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Childhood Cystic Fibrosis in the Era of Highly Effective Modulator Therapy: A Critical Narrative Review of Diagnosis, Multisystem Disease and Evolving Management

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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Abstract

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder among populations of European ancestry, and the childhood years determine much of its long-term trajectory. The therapeutic landscape has been reshaped by cystic fibrosis transmembrane conductance regulator (CFTR) modulators, yet the paediatric evidence base has matured unevenly across the domains that matter most to affected children.

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This critical narrative review evaluates the strength, consistency and limitations of the literature on CF in childhood, spanning pathophysiology, newborn screening and diagnosis, early airway infection and structural lung disease, nutrition and gastrointestinal involvement, CF-related diabetes, CFTR modulator therapy, and mental health. Peer-reviewed studies, professional consensus guidelines and authoritative institutional sources were appraised for methodological quality and translated into a thematic synthesis rather than a study-by-study catalogue. The evidence most strongly supports early diagnosis through newborn screening, the predictive value of early neutrophilic inflammation and infection for structural lung disease, and the short-to-medium-term efficacy and tolerability of triple CFTR modulator therapy in children as young as two years. Confidence is weaker for long-term safety, for outcomes in children ineligible for or unable to access modulators, and for the neuropsychiatric effects attributed to these drugs, where observational signals and case reports remain difficult to disentangle from the psychological burden of chronic illness. Persistent gaps include the management of inconclusive screening results, the durability of modulator benefit initiated in early life, the evolving natural history of CF-related diabetes and pancreatic disease under modulator therapy, and equity of access across health systems. The review concludes that childhood CF is being transformed rather than solved, and that surveillance, nutritional and psychosocial frameworks developed in the pre-modulator era require deliberate re-evaluation rather than uncritical continuation.

Keywords: Cystic fibrosis; children; CFTR modulators; newborn screening; Pseudomonas aeruginosa; cystic fibrosis-related diabetes; mental health.

1. Introduction

Cystic fibrosis (CF) is a multisystem, autosomal recessive disorder caused by pathogenic variants in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial anion channel that regulates chloride and bicarbonate transport across the apical membrane of secretory epithelia (Riordan et al., 1989). Loss or reduction of CFTR function dehydrates airway surface liquid, impairs mucociliary clearance and disturbs secretion in the pancreas, intestine, hepatobiliary tract, sweat glands and reproductive system, producing a disease that, although monogenic in origin, expresses itself across almost every organ (Grasemann & Ratjen, 2023; Mall et al., 2024). Although CF was historically framed as a paediatric condition with limited survival, the demographic centre of gravity has shifted decisively towards adulthood in high-income settings. That shift does not diminish the importance of childhood; rather, it reframes the early years as the period during which the foundations of lifelong health, or of irreversible organ injury, are laid down. Recent global analyses further indicate that this therapeutic transition is occurring unevenly, with persistent disparities in both diagnosis and access to highly effective modulator therapy across health systems (Guo et al., 2024).

The clinical significance of childhood CF derives from the observation that damage frequently begins before symptoms appear. Structural airway change, including bronchiectasis, has been documented in infants and preschool children identified through newborn screening, often in the absence of overt respiratory illness (Sly et al., 2013). The recognition that early neutrophilic inflammation and infection precede and predict later structural disease has motivated a surveillance-oriented model of paediatric care and a search for interventions capable of altering the disease trajectory at its inception (Pillarisetti et al., 2011). The central therapeutic development of the past decade, the advent of small-molecule CFTR modulators, has extended progressively to younger age groups and now reaches children as young as two years for eligible genotypes (Goralski et al., 2023; Zemanick et al., 2021). This progression has generated optimism that the natural history of the disease might be fundamentally rewritten if effective therapy is introduced early enough. Real-world paediatric evidence has likewise reported improvements in CFTR function and sensitive lung-function measures after triple-therapy initiation in school-age children, while underscoring the need for continued safety surveillance beyond controlled trials (Daccò et al., 2024).

That optimism must be tempered by several unresolved tensions. First, the evidence supporting modulator use in young children rests largely on short open-label studies with surrogate endpoints, and the durability of benefit initiated in early life remains uncertain (Wainwright et al., 2025). Second, a minority of children carry genotypes that are unresponsive to currently licensed modulators, or live in health systems where access is constrained, and their needs risk being eclipsed by enthusiasm for the responsive majority (Taylor-Cousar et al., 2023). Third, several domains of childhood CF care, including nutritional targets, airway clearance regimens and infection surveillance, were developed in an era of progressive nutritional failure and inexorable lung

decline, and their continued applicability under modulator therapy has not been established. Fourth, newer concerns, particularly the neuropsychiatric effects attributed to modulators, illustrate how rapidly the clinical questions are evolving relative to the pace of rigorous evidence generation (Bathgate et al., 2023). Implementation research also shows that efforts to make newborn screening more equitable can be constrained by logistical, financial and data-related barriers, limiting the consistent translation of recommendations into practice (Madden et al., 2025). Recent reports of behavioural and sleep disturbances after triple-therapy initiation in preschool children further reinforce the need for age-specific prospective safety assessment (Sermet-Gaudelus et al., 2024).

Terminology used throughout this review follows current conventions. The term children denotes individuals from birth to the eighteenth birthday, with preschool referring to those below approximately six years, and school-age to those between six and eleven years, reflecting the age bands used in the pivotal modulator trials. Highly effective modulator therapy refers principally to the triple combination of elexacaftor, tezacaftor and ivacaftor, abbreviated ELX/TEZ/IVA. Pancreatic exocrine insufficiency describes the failure of enzyme delivery to the duodenum that necessitates pancreatic enzyme replacement therapy (PERT). These conventions are applied consistently to avoid the ambiguity that has occasionally hampered cross-study comparison.

Cystic fibrosis has been reviewed extensively, including authoritative general overviews (Elborn, 2016; Grasemann & Ratjen, 2023; Mall et al., 2024; Ong & Ramsey, 2023) and a dedicated series charting the modulator era (Taylor-Cousar et al., 2023). These treatments are comprehensive but predominantly lifespan-oriented, and the specific circumstances of the developing child, whose airways, pancreas, endocrine function and psychological life are still forming, are frequently subsumed within adult-dominated narratives. Annual topic surveys capture incremental developments but, by design, do not attempt a critical integration across paediatric domains (Savant, 2025). A synthesis focused on childhood, attentive to where paediatric evidence is genuinely robust and where it has been extrapolated from adults, therefore remains warranted.

1.1 Scope, Research Gap and Objectives

This review concentrates on cystic fibrosis during childhood, from antenatal and newborn identification through to adolescence, and integrates evidence across the respiratory, gastrointestinal, endocrine, nutritional and psychological domains that jointly determine paediatric outcomes. It privileges questions in which the developmental context materially changes interpretation, including the timing and consequences of early airway infection, the nutritional and endocrine sequelae of pancreatic disease, the paediatric evidence for CFTR modulators, and the mental health of children and their families. The review deliberately foregrounds areas of disagreement and uncertainty rather than presenting a settled account.

The specific gap addressed is the absence of a childhood-focused critical synthesis that evaluates, rather than merely summarises, how strongly the paediatric evidence supports current practice as the field transitions into the modulator era. Existing reviews tend either to span the whole lifespan or to examine single domains in isolation, leaving the cross-domain tensions of childhood care underexamined. The principal objectives are to define the current state of knowledge in paediatric CF; to distinguish well-supported conclusions from those extrapolated from adults or from surrogate endpoints; to appraise the methodological quality and consistency of the evidence within each domain; to represent conflicting findings fairly, particularly regarding modulator safety and neuropsychiatric effects; and to identify defensible research priorities for the coming decade. The intended contribution is an integrated, critically calibrated map of childhood CF that clinicians and researchers can use to locate the boundaries of current certainty. Conditions primarily affecting adults, such as CF-related infertility management and lung transplantation outcomes, are excluded except where they bear directly on paediatric decision-making, as are laboratory studies without a demonstrable link to childhood clinical outcomes.

2. Methods for Literature Selection

2.1 Review Design and Rationale

A critical narrative review was selected in preference to a systematic review or meta-analysis because the review question is deliberately broad and cross-disciplinary, spanning heterogeneous study designs, outcome measures and clinical domains that do not share a common quantitative metric. A systematic review with meta-

analysis is best suited to a focused question addressed by comparable studies, whereas the present aim is interpretive integration across domains in which randomised, observational, registry-based and consensus evidence must be weighed against one another. The narrative approach permits the inclusion of foundational and conceptual sources alongside recent trials, and allows explicit critical commentary on methodological quality and on the tensions between domains. This choice does not exempt the review from methodological transparency or critical appraisal; the search sources, eligibility principles and appraisal criteria are stated so that the reasoning can be scrutinised, consistent with recognised expectations for the conduct and reporting of narrative reviews. The trade-off is that the review does not generate pooled effect estimates and is more exposed to selection and interpretive bias, a limitation addressed directly in the final section.

2.2 Information Sources

Evidence was identified through structured searching of PubMed and MEDLINE for biomedical literature, supplemented by the multidisciplinary indexes Google Scholar, Semantic Scholar, OpenAlex and the Crossref metadata registry. Bibliographic details and digital object identifiers were verified against the Crossref registry and, where necessary, against publisher landing pages and the National Library of Medicine records. Authoritative institutional and professional sources were consulted directly, including the clinical care guidelines of the United States Cystic Fibrosis Foundation and the guidance of the European Cystic Fibrosis Society, the International Society for Pediatric and Adolescent Diabetes, and the joint European nutrition societies. These bodies were treated as sources of consensus guidance rather than as literature databases. Searching was complemented by backward and forward citation tracking from recent high-quality reviews and pivotal trials, and by targeted checks for corrections, expressions of concern and retractions affecting candidate sources.

2.3 Search Strategy and Search Period

Search concepts combined the population, the condition and the domain of interest. The core concept set paired terms for cystic fibrosis with terms for childhood, including child, children, paediatric, infant, preschool, adolescent and newborn. This set was then combined with domain-specific terms addressing CFTR modulators (elexacaftor, tezacaftor, ivacaftor, lumacaftor, modulator), diagnosis and screening (newborn screening, immunoreactive trypsinogen, sweat chloride, inconclusive diagnosis), airway disease (Pseudomonas aeruginosa, eradication, bronchiectasis, inflammation, lung clearance index), nutrition and gastrointestinal disease (pancreatic insufficiency, enzyme replacement, growth, nutrition), endocrine complications (CF-related diabetes, glucose tolerance) and psychological outcomes (depression, anxiety, mental health, neuropsychiatric). Representative Boolean strings took the form ("cystic fibrosis" AND (child *OR paediatric OR infant OR adolescen*) AND ("CFTR modulator" OR elexacaftor OR ivacaftor)) and analogous constructions for each domain, adapted to the syntax of each interface. The search period extended from 1989, the year in which the CFTR gene was identified and the modern molecular understanding of the disease began, to 23 May 2026. Foundational publications predating 1989 were eligible where necessary to explain historical or conceptual development.

2.4 Eligibility Criteria

Sources were eligible when they addressed cystic fibrosis in children or in mixed populations from which paediatric inferences could reasonably be drawn, and when they contributed to one of the review domains. Peer-reviewed original research, high-quality reviews, and consensus or clinical practice guidelines were prioritised, together with reports from recognised professional and institutional bodies. English-language publications were included. Preference was given to studies employing recognised paediatric outcome measures, including spirometry expressed as percentage predicted forced expiratory volume in one second (ppFEV1), the lung clearance index derived from multiple-breath washout, sweat chloride concentration, validated growth metrics and structured mental health instruments. Sources were excluded when they were not peer-reviewed and no peer-reviewed alternative was required, when their bibliographic identity could not be verified, when they consisted of promotional or non-scholarly material, or when they addressed exclusively adult or laboratory questions without paediatric relevance. Preprints were not relied upon where peer-reviewed evidence was available.

2.5 Screening, Duplicate Handling and Study Selection

Retrieved records were screened by title and abstract for relevance to the paediatric review question, after which candidate full texts were examined for methodological adequacy and for the strength of the link between the source and the claim it would support. Duplicate records arising from indexing in more than one source were consolidated by matching digital object identifiers and bibliographic details, so that each study was represented once. Because this is a narrative rather than a systematic review, no formal record-count flow diagram was constructed and no numerical screening tally is reported; doing so would imply a completeness of enumeration that the design does not claim. Sources whose full text or bibliographic metadata could not be verified were not cited. Where a claim could be supported by more than one study, preference was given to the most rigorous and most directly paediatric evidence, with additional sources cited for contested or broad assertions.

2.6 Critical Appraisal and Evidence Synthesis

Each candidate source was appraised against criteria appropriate to its design, including the suitability of the study design to the question, sample size and representativeness, the presence and adequacy of comparison groups, the validity of outcome measurement, the handling of confounding, analytical robustness, external validity and consistency with other evidence. Particular attention was paid to the distinction between surrogate endpoints, such as sweat chloride and the lung clearance index, and patient-important outcomes, and to the difference between open-label and controlled designs, which is especially consequential in the paediatric modulator literature. Formal risk-of-bias scoring tools were not applied, because the heterogeneity of designs and the interpretive aims of the review did not warrant the false precision of a single instrument. Evidence was organised thematically around mechanisms, controversies and clinical problems. For each theme, the strongest supporting evidence was synthesised, conflicting findings were examined, likely reasons for disagreement were considered, the confidence that could reasonably be placed in current conclusions was assessed, and the residual knowledge gap was stated.

3. Pathophysiology and Genetic basis in the Paediatric Context

3.1 CFTR Dysfunction and the Emergence of Childhood Disease

The identification of the CFTR gene established that a single gene product governs a disease of remarkable phenotypic breadth (Riordan et al., 1989). CFTR functions principally as a cyclic adenosine monophosphate-regulated channel conducting chloride and bicarbonate, and its dysfunction reduces the volume and alters the composition of epithelial surface liquid. In the airway, the resulting dehydration of the periciliary layer impairs mucociliary clearance, favours mucus adhesion and creates conditions conducive to persistent infection and neutrophilic inflammation (Grasemann & Ratjen, 2023). Bicarbonate deficiency additionally disturbs the pH-dependent unfolding and mobilisation of secreted mucins, providing a mechanistic account of why secretions across multiple organs become abnormally viscous. This mechanistic picture is well supported and provides the rationale for therapies that restore CFTR function rather than merely treating downstream consequences (Mall et al., 2024).

The developmental dimension is central to paediatric interpretation. Longitudinal surveillance of newborn-screened infants has demonstrated that inflammation and infection are detectable in the lower airway within the first months of life and that free neutrophil elastase activity in bronchoalveolar lavage fluid is associated with the subsequent development of bronchiectasis (Pillarisetti et al., 2011; Sly et al., 2013). The implication, that the childhood airway is a site of early and partly silent injury, reframes the therapeutic target from established disease towards its prevention. It is important, however, not to overstate the inevitability of this sequence. The relationship between early inflammation and later structural change, although consistent across cohorts, is probabilistic rather than deterministic, and the extent to which restoring CFTR function in the first years of life interrupts it remains an open empirical question rather than a demonstrated fact.

3.2 Genotype–Phenotype Relationships and Their Limits

More than two thousand CFTR variants have been catalogued, and the functional consequences of these variants are conventionally grouped into classes reflecting defects in protein production, processing, gating,

conductance, quantity or stability. This classification has proved clinically valuable because it maps variants to modulator responsiveness: gating variants such as G551D respond to potentiation, whereas the common F508del processing variant requires correction in addition to potentiation (Ramsey et al., 2011; Middleton et al., 2019). The classification therefore underpins the increasingly genotype-directed structure of paediatric therapy. Its limits are equally important. Pancreatic status correlates reasonably well with genotype, but pulmonary phenotype, the trait that most determines prognosis, correlates poorly, and children sharing a genotype may follow divergent respiratory courses (Grasemann & Ratjen, 2023). Modifier genes, environmental exposures, infection history and socioeconomic circumstances all contribute to this variability, and the resulting uncertainty means that genotype informs but does not dictate the individual child's trajectory. Overreliance on genotype as a prognostic instrument risks both false reassurance and premature pessimism.

4. Diagnosis and Newborn Screening

4.1 Newborn Screening Algorithms and the Problem of Equity

Newborn screening has become the principal route to CF diagnosis in many high-income countries, and its central justification is that presymptomatic identification permits early nutritional and respiratory intervention during the window in which the disease is most amenable to modification. Most programmes begin with measurement of immunoreactive trypsinogen in dried blood spots, followed by CFTR variant analysis and, where indicated, sweat chloride testing to confirm the diagnosis (Farrell et al., 2017). The logic of early detection is sound and is supported by the demonstration that lung injury begins early, yet the operational details of screening determine whether its promise is realised equitably. Recent systematic-review-driven consensus guidance has highlighted that algorithms restricting variant detection to F508del or to a small legacy panel systematically under-identify infants whose CFTR variants are more common in non-European ancestral groups, generating inequity in the timeliness and sensitivity of diagnosis (McGarry et al., 2025). The recommended shift towards floating trypsinogen thresholds and broader variant panels is a corrective to a screening architecture that was calibrated to historically studied populations.

The strength of this evidence lies in its convergence across programmes and its explicit attention to equity, a dimension frequently neglected in earlier evaluations. Its principal limitation is that screening performance is highly dependent on local genetic epidemiology, laboratory infrastructure and follow-up systems, so that recommendations validated in one health system may not transfer directly to another. Programmes in low-resource settings face a different problem entirely, in which the absence of screening, rather than its imperfect calibration, drives late diagnosis and early mortality. The evidence base is therefore strongest for the refinement of established programmes and weakest for the question of how to extend timely diagnosis to settings without existing screening infrastructure.

Table 1 consolidates the terminology on which the remainder of this review depends, because inconsistent usage across the screening and diagnostic literature has itself been a source of confusion. The entries distinguish measures of CFTR function from screening proxies, and separate confirmed diagnosis from the intermediate categories generated by population screening. The most consequential distinction is between an elevated immunoreactive trypsinogen concentration, which is a probabilistic screening signal, and sweat chloride, which is a direct functional measure; conflating the two has contributed to the mistaken assumption that screen-positive status is diagnostically equivalent to disease. The table also makes explicit that the CRMS/CFSPID category is a designation of diagnostic uncertainty rather than a mild disease phenotype, a point that carries directly into the discussion of follow-up burden in Section 4.2.

Table 1. Core concepts and terminology in the diagnosis and early classification of cystic fibrosis in childhood

Concept	Working definition and paediatric relevance	Supporting references
Immunoreactive trypsinogen (IRT)	Pancreatic enzyme precursor measured in dried blood spots as the first tier of most screening algorithms; elevated in most, but not all, affected neonates, and subject to false negatives with low values.	Farrell et al. (2017); McGarry et al. (2025)
Sweat chloride	Direct measure of CFTR function; a value of 60 mmol/L or above supports the diagnosis, whereas an intermediate range requires further evaluation.	Farrell et al. (2017)

Concept	Working definition and paediatric relevance	Supporting references
CRMS/CFSPID	CFTR-related metabolic syndrome, termed cystic fibrosis screen positive, inconclusive diagnosis in international usage; describes screen-positive infants who do not meet diagnostic criteria and require structured follow-up.	Farrell et al. (2017); Savant (2025)
Variant class	Grouping of CFTR variants by the nature of the molecular defect; determines eligibility for potentiator, corrector or combined modulator therapy.	Grasemann & Ratjen (2023); Middleton et al. (2019)
Pancreatic exocrine insufficiency	Failure of enzyme delivery to the duodenum, present in most children with CF, necessitating enzyme replacement and driving early nutritional risk.	Stallings et al. (2008); Turck et al. (2016)

Note. CFTR = cystic fibrosis transmembrane conductance regulator; CRMS = CFTR-related metabolic syndrome; CFSPID = cystic fibrosis screen positive, inconclusive diagnosis

4.2 Diagnostic Confirmation and the Challenge of Inconclusive Results

Confirmation of the diagnosis rests on evidence of CFTR dysfunction, most directly through an elevated sweat chloride concentration, interpreted in the context of genetic findings and clinical features (Farrell et al., 2017). The expansion of screening has, however, generated a category of infants who screen positive but do not meet diagnostic thresholds, designated CFTR-related metabolic syndrome or, in international terminology, cystic fibrosis screen positive, inconclusive diagnosis. These children present a genuine clinical and ethical difficulty. A proportion will remain healthy, while a minority will later manifest features consistent with CF or CFTR-related disorders, and the current inability to predict which infants belong to which group imposes surveillance and anxiety on families without a clear diagnostic resolution (Savant, 2025). The evidence guiding management of this group is observational and evolving, and the balance between vigilant follow-up and the avoidance of medicalising healthy children has not been settled. This ambiguity is an intrinsic consequence of screening a population for a condition whose milder phenotypic boundaries are themselves indistinct, and it is likely to grow as variant panels widen.

5. Early Airway Disease: Infection, Inflammation and Structural Change

5.1 The Preschool Window and the Surveillance Model

The recognition that structural lung disease begins in early childhood has been among the most influential findings in modern CF research. Cohort studies employing chest computed tomography and bronchoalveolar lavage in newborn-screened infants demonstrated that bronchiectasis and air trapping are detectable in a substantial proportion of children by the preschool years, frequently before clinical signs emerge, and that early neutrophilic inflammation and infection predict this structural progression (Pillarisetti et al., 2011; Sly et al., 2013). These observations established the preschool period as a window of opportunity during which intervention might prevent irreversible damage, and they justified a surveillance-oriented model in which asymptomatic children are monitored actively rather than treated reactively.

The interpretation of this evidence requires care. Computed tomography is sensitive but entails radiation exposure and, in very young children, sedation, and the clinical significance of the mild, sometimes transient, abnormalities it detects is not fully established. The lung clearance index derived from multiple-breath washout offers a radiation-free alternative that is sensitive to early ventilation inhomogeneity, but it does not reliably detect the presence of localised bronchiectasis and cannot substitute for imaging when structural definition is required. The available evidence indicates that these measures are complementary rather than interchangeable, and the choice among them involves trade-offs between sensitivity, specificity, safety and feasibility that no single modality resolves. Confidence in the surveillance model as a description of disease is high; confidence that any particular surveillance protocol improves long-term outcomes is considerably lower, because the interventions triggered by surveillance have not consistently been shown to alter the natural history.

5.2 Pseudomonas Aeruginosa Acquisition and Early Eradication

Chronic infection with Pseudomonas aeruginosa is associated with accelerated lung function decline and increased morbidity, and the initial acquisition of the organism in childhood has therefore been treated as a

critical therapeutic juncture. The rationale for early eradication is that initial isolates are typically non-mucoid and antibiotic-susceptible, offering a window in which the organism may be cleared before it adapts to chronic persistence. Randomised evidence supports the general efficacy of inhaled antibiotic eradication. The ELITE study found that inhaled tobramycin achieved eradication in the large majority of children with newly acquired infection and that a twenty-eight-day course was not inferior to a fifty-six-day course, indicating that more prolonged treatment conferred little additional benefit (Ratjen et al., 2010). The EPIC trial compared cycled and culture-based antibiotic strategies and found no meaningful difference between four regimens in the time to pulmonary exacerbation or to recurrence, suggesting that the act of early treatment mattered more than the particular protocol chosen (Treggiari et al., 2011).

These trials constitute relatively strong paediatric evidence, being randomised and adequately powered for their primary comparisons. Their limitations lie in what they did not establish. Eradication reduces the prevalence of the organism in the short term, but a proportion of children experience recurrence, and the long-term effect of eradication programmes on lung function and survival has not been demonstrated in controlled designs. Moreover, the microbiological context is shifting. As CFTR modulators reduce airway secretion burden, the density and dynamics of airway infection may change, and the epidemiology of early Pseudomonas acquisition established before widespread modulator use may not persist. The evidence for early eradication as an effective short-term intervention is therefore reasonably firm, whereas the evidence for its long-term benefit, and for its continued relevance under modulator therapy, remains incomplete.

Inhaled hypertonic saline illustrates the difficulty of extrapolating airway therapies to young children. Although mucoactive treatment is beneficial in older individuals, a randomised trial of nebulised hypertonic saline in children younger than six years did not reduce the rate of protocol-defined pulmonary exacerbations, its primary endpoint, even though some secondary measures favoured treatment (Rosenfeld et al., 2012). This result is a useful corrective to the assumption that interventions effective in older patients will necessarily benefit younger ones, and it underscores that the preschool airway may respond differently from the mature airway. The broader lesson is that the preschool window, although real, does not guarantee that any given intervention deployed within it will be effective.

Table 2 assembles the controlled paediatric evidence on early airway intervention so that the strength of each trial can be read alongside what it did not establish. Placing the eradication trials next to the hypertonic saline trial makes the pattern visible: randomised evidence supports the short-term microbiological efficacy of early antibiotic treatment, yet no trial in this age group has demonstrated a durable effect on lung function or survival, and the one trial powered for a clinical endpoint in preschool children returned a negative primary result. The final column shows that the surveillance evidence, although influential, is observational and therefore establishes prognostic association rather than the benefit of acting upon it. Read together, the entries indicate that confidence should be graded by endpoint rather than by design alone, since randomisation confers little protection when the outcome measured is a surrogate.

Table 2. Representative controlled evidence on early airway interventions in young children with cystic fibrosis, with principal findings and limitations

Intervention	Design and population	Principal finding and key limitation	Supporting references
Inhaled tobramycin eradication	Randomised comparison of 28- vs 56-day courses in children with new P. aeruginosa infection	High eradication rates and shorter course non-inferior to longer course; recurrence occurs and no long-term functional outcome demonstrated	Ratjen et al. (2010)
Cycled vs culture-based antibiotics	Randomised comparison of four eradication regimens in young children	No significant difference between regimens in exacerbation or recurrence; no untreated control and long-term benefit not assessed	Treggiari et al. (2011)
Nebulised hypertonic saline	Randomised placebo-controlled trial in children younger than 6 years	No reduction in protocol-defined pulmonary exacerbation rate; negative primary endpoint despite some secondary signals	Rosenfeld et al. (2012)

Intervention	Design and population	Principal finding and key limitation	Supporting references
Early surveillance imaging	Longitudinal newborn-screened cohort with chest CT and lavage	Early inflammation and infection predict bronchiectasis; observational, with radiation and sedation concerns and unproven benefit of acting on findings	Pillarisetti et al. (2011); Sly et al. (2013)

Note. CT = computed tomography; P. aeruginosa = Pseudomonas aeruginosa

6. Nutrition, Growth and Gastrointestinal Disease

Nutritional status has long been recognised as a determinant of respiratory outcome and survival in CF, and the childhood years are decisive because early growth failure is associated with poorer subsequent lung function. Most children with CF have pancreatic exocrine insufficiency and require pancreatic enzyme replacement therapy together with an energy-dense diet and fat-soluble vitamin supplementation (Stallings et al., 2008; Turck et al., 2016). The evidence underpinning aggressive early nutritional management is substantial, drawing on registry analyses linking nutritional indices to pulmonary outcomes and on consensus guidance synthesising decades of practice. Observational data indicate that higher initial enzyme dosing in infancy, at or above approximately 1,500 lipase units per kilogram per meal, is associated with more favourable weight gain by the age of two years, providing a practical anchor for early dosing (Schechter et al., 2018).

The quality of this evidence is mixed in an instructive way. The association between nutrition and outcome is robust and consistent, but much of the supporting data is observational and therefore vulnerable to confounding, because families and centres achieving good nutrition may differ systematically in adherence, socioeconomic resources and overall care quality. Randomised evidence for specific nutritional targets and enzyme dosing strategies is comparatively sparse, and recommendations rest heavily on expert consensus and registry association rather than on trial data. This distinction matters because the strength of the nutrition–outcome association has sometimes been read as though it validated particular interventions, when in fact it establishes the importance of the domain rather than the efficacy of any specific strategy within it.

Table 3. Domains of nutritional and gastrointestinal management in childhood cystic fibrosis, the strength of supporting evidence, and modulator-era uncertainties

Domain	Established practice	Evidence character and modulator-era uncertainty	Supporting references
Energy intake	Energy-dense diet exceeding the requirements of healthy peers	Registry association and consensus with limited trial data; risk of overnutrition as energy balance improves	Stallings et al. (2008); Turck et al. (2016)
Pancreatic enzyme replacement	Weight-based dosing with meals and snacks	Observational dose–response and consensus dosing bands; possible preservation of pancreatic function with early therapy	Schechter et al. (2018); Turck et al. (2016)
Fat-soluble vitamins	Routine supplementation and monitoring	Consensus based on deficiency risk; requirements may change with improved absorption	Turck et al. (2016)
Growth monitoring	Serial anthropometry against population references	Strong association with pulmonary outcome; interpretation of gains shifting with modulator use	Stallings et al. (2008)

Note. Enzyme dosing is conventionally expressed in lipase units per kilogram per meal

The advent of CFTR modulators has introduced a genuine discontinuity into this long-standing framework. Modulator therapy is consistently associated with weight and body mass index gains, and in some children pancreatic function may be partially preserved when therapy is initiated very early, raising the previously unfamiliar prospect of overnutrition and its metabolic consequences in a population historically defined by

nutritional failure (Turck et al., 2016; Zemanick et al., 2021). The nutritional paradigm developed to combat undernutrition may therefore require substantial revision, and the high-energy, high-fat dietary advice that was appropriate in the pre-modulator era cannot be assumed to remain appropriate for children whose energy balance has been transformed. The evidence for this transition is still emerging, and current guidance necessarily lags behind the clinical reality it seeks to address.

Table 3 separates what is well established in nutritional and gastrointestinal management from what rests on consensus, and identifies where CFTR modulators have unsettled long-standing practice. The third column is the analytically important one, because it shows that the domains supported by the strongest association evidence are not the domains supported by the strongest interventional evidence; growth monitoring and energy intake illustrate this divergence particularly clearly. The final column indicates that each domain faces a distinct form of modulator-era uncertainty rather than a single generalisable revision, with energy prescription facing the possibility of overcorrection while enzyme replacement faces the possibility of becoming partially unnecessary. The table is therefore best read as a map of where current guidance is likely to require revision first, rather than as a summary of settled recommendations.

7. Cystic Fibrosis-Related Diabetes and Endocrine Complications

Cystic fibrosis-related diabetes (CFRD) is a distinct form of diabetes arising principally from insulin insufficiency secondary to progressive destruction and dysfunction of pancreatic islets, compounded by fluctuating insulin resistance during infection. Its prevalence rises steeply with age, affecting a small proportion of children but a substantial minority of adolescents, and its onset is frequently insidious, so that clinically silent glucose abnormalities may precede diagnosis by years (Anton-Păduraru et al., 2023). Because CFRD is associated with declining nutritional and pulmonary status even before overt diabetes is established, guidelines recommend annual screening with an oral glucose tolerance test from the age of ten, a recommendation grounded in the recognition that the test detects abnormalities that simpler measures such as glycated haemoglobin may miss (Ode et al., 2022).

The evidence base for CFRD in childhood has characteristic strengths and weaknesses. The epidemiological association between CFRD and adverse outcomes is well established, and the pathophysiological account of insulin insufficiency is mechanistically coherent. The optimal screening modality is less firmly settled, because the oral glucose tolerance test is burdensome and imperfectly reproducible, and continuous glucose monitoring, although increasingly used, has not been definitively validated as a screening tool with agreed diagnostic thresholds in this population. The effect of CFTR modulators on glucose metabolism adds a further layer of uncertainty. A systematic review of the paediatric evidence found that modulators may improve glucose tolerance and insulin secretion in some children, particularly those with preserved beta-cell function, but that the number of studies is small, their designs heterogeneous, and their conclusions preliminary (Pietrzykowska et al., 2025). The available evidence indicates a plausible metabolic benefit without establishing its magnitude, durability or clinical importance, and it would be premature to assume that modulators will substantially reduce the future burden of CFRD in children now receiving them.

8. CFTR Modulator Therapy in Children

8.1 From Potentiators to Triple Combination Therapy

The development of CFTR modulators progressed from potentiators, which increase the open probability of CFTR channels reaching the cell surface, to correctors, which improve the processing and trafficking of misfolded protein, and finally to combinations that pair correction with potentiation. The potentiator ivacaftor demonstrated that pharmacological restoration of CFTR function could yield clinical benefit in patients with gating variants such as G551D (Ramsey et al., 2011). Because such variants are uncommon, the therapeutic reach of potentiator monotherapy was limited, and the decisive advance for the majority came with triple therapy combining elexacaftor, tezacaftor and ivacaftor, which produced substantial benefit in patients carrying at least one F508del allele, the most common variant (Middleton et al., 2019). The paediatric significance of this progression is that it converted CF, for responsive genotypes, from a disease managed symptomatically into one addressable at its molecular origin, and it created a strong rationale for initiating therapy as early in childhood as safety permits (Taylor-Cousar et al., 2023).

8.2 Evidence in School-Age Children

The extension of triple therapy to children aged six to eleven years was supported first by an open-label study demonstrating improvements in ppFEV1, in the respiratory domain of the Cystic Fibrosis Questionnaire-Revised, in the lung clearance index and in sweat chloride, with a safety profile consistent with that observed in older patients (Zemanick et al., 2021). A subsequent placebo-controlled trial in children heterozygous for F508del and a minimal-function variant confirmed efficacy against a comparator, strengthening the causal inference beyond that available from open-label data alone (Mall et al., 2022). Real-world observational studies have broadly corroborated the trial findings in routine practice, reporting improvements in lung clearance and nutritional measures among school-age children commencing therapy (Pittman et al., 2025).

The consistency of these findings across trial and observational settings lends confidence to the conclusion that triple therapy improves surrogate and symptomatic outcomes in school-age children over the short to medium term. Two cautions temper this conclusion. First, several of the pivotal endpoints, particularly sweat chloride and the lung clearance index, are biomarkers whose relationship to long-term, patient-important outcomes such as preserved lung function into adulthood is inferred rather than demonstrated. Second, the children studied were, by trial design, relatively stable and eligible by genotype, and the benefits observed in this population cannot be assumed to extend to children with advanced disease, with rare genotypes, or with the comorbidities and adherence challenges that characterise real-world care. The evidence is strongest for efficacy on surrogate endpoints and weakest for the translation of those endpoints into altered lifelong trajectories.

8.3 Evidence in Preschool Children

Therapy has been extended further to children aged two to five years, again primarily through open-label study, which reported improvement in CFTR function as measured by sweat chloride and in lung function measures over twenty-four weeks, with the drug generally well tolerated at weight-adjusted doses (Goralski et al., 2023). The extension of a molecular therapy into the preschool years is conceptually attractive because it targets the very window during which structural lung disease has been shown to begin. The evidentiary difficulty is that the case for treating this age group rests almost entirely on uncontrolled data and on surrogate endpoints, because the clinical events that therapy is ultimately intended to prevent, such as bronchiectasis and lung function decline, unfold over years and cannot be captured in a short trial. The inference that early treatment will prevent later damage is biologically reasonable and is supported by the natural-history evidence on early disease, but it remains an extrapolation. The absence of placebo-controlled data in the youngest children, although understandable on ethical and practical grounds once benefit in older children is established, means that confidence in preschool treatment is founded more on mechanistic coherence than on direct demonstration of long-term benefit.

8.4 Long-term Safety and Next-Generation Therapy

Longer-term data are beginning to accrue. An open-label extension following children aged six years and older for up to one hundred and ninety-two weeks reported that improvements in lung function, CFTR function, respiratory symptoms and nutritional status were broadly maintained, with adverse events that were mostly mild or moderate and generally consistent with the manifestations of CF itself, although a small number of children discontinued therapy, including one for a neuropsychiatric event (Wainwright et al., 2025). These data represent the longest paediatric experience with a modulator and are reassuring as far as they extend, but the sample was small and self-selected, comprising children who had tolerated and continued therapy, so that the extension design tends to underrepresent those who fared poorly. Next-generation combinations, including vanzacaftor–tezacaftor–deutivacaftor, have been studied in school-age children and can reduce sweat chloride below diagnostic thresholds in most recipients, offering the prospect of simplified once-daily regimens and potentially greater CFTR restoration (Hoppe et al., 2025). Whether deeper biochemical correction translates into superior clinical outcomes, and whether the long-term safety of lifelong therapy begun in early childhood is favourable, are questions that current follow-up cannot yet answer.

A recurring limitation across the paediatric modulator literature is its dependence on the pharmaceutical developer for trial conduct and, frequently, for authorship, which, although not evidence of bias, warrants the independent, registry-based and investigator-initiated verification that is only now beginning to accumulate through community-driven post-approval programmes designed to characterise the effects of highly effective

modulator therapy in routine care (Nichols et al., 2021). Equally, the concentration of trial evidence in children eligible by genotype leaves a minority, including those with rare or unresponsive variants and those in health systems where these expensive therapies are unavailable, poorly served by the current evidence and at risk of a widening outcome gap (Taylor-Cousar et al., 2023). The transformation wrought by modulators is real and substantial, but it is neither universal nor fully characterised over the timescales that matter for children.

Table 4 arranges the pivotal modulator studies by age group and design so that the descending gradient of evidential strength with decreasing age becomes apparent. Placebo-controlled evidence exists for school-age children, whereas the evidence supporting use in children aged two to five years is open-label and single-arm, and the endpoints in the youngest groups are predominantly biochemical and safety-related rather than clinical. The table also records duration, which exposes the central limitation of the field: the longest paediatric follow-up derives from an extension study of children who had already tolerated therapy, a design that cannot estimate the risk borne by those who discontinued. Reading down the columns clarifies that regulatory approval has extended to younger children on the strength of extrapolation from older cohorts combined with safety and biomarker data, an approach that is defensible but should not be mistaken for demonstrated clinical efficacy in the youngest recipients.

Table 4. Pivotal and representative studies of CFTR modulator therapy relevant to children, by age group and design

Study	Age group	Design and principal outcome	Endpoint type	Supporting reference
Ivacaftor, G551D	≥6 years (incl. children)	Randomised; potentiation improved lung function and reduced sweat chloride in gating variant	Clinical and surrogate	Ramsey et al. (2011)
ELX/TEZ/IVA, single F508del	≥12 years	Randomised; triple therapy improved lung function in the common genotype	Clinical	Middleton et al. (2019)
ELX/TEZ/IVA, 6–11 years	School-age	Open-label; improved ppFEV1, LCI, CFQ-R and sweat chloride	Surrogate and symptomatic	Zemanick et al. (2021)
ELX/TEZ/IVA, F/MF 6–11 years	School-age	Placebo-controlled; confirmed efficacy against comparator	Clinical and surrogate	Mall et al. (2022)
ELX/TEZ/IVA, 2–5 years	Preschool	Open-label; improved CFTR and lung function, well tolerated	Surrogate	Goralski et al. (2023)
ELX/TEZ/IVA extension	≥6 years	Open-label extension to 192 weeks; benefits maintained	Surrogate and symptomatic	Wainwright et al. (2025)
Vanza–tezac–deutiva (RIDGELINE)	6–11 years	Single-arm phase 3; sweat chloride below diagnostic threshold in most	Surrogate	Hoppe et al. (2025)

Note. ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = heterozygous for F508del and a minimal-function variant; ppFEV1 = percentage predicted forced expiratory volume in one second; LCI = lung clearance index; CFQ-R = Cystic Fibrosis Questionnaire-Revised

9. Mental Health and Neuropsychiatric Considerations

The psychological dimension of childhood CF has moved from the periphery to the centre of clinical concern. Large international screening established that depression and anxiety are substantially more common in adolescents with CF and in the parents of affected children than in community samples, prompting consensus guidance recommending annual screening with validated instruments from the age of twelve, together with attention to the mental health of caregivers (Quittner et al., 2016). This guidance is well founded in prevalence data and represents a genuine advance in the recognition that the burden of a demanding daily treatment regimen, combined with the existential weight of a chronic and historically fatal condition, exacts a psychological toll on children and families. The screening instruments recommended are practical, although their performance characteristics in younger children are less well established, and emerging work suggests that clinically relevant anxiety may be present in children below the age at which screening conventionally begins (Smith et al., 2025).

The most contested question in this domain concerns the neuropsychiatric effects of CFTR modulators. Reports of worsening anxiety and depression after initiation of modulator therapy predate the triple-combination era, having been described with earlier combinations in adolescent girls (McKinzie et al., 2017), and concern has intensified with case reports of serious events, including suicide attempts, in adolescents receiving triple therapy (Arslan et al., 2023). Provider surveys have documented that clinicians observe both improvement and deterioration in mental health among children starting modulators, a pattern that resists simple characterisation (Bathgate et al., 2023). Interpreting these signals is genuinely difficult. The observational and case-based nature of the evidence precludes firm causal inference, because children starting modulators are simultaneously experiencing changes in health, expectations and life circumstances that could independently affect mood, and because both improvement and deterioration are plausible on mechanistic grounds. Ascertainment and reporting biases operate in both directions, and the absence of controlled neuropsychiatric data leaves the question unresolved. The responsible reading of the current evidence is that a neuropsychiatric effect of modulators is possible and warrants vigilance, but is neither established as causal nor quantified, and that this uncertainty should inform monitoring without being overstated as demonstrated harm.

Table 5 sets the conflicting observations on modulator-associated neuropsychiatric effects against the explanations that could plausibly account for them, since the disagreement in this literature is unlikely to be resolved by the accumulation of further uncontrolled reports. The juxtaposition shows that the same observation is compatible with a pharmacological effect, with the psychological consequences of altered illness trajectory and expectation, and with differential ascertainment following heightened clinical vigilance. No entry in the table derives from a controlled design with prespecified neuropsychiatric endpoints, which is the principal reason the question remains open. The table is intended to support proportionate monitoring rather than to adjudicate causation, and the absence of a resolving study is itself the finding that carries forward into the research priorities set out in the Future Directions.

Table 5. Conflicting evidence on the mental health effects of CFTR modulators in young people, with possible explanations

Observation	Evidence type	Possible explanation	Supporting reference
Worsening anxiety and depression after modulator initiation	Case series in adolescent females	Direct drug effect, or coincidental change during a period of transition	McKinzie et al. (2017)
Serious neuropsychiatric events, including suicide attempts	Case reports in adolescents on triple therapy	Possible drug effect versus background psychiatric risk in adolescence	Arslan et al. (2023)
Both improvement and deterioration observed by clinicians	Provider survey across centres	Heterogeneous individual responses; ascertainment and expectation effects	Bathgate et al. (2023)
High baseline anxiety and depression independent of modulators	International screening and consensus	Treatment burden and chronic-illness stress affecting children and caregivers	Quittner et al. (2016); Smith et al. (2025)

Note. The table juxtaposes observations that are not mutually exclusive; heterogeneous individual responses may account for apparently contradictory reports

10. Future Directions

The most pressing research priority is the long-term evaluation of CFTR modulators initiated in early childhood. Current licensing in preschool children rests on short open-label studies and surrogate endpoints, and the question of whether early molecular therapy prevents structural lung disease, preserves pancreatic and endocrine function and alters lifelong trajectory cannot be answered by such designs. Because placebo-controlled trials in young children are no longer ethical where benefit in older children is established, the appropriate instruments are prospective registry-based cohorts and investigator-initiated longitudinal studies with pre-specified structural, functional and neurodevelopmental outcomes, followed over many years and independent of commercial sponsorship. Sensitive endpoints suited to young children, including multiple-breath washout and low-radiation or magnetic resonance imaging, should be embedded prospectively so that structural benefit, if it exists, can be demonstrated rather than assumed.

A second priority is the neuropsychiatric safety of modulators in children and adolescents. The current reliance on case reports and provider observation is inadequate to a question of this importance, and what is required is prospective study using validated mood and suicidality measures administered before and serially after initiation, with comparison against expected trajectories in unexposed or historical cohorts, so that drug-attributable effects can be distinguished from the psychological changes that accompany altered health. Such work should attend explicitly to younger children, in whom screening tools are least validated and in whom emerging data suggest that clinically important anxiety is already present.

A third priority concerns the children whom modulators do not reach. Those with rare or unresponsive genotypes, and those in health systems where these therapies are unavailable, risk a widening outcome gap as the responsive majority improves. Research effort directed towards genotype-agnostic approaches, including strategies aimed at restoring CFTR expression irrespective of variant, and towards the pragmatic optimisation of conventional airway, infection and nutritional management in the absence of modulators, is necessary if the benefits of the modulator era are not to be confined to a genetically and geographically fortunate subset. Equity of access should itself be treated as a researchable outcome rather than a background assumption.

A fourth priority is the deliberate re-evaluation of care frameworks inherited from the pre-modulator era. Nutritional targets calibrated to prevent undernutrition, airway clearance and mucoactive regimens validated in progressive disease, and infection surveillance protocols developed when chronic Pseudomonas infection was near-inevitable may all require revision as the underlying disease is pharmacologically modified. Comparative effectiveness studies that test whether established interventions retain their value, and that identify which can be safely simplified or de-escalated, would reduce treatment burden for children while guarding against the uncritical continuation of practices whose rationale has changed. The management of inconclusive screening results and of CF-related diabetes under modulator therapy similarly requires prospective study, because both sit at the shifting boundary between disease and its absence that the modulator era has made more prominent. Across all these priorities, the immediate need is for independent long-term surveillance, while the longer-term need is for therapies and care models that extend the benefits of the present decade to every child with CF.

11. Conclusion

Childhood cystic fibrosis is being transformed, but it is not being solved, and the distinction is essential to an accurate reading of the current evidence. The review objectives were to define the state of paediatric knowledge, to separate robust conclusions from extrapolations, to appraise methodological quality, to represent conflicting evidence fairly and to identify research priorities. Against these objectives, the evidence most strongly supports several conclusions. Early diagnosis through newborn screening is well justified by the demonstration that lung injury begins in the first years of life, and the refinement of screening algorithms towards greater equity is a defensible and important advance. The predictive relationship between early airway inflammation and infection and subsequent structural lung disease is consistent across cohorts and provides a sound rationale for a surveillance-oriented model of care. Triple CFTR modulator therapy improves surrogate and symptomatic outcomes in children as young as two years over the short to medium term, and its tolerability in this period appears acceptable.

Other conclusions must be held more tentatively. The translation of modulator-induced improvements in biomarkers into altered lifelong trajectories is inferred rather than demonstrated, and the long-term safety of therapy begun in early childhood remains uncharacterised. The nutritional and endocrine frameworks of paediatric CF, developed to combat undernutrition and to detect emerging diabetes, are being unsettled by a therapy that improves absorption and may partially preserve pancreatic function, and the appropriate response to this discontinuity has not been established. The neuropsychiatric effects attributed to modulators remain possible but unproven, and the evidence does not currently permit them to be either dismissed or confirmed. The children least served by the modulator era, those with unresponsive genotypes or without access, occupy a growing and inadequately studied gap. The broader significance of this synthesis is that the tools inherited from an era of progressive decline cannot be applied uncritically to a disease that is being pharmacologically remade, and that the central task of paediatric CF research in the coming decade is to characterise, over the timescales that matter to children, benefits and harms that current evidence can only provisionally describe.

12. Limitations

This review is a critical narrative synthesis and is subject to the limitations intrinsic to that method. The selection of sources and the interpretation of their significance necessarily involve judgement, and despite a transparent search strategy and explicit appraisal criteria, the possibility of selection and interpretive bias cannot be eliminated, because no formal protocol governed inclusion and no independent second reviewer adjudicated eligibility. The review did not undertake a systematic enumeration of records or a quantitative pooling of results, and it does not report screening counts or a formal flow of study selection, so that its conclusions rest on reasoned integration rather than on statistical synthesis.

Several further constraints qualify the findings. The literature was restricted to sources accessible during the review and to publications in English, so that relevant evidence in other languages, and evidence held in subscription resources that could not be fully interrogated, may be underrepresented. The evidence base itself is uneven: the paediatric modulator literature is dominated by open-label designs and by industry-sponsored trials, much of the nutritional and infection evidence is observational and therefore vulnerable to confounding, and the mental health signals rest substantially on case reports and provider observation. Outcomes across studies are heterogeneous, with heavy reliance on surrogate endpoints such as sweat chloride and the lung clearance index whose relationship to long-term clinical outcomes is inferred, and long-term data in young children are scarce because the relevant events unfold over years. The field is developing rapidly, and conclusions calibrated to the present evidence may be overtaken as controlled and long-term data accrue. Finally, the geographical concentration of high-quality evidence in well-resourced health systems limits the generalisability of several conclusions to settings where screening, modulators and specialist multidisciplinary care are not universally available. No quantitative synthesis was possible given this heterogeneity, and the review should be read as a critically reasoned map of current knowledge rather than as a definitive account.

Consent

It’s not applicable.

Ethical Approval

It’s not applicable.

Declaration of AI Use

This manuscript was prepared through the combined contributions of all author(s), including contributions to the study design, data, content development, results, interpretation, and related scholarly work. The author(s) acknowledge the use of Grammarly and ChatGPT to assist with grammar checking, language refinement, reference formatting. These AI-assisted tools were not used as authors and did not replace the intellectual contributions or scholarly judgment of the author(s). All AI-assisted outputs, including content, references, and interpretations, were carefully reviewed, revised, verified, and approved by the author(s). The author(s) accept full responsibility for the accuracy, integrity, and final content of the manuscript.

Competing Interests

Authors have declared that no competing interests exist.

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