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META-ANALYSIS

Zhang et al: cIMT in pediatric nephrotic syndrome

Increased carotid intima-media thickness in pediatric nephrotic syndrome: A meta-analysis

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ABSTRACT

Nephrotic syndrome (NS) in children has been associated with an increased risk of early atherosclerosis, as indicated by carotid intima-media thickness (cIMT). However, the existing literature on the relationship between NS and cIMT in pediatric populations presents inconsistent findings. This meta-analysis aims to compare cIMT measurements between children with NS and healthy controls. A comprehensive search of PubMed, Embase, and Web of Science was conducted through May 22, 2025. Observational studies that compared cIMT in children under 18 years with NS against controls were included. Mean differences (MDs) with 95% confidence intervals (CIs) were aggregated using a random-effects model to account for potential heterogeneity. Thirteen case-control studies involving 578 children with NS and 741 controls were analyzed. The results indicated that children with NS had significantly higher cIMT compared to controls (MD: 0.06 mm; 95% CI: 0.04–0.08; $p < 0.001$; $I^2 = 68\%$). Subgroup analyses revealed that the difference in cIMT was notably larger in studies with ≥ 60% male participants (MD: 0.09 mm) compared to those with < 60% males (MD: 0.03 mm; p for subgroup difference = 0.01). No significant differences were observed based on age, disease duration, or adjustments for body mass index, blood pressure, or lipid profile (all $p > 0.05$). Meta-regression analyses suggested that the proportion of male participants and the rate of steroid-resistant nephrotic syndrome (SRNS) may contribute to observed heterogeneity (adjusted $R^2 = 29.8\%$ and 22.5%, respectively), although the slopes for these meta-regressions were not statistically significant ($p = 0.13$ and 0.87). In conclusion, children with NS exhibit increased cIMT compared to controls, indicating early vascular changes. The predominance of males and the presence of SRNS may partially account for the heterogeneity observed across studies.

Keywords: Nephrotic syndrome, carotid intima-media thickness, atherosclerosis, children, meta-analysis.

INTRODUCTION

Nephrotic syndrome (NS) is a common chronic kidney disorder in children, characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, and edema (1, 2). The diagnosis is clinical and typically confirmed through laboratory tests demonstrating nephrotic-range proteinuria and associated biochemical abnormalities (3). The annual incidence of pediatric NS ranges from 2 to 7 per 100,000 children, with higher rates observed in Asian populations (4). Most cases are idiopathic and respond to corticosteroid therapy (5, 6); however, a substantial subset—particularly those with steroid-resistant nephrotic syndrome (SRNS) or frequent relapses—require prolonged immunosuppressive treatment (7, 8). While kidney function often remains preserved in the short term, NS and its treatments may have systemic consequences, including increased risk of infections (9-11), thromboembolism (12), and cardiovascular complications (13, 14). Accumulating evidence suggests that children with NS may experience early vascular changes, even in the absence of overt cardiovascular disease (15), highlighting the need for sensitive markers of subclinical atherosclerosis in this population (16).

Carotid intima-media thickness (cIMT) is a non-invasive, ultrasound-based measurement of the thickness of the intimal and medial layers of the carotid artery wall (17). It is widely used as a surrogate marker of subclinical atherosclerosis and has been shown to predict future cardiovascular events in adults (18). In children, cIMT is increasingly recognized as an early indicator of vascular remodeling and endothelial dysfunction, especially in those with chronic conditions such as diabetes, obesity, and kidney disease (19, 20). Several mechanisms may link NS to increased cIMT, including persistent dyslipidemia, hypertension, systemic inflammation, endothelial injury, and oxidative stress—all of which may promote early atherogenesis (13, 15). Despite growing interest, studies examining cIMT in children with NS have yielded inconsistent results, likely due to variations in sample size, disease duration, treatment status, and adjustment for confounders (21-33). Therefore, this meta-analysis aimed to quantitatively synthesize available evidence comparing cIMT between children with NS and healthy controls, and to explore whether study-level characteristics such as age, sex, disease duration, and steroid resistance contribute to observed heterogeneity.

MATERIALS AND METHODS

This study followed the PRISMA 2020 (34, 35) and Cochrane Handbook guidelines (36) for conducting systematic reviews and meta-analyses, covering study design, data collection, statistical methods, and interpretation of results. The protocol was also registered in PROSPERO under the ID CRD420251102090.

Database search

To identify studies pertinent to this meta-analysis, we searched PubMed, Embase, and Web of Science databases using an extensive array of search terms, which involved the combined terms of (1) carotid intima media thickness" OR "carotid intima-media thickness" OR "CIMT"; (2) "children" OR "pediatric" OR "paediatric"; and (3) "nephrotic syndrome" OR "nephrosis". The search was restricted to studies on human subjects and included only full-length articles published in English in peer-reviewed journals. We also manually checked the references of related original and review articles to find additional relevant studies. The search covered all records from database inception up to May 22, 2025. The full search strategy for each database is shown in **Supplemental File 1**. We restricted the search to peer-reviewed English-language studies to ensure methodological quality and data completeness; grey literature was excluded because it is often not peer-reviewed and may provide insufficient methodological details for reliable meta-analysis. Search results from all databases were exported and combined in EndNote; duplicate records were automatically identified and manually verified before screening to ensure accurate study selection.

Study eligible criteria

We applied the PICOS framework to define the inclusion criteria:

P (patients): Children (aged < 18 years) diagnosed with NS (including idiopathic, steroid-sensitive, or steroid-resistant types), regardless of sex, ethnicity, or disease duration.

I (exposure): Diagnosis of NS, either active or in remission, as the primary exposure group.

C (comparison): Healthy controls or children without NS.

O (outcome): cIMT, measured via ultrasound as per the protocol of the original studies. Studies must report mean and standard deviation (or sufficient data to calculate them) for cIMT in both groups.

S (study design): Observational studies, including cross-sectional, case-control, or cohort studies.

We excluded reviews, editorials, other meta-analyses, preclinical studies, studies not including patients with NS or controls without NS, studies that involving adult patients, studies that did not assess cIMT, or those that did not report the data of interest. If studies had overlapping populations, we included the one with the largest sample size in the meta-analysis.

Study quality evaluation

Two authors independently performed the literature search, study selection, quality assessment, and data extraction. Inter-reviewer agreement for study selection and quality assessment was assessed using Cohen's κ statistic, with disagreements resolved through discussion with the corresponding author. Study quality was assessed using the Newcastle–Ottawa Scale (NOS) (37), which rates selection, control of confounders, and outcome evaluation. Scores range from 1 to 9, with scores of 7 or higher considered good quality.

Data collection

The data collected for analysis included the study details (author, year, country, and design), patient characteristics (number of children with NS, duration of the disease, proportions of frequent relapser and steroid resistant NS), control characteristics (characteristics of controls, and number of controls in each study), mean age, sex distribution, and mean body mass index (BMI) of overall included children, methods for evaluating cIMT, and covariates matched or adjusted in when the association between NS and cIMT in children was analyzed.

Statistical analysis

The difference between cIMT between children with NS and healthy controls was summarized as difference (MD) with 95% confidence interval (CI) (36). Heterogeneity was assessed using the Cochrane Q test and I^2 statistic (38), with a p value < 0.10 suggesting significant heterogeneity and I^2 values of < 25%, 25–75%,

and > 75% indicating low, moderate, and high heterogeneity. A random-effects model using DerSimonian–Laird (DL) approach was used to pool the data, accounting for heterogeneity between studies (36). To further validate the reliability of the results, a sensitivity analysis with the Restricted Maximum Likelihood (REML) approach was also performed (36). τ^2 was reported as generated by RevMan, which provides values with limited decimals and may round to 0.00; this limitation was acknowledged to prevent misinterpretation. In addition, we calculated 95% prediction intervals (PIs) for the primary analysis using the formula $\hat{\mu} \pm t_{0.975}$, $df=k-2 \times \sqrt{(\tau^2+SE^2)}$, where k is the number of datasets (39). PIs provide an estimate of the likely range of effects in future comparable studies (39). Sensitivity analyses were performed by removing one study at a time. In addition, sensitivity analysis limited to studies with NOS ≥ 8 was also performed. Predefined subgroup analyses were conducted based on mean ages of the patients, proportion of males, disease duration, and whether other factors contributing to atherosclerosis such as obesity (reflected as BMI), blood pressure (BP), or lipids profile was adjusted. Medians of continuous variables were used to divide subgroups evenly. Univariate meta-regression analysis was performed to investigate if the difference of cIMT could be significantly affected by study characteristics in continuous variables, such as age, proportion of males, disease duration, or proportion of children with SRNS (36). Multivariable meta-regression was not performed because the limited number of studies and non-significant findings in univariate analyses would preclude reliable estimation and risk overfitting. For outcomes involving at least 10 datasets, publication bias was assessed using funnel plots and visual inspection for asymmetry, along with Egger's test (40). Potential small-study effects were further examined using the trim-and-fill method, which estimates the number of potentially missing studies due to publication bias and recalculates the pooled effect size after adjusting for these studies (36). All analyses were performed using RevMan (Version 5.4; Cochrane Collaboration, Oxford, UK) and Stata (Version 17.0; Stata Corporation, College Station, TX, USA).

RESULTS

Study inclusion

The study selection process is shown in **Figure 1**. We first identified 94 records from the three databases. After removing 21 duplicates, 73 articles were screened by title

and abstract. Of these, 51 were excluded for not meeting the aims of the meta-analysis. The full texts of the remaining 22 articles were reviewed by two independent authors, and nine were excluded for various reasons (see **Figure 1**). In the end, 13 studies were included in the quantitative analysis (21-33). The κ statistic for inter-reviewer agreement in study selection and quality assessment was 0.83, indicating good consistency between reviewers.

Summary of study characteristics

Table 1 summarizes the characteristics of the 13 studies included in this meta-analysis (21-33). All studies employed a cross-sectional case-control design and were published between 2013 and 2024. These studies were conducted in diverse countries, including Iran, Turkey, India, Saudi Arabia, the UK, Poland, Serbia, and Egypt. For the four Egyptian studies (28-30, 32), we confirmed from the original reports that they were conducted at different centers with distinct recruitment periods and ethics approvals, ensuring independent cohorts. The number of children with NS in each study ranged from 8 to 81 (total: 578), with disease duration spanning 1.0 to 7.9 years. Several studies reported the proportion of frequent relapsers (ranging from 20% to 75%) and steroid-resistant patients (4.5% to 100%). Control groups were generally composed of healthy children, except for one study that recruited children with a history of urinary tract infection (UTI) (21). Control sample sizes ranged from 20 to 150 participants (total: 741). The mean age of participants across studies varied from 7.5 to 13.6 years, and the percentage of male participants ranged from 47.5% to 68.5%. Mean BMI was reported in eight studies (24-26, 29, 33), with means ranging from 15.7 to 21.1 kg/m². The cIMT was evaluated in all studies using B-mode ultrasound. Most studies measured the far wall of the common carotid artery with probe frequencies ranging from 5 to 13 MHz, while a few studies also included the carotid bulb or internal carotid artery (**Supplementary Table 1**). Twelve studies adjusted or matched for age and sex (21, 23-33), while many also accounted for BMI, blood pressure, lipid profiles, or proteinuria to a varying degree (21, 23, 25-31). **Table 2** presents the quality assessment of the included studies using the NOS. Total NOS scores ranged from 7 to 9, indicating high methodological quality. Eleven studies received the maximum score of 8 or 9, reflecting good selection of cases and controls, proper adjustment for confounders, and reliable exposure assessment (21-24, 26-31,

33). The most commonly missing criterion was adjustment for confounders beyond age and sex.

Difference of cIMT between children with NS and controls

The pooled results of 13 studies (21-33) using a random-effects model of DL approach showed that overall, children with NS were associated with a higher cIMT as compared to controls (MD: 0.06 mm, 95% CI: 0.04 to 0.08, $p < 0.001$; **Figure 2**) with significant heterogeneity (p for Cochrane Q test < 0.001, $I^2 = 68\%$). The 95% PIs for the primary analysis was -0.01 to 0.13 mm, indicating that while most future studies are expected to show a positive association, variability across settings could yield near-null effects. In addition, a sensitivity analysis with the REML approach also showed similar results (MD: 0.06 mm, 95% CI: 0.04 to 0.08, $p < 0.001$; $I^2 = 76\%$; **Supplemental Figure 1**). Sensitivity analyses were performed by removing one study at a time, including each Egyptian dataset, and the results remained stable (MD: 0.05 to 0.06 mm, p all < 0.05), indicating no single study disproportionately influenced the overall estimate. Specifically, the sensitivity analysis excluding the only study using children with history of UTI as controls (21) showed similar results (MD: 0.06 mm, 95% CI: 0.04 to 0.08, $p < 0.001$; $I^2 = 71\%$). In addition, the sensitivity analysis limited to studies with NOS ≥ 8 (21-24, 26-31, 33) also showed similar results (MD: 0.05 mm, 95% CI: 0.03 to 0.08, $p < 0.001$; $I^2 = 68\%$). Subgroup analyses indicated that the results were similar for studies of children < and ≥ 9 years (MD: 0.05 vs. 0.07 mm, p for subgroup difference = 0.41; **Figure 3A**). Interestingly, a more remarkably higher cIMT was observed in population of male ≥ 60% as compared to that of male < 60% (MD: 0.09 vs. 0.03 mm, p for subgroup difference = 0.01; **Figure 3B**). The results were consistent for children with the duration of NS < and ≥ 3 years (MD: 0.07 vs. 0.05 mm, p for subgroup difference = 0.66; **Figure 4A**). Further subgroup analyses showed similar results between studies with and without adjustment of BMI (MD: 0.05 vs. 0.08 mm, p for subgroup difference = 0.30; **Figure 4B**), BP (MD: 0.08 vs. 0.04 mm, p for subgroup difference = 0.09; **Figure 5A**), and lipids profile (MD: 0.08 vs. 0.05 mm, p for subgroup difference = 0.31; **Figure 5B**). Finally, results of univariate meta-regression analysis in **Table 3** suggest that mean age, male proportion, disease duration, and SRNS proportion were not significant modifiers (all $p > 0.05$), although male proportion and SRNS showed might explanation of heterogeneity (adjusted $R^2 = 29.8\%$ and 22.5%, respectively). Given the small number of studies

and limited power, these results should be interpreted as exploratory rather than conclusive.

Publication bias

Funnel plots for the meta-analysis comparing cIMT between children with NS and controls are shown in **Figure 6**. Although the plots appeared symmetrical and Egger's test showed no evidence of publication bias ($p = 0.51$), the statistical power of these tests is limited with only 13 studies. Moreover, the trim-and-fill method did not impute additional studies, and the pooled MD remained essentially unchanged (MD: 0.06 mm; 95 % CI: 0.04–0.08; $p < 0.001$), suggesting that small-study effects were unlikely to materially influence the results.

DISCUSSION

This meta-analysis provides pilot evidence that children with NS exhibit increased cIMT compared to their healthy peers, highlighting a potential link between NS and early vascular changes. While subclinical atherosclerosis has been extensively studied in adults with chronic kidney disease, our findings underscore that such vascular alterations may begin as early as childhood in patients with NS. This aligns with growing concerns about the long-term cardiovascular risks associated with chronic glomerular diseases and supports the inclusion of vascular health monitoring in pediatric nephrology. Our results further indicate that specific clinical features, such as male predominance and a higher proportion of SRNS, may partially explain variability in cIMT outcomes across studies, suggesting potential high-risk subgroups for early intervention.

Our findings align with the recent 4C Study (41), which demonstrated a significant longitudinal increase in cIMT in children with chronic kidney disease and highlighted the influence of blood pressure dynamics on vascular progression, underscoring the importance of early cardiovascular risk assessment in pediatric kidney disorders.

Several mechanisms may contribute to increased cIMT in children with NS. From a pathophysiological perspective, persistent proteinuria and hypoalbuminemia can lead to systemic inflammation and oxidative stress (42, 43), both of which contribute to endothelial dysfunction and arterial wall remodeling (44, 45). Hyperlipidemia—a hallmark of NS—is another key contributor, as elevated LDL-C and triglycerides can promote lipid deposition within vessel walls (46). Additionally, NS is frequently

associated with hypertension and volume overload, which may increase shear stress and stimulate intima-media thickening (47). Treatment-related factors, particularly prolonged corticosteroid or calcineurin inhibitor use, may exacerbate cardiovascular risk by promoting insulin resistance, hypertension, or dyslipidemia (48). Notably, recent work has linked interleukin-6 polymorphisms with increased cIMT in children (49), supporting the hypothesis that inflammatory signaling pathways contribute to endothelial dysfunction and vascular remodeling in pediatric kidney disease. Clinically, repeated relapses and frequent exposure to immunosuppressive agents may further compound vascular stress (50). These intertwined mechanisms provide a biologically plausible basis for the observed association between NS and increased cIMT.

Our subgroup and meta-regression analyses offer important insights into sources of heterogeneity and potential effect modifiers. Notably, studies with ≥ 60% male participants demonstrated a significantly larger cIMT difference compared to studies with < 60% males, suggesting sex-based differences in vascular vulnerability or hormonal influence on endothelial function. This is consistent with a previous report, which showed that boys are likely to have adverse changes in vascular health earlier than the age-matched girls (51). Although not statistically significant, a similar trend was observed for studies with a higher proportion of SRNS patients, who typically experience more severe and treatment-resistant disease. Meta-regression showed that male proportion and SRNS rate explained 29.8% and 22.5% of between-study heterogeneity, respectively, indicating their potential relevance despite limited power for detecting significance. On the other hand, subgroup analyses by age, disease duration, and adjustment for BMI, blood pressure, or lipid profile showed no significant differences, implying that the association between NS and cIMT may be relatively consistent across various pediatric subgroups, or that existing studies lacked sufficient granularity to detect these differences. Of note, these subgroup analyses were based on study medians to maintain statistical balance, as no universally accepted cutoffs exist for variables such as age or male proportion. Accordingly, the findings should be regarded as exploratory and hypothesis-generating rather than conclusive.

The strengths of this meta-analysis include a comprehensive literature search across multiple databases, rigorous inclusion criteria, and robust statistical methods, including sensitivity, subgroup, and meta-regression analyses. All included studies

employed ultrasound-based assessment of cIMT, ensuring methodological consistency in outcome measurement. Furthermore, the majority of studies were rated as high quality using the NOS, suggesting a low risk of bias in study design and reporting. However, several limitations should be acknowledged. First, all included studies were cross-sectional, precluding conclusions about the temporal or causal relationship between NS and early vascular remodeling. Future prospective cohort studies or longitudinal ultrasound investigations are warranted to clarify whether increased cIMT precedes clinical cardiovascular events and to explore the dynamics of vascular changes over time. Second, although most studies adjusted for key confounders such as age and sex, the extent of adjustment for other cardiovascular risk factors—such as lipid levels, BP, physical activity, and socioeconomic status—varied widely or was not reported in detail. In addition, early-life (52) and maternal characteristics (53)—such as maternal health conditions, pregnancy complications, and birth parameters—are known to affect vascular phenotypes in offspring, but these factors were not consistently reported across included studies and could not be accounted for in our analysis. Importantly, we did not compare the pooled cIMT difference with age-specific normative values or express it as a percentage of normal childhood cIMT because of the heterogeneity in age, ethnicity, and baseline vascular characteristics across included studies and the absence of standardized pediatric thresholds, which limits meaningful interpretation of absolute cIMT differences in clinical practice. Third, analyses were based on aggregated study-level data rather than individual participant data, limiting the ability to assess within-study interactions or perform detailed stratification by disease phenotype, treatment duration, or comorbidity burden. Moreover, subgroup cut-points were median-based to maintain statistical balance across limited datasets rather than reflecting established clinical thresholds, which may affect the interpretability of subgroup differences. Fourth, heterogeneity remained moderate despite subgrouping and regression analyses, indicating that unmeasured factors may still influence the observed associations. The addition of a 95% PI (–0.01 to 0.13 mm) provides further context for between-study variability. While the lower bound approached the null, the interval remained centered on a positive effect, consistent with our pooled estimate. This suggests that most future studies would likely demonstrate increased cIMT in children with NS, although small or heterogeneous studies may yield attenuated associations. The width of the PI underscores the importance of larger, prospective studies to refine effect estimates.

Furthermore, although funnel plots and Egger's test suggested no major publication bias, these methods have limited power with fewer than 20 studies, and results should therefore be interpreted cautiously. Additionally, the small sample sizes of individual studies may have reduced the precision of effect estimates and limited the ability to standardize results across diverse populations. Moreover, our search was limited to PubMed, Embase, and Web of Science, which are the largest biomedical databases. Although this approach aligns with PRISMA 2020 recommendations, it may have missed studies indexed exclusively in other platforms such as Scopus or EBSCO, introducing a small risk of selection bias. In addition, restricting the search to English-language, peer-reviewed articles and excluding grey literature may have omitted some relevant studies, although this approach is commonly used to maintain methodological rigor and data reliability. Finally, considerable heterogeneity in cIMT measurement protocols existed across studies, including differences in arterial segment selection, probe frequency, and caliper placement, which we could not account for in subgroup analyses due to incomplete reporting.

From a clinical perspective, even modest increases in cIMT during childhood may be meaningful. In adult populations, cIMT differences as small as 0.01–0.02 mm have been associated with elevated cardiovascular risk (54). In our analysis, the mean difference of 0.06 mm between children with NS and controls represents a potentially clinically significant early vascular change, particularly considering the young age of the populations studied (55). These findings underscore the importance of cardiovascular risk monitoring in pediatric NS, especially in patients with SRNS or those with prolonged disease courses. Although adult studies suggest that small absolute increases in cIMT may carry prognostic significance, the clinical relevance of a 0.06 mm difference in children remains difficult to quantify. Because of heterogeneity in age, ethnicity, and measurement protocols across studies, we could not reliably express the pooled difference as a percentage of normative pediatric cIMT or in terms of standardized z-scores. This highlights the urgent need for large normative datasets and standardized pediatric reference values to facilitate clinical interpretation. Clinicians should consider incorporating non-invasive vascular assessments, such as cIMT measurement, into routine follow-up protocols for high-risk children with NS. Moreover, pediatric cIMT assessment lacks standardized protocols and percentile-based reference values, which limits comparability across studies. It has been emphasized in previous studies that there is an urgent need for

standardization of pediatric cIMT evaluation to facilitate reliable interpretation and clinical translation (56). Moreover, optimizing management of modifiable cardiovascular risk factors—such as BP, lipid levels, and obesity—should be a key priority in this population. Future research should focus on prospective, longitudinal studies to clarify the temporal relationship between NS and vascular remodeling. Individual participant data meta-analyses or large cohort studies may help identify which subgroups of children with NS are at greatest cardiovascular risk and determine the clinical utility of cIMT monitoring in guiding therapeutic decisions. Additionally, mechanistic studies are needed to explore the interplay between inflammation, endothelial dysfunction, and treatment effects in driving vascular changes. Interventional trials evaluating the impact of lipid-lowering agents, antihypertensives, or lifestyle modifications on vascular outcomes in pediatric NS could also provide valuable clinical guidance.

CONCLUSION

In conclusion, this meta-analysis demonstrates that children with NS have significantly increased cIMT compared to controls, suggesting early vascular remodeling and heightened cardiovascular risk. The association appears to be stronger in populations with a higher proportion of males and those with SRNS. These findings emphasize the importance of early cardiovascular assessment and risk factor management in children with NS, and call for longitudinal research to elucidate long-term clinical implications.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included observational studies

Study	Country	Design	No. of children with NS	Duration of NS (years)	Frequent relapser (%)	Steroid resistant (%)	Source of controls	No. of controls	Mean age (years) of overall children	Male (%) of overall children	Mean BMI of overall children (kg/m2)	Methods for evaluating cIMT	Variables matched or adjusted
Hooman 2013	Iran	CC	51	2.0	49.0	32.7	Children with history of UTI	75	7.9	58.7	17.2	B-mode Ultrasound, average of bilateral	Age, sex, proteinuria, and SBP/DBP
Candan 2014	Turkey	CC	37	7.9	NR	100.0	Healthy children	22	13.6	47.5	20.6	B-mode Ultrasound, average of bilateral	Age, BMI, proteinuria, ferritin, and LDL-C
Rahul	India	CC	32	5.3	25.1	18.8	Health	32	9.0	54.7	15.7	B-mode	Age, sex,

2015							y childre n					Ultrasound , average of bilateral	BMI, and MDA
Kari 2017	Saudi Arabia, Australi a, UK	CC	8	3.4	NR	100.0	Health y childre n	40	12.0	52.1	NR	B-mode Ultrasound , average of bilateral	Age and sex
Skrzypc zyk 2019	Poland	CC	50	6.4	44.6	26.0	Health y childre n	20	9.5	64.5	NR	B-mode Ultrasound , average of bilateral	Age, sex, and BMI
Mehta 2019	India	CC	66	2.4	24.2	4.5	Health y childre n	128	7.5	59.7	NR	B-mode Ultrasound , average of bilateral	Age, sex, BMI categories, and blood pressure
Paripovi c 2020	Serbia	CC	40	6.4	37.5	20.0	Health y childre n	20	12.0	65.5	21.1	B-mode Ultrasound , average of bilateral	Age, sex, BMI, and blood pressure
Ahmed 2021	Egypt	CC	81	3.6	NR	13.7	Health y	100	8.2	68.5	16.8	B-mode Ultrasound	Age, sex, BMI, blood

							childre n					, average of bilateral	pressure, and lipid profile
Kamel 2022	Egypt	CC	40	3.2	75.0	25.0	Health y childre n	30	7.8	67.0	17	B-mode Ultrasound , average of bilateral	Age, sex, BMI, hypertension, and dyslipidemia
Al Sharaw y 2022	Egypt	CC	20	1.0	20.0	20.0	Health y childre n	25	9.0	60.0	NR	B-mode Ultrasound , average of bilateral	Age, sex, hypertension, dyslipidemia
Das 2024	India	CC	33	2.9	73.0	12.0	Health y childre n	39	8.6	59.0	16.1	B-mode Ultrasound , average of bilateral	Age, sex, BMI and dyslipidemia.
Elsehma wy 2024	Egypt	CC	60	2.9	NR	36.7	Health y childre n	60	9.7	65.0	20.7	B-mode Ultrasound , average of bilateral	Age and sex
Esfandi ar 2024	Iran	CC	60	1.0	NR	NR	Health y	150	8.0	50.9	NR	B-mode Ultrasound	Age and sex

							childre n					, average of bilateral	

Abbreviations: NS: Nephrotic syndrome; CC: Case-control; UTI: Urinary tract infection; BMI: Body mass index; cIMT: Carotid intima-media thickness; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low-density lipoprotein cholesterol; MDA: Malondialdehyde; NR: Not reported.

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale

Study	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for age and sex	Control for other confounders	Exposure ascertainment	Same methods for events ascertainment	Non-response rates	Total
Hooman 2013	1	1	1	1	1	1	1	1	1	9
Candan 2014	1	1	1	1	0	1	1	1	1	8
Rahul 2015	1	1	1	1	1	1	1	1	1	9
Kari 2017	1	1	1	1	1	0	1	1	1	8
Skrzypczyk 2019	1	0	1	1	1	1	1	1	1	8
Mehta 2019	1	0	0	1	1	1	1	1	1	7
Paripovic 2020	1	0	1	1	1	1	1	1	1	8
Ahmed 2021	1	0	1	1	1	1	1	1	1	8
Kamel 2022	1	1	1	1	1	1	1	1	1	9
Al Sharawy	1	1	1	1	1	1	1	1	1	9

2022										
Das 2024	1	0	1	1	1	1	1	1	1	8
Elsehmawy 2024	1	0	1	1	1	0	1	1	1	7
Esfandiar 2024	1	1	1	1	1	0	1	1	1	8

Table 3. Results of univariate meta-regression analysis

Variables	MD in the difference of cIMT between children with NS and controls			
	Coefficient	95% CI	*p* values	Adjusted R^2
Mean age (years)	0.00030	-0.01721 to 0.01780	0.97	0%
Male (%)	0.0033	-0.0011 to 0.0076	0.13	29.8%
Duration of disease (years)	-0.0056	-0.0199 to 0.0086	0.41	0%
Steroid resistant (%)	0.000090	-0.001041 to 0.001220	0.87	22.5%

Abbreviations: MD: Mean difference; CI: Confidence interval; cIMT: Carotid intima-media thickness.

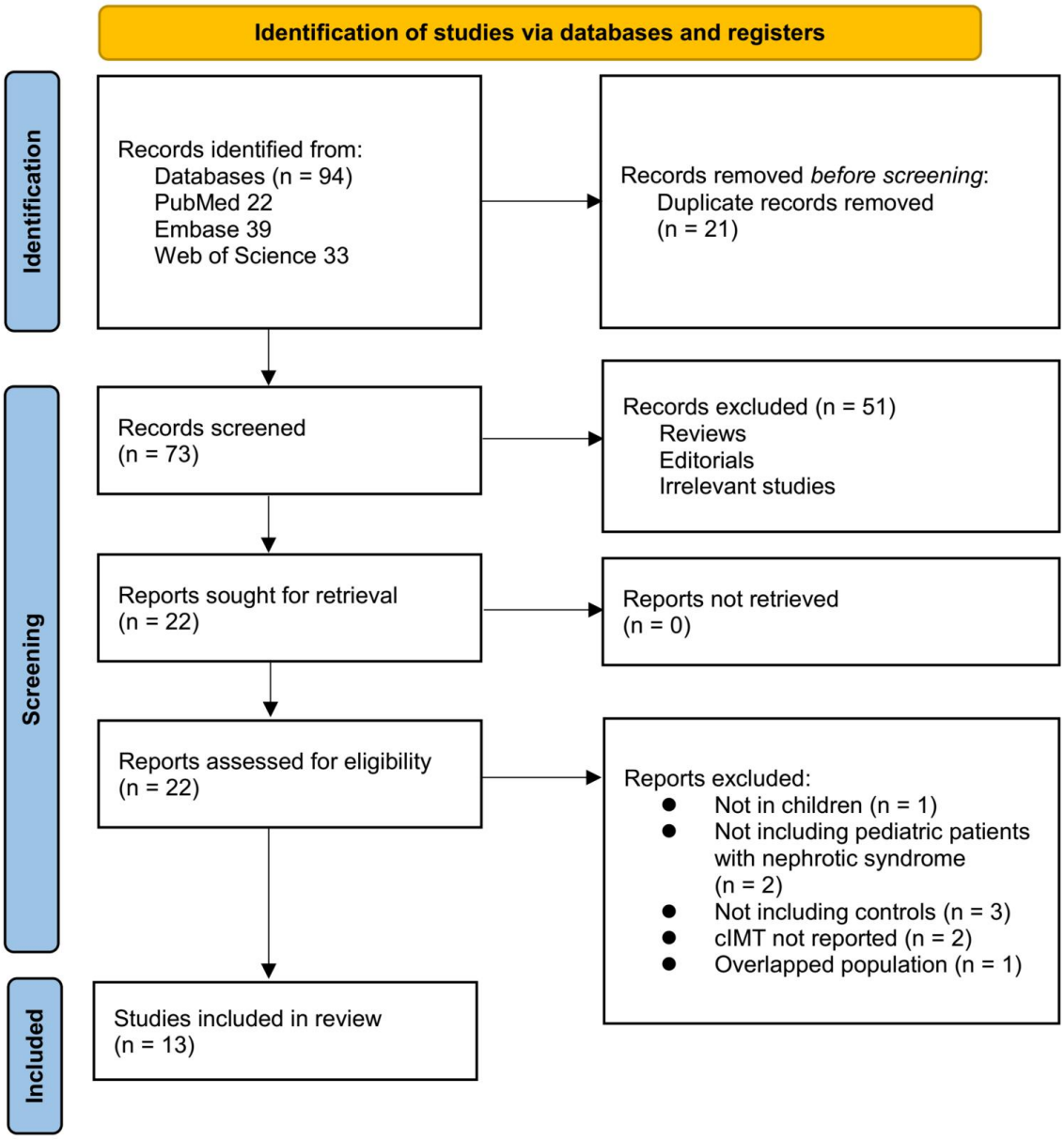

Figure 1. Flowchart of database search and study inclusion. The excluded record with overlapped population was Brachial Artery Flow-mediated Dilatation and Carotid Intima-Media Thickness in Children With Idiopathic Nephrotic Syndrome (Clin Exp Nephrol. 2015;19(1):125–132; PMID: 30595562), which overlapped with the cohort subsequently reported in Assessment of Atherosclerosis in Children with Nephrotic Syndrome (NeuroQuantology. 2022;20(6):8315–8328). The latter study with more complete data was retained.

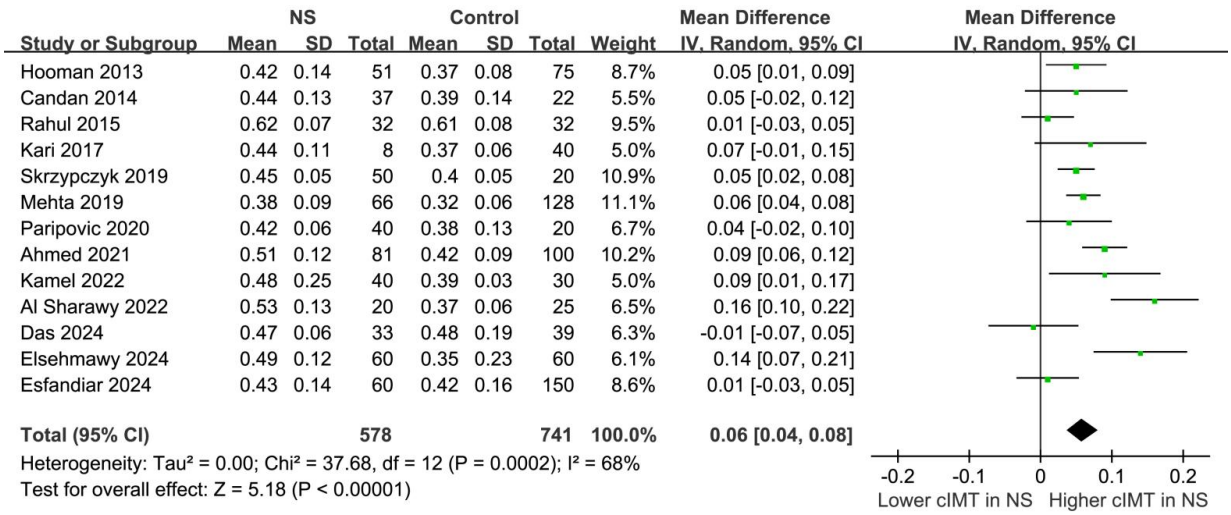

Figure 2. Forest plots for the meta-analysis of the difference of cIMT between children with NS and controls. Children with NS had significantly higher cIMT (MD: 0.06 mm, 95% CI: 0.04 – 0.08, $p < 0.001$) with significant heterogeneity (I^2 = 68%). The 95% prediction interval was – 0.01 to 0.13 mm. Abbreviations: cIMT: Carotid intima-media thickness; NS: Nephrotic syndrome; MD: Mean difference; CI: Confidence interval; I^2: Inconsistency index.

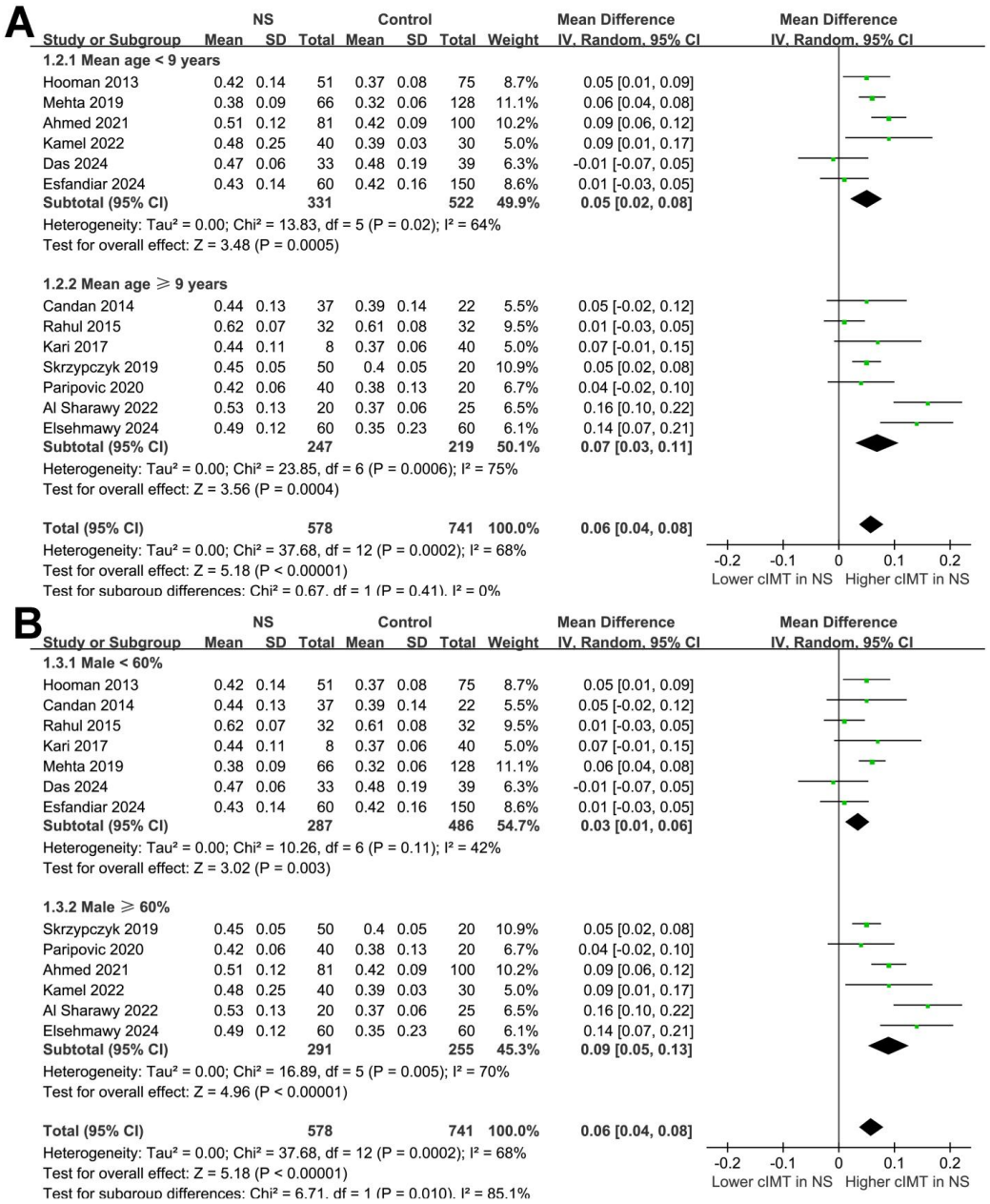

Figure 3. Forest plots for the subgroup analyses of the difference of cIMT between children with NS and controls. (A) Subgroup analysis according to the mean ages of the children; (B) Subgroup analysis according to the proportion of males. Abbreviations: NS: Nephrotic syndrome; SD: Standard deviation; CI: Confidence interval; IV: Inverse variance; cIMT: Carotid intima–media thickness.

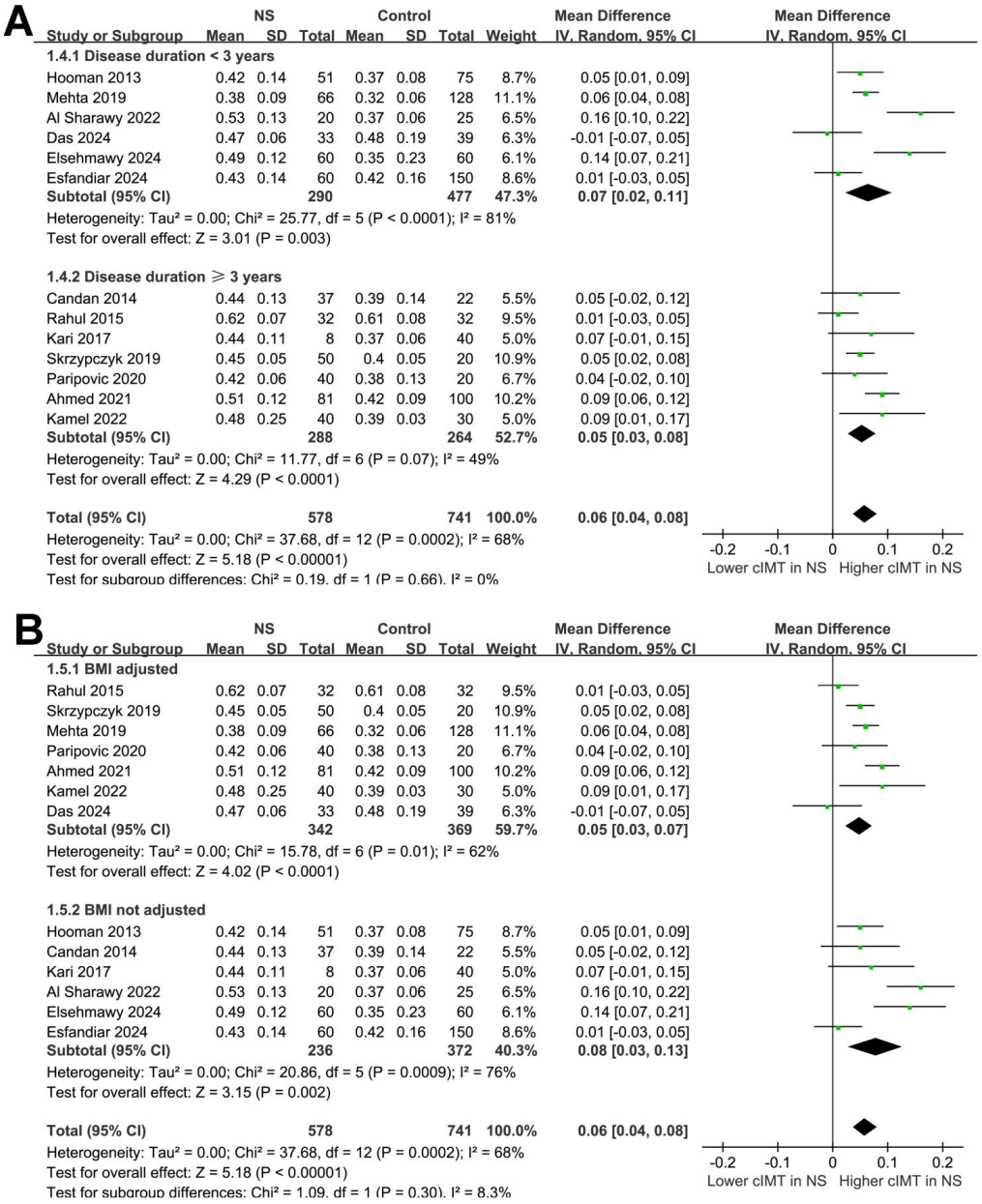

Figure 4. Forest plots for the subgroup analyses of the difference of cIMT between children with NS and controls. (A) Subgroup analysis according to the duration of NS; (B) Subgroup analysis according to whether BMI was adjusted. Abbreviations: NS: Nephrotic syndrome; SD: Standard deviation; CI: Confidence interval; IV: Inverse variance; cIMT: Carotid intima–media thickness; BMI: Body mass index.

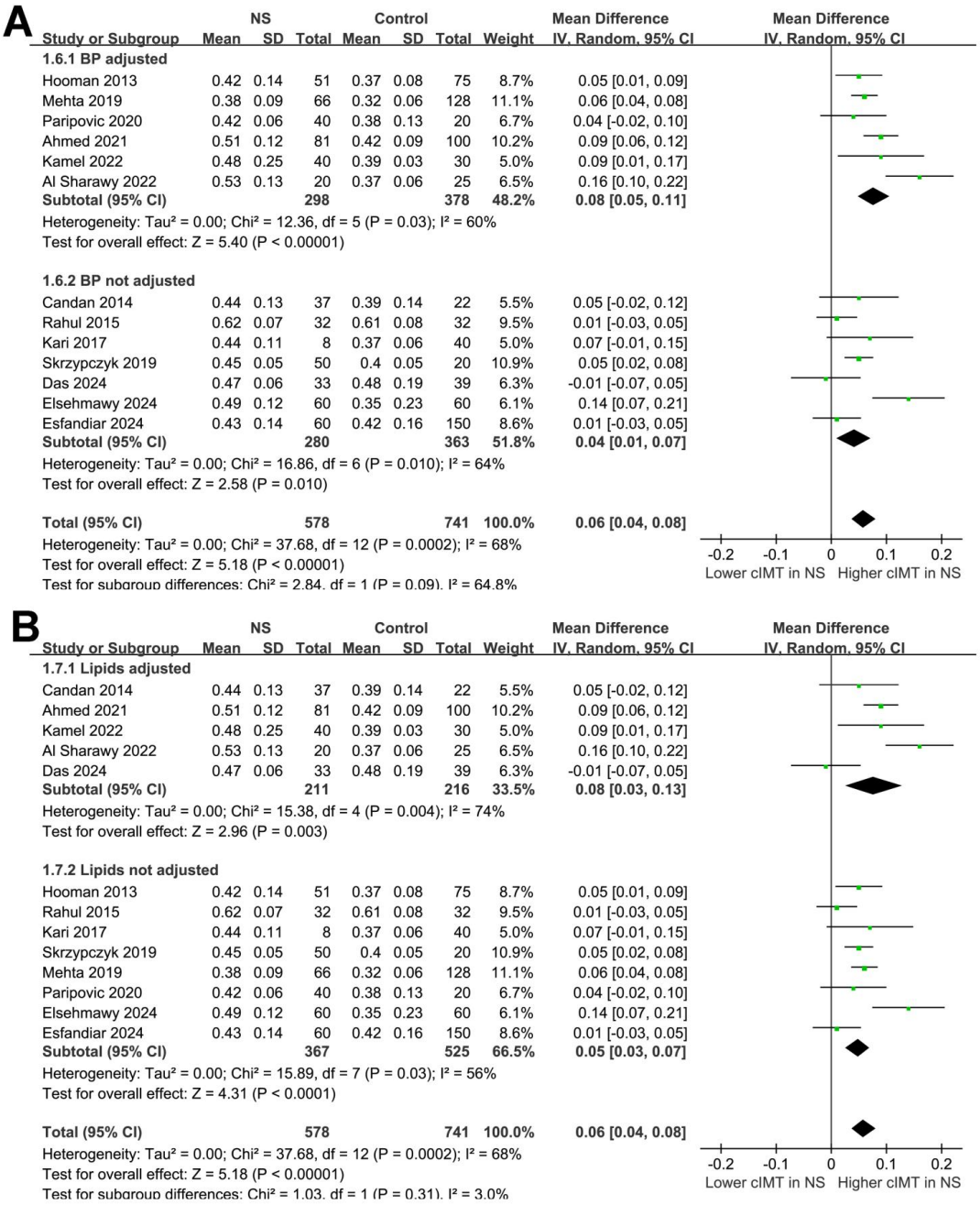

Figure 5. Forest plots for the subgroup analyses of the difference of cIMT between children with NS and controls. (A) Subgroup analysis according to whether BP was adjusted; (B) Subgroup analysis according to whether lipid profile was adjusted. Abbreviations: NS: Nephrotic syndrome; SD: Standard deviation; CI: Confidence interval; IV: Inverse variance; cIMT: Carotid intima–media thickness; BP: Blood pressure.

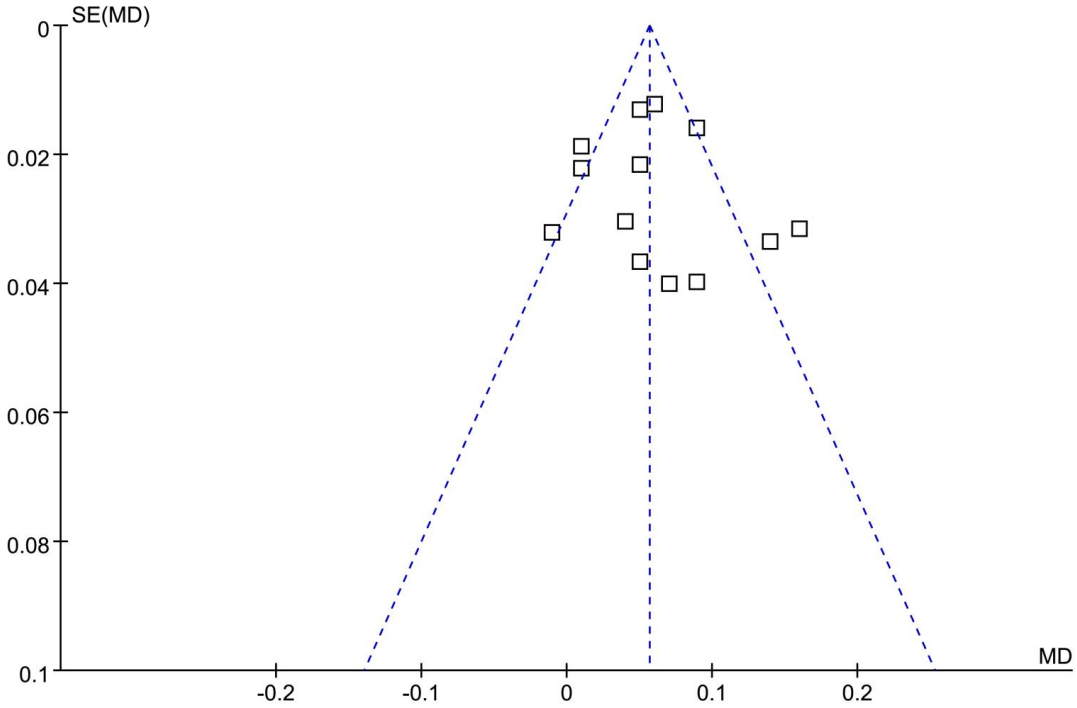

Figure 6. Funnel plots for estimating the potential publication biases underlying the meta-analysis of the difference of cIMT between children with NS and controls. Egger's test $p = 0.51$. The plots appeared symmetrical, with no evidence of publication bias; the trim-and-fill method did not add studies, and the pooled MD remained unchanged. Abbreviations: NS: Nephrotic syndrome; cIMT: Carotid intima–media thickness; MD: Mean difference.

SUPPLEMENTAL DATA

Supplemental data are available at the following link:

https://www.bjbms.org/ojs/index.php/bjbms/article/view/12935/4007