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Review

Association between Circulating Amino Acids and Childhood Obesity: A Systematic Review and Meta-Analysis

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Abstract
This systematic review and meta-analysis aim to synthesize the existing literature to clarify the role of amino acids as potential indicators or contributors to childhood obesity. The study follows the PRISMA 2020 guidelines. A comprehensive search was conducted across multiple electronic databases, including PubMed, Cochrane Library, Embase, Web of Science, Google Scholar, Semantic Scholar, and ResearchRabbit, using relevant keywords such as "childhood obesity," "amino acids," and "branched-chain amino acids (BCAAs)."Heterogeneity among studies was assessed using the chi-square test and the I^2 statistic. Publication bias was evaluated using funnel plots and Egger's test. Five studies involving a total of 1,229 participants met the inclusion criteria. A significant association was observed between amino acid levels and obesity in children. Specifically, glutamine was inversely associated with obesity (SMD = –0.48, 95% CI: –0.85 to –0.11), while leucine (SMD = 0.79, 95% CI: 0.20 to 1.38) and valine (SMD = 0.67, 95% CI: 0.18 to 1.15) were positively associated. Additionally, odds ratio analysis indicated that higher glutamine levels were associated with 56% lower odds of obesity (OR = 0.44, 95% CI: 0.21–0.94, P < .01), suggesting a potential protective role. Elevated levels of specific amino acids, particularly BCAAs, were consistently linked to increased body mass index (BMI) and other obesity-related indicators in children. Future research should focus on longitudinal and interventional studies to better understand these associations and explore targeted strategies involving amino acid metabolism to help prevent and manage childhood obesity.
Keywords: childhood obesity, amino acids, branched-chain amino acids (BCAA), metabolomics.

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Introduction
Obesity is a significant global health issue affecting both adults and children. Pediatric obesity is closely linked to various metabolic abnormalities(1). Obesity can be evaluated using various methods such as body mass index (BMI), waist circumference, waist-to-height ratio, and body fat percentage calculated from skinfold thickness or more precise measures like bioelectrical impedance analysis. Although BMI, adjusted for age and sex, is the most common metric for obesity in children, other measures of central body fat distribution, such as waist circumference and visceral fat, are less frequently studied in children. Metabolite-derived biomarkers offer promising potential for predicting future cardiometabolic diseases more accurately than weight or traditional risk factors, even in early life stages(2). Childhood overweight and obesity greatly increase the risk of developing metabolic diseases in adulthood. This highlights the importance of early preventive measures to tackle obesity, which can lead to better health outcomes later in life. Obesity related conditions include nonalcoholic fatty liver disease, type 2 diabetes, and polycystic ovary syndrome(3). To create effective treatment strategies, it's crucial to thoroughly understand the pathophysiological mechanisms related to obesity. Eating foods high in fat and protein contributes to obesity. Dietary protein contains over 20% branched-chain amino acids (BCAAs), which are notably increased in metabolic-associated fatty liver disease (MAFLD)(4). Branched-chain amino acids (BCAAs), such as valine, isoleucine, and leucine, along with aromatic amino acids (AAAs) like tyrosine, phenylalanine, and tryptophan, are strongly linked to metabolic risk.

It has long been established that plasma levels of amino acids (AAs) are altered in obese adults, Specifically, an elevated pattern in BCAA levels distinctively separates lean individuals from those with obesity(3). Metabolomics has become an influential method for identifying new risk factors, aiding in the early detection of various health traits. Both BCAA and AA serum levels are elevated in obese individuals and animal models(1). Elevated BCAAs could help identify various obesity-related complications, including insulin resistance, dyslipidemia, and MAFLD, as detailed in the review paper. Moreover, a link was observed between daily BCAA intake and a higher risk of overweight and insulin resistance in children of mothers with gestational diabetes mellitus(5).

This study aims to identify metabolomic profiles linked to obesity and metabolic traits. Recent advancements in laboratory techniques and data processing tools have enabled large-scale, simultaneous analysis of numerous metabolites in human biofluids or tissues. The human serum metabolite profile mirrors metabolic processes, including disease-related changes. Studying serum metabolite concentrations in obese children could provide new insights into the biological mechanisms of childhood obesity. Few studies have examined these changes in the serum metabolome of adults and adolescents.

Method
This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy and Reporting
We conducted a comprehensive search for relevant studies in several electronic databases from 2008 to October 2024. The following databases were searched: PubMed, Scopus, Embase, and Web of Science. The search strategy was tailored to each database and included a combination of keywords, subject headings, and Boolean operators.

Search Strings:
PubMed: ("Amino Acids" OR "Circulating Amino Acids") AND ("Childhood Obesity" OR "Childhood Overweight") AND ("Systematic Review" OR "Meta-Analysis")

Scopus: ("Amino Acids" AND "Childhood Obesity") AND ("Systematic Review" OR "Meta-Analysis")
Embase: ('Amino Acid*' AND 'Childhood Obesity') AND ('Meta-Analysis' OR 'Systematic Review')
Web of Science: TS=("Amino Acids" AND "Childhood Obesity") AND TS=("Systematic Review" OR "Meta-Analysis")
Boolean Operators: The searches used Boolean operators (AND, OR) to combine search terms effectively. For example, "Amino Acids" OR "Circulating Amino Acids" was combined with "Childhood Obesity" OR "Childhood Overweight."

Filters Applied:

Language: English-only articles were included.
Publication Date: Studies published between 2008 and October 2024 were considered.
Study Design: We applied filters to select observational studies, systematic reviews, and meta-analyses, as per the eligibility criteria.
The search strategy aimed to capture all relevant studies that examined the association between circulating amino acids and childhood obesity.

Study Selection

The inclusion criteria were:
(a) Studies that investigated the relationship between circulating amino acids in blood and childhood obesity, including those that analyzed the association between amino acid levels and obesity outcomes.
The exclusion criteria were:
(a) Studies that reported only the concentration of amino acids in the blood without linking these concentrations to childhood obesity outcomes (i.e., studies that did not investigate the association between amino acids and obesity, but only reported raw levels).
(b) Studies that did not include participants with obesity, including studies that only involved healthy controls or other conditions.
(c) Studies that did not provide sufficient data for meta-analysis (e.g., missing key statistical information or outcome measures necessary for the analysis).
For studies that involved multiple measurements or time points within a single cohort, we applied the following guidelines:
If the study presented multiple measurements of amino acid levels over time, we included the most relevant measurement (e.g., the first measurement or the measurement closest to the intervention or comparison timepoint).
If the study reported results for distinct subgroups (e.g., different age groups or genders), we included data for the overall population or the subgroup that most closely aligned with our inclusion criteria.
PECOS was defined as:
Population: Children with obesity
Exposure: The relationship between circulating amino acids in blood and childhood obesity
Control: General population without obesity
Outcomes: Comparison of circulating amino acid levels in the intervention and control groups
Study Design: Cross-sectional and case-control studies

Data Extraction

A data extraction form was designed to collect relevant information from the included studies, such as study characteristics (first author, publication year, country, sample size, Participants
Age, type of Study and type of amino acids).

Statistical Analysis

The meta-analysis was performed using STATA Version 17. Dichotomous outcomes were analyzed using odds ratios (OR) with 95% confidence intervals (CI), and continuous outcomes were analyzed using standardized mean differences (SMD) with 95% CI. To combine the results from studies reporting OR, we converted OR to SMD using the following formula:
Ln OR=(3π)×SMD, The formula relates the natural logarithm of the odds ratio (OR) to the Standard Mean Difference(SMD). The formula shows a proportional relationship where SMD is directly related to the log of the OR. Standard error calculations for SMD can be derived using the standard error of the log of OR, multiplied by a factor that may include a variance inflation factor for clustering. This conversion is based on established methods to standardize effect sizes across different types of outcomes. This allows for more consistent comparisons of effect sizes across studies, particularly when outcomes are measured in different units or scales(6).

Heterogeneity Assessment:

The Q test and I^2 index were used to assess the heterogeneity of the studies. High heterogeneity was observed in several outcomes, with I^2 values exceeding 70%(6). To investigate potential sources of this heterogeneity, we performed subgroup analyses based on relevant factors such as:
Age group (e.g., younger children vs. adolescents)
Geographic region (e.g., North America, Europe, Asia)
Measurement methods (e.g., different assays or laboratory techniques used to measure circulating amino acids)

Sensitivity Analysis:

To assess the robustness of our findings, sensitivity analyses were conducted. These analyses examined whether the inclusion of studies with different methodological characteristics (e.g., sample size, quality of reporting) influenced the overall effect estimates.

Meta-regression:

Meta-regression was performed to explore potential sources of heterogeneity further(7). Additional covariates were included in the model, such as:
Study design (e.g., cross-sectional vs. case-control)
Participant characteristics (e.g., BMI thresholds, gender)

Amino acid measurement methods

These analyses helped identify factors that may explain variability among studies and assess the robustness of the findings under different conditions.
A funnel plot was used to assess publication bias. Additionally, Egger's test and meta-regression were used to evaluate the significance of publication bias and other sources of heterogeneity.

Results

Study selection

508 related studies were found by searching in the databases, 132 studies in PubMed, 211 in Google Scholar, 101 studies in Cochrane, and 64 studies in Web of Sciences, 41 studies were found by checking the references, after removing 56 duplicate studies, 493 articles were screened and reviewed. Out of 493 studies, 432 studies were excluded based on non-relevant titles or abstracts, 56 studies were excluded for the following reasons:

No original research, insufficient data, and no relevant outcomes. A total of 5 articles met our inclusion criteria and were finally included in this meta-analysis (Fig. 1).

Characteristics of included studies

In 5 studies, the sample size was 1229 people. The general characteristics of the studies included in the meta-analysis are given in Table 1.

Quality Assessment

The risk of bias assessment in 5 studies was performed using the Newcastle Ottawa Scale checklist (NOS). Table 2 showed the majority of studies were of high quality and there was not a single included study with a high enough overall risk of bias to be removed from the analysis.

Outcomes

From the 5 studies that were reviewed, the following results were obtained:

Glutamine: According to Figure 2A, there is a significant difference between the amount of glutamine amino acid in the blood and obesity, indicating that glutamine levels decrease in individuals with obesity (SMD: -0.48, 95% CI: -0.85, -0.11, P<0.01). Moreover, the odds ratio (OR) analysis suggested that higher glutamine levels are associated with lower odds of obesity by approximately 56% (OR=0.44, 95% CI: 0.21–0.94, P<0.01).

Valine: There is a significant difference between the amount of valine amino acid in the blood and obesity, Figure 2 B shows that valine levels increase in obese people (SMD: 0.79, 95% CI: 0.20, 1.38, P<0.01).

Leucine: There is a significant difference between the amount of leucine amino acid in the blood and obesity, In obese people, the amount of leucine in the blood increases (SMD: 0.67, 95% CI: 0.18, 1.15, P<0.01) Figure 2 C.

Publication bias

Figures 3A to 3C showed funnel plot outcomes of circulating amino acids of blood and childhood obesity. It visually showed an effect of publication bias not significance in all outcomes. To answer this question "Do unpublished studies can change the results of this study?" Regression-based Egger test for small-study effects showed the effect of publication bias was not significant. Comparison effect size estimate (Theta) and 95% CI in Table 3A showed 95% CI in observed and observed+ imputed groups had overlap so we can say the unpublished article did not have a significant effect on the overall effect (Table 3A).

To explore the source of heterogeneity and the effect of the year of publication on effect size multivariate meta-regression was applied, the results of meta-regression showed that there was not significant association between the year of publication and effect size (Table 3B).

Discussion

This meta-analysis examined five studies involving 1,229 participants to explore the relationship between circulating amino acids and obesity, with a focus on glutamine, valine, and leucine. The results revealed significant associations between these amino acids and obesity. Specifically, glutamine levels were lower in obese individuals, while valine and leucine levels were higher compared to those of normal weight individuals. The reviewed studies provided various insights into the role of amino acids in obesity. Moran Ramos et al. identified a serum amino acid signature linked to obesity, including arginine, leucine, isoleucine, phenylalanine, tyrosine, valine, and proline (OR = 1.57, P = 3.84 × 10−31). Campos et al. observed altered amino acid profiles in overweight children, including elevated branched-chain amino acids (BCAAs) and reduced glycine levels, with BMI positively correlating with BCAA and negatively with glycine levels. Bugajska et al. found elevated plasma levels of leucine, isoleucine, valine, and other amino acids in overweight and obese children compared to controls(5). Azab et al. showed that increases in BCAA, glutamic acid, threonine, and oxoproline were associated with a higher likelihood of obesity, while higher glutamine/glutamic acid ratios were linked to a reduced risk of obesity(2). Takashina's study highlighted that visceral obesity was associated with elevated levels of BCAAs, lysine, tryptophan, cystine, and glutamate, while other amino acids like glutamine and glycine were lower(4).

However, these findings must be interpreted with caution due to the limitations of observational studies, including confounding factors such as diet, physical activity, and socioeconomic status. A sensitivity analysis was conducted to exclude studies that lacked adequate adjustment for these confounders, but residual confounding remains a concern.

Biological Mechanisms and Potential Interventions:

Amino acids, especially BCAAs and glutamine, play crucial roles in metabolic processes. Dysregulation of these amino acids can lead to insulin resistance, dyslipidemia, and inflammation—metabolic disturbances commonly seen in obesity. Elevated BCAAs are linked to impaired insulin signaling and disrupted glucose uptake, while glutamine dysregulation contributes to metabolic dysfunction and inflammation.

Interventions targeting amino acid metabolism could offer promising therapeutic strategies for childhood obesity. Dietary modifications, such as protein restriction or amino acid supplementation, may restore balance in amino acid levels and improve insulin sensitivity. Exercise also plays a role in regulating amino acid metabolism. Additionally, metabolic monitoring through techniques like metabolomics could facilitate early detection of obesity-related metabolic disturbances.

Future Research Directions:

Longitudinal Studies: These studies should track changes in amino acid levels over time to establish causal links with obesity and related metabolic disorders.

Dietary Modifications: Further research on how dietary changes impact amino acid levels, including studies on protein-restricted diets or amino acid supplementation (e.g., BCAA restriction or glutamine supplementation), could help prevent or reverse obesity-related metabolic dysfunction.

Gut Microbiota: Understanding how the gut microbiome influences amino acid metabolism is essential, as recent research suggests it may affect amino acid availability and metabolism in the host.

Clinical Trials: Conducting clinical trials on amino acid-targeted interventions, such as BCAA restriction or glutamine supplementation, could assess their effectiveness in treating or preventing obesity and metabolic disorders.

Implications for Intervention and Future Studies:

The findings of this meta-analysis underline the need for further research to explore the role of amino acids in childhood obesity. Future studies should focus on designing intervention trials, including dietary modifications and amino acid supplementation, to assess their impact on childhood obesity and related metabolic markers. Additionally, longitudinal cohort studies could provide more insights into how amino acid levels track with obesity development over time.

Metabolic monitoring programs using advanced techniques like metabolomics could help track amino acid levels and detect early signs of metabolic dysfunction in children at risk for obesity. Finally, multi-faceted interventions that combine dietary changes, exercise, and behavioral therapy may provide a holistic approach to improving both amino acid metabolism and overall health in obese children.

Limitation

The limitations of this study were; few studies were done in this field, so we could not do subgroup analysis, in original article some studies did adjustment for some confounder, but due to small study were done in this field we could not do sensitivity analysis and exclude some study with insufficient adjustment.

Conclusion

Elevated levels of specific amino acids, particularly branched-chain amino acids (BCAAs), were consistently linked to increased body mass index (BMI) and other obesity-related metrics in children, Future research should focus on longitudinal studies to further elucidate these relationships and explore the potential for targeted interventions based on amino acid metabolism to combat childhood obesity.

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Conflicts of interest
The authors have no financial conflicts of interest.

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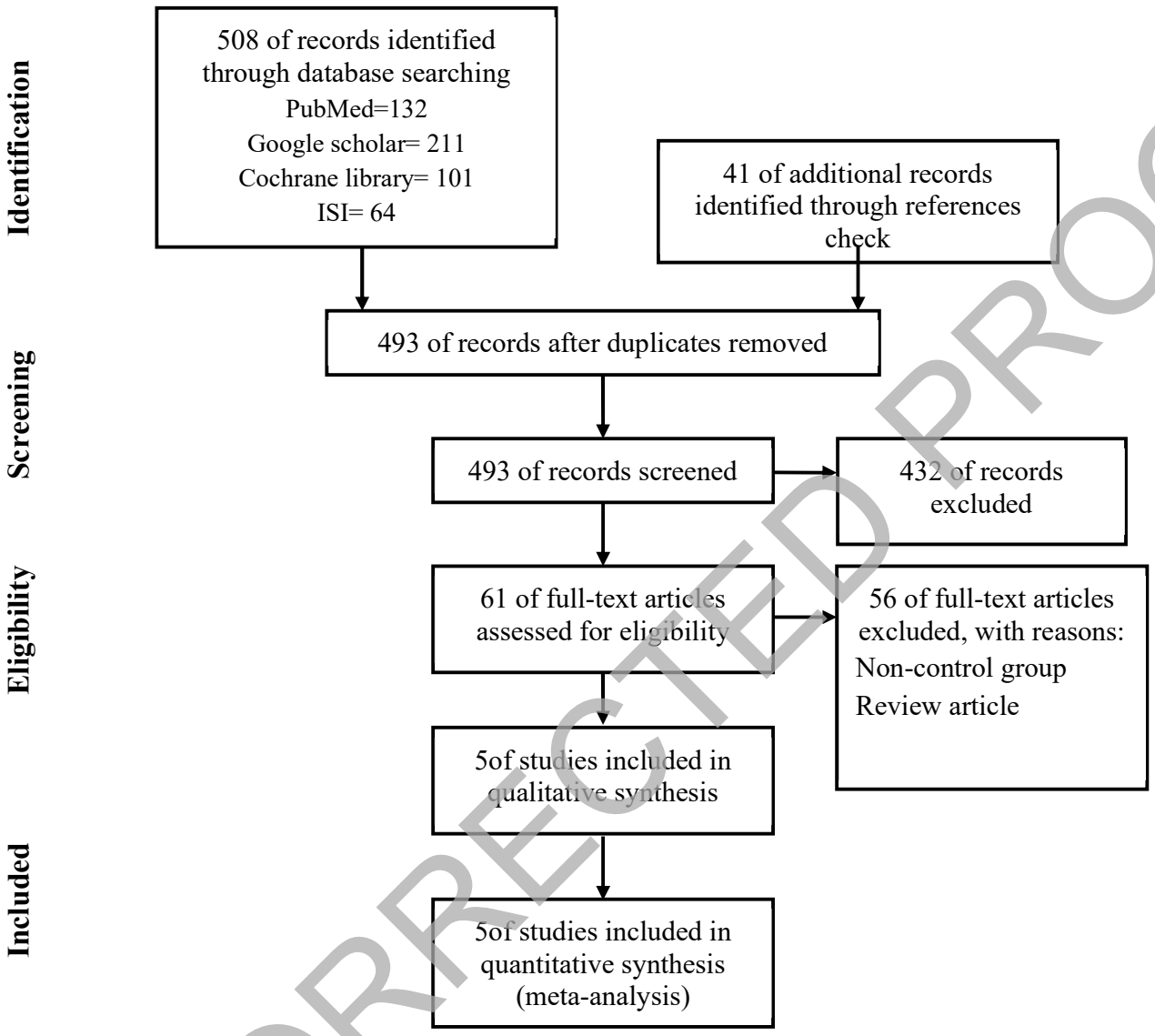

Figure 1: PRISMA flow diagram includes studies
*1 indicate Glutamine, 2 indicate Valine, 3 indicate Leucine

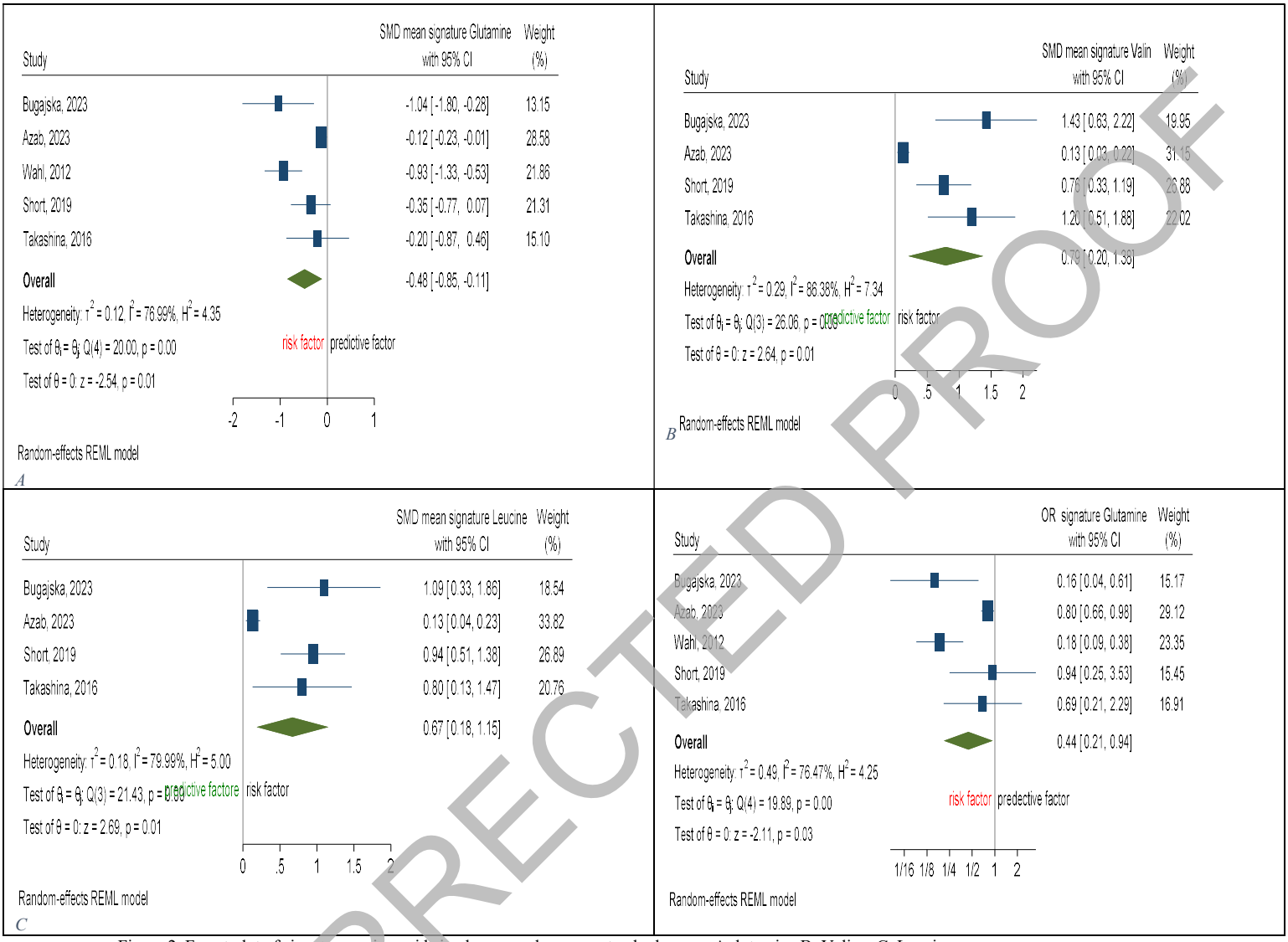

Figure 2. Forest plot of signature amino acids in obese people versus standard group; A: lutamine B: Valine, C: Leucine

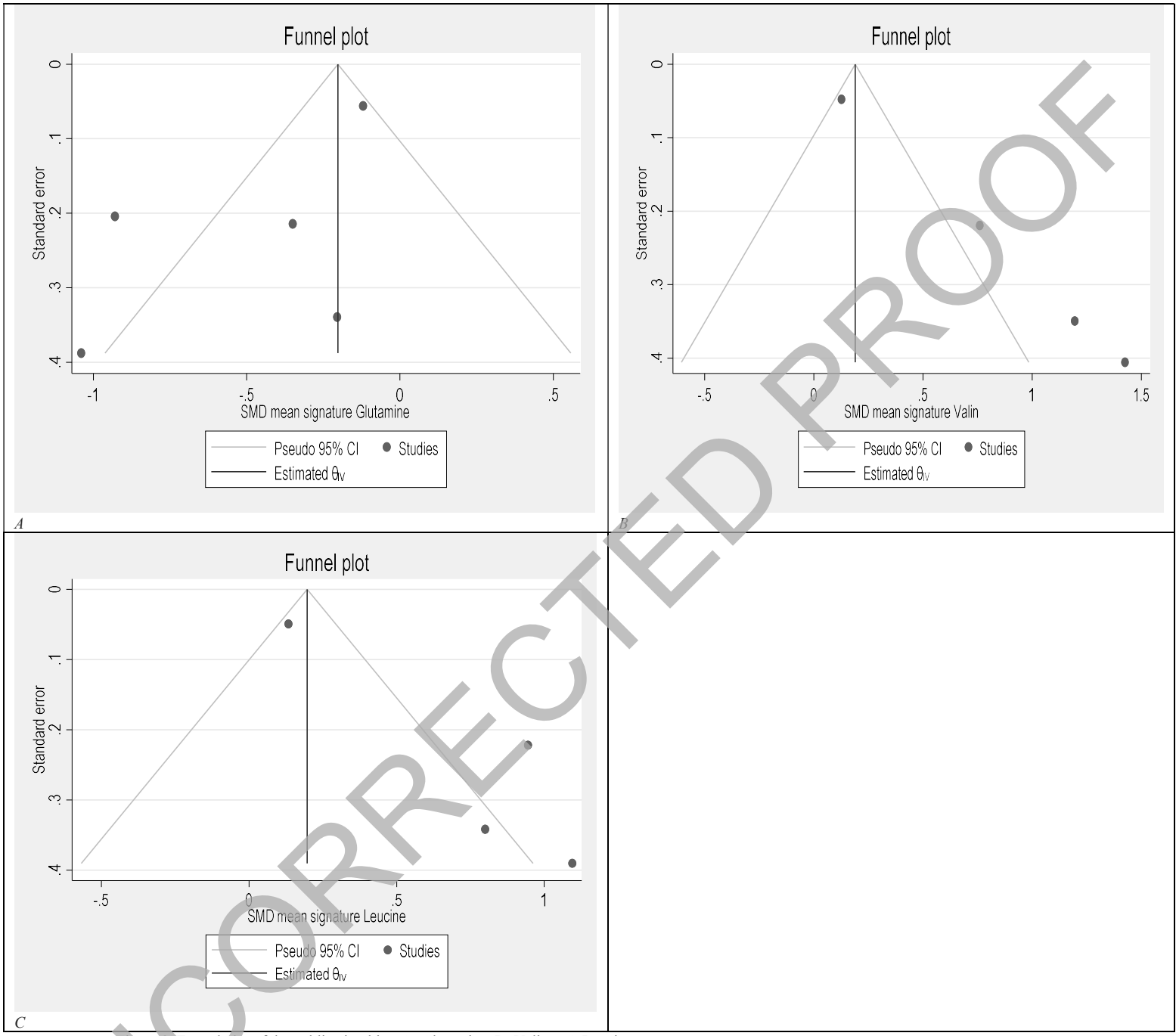

Figure 3. Funnel plot of the publication bias. A: Glutamine, B: Valine, C: Leucine

Table 1. Characteristics of included studies								
Author	**Year**	**Country**	**Sample Size**	**Participants (Age: Mean ± SD)**	**Type of Study**	**Outcomes Assessed***	**Method of Measurement (Amino Acids)**	**Definition of Obesity**
Bugajska(5)	2023	Poland, Hungary	32	Obese children: 7.7 ± 2.3	Case-control	1, 2, 3	**HPLC** or **Mass Spectrometry**, µmol/L	BMI > 95th percentile
Azab(2)	2023	Canada	900	Obese children: 5.02 ± 0.11	Cross-sectional	1, 2, 3	**LC-MS/MS**, µmol/L	BMI > 95th percentile
Short(7)	2019	United States	94	Obese children: 13.9 ± 6.1	Cross-sectional	1, 2, 3	**HPLC** or **Enzymatic Assays**, µmol/L	BMI > 95th percentile
Takashina(4)	2016	Japan	83	Obese children: 35.2 ± 3.8	Cross-sectional	1, 2, 3	**GC-MS** or **LC-MS/MS**, µmol/L	BMI > 25 (adults) or > 95th percentile (children)
Wahl(8)	2012	Germany	120	Obese children: 10.9 ± 2.1	Case-control	1	**LC-MS/MS**, µmol/L	BMI > 95th percentile

Table 2 - Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Author/Year	**Newcastle-Ottawa Scale**											
	Selection					**Comparability**			**Outcome**			**Total**	**Quality**
	1[a]	2[b]	3[c]	4[d]		5[e]	6[f]		7[g]	8[h]	9[i]		
Bugajska(5)	*	*	*	*		*	*		*	*	*	9	good
Azab(2)	*	*	*	*		*	*		*	*	*	9	good
Short(7)	*	*	*	*		*	*		*	*	*	9	good
Takashina(4)	*	*	*	*		*	*		*	*	*	9	good
Wahl(8)	*	*	*	*		*	*		*	*	*	9	good

[a] Representativeness of the exposed cohort
[b] Selection of the non-exposed cohort *
[c] Ascertainment of exposure
[d] Demonstration that outcome of interest was not present at start of study
[e] Comparability of cohorts on the basis of the design or analysis (adjusted for age)
[f] Comparability of cohorts on the basis of the design or analysis (adjusted for any other factor)
[g] Assessment of outcome
[h] Was follow-up long enough for outcomes to occur
[i] Adequacy of follow-up of cohorts

Table 3A. Comparison between observed and observed imputed estimates of effects sizes				
Imputation unpublished study	studies	Theta	95% confidence Interval	
SMD mean signature Glutamine	observed	-0.202	-0.303	-0.102
	Observed+ imputed	-0.123	-0.217	-0.029
SMD mean signature Valine	observed	0.189	0.099	0.279
	Observed+ imputed	0.170	0.081	0.258
SMD mean signature Leucine	observed	0.197	0.104	0.290
	Observed+ imputed	0.174	0.084	0.263

Table 3B. Multivariate meta-regression year and effects sizes					
	covariates	Coefficient	Std. err	Z	P
SMD mean signature Glutamine	year	0.0396753	0.0395884	1.00	0.316
SMD mean signature Valine	year	-0.0689771	0.111275	-0.62	0.535
SMD mean signature Leucine	year	-0.0594674	0.0890073	-0.67	0.504