General Characteristics and Quality Assessment of Pediatric Randomized Controlled Trials Published in Mainland China over the Decades 1999-2018

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General characteristics and quality assessment of pediatric randomized controlled trials published in mainland China over the decades 1999-2018

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Abstract

Objective: Randomized controlled trials (RCTs) are usually the basis of evidence-based medicine and provide important information for pediatric clinical practice, but whether the results of RCTs can be correctly translated into clinical practice depends on the quality of the literature reported. In this study, we evaluated the general characteristics and quality of pediatric RCTs published in mainland China over the decades 1999-2018.

Methods: We individually searched all 20 available pediatric journals published between January 1, 1999, and December 30, 2018 and selected RCTs with participants less than 18 years. Each review author extracted details data from each of the selected RCTs including general characteristics, ethical characteristics, trial characteristics. Using Cochrane Collaboration methods for risk assessment.

Results: Totally, 4093 RCTs were included for analysis. The average annual growth rate of published pediatric RCTs was 35.22% ($p = 0.000$), a notable increase occurred in 2017, and most of the studies were carried out in east China (32%). Only 1.98% of RCTs conducted in multiple-center, and 13.73% of the RCTs reported funding resources, 15.34% of the RCTs stated that it was approved by the ethics committee and 34.99% of the authors stated that the patients signed the informed consent. Comparing RCTs published in 2014-2018 with RCTs published in 1999-2003, we found the quality of RCTs has improved in random sequence generation, blinding participants and personnel, and incomplete outcome data. RCTs stated the approval of the ethics committee and the signing of the informed consent form, conducted in teaching hospitals, with multiple-centers, funding were of better quality in all the analyzed items.

Conclusions: The number of pediatric RCTs has increased significantly over time in mainland China, and the quality have improved over the decades 1999-2018, but quality of the RCTs initiated by investigators published in mainland China still need to be improved,

special attention should be paid to allocation concealment, blinding outcome assessment and selective outcome reporting.

Keywords: Pediatric, Randomized controlled trials, Characteristics, Quality assessment, China.

Introduction

Due to lack of sufficient information on children's medication in the drug labels, off-label prescribing is widespread worldwide. Studies showed the prevalence of off-label prescribing in children was from 28.3 to 46.5% [1-4], and probably more common in China [5, 6], thus, higher risks related to treatment and legal exist in the treatment of children's diseases [7]. In addition to the drug labels, clinical treatment guidelines and expert consensuses based on clinical research have become the main sources and basis of physicians' medication evidence [8, 9], especially pediatricians, and the clinical research evidence in the guidelines and expert consensuses generally graded according to the research design type. However, the clinical applicability of the research results is not only related to the design type of the research but also many other factors, especially the factors that may reflect the reliability of research results in the research report.

Randomized controlled trials (RCTs) are considered the best research protocol for assessing the effectiveness and safety of interventions and have been defined in many guidelines and expert consensuses as evidence of high quality and given a corresponding clinical application recommendation grade [10-12]. However, whether the results of RCTs can be correctly translated into clinical practice also depends on the quality of the literature reported. Previous studies showed there were limited published clinical trials about children, especially randomized controlled trials and multicenter trials [13, 14], and most of the pediatric RCTs were published with high or unclear risk of bias in different ways [15-17]. As everyone knows, low quality reported RCTs can hinder the reader's objective assessment of bias and leads to false estimates of the effect of the intervention, which may lead to harmful clinical decisions [18, 19].

Besides, in recent years, clinical trials in the pediatric population have caused great attention in China, in 2011, the government proposed to encourage research and development and production of drugs for children, and since then, a number of documents or measures were

issued to encourage clinical trials in pediatrics, such as the National Program for Child Development in China (2011-2020) in 2011 [20], the Technical Guidelines for Pharmacokinetic Research in Pediatric Population in 2014 [21], the Technical Guidelines for Drug Clinical Trials in Pediatric Population in 2016 [22], and putting priority assessment of pediatric urgently demand drugs into practice since 2015 [23]. With these policies, the number of industry-sponsored pediatric clinical research in China increased these years, and we found that the number of pediatric clinical studies reported in the literature, including investigator-initiated clinical trials, is also increasing significantly. There was a study analyzed the quality of pediatric RCTs in china before 2011 [24], but we found the included RCTs were not comprehensive enough, and general characteristics such as the characteristics of investigators, geographical distribution of the trials, ethical characteristics were not reported. Thus, the objective of this study was to determine the general characteristics and quality of pediatric randomized controlled trials published in mainland China over the decades 1999-2018, by assessing the trials published on all the pediatric journals in China, to evaluate the quality trends in pediatric clinical trials over the decades, and provide reference for the development and reporting of pediatric clinical research and its application in clinical practice as evidence.

Methods

Selection of journals and RCTs

We searched the currently available pediatric journals in Mainland China from the following databases on 26 February 2019: China National Knowledge Infrastructure(CNKI), www.cqvip.com, wan fang data and China Biology Medicine disc (CBMdisc), journals that were classified as pediatric journal were included, and we excluded English journals and popular science periodical. A total of 20 pediatric medical journals were included in this study,

namely *Chinese Journal of Applied Clinical Pediatrics, Chinese Journal of Pediatrics, Chinese Journal of Contemporary Pediatrics, Journal of Clinical Pediatrics, Chinese Journal of Pediatric Surgery, Chinese Journal of Practical Pediatrics, Chinese Journal of Evidence-Based Pediatrics, Chinese Journal of Neonatology, Journal of Pediatrics of Traditional Chinese Medicine, Women's Health Research, Journal of Clinical Pediatric Surgery, Chinese Pediatric Emergency Medicine, Chinese Journal of Obstetrics & Gynecology and Pediatrics(Electronic Edition), Chinese Pediatrics of Integrated Traditional and Western Medicine, Journal of China Pediatric Blood and Cancer, Chinese Journal of Child Health Care, International Journal of Pediatrics, Journal of Pediatric Pharmacy, Maternal and Child Health Care of China, Journal of Developmental Medicine(Electronic Version).* The first 7 journals are included in the Chinese Science Citation Database(CSCD), which is the Chinese equivalent of Science Citation Index (SCI) and represents the most influential journals in the field of natural sciences [25] , and has earned a good reputation among Chinese scientists [26]. The remaining 13 journals are Non-CSCD journals.

Two authors independently screened the titles, abstracts or full text of all the studies published on the 20 journals from 1999 to 2018, and any disagreements were resolved through discussion or by consulting a third author. Trials were considered for inclusion if all the participants were less than 18 years and the random method was used to assign participants to different intervention groups, no matter the exact random method was stated or not, and only Chinese language studies were included. We excluded overview, meta-analysis, clinical treatment guidelines, expert consensuses, conference proceedings.

Data Extraction and Quality Assessment

Two authors reviewed the full text of all the included trials and extracted study characteristics and doing the quality assessment, and any disagreements were resolved through discussion or

by consulting a third author. We used a data collection form that had been piloted on ten studies, and including the following items :

(1) General characteristics: journal name, publication date, the first affiliation of the authors,

(2) Ethical characteristics: whether ethical approval and informed consent were reported,

(3) Trial characteristics: the city in which the RCT was conducted, multiple-center or single-center trial, funding resources, trial registration information, intervention, control, studying diseases, sample size, length of follow-up. In this study, the studying diseases were coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, International Classification of Diseases (ICD)-10 classification [27]. Besides, we also recorded whether the study reported a method for calculating the sample size, whether the study reported the comparability of baseline characteristics, whether dropouts, adverse events were reported, and whether conflicts of interest were stated.

(4) Quality assessment: the quality evaluation method was based on the Cochrane Collaboration methods for risk assessment [28], including the following 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. We judged each potential source of bias as high, low, or unclear. We used the SRQRreporting guidelines to complete this article[29].

Statistical analysis

Descriptive analyses were used to summarize the data, and the number (%) was used for qualitative variables. The simple regression model was used to analyze the 20-year trends in the number of RCT trials, and we used a binary logistic regression analysis to explore the relationship between the presence of “low risk of bias” or “yes” according to each item and the year of trial publication. We divided all RCTs in four-time strata based on the year of

publication: “1999-2003”, “2004-2008”, “2009-2013”, “2014-2018”, and “1999-2003” was used as reference time stratum, and we used the “low risk of bias” or “yes”as the reference category, and compared to “unclear, high risk of bias” taken together, or “no, not stated” taken together. We reported odds ratios (OR) with 95% confidence intervals (CI). The chi-square test was used for proportions and compare the difference among subgroups. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed on a personal computer with the statistical package SPSS for Windows (version 22.0).

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Results

Publication time trends and geographical distribution of the RCT trials

From January 2009 to December 2018, there were 119101 articles published on the 20 Chinese pediatric journals, after screening of the study design and participants led to 4093 (3.44 %) of the studies being selected for inclusion and data analysis (Figure 1). The majority of the included studies were published on *Maternal and Child Health Care* of China (20.28%), followed by the *Journal of Pediatrics of Traditional Chinese Medicine* (17.91%) and *Journal of Pediatric Pharmacy* (14.88%).

An ascending trend was found concerning the number of published RCTs from 41 in 1999 to 350 in 2018, with an average annual growth rate of 35.22% (p=0.000). A surge was identified beginning in 2011, and a notable increase occurred in 2017, with 443 RCTs published. In the last 5 years from 2014 to 2018 of the period studied, 1840 RCTs were published, which accounting for 44.95% of the RCTs reported in the 20 Chinese pediatric journals we selected over the past two decades (Figure 2).

Geographical distribution analysis showed all the published RCTs were carried out in 30 different cities in China (Figure 3), for multiple-center RCTs, the cities where the

coordinating investigator were located were taken into analysis. Most of the studies were carried out in east China (32%), followed by the central(18%) and south (15%), which was consistent with the distribution of economic prosperity, and over one-third of the RCTs were conducted in Zhejiang, Henan and Guangdong. The most prolific institutions were Beijing Children's Hospital Capital Medical University (n=52), followed by Hunan Children's Hospital (n=51) and Henan Children's Hospital (n=42).

Characteristics of the trials

The characteristics of the included trials are shown in Table 1. Only about one-quarter (26.22%) of RCTs were conducted in teaching hospital, and few (15.34%) of the authors stated that the RCT was approved by the ethics committee, 34.99% of the authors stated that the patients signed the informed consent. Only 1.98% of RCTs conducted in multiple-center, with a number of centers ranged from 2 to 11 (average = 6.5), and 13.73% of the RCTs reported funding resources, in which 10 RCTs trials were subsidized by companies. Very few trials showed that registration had been carried out on relevant websites. Most of the research was conducted on drugs and only a few use of placebo as a control. A median sample size of the RCTs was 86 (range from 11 to 1763), but only 59 (1.44%) of them reported the sample size calculation process. Most of the RCTs reported the comparability of the baseline of the different groups but didn't report the total follow-up time, dropouts of the subjects, and conflict of interest of the trial, and less than half of the RCTs reported adverse events.

The distribution of the studying diseases among the included studies, categorized according to the (ICD)-10 classification, was shown in Figure 4, which was consistent with the distribution of major diseases in children, diseases of the respiratory system accounts for over one-third (36%) of all identified diseases, and followed by certain conditions originating in the perinatal period disease (11%), diseases of the digestive system (10%) and certain infectious and

parasitic diseases (10%). Pediatric asthma and mycoplasma pneumonia were the most commonly studied diseases with 374 (9%) and 322 (8%) trials, respectively. Only 72 RCTs studying major diseases defined as diseases that cost a lot and seriously affect the normal work and life of patients and their families for a long period time, including congenital heart disease (n=32), acute lymphoblastic leukemia (n=8), pediatric tumors (n=7), systemic lupus erythematosus (n=7), etc., and no identified RCT involved rare diseases.

Quality assessment of the trials

Results of quality assessment based on the Cochrane Collaboration methods for risk assessment were shown in Table 2. Only 1177 (28.76%) of the RCTs reported a truly random method, and 66 (1.61%) RCTs used adequate methods for allocation concealment, 144(3.52%) RCTs ensured blinding of participants and personnel and 50(1.22%) ensured blinding of outcome assessment. More than one-third of RCTs (38.53%) showed 'low risk' of bias of incomplete outcome data, of which 5.23% reported dropouts, but only 0.89% used intention-to-treat analysis. 851 (20.79%) of the RCTs were judged as obvious selective outcome reporting due to the outcome that was explicitly reported in the methodology was not shown in the result. For other bias, very few studies (0.12%) were considered as low risk of bias, they were mostly registered and company-funded trials.

Trends of Quality and influence factors analysis

Table 3 showed when using "low risk of bias" or "yes" as the reference category, and time stratum '<1990' as the reference time stratum, the trends of the quality of the RCTs over time. We identified that there was statistically significantly improved in the odds for low risk of bias for three items (random sequence generation, blinding participants and personnel,

incomplete outcome data). For other related quality assessment items, four items (ethical approval, signed informed consent, funding reported, and report of adverse events) significantly improved over time.

Results of quality influence factors analysis were shown in Table 4. For “other bias”, due to only 5 RCTs were judged to be low risk, we didn’t analyze the influence factors. Overall, we found that RCTs stated the approval of the ethics committee and the signing of the informed consent form, conducted in teaching hospital, with multiple-centers, funding were of better quality in all the analyzed items. RCTs published from CSCD journals were of better quality in respect of adequate allocation concealment, blinding participants and personnel, blinding of outcome assessment and selective outcome reporting, but of lower quality in respect of random sequence generation and incomplete outcome data. RCTs conducted in the northeast were of better quality in respect of random sequence generation, but of lower quality in respect of blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. RCTs with follow-up time $<$ 1 year were of better quality in respect of random sequence generation, but RCTs with follow-up time 1-3 year were of lower quality in respect of adequate blinding of outcome assessment.

Discussion

The number of pediatric RCT trials demonstrated prominent increase in mainland China, with an average annual growth rate of 35.22%, it is likely to be related to significant efforts and support from the Chinese government, and reflecting researchers' growing interest in pediatric RCTs as the gold standard for evidence-based medicine to guide treatment decisions. 4093 RCTs came from 21 cities and 1325 (32%) of RCTs distributed in the east, while only 308

(8%) RCTs distributed in the northwest. Compared with in developed countries, markedly uneven geographical distribution of pediatrics clinical trials across mainland China, however, geographical disparity are not related to population or disease distribution, but rather a direct reflection of the uneven distribution of high-quality medical resources for clinical research across China. It is possible to be the government's hope that major clinical trial units will play a leading role in creating a dynamic environment for medical innovation [30].

By using a Cochrane Collaboration risk of bias tool, we conducted an in-depth analysis of the methodological characteristics and risk of bias of RCT trials published on the 20 pediatric journals in mainland China from 1999 and 2018. Published clinical trials are usually applied to clinical treatment as evidence of treatment, and high-quality RCT is the basic foundation of evidence-based medicine [31]. However, poorly reported research may distort the authenticity of the experiment results to some extent. Comparing RCTs published in 2014-2018 with RCTs published in 1999-2003, we found the quality of RCTs has improved in random sequence generation, blinding participants and personnel, and incomplete outcome data. it seems to be a positive development, but there is still large room to improve the methodological reporting quality of RCTs in pediatrics journals in Mainland China, including detailed description of allocation concealment, it is one of the key factors that make RCTs the most valuable study design to evaluate the effectiveness of therapeutic interventions [32], and the use of blinding of outcome assessment was often neglected, part of investigators only marking the RCTs as single, double, or triple-blind, we think these bias could easily decrease if authors truthfully report why they were not blind to the outcome assessors, to make readers have a clear understanding of the risk of bias. Only 5.23% of trials reported dropouts, but reporting the drop-out rates from RCTs is important to reflect the patients overall assessment of the balance between benefits and harms [33], and ensure that other recorded outcomes are not biased due to differential drop-out rates and reasons between the treatment arms [34]. We

also found more than half of the trials did not report adverse effects, children as vulnerable individuals, we should pay more attention to the safety and efficacy of interventions, any therapeutic effect must be balanced with adverse effects to support a clinical diagnosis by the pediatrician. Only 1.44% of trials reported or performed their sample-size calculation, it is substantially low. As lack of sample size calculation before enrollment could lead to an increase in the risk of random errors and reflect statistical significance [35]. Moreover, we found that the quality for pediatric RCTs published on CSCD journals was not significantly better than those published on the Non-CSCD journal, thus, publication in a journal with a good reputation in china does not ensure that it with a high quality. Therefore, Chinese pediatric journals should standardize RCTs reporting standards, such as report the full text complying with reporting criteria CONSORT (Consolidated Standards of Reporting Trials) checklists [10], to reduce the risk of making incorrect conclusions about interventions effects.

The informed consent is an important medical ethical principle to be followed in pediatric clinical trials [36], but we found approximately 85% of the included in this study failed to report ethically approved, and RCTs stated the approval of the ethics committee and the signing of the informed consent form were of better quality. Poor recruitment and ethical issues are unique challenges for conducting pediatric RCTs [37]. Clearly understanding of risks and benefits are two of the most important elements required by parents in to make informed decisions about their child's participation in a research study [38]. Researchers can use graphical presenting (such as hieroglyphs, short videos, comics)instead of traditional verbal expressions [39], so parents can make informed decisions about participation and avoid negatively affecting their decision-making. Besides, it is more challenging to use a placebo in RCTs without a reference-validated drug as a control, which may cause significant ethical issues both in clinical research and clinical practice. Thus, the placebo may be an option only when the principle of clinical balance and the health of patients are respected [40].

In 2007, The Chinese Clinical Trial Registry (ChiCTR, www.chictr.org) was recognized as a Primary Registry of the World Health Organization's International Clinical Trial Registry Platform (WHO ICTRP) [41]. The purpose of ChiCTR is to improve the quality of clinical research in China and provide reliable evidence for clinical decision-makers. In recent years, the prevalence of registered trials in the registry has continued to increase, however, only 0.32% were found to be registered in this study, and we failed to compare the quality difference between registered and unregistered trials. Previously studies showed clinical trial registration might be a marker for reducing the risk of bias [35], and trial discontinuation and non-publication were common among interventional trials conducted in children [42], and more than a third of RCTs completed in newborns might have not yet been published [43]. Moreover, on clinicaltrials.gov, only 29% of pediatric intervention trials were completed and published on the corresponding journal, those results raised another major concern that the unpublished or unreported of trial findings bring substantial publication bias into the medical literature, and that may disrupt clinical guidelines and evidence-based clinical practices, and lead to false medical decisions. Further efforts to improve the registration of pediatric RCT trials are needed, Chinese medical journals should learn from the policy of the International Committee of Medical Journal Editors that the information about clinical trial reports should be submitted in a clinical trial registry [44].

With regard to funding, most of the included trials were funded by national and provincial resources, only ten trials were funded by the industry, indicating the higher cost of pediatric trials and the absence of commercial profit in this research area. Lack of funding is one of the major barriers to conducting pediatric RCTs worldwide [45]. To further facilitate the innovation of pediatric drugs and motivate the efficiency of pediatric clinical trials, the newly revised Drug Administration Law of the People's Republic of China came into effect on December 1, 2019. It clearly states that it encourages the development and innovation of

children's medicine, supports the development of special medicines that are consistent with children's physiological characteristics, and gives priority to the approval of children's medicine [46]. However, the previous work suggested that clinical trials funded by corporate sponsorship may overstate the results or only report favorable findings [47, 48], and how to improve the bias of clinical trials funded by industry is an important issue worthy of exploration.

There were some limitations in our study: we only studied articles in pediatric professional journals, we may have missed RCTs published on other non-pediatric related journals. Given the extremely large number of articles retrieved, we believe that our results are representative. We used the Cochrane Collaboration tool to assess the risk of bias can be subjective. We failed to contact the author to solve the confusing information when judging the risk of bias, as we hope to objectively present the quality of the research report, and two independent authors assessed the included studies to avoid potential biases. At present, many Chinese industry-sponsored pediatric clinical researches were published on foreign journals, and our study mainly reflected the quality of pediatric RCT trials initiated by Chinese investigator, with only10 RCTs trials were subsidized by companies.

Conclusions

The number of pediatric randomized controlled trials has increased significantly over time in mainland China, and the quality have improved over the decades 1999-2018. RCTs stated the approval of the ethics committee and the signing of the informed consent form, conducted in teaching hospital, with multiple-centers, funding were of better quality in all the analyzed items. However, the proportion of trials judged as having a low risk of bias did not exceed 40% in the majority of the risk of bias domains, and quality of the RCTs initiated by investigators published in mainland China still need to be improved, special attention should

be paid to allocation concealment, blinding outcome assessment and selective outcome reporting. Potential barriers can be uncovered and addressed through promoting government policies, strengthening the standardization of journal publishing and advancing registration of clinical trials.

Abbreviations

RCTs: Randomized Controlled Trials; CNKI: China National Knowledge Infrastructure; CBMdisc: Wan Fang Data and China Biology Medicine disc; Chinese Science Citation Database(CSCD); Science Citation Index (SCI); ICD: International Classification of Diseases; OR: Odds Ratios; CI: Confidence Intervals; CONSORT: Consolidated Standards of Reporting Trials; ChiCTR: Chinese Clinical Trial Registry; WHO ICTRP: World Health Organization's International Clinical Trial Registry Platform.

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Authors' contributions

LS and BH conceived and designed the study, BH, MA and NY performed searches, extracted the relevant data and carried out the quality assessment. YL, SR and YJ verified the data and results of quality assessment, LS, YJ and BH analyzed data and wrote the paper. All authors contributed to the interpretation of study data, revised paper critically for content and approved the final version.

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Availability of data and materials

The data from the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Figures

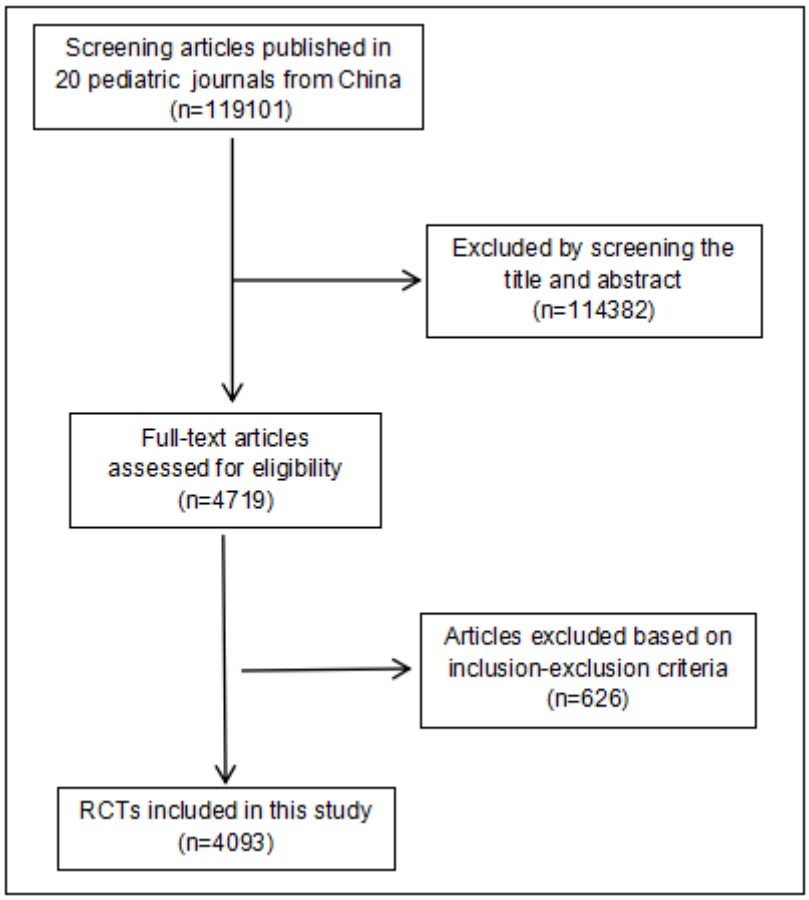


Figure 1

PublicationtimetrendsandgeographicaldistributionoftheRCTtrials1 78 From January 2009 to December 2018, there were 119101 articles published on the 201 Chinese pediatric journals, after screening of the study design and participants led to 40931 (3.44 %) of the studies being selected for inclusion and data analysis (Figure 1). The majority1 oftheincludedstudieswerepublishedonMaternalandChildHealthCareofChina(20.28%),1 followed by the Journal of Pediatrics of Traditional Chinese Medicine (17.91%) and Journal1 ofPediatricPharmacy(14.88%).

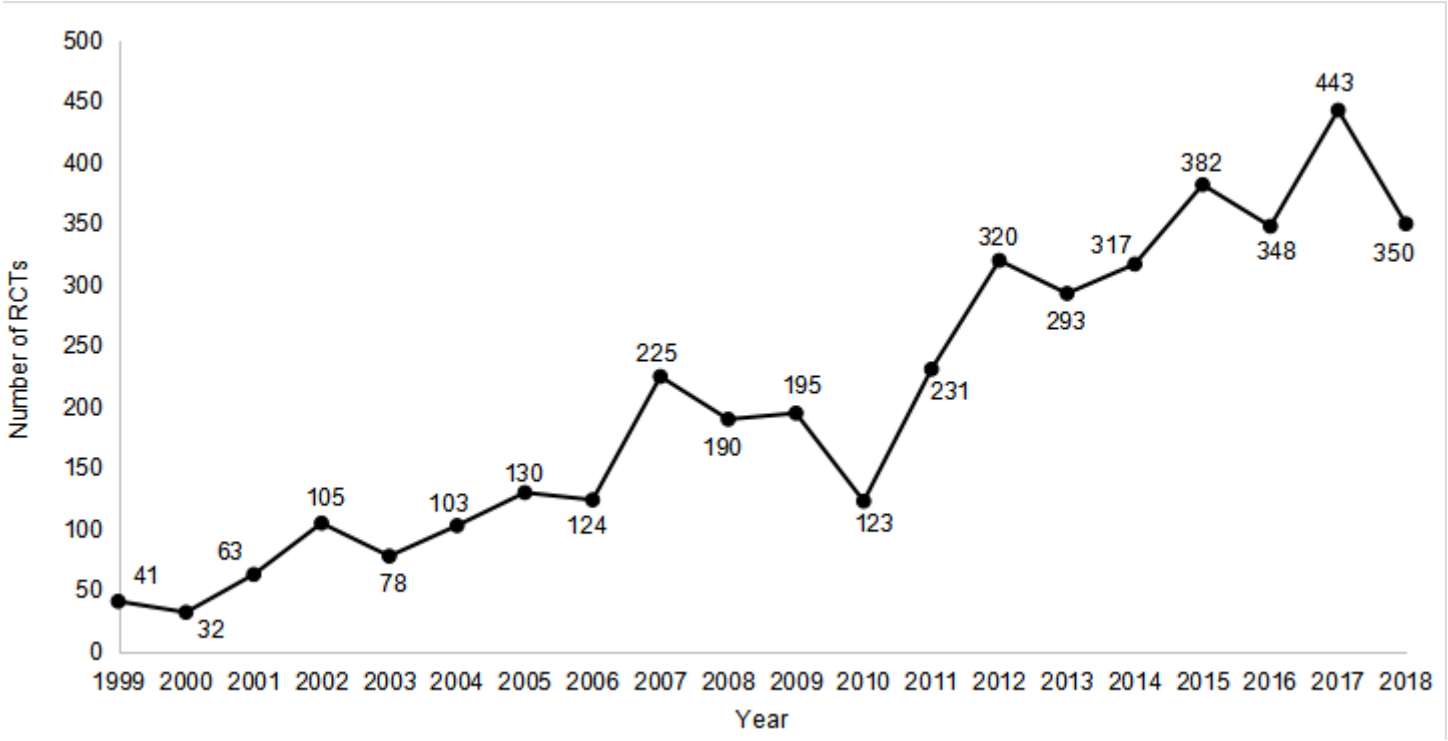
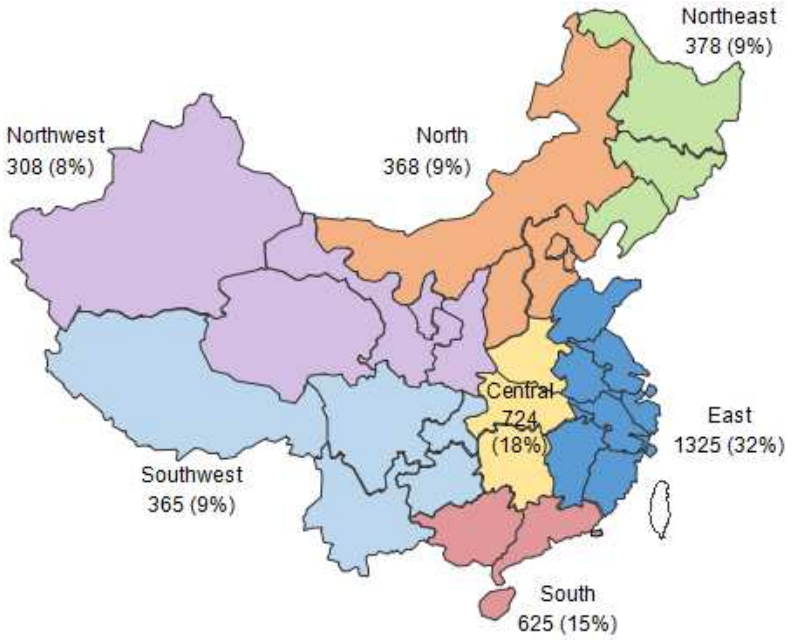


Figure 2

350 in 2018, with an average annual growth rate of 35.22% (p=0.000). A surge was identified1 beginning in 2011, and a notable increase occurred in 2017, with 443 RCTs published. In the1 last 5 years from 2014 to 2018 of the period studied, 1840 RCTs were published, which1 accounting for 44.95% of the RCTs reported in the 20 Chinese pediatric journals we selected1 overthepasttwodecades



Region and province	Number of pediatric RCTs (n=4093)	Region and province	Number of pediatric RCTs (n=4093)
East	1325	Central	724
Zhejiang	507	Henan	411
Jiangsu	329	Hubei	199
Shandong	196	Hunan	114
Shanghai	116	Northeast	378
Fujian	70	Liaoning	208
Anhui	65	Jilin	100
Jiangxi	42	Heilongjiang	70
North	368	Northwest	308
Beijing	141	Gansu	140
Hebei	135	Shanxi	98
Tianjin	47	Xinjiang	41
Shanxi	23	Ningxia	21
Neimenggu	22	Qinghai	8
Southwest	365	South	625
Sichuan	178	Guangdong	489
Chongqing	99	Guangxi	106
Guizhou	47	Hainan	30
Yunnan	41		

Figure 3

Geographical distribution analysis showed all the published RCTs were carried out in 30 different cities in China (Figure 3), for multiple-center RCTs, the cities where the coordinating investigator were located were taken into analysis. Most of the studies were carried out in east China (32%), followed by the central(18%) and south (15%), which was consistent with the distribution of economic prosperity, and over one-third of the RCTs were conducted in Zhejiang, Henan and Guangdong. The most prolific institutions were Beijing Children's Hospital Capital Medical University (n=52), followed by Hunan Children's Hospital(n=51)andHenanChildren'sHospital(n=42). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

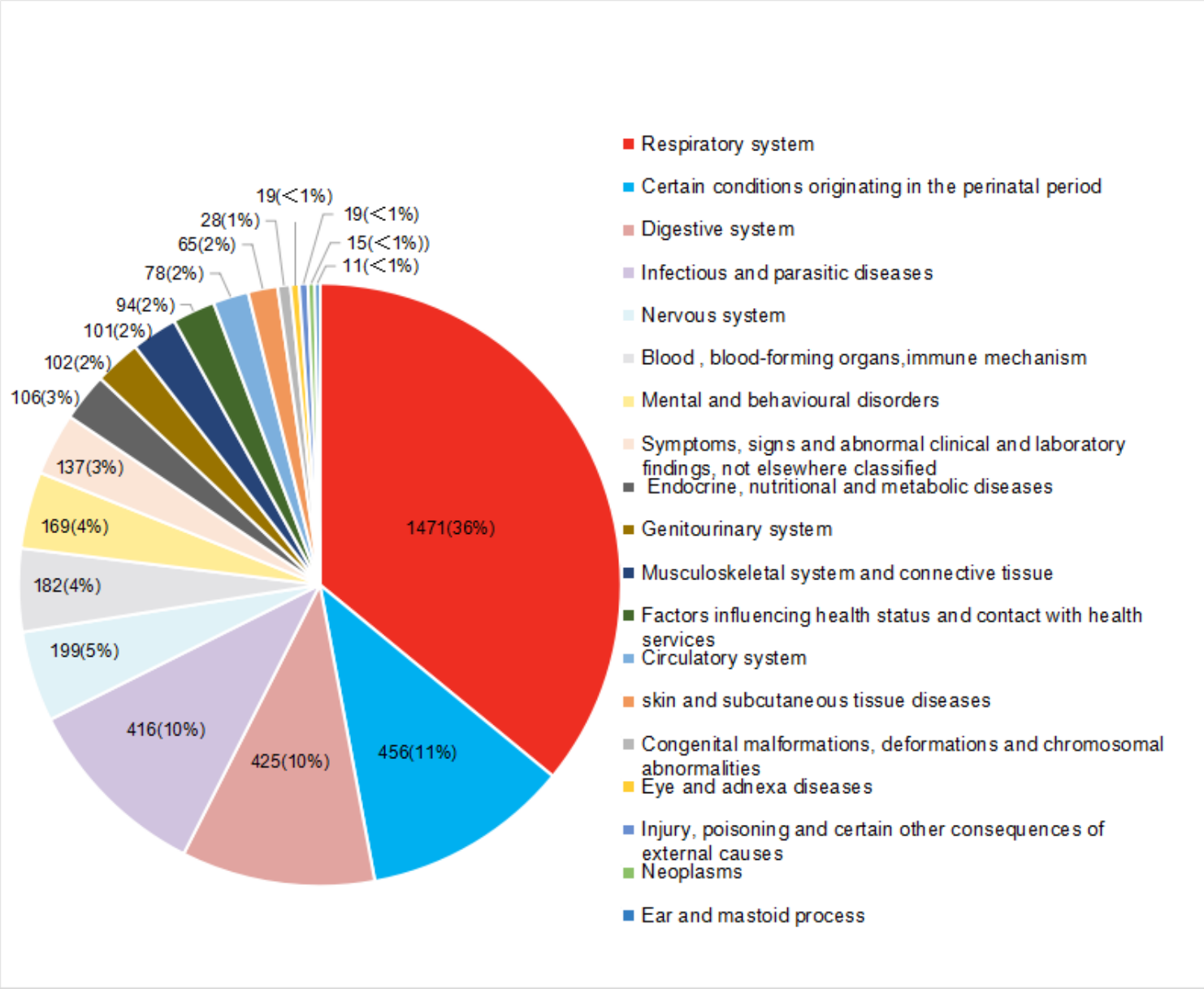


Figure 4

The distribution of the studying diseases among the included studies, categorizedaccording to the (ICD)-10 classification, was shown in Figure 4, which was consistent with the distribution of major diseases in children, diseases of the respiratory system accounts for over one-third (36%) of all identified diseases, and followed bycertain conditions originatingin the perinatal period disease (11%), diseases of the digestive system (10%) and certain infectious and parasitic diseases (10%). Pediatric asthma and mycoplasma pneumonia were the most commonly studied diseases with 374 (9%) and 322 (8%) trials, respectively. Only 72 RCTs studying major diseases defined as diseases that cost a lot and seriously affect the normal work and life of patients and their families for a long period time, including congenital heart disease (n=32), acute lymphoblastic leukemia (n=8), pediatric tumors (n=7), systemic lupus erythematosus(n=7),etc.,andnoidentifiedRCTinvolvedrarediseases

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SRQRchecklist.pdf