

# The Quality Of Cluster Randomized Controlled Trials Of Pediatrics Should Be Improved: An Integrative Literature Review

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## Research Article

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# Abstract

**Background:** The number of cluster Randomized Controlled Trials (cRCTs) have been increasing and application in pediatrics is also growing. However, we did not know the quality of cRCTs in pediatrics and no previous study has comprehensively analyzed cRCTs in pediatrics. To investigate the status of cRCTs in pediatrics and analyzed influencing factors of the methodological quality.

**Methods:** Through a search of 10 highest-impact-factor journals from PEDIATRICS and MEDICINE, GENERAL & INTERNAL, we identified cRCTs published from 1 January 2015 to 7 June 2020. The associations between study factors and grade of ROB (Risk of Bias) quality were analyzed by Pearson's chi-squared test.

**Results:** A total of 73 cRCTs were included. For the number of cRCTs, it has fluctuated in the past five years. For the International Classification of Diseases Eleventh Revision (ICD-11), 34.2% cRCTs could not be classified, of which more focused on vaccines; 15.1% cRCTs were classified into "X Extension Codes", of which more focused on vaccines and school bullying. For research settings, studies were concentrated in schools, communities, hospitals, clinics, and kindergartens, of which schools (36.5%) were the most. The number of clusters ranged from 1 to 1533 (M=28) and the participants ranged from 135 to 190,238 (M=1903). For the results of ROB assessment, 31 cRCTs were in high-quality, 28 were in low-quality, and 14 were unclear. The majority of cRCTs provided flow diagrams (87.8%), registered (98.6%), and made a distinction between primary and secondary outcomes (86.5%).

**Conclusions:** The further improvement of the quality of cRCTs in pediatrics is needed, particularly in the terms of randomization, allocation concealment, and blinding. Writing and publishing the protocol can enhance transparency. Comply with of CONSORT statement for future studies is needed.

## Background

Because of the strong argument strength, randomized trials usually help researchers determine the efficacy of interventions in evidence-based medicine<sup>[1]</sup>. The multi-center design is a common method used in clinical trials, particularly in randomized controlled trials (RCTs). It is also widely used in evaluating the intervention's efficacy because of interventions in clusters<sup>[2]</sup>, which makes it possible not only to avoid contamination<sup>[3]</sup>, but also to combine the advantages and characteristics of RCTs. Based on the above, and take into account the particular characteristics of children, cRCTs are also particularly appropriate for applications in pediatric studies. In recently, the number of cRCTs have been increasing and application in pediatrics is also growing. A cross-sectional survey in 2021, however, find that both the methodological quality and reporting quality of cRCTs need to be improved, particularly the selection bias of methodological quality<sup>[4]</sup>. Currently, no previous study has comprehensively analyzed cRCTs in pediatrics; indeed, no study has identified what characteristics affecting the quality of cRCTs. Therefore, in this survey, cRCTs in the high-quality journals in the field of PEDIATRICS and MEDICINE, GENERAL & INTERNAL were included to summarize the characteristics, to assess of quality based on the Cochrane risk of bias assessment tool (ROB), and to analyze the influencing factors of the methodological quality of cRCTs in pediatrics.

## Methods

### Data Sources and Search

Ten journals, namely Journal of the American Medical Association (JAMA), British Medical Journal (BMJ), Lancet, New England Journal of Medicine (NEJM), Annals of Internal Medicine, JAMA Pediatrics, Lancet Child & Adolescent Health, Journal of the America Academy of Child and Adolescent Psychiatry, Archives of Disease in Childhood-Fetal and Neonatal and Pediatrics were systematically searched from 1 January 2015 to 7 June 2020 in PubMed. We selected the top ten journals According to the impact factors in the PEDIATRICS and MEDICINE, GENERAL & INTERNAL in JCR 2019 (Journal Citation Reports) respectively. The search terms were "pediatric\*", "paediatric\*", "child\*", "infant\*", "adolescent\*", "baby", "babies", "trottie\*", "youth\*", "kids", "toddler\*", "pre-school\*", "preschool\*", "kindergarten\*", "kinder-garten\*", "girl\*", "boy\*", "student\*", "junior\*", "juvenile\*", "neonat\*", "newborn\*", "teenager\*", "pubescent", "preterm", "puberty", "young\*"; "cluster", "crossover trial", "cluster-crossover trial", "cluster crossover trial", "cluster-randomized", "cluster randomized", "cluster-randomised", "cluster randomised", "cluster RCT".

### Selection Criteria

Studies fulfilling all the following criteria were considered eligible: (1) the study was a cRCT; (2) the study subject was about newborn, infant, toddler, child, and adolescent; and (3) studies published in Chinese or English.

The following types of studies were excluded: (1) conference proceedings, abstracts, letters, or protocols; (2) studies for which the full text was not available; (3) studies were duplicated; and (4) RCTs at the individual level.

### Study Selection

After eliminating duplicates, four researchers independently in pairs in two steps as described below. Before the formal selection, a training exercise of a random sample of 200 citations was conducted to ensure the reliability and feasibility of selection, until adequate agreement on the selecting methods was reached. Firstly, the titles and abstracts of the records were independently screened by four researchers based on selection criteria, and then the full texts of potential suitable articles were retrieved for further assessment. Disagreements were resolved by discussion or consultation with a third researcher.

### Data Extraction

Using a pre-developed data extraction form, six researchers independently in pairs extracted study characteristics including: (1) Basic information: publication year, title, journal of publication, country of the first author, funding, conflicts of interest, study topic, ICD-11 classification, the country in which the study was conducted, study setting, and whether multi-center; (2) Study design: whether the trial registered, wrote a protocol, published protocol, had a diagram, conducted repeat observations, conducted evaluator training, conducted additional analyses, distinguished primary and secondary outcome indicators (yes or no), and type of intervention, number of centers, number of participants.

### Quality of Evidence Assessment

Six researchers independently evaluated the methodological quality of included studies using the Cochrane risk of bias assessment tool [5] in pairs. Disagreements are resolved by consensus or consultation with a third researcher. The overall Cochrane ROB tool grades methodological quality of included studies as high, low, and unclear [6, 7] according to the risk of bias of following 8 items: sequence generation (randomization) , allocation concealment, blinding of participant, blinding of personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. See **Table 1 The grade of ROB** for details.

Table 1 The grade of ROB

The grade of methodological quality	Conditions
High Quality	Two or more of the five key items <sup>a</sup> have low bias, and three common items <sup>b</sup> without high bias.
Low Quality	One or less of the five key items with low bias, and regardless of other common items.
Unclear	Other conditions.

a: The five key items included sequence generation, allocation concealment, blinding of participant , blinding of personnel , blinding of outcome assessors.

b: three common items were incomplete outcome data, selective outcome reporting, and other sources of bias.

### Statistical Analysis

We established the database with Microsoft Excel 2019 software, and descriptive statistics were performed by SPSS software, version 25.0 (Statistical Package for the Social Sciences version 25.0). Qualitative variables were described by absolute numbers (percentages). Quantitative variables were expressed as mean  $\pm$  standard deviation (SD). We then conducted chi-square test to assess the associations between study factors and rates of ROB. A difference was considered statistically significant effect when the *P*-value equal to or less than 0.05.

## Financial Support

The funding source had no role in design of study, the collection, analysis, interpretation, and the decision to approve publication of the finished manuscript.

## Ethical Approval

Not applicable. All the work was developed using published data.

# Results

## Study Selection

We identified 5,147 records from database. A total of 73 cRCTs were included eventually. More details of the search and selection are shown in **Figure 1 Flow chart summarizing the process of identifying the eligible studies.**

## Study Characteristics

The number of included cRCTs fluctuated from 2015 to 2020. The 73 cRCTs included 6,391 clusters ( $\mu=89$ ,  $SD=213$ ) and 863,916 participants ( $\mu=11,834$ ,  $SD=32,339$ ). Most cRCTs were from Pediatrics (27, 37.0%), Lancet (12, 16.4%), and JAMA Pediatrics (13, 17.8%). Most cRCTs were focused on vaccines (11, 15.1%) and growth and obesity of child and adolescent (11, 15.1%). According to ICD-11, most cRCTs cannot be classified (25, 34.2%), of which more focused on vaccines (5, 20%); many cRCTs focused on the most was "X Extension Codes" (11, 15.1%), of which more focus on vaccines (6, 54.5%); then a part of studies concerned about "Endocrine, nutritional or metabolic diseases" (9, 12.3%) and "Certain infectious or parasitic diseases" (7, 9.6%). Most studies were from United States (31, 42.5%) and United Kingdom (56.8%), and there were only 3 cRCTs from China (4.1%). The first author was mostly from the United States (35, 48.0%) and the United Kingdom (12, 16.4%). Studies were conducted in community (25, 34.2%) and school (25, 34.2%), hospital (17, 23.3%), clinic (5, 6.8%), and nursery (1, 1.4%). All 73 cRCTs had financial support. More details of characteristics are shown in **Table 2 Characteristics of included studies** at the end of the text.

Table 2 Characteristics of included studies

Study ID	First author's country	Research topic	ICD-11	Country	Setting	Cluster (n)	Participants (n)
Weisleder 2015	America	Abusive relationship of adolescent	23 External causes of morbidity or mortality	America	School	7	1,012
Yousafza 2015	Pakistan	Parenting skills	24 Factors influencing health status or contact with health services	Pakistan	Community	1	1,489
Sikander 2015	America	Vaccination reminder	Unable to classify	America	Clinic	4	6,593
Kempe 2015	China	Sleep	Unable to classify	Hong Kong, China	School	15	8,856
Pinder 2015	Pakistan	Breast feeding	Unable to classify	Pakistan	Community	40	454
Andersson 2015	America	Immunization coverage rate	Unable to classify	America	Community	16	50,549
Chang 2015	America	Children's obesity	21 Symptoms, signs or clinical findings, not elsewhere classified	America	Clinic	14	549
Brotman 2015	China	Myopia	09 Diseases of the visual system	China	School	12	1,903
Döring 2015	Britain	Malaria	01 Certain infectious or parasitic diseases	Gambia	Community	70	7,845
Kempe 2015	Mexico	Prevention of dengue fever	01 Certain infectious or parasitic diseases	Nicaragua Mexico	Community	150	20,455
Mortimer 2015	America	Brief intervention and referral	Unable to classify	America	Hospital	52	5,183
Soofi 2015	Jamaica	Vaccination	Unable to classify	Jamaica, Antigua, Saint Lucia	Community	29	707
Keenan 2015	America	Vaccination	Unable to classify	America	Hospital	56	347
Tofail 2015	America	Effect of sedatives on clinical outcome in children	X Extension Codes	America	Hospital	31	2,449
Azor-Martinez 2015	Britain	Reduce salt intake for children and families through education	Unable to classify	China	School	28	832
Stewart 2015	Swedish	Prevention of Adolescent suicide through Education	21 Symptoms, signs or clinical findings, not elsewhere classified	10 countries in the European Union	School	168	11,110
Tiono 2015	Australia	Cardiovascular disease in primary school students	Unable to classify	Australia	School	20	264

Ordway 2016	America	Mental health and academic achievement of young children	23 External causes of morbidity or mortality	America	School	10	1,050
Shet 2016	Canada	Improve pain assessment and management of hospitalized children	21 Symptoms, signs or clinical findings, not elsewhere classified	Canada	Hospital	16	1,440
Pullan 2016	America	Attention deficit / hyperactivity disorder	06 Mental, behavioural or neurodevelopmental disorders	America	School	23	135
Foy 2016	America	Infant's weight	21 Symptoms, signs or clinical findings, not elsewhere classified	America	Hospital	4	1,173
Prendergast 2016	Australia	Safety of Baby Simulator in preventing Adolescent pregnant Children from being vaccinated	Unable to classify	Australia	School	57	5,327
Ojha 2016	Canada	Safety of Baby Simulator in preventing Adolescent pregnant Children from being vaccinated	X Extension Codes	Canada	Community	48	3,451
Skjerven 2016	Swedish	Children's obesity	05Endocrine, nutritional or metabolic diseases	Swedish	Community	59	1,369
Staedke 2016	America	Vaccine recall	X Extension Codes	America	Community	7	1,422
Brayn 2016	Netherland	The influence of physical exercise on Children's academic achievement	Unable to classify	Netherland	School	12	499
Miller 2016	America	Physical exercise	Unable to classify	America	School	20	1,143
Wing 2016	America	Influenza vaccine	X Extension Codes	America	School	44	19,776
He 2016	America	Vaccine supply	X Extension Codes	America	Hospital	35	3,147
He 2017	Uganda	evaluate an intervention designed to teach primary school children to assess claims about the effects of treatments	Unable to classify	Uganda	School	120	12,798
Wasserman	Malawi	Children's	12 Diseases of the	Malawi	Community	150	10,750

2016		pneumonia	respiratory system				
Robinson 2017	French	omphalitis	19 Certain conditions originating in the perinatal period	French	Hospital	6	8,698
Brotman 2017	New Zealand	Campus bullying	X Extension Codes	New Zealand	School	16	1,663
Pfiffner 2017	America	Children's obesity	05 Endocrine, nutritional or metabolic diseases	America	Hospital	9	378
Brinkman 2017	America	Type 2 diabetes in children	05 Endocrine, nutritional or metabolic diseases	America	Hospital	4	1,369
Mullender-Wijnsma 2017	Pakistan	Take vitamin A	X Extension Codes	Pakistan	Community	390	13,225
Cradock 2017	America	Vision screening	24 Factors influencing health status or contact with health services	America	Hospital	12	1,166
Szilagyi 2017	America	Obesity	05 Endocrine, nutritional or metabolic diseases	America	School	6	697
Nsangi 2017	America	Infant sleep habits	Unable to classify	America	Hospital	16	3,733
Farme 2017	Britain	Breastfeeding for asthma, lung function and atopic eczema	12 Diseases of the respiratory system, 14 Diseases of the skin	Belarus	Hospital	34	17,046
Lumeng2018	Britain	Financial incentives for breastfeeding	19 Certain conditions originating in the perinatal period	Britain	Hospital	92	10,010
Lloyd 2018	Britain	Healthy lifestyle prevents obesity in primary school children	05 Endocrine, nutritional or metabolic diseases	Britain	School	32	1,324
Adab 2018	America	vaccination	X Extension Codes	America	Hospital	5	1,621
Bonell 2018	America	Azithromycin reduces mortality	X Extension Codes	Malawi, Niger, Tanzania,	Community	1533	190,238
Shinde 2018	Canada	Pediatric early warning system	Unable to classify	Belgium, Canada, Britain, Ireland, Italy, New Zealand, Netherland	Hospital	21	144,539
Pfiffner 2018	America	Effects of alcohol and cannabis on sexually transmitted infections in adolescents	01 Certain infectious or parasitic diseases	America	Community (Detention facility)	145	460

Polonsky 2018	Bangladesh	Child development	Unable to classify	Bangladesh	Community	720	5,551
Gerald 2018	Britain	Childhood Obesity Prevention Program	05 Endocrine, nutritional or metabolic diseases	Britain	School	54	2,462
Marshall 2018	Spain	Respiratory infection	12 Diseases of the respiratory system	Spain	Community	25	1,176
Link 2018	Britain	Campus bullying	X Extension Codes	Britain,	School	40	6,667
Miller 2018	America	Child development	Unable to classify	Kenya	Community	702	7,960
Sterling 2018	Burkina Faso	Malaria	01 Certain infectious or parasitic diseases	Burkina Faso	Community	40	1,980
Henrikson 2018	America	Parenting programs and children's obesity	05 Endocrine, nutritional or metabolic diseases	America	Community	6	237
Curley 2018	Britain	School environment affects students' health and scholarship	Unable to classify	India	School	75	13,035
Stevens 2018	America	Reading aloud promotes parent-child interaction and children's development	Unable to classify	Brazil	Educational nursery	12	612
Wood 2018	America	Collaborative Lifeskills Program in the treatment of Children with attention Disorder	06 Mental, behavioural or neurodevelopmental disorders	America	School	23	135
Fu 2019	America	Mental health referral	Unable to classify	America	Clinic	6	342
Guen 2019	America	Breakfast affects children's obesity	05 Endocrine, nutritional or metabolic diseases	America	School	16	1,362
Sharifi 2019	India	The effect of parent consultation Education on the treatment rate of Children's anemia	03 Diseases of the blood or blood-forming organs	India	Community	56	1,625
Hannon 2019	Britain	Worm infection	01 Certain infectious or parasitic diseases	Kenya	Community	120	147,463
Modest 2019	America	Malaria	01 Certain infectious or parasitic diseases	Burkina Faso	Community	8	590
Moon 2019	Zimbabwe	HIV infection	24 Factors	Zimbabwe	Community	211	5,270

		and anemia in children	influencing health status or contact with health services				
Flohr 2019	America	Smoking	Unable to classify	America	Clinic	18	8,184
Relton 2019	America	Infant sleep	Unable to classify	America	Hospital	16	1,263
Dixon 2019	America	Vaccination for children	Unable to classify	America	Clinic	24	156
Parshuram 2019	America	Children's asthma	12 Diseases of the respiratory system, 14 Diseases of the skin	America	School	20	8,916
Lumeng 2020	Britain	Financial incentives for breastfeeding	19 Certain conditions originating in the perinatal period	Britain	Hospital	92	10,010
Anokye 2020	Australia	Meningococcal infection rate of students after vaccination	X Extension Codes	Australia	School	237	24,269
Stockwell 2020	Britain	Child nutrition	05 Endocrine, nutritional or metabolic diseases	India	Community	56	2,469
Taveras 2020	Norwegian	Infantile specific dermatitis	14 Diseases of the skin	Norwegian, Swedish	Community	92	2,397
Coker 2020	America	Mental illness	Unable to classify	America	School	14	751
Nabi-Burza 2020	America	Prevention of adolescent abuse	Unable to classify	America	School	48	973
Opel 2020	Britain	Malaria	01 Certain infectious or parasitic diseases	Uganda	Community	104	27,817

Note: ICD-11 is International Classification of Diseases 11th Revision.

### Quality of Evidence Assessment

There were variabilities across various RoB items. A total of 31 (42.5%) had high quality, 28 (38.4%) had low quality, 14 (19.2%) had unclear. Across five key RoB items, including randomization, allocation concealment, blinding of participant, blinding of personnel and blinding of outcome assessors, of which the blinding of personnel and blinding of participant had the highest bias. From the randomization process, there were 50 (68.5%) trials have high bias, and others have unclear. From the allocation concealment, there were 39 (53.4%) studies have unclear, 28 (38.4%) have low bias and only 6 (8.2%) have high bias. From the blinding of participant and personnel, there were 34 (46.6%) studies have unclear, 26 (35.6%) have high bias, and 13 (17.8%) have low bias. From the blinding of outcome assessors, there were 38 (52.1%) studies have low bias, 26 (35.6%) have unclear, and 9 (12.3%) have high bias. Across three common RoB items, including incomplete data, reporting bias, and other bias, of which the other bias had the lowest bias. From the incomplete outcome data, there were 59 (80.82%) have low bias, 9 (12.33%) have high bias, and 5 (6.85%) have unclear. From the selective outcome reporting, there were 63 (86.30%) have low bias, and others (13.70%) were high bias. From the other sources of bias, there were 65 (89.04%) have low bias, 7 (9.59%) have high bias, and only 1 (1.37%) has unclear. More details are shown in **Table 3 The results of ROB assessment**.

Table 3 The results of ROB assessment

Items	Low bias [n (%)]	Unclear [n (%)]	High bias [n (%)]
Randomization	23 (31.51)	50 (68.49)	0 (0.00)
Allocation concealment	28 (38.36)	39 (53.42)	6 (8.22)
Blinding of participant	9 (12.33)	41 (56.16)	23 (31.51)
Blinding of personnel	13 (17.81)	37 (50.68)	23 (31.51)
Blinding of outcome assessors	38 (52.05)	26 (35.62)	9 (12.33)
Incomplete outcome data	59 (80.82)	5 (6.85)	9 (12.33)
Selective outcome reporting	63 (86.30)	0 (0.00)	10 (13.70)
Other sources of bias	65 (89.04)	1 (1.37)	7 (9.59)

### Comparisons of ROB Between Groups

We evaluated the association between each of the trial characteristics on trial quality. The Chi-square test showed that produced a protocol has a statistically significant impact on the methodological quality of cRCTs ( $OR=0.261$ ,  $P=0.014$ ), and other trial factors had no statistically significance. See **Table 4 Chi-square analysis results of each research factor** at the end of the text for details.

Table 4 Chi-square analysis results of each research factor

Research factors	OR	95%CI	P-value
Protocol produced			0.014
Yes	1.000		
No	0.261	0.087-0.783	
Repeat observations conducted			0.562
Yes	1.000		
No	0.733	0.257-2.095	
Additional analysis conducted			0.141
Yes	1.000		
No	0.458	0.160-1.305	
Primary and secondary outcomes distinguished			0.071
Yes	1.000		
No	0.207	0.039-1.098	
Single vs. multicenter			
Single-center	1.000		
Multicenter	0.686	0.226-2.070	0.505
Not reported	1.800	0.139-23.374	0.571
Staff training conducted			
Yes	1.000		
No	0.348	0.034-3.584	0.612
Not reported	0.959	0.214-4.292	0.626
Protocol published			
Yes	1.000		
Not reported	3.684	0.678-20.012	0.151
Not applicable	4.200	0.586-30.095	0.197
Flow diagram conducted			0.148
Yes	1.000		
No	/	/	
Registration reported			0.325
Yes	1.000		
No	/	/	

Note: The OR of all research factors is not calculated because the value of these research factors contains 0 can not be calculated.

## Discussion

In this cross-sectional survey of cRCTs published in 10 top journals in recent years. We found that the number of included cRCTs fluctuated in past five years, the fields of concern were wide, and the methodological quality of cRCTs still needed to be improved.

We found that the number of cRCT literatures in pediatrics in recent five years fluctuated, which may be related to the reason that we only included literatures published in Chinese and English, and exclude the literatures that inability to obtain full-text and those none periodical. The reasons listed above may affected the amount of literature in different years, thus affecting the overall trend. Another reason is that we limited retrieval time to June 2020. Whatever the publishing trend, we can find that the pediatric field has continued to pay attention to the application of cRCTs in recent years. According to the data released by WHO, by the end of 2018, the top three diseases in the mortality of children under the age of five were acquired immunodeficiency syndrome, diarrhoeal disease, and tetanus [8]. It can be seen that children's health and life safety still threatened by infectious diseases. However, vaccination is the key to reduce child mortality in low and middle-income countries [9-11]. In this study, we found that most cRCTs pay high attention to vaccines, which is consistent with the above situation. In addition, obesity has always been the focus of public health all the world [12, 13], which is also consistent with the more attention paid to the development and obesity of children and adolescents in this study.

In this study, we found that the quality of cRCTs still needs to be improved. There were few descriptions of randomization, allocation concealment, and blinding in cRCTs. The risk of bias is generally high, from previous studies we found that more than half of RCTs do not implement appropriate blinding or undescribed blinding [14-18]. A study in 2021 showed that a better methodological design is needed to improve the quality of cRCTs, such as calculation of sample size and balance randomization [19]. Therefore, we can conclude that the methodological quality of cRCTs still needs to be improved. In addition, the reporting quality of cRCTs should be improved too. From the previous study, we found that the reporting of RCTs is still insufficient [20] and imperfect [21], which is difficult to provide readers with necessary information. Published RCTs rarely reported the details of blinding and allocation concealment [22-24]. The same as cRCTs, a study published in 2021 found that the current reporting quality of multi-center RCTs is not optimal when evaluating the reporting quality of cRCTs from 1975 to 2021 [25].

With regard to the influencing factors, more than half of the literatures in this study wrote a protocol. The protocol is the basis for clinical trial planning, implementation, reporting, and evaluation [26]. Furthermore, the Consolidated Standards Of Reporting Trials statement 2010 (CONSORT) extension to cluster randomized trials stated that the protocol should be written in advance, registered on the clinical trial registration, and the complete version of the protocol should be provided in the text. Moreover, strictly following the CONSORT statement can improve the reporting quality [27] and provide readers with more comprehensive information. In this study, we found that the quality of trials with protocol was higher than that of without, which was consistent with the above researches. cRCTs are prone to loss of follow-up and missing data during the implementation of the study due to a large number of participants and long follow-up time. In this situation, some studies suggested to reduce bias and improve the quality of studies by using intention analysis and sensitivity analysis in the analysis of cRCTs [28]. This study found that most of the pediatric cRCTs reported the flowcharts and adopted the additional analyses. However, the quality difference between studies was small, because included studies were from high impact factor journals, thus we didn't find out the impact of the flowcharts or use of additional analyses on the research quality.

Based on the findings of this study, we put forward the following suggestions for carrying out pediatric cRCT researches, which is also applicable to other disciplines to a certain extent. Firstly, we suggest that cRCTs should write a protocol to help the effective implementation of the research and increase the transparency of the research. Secondly, we suggest researchers should fully master the methodology of the trial, especially the implementation of a strict randomization, allocation concealment and blinding before the implementation of cRCTs, epidemiological professionals or methodologists can also be included in the trials for full guidance. Finally, we suggested to increase the training and use of CONSORT and its extended version for researchers, and further urge the standardized reporting of the trials.

### **Strengths and Limitations**

This study has several strengths. We performed a comprehensive analyses of cRCTs in the field of pediatrics for the first time as we know. The blinding is divided into the blinding of participant, blinding of personnel and the blinding of outcome assessors, instead of the joint evaluation method when assessing the risk of bias of the study. In this way, we increased the reliability of the evaluation results [29]. In order to provide references and suggestions for future research, we also analyzed the factors affecting the ROB of cRCTs. At the same time, this study has several limitations. Firstly, the evaluation of the current research hotspots in the field of pediatrics may be affected, that many included studies could not be distinguished to the specific disease classification according to

ICD-11, of which 34.2% cRCTs involved diseases that could not be classified, and 15.1% cRCTs involved diseases classified as “X Extension Codes”. In addition, we may omit some important factors that affect the research quality, due to the cRCTs included in this study are all from high impact factor journals and the methodological quality heterogeneity between studies is small. Furthermore, the analysis results may be affected by publication bias, for this study excluded the literatures published in no Chinese and English.

## Conclusion

Overall, nearly half of the pediatric cRCTs published in journals with high impact factors in the past five years are of high quality. However, the five key items of the ROB still need to be improved. As to increase the standardization and normalization of cRCTs and eventually improve the quality, we recommended to write a protocol before the experiment, strengthen methodological training for researchers, and in accordance with the CONSORT statement when reporting.

## Abbreviations

$\mu$ : Mean

M: Median

SD: Standard Deviation

cRCT: Cluster randomized controlled trial

CONSORT: Consolidated Standards Of Reporting Trials statement

ROB: Risk of bias

RCT: Randomized controlled trial

WHO : World Health Organization

## Declarations

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Not applicable.

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### Availability of data and material

Data Availability Statement: The raw data of this study come from data extraction and ROB results. The extracted data is shown in Table 2, and the ROB assessment results of every single study are shown in additional file 1.

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable.

**Competing Interests:** The authors declare no conflicts of interest.

### Author contributions

Hui Lan: Data extraction, quality assessment, statistical analysis, wrote the draft and the full text. Jianjian Wang: Searched and screened researches, data extraction, quality assessment, draft modification. Shouyuan Wu: Data extraction, quality assessment, draft modification. Qiangqiang Guo: Data extraction, quality assessment, draft modification. Ping Wang: Data extraction, quality assessment. Juanjuan Zhang: Data extraction, quality assessment. Siya Zhao: Screened researches. Xiao Liu: Screened researches. Xingrong Liu: Study design, methodology support, supervision, manuscript modification. Yaolong Chen: Study design, methodology support, supervision, manuscript modification, funding acquisition.

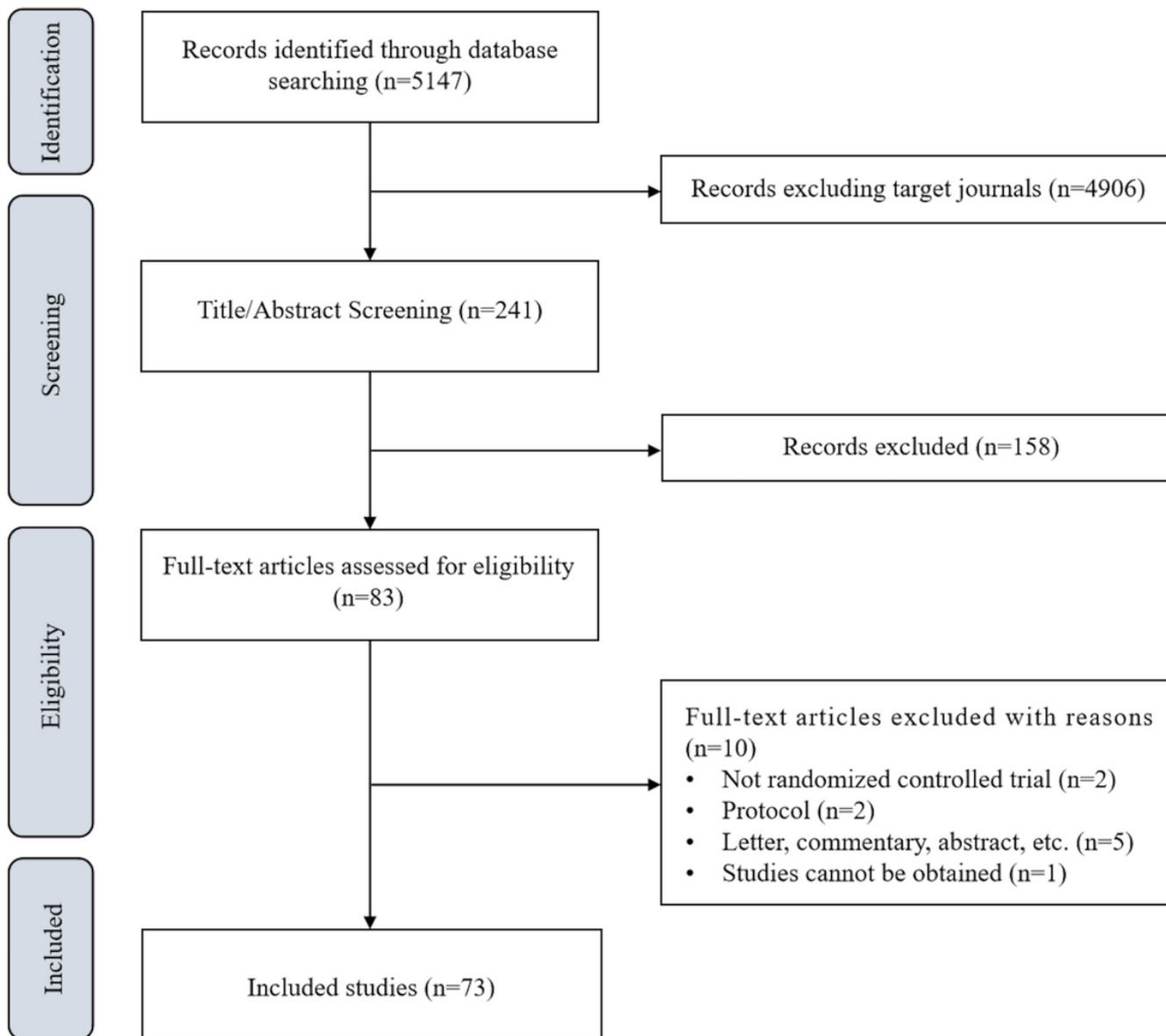
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## Figures



**Figure 1**

Flow chart summarizing the process of identifying the eligible studies.

## Supplementary Files

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