

Associations between functional gastrointestinal disorders and mental health in children and adolescents

A systematic review

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Laatija:
Maria Korpela

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Vastuuhenkilöt: Linnea Karlsson ja Anna Aatsinki

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Functional gastrointestinal disorders (FGIDs) represent a varying group of conditions characterized by chronic gastrointestinal symptoms such as abdominal pain, constipation, and bloating. These disorders are relatively common among children and adolescents, and there are several research examining their impact on comorbidities and overall health in pediatric patients. Studies consistently demonstrate that children with FGIDs are more likely to exhibit psychiatric symptoms, such as depression and anxiety, compared to healthy peers. The association between FGIDs and psychiatric symptoms may be explained in part by shared pathophysiological mechanisms and the overall burden of disease. Both FGIDs and psychiatric disorders are associated with reduced quality of life, increased school absences, and greater psychosocial burden on families and society.

This systematic review aims to examine the literature on the relationship between FGIDs and mental health in pediatric populations. A systematic literature search was conducted in the PubMed database, focusing on the studies that investigated associations between predefined subtypes of FGIDs and various domains of mental health. Inclusion criteria required studies to be published in the 2000s, to diagnose both FGIDs and psychiatric disorders using structured methods, and to include participants between 1 and 18 years. A total of 28 articles meeting these criteria were included in the review.

The main finding of this review is that FGIDs and mental health are frequently associated with pediatric patients. The strongest association was reported in studies focusing on the current association, whereas prospective studies reported more variable results, suggesting that the strength of the association may fluctuate over time. These findings emphasize the importance of early identification and integrated care approaches that address both gastrointestinal and mental health symptoms in children and adolescents.

Keywords: Functional gastrointestinal disorders, mental health in adolescents and children

Abbreviations

FGID = Functional gastrointestinal disorder

FAP = Functional abdominal pain

IBS = irritable bowel syndrome

RAP = Recurrent abdominal pain

SDQ = Strengths and difficulties questionnaire

CBCL = The child behavior checklist

BASC = Behavior Assessment System for Children

CDI = Children's Depression Inventory

DAWBA = Development and well-being assessment

HRQOL = Health-related quality of life

YSR = Youth self-report

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1 Introduction

Functional gastrointestinal disorders (FGIDs) are often encountered in pediatric primary care. Up to 12-25% of children and adolescents meet the diagnostic criteria for functional abdominal pain (1) (2). The diagnosis of FGID is based on the Rome IV criteria (3). These criteria consider the continuity of abdominal symptoms, their impact on quality of life, and the specific characteristics of abdominal pain without any structural or biochemical abnormalities. In addition, psychiatric disorders in children and adolescents are a relatively common pediatric diagnosis. Up to 5-10% of patients under the age of 18 years suffer from anxiety. Severe depression occurs in 0.5-3% before puberty (4). During follow-up, the number of pediatric healthcare contacts caused by psychiatric symptoms has been on the rise (5).

Past research has identified a significant number of psychological characteristics of children and adolescents with FGID (6). In addition, the coexistent presence of FGID and mental disorders complicates their management in primary care (7). Up to 50% of children with FGID suffer from clinically significant depression or anxiety (2). Both FGID and psychiatric disorders significantly reduce quality of life, increase school absences (8), and increase anxiety among family members (9). This represents a large pediatric patient population whose symptoms impact not only the individual but also their families and society.

It is commonly suggested, that the gut-brain axis has a role in the co-morbidity of FGIDs and mental health (10) and the symptoms and comorbidities have been studied increasingly. It is commonly found that the changes in visceral sensation and intestinal motility are associated with provoking each other (11). On the other hand, the role of inflammatory cells in the pathogenesis of comorbidity was studied in several studies (Schurman et al 2010). Despite this, the individual connection between the FGID subtype and the psychiatric symptom is still widely unknown.

This work aims to clarify the current knowledge of the connection between FGID and psychiatric disorders in children and adolescents based on scientific evidence. This systematic review was conducted through a literature search in the PubMed database, focusing on the main findings related to the co-occurrence of FGID symptoms and psychiatric symptoms.

2 Methods

2.1 Search strategy

The database search of this systematic review was conducted in October 2022 on PubMed. The search consisted of filters with requirements for the English language and a publication date later or equal to the year 2000. In addition, the following search query was used: ("functional gastrointestinal disorder*" OR "functional gastrointestinal" OR "functional gastrointestinal disease" OR "functional bowel disorder*" OR "functional abdominal" OR "functional constipation" OR "FGIDS" OR "FAPDs" OR "abdominal pain" OR "irritable bowel") AND ("depression*" OR "anxiety" OR "internalizing" OR "mental health*") AND ("child*" OR "childhood" OR "children" OR "adolescence" OR "infant" OR "infancy"). In total 692 articles were found.

2.2 Selection criteria

This systematic review excluded studies about non-human subjects as well as reviews, controlled trials, and case reports. Therefore, the included articles were observational prospective or retro-prospective studies, case-control studies, or cohort studies.

Furthermore, the review was conducted with the following inclusion criteria: 1) Children aged 1-17 years. Patients under the age of one year are excluded because the colic symptoms are not studied in this review. 2) FGID phenotype measured using a structured questionnaire such as Rome 2-4 criteria or Apley's criteria or diagnosed by a physician. 3) Psychiatric phenotype was measured using structured questionnaires, such as SDQ and CBCL, for children or their parents. Therefore, studies lacking structural measurements for FGID or psychiatric disorders were excluded.

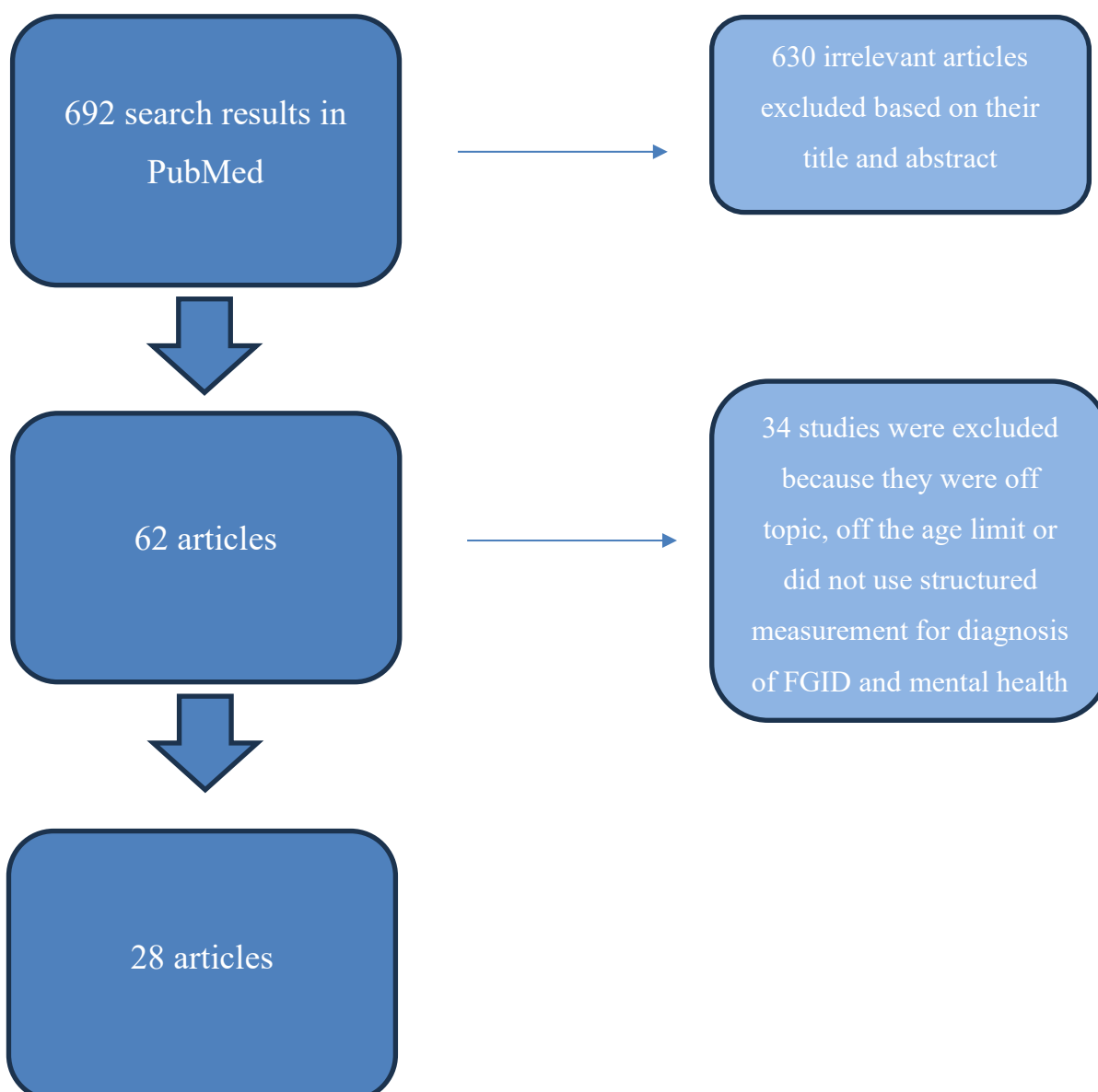
One person reviewed the material without blinding. Inclusion and exclusion criteria were agreed upon by a group that included a post-doctoral and a senior researcher. The information on the studies was collected on the spreadsheet, including the publishing year, the number of participants, gender, geographical distribution, FGID phenotype, FGID measure, psychiatric phenotype, psychiatric measure, and main findings were acknowledged. Furthermore, the results are summarized in Table 1. The literature search was carried out to October 2022.

3 Results

3.1 Study selection

Of the 692 search results, 90 articles were chosen by reading the title and abstract. Studies unrelated to the topic, participants off the age limit, reviews, inventory trials, and case reports were excluded. Further 62 articles were excluded after reading the full text because they were off-topic, off the age limit, or did not use the specific measurement for FGID and psychiatric disorders. Finally, there were 28 eligible articles included in this review.

Table 2. Flow chart of study selection



3.2 Study characteristics

Among the 28 selected articles, 15 were case-control studies, 13 were cohort studies. A prospective or retrospective study design was used in five studies. Subject numbers including control groups ranged from 27 to 14094. However, number of subjects with FGID ranged from 19 to 406. In 21 studies a specific study group was defined for participants diagnosed with FGID. The group of FGID-diagnosed patients was the only studied group in 8 cohort studies and one of the studied groups in 12 case-control studies. Therefore, 7 studies considered only one group conducted from the general population. Healthy control groups were used in 11 case-control studies. In addition, 6 case-control studies included other control groups, such as patients diagnosed with anxiety, migraine, asthma, or organic reasons for abdominal pain.

The study samples consisted of patients from clinics in 17 studies and in 6 studies the sample was conducted from the general population. In 5 articles, there were both patient and general-based populations studied. The ages of all participants ranged from 5 to 17 years. Gender diversity varies between studies, with females being the biggest part of the study groups. However, gender diversity was not reported in 5 studies, and notably, in 2 articles males formed a bigger group than females. The gender diversity varied between 10%-56%. Geographically, most of the studies were conducted in the USA. Nevertheless, there were also studies in Australia, China, Germany Iran, Israel, Netherlands, Norway, Sri Lanka, and Turkey. The articles were published between the years 2000 and 2021.

19 articles of a total of 28 articles considered only FAP. In 3 articles, alongside FAP, researchers also studied a wider range of FGIDs, including IBS, functional constipation, and functional dyspepsia. In 6 studies, the focus was on IBS. Additionally, two studies focused on functional constipation and two studies examined functional dyspepsia. In 19 articles for the diagnosis of FGIDs Rome II, Rome III, or Rome IV criteria were used. Additionally, the Apley criteria were used in 5 studies. In 2 studies the diagnosis was made by a physician, and a more detailed questionnaire was not mentioned. In one study the questionnaire on Gastrointestinal Symptoms in Children was used, as well one study used the MM-RAP questionnaire. However, the diagnosis was made by a physician in 16 studies, and in 2 studies a physician was consulted in difficult cases.

Anxiety was studied in 22 out of 28 articles, while depression was examined in 15 articles. Additionally, somatization was studied in 9 articles, and quality of life was studied in 3 studies. For psychiatric disorders diagnosis structured questionnaires were used, such as BASC, BASC-2, CBCL, CDI, DAWBA, DSM-IV, GHQ, HRQOL, K-SADS, PIC, RCAD, SCARED, SDQ, STAIC, PedsQL and YSR. Only in one study the diagnosis of anxiety was made by a physician, meaning that the structured questionnaires were used for the psychiatric diagnoses in 27 studies.

3.3 Associations between FGIDs and psychiatric disorders

The mean results of the association between FGIDs and psychiatric disorders are summarized in the table Table 3.

Table 4. Associations between FGIDs and mental health

	IBS	Dyspepsia	Constipation	FAP	FGIDs in total
Depression					
Positive association	(12)* (13)**, (14), (15)	(15), (16),	(17)	(6), (8), (14), (16), (18)***, (19), (20), (21), (22), (23), (24)	15 articles
Negative association	(12)*				1 article
No association			(22)	(18)***, (25), (26), (27)	5 articles
Anxiety					
Positive association	(12)*, (13)**, (14), (15), (28)	(15)	(17)	(1), (6), (8), (9), (14), (15), (18)***, (19), (20), (22), (23), (24)****, (26), (27), (29)****, (30), (31), (32)0/0/0000 0:00:00 AM	22 articles
Negative association					No articles
No association			(22)	(18)**, (24)****, (25), (29)****, (33)	6 articles
Somatization					

Positive association	(12)* (13)** , (15)	(15)	(17)	(8), (9), (15), (23), (31), (32)	9 articles
Negative association	(12)*				1 article
No association					No articles
Life Quality					
Positive association					No articles
Negative association	(34)		(17)	(35)	3 articles
No association					No articles

*) Depending on IBS symptom and subtype. Bloating, early satiety, and postprandial distress syndrome had a positive association with anxiety and depression. Bloating and somatization had a positive association. Epigastric pain -subtype was negatively associated with somatization and depression compared to other subtypes. **) Abdominal pain IBS subtype was studied. ***) A current positive association was found, but no prospective association was found. ****) No association between generalized anxiety, and a positive association between the separation anxiety subtype. *****) Individual variation in anxiety was studied.

3.4 Depression and FGIDs

Positive associations were reported between depression and FGIDs overall in 15 studies, while no association was identified in 5 studies, and negative association was reported in one study. One study found both positive and negative associations, depending on the IBS subtype. Four studies reported a positive association between depression and IBS, while no association was found in any study. Two studies found positive associations between depression and dyspepsia, while no negative associations were reported in any study. A positive association between depression and constipation was identified in one study, though as well one study did not find an association. In all, 10 studies reported positive associations between depression and abdominal pain, whereas 3 studies found no association. One study reported a current positive association but found no association in prospective study design.

Among 13 studies reporting positive associations, 8 were cohort studies and five were case-control studies. Of the five studies reporting no associations, all were case-control studies. Of the two studies with a prospective study design, one reported an association while the other found no association.

3.5 Anxiety and FGIDs

Positive associations between anxiety and FGIDs overall were reported in 22 studies, and no associations were reported in 6 studies. Both positive and neutral associations were found in two studies study, depending on the anxiety subtype. Five studies reported positive associations between anxiety and IBS, whereas negative associations or no associations were not found in any studies. Positive associations between anxiety and dyspepsia were reported in one study and no studies reported finding no associations. Between anxiety and constipation, positive associations were reported in one study, and respectively one study reported neutral association. Between anxiety and abdominal pain, 15 studies reported a positive association, while three studies reported no association. Two studies found both a positive association and no association between anxiety and abdominal pain, and one study depending on the study design

Of the 22 studies reporting positive associations, 12 were cohort studies and 10 were case-control studies. Among the six studies reporting no association, four were case-control studies and two studies were cohort studies. One study using a prospective study design found an association, while no association was found in two studies using a prospective study design.

3.6 Somatization and FGIDs

Positive associations between somatization and FGIDs overall were reported in 9 studies. Two studies found positive associations between somatization and IBS, while in one study both positive and negative associations were found depending on the IBS subtype. A positive association between somatization and dyspepsia was found in one study. Similarly, a positive association between somatization and constipation was reported in one study. Additionally, six studies reported positive associations between somatization and FAP. No studies reported results with no association between somatization and FGIDs.

Out of the 9 studies reporting associations five were cohort studies, and three were case-control studies. One study reporting both positive and negative associations was a cohort study. No study used a prospective study design.

3.7 and FGIDs

Negative associations between quality of life and FGIDs overall were identified in three studies, while no studies reported either positive associations or no associations. One study reported a negative association between quality of life and IBS, as well one study reported a negative association between quality of life and constipation. Additionally, one study found a negative association between quality of life and FAP.

Of the three studies reporting negative associations, two utilized a case-control study design, while one represented a cohort study design. No study used a prospective study design.

4 Discussion

This systematic review aimed to determine the current knowledge on the association between FGIDs and mental health in children and adolescent patient groups. The results of this study show a clear relationship between FGIDs and mental health, meaning children and adolescents often suffer comorbidity of FGID and psychiatric symptoms. While research on this co-morbidity is widely available, the number of eligible studies was moderate due to the limited focus on pediatric patients and the use of structured questionnaires. However, the consistency of findings across studies allows for meaningful comparisons and strengthens the overall conclusions.

Every study had structured questionnaires for diagnosis of FGID and mental health conditions. The diagnosis of FGID was commonly made using Rome or Apley criteria. In older studies from the early 2000s' Apley criteria were used, while in later studies Rome criteria were used. Apley criteria considered abdominal pain which led to the significant appearance of diagnosis of functional or recurrent abdominal pain in the literature in the early 2000s'. Rome criteria consider FGIDs in more defined subtypes. Thus, in the literature where IBS, dyspepsia, and functional constipation are studied, the Rome criteria were primarily used. In contrast, studies that used the Apley criteria mainly studied FAP. Notably, studies that used Apley criteria, found more often reported no associations between FGIDs and mental health conditions than studies using the Rome criteria. At least as part of their findings, 40 % of studies using the Apley criteria (2 out of 5 studies) reported no association, compared to 27 % (5 out of 19 studies) studies using the Rome criteria.

Most studies in this review focused on school-aged children, with participant ages ranging from 7 to 17 years. The youngest children studied were four years old. The focus on older children and adolescents may reflect the difficulty of studying younger children. Notably, making an accurate FGID or mental health diagnosis in toddlers is challenging with current diagnostic tools. Only three studies in this review included children only seven years old or younger children, and all three reported an association between FGIDs and mental health. However, since most of the studies included participants ranging from early childhood to adolescence, it is challenging to determine age-specific differences in the association between FGIDs and mental health.

The sample sizes varied widely across studies, with most having over 100 participants, while only 3 studies included fewer than 50 participants. The largest sample sizes were found in epidemiological cohort studies and smaller sample sizes were primarily seen in case-control studies. In 26 studies out of the 28 studies, girls represented a larger proportion of the study group than boys. Especially in the studies where the sample consisted solely of FGID patients, the proportion of girls was particularly prominent. This finding aligns with previous research that has reported a female-dominant gender distribution in FGID populations. Additionally, most of the studies were carried out in Western countries, primarily in the USA. These gender and geographical imbalances may limit the generalizability of the findings presented in this review.

This review found that FGIDs were most associated with anxiety and depression, with positive associations reported in 21 and 13 studies. This result is influenced by the fact that anxiety and depression were the most studied mental health conditions in the literature. However, there was notable variation in the associations for both conditions. Among studies on anxiety, six (29 %) did not find a positive association with FGIDs, and among studies on depression, nine (32 %) did not find a positive association. Fewer articles addressed the relationship between FGIDs and somatization (11 studies) or quality of life (3 studies). The associations with somatization and quality of life were more consistent, with 10 studies (91%) reporting a positive association between FGIDs and somatization, and three studies finding a negative association between FGIDs and quality of life.

Although the overall findings of the review are primarily consistent, discrepancies exist regarding the association between mental health and FGIDs. The consistency of this association appears to vary depending on whether the study design focuses on a current or prospective association. In the literature, the current association appears strong, whereas in prospective studies the association is less clear. In all, 19 articles (83 %) out of 23 focusing on current associations reported an association between mental health and FGIDs in at least part of their findings. In contrast, only one article (20 %) out of a total of five with a prospective or retrospective study design reported an association in follow-up as part of the study findings. This suggests that although the association appears significant at present, FGIDs or mental health problems may not necessarily predict future FGID or mental health symptoms. For example, Gieteling et al. (18) found that although a current association was present, only one-third of children with depression and anxiety continued to exhibit the symptoms at one-year

follow-up, and the characteristics of abdominal pain did not predict the persistence of these psychiatric symptoms.

There is notable individual variance and different intensities in the association of FGIDs and psychiatric symptoms. This association may differ depending on the FGID subtype and the predominant symptom. For example, Schurman et al. (12) found that the association with mental health varied depending on the leading symptom of IBS. Specifically, bloating, early satiety, and postprandial distress syndrome as predominant symptoms were associated with anxiety and depression, whereas epigastric pain as the leading symptom was negatively associated with somatization and depression compared to other IBS symptoms. Similarly, the association varies depending on the predominant psychiatric symptom. Ghanizadeh et al. (24) demonstrated variation in the presentation of FAP depending on the subtype of anxiety. Notably, they reported no association between generalized anxiety and FAP, but a positive association between separation anxiety and FAP. Therefore, the associations between FGIDs and mental health conditions differ significantly within their respective subtypes leading to notable individual differences.

Notably, FAP as a subtype of FGID was the most studied subtype in the literature. In this review, FAP was studied in 19 articles out of total 28 articles. Additionally, abdominal pain as a predominant symptom of a FGID subtype of IBS was studied in two studies (12), (13). This highlights the fact, that abdominal pain seems to be the most studied FGID subtype in pediatric patient groups. Diagnosis of other FGID subtypes might be also hard to make with parental questionnaires because the symptoms of FGIDs often overlap and children tend to manifest the symptoms as pain. Abdominal pain as a subtype of FGID tends to be a common clinical symptom, that is associated with mental health problems. In addition, multisite pain overall is found to be connected to higher levels of psychiatric symptoms, especially anxiety (36) (23). Considering these findings, future research examining psychiatric symptoms in young children may benefit from focusing on multisite pain, rather than limiting the analyses to pain localized to a single site.

The strong association between FGIDs and mental health is clinically significant and should be carefully considered. As it is shown in this review, FGIDs are associated with a lower quality of life. This clinically common pediatric patient group often experiences additional challenges. For example, FAP has been linked to cognitive difficulties, including slower

processing speed and poorer executive functioning. Children with FAP tend to perform worse in school (8) (16) and have higher rates of school absences (1), (37). Moreover, anxiety and depression as co-morbidities of FAP predict functional disability (19) and patients with FGIDs are more likely to experience an earlier onset of anxiety (6). These findings highlight the critical need for early identification and comprehensive management of FGIDs, considering their relation to mental health, cognitive function, and overall well-being in pediatric patients. Children and adolescents with FGIDs could benefit from psychiatric assessment as part of a more complete and supportive treatment plan.

The literature search has several limitations. It was conducted by a single researcher, which may introduce bias. Additionally, only one database (PubMed) was used, potentially limiting the scope of the included studies. Most of the literature was conducted mostly in Western countries, which may affect the generalizability of the findings.

In conclusion, the results of this systematic review suggest that FGIDs and mental health are strongly and rather consistently associated in pediatric patient groups. Children and adolescents suffering from FGIDs or psychiatric symptoms should be treated comprehensively, not only focusing on the leading symptom. Improving knowledge and treatment for this large population of children and adolescents is very important in reducing and preventing long-term and present personal, social, and societal costs of FGIDs and mental health problems.

5 Use of artificial intelligence

In this work, artificial intelligence was used for grammar correction. The platform used was ChatGPT. Artificial intelligence was not utilized in data collection, text or data analysis, or in summaries.

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