Diagnostic test accuracy of waist-to-height ratio as a screening tool for cardiovascular risk in children and adolescents: a meta-analysis

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ABSTRACT

\textbf{Context:} Waist-to-height ratio (WHtR) is a controversial evaluation index of cardiovascular risk factors (CVRFs) in children and adolescents.

\textbf{Objective:} To assess the accuracy of WHtR as a measure to screen for clusters of at least one CVRF (CVRF\textsubscript{1}), two CVRFs (CVRF\textsubscript{2}), and three CVRFs (CVRF\textsubscript{3}) in different ages, sexes, regions and cut-offs.

\textbf{Methods:} The PubMed, Web of Science, EBSCOhost, Springer, Taylor & Francis Online, Wiley Online Library, Wanfang, and CNKI databases were searched for eligible publications up to June 2021. The QUADAS-2 checklist was used to assess the methodology of the included studies.

\textbf{Results:} Twenty-two studies that evaluated 85281 children and adolescents aged 5–19 years were included in the meta-analysis. The AUSROC values were 0.56 (95% CI: 0.54–0.57), 0.82 (95% CI: 0.81–0.83), and 0.89 (95% CI: 0.89–0.90) for CVRF\textsubscript{1}, CVRF\textsubscript{2}, and CVRF\textsubscript{3}, respectively. Higher AUSROC values were found for adolescents (12–19 years), that is, 0.91 (95% CI: 0.88–0.93), 0.90 (95% CI: 0.87–0.92) for males, and 0.91 (95% CI: 0.90–0.91) for a cut-off of ≥ 0.51 in the identification of CVRF\textsubscript{3}.

\textbf{Conclusion:} WHtR can be used as an accurate screening tool for CVRF\textsubscript{3} and CVRF\textsubscript{2} in children and adolescents, and it is recommended to select different cut-offs according to different ages, sexes, and regions.

Introduction

With approximately 370 million children and adolescents being overweight or obese worldwide, childhood obesity has become a worldwide concern and increasingly a global public health problem (Di Cesare et al. 2019). Overweight and obesity increase metabolic and cardiovascular risk factors (CVRFs) in children and adolescents (Friedemann et al. 2012; World Health Organization 2016) and increase cardiovascular mortality in adulthood (Twig et al. 2016; Lee and Yoon 2018). Because of the strong association between obesity and CVRFs (Hubert et al. 1983; Smith 2007), there has been a tendency to use obesity or obesity indicators as screening tools for CVRFs in children and adolescents to achieve prevention and intervention for cardiovascular disease (CVD) early in life. Compared with blood lipids, blood glucose, and other blood test indicators commonly used in cardiovascular risk factor screening, anthropometric indicators have the advantages of non-invasiveness, low cost, and good compliance and are more suitable for large-scale screening of children in the field of public health (Grassi et al. 2009; Zheng et al. 2016). The most common anthropometric indicators, body mass index (BMI) and waist circumference (WC), although well-known screening tools for CVRFs, still have deficiencies in practical application. The disadvantage of BMI is that it cannot differentiate fat distribution, it is less effective at measuring CVRFs associated with central obesity, and it isn't effective in assessing cardiovascular risk in normal-weight children and adolescents (Prentice and Jebb 2001; Heymsfield et al. 2009). WC, although a representative indicator of central obesity, cannot distinguish among visceral fat differences in individuals of different heights (Hsieh and Yoshinaga 1999).

WHtR, a measure of central adiposity, is expressed as WC divided by height (Hsieh and Yoshinaga 1995; Ashwell et al. 1996). Compared with BMI and WC, WHtR has more practical advantages in identifying CVRFs for overweight and obese children and adolescents. First, it effectively combines the benefits of the first two, taking into account account height and central obesity. Second, compared with BMI, it does not need to be adjusted depending on age and sex and is simpler to operate and easier to interpret (Goulding et al. 2010; Bauer et al. 2015), which makes it more suitable for widespread screening in the clinical and public health domains. In the early stage of cardiovascular injury, the development of CVD is still reversible, and the identification of CVRFs and the development of preventive strategies during this period are the leading measures to reduce CVD morbidity and mortality in the general population (Drozd et al. 2021). Despite the advantages of WHtR being non-invasive, low cost, simple,
and easy to interpret, its diagnostic accuracy as a screening tool for CVRFs in children and adolescents has been controversial (Bauer et al. 2015; Aristizabal et al. 2019; Dou et al. 2020; Yang et al. 2020). Although relevant meta-analysis studies have appeared (Jiang et al. 2021; Ezzatvar et al. 2022), there are still few, and there is no comprehensive and systematic analysis combined with different levels of risk factor clustering.

A comprehensive and systematic understanding of the identification effect of WHtR on the clustering of CVRFs at different levels in children and adolescents is more conducive to the early prevention and treatment of cardiovascular disease. However, there is a lack of meta-analysis studies on the diagnostic accuracy of WHtR under different levels of CVRF clustering in children and adolescents, primarily a comprehensive survey of children and adolescents of different ages, sexes, and ethnic/geographical regions under varying levels of CVRF clustering. Earlier meta-analysis studies focussed on CVRFs but lacked attention to CVRF1 and CVRF2 (Lo et al. 2016; Ochoa Sangrador and Ochoa-Brezmes 2018). Although the study by Ezzatvar et al. considered the influence of factors, such as sex and ethnicity/geographical region, on the identification of CVRFs in children and adolescents and conducted a subgroup analysis, it did not analyse the abovementioned indicators in combination with the clustering of CVRFs at different levels (Ezzatvar et al. 2022). Similarly, while Jiang et al.’s study explored the effect of WHtR on identifying the clustering of CVRFs at different levels in children and adolescents, they did not perform a subgroup analysis on factors such as age, sex, and ethnicity/geographical region (Jiang et al. 2021). A single cut-off of 0.50 for WHtR may not be appropriate, and suitable cut-offs should be set by considering factors such as CVRF cluster levels, age, sex, and ethnicity/geographical regions (Jiang et al. 2021; Ezzatvar et al. 2022).

Methods and literature review

We performed the systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) checklist (McInnes et al. 2018). The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Registration number CRD42021257521).

Eligibility criteria

Eligible studies should be consistent with the following inclusion criteria: (i) the included studies aim to evaluate the performance of WHtR as a screening standard in diagnosing cardiovascular disease (CVD) risk factors in children and adolescents whose ages range from 5 to 19 years; (ii) the 2 x 2 contingency table can be extracted to allow for meta-analysis or information (e.g., sensitivity, specificity, predictive value, or prevalence) to calculate these values; (iii) at least one component of metabolic syndrome (MetS) should be included as follows: elevated total cholesterol (TC), elevated triglycerides (TGs), low high-density leptin cholesterol (HDL-C), elevated low-density leptin cholesterol (LDL-C), hyperglycaemia, high blood pressure (BP) and central obesity.

We excluded articles if they had the following characteristics: (i) nonoriginal articles, e.g. review studies; (ii) not in English or Chinese; (iii) studies of people who were classified as obese or nonobese before a diagnostic test; (iv) studies without blood tests; (v) duplicate articles.

Information sources and search strategy

We researched the following electronic bibliographic databases: (i) PubMed; (ii) Web of Science; (iii) EBSCOhost; (iv) Springer; (v) Taylor and Francis Online; (vi) Wiley Online Library; (vii) China National Knowledge Infrastructure; and (viii) Wanfang databases. The search strategy only included related terms or the description of the association and was conducted in English and Chinese terms from inception to June 2021.

The search strategy descriptor groups were ("W-HtR" OR "WC/height" OR "WHtR" OR "waist: height ratio" OR "waist-to-height ratio" OR "wthr" OR "Waist-Height Ratio" OR "W-Height-To-Height" OR "waist to height" OR "waist height" OR "waist circumference to height") AND ("Heart Disease Risk Factors" OR "Cholesterol, HDL" OR "Triglycerides" OR "Insulin Resistance" OR "Hyperlipidaemias" OR "Hyperglycaemia" OR "Hypertension" OR "Blood Pressure") AND ("adolescent" OR "child" OR "paediatrics").

Study selection and quality assessment

The literature selection process was performed by two independent reviewers (F.S.Z. and Y.B.H.). Literature that did not meet the inclusion criteria by reading titles and abstracts was excluded. Therefore, the full texts of the selected articles were read to determine which studies met the inclusion criteria. Discrepancies between reviewers were settled through discussions with the reviewer team (H.L.W., Y.L., Z.W.Y.). After selecting the studies, two authors (F.S.Z. and Y.B.H.) conducted manual searching of reference lists of selected articles. We used Endnote X9 software to screen and manage the articles.

Data collection process and data items

One author (Y.L.) extracted the following characteristics of the included studies: author, year of publication, country, sample size, study design, age, sex, reference standard, optimal WHtR cut-off, and 2 x 2 contingency table. The second author (Z.W.Y.) cross-checked all collected information. A third author (H.L.W.) participated in the process to make a final decision when necessary.

Risk of bias in individual studies

Two authors (F.S.Z. and Y.B.H.) independently assessed the quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (Whiting
et al. 2011). QUADAS-2 is a revised tool for systematic reviews used to evaluate the quality of the diagnostic test studies in the areas of bias and applicability, involving four domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing. Applicability questions were applied to the first three domains, and the answer to each question was determined by "yes", "no" or "unclear". The risk of bias and concerns about applicability were estimated as "high", "low" or "unclear" (see Table S6). Discrepancies were resolved by discussion or by consulting the reviewer team (H.L.W., Y.L., Z.W.Y.).

**Synthesis of results**

We conducted this meta-analysis following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement (McInnes et al. 2018). To evaluate the diagnostic accuracy of WHtR for detecting CVRFs, we extracted sensitivity and specificity parameters from each study and extracted or calculated true positive (TP), false positive (FP), false negative (FN), and true negative (TN) from each included article. Meta-analysis was performed using Stata statistical software version 16.0 (Stata Corp, College Station, TX, USA) based on 2 × 2 tables. Pooled sensitivity (SEN), specificity (SPE), positive likelihood ratio (LRþ), negative likelihood ratio (LR−), diagnostic odds ratio (DOR), and the area under the summary receiver operating characteristic curves (AUSROC) were assessed using a bivariate mixed-effects model (see Tables 1, S2, and S3 for details). The bivariate model is a random effects model (Leeflang et al. 2008) that is suitable for diagnostic meta-analyses with data heterogeneity (Liu et al. 2013). SEN refers to the probability of a positive result being detected in a subject; SPE is the probability of a negative test result in a subject without disease. LRþ refers to the ratio between the occurrence of a positive test result in a subject with disease and the occurrence of the same result in a subject without disease; LR− refers to the ratio of the occurrence of a negative test result in subjects with disease to the occurrence of the same result in subjects without disease (Akobeng 2007; Simundic 2009). The AUSROC has been considered a global measure of test performance. AUSROC values of 0.5–0.7, 0.7–0.9, and 0.9–1.0 were used to suggest low, moderate and high diagnostic accuracy, respectively (Swets 1988).

**Risk of bias across studies**

The Cochran Q test and inconsistency index ($I^2$) were used to explore the heterogeneity of the included studies. If the value of $I^2$ is greater than 50%, it indicates the possibility of significant heterogeneity, in which case a random-effects model is applied to subsequent pooling, or a fixed-effects model is applied when $I^2$ is less than 50% (Higgins and Thompson 2002; Higgins et al. 2003; see Figure 2). Diagnostic thresholds were analysed by Spearman’s correlation coefficient and p values. If there was no significant threshold effect, the diagnostic accuracy was estimated by pooled AUSROC, Q index, SEN, SPE, LRþ, LR−, and DOR. If there was a significant threshold effect, diagnostic accuracy was evaluated only by AUSROC and Q index rather than SEN, SPE, LRþ, LR−, and DOR (Devillé et al. 2002; Reitsma et al. 2005; see Tables 1 and Table S2). Deeks’ funnel plot was used to measure the publication bias in the meta-analysis, and the regression line associated with p values of less than 0.05 indicated a statistical publication bias (Deeks et al. 2005; see Figure 4).

To decrease heterogeneity, we further performed subgroup analyses based on age status (children ≥ 5–12 years, adolescents ≥ 12–19 years) (Musa-Veloso et al. 2016; Sardinha et al. 2016), sex, geographical region, and cut-off group for CVRF3 (see Table 1). At the same time, the different levels of CVRFs and their components were also analysed (see Table S2). To further explore the potential sources of heterogeneity, the outcomes of reference standards, for example, fasting blood glucose (FBG), BP, TG, HDL-C, and central obesity, as well as index test (whether the test was blinded), WHtR cut-off group, and geographical region were included in the meta-regression analysis (see Table S5, Figure S2).

We specifically classified the diagnostic criteria for each outcome as follows: FBG ≥ 5.6 mmol/L (100 mg/dL) or ≥110 mg/dL vs. other risk thresholds as a group; systolic BP (SBP) ≥130 mmHg or diastolic BP (DBP) ≥ 85 mmHg or SBP and/or DBP ≥ 90th percentile for age, sex and height vs. other risk thresholds as a group; TG ≥ 150 mg/dL (1.69 mmol/L) or TG ≥ 110 mg/dL (1.25 mmol/L) vs. other cut-

| Table 1. Subgroup analysis of WHtR screening for the clustering of CVRF3. |
|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| **Outcome**     | **Threshold effect** | **p-value** | **SEN (95% CI)** | **SPE (95% CI)** | **AUSROC (95% CI)** | **DOR (95% CI)** | **Publication bias (p-value)** |
| **Age status**  |                 |                 |                 |                 |                 |                 |                 |
| Children        | 0.10            | 0.01            | 0.76 (0.58–0.88) | 0.76 (0.75–0.78) | 0.78 (0.76–0.79) | 10 (4–25)       | 0.146           |
| Adolescents     | 0.54            | 0.29            | 0.84 (0.78–0.89) | 0.84 (0.79–0.88) | 0.91 (0.88–0.93) | 29 (15–55)      | 0.536           |
| **Sex**         |                 |                 |                 |                 |                 |                 |                 |
| Female          | 0.67            | 0.45            | 0.81 (0.73–0.87) | 0.80 (0.75–0.85) | 0.87 (0.84–0.90) | 18 (9–36)       | 0.080           |
| Male            | 0.28            | 0.08            | 0.85 (0.77–0.90) | 0.83 (0.77–0.87) | 0.90 (0.87–0.92) | 27 (14–52)      | 0.060           |
| **Geographical region** |     |                 |                 |                 |                 |                 |                 |
| Asian           | 0.60            | 0.36            | 0.85 (0.78–0.91) | 0.79 (0.76–0.81) | 0.85 (0.84–0.86) | 22 (12–39)      | 0.011           |
| Non-Asian       | 0.62            | 0.38            | 0.83 (0.76–0.88) | 0.84 (0.78–0.88) | 0.90 (0.89–0.91) | 25 (13–48)      | 0.113           |
| **Cut-off group** |                |                 |                 |                 |                 |                 |                 |
| Cut-off 0.43 to 0.46 | 0.82           | 0.67            | 0.79 (0.62–0.90) | 0.77 (0.76–0.79) | 0.79 (0.78–0.80) | 13 (5–31)       | 0.029           |
| Cut-off 0.47 to 0.50 | 0.40           | 0.16            | 0.86 (0.79-0.90) | 0.79 (0.76–0.82) | 0.87 (0.84–0.90) | 23 (13–40)      | 0.086           |
| Cut-off ≥ 0.51  | 1.00            | 1.00            | 0.86 (0.81–0.89) | 0.86 (0.78–0.91) | 0.91 (0.90–0.91) | 37 (17–81)      | 0.148           |

WHR, waist-to-height ratio; CVRF, cardiovascular risk factor; CVRF3, clustering at least three CVRFs; SEN, sensitivity; SPE, specificity; AUSROC, area under the summary receiver operating characteristic; DOR, diagnostic odds ratio; CI, confidence interval.
offs as a group; HDL-C < 40 mg/dL (1.03 mmol/L) or not; central obesity according to the WC ≥ 90th percentile of the age- and sex-specific reference or not; index test is blind or not; cut-offs of WHtR ≥ 0.51 vs. cut-offs of WHtR between 0.43 to 0.50; Asian or non-Asian populations. All analyses were performed using Stata Statistical Software Version 16.0 (Stata Corp, College Station, TX, USA).

Results

Study selection

Figure 1 shows the search and selection process of the studies. In total, 4295 articles were identified from the primary literature search strategy, of which 577 were from PubMed/MEDLINE, 208 were from EBSCO, 1940 were from Springer, 160 were from Taylor and Francis, 729 were from Web of Science, 674 were from Wiley Online Library, and seven were from the Chinese databases of Wan Fang and Chinese National Knowledge Infrastructure. In addition, 36 references were identified from reference lists and other sources. After the removal of 811 duplicate references, 3520 different articles were identified. A comprehensive evaluation of the title and abstracts was conducted, and 3454 papers were excluded, resulting in 66 articles for full-text eligibility assessment. 44 studies were excluded after the full-text article was assessed for eligibility (Supplementary Method S2). Finally, we included a total of 22 articles for meta-analysis (Figure 1).

Study characteristics

Twenty-one cross-sectional studies and one cohort study which were published from 2008 to 2020 (the research date started from 1999 to 2015) and included 85281 children and adolescents (49% females) aged between 5 and 19 years, were included in the meta-analysis. The studies were conducted in 30 countries. Of these studies, 15 studies were conducted for CVRF3 in countries from the Asian region (Korea, China, Vietnam) (Liu et al. 2017; Seo and Kim 2017; Jiang et al. 2018; Zhang et al. 2019; Dou et al. 2020; Li et al. 2020; Mai et al. 2020), and 16 studies were conducted for CVRF3 in countries from the non-Asian region (i.e. USA, Algeria, Mexico, UK, Argentina, South Africa, Italy, Spain, Brazil, and Chile) (Elizondo-Montemayor et al. 2011; Graves et al. 2014; Bauer et al. 2015; Benmohammed et al. 2015; Perona et al. 2017; Zhao et al. 2017; Vasquez et al. 2019). Sample sizes ranged from 178 (Kruger et al. 2013) to 18529 (Dai et al. 2014).

Five studies involved children aged 5-12 years according to the CVRF3 subgroup (Elizondo-Montemayor et al. 2011; Dou et al. 2020; Li et al. 2020), and sixteen studies involved adolescents aged > 12-19 years (Benmohammed et al. 2015; Perona et al. 2017; Zhao et al. 2017; Vasquez et al. 2019; Dou et al. 2020). WHtR cut-offs ranged between 0.43 (Li et al. 2020) and 0.59 (Elizondo-Montemayor et al. 2011) according to the CVRF3 subgroup as follows: six studies showed cut-offs of 0.43 to 0.46 (Liu B et al. 2017; Dou et al. 2020; Li et al. 2020); 15 studies showed cut-offs of 0.47 to 0.50 (Graves et al. 2014; Benmohammed et al. 2015; Liu B et al. 2017; Seo and Kim 2017; Zhao et al. 2017; Jiang et al. 2018; Zhang Y et al. 2019; Dou et al. 2020; Mai et al. 2020); and 10 studies showed cut-offs of ≥ 0.51 (Elizondo-Montemayor et al. 2011; Bauer et al. 2015; Benmohammed et al. 2015; Perona et al. 2017; Zhao et al. 2017; Vasquez et al. 2019). The descriptive characteristics of the included studies are summarised in Table S1.
Risk of bias within studies
We assessed the risk of bias in the included studies by QUADAS-2, as detailed in Figure S1 and Table S6 in the supplementary document. All included studies were methodologically homogeneous, with six studies meeting the QUADAS-2 quality assessment criteria. 15 studies were classified as “unclear” for the first question in the second domain (Index test, “Could the conduct or interpretation of the index test have introduced bias?”) because they did not specify whether the implementation and interpretation of the index test was conducted in a blinded context, potentially creating bias as a result. The reasons were similar to the previous question because of concerns about whether the index test was conducted in a blinded context, and 13 studies were classified as “unclear” in the second question in the second domain (Index test, “Is there concern that the index test, its conduct, or interpretation differ from the review question?”). One study was classified as “unclear” for the first question in the third domain (Reference standard, “Could the reference standard, its conduct, or its interpretation have introduced bias?”) because it used an uncommon reference standard, and the second question for the domain (Reference standard, “Is there concern that the target condition as defined by the reference standard does not match the review question?”) was answered as “high” (see Figure S1 and Table S6 for supporting information).

Results of individual studies
Characteristics of the studies and the accuracy evaluation results, including optimal cut-off, SEN, SPE, positive predictive value (PPV), negative predictive value (NPV), prevalence, LR+, LR−, DOR, and Youden’s index were confirmed to be extracted from the included articles, which were involved in the identification of WHtR for CVRFs and its components, as shown in Tables S3 and S4.

Synthesis of results and additional analyses
The total sample size of the meta-analysis was 85281. A total of 86 diagnostic analyses (4 analyses for CVRF1, 11 analyses for CVRF2, 31 analyses for CVRF3, and 40 analyses for the components of CVRFs) were performed in 22 studies included in the meta-analysis. The results of the Spearman correlation coefficient are shown in Table 1 and Table S2, and no significant difference (p < 0.001) was found, which indicated there was no heterogeneity from threshold effects in this meta-analysis.

Regarding the DTA of WHtR screening for CVRF1, the pooled SEN, SPE and AUSROC values were 0.47 (95% CI: 0.44-0.51), 0.87 (95% CI: 0.75-0.94), and 0.56 (95% CI: 0.54-0.57), respectively (Figure 3(a) in the supporting information). High heterogeneity was observed in both sensitivity (I² = 95.06%) and specificity (I² = 99.34%) (Figure 2(a) in the supporting information). The DOR was 6 (95% CI: 3 to 12) (Table S2), and the pooled Deeks’ test result was t = −0.21, p = 0.853, which indicated no significant publication bias of WHtR screening for CVRF1 (Figure 4(a) in the supporting information). Subgroup analyses for CVRF1 were not performed due to limited data.

Concerning the DTA of WHtR screening for CVRF2, the pooled SEN, SPE and AUSROC values were 0.62 (95% CI: 0.53-0.70), 0.83 (95% CI: 0.80-0.85), and 0.82 (95% CI: 0.81-0.83), respectively (Figure 3(b) in the supporting information). High heterogeneity was observed in both sensitivity (I² = 95.96%) and specificity (I² = 98.72%) (Figure 2(b) in the supporting information). The DOR was 8 (95% CI: 5 to 11) (Table S2). The pooled Deeks’ test result was t = −0.82, p = 0.434, which indicated no significant publication bias of WHtR screening for CVRF2 (Figure 4(b) in the supporting information). Subgroup analyses for CVRF2 were not performed due to limited data.

Regarding the DTA of WHtR screening for CVRF3, the pooled SEN, SPE and AUSROC values were 0.84 (95% CI: 0.80-0.88), 0.81 (95% CI: 0.78-0.84), and 0.89 (95% CI: 0.89-0.90), respectively (Figure 3(c) in the supporting information). High heterogeneity was observed in both sensitivity (I² = 95.13%) and specificity (I² = 98.69%) (Figure 2(c) in the supporting information). The DOR was 24 (95% CI: 15 to 37) (Table S2), and the pooled Deeks’ test result was t = 3.26, p = 0.003. The funnel plot displayed an asymmetric distribution, showing publication bias of WHtR screening for CVRF3 (Figure 4(c) in the supporting information). The subgroup analyses are shown in Table 1, which were performed to find possible sources of heterogeneity. Our subgroup analysis outcomes suggested that studies on adolescents (age group: 12-19 years) showed a better diagnostic accuracy than those on children (age group: 5–12 years), with a SEN of 0.84 vs. 0.76, SPE of 0.84 vs. 0.76, DOR of 29 vs. 10 and AUSROC of 0.91 vs. 0.78. In addition, studies on males had a slightly higher diagnostic value than those on females: SEN (0.85 vs. 0.81), SPE (0.83 vs. 0.80), DOR (27 vs. 18) and AUSROC (0.90 vs. 0.87).

Moreover, when subgroup analysis by geographic region was performed, the diagnostic accuracy of WHtR for CVRFs in the non-Asian population was found to be slightly higher than that in the Asian population in terms of SEN (0.83 vs. 0.85), SPE (0.84 vs. 0.79), DOR (25 vs. 22) and AUSROC (0.90 vs. 0.85). According to the subgroup analysis of the cut-off group, it was found that the diagnostic accuracy of WHtR for CVRFs increased with increasing cut-off value, which was reflected as cut-off 0.43 to 0.46 < cut-off 0.47 to 0.50 < cut-off ≥ 0.51, with a SEN of 0.79 vs. 0.86 vs. 0.86, SPE of 0.77 vs. 0.79 vs. 0.86, DOR of 13 vs. 23 vs. 37 and AUSROC of 0.79 vs. 0.87 vs. 0.91.

We explored the potential sources of between-study heterogeneity of WHtR to detect CVRF3. We also conducted a meta-regression analysis according to the covariates of FBG, BP, TG, HDL-C, and central obesity, as well as index test, WHtR cut-off group, and geographical region. Univariable meta-regression analysis revealed that TG, HDL-C, geographical region, index text and WHtR cut-off group may explain heterogeneity in sensitivity (p < 0.05), while all abovementioned covariates may also be potential sources of heterogeneity in specificity (p < 0.05; Table S5, Figure S2). However,
in the joint analysis model, meta-regression analysis revealed that FBG, BP, TG, and central obesity were responsible for heterogeneity ($p < 0.05$; Table S5).

Regarding the DTA of WHtR screening for components of CVRFs, WHtR showed higher accuracy in detecting TG and central obesity (Table S2). The pooled SEN, SPE and AUSROC...
values of WHtR screening for TG were 0.64 (0.57-0.71), 0.71 (0.68-0.73), and 0.74 (95% CI: 0.71-0.76), respectively. The pooled Deeks’ test result of TG was $t = -0.18$, $p = 0.87$, and the pooled Deeks’ test result of central obesity was $t = 3.57$, $p = 0.07$, which indicated no significant publication bias of WHtR screening for TG and central obesity (see Table S2). Subgroup analyses for TG and central obesity were not performed due to limited data.

Discussion

This meta-analysis aimed to comprehensively assess the diagnostic test accuracy (DTA) of WHtR as a screening tool to detect various levels of clustering CVRFs in school-aged children and adolescents aged 5–19 years. CVRFs and risk behaviours can be identified in childhood, and the extent of their existence has been related to the severity of atherosclerosis in childhood and adulthood. Therefore, it is critical to detect early children and adolescents who are at increased risk of developing CVDs to potentially intervene and prevent the development of chronic diseases in adulthood.

To our knowledge, this is the first study to evaluate the diagnostic accuracy of WHtR for cardiovascular risk factors in children and adolescents aged 5-19 years from multiple perspectives of different levels of cardiovascular risk factor clustering in both sexes in different ages, geographical regions and cut-off groups. A previous similar study in children did not analyse the effect of WHtR diagnosis for different ages, sexes, geographical regions and cut-offs (Jiang et al. 2021). Our research found that the performance of WHtR in the diagnosis of CVRFs with different levels of clustering is CVRF1 < CVRF2 < CVRF3, indicating that as the levels of clustering of cardiovascular risk factors increase, the diagnostic accuracy of WHtR for its diagnosis begins to increase. The results showed that the AUSROC of WHtR to detect CVRF1 and CVRF2 was 0.56 (95% CI: 0.54–0.57) and 0.82 (95% CI: 0.81–0.83), respectively. Previous studies on Chinese children and adolescents showed that the two results were 0.62 (95% CI: 0.58-0.65) and 0.74 (95% CI: 0.69-0.79), respectively (HOU et al. 2018), which is consistent with our research, indicating that WHtR has a good diagnostic performance on CVRF2 but a fair performance on CVRF1. Our research found that WHtR showed better diagnostic accuracy in the identification of CVRF3, both in overall and in subgroup analyses by age, sex, geographical region and cut-off group. In addition, compared with BMI and WC, WHtR is more simply applicable because it is independent of age and sex (Lee et al. 2008; Browning et al. 2010; Mokha et al. 2010; Khoury et al. 2013).

In the subgroup analyses, the lower accuracy of WHtR in diagnosing CVRF3 in children (5-12 years) may be related to the rapid growth and development and instability of various physical functions during childhood. In addition, after entering puberty, the speed of human growth and development accelerates, which is especially clear in adolescent (12–19 years) boys, and the performance of WHtR in detecting CVRF3 in
adolescents is slightly higher than that in childhood boys (Dou et al. 2020). The cohort studies in the International Childhood Cardiovascular Cohort (I3C) consortium showed a stronger effect of CVD risk factors in late childhood and adolescence (≥ 10 years) in predicting subclinical cardiovascular outcomes in adulthood relative to early childhood (<9 years) (Xi and Hu 2020). Analysis of the trajectory change from childhood to adulthood for BMI and blood pressure showed that, relative to childhood (4-11 years), adolescence (12–19 years) was the prevention gateway for left ventricular hypertrophy (Zhang et al. 2018) and diabetes (Zhang et al. 2019) in adulthood. The abovementioned analysis shows that with increasing age, the clustering of cardiovascular risk factors in children and adolescents increases. Our study also verifies the abovementioned point of view to some extent, indicating that WHtR has a stronger ability to identify cardiovascular risk factors in adolescents than in children.

With respect to sex, this measure is more accurate in males; this result is consistent with previous findings (Li et al. 2020), and may be related to excess fat accumulation in boys after entering puberty (Tzotzas et al. 2011), with boys having greater abdominal fat than girls at all puberty stages, and girls having a greater amount of fat at the hip (i.e. gynoid fat) than boys (Taylor et al. 2010). Studies from multiple countries have shown that male children and adolescents in prepubertal stage and adolescence have higher rates of overweight and obesity than females (Chhatwal et al. 2004; Gupta et al. 2011; Ahmed et al. 2013; Guo et al. 2013; Piryani et al. 2016).

To understand the identification ability of WHtR for CVRFs in children and adolescents from different geographic regions, we performed subgroup analysis of Asian and non-Asian populations based on limited data. Our study found that WHtR had a slightly better discriminatory ability for CVRFs in non-Asian children and adolescents than in Asian children and adolescents, which may be related to the higher prevalence of childhood obesity in non-Asian countries. Mexico and Brazil are the countries with the highest rates of obesity in the world (Di Cesare et al. 2019), and obesity is accompanied by an increased risk of cardiovascular disease, which is ultimately reflected in the improved ability of WHtR to detect CVRFs (Khoury et al. 2013; Saydah et al. 2013; Rodea-Montoro et al. 2014).

In addition, we combined different cut-off values of WHtR for subgroup analysis, and because there are studies showing that the optimal cut-off value applicable to Chinese children and adolescents is 0.47 (Jiang et al. 2018; Dou et al. 2020), we divided the cut-off range of WHtR into three groups, 0.43–0.46, 0.47–0.50, and ≥0.51, for analysis. We found that the majority of applications with a cut-off range of 0.43–0.46 were in China, those with 0.47–0.50 in Asia, Europe, and America, but mainly Asia, and those with cut-off ≥0.51 were mainly in Europe, America, and Africa. This discrepancy in WHtR for different geographic regions/ethnicities is said to be related to height because Asian children tend to be shorter than white or black children for the same sex and age, and therefore a lower WHtR cut-off has been suggested (Nawarycz et al. 2016). Our study showed that the diagnostic accuracy of WHtR for CVRFs showed a tendency to increase with higher cut-off values. Compared with 0.43–0.46, the diagnostic accuracy of the 0.47–0.50 cut-off range is higher. However, excessive pursuit of diagnostic

Figure 4. Deeks’ funnel plot of WHtR for diagnosing CVRFs. (a) CVRF1; (b) CVRF2; (c) CVRF3.
accuracy would miss some individuals with existing cardiovascular risk factors and be detrimental to the early prevention and treatment of cardiovascular disease; moreover, the AUSROC value of the cut-off range of 0.43-0.46 was 0.79 (95% CI: 0.78-0.80), which is an acceptable value.

In conclusion, the cut-off values for WHtR should be set in conjunction with different ages, sexes, and geographic regions with the aim of achieving the best combination of preventive and accurate outcomes. For Chinese and Mexican Hispanic children and adolescents, a cut-off value of 0.50 is a practical but crude cut-off (Zhou et al. 2014; Seo and Kim 2017); for practical application, a more reasonable cut-off value must be set in combination with demographic characteristics to achieve early prevention of CVD.

Limitations
The limitations of this meta-analysis mainly lie in the presence of heterogeneity. Due to the limited number of studies, we only performed subgroup analysis and meta-regression analysis for CVRF\textsubscript{3} in the presence of heterogeneity, while CVRF\textsubscript{2} and CVRF\textsubscript{1} did not perform the abovementioned analysis due to the small number of studies. Moreover, children and adolescents are in the stage of growth and development, with a large age span, and the performance of WHtR in the identification of different pubertal stages needs to be investigated. In this study, we only performed subgroup analyses of ≥5–12 years (children) and >12–19 years (adolescents), but the performance of WHtR identification of other pubertal stages was not conducted due to the limited number of included studies and the varied criteria for demarcation of age groups in the studies.

Conclusion
This meta-analysis demonstrates that the diagnostic accuracy of WHtR increases with the increase in the clustering of cardiovascular risk factors, and WHtR can be used as a screening tool for CVRF\textsubscript{3} and CVRF\textsubscript{2}. When applying WHtR to CVRF\textsubscript{3} screening, it is recommended to select different cut-off values according to age, sex, and region.

Acknowledgements
The authors thank the National Social Science Foundation of China for the financial support.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
This work was supported by the National Social Science Foundation of China [Grant 19XYY011].

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