighted a preference for a hybrid approach, in which digital tools are accompanied by human oversight.

4) Build evidence-based understanding of engagement with digital interventions

Challenge

Emerging digital interventions such as conversational AI chatbots and VR are often described as highly engaging and well-suited to young people with anxiety and depression. Yet, current research rarely examines the mechanisms through which engagement translates into symptom improvement, or the role that moderation by a clinician might play. Without this knowledge, it is difficult to assess their potential benefits, risks, and best practices for implementation.

Mechanistic Opportunities

To advance this promising area of research, studies should:

- Determine which features of novel technologies (e.g. interactivity, immersive experiences) drive engagement and subsequent symptom improvement.
- Conceptualise and operationalise engagement mechanisms (e.g. using systems design or realist evaluation frameworks) and examine their interaction with individual characteristics and outcomes.
- Co-create interventions with young people to ensure formats are accessible, engaging, and aligned with their needs and priorities.

Supporting evidence

Evidence from systems design literature, qualitative analyses and realist evaluations has begun to conceptualise and develop theoretical models of youth engagement with digital interventions[88,93]. Evidence for chatbot interventions in young people is currently limited, with research focusing on feasibility and acceptability rather than efficacy or mechanisms[89]. VR interventions have demonstrated efficacy in adults; however, research in young people is limited. Promising early findings include a meta-analysis showing reduced anxiety symptoms in young people undergoing cancer treatment[81], and one study demonstrated reductions in public speaking anxiety among adolescents following exposure therapy[80].

4.4 Social & Interpersonal Interventions

Most reviews of social and interpersonal interventions focused on parenting and family-based approaches, with less evidence on peer, group, or community interventions. Other approaches included mass trauma interventions and interventions targeting loneliness and self-evaluation. Meta-analyses suggest that parenting interventions produce small but significant improvements in children's socio-emotional outcomes, particularly in reducing internalising symptoms[96–100]. Family interventions (involving the child/adolescent and other family members) have demonstrated effectiveness across multiple conditions, including depression[24], anxiety[101], OCD[102], and PTSD[103], though brief family interventions show only weak support[104], and those targeting youth with co-occurring alcohol and mental health difficulties showed no significant benefit[105].

The impact of parental involvement on outcomes is mixed. Several reviews found no difference between interventions with and without parental involvement[101,106–108], although one meta-analysis suggested potential benefits for externalising but not internalising symptoms[109]. Evidence for group or peer-led interventions was limited, with fewer trials and less consistent findings. While much of the literature comes from HICs, some reviews demonstrated effective psychosocial interventions in LMICs, including sub-Saharan Africa[24,25,110], suggesting broader applicability.

Key Gaps & Challenges

Review articles noted a lack of rigorous, large-scale studies, with significant variability in the quality of evidence and the mechanisms explored. Some focused on elaborating clearly articulated theoretical models supported by qualitative findings and experiential accounts of perceived mechanisms of change. However, many reviews highlighted the insufficient quantitative analysis of moderators and mediators. Research was conducted in a broader range of countries than for other intervention categories, including one review in sub-Saharan Africa[24,25,110]. Yet, evidence remained over-representative of HICs, with a need for more data in diverse populations. Additionally, studies are often centred on mothers, neglecting the role of fathers or other family members, and lack long-term follow-ups.

Insights from young people with lived experience

Young people consistently highlighted the importance of peer support, family relationships, and broader social connections for their mental health. Peer groups were consistently described as empowering, especially when identity-based (such as LGBTQ+ or neurodivergent) or peer-led, offering belonging, reducing isolation, and creating safe spaces

to speak openly. In contrast, family involvement was seen as more variable. It could be beneficial when relationships were supportive and culturally attuned, but harmful when parents were unsupportive, stigmatising, or the source of stress.

In Brazil, young people highlighted friendships and genuine, trust-based relationships as protective factors, particularly against loneliness and poor self-image. UK participants emphasised the value of peer groups and family involvement as a stepping stone to therapy, while also warning of risks where families lacked trust or mental health literacy. African Youth in Mind groups described families as both sources of help and harm, with Ghanaian participants specifically calling for parental education and psychological support for caregivers. Zimbabwean participants from the Zvandiri group strongly advocated for expanding peer-led safe spaces and "third spaces" such as camps or retreats, alongside school-based mental health literacy, but cautioned against family approaches that could create "double stigma."

Overall, peer support was almost universally valued by young people. However, family involvement must be handled with cultural competence and safeguards. Safe, youth-centred spaces are critical, whether in schools, communities, or dedicated retreats. The main regional differences lie in the emphasis: UK and Brazil participants emphasised belonging and trust in peer and family relationships, while Zimbabwe and Ghana participants highlighted the risks of stigma, lack of privacy, and the need for structural supports like peer educators, teacher training, and caregiver support.

4.4.1 Recommendations for Social & Interpersonal Interventions

	Recommendation	Challenge	Strategic Fit
1	Strengthen the evidence and generalisability by testing and adapting interventions to diverse populations and settings, taking into account local preferences, attitudes and stigma	Evidence is dominated by HICs, limiting understanding of cultural, contextual, and developmental factors that shape outcomes in LMICs	Better understanding of how to target interventions to stratified populations, including the role of family and cultural adaptations
2	Prioritise research that systematically investigates moderators of efficacy to personalise interventions	It remains unclear which subgroups benefit most, as most moderator analyses are demographic characteristics, rather than treatment-relevant variables	Better understanding of how to target interventions to stratified populations, including moderators directly related to intervention features
3	Empirically test and refine existing theoretical models, integrating qualitative data and lived experience insights	Existing models have a strong theoretical basis but lack empirical and lived experience validation, leaving uncertainty about which mechanisms drive change in real-world contexts	Non-pharmacological interventions that are based on a clear mechanistic understanding; Good and systematic use of the evidence, including living evidence synthesis

1) Strengthen the evidence and generalisability by testing and adapting interventions to diverse populations and settings, taking into account local preferences, attitudes and stigma

Challenge

Although psychosocial interventions show broad efficacy, most evidence comes from HICs and relatively homogenous populations. This limits understanding of how cultural, developmental, and contextual factors shape engagement and outcomes. Without this knowledge, it remains unclear which core intervention features are potentially generalisable across multiple contexts and which require cultural or contextual adaptation.

Mechanistic Opportunities

To strengthen the evidence base for this field, funding should prioritise studies that:

- Test social and interpersonal interventions across diverse groups and contexts to assess generalisability and equity of impact, particularly in LMICs.
- Examine cultural, developmental, and contextual adaptations as potential moderators of effectiveness.
- Embed co-production with local young people with lived experience and their families or communities to identify and test adaptations.

Supporting evidence

Most reviews noted that current evidence lacks diversity in participant demographics and is heavily weighted toward HICs[99,104,107]. There are few studies in LMICs or diverse cultural settings, although some exceptions exist, including reviews of interventions in sub-Saharan Africa[25] and among adolescents living with HIV across HICs and LMICs[110]. One review suggested that cultural differences, including parental participation and extended family or community roles in raising children, may be important in explaining why interventions show varying effects across studies[99].

2) Prioritise research that systematically investigates moderators of efficacy to personalise interventions

Challenge

Social and interpersonal interventions may be particularly valuable for certain groups, such as younger children, who might not engage well with psychological therapies. However, there is a lack of robust evidence identifying which populations and contexts benefit most from these approaches, making it difficult to tailor interventions and ensure they meet the needs of those most likely to benefit.

Mechanistic Opportunities

To address this gap, future research should:

- Recruit sufficiently large samples to systematically test moderators such as delivery context (e.g. home, school, or clinical settings) and intervention features.
- Identify subgroups that derive the greatest benefit, focusing on treatment-related and intervention-specific variables (e.g. delivery components, parental involvement) rather than relying on broad demographic characteristics.
- Investigate how developmental stages (rather than chronological age) and neurodiversity influence responsiveness to interventions.

Supporting evidence

Moderator analyses to date have found no robust evidence of differences in response by age, gender or ethnicity[25,96,98–100,103–105,107]. However, small samples, insufficient variance, and poor reporting limited the statistical power to conduct moderator analyses and meta-regression. Reviews highlighted substantial heterogeneity and criticised reliance on demographic variables of convenience rather than theory-driven factors[91]. Promising signals include differential effects of displacement status in trauma interventions[111], communication problems in attachment-based interventions[112], and parental involvement in digital interventions[113]. Developmental stage, rather than chronological age, may be a more appropriate measure of age-related effects[91]. Neurodivergence has also been highlighted as a potential moderator, as some psychosocial approaches may create barriers to engagement. These findings suggest that intervention-specific features and delivery may be more critical moderators than broad demographics[4].

3) Empirically test and refine existing theoretical models, integrating qualitative data and lived experience insights

Challenge

Many social and interpersonal interventions already have clearly articulated theoretical models and proposed mechanisms of change, yet these have rarely been systematically validated. Without empirical testing, it remains unclear which mechanisms drive change, for whom, and in which contexts. Incorporating lived experience can further strengthen these models, ensuring they accurately reflect the real-world challenges and preferences of young people.

Mechanistic Opportunities

To strengthen the evidence of social and interpersonal models, future research should:

- Conduct mediation and other quantitative analyses to empirically test proposed mechanisms of change.
- Apply mixed-methods and qualitative approaches (e.g. theory of change, realist evaluation) to refine models and specify how components lead to outcomes.
- Create or update mechanistic frameworks by incorporating insights from lived experience advisors, ensuring they are grounded in the perspectives of young people and families.

Supporting evidence

Several interventions already exemplify how theory can be integrated with qualitative and experiential evidence. For example, Attachment-Based Family Therapy builds on a well-defined attachment theory model and clearly articulates mechanisms of change[112].

Loneliness interventions have also combined qualitative and quantitative data with lived experience input to develop conceptual frameworks that map components and proposed mechanisms[114]. Other reviews highlight intervention-specific targets, such as family accommodation for OCD treatment, that could serve as ideal candidate measures for mediation analyses[102]. Integrated approaches such as these ensure that theoretical models are both scientifically grounded and relevant to young people.

4.5 Lifestyle Interventions

Lifestyle interventions, encompassing exercise, sleep optimisation, and nutritional strategies, have gained recognition as promising, accessible, and lower-risk approaches for addressing symptoms of youth depression and anxiety. While some of these interventions are increasingly recommended in clinical guidelines, they are often based on general health principles or expert opinion rather than robust mechanistic evidence specific to youth mental health[23]. Recent global youth mental health frameworks emphasise that lifestyle interventions are most effective when embedded within multi-level prevention strategies that address individual, family, school, and community contexts[115]. Co-design with young people and local cultural adaptations that take into account structural realities are critical for ensuring relevance, scalability, and sustainability.

Physical Activity

Physical activity interventions were associated with a moderate reduction in depressive symptoms in young people compared with control conditions[116]. Benefits were greatest in adolescents aged 13 years or older and in those with a depression diagnosis or other mental illness, with additional gains observed for interventions delivered three times per week and lasting fewer than 12 weeks. Moderate-to-vigorous aerobic activity has demonstrated significant potential to reduce depressive symptoms in youth[116–123], including subgroups (e.g. those with overweight/obesity or neurodivergence). This reinforces the importance of testing optimal "dose" and intensity parameters in future trials. Emerging evidence suggests that mind–body approaches, such as yoga, may reduce internalising symptoms in young people[124–126].

Sleep

Sleep and nutrition interventions show early promise but remain under-researched compared to exercise. Sleep disturbances are prevalent among young people with depression and anxiety. Targeted interventions, such as a pilot RCT of CBT for insomnia and an RCT sleep extension protocol, have demonstrated medium-sized improvements in depressive symptoms[23,127,128].

Nutrition

Nutrition-focused interventions are still underresearched, with most evidence from observational or small-scale studies linking poor diet quality to higher rates of depression and anxiety symptoms in youth[23]. Some evidence also links higher dietary fibre intake with better cognitive function and mental health outcomes in youth, though the available trials are few and heterogeneous[129]. Limited evidence suggests that specific

nutrients and microbiome-targeted approaches, such as omega-3 fatty acids, vitamins, minerals, and probiotics, may benefit youth mental health through anti-inflammatory, neuroplasticity, and neurotransmitter pathways, although high-quality paediatric trials are scarce[130,131].

Key Gaps & Challenges

For depression and anxiety, some mechanistic pathways for interventions like exercise have been proposed. For PTSD and OCD, the evidence base for the efficacy and mechanisms of interventions in youth is scarce. Neurobiological pathways implicated in exercise-mediated mental health improvements include increased expression of neurotrophins, improved connectivity between the prefrontal cortex and amygdala, and reduced systemic inflammation[132]. Potential psychosocial mediators, such as enhanced self-efficacy, self-esteem, perceived competence, and social support, may also influence outcomes[132,133]. In nutritional psychiatry, mechanisms of interest include inflammation, oxidative stress, gut microbiota, and deficiencies in key nutrients. Integrated studies that examine the combined and independent contributions of neurobiological and psychosocial mechanisms are also needed to obtain the overall picture.

A deeper mechanistic understanding would inform personalisation, strengthen the case for their integration into clinical care, and help identify when lifestyle interventions alone are sufficient or best used alongside other treatments. Mechanistic research will also clarify whether lifestyle factors interact with or modify responses to pharmacological and psychological interventions, supporting more precise and synergistic approaches in future mental health strategies.

Insights from young people with lived experience

Young people across regions viewed lifestyle strategies as important supports for their mental health, particularly exercise, sleep, and maintaining routines. In the UK, participants found physical activity, structured sleep, and mindfulness effective for improving mood and managing stress, but raised concerns about financial barriers and the risk that sometimes “healthy living” advice could trigger or worsen eating disorders.

In Brazil, participants valued routines, balanced nutrition, and physical activity, but emphasised that no single approach works for everyone. In fact, what helps one young person may feel unhelpful to another. In the African groups, young people agreed that lifestyle changes were foundational to mental health. In Zimbabwe, participants strongly advocated for sports, nature walks, breathing techniques, and creative outlets as culturally resonant strategies for managing stress and insomnia. In Ghana, young people urged funders to adopt a holistic approach and examine the role of nutrition in mental health more closely. Across

contexts, young people said lifestyle strategies are relevant and valued, but they must be accessible, affordable, and adapted to individual needs and cultural settings. The main cautions relate to equity of access and avoiding harm through overly prescriptive or generic health messages.

4.5.1 Recommendations for Lifestyle Interventions

Physical Activity

	Recommendation	Challenge	Strategic Fit
1	Prioritise mechanistic research in physical activity interventions that measure transdiagnostic symptoms and collect comprehensive biopsychosocial data	Current evidence focuses mainly on symptom reduction, without clarifying the underlying neurobiological, psychosocial, or behavioural pathways	Improved non-pharmacological interventions grounded in measurable biological and psychological characteristics
2	Investigate age-specific and dose-response relationships with key moderators of physical activity effects	Limited understanding of how intensity, frequency, and duration of exercise interact with age, sex, baseline fitness, and prior activity levels	Greater mechanistic understanding of non-pharmacological interventions an d how to target them to stratified populations
3	Examine the interaction effects of delivery format, supervision, setting, and activity type	Factors like delivery, degree of supervision, intervention setting, and type of activity may influence both symptom outcomes, but interactions are currently underexplored	Better understanding of how to target non-pharmacological interventions to stratified populations

Sleep

	Recommendation	Challenge	Strategic Fit
1	Conduct rigorous experimental studies to determine how restoring sleep architecture and circadian rhythm regulation affects mood symptoms	Limited evidence on how sleep architecture and circadian rhythms interventions lead to symptom change, particularly in young people	Improved non-pharmacological interventions and better understanding of how to target sleep interventions to stratified populations
2	Investigate mechanisms and added value of sleep interventions as adjunctive versus standalone treatments	Adjunctive sleep interventions hold potential for comorbid conditions, but there is limited research comparing standalone versus combined intervention models	Improved non-pharmacological interventions; greater understanding of which transdiagnostic targets to focus on; understanding of how depression resolves

Nutrition

	Recommandation	Challenge	Strategic Fit
1	Conduct mechanistic research on how dietary patterns and specific nutrients influence biological and neurodevelopmental pathways	Research is currently limited in understanding how dietary patterns and specific nutrients modulate inflammation, neurotransmission, gut-brain signalling and neurodevelopmental trajectories	Improved non-pharmacological interventions grounded in measurable characteristics; unders tanding of how depression and anxiety resolve
2	Investigate nutritional stratification strategies to identify subgroups of youth who may benefit most from dietary interventions	Most nutrition studies do not test whether specific subgroups respond differently to dietary interventions, limiting opportunities for personalisation	Better understanding of how to target non-pharmacological interventions to stratified populations
3	Explore contextual barriers and facilitators of dietary behaviour change that may limit adherence or impact	Dietary interventions often neglect contextual barriers that affect adherence and impact, such as food insecurity, family dynamics, cultural preferences, and media influences	Interventions developed with and meeting the needs and priorities of end beneficiaries with lived experience

Combined Lifestyle

	Recommendation	Challenge	Strategic Fit
1	Develop and test multi-component lifestyle interventions using innovative trial designs	Lifestyle factors are known to interact, yet most research examines them in isolation. Combining interventions may produce additive effects	Cutting-edge clinical trials designed and powered to provide rigorous results; greater understanding of which transdiagnostic targets to focus on
2	Address motivational and placebo-related factors to clarify how these shape outcomes in real-world settings	Interventions often depend on self-directed factors, but it is unclear how these factors interact with biopsychosocial pathways or shape outcomes in real-world contexts	Developed with, and meet the needs and priorities of end beneficiaries; better understanding of how to target interventions to stratified populations.
3	Incorporate youth perspectives in defining meaningful outcomes and mechanisms	Current research overlooks the priorities of young people. Understanding what is most meaningful to youth is crucial to promote engagement and real-world efficacy	Interventions developed with and meeting the needs and priorities of end beneficiaries with lived experience

Physical Activity

1) Prioritise research that measures transdiagnostic symptoms and collects comprehensive biopsychosocial data

Challenge

Although physical activity has shown promise for improving mood in young people, we still lack a robust mechanistic understanding of how exercise achieves these effects. Current evidence focuses mainly on symptom reduction, without clarifying the underlying neurobiological, psychosocial, or behavioural pathways. This limits our ability to develop optimally targeted and effective interventions.

Mechanistic Opportunities

Integrated research that examines both neurobiological and psychosocial mechanisms (separately and together) is needed to clarify how interventions work and to identify the most impactful targets. Future research should:

- Go beyond symptom change and measure transdiagnostic constructs such as mood regulation, cognitive control, and emotional resilience.

- Investigate how physical activity modulates neurobiological pathways such as neurotrophin expression, brain activity, brain function, and inflammatory markers.

- Examine psychosocial mediators, including self-efficacy, body image, social support, and perceived competence.

Supporting evidence

Evidence indicates that moderate-to-vigorous aerobic exercise can reduce depressive symptoms in youth[117]. Research on state anxiety is promising, with moderate effects and increased efficacy in clinical populations[134]. Potential neurobiological pathways include increased expression of neurotrophins, improved connectivity between the prefrontal cortex and amygdala, and reduced systemic inflammation[132,135]. In parallel, psychosocial mediators such as self-efficacy, self-esteem, perceived competence, and social support also play key roles[132,133]. Despite these insights, most studies do not comprehensively assess these multiple pathways or how they interact.

2) Investigate age-specific and dose-response relationships with key moderators of physical activity effects

Challenge

Current evidence supports the benefits of physical activity for youth mental health, but there is limited understanding of how factors such as intensity, frequency, and duration of exercise interact with age, sex, baseline fitness, and prior activity levels. Without clearer evidence on these dose-response relationships and moderators, it is difficult to tailor exercise interventions for maximum benefit in different subgroups.

Mechanistic Opportunities

Defining clearer age or developmental-specific and intensity-specific thresholds would help tailor interventions more precisely. Studies should:

- Define evidence-based thresholds for intensity, frequency, and duration of physical activity that optimise mental health outcomes in different age and demographic groups.

- Build mechanistic models incorporating moderators such as sex, baseline fitness, and prior activity levels to inform personalised intervention design.

Supporting evidence

Meta-analyses show that structured exercise interventions can reduce depressive symptoms in youth[117,118]. However, many studies use different

definitions of “moderate-to-vigorous” activity, with limited exploration of how these activity thresholds translate into consistent outcomes across different populations.

3) Examine the interaction effects of delivery format, supervision, setting, and activity type

Challenge

The effectiveness of physical activity interventions likely depends not only on the activity itself but also on how it is delivered and contextualised. Factors such as group versus individual delivery, degree of supervision, intervention setting and type of activity may influence both symptom outcomes and the underlying mechanistic pathways. These interactions are currently underexplored, which limits the ability to identify the most effective intervention formats for specific populations.

Mechanistic Opportunities

Future research should:

- Investigate how delivery formats (e.g. group vs. individual) and supervision levels influence engagement, adherence, and therapeutic outcomes.
- Compare different activity types (e.g. aerobic vs. mixed) and settings to determine which combinations most effectively promote symptom reduction.
- Test interaction effects to pinpoint how these factors work together to produce changes in mental health symptoms and underlying mechanisms.
- Identify which combinations of delivery format, supervision level, setting, and activity type maximise both engagement and symptom improvement in youth.
- Integrate contextual factors (e.g. school vs. community) into mechanistic research to develop scalable and culturally relevant physical activity programmes.

Supporting evidence

While group-based and supervised exercise programs have shown promise in improving outcomes for youth[117,118], there is limited systematic comparison of different formats and activity types in youth mental health contexts. Understanding how these delivery factors shape the outcomes and underlying pathways of exercise-based interventions is critical to designing effective, contextually relevant approaches.

Sleep

1) Conduct rigorous experimental studies to determine how restoring sleep architecture and circadian rhythm regulation affects mood symptoms

Challenge

While sleep disruption is strongly linked to anxiety and depression in young people, there is limited rigorous evidence on how interventions targeting sleep architecture and circadian rhythms lead to symptom change. The causal and mechanistic links remain unclear, particularly in children and adolescents whose sleep patterns are developmentally distinct from adults.

Mechanistic Opportunities

Tailoring sleep interventions to developmental stage and context will inform early intervention strategies and stratified care approaches. Future research should:

- Examine how circadian rhythm regulation interventions impact neurobiological pathways.
- Identify moderators (e.g. sex/gender, developmental stage, chronotype) and potential differential effects across subgroups.
- Examine the role of family and school routines as integral components of sleep-related mechanistic pathways, recognising that daily schedules and environmental cues influence both sleep patterns and mood outcomes.
- Identify and validate moderators (e.g. chronotype, developmental stage, gender, family and school routines) to guide personalisation and improve intervention effectiveness across diverse populations.

Supporting evidence

Sleep disturbances are prevalent among adolescents with depression and correlate with symptom severity[23]. For example, evidence from an RCT testing a sleep extension protocol (bedtime scheduling and hygiene guidance) reported significant reductions in depressive symptoms[127].

2) Investigate mechanisms and added value of sleep interventions as adjunctive versus standalone treatments

Challenge

Adjunctive sleep interventions, like CBT for insomnia and depression, may hold potential as treatments for young people with comorbid conditions.

However, the specific mechanisms through which these adjunctive approaches contribute to symptom reduction are not well understood. In particular, there is limited research comparing their standalone impact versus their synergistic contribution within combined intervention models.

Mechanistic Opportunities

Future research should use mechanistic insights to inform personalised, scalable, and context-sensitive early intervention models for sleep by:

- Examining how combining adjunctive sleep interventions with other treatments influences outcomes and contributes to recovery.
- Comparing standalone versus combined models to determine if adjunctive sleep-focused interventions add unique or synergistic benefits.
- Testing whether combining interventions leads to synergistic benefits in subgroups of young people with sleep disruption and comorbid depression.

Supporting evidence

Sleep disturbances are prevalent among adolescents with depression and strongly correlate with symptom severity. Meta-analyses confirm this association and clinical trials have shown that interventions targeting sleep can improve depressive symptoms[23].

Nutrition

1) Conduct mechanistic research on how dietary patterns and specific nutrients influence biological and neurodevelopmental pathways

Challenge

The field of nutritional psychiatry is still emerging, with limited evidence in young people. More research is needed to understand how dietary patterns and specific nutrients modulate inflammation, neurotransmission, gut-brain signalling, and neurodevelopmental trajectories in youth with depression and anxiety.

Mechanistic Opportunities

- Generate high-quality mechanistic evidence on how dietary patterns and specific nutrients influence biological and neurodevelopmental pathways linked to youth depression and anxiety.

- Identify measurable biological and psychosocial markers to guide the design of nutrition-based interventions.
- Use these insights to develop targeted, non-pharmacological strategies for early intervention and recovery.
- Examine how dietary changes and individual nutrients influence inflammation, neurotransmission, gut-brain signalling, and neurodevelopmental trajectories.
- Compare how dietary patterns (e.g. Mediterranean diet, Western diet) affect inflammatory markers.

Supporting evidence

Observational studies show that poor diet quality is associated with increased depressive symptoms in adolescents, but high-quality interventional evidence is lacking[23,136]. Two systematic reviews without meta-analyses identified consistent correlations between unhealthy dietary patterns and higher rates of depression and anxiety symptoms[137,138]. Mechanisms of interest include inflammation, oxidative stress, gut microbiota, and deficiencies in key nutrients.

2) Investigate nutritional stratification strategies to identify subgroups of youth who may benefit most from dietary interventions

Challenge

Current nutritional intervention studies in youth rarely explore whether specific biological or psychosocial subgroups respond differently to dietary changes. Without this knowledge, it is difficult to personalise dietary interventions or understand why some young people respond more positively than others.

Mechanistic Opportunities

Mechanistic insights will enable the design of targeted, scalable dietary interventions for early intervention and treatment of youth depression. Studies should:

- Examine whether baseline inflammatory markers, metabolic risk or micronutrient deficiencies predict response to dietary interventions.
- Use stratified analysis or targeted recruitment to provide tailored interventions to specific subgroups (e.g. anti-inflammatory diets for young people with higher inflammation).
- Build mechanistic evidence to identify which biological or psychosocial subgroups of young people benefit most from dietary interventions.

- Determine how factors such as inflammation, metabolic risk, and micronutrient deficiencies can guide personalised nutrition strategies.

Supporting evidence

Evidence suggests that specific micronutrients and dietary patterns influence depression risk in youth, though more longitudinal research is needed to clarify these relationships. Data also highlight biologically plausible pathways, such as adiposity and inflammation, through which unhealthy diets may exacerbate depressive symptoms, supporting the potential value of stratified nutritional interventions[139,140].

3) Explore contextual barriers and facilitators of dietary behaviour change that may limit adherence or impact

Challenge

Dietary interventions for depression and anxiety in youth often overlook key contextual factors that shape dietary behaviour. Factors such as food insecurity, family dynamics, cultural preferences, and media influences can limit adherence to dietary interventions or reduce their impact.

Mechanistic Opportunities

- Identify how social, cultural, and family factors interact with dietary behaviour change.
- Examine how these factors influence the feasibility, acceptability, and outcomes of dietary interventions.
- Integrate lived experience insight into efficacy evaluations of interventions and explore young people's perspectives on these factors.
- Co-develop dietary interventions with young people to ensure they address lived experience priorities, cultural preferences, and contextual realities.
- Incorporate evidence synthesis and real-time evidence updates to adapt interventions as new findings emerge.
- Integrate strategies that address social determinants, such as food insecurity and digital/media influences, into nutrition-based mental health programmes.

Supporting evidence

Trials are needed that assess the benefits of using these interventions in different care settings (e.g. primary care, specialist services), and across different socioeconomic and ethnic groups[23,139]. Emerging evidence on

the impacts of social media use among adolescents[141] indicates the need for interventions that address digital influences, particularly those related to body image, anxiety, and disordered eating, as part of comprehensive mental health strategies. Given associations between food insecurity and psychological distress across diverse populations and study designs[142], future trials should also evaluate how mental health interventions can address social determinants such as food insecurity.

Combined Lifestyle

1) Develop and test multi-component lifestyle interventions using innovative trial designs

Challenge

Youth depression and anxiety are influenced by multiple, interacting lifestyle factors, including sleep, exercise, and nutrition. However, most research to date has examined these factors in isolation. Little is known about how combining these interventions could produce additive or synergistic effects.

Mechanistic Opportunities

Future research should go beyond isolated interventions and systematically test how lifestyle components interact within multi-component models. Studies should:

- Conduct factorial or adaptive trials to test individual and combined effects of sleep, exercise, and nutrition interventions.
- Differentiate additive vs synergistic outcomes, clarifying whether benefits are independent or amplified when combined.
- Identify biological and psychosocial mechanisms underpinning combined effects (such as whether morning physical activity enhances circadian alignment and mediates improvements in sleep and mood).
- Test moderators such as age, sex, and developmental stage to guide personalised combinations of lifestyle strategies.
- Validate mechanistic targets (e.g. sleep architecture, activity timing, diet quality) that reliably drive improvements across outcomes.

Supporting evidence

Clinical practice guidelines for pediatric mental health often include general advice on healthy eating, sleep, and physical activity. However, recommendations are frequently brief, qualitative, based more on expert

opinion or general health principles than on robust evidence from specific intervention trials in paediatric mental health populations, and rarely delve into the underlying mechanisms[23]. This underscores a significant gap between the intuitive appeal of lifestyle interventions and the scientific understanding needed for their targeted and evidence-based application in youth mental healthcare.

2) Address motivational and placebo-related factors to clarify how these shape outcomes in real-world settings

Challenge

Many lifestyle interventions for depression and anxiety rely on self-directed or externally encouraged participation, making motivation, adherence, and enjoyment crucial factors for success. However, little is known about how these psychological and contextual factors interact with mechanistic pathways or contribute to observed outcomes.

Mechanistic Opportunities

- Examine how motivation and expectancy affect treatment outcomes, potentially through biological or psychological mechanisms.
- Investigate the role of enjoyment as a mediator of intervention engagement and sustained behaviour change.
- Evaluate the level of adherence required for an intervention to be effective in real-world settings.
- Co-develop lifestyle interventions with young people to ensure they address motivational drivers, enjoyment, and real-world barriers to adherence.
- Generate mechanistic evidence on how expectancy, motivation, and enjoyment influence biological and psychological pathways to recovery.
- Identify adherence thresholds and contextual factors that optimise outcomes for different subgroups and delivery formats.

Supporting evidence

Reviews note that structured, supervised, and group-based interventions (e.g. team sports, dance) tend to yield better outcomes than unstructured or solitary formats[117,118]. This raises the question of how much self-directed or externally encouraged participation in physical activity contributes to success, and how motivation, adherence, and enjoyment may moderate this relationship.

3) Incorporate youth perspectives in defining meaningful outcomes and mechanisms

Challenge

Current research on lifestyle interventions often overlooks the insights and priorities of young people themselves. Understanding what outcomes and mechanisms are most meaningful to youth, including elements like sense of agency, social connectedness, or identity, can better align interventions with their lived experiences and promote engagement and real-world efficacy.

Mechanistic Opportunities

Incorporating lived experience input can ensure that research better reflects young people's perspectives to improve treatment adherence and outcomes. Future research should:

- Actively involve young people in defining outcomes and mechanisms most relevant to them (e.g. agency, identity, social connectedness, autonomy, confidence, relationships).
- Co-create and test interventions with young people so outcomes, mechanisms, and implementation strategies reflect their priorities, values, and lived experiences, while minimising potential harms (e.g. overtraining, sleep disruption).
- Integrate youth-defined outcomes into trial design, evaluation, and guideline development to ensure findings are meaningful and applicable.
- Use qualitative and mixed-methods approaches to capture nuanced, developmentally appropriate insights that standardised scales may miss.

Supporting evidence

Evidence highlights psychosocial mechanisms, such as self-efficacy, self-esteem, and social support, as key mediators of physical activity intervention effects[132,133]. However, these are often defined by researchers rather than young people themselves. It is important to include youth with lived experience of depression and their families in the design and interpretation of future studies, as well as in the formulation of future clinical practice guidelines, to ensure relevant interventions are acceptable and meaningful to youth[23].

4.6 Other Interventions

Interventions classified as 'other' included a wide range of approaches that did not fit into established categories. They encompassed interventions likely to involve multiple mechanisms, such as play, drama, music, religious and spiritual interventions, and interventions that focused on one component or mechanism such as collaborative goal-setting, light therapy, and transcranial magnetic stimulation (TMS). Literature was limited by the small number of studies, especially in LMICs, and the lack of replication in youth.

Drama therapy showed potential benefits for depression, anxiety, and PTSD in young people, although the studies were often underpowered[143]. Non-therapeutic/child-centred play effectively reduced anxiety in younger children and in adolescents[144,145]. Religious and spiritual interventions mostly reduced anxiety and depression in 10-24 year olds[146], as did musical interventions in adolescents[147]. Light therapy/bright light therapy following either standalone or treatment adjunct approaches reduced depression symptoms, although evidence was limited[148].

Key Gaps & Challenges

Some reviews discussed potential mechanisms and applications to adolescents, but with limited evidence on efficacy[149,150]. As observed in the Social/Interpersonal section, some interventions falling in the 'other' category had clearly defined theoretical models, or qualitatively-informed proposed mechanisms (e.g. non-therapeutic play, collaborative goal setting, drama therapy, religious, spiritual, and musical interventions). These interventions are therefore well-positioned for examination of theoretical models to support or refine the proposed mechanisms.

Certain interventions targeted specific mechanisms. For example, TMS was based on the neural correlates of depression[149], and light therapy drew on literature showing efficacy in adults[148]. In these instances, examination of efficacy by nature provided a test of the role of the proposed mechanism targeted. Light therapy research robustly explored mechanisms, assessing it as an adjunct to isolate specific effects[151], and exploring dose-response relationships[148].

Insights from young people with lived experience

Across regions, young people consistently valued creative and spiritual approaches as important supports for mental health, but noted these are rarely researched or formally provided. Prayer, meditation, and other spiritual practices were seen as calming and supportive in the UK, Zimbabwe, and Ghana, with strong calls for culturally relevant interventions that reflect community and religious contexts.

Creative outlets such as art, music, dance, and journaling were emphasised in Brazil and Zimbabwe as powerful tools for expression, identity-building, and emotional regulation. While young people in the UK stressed expanding options beyond CBT to include peer and spiritual support, African groups highlighted the need for research and funding that recognises both scientific and spiritual models, and for interventions co-designed with communities and traditional leaders.

4.6.1 Recommendations for Other Interventions

	Recommendation	Challenge	Strategic Fit
1	Conduct mechanistic research on creative and spiritual interventions	Early efficacy research indicates promising effect s and many are supported by theoretical models, but these interventions lack mechanistic evaluation	Improved non-pharmacological interventions; better understanding of how to target interventions to stratified populations
2	Conduct mechanistic studies of targeted interventions such as TMS and light therapy using rigorous, comparative designs	TMS and light therapy show potential, but the evidence base is limited in young people and there is a lack of comparative and mechanistic studies	Non-pharmacological interventions grounded in measurable, observable characteristics; cutting-edge clinical trials designed and powered to provide rigorous results

1) Conduct mechanistic research on creative and spiritual interventions

Challenge

Early efficacy research on interventions focused on play, drama, music and religious/spiritual interventions shows promise of efficacy. However, they likely involve multiple mechanisms, and these remain untested. Many of these interventions are supported by theoretical models, making them well-suited to mechanistic evaluation to allow further development and refinement of models.

Mechanistic Opportunities

- Use rigorous quantitative and qualitative approaches and young people with lived experience to test and refine the theoretical models underlying these interventions.

- Examine whether these interventions are especially effective in certain populations and contexts (e.g. play for younger children, religious/spiritual practices for youth with aligned beliefs).

Supporting evidence

Emerging evidence indicated promising effects within groups of individuals, for example: non-therapeutic/child-centred play for reducing anxiety in younger children and in adolescents[144,145]; religious and spiritual interventions in reducing anxiety and depression in 10-24 year olds[146]; and musical interventions in adolescents[147]. Evidence for drama therapy shows promise for reducing symptoms of anxiety, depression, and PTSD in young people, but larger, well-powered studies were lacking[143]. Most reviews of these interventions discussed proposed mechanisms of change, but were lacking in empirical support for mechanisms/theoretical models.

2) Conduct mechanistic studies of targeted interventions such as TMS and light therapy using rigorous, comparative designs

Challenge

Targeted interventions such as TMS and light therapy have shown potential in addressing anxiety and depression in young people. However, the existing evidence base is limited in children and adolescents, and mechanistic insights into how these interventions exert their effects in these age groups are scarce. Additionally, there has been a lack of direct comparisons and studies designed specifically to explore underlying mechanisms.

Mechanistic Opportunities

- Implement head-to-head trials comparing these targeted interventions directly with existing treatment modalities or each other.

- Conduct adjunct studies (e.g. testing TMS/light therapy combined with standard treatments) to examine whether mechanistic synergy or unique pathways contribute to improved outcomes.

- Use dose-response studies to identify optimal treatment guidelines for young people and clarify how variations in exposure influence efficacy.

Supporting evidence

Studies exploring light therapy/bright light therapy have demonstrated reduced symptoms of depression following either standalone treatment or treatment adjunct, although evidence is

limited[148,151]. Reviews of TMS to directly target prefrontal brain neurocircuitry suggest that this approach holds much promise; however, only one large-scale RCT has been conducted to date, which demonstrated no difference compared to a 'sham' stimulation protocol[152,153].

4.7 Prevention Research

Reviews and meta-analyses show small but significant effects of prevention programmes for youth anxiety and depression[26,28–30]. Most existing programmes are better described as secondary prevention, since they adapt early treatment approaches for young people with emerging or subclinical symptoms rather than addressing underlying risk factors. More recent work in LMICs[133] suggests that universal and selective psychological prevention approaches can reduce anxiety and depression symptoms and improve quality of life, while indicated prevention reduced depressive symptoms and functional impairment.

At the same time, there is concern regarding the potential harms of prevention initiatives. School-based mental health interventions have reported unintended negative outcomes such as a decrease in well-being or an increase in depression or anxiety, with particular subgroups having a higher risk of experiencing negative effects compared with their peers[154]. These conflicting findings highlight the importance of understanding how and why prevention works, for whom, and under what conditions. A mechanistic focus will be crucial for determining which prevention interventions are most effective and safe.

4.7.1 Recommendations for Preventative Interventions

	Recommendation	Challenge	Strategic Fit
1	Fund rigorous prevention trials to identify mechanisms targeting risk factors and optimal developmental periods or subgroups to focus efforts on	Most prevention interventions show modest and inconsistent effects, are constrained by methodological weaknesses and typically focus on symptom reduction rather than causal risk factors	Improved non-pharmacological interventions; better understanding of how to target interventions to stratified populations

1) Fund rigorous prevention trials to identify mechanisms targeting risk factors and optimal developmental periods or subgroups to focus efforts on

Challenge:

Most existing prevention interventions show only modest and inconsistent effects. Studies are frequently constrained by methodological

weaknesses, short follow-up periods, and insufficient screening of participant groups to distinguish preventative and therapeutic effects. Interventions typically focus on symptom reduction (i.e. indicated prevention) rather than targeting causal risk factors, and engaging families and young people remains difficult.

Mechanistic Opportunities:

Future prevention research should adopt designs aimed at reducing incidence and clarifying mechanisms of change. Specifically, studies should:

- Prioritise interventions that specifically target evidence-based underlying risk and protective factors to examine their causal role in the onset of anxiety and depression.
- Measure depressive or anxiety disorder onset as a primary outcome, alongside long-term symptomatology and functional impairment.
- Distinguish prevention and treatment effects by stratifying asymptomatic, at-risk and diagnosed groups at baseline to clarify whether long-term changes represent incidence reduction, relapse prevention, or symptom improvement.
- Strengthen trial design by carefully distinguishing by age/developmental stage (e.g. preschool, middle years, adolescence) to avoid masking effects through aggregation.
- Ensure interventions are developmentally timed to maximise engagement and acceptability for families, including in preschool and early childhood contexts where risk processes may already emerge.
- Consider scalability and potential harms from the outset, and adapting interventions for distinct contexts, such as HICs and LMICs.

Supporting Evidence:

Prevention research is scarce and constrained by methodological limitations, including insufficient screening, short follow-up periods and the pooling of symptomatic and diagnosed participants[28,31,32]. Importantly, the few interventions that directly target underlying risk factors, such as those addressing both behavioural inhibition and parental anxiety, have shown stronger effects, including reduced incidence of anxiety disorders at follow-up[29]. High-quality mechanistic trials are therefore needed to establish whether preventative interventions can reduce incidence and relapse, and to clarify the pathways through which they operate.

4.8 Lived Experience Research Priorities

Matching Support to Individual Needs

Young people across all regions prioritised personalised, context-sensitive care over blanket approaches. They stressed that support should not be determined by age alone, but tailored to individual characteristics, including culture, ethnicity, neurodiversity, gender identity, disability, personal history of trauma, and whether they live in rural or urban settings. In the UK, participants expressed frustration that standardised treatments are offered by default, even when they are a poor fit or not tailored to the individual's context (such as neurodivergent or LGBTQ+). Similarly, in Brazil, young people highlighted the importance of tailoring to marginalised populations (such as LGBTQ+ and Indigenous youth) whose experiences of discrimination are rarely addressed in research or service provision. In Zimbabwe and Ghana, there was an emphasis on the need for personalised medicine and culturally adapted interventions. Zimbabwean young people from the LGBTQ+ community emphasised research that provides psychoeducation for caregivers who still believe they need to be "healed".

Access and Equity

Access was a pressing concern everywhere. Participants described long waiting times, the high cost of private care, and the absence of services in rural areas. Zimbabwean and Ghanaian groups emphasised that young people in rural areas often have no access to mental health services at all, and called for research that explicitly involves local leaders and community networks to make care more available and acceptable. UK participants also contrasted the diversity of provision in cities with the limited options in rural communities. Brazilian youth pointed to structural inequities, noting that marginalised groups, including racially minoritised and autistic youth in underserved areas, face additional barriers.

Early Identification and Developmental Relevance

Many participants wanted mental health difficulties to be recognised and addressed earlier, with Ghanaian and Zimbabwean youth recommending support from as young as age seven. They argued that interventions should be designed with the developmental stage in mind and adapted for younger children, for example, through school-based supports, parent and teacher education, and play-based approaches. UK participants also highlighted misdiagnosis and missed recognition of co-occurring or neurodivergent conditions, which result in young people receiving inappropriate interventions.

Relationships and Trust

Trust, respect, and feeling listened to were central concerns. Across African groups, young people emphasised that adults often fail to understand or respect their perspectives, and that sometimes simply being heard can be transformative. Privacy was also a recurring theme: breaches of confidentiality, such as services informing parents without consent, were seen as damaging, particularly where family relationships were unsupportive. Stigma, whether cultural, familial, or institutional, was another barrier that deterred many from engaging with services. In the UK, participants also described invalidating experiences with clinicians who dismissed their difficulties or minimised symptoms, which reduced willingness to seek help again.

Social and Peer Support

Peer and identity-based supports were strongly valued, with participants emphasising their potential to reduce stigma, build belonging, and offer age-relevant perspectives. UK youth highlighted the need for more identity-based peer groups, while in Zimbabwe, young people advocated for weekly peer-led rather than adult-led activities, such as sports, storytelling, and retreats. Ghanaian participants stressed the role of family and educators in creating supportive environments, alongside peer interventions, and called for interventions that strengthen community belonging as a protective factor.

Creative, Spiritual and Religious Approaches

Creative and spiritual practices were widely endorsed but seen as under-researched. Brazilian participants described music, dance, journaling, poetry, and art as powerful tools for emotional expression and identity-building. In Zimbabwe and Ghana, prayer, church attendance, and spiritual or cultural traditions were highlighted as central to wellbeing, with participants calling for recognition of both scientific and spiritual models of care. UK participants also reported benefits from prayer and spiritually framed meditation, but stressed that such practices need to be offered as options within mainstream provision, not only privately. Across regions, young people wanted research to take these approaches seriously, testing their mechanisms and effectiveness alongside conventional therapies.

Summary of Research Priorities

Overall, the most consistent priorities were for personalised, culturally relevant interventions; equitable access, especially in rural and marginalised communities; earlier identification and support from childhood; and greater recognition of creative, spiritual, and peer-based approaches alongside conventional models. Across all regions, young people urged researchers to involve them directly in the design of studies

and interventions, to ensure that future research is relevant, acceptable, and accessible.

5. Conclusion

This report found that while a wide range of interventions reduce symptoms of youth anxiety and depression, their mechanisms of action remain poorly understood. Four overarching challenges emerged: 1) weak mechanistic evidence and gaps between theory and practice; 2) a lack of primary prevention research targeting underlying risk factors; 3) a narrow evidence base concentrated in HICs, with limited adaptation and evaluation in LMICs and culturally diverse settings; and 4) limited integration of lived experience, resulting in a mismatch between what studies measure and what youth find meaningful and relevant to their real-world needs.

Our recommendations call for research that explicitly tests mechanisms of change, prioritises prevention and resilience, and advances underexplored but promising areas such as lifestyle, social, and creative interventions. Strengthening mechanistic evidence requires designs that isolate active ingredients, examine subgroup and contextual differences, and integrate youth perspectives into defining outcomes and models of change. For policymakers, this means enabling investment in mechanistically informed, contextually relevant and youth-centred approaches that can be adapted globally. With coordinated effort, these steps can move the field beyond symptom reduction toward a clearer understanding of what works, for whom, and why, advancing progress towards Wellcome's vision of a world where no one is held back by mental health problems

6. References

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7. Conflict of Interest Statement

CK is the founder of Wida, a digital mental health initiative.

8. Appendix

8.1 Results

These results are based solely on review articles included for data extraction. As we did not extract data directly from primary studies, the findings reflect what was discussed in the reviews and are not necessarily representative of the primary research studies.

The most consistently examined moderators were age, gender, and baseline symptom severity. A small number of studies examined socioeconomic status, ethnicity, delivery mode and treatment-related moderators, though reporting was inconsistent. Where mediators were assessed, the majority related to cognitive or psychological processes. Behavioural and social mediators were less common, while investigation of biological pathways as mediators was rare.

Lived experience involvement was nearly absent from reviews as only 6% of reviews discussed engagement of young people with lived experience in their methodology. Of the 11 reviews that did so, 10 were published in 2021 or later, with a single earlier example in 2002, indicating only very recent attention to this area.

Although many reviews did not explicitly state the setting, of those that did, most interventions took place in clinical services (outpatient clinics, hospitals, research centres) or educational environments (schools, colleges, universities). A smaller number were delivered in community or home contexts, including youth services, welfare facilities, shelters, or via mobile and telehealth platforms.

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Wellcome Trust, 215 Euston Road, London NW1 2BE, United Kingdom
T +44 (0)20 7611 8888, E contact@wellcome.org, wellcome.org