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BMJ Paediatrics Open

Impact of physical inactivity and sedentary behaviour on functional constipation in children and adolescents: a systematic review

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ABSTRACT

Objective Lack of physical activity (PA) and sedentary behaviour (SB) have emerged as critical global health concerns in children and are believed to be associated with functional constipation (FC). The present study aims to explore this potential association.

Design A comprehensive search of PubMed, Scopus, Web of Science, Embase, Cochrane Library and PsycInfo databases was conducted through 2023 using terms related to constipation and PA and SB in ages 0–18 years. Titles and abstracts were screened against eligibility criteria. Constipation was diagnosed using Rome (II–IV) criteria. Full-text reviews were reviewed, and data were extracted. Risk of Bias in Non-randomized Follow-up Studies of Exposure quality assessment tool was used to evaluate the risk of bias of studies.

Main outcome measures We assessed the association between lack of PA/SB and FC.

Results A total of 2170 titles were screened. Nine studies encompassing 3849 children from six countries were included. Of these, four were community/schoolbased studies, one was a birth cohort, three were case series and two were hospital-based case-controlled studies. All 10 studies assessed the association between PA and FC. Only three showed an association between lack of PA and FC. Five studies evaluated the effects of SB on FC, and only two reported a positive association. The methods used to assess PA/SB differed across the studies. All nine studies included in the systematic review were rated as having high risk of bias.

Conclusions Despite numerous studies suggesting a link between insufficient PA/SB and FC, this systematic review did not uncover compelling evidence supporting such an association.

INTRODUCTION

The lack of physical activity (PA) and engaging in sedentary behaviour (SB) has become a significant universal health concern in children and adolescents. It has been reported that 81.0% of children and adolescents worldwide do not engage in sufficient PA.¹ The lack of PA has a detrimental influence on health, including increased risk of obesity, cardiometabolic diseases and colonic and breast

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is widely believed that inadequate physical activity and prolonged sedentary behaviour play a crucial role in the development of constipation in children.

WHAT THIS STUDY ADDS

- ⇒ Our findings indicate a lack of solid evidence supporting the notion that physical inactivity and sedentary behaviour are causally linked to the development of constipation in children.
- ⇒ Encouraging healthy habits like increased physical activity and reducing sedentary behaviour may not positively impact the management of childhood constipation with current evidence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- $\Rightarrow\,$ This study helps to promote normal physical activity in children with constipation.
- ⇒ Researchers must be encouraged to explore these associations by employing clear definitions and robust scientific methodology.

cancers, and tends to reduce the life span.² In addition, more recently, several studies have suggested the possibility of an association between lack of PA and engaging in SB and functional constipation (FC) in children, adding another new dimension to this complex problem.³⁴

FC is a global public health problem affecting children. The estimated prevalence of FC in children is 9.5%.⁵ Some of them experience numerous psychological issues, including anxiety, depression, maladjustment, abnormal personality traits and internalisation.^{6–8} Furthermore, their health-related quality of life is significantly lower in all domains than their healthy peers.⁹ FC also imposes a substantial financial burden on public funds due to healthcare expenditure in patient and outpatient care.^{10 11}

No comprehensive systematic review has been conducted on the potential association between PA/SB and FC in children. Therefore, we aimed to systematically review the currently available scientific literature on the association between FC and PA/SB.

METHODS

Review design

This systematic review was designed and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹² A prospective methodology was agreed, and no major deviations were made from this prior to completion of the review.

Literature search

PubMed, Scopus, Web of Science, Embase, Cochrane Library and PsycInfo databases were searched from their inception to February 2023 by CK, a medical librarian with extensive experience. The search strategy in full is available in online supplemental material 1.

Inclusion criteria

- 1. Studies that assessed the association between FC and PA/inactivity.
- 2. Studies that assessed the association between FC and sedentary lifestyle.
- 3. Included infants/children from 0 year to 18 years.
- 4. With a diagnosis of FC using any iteration of the Rome (II–IV) criteria.
- 5. Published in complete manuscript form in the English language.

Screening and selection of articles

Two authors (SA and WH) screened all abstracts independently using Rayyan QCRI—a web and mobile app for systematic reviews (www.rayyan.qcri.org).¹³ When a disagreement occurred, the senior author (SR) was consulted to reach an agreement. All eligible titles were chosen after removing irrelevant titles and abstracts, and full-text articles were retrieved. The same two authors (SA and WH) reviewed all these articles independently before deciding whether to include them based on the above qualifying criteria. Yet again, the disparities of opinions were discussed with the senior author (SR) to reach a conclusion.

Data extraction

Once selected as eligible for inclusion, data were extracted by the same authors (SA and WH) once again independently and in duplicate using a standard Microsoft Excel sheet, followed by involvement of a senior author for any disagreements. Extraction included basic study details (authors, year of publication, country of origin, study design, settings), details of the population (sample size, number of children with FC, number of controls, age range, sex distribution), diagnostic criteria for FC, study results related to PA and sedentary lifestyle (PA, SB, television (TV) watching, video gaming, including percentages among cases and controls, data on univariate analysis, data on multivariate analysis and p values).

Quality assessment

Ouality assessment of all included articles was conducted independently using standard methods by two authors (SA and WH). We used the Risk of Bias in Non-randomized Follow-up Studies of Exposure (ROBINS-E) tool to assess the risk of bias in selected studies.¹⁴ The tool has five parts (A–E). Section A specifies the results being assessed. Section B provides basic assessment tool (screening tool) to assess the risk of bias in studies to decide whether to proceed with full assessment. This might be the case if the screening questions identify that there is substantial confounding and the study has made no attempt to control for them, it may not be necessary to proceed with full risk of bias assessment and the study can be judged as having substantial high risk of bias. Section C provides a detailed tool to assess risk of bias using seven domains. Section D defines causal effect of interest specific to the result being assessed. Section E examines whether the confounders that should have been controlled for were controlled in that analysis to produce the final results.¹⁴

Statistical methods

We used a descriptive analytical model to present the data. The studies included in the review were heterogeneous in many ways; therefore, we could not perform any statistical analysis of the data.

Patient involvement

There was no patient involvement in this review.

RESULTS

Literature search

The literature search identified 2170 abstracts. Out of them, 2137 were judged to be not relevant to the topic and therefore excluded. The full texts of the 33 abstracts were reviewed in detail to assess eligibility. Of the 32 articles, 23 were rejected (seven did not use Rome criteria to diagnose constipation, nine studies did not provide data on constipation and six did not have relevant data to assess the association between constipation and PA). One article was rejected after an in-depth review as it contained duplicate data.¹⁵ Nine articles were included in the final systematic review^{16–24} (figure 1).

Characteristics of the included studies

There were 3849 children in the nine studies, and out of them, 1637 had FC and other 2212 were serving as controls. Five studies used the Rome III criteria for diagnosing FC,^{16–20} whereas three used the Rome IV criteria.^{21–23} The other study used the Rome II criteria.²⁴ One study was observational and, therefore, had no control group.¹⁶ There were four school/communitybased studies,¹⁸ ¹⁹ ²¹ ²⁴ one birth cohort study²³ and four hospital-based cohort studies.¹⁶ ¹⁷ ²⁰ ²² Regarding geographical location, three studies were from

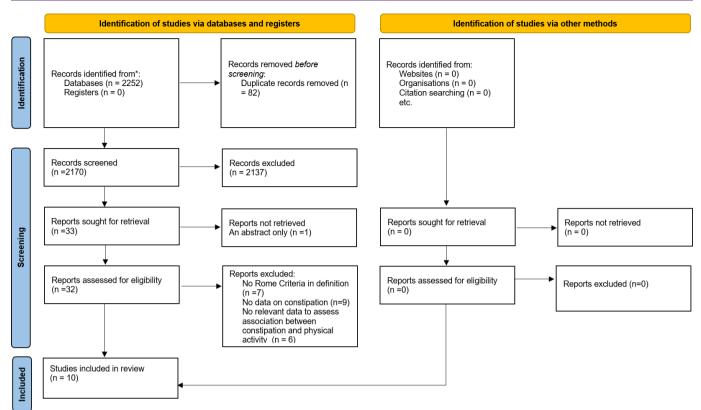


Figure 1 Flow chart of the study selection.

Asia,^{16 20 22} three from South America^{18 21 23} and three from Europe^{17 19 24} (online supplemental material 2).

Quality assessment

We used ROBINS-E tool to assess the risk of bias of selected nine studies. As the first step, the screening tool (section B) was implemented to determine whether there were substantial confounding and the attempt that the authors made to control them during the planning, analysis and reporting the study. All nine studies were shown to have high risk of bias. Only three studies have made at least a statistical attempt to control for confounding variables.^{16 19 22} Apart from two studies,^{18 24} all other studies had problems in measuring the exposure (PA/SB) in a standard and validated way (table 1). Therefore, all nine studies failed to obtain adequate priority for full risk of bias assessment.

Physical inactivity and FC

Definition of physical inactivity

Table 2 describes the definitions used to define PA. PA can objectively be measured by using an accelerometer or standard questionnaires such as the International Physical Activity Questionnaire (IPAQ) and Health Behavior in School Children questionnaire.^{25 26} All 10 studies used questionnaires to identify the time spent on PA/inactivity. Only one study used an objective questionnaire (the IPAQ) to define PA.¹⁸ A Brazilian study used a nonvalidated method to calculate a PA score by evaluating and scoring activities according to their intensity,²¹ while others were found to be with poor validity and reliability.

Similarly, the cut-off value for PA is defined as a minimum of 60 min of moderate to vigorous PA per day.²⁷ Most of the studies have not included such a definition in their protocol. For example, Andreoli *et al* assessed the PA using a yes/no question of whether their subjects were involved in regular PA.²³ A Thai study defined adequate PA as a weekly energetic activity of more than 2 hours/ day.²²

Association between physical inactivity and FC

Only one study reported an association between physical inactivity and FC after multiple logistic regression. PA of 4-7 days/week versus no PA had an OR of 0.53 (95% CI 0.36 to 0.77, p=0.001), indicating higher odds of developing FC in children with physical inactivity.¹⁹ Another study measured PA using a questionnaire that measured the number of days per week with more than 60 min of moderate to vigorous PA. Children with FC had less PA than controls.¹⁷ One study, however, reported more PAs in children with FC compared with children without constipation (moderate PA (hours/ day) children with constipation had more activity than controls $(1.3\pm1.0 \text{ vs } 1.0\pm0.7)$) and vigorous PA (vigorous activity was also more prevalent in children with constipation compared with controls $(0.2\pm0.3 \text{ vs } 0.1\pm0.2))$.²⁴ An Iranian study without a control group reported no significant increase in FC duration in children with inadequate PA.¹⁶

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Tab	Table 1 Assessment of risk and bias of studies using ROBINS-E tool	ROBINS	h-E tool							
		Studies								
	Factor in the ROBINS-E, section B	Dias 1992 ²¹	Chouliaras et al ¹⁹	Chouliaras Wanichsetakul and Macedo Andreoli Rezaianzadeh Dehghani Olaru Jennings et al^{19} Wongteerasut ²² 2020 ¹⁸ et al^{23} et al^{16} et al^{20} 2017 ¹⁷ et al^{24}	Macedo 2020 ¹⁸	Andreoli et a/ ²³	Rezaianzadeh et al ¹⁶	Dehghani et al ²⁰	Olaru Jennir 2017 ¹⁷ et al ²⁴	Jennings et al ²⁴
B1	Did the authors make any attempt to control for N confounding?	z	~	٨	z	~	z	z	z	z
B2	If N/PN to B1: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	≻	z	ΡΥ	~	Ъ	7	≻	≻	~
B3	Was the method of measuring exposure inappropriate?	≻	~	7	z	≻	~	≻	≻	z
B4	Was the method of measuring the outcome inappropriate?	z	z	Z	z	z	z	z	z	z
lf th∈ N, N	lf the answer to any of B2, B3, B4 is Yes or Probably yes, the result should be considered to be very high risk of bias and no further assessment is required. N, No; PN, Probably no; PY, Probably yes; ROBINS-E, Risk of Bias in Non-randomized Follow-up Studies of Exposure; Y, Yes.	result sho f Bias in N	uld be consider on-randomized	iould be considered to be very high risk of bias and no fu Non-randomized Follow-up Studies of Exposure; Y, Yes.	bias and no oosure; Y, Ye	further asses s.	sment is required.			

SB and FC Definition of SB

Four studies assessed the association between FC and sedentary activities.¹⁶¹⁷¹⁹²³ The leading sedentary lifestyle was exposure to TV. Other sedentary activities studied included video gaming and playing with toys and dolls. The time used as the cut-off value varied from study to study. A European study reported a timescale of watching the TV (<1, 1–3 and >3 hours).¹⁹ Another study used a cut-off value of 3 hours to define excess TV watching.²³ The measurement of engaging in these activities was diverse and, therefore, could not be included in a meta-analysis.

Association between SB and FC

Four studies assessed the effects of screen time as a risk factor for FC.^{16 17 19 23} One study assessed TV exposure using a non-validated questionnaire and showed that exposure to TV for more than 3 hours compared with less than 1 hour has higher odds of developing FC (OR 1.88 (95% CI 1.11 to 3.18), p=0.019).¹⁹ Olaru *et al* reported longer screen time in children with FC than controls.¹⁷ A study from Brazil noted that children exposed to screen more than 3 hours have no higher risk of developing FC than children exposed to screen under 3 hours (p=0.556). In addition, this study reported that engaging in sedentary activities, such as playing with dolls and other toys for more than 4 hours, had no higher odds of developing FC than children exposed to similar activities for less than 4 hours (p=0.727).²³

DISCUSSION

Consistent PA is considered one of the cornerstones of overall child health, and guidelines recommend daily kinetic activities for healthy children.²⁵ The prevailing notion is that children who lead sedentary lifestyles characterised by a lack of PA and extended screen exposure are more prone to experiencing FC. Consequently, engaging in PA is often recommended for children with FC to alleviate their symptoms. Therefore, this systematic review evaluated the association between lack of PA and SB and FC in children.

Nine studies were included in the systematic review, and we could not find adequate evidence to state that physical inactivity predisposes children to develop FC. It is vital to clarify that lack of evidence of association is not evidence of no association. This finding instead highlights that currently there is a paucity of evidence to support either way. This review can say that based on a rigorous and standardised synthesis of the current literature, it is not possible to identify physical inactivity or prolonged screen time as a significant risk factor for FC in children.

There were several potential reasons for this finding. First, the measurement and definition of PA were diverse across studies, and this led to clinical heterogeneity which significantly impacts any potential for meta-analysis to increase the precision of findings. Except for two studies,

Author, year	Number of children with constipation	Controls	Age range	Sample size	Measurement of physical activity/TV exposure	Statistical measures in original studies
Dias, 1992 ²¹	101	351	6–12 years	452	Active commuting to school Physical activity score	There was no statistically significant relationship between functional constipation and active commuting to school (48.5% and 56.7% of children with and without constipation, respectively; $p=0.179$). There was no difference between physical activity scores between children with constipation (17.3±11.9) and children with no constipation (17.3±10.3), $p=0.601$.
Wanichsetakul and Wongteerasut, ²² 2021	45	45	1-4 years	90	Weekly energetic (sweating) movement or activity ≥4 days	Univariate logistic regression analysis revealed no significant differences between the constipated and non-constipated groups in weekly energetic (sweating) movement or activity ≥4 days (38 vs 44, p=0.055) and sedentary activity >2 hours/day (31 vs 36, p=0.230).
Macêdo e <i>t al,¹⁸</i> 2020	96	290	14–19 years	386	Physical activity Using the short version of the International Physical Activity Questionnaire. The physical activity score was calculated in minutes per week by adding the minutes spent in walking and moderate-intensity activities and the minutes spent in vigorous- intensity activities. Physical inactivity was defined as a physical activity score lower than 300 min.	Physical inactivity (<300 min/week) was found in 204 (52.8%) of the 386 participants and was more frequent in females (62.7%; 126/201) than in males (42.2%; 78/185; p<0.0001). Physical inactivity among males with constipation versus without constipation: 19 (45.2%) vs 59 (41.3%), p=0.778 Physical inactivity among females with constipation versus without constipation: 32 (59.3%) vs 94 (63.9%), p=0.657 Physical inactivity among total children with constipation and without constipation: 51 (51.3%) vs 153 (52.8%), p=0.956
Andreoli <i>et al</i> , ²³ 2019	49	103	4-7 years	152	Physical activity Regular physical activity: Yes/No Screen time: <3 hours >3 hours/day Sedentary activities: <4 hours >4 hours Time spent playing with toy cars, dolls and playhouse, and doing homework. Non-sedentary activities: <2 hours >2 hours Riding a bike, playing with a ball, running and other things	Regular practice of PA: Yes, 43 (28.3%) Constipation 13 (26.5%) versus No constipation 30 (29.1%): No, 109 (71.7%) Constipation 36 (73.5%) versus No constipation 73 (70.9%): X^2 test, p=0.741 Screen time: <3 hours, 60 (39.5%) Constipation 21 (42.9%) versus No constipation 64 (62.1%): \geq 3 hours, 92 (60.5%) Constipation 28 (57.1%) versus No constipation 39 (37.8%): X^2 test, p=0.556 Poisson regression, p=0.555 Sedentary activities: <4 hours, 59 (38.8%) Constipation 20 (40.8%) versus No constipation 39 (37.9): \geq 4 hours, 93 (61.2%) Constipation 29 (59.2%) versus No constipation 64 (62.1%): X^2 test, p=0.727 Non-sedentary activities: <2 hours, 82 (54%) Constipation 27 (55.1%) versus No constipation 55 (53.4%): \geq 2 hours, 70 (46%) Constipation 22 (44.9%) versus No constipation 48 (46.6%): X^2 test, p=0.844 Poisson regression, p=0.121
Rezaianzadeh et al, ¹⁶ 2018	826	No control group	6.96 months to 17.75 years	826	Physical activity: Measured as <1 hour, 1–2 hours, >2 hours/day <i>TV exposure:</i> <2 hours 2–3 hours >3 hours/day <i>Video garnes:</i> <2 hours 2–3 hours >3 hours/day	The results of univariate linear regression analysis indicated that the duration of chronic constipation was related to physical activity (B=0.101, p=0.038) and duration of watching TV (B=0.033, p<0.001). Both physical activity and TV exposure are not significant in multivariate analysis.

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Table 2 Con	tinued					
Author, year	Number of children with constipation	Controls	Age range	Sample size	Measurement of physical activity/TV exposure	Statistical measures in original studies
Olaru et al, ¹⁷ 2016	234	112	4–18 years	346	Physical activity: Number of days per week with more than 60 min of moderate to vigorous physical activity <i>TV exposure:</i> Quantified the time they spend watching TV or using a computer	When physical activity was concerned, 52.99% of the children in the patient sample were not involved in physical activity, and 39.32% reported only 2 days/week of 60 min moderate to vigorous physical activity at the most. In the control sample, 33.93% had no physical activity, and 59.82% reported 2–4 days/week of 60 min moderate to vigorous physical activity. The statistical analysis of the cases studied based on the level of physical activity in the two samples revealed a significant difference (χ^2 =18.419, df=3, p<0.001). When sedentary behaviour (watching television or using the computer) was concerned, 50% of the children in the patient sample spent around 4–6 hours/day watching television or using the computer, as compared with the control sample (84.82%) spent around 1 and 3 hours/day doing these activities, compared with the 50% of the children in the patient sample. A significant statistical correlation has been determined between the number of hours spent watching television/ using the computer and the occurrence of constipation (<i>F</i> =92.162, p<0.001, 95% CI).
Chouliaras <i>et al</i> , ¹⁹ 2021	221	1218	6–18 years	1439	TV exposure was determined using a daily time scale (<1, 1–3, >3 hours). Level of physical activity was determined on a time scale per week (none, 1–3 days, 4–7 days).	After multiple backward, stepwise logistic regression analyses, physical activity (4–7 days/week vs none, OR 0.53, 95% Cl 0.36 to 0.77, p=0.001) was significantly less in children with FC. TV exposure (>3 hours/day vs <1 hour/day, OR 1.88, 95% Cl 1.11 to 3.18, p=0.019) was also significantly associated with FC.
Dehghani <i>et al</i> , ²⁰ 2015	37	37	6 months to 18 years	74	Physical activity measures: Physical activity of more than 20 min/day on at least 3 days/week	Physical activity and vegetable consumption were seen more frequently in the control group compared with the cases, but these differences were statistically insignificant.
Jennings <i>et al</i> , ²⁴ 2009	28	56	7–10 years	84	Physical activity: The method involved children completing a 7-day diary that asked for information on each activity that they participated in, as well as information on the time spent in sedentary activity.	Of the 84 participants, 28 were classified as having constipation. When comparing moderate physical activity (hours/day), children with constipation had more activities than controls ($1.3\pm1.0 \text{ vs} 1.0\pm0.7$). Similarly, vigorous activity was more prevalent in children with constipation ($0.2\pm0.3 \text{ vs} 0.1\pm0.2$).

others did not measure PA in a universally acceptable objective way.^{18 21} Most of the studies have not included a minimum cut-off value to define adequacy of PA in their protocol. Second, there may be no association and despite weaknesses in studies, the finding could be accurate. Only two community-based and one hospital-based studies reported an association between inadequate PA and FC in children.^{16 17 19} Contrast to these studies, Tuteja et al, studying 773 adults (24-77 years) using validated diagnostic criteria and a validated PA questionnaire, found no association between reduced PA and FC.²⁸ There are no systematic reviews assessing the association between PA and FC in adults. However, one meta-analysis on the effects of exercise therapy in patients with constipation found meagre benefits.²⁹ However, the included studies were reported to have number of biases including random allocation, concealment of allocation and nonblinded outcome measures. Furthermore, there were

also concerns regarding the exercise plan and supervision. Therefore, it is difficult to conclude that PA is a useful therapeutic modality for constipation. SB is characterised by excessive screen time (watching TV and time spent on computers and tablets). The cut-off value for SB is 2 hours.²⁵ Only two studies found a significant association between screen time and FC.¹⁷¹⁹

Finally, outcome measures were another source of heterogeneity, as well as raising questions of validity, reliability and indirectness. The methods of acquiring outcome data are not standard, with no consensus or core outcome set. Cut-offs were variable, tools often invalidated and the question as to whether the measured items were direct or perhaps surrogate markers of the measure of interest was apparent in a number of studies.

It is imperative to understand the underpinning thinking of why both the general public and paediatricians believe that lack of PA and engaging in SB, including TV watching, predisposes children to develop FC. First, there is a sizeable literature regarding these associations. While most of these studies found an association between lack of PA and FC, the definitions the researchers used to define FC were not robust enough to be included in this systematic review. Three papers from the Toyama birth cohort study reported an association between poor PA and FC. However, their definition of FC was nondaily and irregular bowel movements in one publication and occurrence of bowel movements less frequently than once every 2 days in another publication.^{3 30 31} The Generation R birth cohort from Rotterdam measured PA with an accelerometer, and their definition of FC was having a defecation frequency <3 times a week for at least 2weeks or predominantly hard stools for most stools for at least 2 weeks.^{32 33} It has been shown that 6.6% of otherwise healthy children have stool frequency <3 per week and 3.8% hard stools.³⁴ Therefore, diagnosing FC using a single criterion would grossly exaggerate the prevalence of FC and overemphasise the association between lack of PA and FC. All these could have contributed to the belief that children who do not engage in PA and live sedentary lives are at a higher risk of developing FC.

Several authors have studied the effects of PA on colonic transit times in healthy adults and reported reduced pressure waves in the colon during exercise and reduced colonic transit time without increasing defecation frequency.^{35 36} Most of these studies were conducted in experimental settings with few healthy subjects, and therefore, it may not be possible to assume that the colon may function in children suffering from constipation. These conflicting results possibly indicate that PA has minimal effect on colonic motility and can hardly increase defecation frequency in a clinically meaningful way.

This systematic review has strengths, including the meticulous inclusion of studies employing Rome criteria for diagnosing FC and substantial sample size. A notable drawback is the inconsistency in defining inadequate PA and SB across the studies. Standardised methods like using the IPAQ or accelerometer, and internationally recognised PA and SB thresholds are essential for future research to meet global standards. Additionally, the validity and precision of PA and SB assessment tools were not consistently addressed in most of the studies reviewed in this systematic review. The exclusion of non-English articles also limits the comprehensiveness of our findings, potentially overlooking valuable insights.

Finally, the assessment of risk of bias using a standard tool showed all studies included in the systematic review failed screening test for full assessment of risk of bias. The screening process revealed that most of the studies have not attempted to control for confounding factors in a systematic way indicating the possibility of serious risk of bias. Only three studies have used some form of a multiple logistic regression analysis to control for confounding factors.^{19 22 23} Two studies have used a standard method to assess the exposure (inadequate PA or SB).^{18 24} Despite

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these significant methodological and analytical deficiencies, some studies have suggested association between lack of PA and SB and FC. Addressing these limitations in future research endeavours will improve the validity and generalisability of findings regarding the association between PA, SB and FC in paediatric populations.

CONCLUSIONS

Despite prevailing beliefs, we failed to establish a conclusive link between engaging in SB and lack of PA and the development of FC in children. Methodological disparities in PA and SB measurement likely contribute to this lack of association. Given the contemporary decline in PA among adolescents and the rise in SB due to global sociocultural shifts, there may indeed exist a potential connection between inadequate PA, SB and FC. Researchers must undertake further investigations with enhanced scientific rigour, employing internationally recognised standards for PA and SB assessment and defining FC parameters. Increased evidence elucidating these inter-relations could lead to developing clinically effective therapeutic interventions and preventive measures for FC.

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