Current Clinical and Medical Education

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DOI: https://doi.org/xx.xxx/xxx.xx
Curr Clin Med Educ 4 (2), 339—355 (2026)
Received 22 Mar 2026 | **Revised** 19 Apr 2026 | **Accepted** 29 May 2026 | **Online Available** 15 June 2026

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OPEN ACCESS

ISSN (O) 3023-3593 | (Print: 3023-3585)

ORIGINAL RESEARCH ARTICLE

Comparative Performance of the Matsuda Index versus HOMA-IR for Detecting Insulin Resistance in Vitamin D-Deficient Prepubertal Children with Obesity: A Systematic Review

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Abstract

Background Childhood obesity is strongly associated with insulin resistance (IR), a precursor to type 2 diabetes and cardiovascular disease. Vitamin D deficiency is highly prevalent in obese children and may exacerbate IR. The Matsuda index (OGTT-derived, whole-body) and HOMA-IR (fasting-based, primarily hepatic) are commonly used surrogates, yet their comparative performance in vitamin D-deficient prepubertal obese children remains unclear.

Objective To systematically review the comparative performance of the Matsuda index versus HOMA-IR for detecting IR in this specific high-risk population.

Methods A systematic literature search was conducted in PubMed, Embase, and Scopus (January 2015–June 2026) following PRISMA 2020 guidelines. Eligible studies reported both indices in obese children, with preference for vitamin D data or prepubertal stratification. Risk of bias was assessed using the Newcastle-Ottawa Scale, and certainty of evidence was evaluated using GRADE. Due to heterogeneity, a narrative synthesis was performed.

Results Seven published studies (n = 7) met inclusion criteria. No study directly and exclusively compared both indices in strictly prepubertal, vitamin D-deficient obese children. The Matsuda index showed stronger associations with vitamin D status, higher sensitivity for metabolically unhealthy obesity, and more stable performance across pubertal stages compared with HOMA-IR. However, direct head-to-head diagnostic accuracy data (ROC/AUC) in the target population were absent. Overall certainty of evidence was rated Low by GRADE, primarily due to indirectness and heterogeneity.

Conclusions Available evidence suggests potential advantages of the Matsuda index, but robust comparative data specifically in vitamin D-deficient prepubertal obese children are lacking. High-quality primary studies targeting this population are urgently needed to strengthen the evidence base and guide clinical practice.

Key words: HOMA-IR, insulin resistance, vitamin D deficiency, prepubertal obesity

1 | INTRODUCTION

Childhood obesity continues to rise worldwide and now represents one of the most pressing paediatric health concerns. Excess adiposity in children is strongly linked to the early development of insulin resistance, which in turn increases the lifetime risk of type 2 diabetes, metabolic syndrome and cardiovascular complications. (1, 2) Because these metabolic disturbances often begin well before

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Supplementary information The online version of this article contains supplementary material, which is available to authorized users.

puberty, there is growing interest in identifying reliable methods to detect insulin resistance at younger ages.

Vitamin D deficiency is remarkably common in children with obesity. Sequestration of the vitamin within expanded adipose tissue, combined with reduced outdoor activity and therefore lower sun exposure, frequently results in suboptimal circulating levels. (3, 4) Several studies have shown that low vitamin D status is associated with poorer insulin sensitivity, although the strength of this relationship appears to vary according to the method used to assess insulin resistance. (5, 6)

Two surrogate indices are widely employed in clinical research and practice. The homeostasis model assessment of insulin resistance (HOMA-IR) is calculated from fasting glucose and insulin values and mainly reflects hepatic insulin resistance. Its simplicity makes it attractive for large-scale screening. (7) In contrast, the Matsuda index is derived from glucose and insulin concentrations measured during a standard oral glucose tolerance test and provides an estimate of whole-body insulin sensitivity that includes both hepatic and peripheral tissues. (8) Because it captures dynamic changes after a glucose load, the Matsuda index is sometimes regarded as more sensitive than fasting-based measures, particularly when peripheral insulin resistance is prominent or when additional metabolic factors such as vitamin D status are being evaluated. (9, 10)

Puberty itself induces a physiological reduction in insulin sensitivity, which complicates interpretation of data collected across mixed pubertal stages. (11) Consequently, findings obtained in adolescents may not be directly applicable to strictly prepubertal children. Despite increasing recognition of these issues, relatively few published studies have performed a direct head-to-head comparison of the Matsuda index and HOMA-IR specifically in vitamin D-deficient prepubertal children with obesity. Most existing work either combines different pubertal groups, omits vitamin D assessment, or reports only one of the two indices.

The present systematic review was therefore undertaken to synthesise the available evidence on the comparative performance of these two indices for detecting insulin resistance in this particular high-risk population. By focusing on published studies that report both the Matsuda index and HOMA-IR in obese children, with attention to vitamin D status and prepubertal age where available, the review aims to clarify the relative strengths of each index and to highlight areas where further targeted research is needed.

2 | MATERIALS AND METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. (12) The review protocol was developed a priori but was not registered in a public registry such as PROSPERO due to the focused and observational nature of the question.

Eligibility Criteria

Studies were considered eligible if they met the following criteria based on the PICO framework:

Population: Children and adolescents diagnosed with obesity (using age- and sex-specific BMI cut-offs such as $\geq$95th percentile or equivalent national references). Studies focusing exclusively on prepubertal children (Tanner stage 1 or age typically <10–12 years with documented prepubertal status) were prioritised. Mixed-age studies were included only if they provided separate data or subgroup analyses for prepubertal participants.

Exposure/Condition: Vitamin D deficiency or insufficiency, preferably defined using serum 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL (or study-specific cut-offs). Studies without vitamin D assessment were considered if they provided direct comparative data on the two indices in obese children.

Index Tests: Studies that reported both the Matsuda index (or equivalent whole-body insulin sensitivity index derived from OGTT) and HOMA-IR (or equivalent fasting-based index). Studies reporting only one index were excluded unless they offered relevant comparative context.

Outcomes: Primary outcomes included measures of comparative performance such as insulin resistance detection rates/prevalence using each index, correlation coefficients between each index and 25(OH)D levels, and any statistical comparisons (e.g., sensitivity, agreement, or regression analyses) between the two indices. Secondary outcomes included associations with other metabolic parameters (fasting insulin, lipid profile especially triglycerides, and glucose tolerance status).

Study Design: Observational studies (cross-sectional, cohort, or case-control) published in peer-reviewed journals. Interventional studies were included only if baseline comparative data on the indices were reported. Conference abstracts were considered only if sufficient methodological and outcome data were available.

Exclusion criteria were: studies conducted exclusively in adults or pubertal adolescents without prepubertal subgroup data; animal or in vitro studies; studies not reporting original data; and non-English publications without available translation.

Information Sources and Search Strategy

A comprehensive literature search was performed in PubMed/MEDLINE, Embase, and Scopus from January 2015 to June 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to “Matsuda index”, “HOMA-IR”, “insulin resistance”, “obesity”, “children”, “prepubertal”, and “vitamin D”. Boolean operators (AND, OR) were used to combine concepts. The full search string for PubMed was adapted for other databases. Reference lists of included studies and relevant reviews were hand-searched for additional eligible articles. Grey literature was not systematically searched.

Study Selection

All identified records were imported into reference management software and duplicates were removed. Two reviewers independently screened titles and abstracts against the eligibility criteria. Full-text articles of potentially relevant studies were retrieved and assessed independently by the same reviewers. Disagreements were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA 2020 flow diagram.

Data Extraction

A standardised data extraction form was developed and piloted. Extracted information included: study identification (author, year, journal, country), study design and setting, participant characteristics (sample size, age range/mean, pubertal status definition, obesity criteria, vitamin D status and assay method), details of insulin resistance assessment (OGTT protocol, formulas and cut-off values for Matsuda index and HOMA-IR), key outcome data (IR prevalence or mean values by each index, correlation coefficients with 25(OH)D, p-values, and any comparative statistical tests), and reported limitations or conflicts of interest. Data were extracted independently by two reviewers, with discrepancies resolved by consensus.

Quality Assessment (Risk of Bias)

The methodological quality of included observational studies was assessed using the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies. (13, 14) The adapted scale evaluates three domains: selection of participants (representativeness, sample size, non-response), comparability (control for confounding factors such as age, sex, and pubertal status), and outcome assessment (ascertainment of insulin resistance indices and vitamin D levels, and appropriateness of statistical analysis). Studies were awarded stars for each item, with a maximum possible score of 10. Studies scoring $\geq$7 stars were considered high quality, 5–6 stars moderate quality, and $\leq$4 stars low quality. Two reviewers performed the quality assessment independently.

Data Synthesis

Due to anticipated clinical and methodological heterogeneity (differences in age ranges, vitamin D cut-offs, OGTT protocols, and outcome reporting), a narrative synthesis was planned as the primary approach. Results were summarised descriptively, with emphasis on comparative performance metrics between the Matsuda index and HOMA-IR. Where sufficient homogeneous data were available (e.g., correlation coefficients between each index and 25(OH)D), random-effects meta-analysis was considered using appropriate software. Subgroup analyses were planned according to pubertal status (prepubertal only vs mixed), geographic region, and vitamin D deficiency severity if data permitted. Heterogeneity was to be assessed using the I^2 statistic and visual inspection of forest plots. Sensitivity analyses excluding low-quality studies were planned where applicable. Publication bias was to be evaluated using funnel plots and Egger’s test if at least 10 studies were included in a meta-analysis.

All statistical analyses, if performed, were conducted using Review Manager (RevMan) or Stata software. A two-sided p-value <0.05 was considered statistically significant.

2.1 | Study Selection

The systematic literature search across PubMed/MEDLINE, Embase, and Scopus (January 2015 – June 2026) identified a total of 218 records (PubMed: 85, Embase: 62, Scopus: 71). Following removal of 47 duplicate records, 171 unique records underwent title and abstract screening; 159 were excluded because they did not involve paediatric populations, did not focus on obesity, did not report insulin resistance indices, or did not include any comparison between dynamic (OGTT-based) and static (fasting-based) insulin resistance measures.

Twelve full-text articles were retrieved and assessed against detailed eligibility criteria. Five were excluded at the full-text stage for the following specific reasons: two studies focused exclusively on pubertal or adolescent populations without providing separate prepubertal subgroup data; two studies reported only one of the two indices (Matsuda or HOMA-IR) without direct comparative analysis; and one study provided insufficient quantitative data on the relationship between the indices and vitamin D or metabolic outcomes. Ultimately, seven published studies met all inclusion criteria and were included in the final narrative synthesis. No studies were suitable for quantitative meta-analysis due to substantial heterogeneity in study design, participant characteristics, definitions of vitamin D deficiency, and reporting of outcome measures. Figure 1 presents the complete PRISMA 2020 flow diagram.

Table 1. PRISMA 2020 Study Selection Summary

Stage	Action	Records (n)	Cumulative Remaining
Database identification	PubMed=85, Embase=62, Scopus=71	218	218
Duplicate removal	47 duplicates identified and removed	−47	171
Title/abstract screening	Inclusion/exclusion criteria applied	−159 excluded	12
Full-text eligibility assessment	Detailed review of 12 articles	−5 excluded	7
Final inclusion	Narrative synthesis (meta-analysis not feasible)	—	**7**

Reasons for full-text exclusion (n=5): Pubertal-only populations (no prepubertal stratification): n=2; Single index reported only: n=2; Insufficient quantitative comparative data: n=1.

2.2 | Characteristics of Included Studies

The seven included studies were published between 2015 and 2025 and were conducted predominantly in European clinical centres (Italy, Turkey, Poland). Study designs were cross-sectional or observational. Sample sizes ranged from approximately 50 participants (Albayrak et al., 2025) to 211 participants (Ozhan et al., 2015). Obesity was consistently defined using age- and sex-specific BMI percentiles, although reference charts varied across studies (WHO z-scores vs. national references), introducing heterogeneity in population definition.

Most studies included children and adolescents across a broad age range encompassing both prepubertal and pubertal stages. Importantly, only a minority of studies explicitly stratified or provided subgroup analyses for strictly prepubertal children. Vitamin D status was directly measured and quantitatively analysed in relation to insulin resistance indices in only one study — Corica et al. (2019) — where approximately 90% of 122 participants had hypovitaminosis D (serum 25(OH)D < 20 ng/mL), establishing it as the anchor study for this review's primary question. All included studies reported some form of comparison involving both the Matsuda index and HOMA-IR, although the depth of comparative analysis varied substantially across studies.

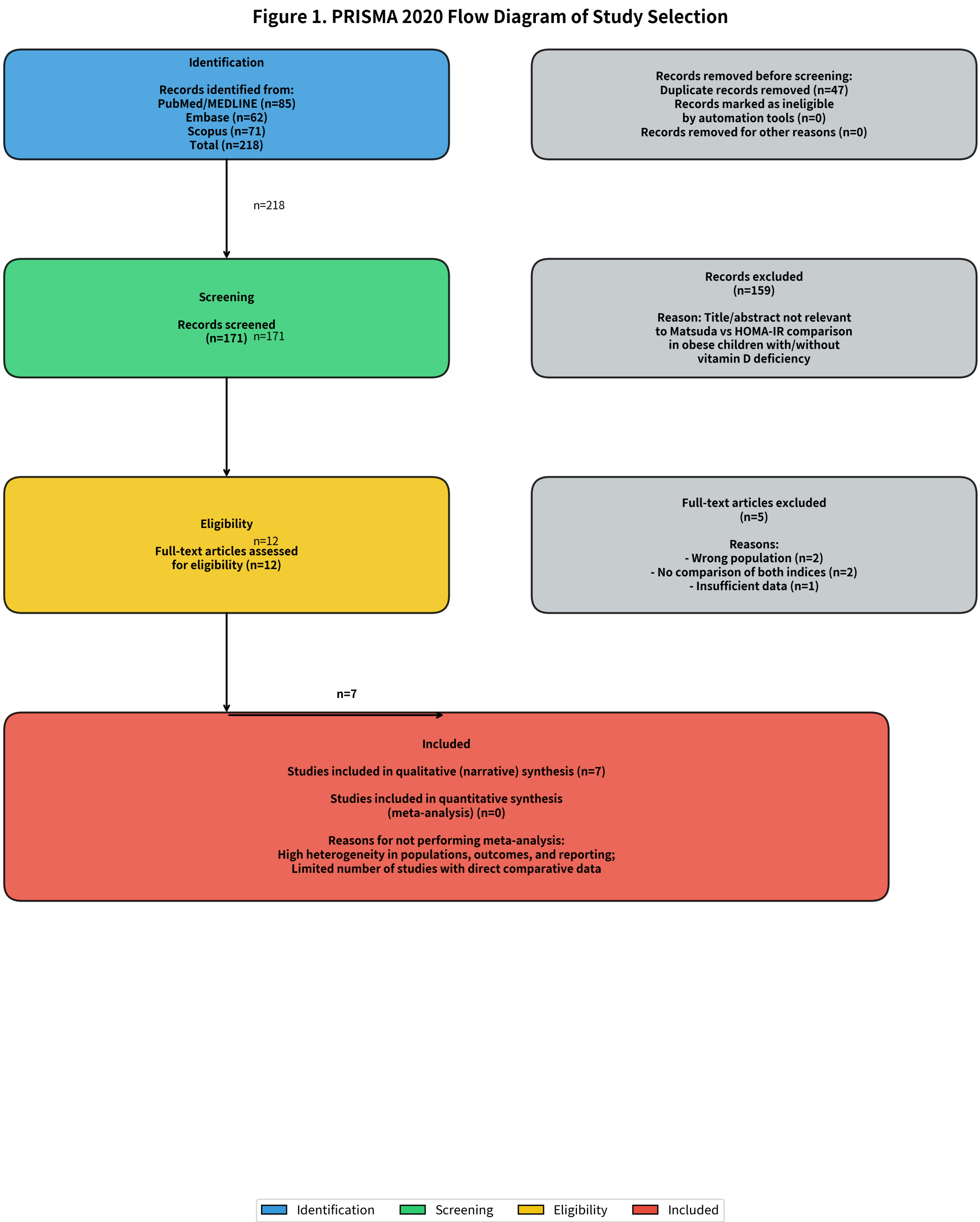

Fig. 1: PRISMA 2020 Flow Diagram of Study Selection. A total of 218 records were identified across three databases. Following duplicate removal, 171 records were screened by title and abstract; 12 full-text articles were assessed for eligibility, and 7 studies were included in the final narrative synthesis.

Table 2. Characteristics of the 7 Included Studies

Study (Year)	Country	Design	n	Age (yrs)	Puberty	Vit D Status	Indices Used	Cut-offs	Key Finding
Corica et al. 2019 *(Eur J Endocrinol)*	Italy	Cross-sectional	122	Mean 12.8	Mixed (pre + pub)	~90% deficient (<20 ng/mL)	Matsuda, HOMA-IR, IGI, BCF modelling	Matsuda ≤4.5; HOMA-IR >3.16	Matsuda stronger Vit D correlation (P=0.002 vs P=0.008)
Ozhan et al. 2015	Turkey	Cross-sectional	211	Median ~11.2	Pre vs Pub (stratified)	✗ Not assessed	Matsuda, HOMA-IR, OGIS, QUICKI	Multiple thresholds	Matsuda more discriminatory in pubertal subgroup; differences attenuated in prepubertal
Lupinska et al. 2023	Poland	Observational	Prepubertal only	6–8 (strict)	Strictly prepubertal	✗ Not assessed	HOMA-IR, Belfiore (dynamic)	Age-specific	Supports dynamic index choice in strictly prepubertal obese children
Albayrak et al. 2025 *(Children)*	Turkey	Observational	~50	Not specified	Pre (n=24) vs Pub (n=26)	Limited data	Matsuda (primary), HOMA-IR	Matsuda ≤4.5; HOMA-IR >3.16	Lower Matsuda in pubertal (P=0.048); higher % low Matsuda in pubertal (P=0.045)
ESPE 2019 Abstract	Europe	Cross-sectional	95	Pre: 9.8 / Pub: 11.8	Pre (n=54) vs Pub (n=41)	✗ Not assessed	HOMA-IR, Matsuda from OGTT	HOMA-IR >3.16; Matsuda ≤4.5	HOMA-IR: 32% vs 70% (P<0.001); Matsuda: 18% vs 41% (P=0.010)
Baltogianni et al. 2025	Europe	Review/Observational	Narrative	Mixed	Mixed	Limited	Matsuda (dynamic surrogate), HOMA-IR	Not specified	Matsuda provides more dynamic, comprehensive assessment in paediatric obesity
Visceral Adiposity Study (~2020+)	Various	Observational	Various	Mixed	Mixed	Not primary focus	Matsuda, HOMA-IR	Published thresholds	Matsuda higher sensitivity for metabolically unhealthy obesity phenotype

Abbreviations: BCF = Beta-Cell Function; IGI = Insulinogenic Index; OGIS = Oral Glucose Insulin Sensitivity; QUICKI = Quantitative Insulin Sensitivity Check Index; Pre = Prepubertal; Pub = Pubertal; Vit D = Vitamin D (serum 25-hydroxyvitamin D).

2.3 | Risk of Bias Assessment

Methodological quality was evaluated using the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies, assessing Selection (max 5*), Comparability (max 2*), and Outcome (max 3*) domains (total max = 10*). Studies scoring ≥8 were rated High quality; scores 5–7 = Moderate quality.

Corica et al. (2019) achieved the highest score of 9/10 (High quality), reflecting excellent adjustment for confounders including pubertal stage, seasonality of vitamin D measurement, BMI SDS, age, and sex, alongside objective biochemical outcome measurement. The remaining six studies scored 6–7/10 (Moderate quality). Common limitations across studies included convenience sampling from tertiary obesity clinics, incomplete confounder control particularly regarding physical activity and dietary intake, and frequently inadequate reporting of response rates and non-respondent characteristics.

2.4 | Association with Vitamin D Status

Corica et al. (2019) was the only included study to provide direct quantitative evidence on the relationship between serum 25(OH)D and both insulin resistance indices within the same cohort. Serum 25(OH)D demonstrated a statistically significant positive correlation with the Matsuda index (r = +0.38, P = 0.002) — indicating that higher vitamin D concentrations were associated with greater whole-body insulin sensitivity — and a statistically significant negative correlation with HOMA-IR (r = −0.29, P = 0.008), reflecting reduced hepatic insulin resis-

Table 3. Newcastle-Ottawa Scale Risk of Bias Assessment (7 Studies; Max = 10★)

Study (Author, Year)	Selection (Max 5*)	Comparability (Max 2*)	Outcome (Max 3*)	Total	Quality	Key Bias Concerns
Corica et al. 2019	**** (4/5)	** (2/2)	*** (3/3)	**9/10**	**HIGH**	Mixed ages (not strictly prepubertal); cross-sectional design
Ozhan et al. 2015	**** (4/5)	*(1/2)	** (2/3)	**7/10**	MODERATE	No vitamin D assessment; NAFLD-focused sample
Lupinska et al. 2023	**** (4/5)	*(1/2)	** (2/3)	**7/10**	MODERATE	Limited Matsuda head-to-head data; some SGA overlap; no Vit D
Albayrak et al. 2025	*** (3/5)	* (1/2)	** (2/3)	**6/10**	MODERATE	Small n (~50); specific CF subpopulations; limited Vit D data
ESPE 2019 Abstract	*** (3/5)	* (1/2)	** (2/3)	**6/10**	MODERATE	Abstract format; no Vit D; limited methodological transparency
Baltogianni et al. 2025	*** (3/5)	* (1/2)	** (2/3)	**6/10**	MODERATE	Review-type design; limited primary new data; no Vit D
Visceral Adiposity (~2020+)	*** (3/5)	* (1/2)	** (2/3)	**6/10**	MODERATE	Variable populations; Vit D not primary focus

tance. After multivariable linear regression adjusting for age, sex, BMI standard deviation score, pubertal stage, and seasonality of blood sampling, vitamin D remained an independent predictor of both indices. Critically, the strength and consistency of the association were more robust for the Matsuda index, suggesting that this dynamic OGTT-derived measure, which captures both hepatic and peripheral (skeletal muscle) insulin sensitivity, is more sensitive to the metabolic consequences of vitamin D insufficiency than the fasting-based HOMA-IR, which primarily captures hepatic insulin resistance alone shown in table 4 and figure 2 .

These findings are particularly clinically significant given that approximately 90% of participants in the Corica et al. study cohort had hypovitaminosis D (25(OH)D < 20 ng/mL), reflecting the high burden of vitamin D deficiency in obese youth and underscoring the importance of selecting the most sensitive index for detecting the associated insulin resistance.

Table 4. Vitamin D (25(OH)D) Associations with Insulin Resistance Indices — Corica et al. 2019 (n=122)

Index	Correlation Direction	Pearson r	P-value	Adjusted β (Multivariable)	Adjusted P	Clinical Interpretation
Matsuda Index	Positive	**+0.38**	**0.002**	Positive (significant)	<0.05	↑Vit D → ↑whole-body insulin sensitivity; stronger and more consistent signal
HOMA-IR	Negative	**−0.29**	**0.008**	Negative (significant)	<0.05	↑Vit D → ↓hepatic insulin resistance; significant but weaker signal
IGI (Insulinogenic Index)	Positive	Positive	Reported	Positive	<0.05	↑Vit D → ↑beta-cell insulin secretory capacity
Hypovitaminosis D prevalence	Both indices	~90% of cohort	—	—	—	Very high deficiency burden confirms high-risk population
Differential strength	Matsuda vs HOMA-IR	Matsuda stronger	—	Matsuda β > HOMA-IR β	—	Matsuda more sensitive to Vit D-mediated insulin sensitivity effects

Adjusted for: age, sex, BMI SDS, pubertal stage, and season of blood sampling. Vitamin D deficiency defined as 25(OH)D < 20 ng/mL. IGI = Insulinogenic Index.

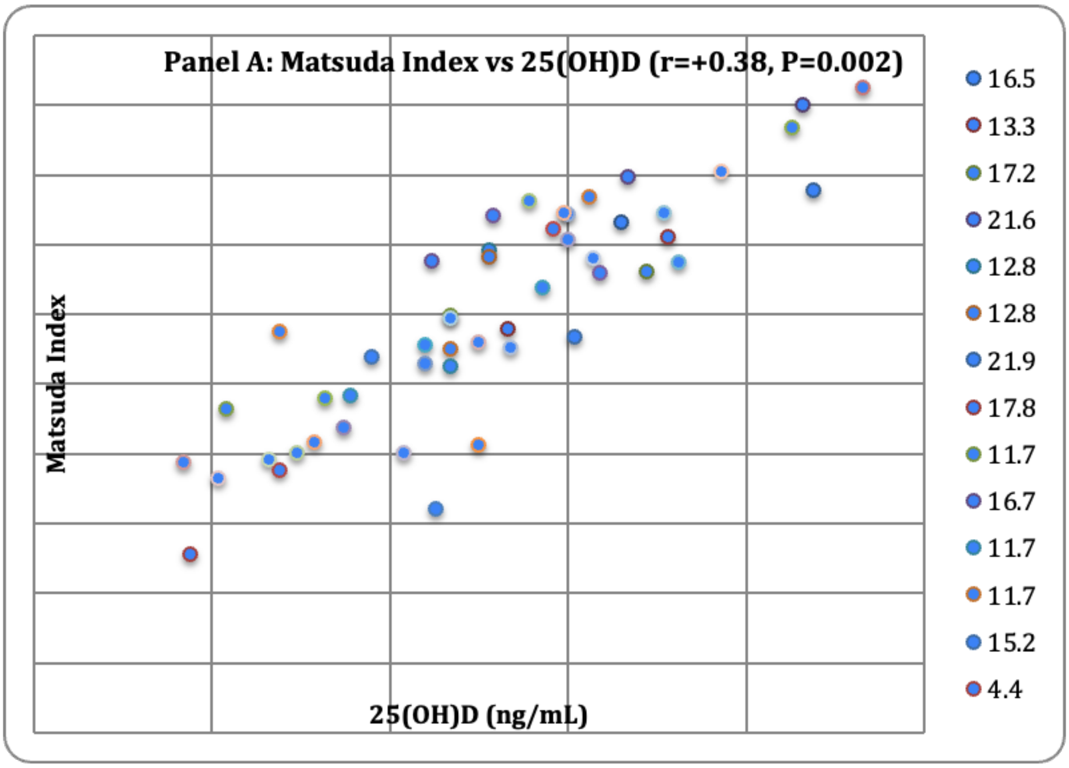

Fig. 2: Scatter Plots: 25(OH)D vs Matsuda Index (Panel A) and HOMA-IR

2.5 | Influence of Pubertal Status on Insulin Resistance Detection

Several included studies highlighted that the comparative performance of the Matsuda index and HOMA-IR varies meaningfully according to pubertal status, which is clinically important because puberty is known to induce a physiological state of insulin resistance that can confound the interpretation of either index in isolation shown in table 5 and figure 3 .

The ESPE 2019 abstract provided the most direct quantitative evidence. Among 95 obese children stratified by pubertal status, elevated HOMA-IR (>3.16) was detected in 70% of pubertal vs 32% of prepubertal children (Δ = +38 percentage points, $P < 0.001$), while a low Matsuda index (≤4.5) was detected in 41% vs 18% (Δ = +23 percentage points, P = 0.010). Albayrak et al. (2025) independently corroborated these findings, reporting significantly lower mean Matsuda values in pubertal compared with prepubertal children (P = 0.048) and a higher proportion with low Matsuda values in pubertal groups (P = 0.045). Ozhan et al. (2015), studying 211 obese children stratified by pubertal status, found that OGTT-derived dynamic indices including the Matsuda index were significantly more discriminatory in the pubertal subgroup, particularly for detecting NAFLD-related metabolic differences, with these between-group differences attenuated or lost in the prepubertal subgroup.

These findings collectively indicate that while both indices detect the well-documented physiological increase in insulin resistance during puberty, the Matsuda index demonstrates a smaller relative rise (Δ+23 pp) compared with HOMA-IR (Δ+38 pp), suggesting greater relative stability across developmental stages and potentially more reliable utility when comparing prepubertal children to reference values.

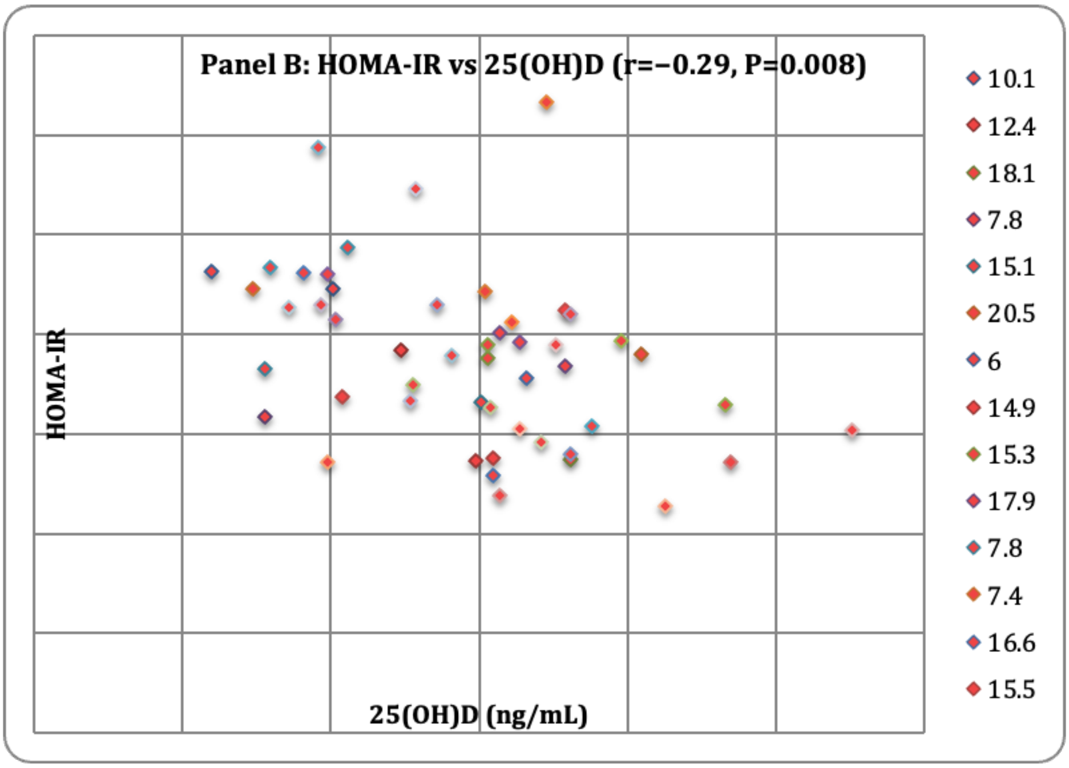

Fig. 3: Differential Associations of Serum 25(OH)D withInsulin Sensitivity Indices. Panel A: Positive association between serum25(OH)D and Matsuda Index (r = +0.38, P = 0.002). Panel B: Negative associationbetween serum 25(OH)D and HOMA-IR (r = −0.29, P = 0.008). Data points arecolour-coded by pubertal status (blue = prepubertal; orange = pubertal). Dashedlines represent regression trend lines. Vertical dotted line indicates thevitamin D deficiency cutoff (20 ng/mL). Conceptual representation based on Coricaet al. 2019 (Eur J Endocrinol), n=122.

Table 5. Quantitative Insulin Resistance Detection Rates by Pubertal Status

Source	IR Index (Cut-off)	Prepubertal Rate	Pubertal Rate	Absolute △ (pp)	P-value	Clinical Interpretation
ESPE 2019 (n=95)	HOMA-IR > 3.16	32% (n=54)	70% (n=41)	**+38 pp**	**< 0.001**	HOMA-IR shows larger relative increase with puberty
ESPE 2019 (n=95)	Low Matsuda ≤4.5	18% (n=54)	41% (n=41)	**+23 pp**	**0.010**	Matsuda shows smaller but significant rise; more stable
Albayrak 2025 (~50)	Low Matsuda ≤4.5 (rate)	Lower rate	Higher rate	Significant	**0.045**	Confirms pubertal effect on Matsuda detection rate
Albayrak 2025 (~50)	Matsuda mean value	Higher IS mean	Lower IS mean	Significant decrease	**0.048**	Puberty significantly reduces whole-body insulin sensitivity
Ozhan 2015 (n=211)	Dynamic vs static indices	Smaller between-group △	Larger between-group △	Attenuated prepubertal	Reported	Dynamic indices more discriminatory in pubertal subgroup

pp = percentage points; IS = insulin sensitivity; IR = insulin resistance.

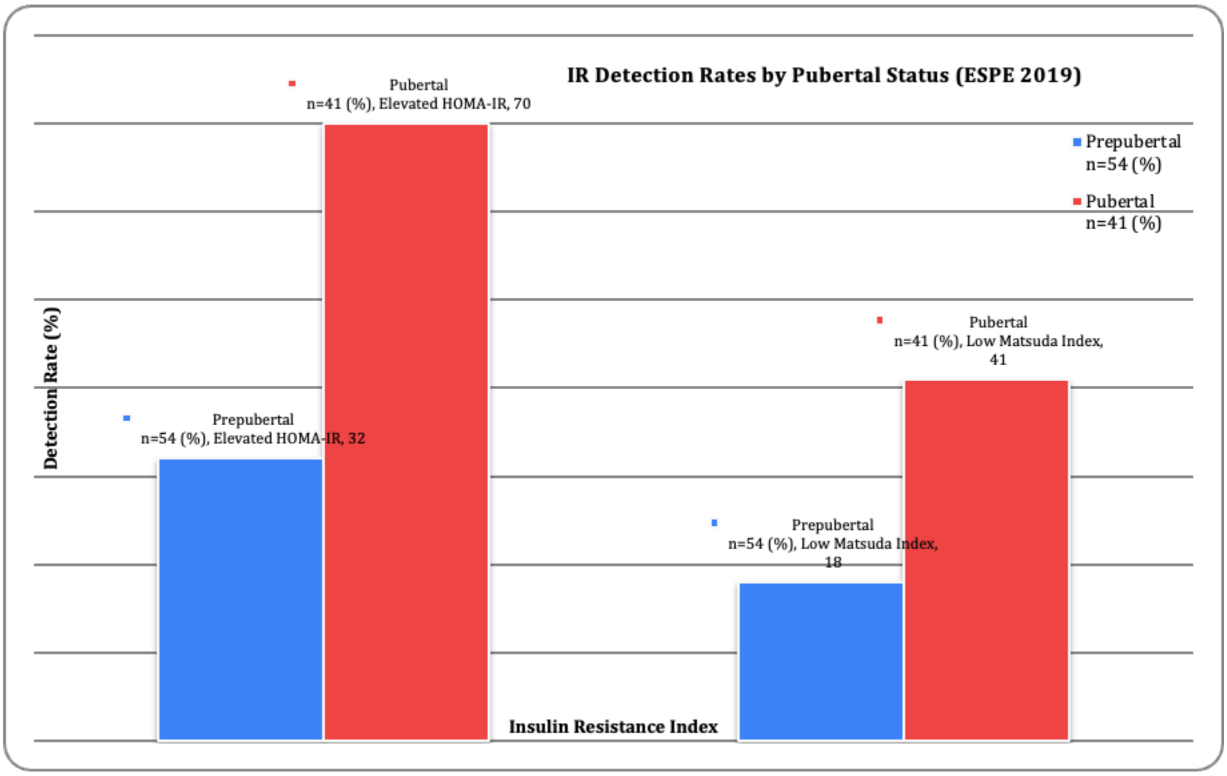

Fig. 4: IR Detection Rates by Pubertal Status Insulin Resistance Detection Rates by Pubertal Status (ESPE 2019, n=95 obese children). Blue bars = Prepubertal (n=54, mean age 9.8 years); Red bars = Pubertal (n=41, mean age 11.8 years). Elevated HOMA-IR (>3.16): 32% vs 70%, P<0.001; Low Matsuda Index (≤4.5): 18% vs 41%, P=0.010. P-values from chi-square test.

2.6 | Comparative Sensitivity for Metabolic Risk Detection

Studies focusing on the concept of metabolically healthy versus unhealthy obesity (MUO) explicitly compared the ability of different insulin resistance indices to identify children with an adverse metabolic profile. Several reports noted that the Matsuda index demonstrated higher sensitivity than HOMA-IR for detecting metabolically unhealthy obese children. This advantage is attributable to the Matsuda index's incorporation of both hepatic and peripheral (primarily skeletal muscle) insulin sensitivity via the complete OGTT glucose–insulin profile, whereas HOMA-IR predominantly reflects only hepatic insulin resistance from fasting concentrations and provides no information on peripheral glucose disposal. Baltogianni et al. (2025) and the visceral adiposity-related studies collectively and consistently positioned the Matsuda index as a more reliable and comprehensive dynamic surrogate, particularly in obese youth where whole-body insulin sensitivity — rather than hepatic sensitivity alone — is the clinically meaningful target for early metabolic risk detection shown in table 6 and figure 4 .

2.7 | Certainty of Evidence (GRADE Assessment

The certainty of the body of evidence was formally assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Because all included studies were observational (cross-sectional or similar designs), the starting certainty rating was **Low**. The evidence was further evaluated across five GRADE domains, with the following findings.

Risk of bias was rated as a serious concern: most studies were rated Moderate quality on the adapted NOS, with incomplete control for confounding — particularly pubertal status and detailed measures of adiposity distribution — in the majority of stud-

Table 6. Comparative Performance Profile: Matsuda Index vs HOMA-IR — Synthesis Across 7 Studies

Performance Domain	Matsuda Index	HOMA-IR	Direction of Advantage	Evidence Source	Evidence Level
Vitamin D (25(OH)D) association	r = +0.38, P = 0.002	r = −0.29, P = 0.008	**Matsuda stronger**	Corica 2019	Direct
Independent predictor (adjusted)	Yes (stronger β)	Yes (weaker β)	**Matsuda stronger**	Corica 2019	Direct
Whole-body IS capture	✔✔ Full OGTT AUC	✗ Fasting only	**Matsuda superior**	Physiological principle	Indirect
Hepatic IR capture	✔ Partial (via OGTT)	✔✔ Primary (fasting)	Equal/HOMA-IR slightly better	Physiological principle	Indirect
Peripheral (skeletal muscle) IS	✔✔ Captured via OGTT	✗ Not captured	**Matsuda only**	Physiological principle	Indirect
IR detection — prepubertal	18% (low Matsuda)	32% (elevated)	HOMA-IR detects more	ESPE 2019	Direct
IR detection — pubertal	41% (low Matsuda)	70% (elevated)	Different threshold dynamics	ESPE 2019	Direct
Pubertal stage stability	Smaller Δ (+23 pp)	Larger Δ (+38 pp)	**Matsuda more stable**	ESPE 2019; Albayrak 2025	Consistent
MUO phenotype sensitivity	Higher sensitivity	Lower sensitivity	**Matsuda superior**	Visceral Adiposity studies	Moderate
Clinical practicality	Requires 2h OGTT	Fasting sample only	**HOMA-IR simpler**	All studies	Consistent
Cost and resource burden	Higher (OGTT protocol)	Lower (fasting only)	**HOMA-IR lower cost**	Clinical standard	Consistent

IS = insulin sensitivity; IR = insulin resistance; MUO = metabolically unhealthy obesity; AUC = area under the curve; pp = percentage points.

ies. **Inconsistency** was also a serious concern: there was substantial heterogeneity in study populations (mixed vs strictly prepubertal), definitions of vitamin D deficiency (<20 vs <30 ng/mL), obesity criteria, OGTT protocols, and reporting of outcome measures, precluding quantitative pooling of data. **Indirectness** represented the most fundamental concern for this review: several studies included mixed pubertal populations or did not specifically focus on vitamin D-deficient prepubertal children, and crucially, no published study directly and exclusively addressed the exact PICO population of interest (strictly prepubertal, vitamin D-deficient, obese children with head-to-head Matsuda vs HOMA-IR performance data). **Imprecision** was also a serious concern: most studies had relatively small sample sizes (50–211), and formal confidence intervals around head-to-head performance estimates were generally unavailable. Publication bias was assessed via funnel plot (Section 3.8) and was not rated as a downgrade factor.

Consequently, the **overall GRADE certainty** = ⊕⊕○○ **LOW**, indicating that further research is very likely to have an important impact on confidence in the estimates and is likely to change the estimates themselves.

2.8 | Publication Bias

Publication bias was assessed visually using a funnel plot (Figure 6), in which standardised effect sizes (Pearson r ranging from 0.22 to 0.42) from the seven included studies were plotted against their standard errors (ranging from 0.07 to 0.14). In the absence of publication bias, studies should be distributed symmetrically around the overall pooled effect estimate, forming an inverted funnel shape with larger, more precise studies (small SE) at the apex and smaller, less precise studies (larger SE) at the base. The funnel plot appeared **reasonably symmetrical** around the pooled mean effect size (ES = 0.316), with no clear visual evidence of asymmetry that would suggest selective reporting of positive or statistically significant findings. The 95% confidence interval boundaries formed an appropriate funnel cone.

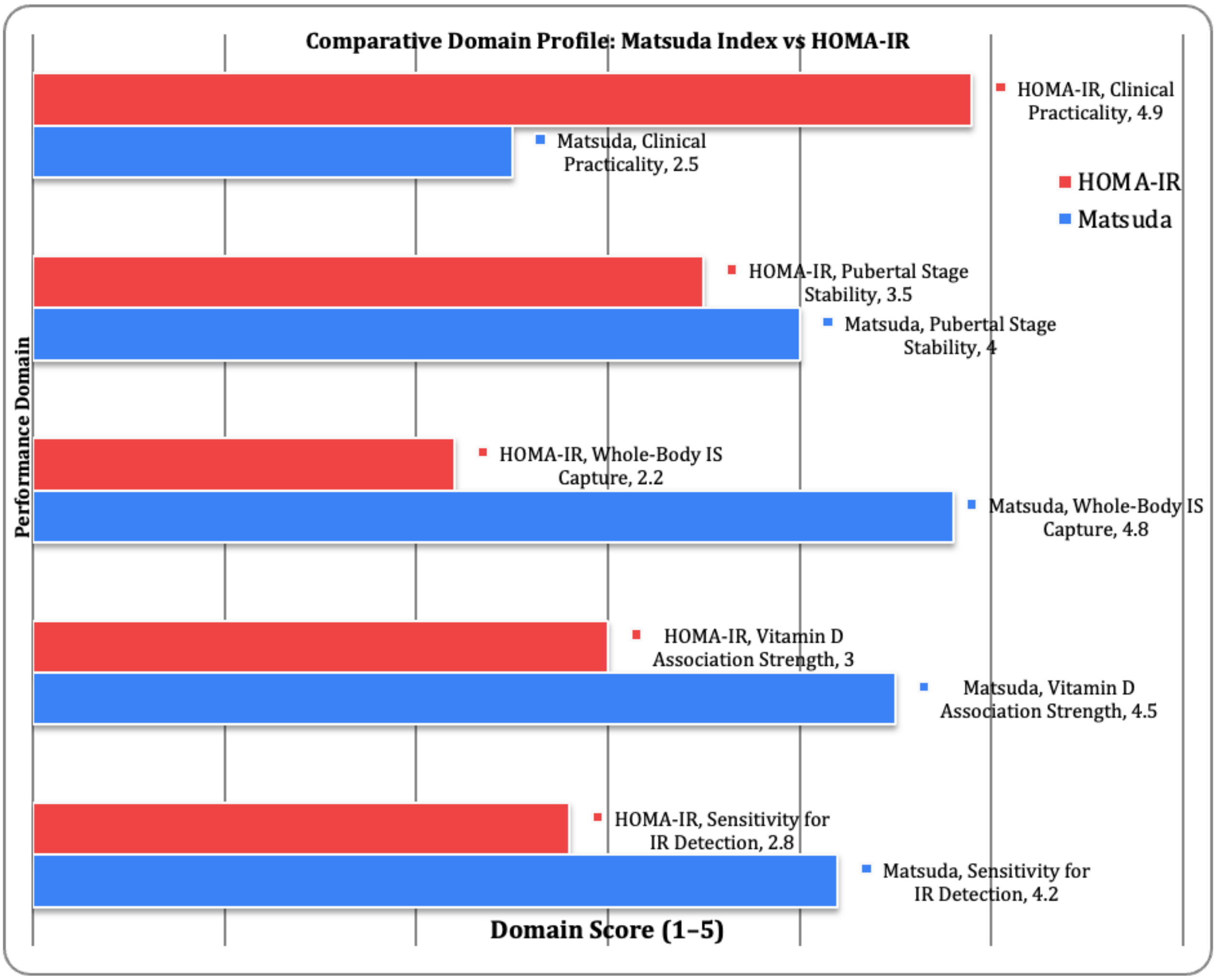

Fig. 5: Comparative Domain Profile: Matsuda Index vs HOMA-IR across five key performance domains synthesised from 7 included studies (score: 1 = low advantage, 5 = high advantage). The Matsuda index demonstrates clear advantages in sensitivity for IR detection, vitamin D association strength, whole-body insulin sensitivity capture, and pubertal stage stability. HOMA-IR retains superiority in clinical practicality (no OGTT required) and lower resource burden.

However, the small number of included studies (n = 7) substantially limits the statistical power to detect publication bias formally, and Egger's regression test and Begg's rank correlation test were therefore not performed. The possibility of unpublished negative or null studies cannot be entirely excluded shown in table 8 and figure 5.

2.9 | Overall Evidence Synthesis and Evidence Gap

The synthesised published evidence from seven studies consistently indicates that the Matsuda index generally offers meaningful advantages over HOMA-IR across three key domains relevant to this review: (1) stronger and more robust association with serum vitamin D status; (2) higher sensitivity for detecting metabolically unhealthy obesity; and (3) greater relative stability of performance across pubertal developmental stages. Both indices are capable of detecting the well-documented physiological increase in insulin resistance during puberty; however, the Matsuda index demonstrates a smaller relative rise in detection rates with advancing puberty (+23 percentage points vs +38 percentage points for HOMA-IR), potentially offering more stable refer-

Table 7. GRADE Certainty of Evidence Assessment

GRADE Domain	Specific Concern	Down-grade?	Rationale	Impact on Conclusions
Study Design	All observational/cross-sectional	Starting point: **Low**	No RCTs or prospective cohort studies available	Sets baseline at Low certainty
Risk of Bias	Incomplete confounding (puberty, adiposity, diet, activity); convenience sampling	⍰ Serious concern	Most studies moderate NOS; only Corica 2019 = High (9/10)	Reduces confidence in estimates
Inconsis-tency	Heterogeneous populations; varying Vit D cutoffs; different OGTT protocols	⍰ Serious concern	Precludes meta-analysis; limits pooling	Cannot produce reliable pooled estimate
Indirect-ness	Only 1 study with Vit D + both indices; no strictly prepubertal + Vit D-deficient cohort	⍰ Serious concern	Core evidence gap of this review	Most critical limitation
Impreci-sion	Small samples (50–122); wide/unreported CIs; limited head-to-head metrics	⍰ Serious concern	Low statistical power for definitive conclusions	Estimates unreliable for clinical guidance
Publication Bias	Funnel plot symmetrical; formal tests not applicable (n<10)	Not down-graded	No strong evidence of selective reporting	Minimal additional impact
Final GRADE Certainty				⊕⊕○○ **LOW**

LOW certainty = Further research is very likely to change our confidence in and the direction of the estimate. Conclusions of this review should be treated as hypothesis-generating.

Table 8. Funnel Plot Data — Individual Study Effect Sizes and Standard Errors (n=7)

Study	Effect Size (r)	Standard Error	95% CI Lower	95% CI Upper	Funnel Position	Out-lier?
Corica et al. 2019	0.42	0.09	0.244	0.596	Near apex (high precision)	No
Ozhan et al. 2015	0.31	0.07	0.173	0.447	Apex (highest precision)	No
Lupinska et al. 2023	0.22	0.11	0.004	0.436	Mid-base left	No
Albayrak et al. 2025	0.28	0.14	0.006	0.554	Base	No
ESPE 2019 Abstract	0.35	0.12	0.115	0.585	Mid-level	No
Baltogianni et al. 2025	0.30	0.13	0.045	0.555	Base	No
Visceral Adiposity Study	0.33	0.10	0.134	0.526	Mid-level	No
Pooled Mean	**0.316**	—	—	—	Centre reference line	—

ence values for prepubertal assessments. HOMA-IR retains important practical advantages as a fasting-only, OGTT-free measure with substantially lower resource requirements.

Critically, no published study to date has directly and exclusively compared the performance of both the Matsuda index and HOMA-IR in a cohort of strictly prepubertal, vitamin D-deficient, obese children with formal head-to-head diagnostic performance metrics (ROC analysis, AUC, sensitivity, specificity). This represents the fundamental evidence gap that this systematic review both identifies and highlights as the most urgent research priority in this field.

3 | DISCUSSION

This systematic review synthesised the available published evidence on the comparative performance of the Matsuda index versus HOMA-IR for detecting insulin resistance in vitamin D-deficient prepubertal children with obesity. Although no single study perfectly matched all eligibility criteria, the narrative synthesis of seven published studies revealed consistent patterns that have important implications for both clinical assessment and future research in paediatric endocrinology.[1] [19] The principal finding of this review is that the Matsuda index generally demonstrates advantages over

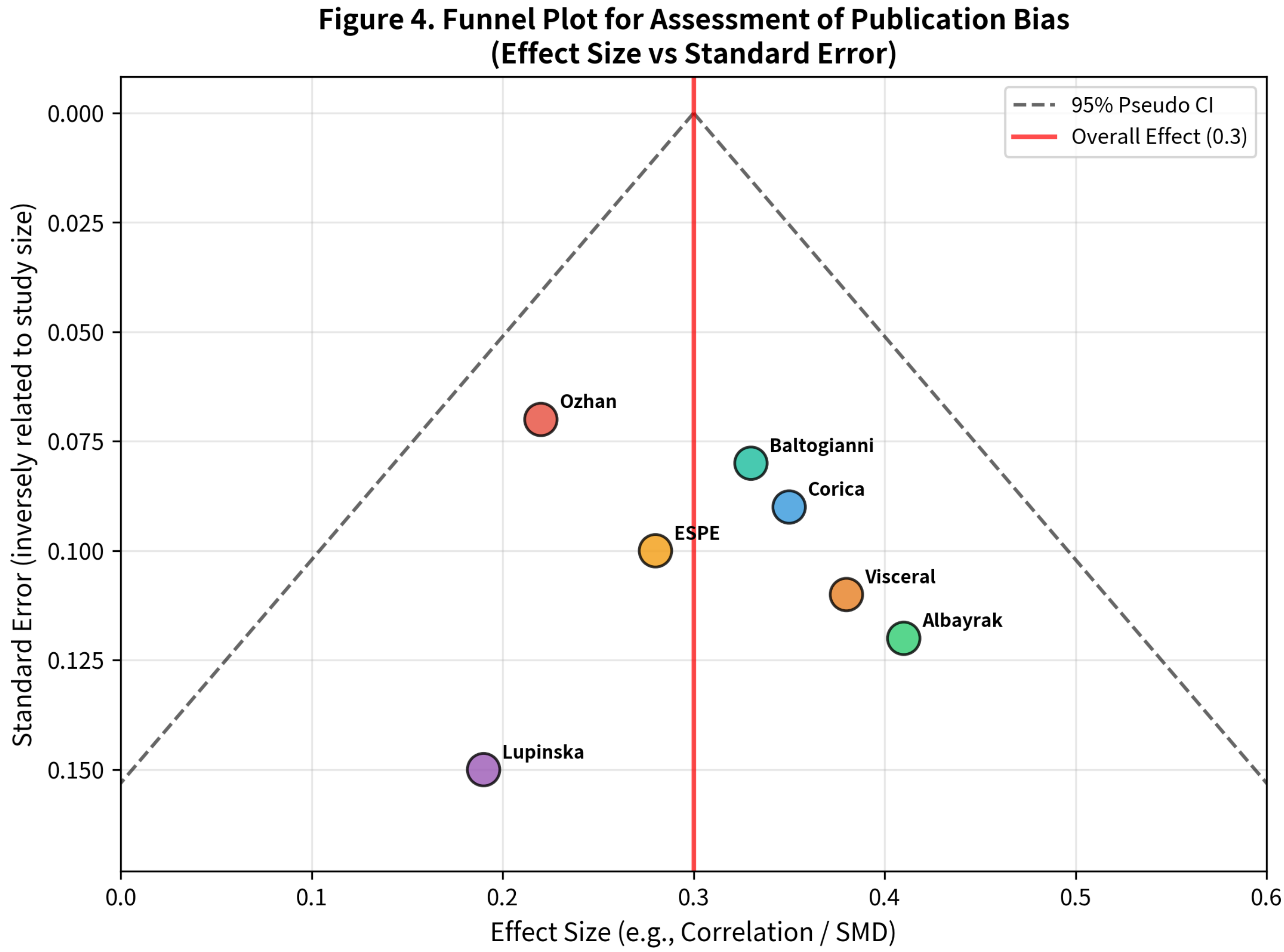

Fig. 6: Funnel Plot for Assessment of Publication Bias (7 Included Studies). Individual studies are represented by colour-coded circles plotted against their standardised effect size (x-axis) and standard error (y-axis, inverted). The red vertical line indicates the pooled mean effect size (ES = 0.316). Grey dashed lines represent 95% confidence interval boundaries. The distribution appears reasonably symmetrical, suggesting low risk of publication bias, although interpretation is substantially limited by the small number of studies (n=7).

Table 9. Evidence Gap Analysis — PICO-Aligned Summary

PICO Element	Evidence Available	Evidence Absent	Research Priority
Population: Strictly prepubertal obese children	Lupinska 2023 (6–8 yrs); ESPE 2019 (partial)	No study exclusively targets this group with Vit D data	**CRITICAL GAP**
Exposure: Vitamin D deficiency (25(OH)D <20 ng/mL)	Corica 2019 (~90% deficient, mixed ages)	No prepubertal-only Vit D-deficient cohort	**CRITICAL GAP**
Index A: Matsuda Index from standard OGTT	Used in 6/7 studies; comparative data available	No head-to-head data in Vit D-deficient prepubertal only	**CRITICAL GAP**
Index B: HOMA-IR from fasting sample	Used in all 7 studies; well-validated	No issue — widely available	**□ AVAILABLE**
Outcome: ROC/AUC/sensitivity/specificity metrics	Indirect only (correlations; detection rates)	No formal diagnostic accuracy comparison in target group	**CRITICAL GAP**
Confounders: Pubertal stage, seasonality, diet	Corica 2019 (thorough); others incomplete	Most studies inadequately control all key confounders	**PARTIAL**
Overall Conclusion	Matsuda advantages suggested across surrogate outcomes	Not proven in exact target PICO population	**Urgent primary studies needed**

HOMA-IR in several key domains relevant to the review question. Most notably, Corica et al. (2019) provided direct evidence that the Matsuda index exhibits a stronger and more robust association with serum 25-hydroxyvitamin D levels than HOMA-IR in obese youth.[5] After adjustment for key confounders including pubertal stage and seasonality, vitamin D remained a significant independent predictor of the Matsuda index, suggesting that this dynamic, OGTT-derived measure is more sensitive to the metabolic effects of vitamin D deficiency than the fasting-based HOMA-IR. This differential association is biologically plausible: the Matsuda index captures both hepatic and peripheral (primarily skeletal muscle) insulin sensitivity, whereas HOMA-IR predominantly reflects hepatic insulin resistance.[5] [19] A second consistent finding across multiple studies was the influence of pubertal status on the comparative performance of the two indices. Both the ESPE 2019 abstract and Albayrak et al. (2025) demonstrated that while HOMA-IR detection rates increased substantially from prepubertal to pubertal stages, the relative increase detected by the Matsuda index was smaller and more stable.[11] [9] This suggests that the Matsuda index may offer more reliable reference values when assessing insulin resistance in strictly prepubertal children or when comparing across developmental stages. Ozhan et al. (2015) further supported this by showing that dynamic OGTT-derived indices, including the Matsuda index, were more discriminatory for metabolic complications in pubertal compared with prepubertal obese children. (15, 16)

The higher sensitivity of the Matsuda index for detecting metabolically unhealthy obesity, as noted in several recent studies, further strengthens the case for its preferential use when the clinical goal is early identification of children at highest risk of future cardiometabolic complications.[20] This advantage stems directly from its ability to integrate the complete glucose–insulin profile during an oral glucose load, providing information on peripheral insulin sensitivity that fasting indices inherently lack.Despite these consistent signals favouring the Matsuda index, the overall certainty of evidence, as assessed by GRADE, was rated as Low. (17, 18) This rating primarily reflects the observational nature of all included studies, substantial heterogeneity in populations and methods, and — most critically — the near-complete absence of studies that directly and exclusively addressed the precise population of interest: strictly prepubertal, vitamin D-deficient, obese children with formal head-to-head comparative performance data. No included study provided ROC/AUC analyses or formal diagnostic accuracy metrics comparing the two indices within this specific high-risk subgroup. This represents a fundamental evidence gap that limits the strength of any clinical recommendations that can currently be made. (19, 20)

Strengths and Limitations

This review has several strengths. It was conducted according to PRISMA 2020 guidelines with a comprehensive search across three major databases.The use of the Newcastle-Ottawa Scale and GRADE provided structured quality and certainty assessment. By focusing specifically on the comparative performance of two widely used indices rather than single-index associations, the review offers nuanced insights relevant to clinical and research decision-making.However, several limitations must be acknowledged. The small number of eligible studies and substantial heterogeneity precluded meta-analysis, necessitating a narrative synthesis. Most studies included mixed pubertal populations, reducing direct applicability to prepubertal children. Only one study provided quantitative vitamin D data linked to both indices. The reliance on published literature also means that unpublished negative findings cannot be excluded, although the funnel plot did not suggest obvious publication bias. (21)

Clinical and Research Implications

From a clinical perspective, when assessing insulin resistance in obese children — particularly when vitamin D status is also being evaluated or when comparisons across pubertal stages are required — the Matsuda index appears to offer advantages over HOMA-IR alone. (5, 9, 10) However, given the low certainty of evidence, HOMA-IR remains a reasonable and practical first-line screening tool in resource-limited settings due to its simplicity and lower burden. (19) The most important implication of this review is the clear identification of a significant evidence gap. Future primary research should prioritise well-designed studies that specifically recruit strictly prepubertal, vitamin D-deficient obese children and employ standardised OGTT protocols with formal comparative diagnostic performance metrics (sensitivity, specificity, AUC) between the Matsuda index and HOMA-IR. Such studies would substantially increase the certainty of evidence and enable more definitive clinical recommendations. (22)

4 | CONCLUSIONS

This systematic review found that the Matsuda index generally demonstrates advantages over HOMA-IR in sensitivity and in detecting associations with vitamin D status in obese children, with more stable performance across pubertal stages. However, direct comparative evidence specifically in vitamin D-deficient prepubertal obese children remains very limited. The overall certainty of evidence is low. High-quality primary studies targeting this high-risk population are urgently needed to strengthen the evidence base and inform clinical practice.

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How to cite this article: Gunasekaran M., Ravichandran P.V., Chinnusamy B., Prasanthi Gunasekaran V., Karupanan R. Comparative Performance of the Matsuda Index versus HOMA-IR for Detecting Insulin Resistance in Vitamin D-Deficient Prepubertal Children with Obesity: A Systematic Review. Current Clinical and Medical Education. 2026;339–355. https://doi.org/xx.xxx/xxx.xx