## Childhood Obesity in China 2

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# Public health interventions against childhood obesity in China

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China is confronted with the challenge of increasing childhood obesity. Although interventions for childhood obesity have been developed, their effectiveness and implementation can vary considerably across nations. In this paper, we review and consolidate the evidence on childhood obesity intervention strategies aimed at multiple levels and components across life, in China. School-based interventions, primarily delivered with group-based dietary and physical education, have shown potential efficacy and can be enhanced by integrating food environment reform and family support. However, most interventional studies were done in eastern and urban areas of China, which highlights the need for attention in regions with insufficient health resources where policies and initiatives are less accessible. In addition, the sparse reporting on implementation design and delivery might hinder the scalability of potentially effective strategies. Amid rapid social and economic development over the past few decades, China faces unique challenges on urbanisation, physical inactivity, and nutritional transitions, necessitating an updated policy agenda for primary prevention of childhood obesity. Structural longitudinal evaluations of public initiatives led by the government and organisations along with inclusive and equitable interventions targeting children of different ages, urban—rural regions, and different ethnic and socioeconomic groups are warranted. Tackling childhood obesity in China needs a cohesive approach that integrates social, economic, cultural, and environmental strategies, combining school-based, family-based, and individual-based approaches, and concerted efforts from multiple sectors and entities within China.

#### Introduction

To address childhood obesity, intervention strategies have been extensively studied and prioritised in public health practice worldwide. 1-5 With the specific social, cultural, and environmental contexts of China, it is important to address the unique challenges and leverage opportunities inherent to the region to curb the escalating childhood obesity rates and associated health effects.6 There is mounting evidence on intervention efforts to tackle the epidemic of childhood obesity,6 encompassing various levels, such as nationwide policy making, community revitalisation, school-based initiatives, family guidance programmes, and individual-targeted interventions. These efforts engage diverse stakeholders including the government, health-care professionals, educational institutions and teachers, communities, parents, and children themselves.7-9

While the strategies to tackle childhood obesity might be universal, their effectiveness varies across nations. For example, school-based intervention programmes have been shown to have minor effects on the children's weight status in several trials in high-income countries, <sup>10–12</sup> but proved to be successful in China. <sup>7,13,14</sup> Translating globally successful measures to the Chinese context remains challenging considering the distinct cultural norms, economic disparities, and regional differences. <sup>15</sup> Moreover, China's rapid urbanisation and socioeconomic progress accompanied lifestyle changes that further complicate the implementation of strategies with large variations across regions, areas, ages, and sex. <sup>16</sup> Although standardised approaches might scale up into the large

child population in China, a nuanced and context-specific review of current interventions is needed.

In the first paper in this Series,<sup>17</sup> we provide a landscape of the trends and epidemiology of childhood obesity in China and evaluate the individual-level risk factors and population-level determinants. Here, we review population-level and individual-level intervention strategies that are implemented or studied in China. We discuss data from studies worldwide and their applicability to the Chinese context. For strategies showing promise, we also discuss their facilitators and barriers within an implementation framework. By analysing the existing evidence and identifying the strengths and limitations, we propose future directions in studying and scaling up of interventions of childhood obesity in China. These efforts should inform policies, as discussed in the third paper in this Series.<sup>18</sup>

## Framework of obesity interventions for Chinese children

Existing interventions span from population-level to individual-level strategies (figure 1). 3.6 Society-wide interventions mainly include policy measures for food industry reform, food environment improvement, better urban planning to encourage exercise, and increasing society-wide health-care accessibility. School-based approaches mainly include improved diet quality and promotion of physical activity with education and environment reconstruction. For individuals and families, the framework targets lifestyle—for example, encouraging healthy eating habits and improving physical activity profiles; or clinical interventions for severe obesity cases

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This is the second in a **Series** of three papers about childhood obesity in China

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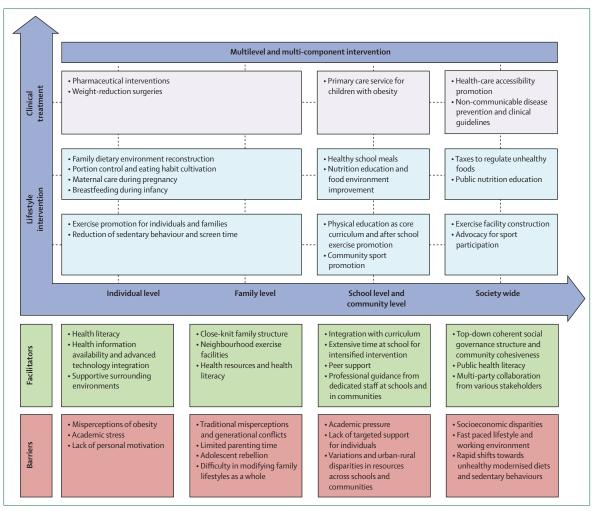


Figure 1: Framework of childhood obesity intervention strategies in China
The upper panel presents the intervention strategies at multiple levels targeted to different aspects. The lower panels present facilitators and barriers to these interventions.

See Online for appendix

and comorbidities. There is emerging support given for combining strategies across levels and involving various stakeholders, such as the government, health-care system, educational institutions, caregivers, and children themselves. Contextual factors can be powerful facilitators and barriers in the implementation of such efforts. We identify several potential facilitators and barriers for intervention strategies in each category, including the attributes of the intervention itself, external factors that could influence implementation, characteristics of the primary setting, entities involved in the implementation process, and implementation procedures. 19,20 Primary prevention harnesses cross-level strategies for healthy lifestyles and maternal-infancy health, facilitated by individual and family health literacy. In secondary and tertiary prevention, health-care access and facilities drive monitoring, intervention, pharmaceutical, and surgical strategies, potentially affecting childhood obesity and health equity.21,22 Given China's vast territory, ethnic diversity, and large population, a tailored and nuanced approach that balances population-wide initiatives with targeted and individualised measures is crucial to improve efficacy while mitigating potential health inequalities. Furthermore, we reviewed international and Chinese guidelines on childhood obesity (appendix pp 3–8) to compare strategies across life stages (appendix p 17). The analysis illustrates that while the guidelines in Chinese childhood obesity interventions are generally aligned with the international agenda, they have specifically emphasised the important role of schools.

To better understand and estimate the efficacy of interventions on childhood obesity in China, we reviewed, summarised, and meta-analysed the randomised controlled trials (RCTs) done in Chinese children (see appendix pp 2, 9–14).<sup>23,24</sup> Most (22 [91·7%] of 24) RCTs were school-based and two [8·3%] were hospital-enrolled. Overall, the intervention strategies significantly reduced childhood obesity prevalence (odds

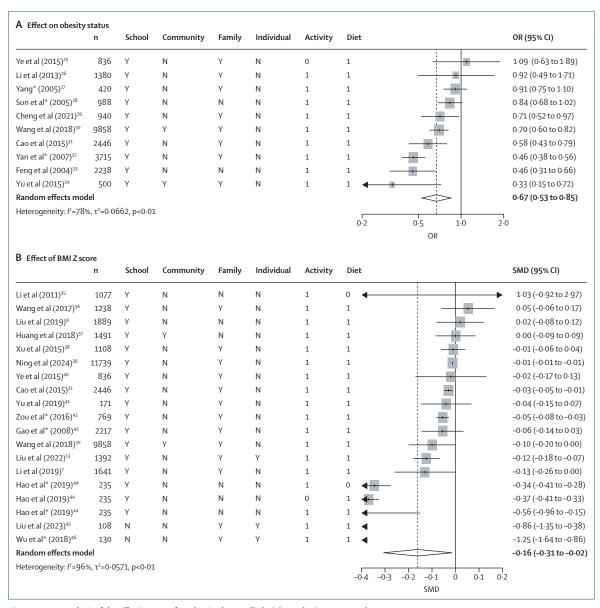


Figure 2: Meta-analysis of the effectiveness of randomised controlled trials on obesity status and BMI Z score

Meta-analysis of the effectiveness of randomised controlled trials on obesity rate (A) and BMI Z score (B). We pooled the ORs for obesity and SMD between the intervention and control groups from the randomised controlled trials conducted among children in China with a sample size of at least 50 per group using random effect models. Because most studies used mixed intervention strategies, we did not pool estimates by intervention strategy but presented their involved levels and strategies. The columns of school, community, family, and individual indicate whether population-level or individual-level strategies were adopted. The columns of activity and diet indicate whether physical activity and dietary interventions were implemented. No study involved pharmacological or surgical interventions. 1 and 0 in Activity and Diet indicate whether the study involved interventions on physical activity or diet. N=no. OR=odds ratio. SMD=standardised mean difference. Y=yes.

\*Studies with a high risk of bias in more than one study design component. See appendix p 2 for details.

ratio 0.67,95% CI 0.53 to 0.85) and lowered BMI Z score (standardised mean difference -0.16, 95% CI -0.31 to -0.02; figure 2). Moreover, the geographical distribution reveals that high-quality and large-sample studies were primarily concentrated in high-income (or more developed) cities, especially in eastern China. Meanwhile, there is a considerable disparity in urban-rural research efforts, with studies in rural areas being notably scarce. In these studies, reporting of

implementation design and maintenance was less comprehensive and should be improved, with an average reporting rate of maintenance of only  $19\cdot2\%$  (appendix p 20). This limitation undermines the ability to evaluate the scalability and long-term efficacy of targeted intervention studies within practical settings. Therefore, it is imperative to adopt a pragmatic approach that integrates all dimensions during planning, evaluation, and decision-making phases.

### Population-level intervention strategies

#### Society-wide intervention

Long-standing social and policy initiatives aimed at reducing childhood obesity encompass legislation, environmental modifications, accessible resource allocation, and economic measures (eg, sugar taxes and food subsidies).47,48 Although quantification of these policies and strategies remain scarce in China, several studies in high-income nations have shown their potential on childhood obesity trends. For example, the soft drinks levy in the UK correlated with a decline in obesity incidence among girls, particularly in low-income regions. 15,49 A modelling analysis suggested that these measures disproportionately benefit children, reinforcing the importance of evidence-based policies for obesity control. 50 In China, there is an urgent need for elucidating the potential challenges and practical considerations of such measures. Reducing sugar-sweetened beverage intake might be beneficial, but due to substitution effects between foods<sup>51</sup> and the uncertain long-term health effects of current non-nutritive sweeteners and sugar substitutes, 52 the exogenous consequences of this strategy warrant examination. A modelling study in China estimated that taxing sugar-sweetened beverage consumption would reduce beverage consumption, but increase the intake of diet drinks (typically artificially sweetened).53 Given China's socioeconomic landscape and varied regional development, sugar taxation could considerably reshape the food industry, extending bevond sugar-sweetened beverage consumption reduction. Thus, nuanced explorations into regional feasibility and health outcomes are crucial to crafting effective and equitable strategies.

Various other society-wide strategies, such as breastfeeding promotion, subsidies for healthy food, food formulation standard development, sport-friendly urban planning, and the development of public recreational facilities can exert varying degrees of influence on childhood obesity. Enhancing the agricultural sector and food supply chains are also pivotal, as they directly shape food provision. These comprehensive societal measures stem not only from government policies, but also from the efforts of non-governmental organisations that contribute to a wide array of programmes.<sup>54</sup> Programme evaluation remains challenging and scarce but is necessary for implementation and scaling of these programmes.55 China's top-down governance structure expedites public health policy implementation and enables society-wide interventions and multisectoral collaboration. However, socioeconomic disparities, urban lifestyles, a modernised dietary pattern with higher processed food consumption, and sedentary trends pose barriers to the implementation of interventions.

#### School-based interventions

Globally, school-based strategies combining diet and physical activity interventions have shown inconsistent effectiveness for children.<sup>11,56</sup> In some settings, these interventions led to improvements in obesity-related outcomes, while in others, the effect was minimal or difficult to sustain.11 A meta-analysis showed that shortterm school-based intervention programmes lowered the odds of overweight and obesity by 26%.57 However, a previous RCT assessing school-based intervention in 1324 UK primary school children found no significant reduction in BMI. This highlights the complexities and challenges to change children's unhealthy behaviours within the school environment, 10 which echoed a previous study in 200 UK schools<sup>12</sup> and another in the USA.<sup>58</sup> A recent review concluded that school-based interventions, with or without dietary intervention components, might only have modest benefits at short and medium terms that usually disappeared with long-term follow-up.59 These inconsistencies suggest that the success of schoolbased interventions might be highly dependent on cultural, environmental, and logistical contexts and delivery strategies.

In China, school-based intervention programmes are among the most frequently chosen strategies in obesity intervention studies, primarily due to the feasibility of implementing and monitoring these interventions within a controlled environment.14 Schools provide a unique setting where children can be consistently exposed to health promotion, and interventions could be integrated into daily education routines. Common strategies include enhanced physical and nutrition education, encouraging outdoor exercise, provision of healthy school meals, and improvements in the overall food environment (eg. school canteen redesign). Some school-based interventions have shown success in China. In a cluster RCT, a school-based intervention programme targeting children's healthy diet and physical activity reduced the mean BMI and obesity incidence.13 In another RCT, 8 months of nutrition education and physical activity intervention improved metabolic and mental health among children with obesity.58 These findings suggest that school-based interventions in China could be effective.60

A pivotal factor underpinning the success for reducing childhood obesity is the substantial time students devote to schooling, which is distinct from high-income nations. 13,61 China boasts a large number of students residing in dormitories, enhancing constant immersions in the school and enabling comprehensive and sustained intervention implementation. Robust government backing, curriculum-integrated health education, and community engagement foster a favourable climate for advocating healthy practices in addressing childhood obesity. However, high-quality evidence from China is still scarce, necessitating large-scale and long-term studies to evaluate efficacy and sustainability of such interventions. Complementary community-based initiatives, while largely unexplored, could augment school-based efforts. Concurrently, as previously highlighted, prolonged school hours might affect the influence of other risk factors, necessitating measures beyond nutrition and physical activity promotion. Challenges encompass intense academic pressures, resource disparities (eg, physical facilities) across schools, and the absence of targeted support for individuals, which could hinder rural schools' progress, as evidenced in previous RCTs.<sup>13</sup> Additionally, knowledge disparities between urban and rural schools, and the absence of standardised training procedures among staff can often hinder consistency and effectiveness of such programmes.

#### Family-based intervention

Family-based intervention strategies—eg, nutrition and physical activity promotion and parenting skill improvement—might be effective for child weight management, especially at an early stage when children spend most of the time with family. 62 Globally, familybased interventions were generally successful in improving weight-related behaviours and reducing weight among children.62 While family involvement and education are common practice in the prevention of overweight, they are not necessarily the primary setting of childhood obesity interventions in China. Family-based interventions are more often integrated into broad, primarily school-based interventions rather than being standalone approaches, potentially due to challenges of reaching families directly and the key role of schools in child development. Several Chinese RCTs have integrated family-based components within school-based frameworks, 6,7 suggesting that this combined approach can further enhance effectiveness. The CHIRPY DRAGON study, featuring two education programmes for caregivers in a family alongside those programmes for children, effectively enhanced intervention efficacy, proved to be a costeffective strategy, and highlighted parental cooperation as an instrumental propellant.7 International guidelines recommend maternal care during pregnancy and breastfeeding to prevent excessive fetal weight growth and reduce macrosomia, and evidence from China showed the potential of text message intervention.63

The implementation of family-based interventions for childhood obesity in China is facilitated by strong family ties and the central role of parents (or sometimes grandparents) in children's lives, while households with less family involvement could pose challenges to reducing childhood obesity. Improving health resources and literacy at the family level enables parents and caregivers to make informed decisions for children's health. However, obstacles include traditional cultural perceptions<sup>64,65</sup> that favour heavier children as healthier and lead to overfeeding<sup>64</sup> and the challenge of altering established dietary and lifestyle habits within families. Furthermore, regional disparities in health literacy and access to resources can hinder the consistent application

of interventions and challenge their widespread and lasting effects. Family structure (such as dual-income or single-parent families) can affect the time spent parenting, preparing healthy meals, or engaging in physical activities with children. 68

Interventions solely involving parents yielded similar or even superior outcomes in managing child weight compared with interventions including both parents and children, 62,69 which highlights the pivotal role parents have in decision making and modelling behaviours for their offspring. While family-centred approaches appear economically viable, empirical data from Chinese children, particularly compared with schoolbased and other intervention modalities, remain scarce. Multilevel and multi-component interventions involving collaborations among schools, families, communities, and health-care providers, appear to be successful in China. A school-based RCT was designed to be delivered by on-campus settings and intended to involve specific strategies to engage families and other stakeholders.13 Moreover, the family-individual-school model used in a 3-year RCT, showed both immediate and long-lasting effectiveness in preventing childhood obesity.70 Notably, the existence of disparities between males and females in intervention responsiveness underscores the need for tailored intervention frameworks accounting for sex in childhood obesity prevention.

#### Individual-level interventions

#### Lifestyle interventions

Lifestyle modification is globally recognised as the firstline strategy for childhood obesity. Multi-component lifestyle interventions typically involve various elements, such as dietary modification, increased physical activity, and overall healthy lifestyle habits,4 and they have been extensively studied and implemented in Chinese children with promising results.31 Dietary interventions typically focus on promoting a balanced diet rich in fruits, vegetables, and whole grains while reducing the intake of calorie-dense processed foods and training in meal planning and portion control.7,13 Among children, physical activity interventions focus on increasing regular exercise and reducing sedentary behaviours by promoting after school exercise or community-based recreational activities. 41 The growing availability of health information and resources via media and digital platforms also supports these efforts.71 Nonetheless, major obstacles exist, including the academic workload that restricts exercise time and the effects of large-scale marketing and easy access to unhealthy foods. These challenges call for a holistic approach that considers both cultural and socioeconomic factors when designing individual-based interventions.

However, it is crucial to acknowledge that the majority of lifestyle intervention studies in China are circumscribed within the confines of schools or familial milieus, with a notable absence of direct and child-centred engagement that fully appreciates their roles as autonomous agents. If focusing on educating parents, caregivers, and educators, these interventions could be more effectively disseminated and internalised by children. Conversely, the reliance on schools and families means that intervention strategies might be less available to children who are outside the traditional educational system or those from households where parents are less willing or able to participate, especially given the vast geographical and cultural varieties of China. As such, it is crucial to develop childcentred intervention strategies that empower children themselves. Technological advances, such as e-Health and generative artificial intelligence, provide opportunities for multimodal lifestyle intervention and management in tracking behaviours, providing real-time feedback and positive reinforcement to encourage healthier habits,72-74 and interactive and personalised engagement with nutrition and physical activity programmes.75,76

#### Clinical interventions

Although for this Series, we focus on public health, clinicians have a crucial role in managing childhood obesity, especially in providing medical assessments and guidance for affected children and their families, that cannot be ignored.77 Clinicians are also central to nonpharmacotherapeutical efforts, particularly within the so-called 5A (assess, advise, agree, assist, and arrange) framework to guide behavioural changes. 69,78 Health-care workers' roles go beyond assessing and advising patients; they are essential to guide families along the entire process of developing and implementing personalised interventions. By assisting and arranging tailored support and treatment plans, health-care workers ensure that each child receives care that is comprehensive and appropriate to their unique needs. For clinical interventions, the knowledge and capability of healthcare providers can be an important determinant of the effectiveness of their practice, while the absence of knowledge, inadequate training, and lack of motivation could become key barriers.79

The use of pharmacological treatments in Chinese children, however, remains generally reserved for severe cases of obesity where lifestyle interventions have been ineffective and is considered a fourth-line treatment option. As in other countries, there is an absence of comprehensive long-term data on potential adverse events. This cautious stance reflects global concerns over the safety and appropriateness of pharmacotherapy in young populations, where weighing risks and benefits remains challenging in the absence of robust evidence, and only given priority when lifestyle modifications have proven insufficient in mitigating cardiometabolic risks.

In China, medications such as phentermine and orlistat, are sparingly prescribed under expert guidance, and combined with rigorous lifestyle modifications

to maximise efficacy while mitigating risks, as is emphasised in studies from other populations. 82-84 In recent years, GLP-1 agonists such as liraglutide and semaglutide, showed promising BMI reduction; although lingering safety concerns persist. 5,80,85-87 As of now, China remains cautious on incorporating these advances into paediatric weight management.

Severe cases of obesity coupled with escalating complications, such as diabetes and hypertension, can necessitate use of rigorous therapeutic measures and bariatric surgery. As an invasive yet effective approach, bariatric surgery entails modifications to the digestive system aimed at facilitating weight loss. However, bariatric surgery in paediatric populations requires stringent oversight and regulation due to the inherent risks and profound repercussions on young patients. In China, this surgical option is not broadly used or prioritised among children and adolescents over other weight-modifying methods.

#### Crucial gaps and unique opportunities

Chinese guidelines emphasise distinct strategies, especially school-based ones, highlighting the importance of context specificity for best practice alignment within China's unique sociocultural landscape. S2.91 China's policies, culture, and economic development offer unique opportunities for addressing childhood obesity. However, crucial gaps persist.

Children can have age-specific risk factors for obesity, meaning that it might be valuable to tailor interventions to individuals of different ages. For example, dietary optimisation has been widely recognised to have an important role, but a recent review found uncertain evidence for whether dietary optimisation alone had an effect on bodyweight status for children aged 12-18 years.<sup>59</sup> Therefore, tailored and targeted interventions are needed for children across their life. Furthermore, there is a pressing concern regarding the representativeness of RCTs and the inadequate focus on socioeconomic status disparities within current frameworks. A notable discrepancy exists as RCTs conducted in China predominantly involve populations from high-income urban areas. This limitation in inclusiveness poses substantial challenges in translating evidence-based interventions to reach and benefit the most susceptible populations with low resources. Standardised intervention operation procedures need to be combined with individualised intervention schemes, which require concerted efforts from multiple sectors and entities in China. We present our recommendations for future research and directions for childhood obesity intervention in China in the panel.

China has gone through a rapid economic development over the past few decades, resulting in unique perspectives on urbanisation, physical activity, and nutritional transitions. Meanwhile, governments

#### Panel: Implications for future research in childhood obesity interventions in China

#### Country-specific contexts

Evidence on the feasibility, efficacy, and cost-effectiveness of multilevel interventions against childhood obesity in the different cultural and economic contexts of China remains scarce. There should be investigations to design and evaluate interventions that are culturally relevant and consider traditional dietary practices and social norms and adapt successful interventions from other regions or countries to the Chinese context to assess their effectiveness.

#### Inclusive design to promote health equity

China is a large country with considerable variation in resources across geographical regions, between rural and urban areas, and between males and females. Future studies should take these factors into account to devise inclusive and targeted strategies for effective obesity control across the whole nation.

#### Efficient delivery assisted by advanced technology

The use of digital tools and artificial intelligence for effective and scalable interventions could be further expanded, including

mobile apps and online platforms that provide personalised dietary and physical activity recommendations for children, wearable fitness trackers to monitor and motivate physical activity in children, and telehealth services that provide remote counselling and support for weight management.

Multilevel and multi-component intervention strategies
Current intervention programmes are mostly based on schools;
future studies are needed to incorporate family, community,
society, and other stakeholders to design multifaceted
interventional approaches. Partnerships between government,
schools, health-care providers, and private sectors to develop
and implement comprehensive intervention programmes
would be a unique opportunity.

#### Cost-effectiveness and implementation

There is a need for rigorous evaluations of existing intervention programmes to identify best practices, areas for improvement and feasibility, and evaluate the effect of scaling up successful pilot programmes to a national level.

have a crucial role in refocusing the policy agenda to prevent further weight gain. This issue is particularly evident in countries where populations have shifted from high physical activity to an increasingly sedentary lifestyle. 92,93 During this transition period, evidencebased practice is warranted to standardise the evaluation of government-led initiatives. Although there are a multitude of initiatives and promotional programmes embarked upon by various government and nongovernment entities, a comprehensive evaluation framework to ascertain their efficacy and scalability (when juxtaposed with investigator-initiated trials centred around school-based or family-based methods) remains elusive. This void undermines the capacity to discern best practices and comprehend which interventions thrive in diverse settings. Notably, for most intervention modalities, safety data particularly pertaining to long-term effects, are scarce. Although primarily lifestyle modification measures are less likely to induce severe adverse events compared with pharmacological or surgical strategies, future research should focus on providing data to test the long-term effects before scaling up.94

While lifestyle modifications remain the cornerstone of interventions aimed at childhood obesity, there is a noticeable absence of a consensus on tailored pharmacological and surgical treatments specifically addressing severe childhood obesity. This gap underscores the urgency to embrace advanced digital health technologies, enhance health-care accessibility, and devise comprehensive and evidence-based guidelines. These components are pivotal in crafting a more efficient and holistic strategy for childhood obesity in China. An

#### Search strategy and selection criteria

In this Series, we primarily focused on obesity among Chinese children aged 6–18 years. To evaluate the effectiveness of the intervention approaches in Chinese children, we systematically searched for randomised controlled trials on childhood obesity in China from five English and Chinese databases—PubMed, Embase, Web of Science, CNKI, and Wanfang—from initiation to May 3, 2024 (n=1059). For comprehensiveness, we also included interventions for children younger than 6 years in this review because these studies also serve as important examples for interventions in difference scenarios. After title, abstract, and full-text review on the relevance of the topic investigated, the population included and corresponding sample size, intervention and outcome definitions, and study design were reviewed from which we included 24 papers for further analysis. The search terms for each database and the summary of the search are listed in the appendix (pp 9-11). Considering the absence of high-quality studies, instead of including all studies for quantitative synthesis, we prioritised those that had a larger sample size, longer intervention and follow-up durations, and with better representativeness of data sources of childhood obesity in China in the narrative summarisations. We also reviewed the articles describing evidence in non-Chinese populations that were high quality and the potential to translate into the Chinese context where applicable and compared studies that both addressed high-income country and Chinese populations.

integrated response that combines medical, technological, and environmental solutions, coupled with the dedicated engagement of health-care professionals, is imperative to effectively confront this pressing issue.

#### Conclusion

Our Series paper offers a prospective outlook and emphasises the potential importance of China's policy landscape in shaping childhood obesity interventions. Policy interventions often transcend traditional research frameworks and necessitate evidence-based evaluation methodologies. We have identified knowledge gaps and urge researchers to invest in rigorous RCTs and meticulously designed quasi-experimental studies to fortify evidence-based policy making and public health interventions.

Our examination of both population-wide and individual-level obesity interventions in Chinese children has revealed varied effectiveness across diverse levels of evidence, mirroring global trends, yet underscoring China's unique characteristics. Tackling childhood obesity necessitates a comprehensive approach that integrates social, economic, cultural, and environmental strategies, combining family-based, school-based, and individual-based approaches, requiring concerted efforts from multiple sectors and entities within China.

#### Contributors

CY and YD conceptualised and designed the report, drafted the initial manuscript, and reviewed and revised it to ensure clarity and coherence. YS and JM contributed to the conceptualisation and design, research reviews analyses, and participated in the initial drafting of the manuscript, and its review and revision process. HC, LM, LJ, JL, QL, and YH provided valuable insights into the interpretation of the review and revisions of the manuscript. All authors gave their approval for the final version submitted and accept responsibility for every aspect of this collaborative work.

#### **Declaration of interests**

We declare no competing interests.

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