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Review

Amino Acid Pattern Signatures in Pediatric Obesity, Dysglycemia, and Fatty Liver Disease: Links to Insulin Resistance and the IGF-1 Axis

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ABSTRACT

Amino acid (AA) pattern shifts are increasingly recognized as early biochemical fingerprints of pediatric obesity and its metabolic sequelae. In children and adolescents, elevations in branched-chain AAs (BCAAs: leucine, isoleucine, valine), aromatic AAs (AAAs: phenylalanine, tyrosine), and glutamate—often coupled with reductions in glycine and serine—have been repeatedly linked to insulin resistance (IR), dysglycemia, and metabolic dysfunction-associated fatty liver disease (MASLD/NAFLD). These signatures may reflect impaired BCAA catabolism, altered mitochondrial substrate handling, hepatic nitrogen flux, and adipose-liver crosstalk, and they may provide complementary risk stratification beyond standard clinical markers. (1) To summarize AA pattern changes characteristic of pediatric/adolescent obesity, prediabetes, diabetes, and fatty liver disorders and their relationship to insulin resistance. (2) To synthesize evidence linking AA signatures to IGF-1 biology and developmental covariates (age, sex, puberty), and to discuss management implications. A structured review (last 20 years) of PubMed/Scopus-indexed literature was performed, prioritizing pediatric/adolescent studies. We included targeted and untargeted metabolomics studies reporting fasting or standardized AA measures in: (i) obesity/obesity phenotypes, (ii) prediabetes/abnormal glucose tolerance, (iii) Type 1 or Type 2 diabetes, and (iv) NAFLD/MASLD, with outcomes involving IR (HOMA-IR, clamp-derived indices), hepatic steatosis (MRI/MRS, ultrasound, biopsy), or cardiometabolic risk clustering. We narratively synthesized AA directionality and consistency across conditions and platforms. Risk of bias was assessed using RoB 2 for randomized trials and ROBINS-I for non-randomized studies. Across multiple pediatric cohorts, obesity was most consistently associated with higher BCAAs, AAAs, glutamate, and several BCAA-derived intermediates, with lower glycine/serine in metabolically higher-risk phenotypes. Several studies linked AA signatures to future IR or hypertriglyceridemia and identified associations with metabolically unhealthy obesity. In youth with dysglycemia or Type 2 diabetes risk, AA profiles were heterogeneous across studies but increasingly support combined panels (BCAA/AAA elevation with glycine reduction and glutamine-glutamate imbalance) to capture β-cell stress and IR-related trajectories. In pediatric NAFLD, AA signatures (notably BCAA dysregulation and glutamate-related indices) were associated with steatosis burden and, in some studies, predicted liver fat independent of BMI and conventional risk factors. Developmental effects were substantial: age, sex, and pubertal stage modified AA distributions, and IGF-1-linked metabolomic relationships suggest GH/IGF axis-metabolism coupling. AA patterns provide biologically plausible, developmentally modulated candidate biomarkers which align with IR, dysglycemia, and pediatric fatty liver risk. Future pediatric studies should standardize sampling, puberty adjustment, and analytic pipelines, and should test whether AA-informed risk stratification improves prevention and treatment response monitoring.

Keywords: Amino acids, insulin resistance, pediatric obesity, NAFLD/MASLD, IGF-1

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Introduction

Amino acids are not only building blocks for protein synthesis, but also key metabolic signals integrated with mitochondrial function, hepatic nitrogen handling, and nutrient-sensing pathways. Modern metabolomics has expanded the clinical view of AAs by revealing reproducible, disease-linked shifts in circulating AA patterns across metabolic disorders (1). Among these, elevations in BCAAs and AAAs have emerged as particularly robust correlates of insulin resistance and future diabetes risk in adult and pediatric populations, suggesting shared upstream mechanisms such as impaired BCAA catabolism, altered substrate competition, and dysregulated nutrient signaling (2-5).

Beyond BCAAs, several 'counter-pattern' AAs, especially glycine and serine, often show reductions in metabolically at-risk states. Glycine deficiency states may reflect increased one-carbon demand, oxidative stress buffering, and constrained conjugation capacity for acyl-group disposal, while the glutamine-glutamate axis can reflect altered transamination, hepatic metabolism, and mitochondrial flux (6,7). Evidence syntheses indicate that AA panels (BCAA/AAA elevation plus lower glycine/serine and glutamine-glutamate imbalance) are among the most consistent metabolite features linked to prediabetes/diabetes risk, supporting their role as integrated markers of early metabolic dysfunction (8).

In pediatrics, obesity is a heterogeneous condition with variable cardiometabolic risk clustering; therefore, metabolite-based fingerprints are appealing adjuncts to BMI-based classification. Systematic reviews of pediatric obesity metabolomics consistently highlight AA disturbances, particularly BCAAs, AAAs, and related intermediates, alongside lipid and acylcarnitine changes (9,10). Pediatric-focused reviews similarly emphasize that AA alterations can be detectable early in life, may precede overt dysglycemia, and plausibly connect adiposity to hepatic and muscle insulin resistance through impaired BCAA catabolism and nutrient signaling (11-13).

Multiple pediatric cohort and case-control studies have reported higher BCAAs and AAAs in children and adolescents with obesity and have linked these elevations to insulin resistance metrics and future metabolic risk (14-16). Metabolomics studies in obese prepubertal children indicate sex-dependent patterns and suggest that hyperinsulinemia/IR phenotypes are accompanied by distinct AA and related metabolite shifts (17,18). In addition, pediatric studies have shown that tyrosine and related signatures can track longitudinal IR trajectories, supporting AA measures as candidate early markers rather than mere epiphenomena (19,20).

Dysglycemia in youth spans impaired fasting glucose, impaired glucose tolerance, and youth-onset diabetes, with unique developmental considerations (puberty-related physiological IR, growth demands, and evolving β-cell compensation). Pediatric metabolomics studies evaluating AA profiles in dysglycemia and youth-onset diabetes have produced both convergent and divergent findings, likely reflecting differences in age, adiposity, diabetes type, pubertal stage, and analytic platform (21-25). Nevertheless, recent youth-focused work suggests that composite AA signatures may help identify youth at risk for β-cell failure and may distinguish diabetes types, which could support phenotype-aligned prevention and management strategies (23-25).

Pediatric fatty liver disease (NAFLD/MASLD) is closely linked to obesity and insulin resistance and is now a major concern in pediatric practice. As most cited pediatric studies predate the 2023 nomenclature revision, we retain the original study-reported terms (typically NAFLD) when summarizing individual investigations, while using the combined NAFLD/MASLD designation in synthesis statements which span the terminology transition; MASLD is used specifically when a cited study explicitly adopted the revised nomenclature. Clinical guidelines emphasize early identification and risk stratification, typically using clinical risk factors and imaging, yet blood-based metabolic fingerprints remain an active translational gap (26). Pediatric NAFLD metabolomics studies demonstrate AA pathway disruptions often involving BCAA dysregulation and glutamate-related patterns which can associate with hepatic fat independent of BMI and conventional risk markers (27-35). Importantly, normal developmental variation (age, sex, puberty) strongly influences AA distributions and intersects with growth biology and IGF-1 signaling (36,37). This creates a need for pediatric-specific interpretation frameworks and motivates this review's focus on AA pattern characteristics across obesity, dysglycemia, diabetes, and fatty liver disorders in relation to IR and the IGF-1 axis.

Objectives

1. To characterize AA pattern changes reported in pediatric/adolescent obesity, prediabetes, diabetes, and fatty liver disorders, and to summarize their associations with insulin resistance and metabolic risk phenotypes.

2. To integrate developmental and endocrine context, focusing on IGF-1 and puberty-related modifiers of AA signatures, and to discuss practical management implications and research priorities.

Materials and Methods

PRISMA 2020 principles were used to improve transparency of literature identification and study selection (14-53). As the included literature used heterogeneous analytic platforms (targeted versus untargeted metabolomics), varied sampling conditions (fasting versus standardized sampling windows), and reported outcomes which were not directly comparable across studies, we prioritized a structured narrative synthesis supported by tabulation rather than conducting a pooled meta-analysis (54-56).

We searched PubMed and Scopus for English-language articles published from January 1, 2006 through March 1, 2026. Search terms were built around four concept blocks: (i) amino acid exposure terms ('amino acid*,' 'branched chain amino acid*,' 'aromatic amino acid*,' 'glycine,' 'glutamate,' 'glutamine'), (ii) pediatric population terms ('child*,' 'adolescent*,' 'pediatric'), (iii) target conditions and outcomes (obesity, insulin resistance, prediabetes, impaired glucose tolerance, diabetes, fatty liver, NAFLD, MASLD), and (iv) metabolomic methods (metabolomics, mass spectrometry, LC-MS, GC-MS, NMR). In addition, reference lists of key reviews and eligible studies were hand-searched to identify relevant pediatric metabolomics papers that might not have been retrieved by the database terms alone. Titles and abstracts were screened for pediatric relevance and amino-acid content, followed by full-text assessment against the eligibility criteria described below.

Study selection and evidence identification. The database and reference-list searches identified literature addressing amino-acid and metabolomic patterns in pediatric obesity, dysglycemia/diabetes, fatty liver disease, and developmental or IGF-1-related metabolic phenotypes. Because the original record-level PubMed and Scopus search exports were not retained, exact database-specific identification, deduplication, and title/abstract screening counts could not be reliably reconstructed retrospectively and were therefore not estimated. A retrospective audit of the final evidence set identified 58 cited references. Three references were methodological/reporting sources relating to PRISMA 2020, RoB 2, and ROBINS-I and were not considered substantive evidence. Of the remaining 55 substantive references assessed, 23 consisted of systematic or narrative reviews, clinical practice guidelines, predominantly adult mechanistic/context studies, or other supporting sources that were not counted as primary pediatric studies. The final primary-study synthesis therefore comprised 32 unique pediatric or pediatric-relevant primary studies. Additional reviews, guidelines, and mechanistic studies were retained exclusively to provide biological, methodological, and clinical context and were clearly distinguished from the primary pediatric evidence (Figure 1).

Eligible studies primarily included children and adolescents (typically ≤18 years); however, we also included studies enrolling youth/young adults up to 24 years when the cohorts were clearly pediatric-relevant (for example, bariatric surgery cohorts initiated in adolescence). We included observational (cross-sectional, case-control, and cohort) and interventional designs which reported circulating amino acids measured under fasting or otherwise standardized sampling conditions. The included studies were required to report at least one relevant metabolic outcome, including insulin resistance (HOMA-IR, clamp-derived indices, or validated surrogates of insulin sensitivity), glycemic phenotypes (prediabetes, impaired glucose tolerance, youth-onset diabetes), and/or hepatic steatosis assessed by MRI/MRS, ultrasound, or histology. Studies using targeted amino-acid panels, untargeted metabolomics with explicit amino-acid outputs, or broader metabolite profiling which clearly reported amino-acid findings were all eligible. We excluded adult-only cohorts without pediatric stratification (unless used solely for mechanistic context in the IGF-1, NAFLD/MASLD, or intervention-focused sections, where they are explicitly labeled as adult/context-only and are not treated as pediatric evidence), non-human studies (not tabulated in this review), and reports which did not provide extractable directionality for amino-acid changes or did not include relevant metabolic outcomes.

For each eligible study, we extracted the study design, sample size, age range, phenotype definitions (obesity class, metabolic-risk clustering, dysglycemia definition), metabolomic platform, key amino-acid directionality (increase/decrease), and primary associations with insulin resistance and/or liver fat. As effect measures and analytic strategies varied widely, we synthesized findings using a structured qualitative framework. This included consistency mapping (whether a given amino-acid pattern was directionally replicated across multiple pediatric studies), phenotype anchoring (whether the pattern aligned more closely with metabolically unhealthy obesity, dysglycemia risk, or NAFLD/MASLD), and assessment of context

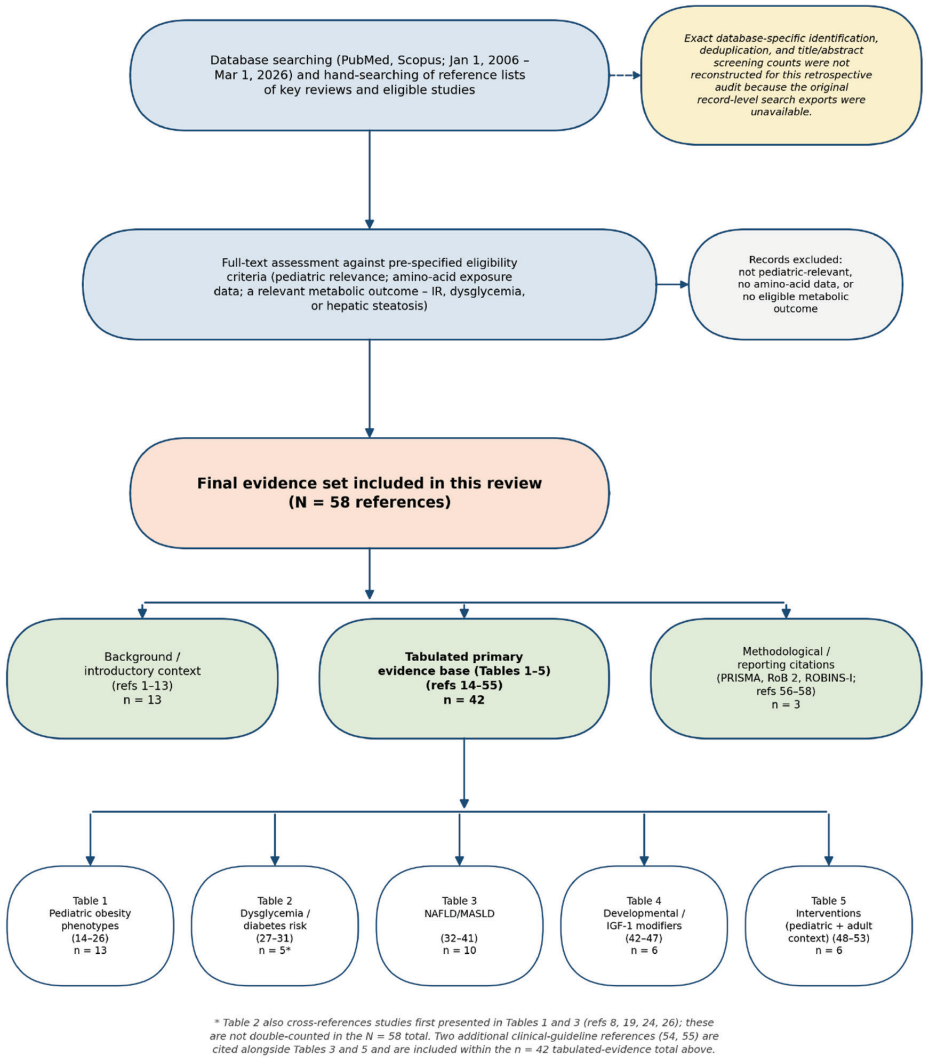

Figure 1. PRISMA 2020-style flow diagram of study selection (retrospective evidence-set audit). The diagram reports a retrospective audit of the final evidence set. Exact database-specific identification, deduplication, and title/abstract screening counts were not reconstructed because the original record-level search exports were unavailable

Algorithm (for figure box)

Step 1 - Identify the at-risk patient: Child/adolescent with overweight/obesity or metabolic risk (family history, rapid weight gain, acanthosis, elevated BP, dyslipidemia, or elevated ALT). Document age, sex, and pubertal stage.

Step 2 - Standard metabolic phenotyping: Fasting glucose and HbA1c (± OGTT if indicated), fasting insulin (HOMA-IR), lipids, ALT/AST (± GGT), and blood pressure; consider hs-CRP and uric acid when relevant.

Step 3 - Add endocrine context when indicated: If growth or pubertal concerns are present, measure IGF-1 (standard deviation score, SDS) and interpret metabolite findings with developmental context.

Step 4 - Trigger AA profiling (adjunct tool): Use fasting, standardized sampling for targeted AA panel (± acylcarnitines) when phenotype is metabolically unhealthy, IR is rising, dysglycemia risk is high, or NAFLD/MASLD is suspected.

Step 5 - Interpret the AA signature (puberty/sex-adjusted): Core IR-risk pattern: BCAAs (Val/Leu/Ile) increased, often AAAs (Phe/Tyr) increased, glycine decreased (± serine decreased), and glutamine-to-glutamate ratio decreased (and/or glutamate increased). Consider validated indices when available (e.g., GSG index, BCAA-based liver fat score).

Step 6 - Anchor interpretation to clinical phenotype: Normal glycemia: intensify lifestyle and monitor closely. Dysglycemia/prediabetes: follow pediatric dysglycemia pathway focusing on IR reversal. NAFLD/MASLD suspicion or ALT elevation: proceed to liver imaging (US or MRI-PDFF where available) and hepatology pathway when indicated.

Step 7 - Follow-up and response assessment: Reassess at 3-6 months (BMI-z/waist, glycemia, HOMA-IR, ALT, lipids). If AA profiling is used, repeat under identical conditions and interpret changes alongside clinical improvement.

modifiers such as pubertal stage, sex, ethnicity, fasting status, and sampling conditions.

No quantitative pooling of effect sizes was performed. Instead, we summarized whether each study reported an association, the direction of the effect, and whether the association persisted after adjustment for adiposity and other covariates when such models were reported. When studies developed composite scores or indices (for example, amino-acid-based prediction models for liver fat), we extracted the reported discrimination or predictive performance and described these findings narratively in order to maintain comparability across heterogeneous designs.

Risk of bias was assessed using RoB 2 for randomized trials (57). For non-randomized observational and interventional studies, we used ROBINS-I (58) domains covering confounding, participant selection, classification of exposures/interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Study-level judgments were summarized as low, moderate, or serious risk of bias and then condensed across evidence themes in order to contextualize confidence in the overall patterns described.

Results

Overview of Included Evidence

Across pediatric and youth studies, the most frequently observed AA pattern in metabolic risk states was BCAA/AAA elevation with lower glycine/serine and glutamine-glutamate imbalance, although the magnitude and specific AAs varied by phenotype definition, pubertal stage, and analytic platform (9-13). Evidence was strongest for obesity and NAFLD signatures (14-20,27-35) and increasingly supportive for dysglycemia risk signatures in youth (21-25).

Across diverse pediatric cohorts, obesity, especially metabolically higher-risk obesity, shows reproducible AA shifts centered on BCAA/AAA elevation and related intermediates, with additional signals involving glutamate, tyrosine, and BCAA-derived metabolites (e.g., 3-hydroxyisobutyrate). Longitudinal data suggest some AA changes (e.g., tyrosine) may appear early along the IR trajectory (14-26).

Pediatric dysglycemia evidence supports composite AA signatures rather than single AAs, but findings vary by developmental stage and diabetes subtype (27-31). Newer pediatric studies suggest AA panels may help capture β-cell stress risk and differentiate T1D vs T2D signatures (29,31), while systematic evidence synthesis provides interpretive scaffolding (8).

Pediatric NAFLD studies consistently implicate BCAA dysregulation and glutamate-related indices, with some approaches showing promise for non-invasive prediction of liver fat (34,36-38). Dietary AA composition may also play a role, but causal direction and pediatric intervention evidence are still limited (39-41).

AA signatures are developmentally dynamic and influenced by the GH/IGF axis. Pediatric interpretation of AA risk panels should therefore consider pubertal stage and IGF-1 status, especially when comparing across cohorts or tracking individuals longitudinally (42,43,51,52).

Pediatric intervention data suggest AA profiles, particularly BCAAs, can shift with substantial metabolic improvement (e.g., bariatric surgery), while lifestyle programs may yield broader metabolomic shifts reflecting improved cardiometabolic biology. Mechanistic adult data caution that tissue BCAA catabolism can change without large plasma BCAA shifts, and that glycine context matters for interpreting BCAA-IR relationships.

Evidence is moderate for obesity and NAFLD AA signatures because findings are consistent across cohorts and NAFLD studies often use imaging. Evidence is low-moderate for dysglycemia/diabetes and IGF-1 links due to heterogeneity (definitions, puberty effects, treatments) and fewer robust pediatric datasets. Intervention evidence is low-moderate because most studies are non-randomized, but AA signatures improve when metabolic state improves (especially after surgery). At the individual-study level, each reference in Tables I-VI inherits the risk-of-bias judgment of the evidence cluster to which it is assigned above (Ref numbers listed in the 'Studies included' column); studies which contribute only adult or mechanistic context (explicitly labeled as such in Tables I-VI). are excluded from the pediatric-evidence certainty ratings shown here.

Table I. Amino acid pattern changes in pediatric obesity and obesity phenotypes

Ref	First author (Year)	Design/population	Platform	Key amino-acid findings (direction)	Metabolic association (IR/risk phenotype)
(14)	McCormack (2013)	Cohort; children/adolescents (n=69, ages 8-18 y cross-sectional; longitudinal subset n=17, ages 8-13 y, followed 18 months)	Targeted AAs	↑BCAAs/AAAs in obesity	Baseline BCAA pattern associated with future insulin resistance
(15)	Butte (2015)	Cross-sectional; Hispanic children (n=803; mean age 11.1±3.9y; 56% with obesity)	Untargeted metabolomics	AA clusters (incl. BCAA/AAA) differed by obesity	AA PCs associated with hyperinsulinemia and TG risk
(16)	Mangge (2016)	Cross-sectional; lean/overweight/obese youth [cohort spanned adults and juveniles, mean age 25.3±12.8y; pediatric-relevant subset only]	Targeted BCAAs	↑BCAAs across adiposity strata	BCAAs associated with cardiometabolic risk profiles
(17)	Mastrangelo (2016)	Case-control; obese prepubertal	Targeted metabolomics	Sex-dependent AA shifts; ↑BCAA/AAA patterns in IR	Metabolomic profile correlated with IR severity
(18)	Martos-Moreno (2017)	Targeted metabolomics; obese prepubertal	Targeted metabolomics	Discriminative metabolome in hyperinsulinism	Metabolome separated hyperinsulinemic vs less-affected phenotypes
(19)	Suzuki (2019)	Cross-sectional; childhood obesity (n=26; ages 9-10y)	AA + lipid panels	AA profile linked to IGT; BCAA/AAA signals prominent	AA profile reflected early IGT and HOMA-IR variation
(20)	Hellmuth (2016)	Longitudinal; obese children	Longitudinal metabolomics	Tyrosine tracked IR trajectory; later BCAA shifts	Suggests early AA changes may precede broader BCAA disruption
(21)	Bugajska (2023)	Cross-sectional; overweight/obese prepubertal	AA profiling	Abnormal AA profile in OW/OB	Linked with early markers of cardiometabolic risk and MAFLD signals
(22)	Moran-Ramos (2017)	Cross-sectional + longitudinal school-age cohort	AA signature score	AA signature (incl. BCAA/AAA/proline/arginine)	Predicted 2-year hypertriglyceridemia risk
(23)	Perng (2020)	Cross-sectional adolescents (Project Viva)	Metabolomics	Metabolomic differences across OWOB-MetRisk phenotypes	MetRisk phenotype associated with AA differences incl. BCAA/AAA
(24)	Short (2019)	Cross-sectional + exercise intervention; American Indian adolescents	42 AA panel	Obesity: ↑BCAA/AAA/glutamate; ↓BAIBA; ↑2-AAA	AA levels correlated with adiposity and inversely with insulin sensitivity
(25)	McCann (2021)	Cohort biorepository (POMMS)	Metabolomics/microbiome	Adolescents with obesity show metabolomic patterns overlapping adult risk	Provides pediatric baseline metabolomic context for obesity interventions
(26)	Ng (2025)	Untargeted metabolomics; MHO vs MUO	Metabolomics	MUO linked to AA/FA differences; 3-HIB and BCAA signals	Differences primarily aligned with abnormal glucose homeostasis

AA: Amino acid(s), BCAA: Branched-chain amino acid(s), AAA: Aromatic amino acid(s), IR: Insulin resistance, TG: Triglycerides, IGT: Impaired glucose tolerance, HOMA-IR: Homeostasis model assessment of insulin resistance, MUO: Metabolically unhealthy obesity, MHO: Metabolically healthy obesity, 3-HIB: 3-hydroxyisobutyrate, BAIBA: β-aminoisobutyric acid, 2-AAA: 2-aminoadipic acid

Across these studies, BCAA/AAA elevation with reduced glycine is the most consistent amino-acid signature distinguishing metabolically unhealthy from metabolically healthy obesity.

This pattern is detectable in cross-sectional pediatric cohorts and, in longitudinal data, appears to precede measurable insulin resistance.

Table II. Amino acid patterns in pediatric prediabetes, dysglycemia risk, and diabetes phenotypes

Ref	First author (Year)	Phenotype/population	Platform	Key amino-acid findings	Clinical implication
(8)	Guasch-Ferré (2016)	Evidence synthesis (human studies)	Review/meta-analysis	AA panels (BCAA/AAA ↑; glycine ↓; glutamine-glutamate imbalance) linked to prediabetes/T2D risk	Framework for interpreting AA panels as risk markers
(27)	Michaliszyn (2012)	Obese adolescents ± dysglycemia	Targeted AAs	AA concentrations related to β-cell function relative to insulin sensitivity	Highlights developmental differences vs adults in AA-risk interpretation
(28)	Mihalik (2012)	NW vs obese vs T2D adolescents	Acylcarnitine + AA profiling	T2D youth showed distinct AA/acylcarnitine patterns vs obese/NW	Suggests youth T2D metabolome differs from adult paradigm
(19)	Suzuki (2019)	Childhood obesity with early metabolic abnormalities	AA + lipids	AA profile reflected impaired glucose tolerance early	Supports AA panels for early dysglycemia risk stratification in obesity
(24)	Short (2019)	Obese vs NW adolescents	Targeted AAs	↑BCAA/AAA/glutamate; ↓BAIBA; ↑2-AAA	Candidate AA markers for insulin sensitivity in adolescents
(26)	Ng (2025)	Obesity with abnormal glucose tolerance	Untargeted metabolomics	↑BCAA and 3-HIB; ↓1,5-Anhydroglucitol in abnormal glucose tolerance	Links AA changes to glycemic dysregulation phenotype
(29)	Bacha (2024)	Youth with or at risk for T2D	Targeted AAs	Higher BCAA/AAA and lysine; lower glycine/glutamine-glutamate signals	AA profile proposed to identify risk for β-cell failure
(30)	Perng (2022)	Two youth cohorts; fasting glucose outcomes	Metabolomics + RRR	Sex-specific metabolite predictors of future dysglycemia	Demonstrates predictive modeling using metabolite panels including AAs
(31)	Tosur (2023)	Pediatric T1D vs T2D	Targeted AA metabolomics	Distinct fasting AA signatures by diabetes type	Potential biomarker support for classification/phenotyping

AA: Amino acid(s), BCAA: Branched-chain amino acid(s), AAA: Aromatic amino acid(s), T1D: Type 1 diabetes, T2D: Type 2 diabetes, RRR: Reduced rank regression

Amino-acid signatures differ by diabetes type, with distinct fasting profiles distinguishing pediatric type 1 from type 2 diabetes.

Glycine reduction and BCAA/AAA elevation track with declining insulin sensitivity across the dysglycemia spectrum, supporting their use as early risk markers.

Table III. Amino acid signatures in pediatric NAFLD/MASLD and related fatty liver disorders

Ref	First author (Year)	Study/population	Steatosis assessment	Key amino-acid findings	Clinical signal
(32)	Vos (2017)	NASPGHAN guideline	Guideline	Recognizes NAFLD as obesity/IR-linked	Supports need for better non-invasive biomarkers
(33)	Jin (2016)	Obese adolescents; case-control	MRS	AA metabolism pathways disturbed in NAFLD	Early evidence that AA pathways integral to pediatric NAFLD
(34)	Goffredo (2017)	Obese adolescents with NAFLD (n=78; mean age 13.3±3.0y, range 8-18y)	Imaging + follow-up	BCAA-related metabolomic signature in NAFLD	Signature associated with NAFLD independent of obesity/IR
(35)	Tricò (2018)	Multiethnic obese adolescents	Imaging + metabolic phenotyping	NAFL associated with metabolic features including AA signals	Highlights ethnicity/race and IR interplay in NAFL risk
(36)	Lischka (2021)	Youth with severe obesity	Liver fat prediction	BCAA-based metabolic score predicted liver fat	Practical candidate-biomarker approach for risk stratification
(37)	Leonetti (2020)	Pediatric at-risk cohorts	NAFLD detection	'GSG index' (glutamate-serine-glycine) detected NAFLD	Index associated with NAFLD independent of traditional risks
(38)	Chae (2022)	Overweight pediatric population	Biopsy-proven NAFLD	NAFLD-specific metabolic features included valine/tyrosine/glutamate/glycine	Machine-learning models achieved high AUROC using metabolite features

Table III. Continued

Ref	First author (Year)	Study/population	Steatosis assessment	Key amino-acid findings	Clinical signal
(39)	Nikparast (2024)	Overweight/obese children	Ultrasound + clinician dx	Higher dietary BCAA (esp. leucine) associated with NAFLD odds	Suggests dietary AA composition may modulate NAFLD risk
(40)	Lake (2015)	Progressive human NAFLD [Adult; mechanistic context only] (context)	Histology spectrum	Hepatic BCAA metabolite changes with NAFLD→NASH progression	Mechanistic support for BCAA pathway involvement
(41)	Deng (2024)	Review (MAFLD mechanisms) [Not pediatric-specific; mechanistic context only]	Synthesis	Essential AA signaling intersects lipid handling, inflammation	Frames therapeutic interest but pediatric trials remain limited

AA: Amino acid(s), BCAA: Branched-chain amino acid(s), NAFLD: Non-alcoholic fatty liver disease, MASLD: Metabolic dysfunction-associated steatotic liver disease, NASH: Non-alcoholic steatohepatitis, IR: Insulin resistance, MRS: Magnetic resonance spectroscopy, AUROC: Area under the receiver operating characteristic curve, GSG index: Glutamate-serine-glycine index

BCAA-related amino-acid alterations associate with hepatic steatosis independently of BMI and conventional risk markers in several pediatric cohorts.

Amino-acid-based indices show early promise as noninvasive adjuncts to imaging for pediatric NAFLD/MASLD risk stratification, though external validation remains limited.

Table IV. Amino acids, IGF-1 axis, and developmental modifiers relevant to pediatric interpretation

Ref	First author (Year)	Population/context	Key observation	Importance for this review
(42)	Jensch (2024)	Healthy children/adolescents	Whole-blood AA/acylcarnitines associated with anthropometry and IGF-I	Supports developmental and endocrine coupling of AA patterns with IGF-I
(43)	Hirschel (2020)	Children/adolescents	AA/acylcarnitine levels vary with age, sex, BMI, puberty and correlate with metabolic markers	Puberty and sex must be adjusted when interpreting AA signatures
(44)	Knacke (2016)	Metabolomics + IGF-1 (multifluid; context) [Adult/general population; mechanistic context only]	IGF-1 associated with metabolites linked to AA metabolism (e.g., pipecolate)	Provides mechanistic plausibility for IGF-linked AA fingerprints
(45)	Barazani (2020)	IGF-I deficiency (Laron syndrome) ± IGF-I therapy	IGF-I deficiency associated with abnormal plasma AA metabolism partially reversed by IGF-I	Direct evidence that IGF-I status can shape AA profiles
(46)	Aggelaki (2025)	Children with GHD before/after GH therapy	Metabolomic fingerprint differs in GHD; correlations explored with IGF-1	Reinforces endocrine context for metabolomic interpretation
(47)	Inoue (2025)	SGA infants (cord metabolomics)	Cord AA alterations associated with impaired linear growth	Demonstrates early-life AA-growth links relevant to IGF biology

AA: Amino acid(s), IGF-I/IGF-1: Insulin-like growth factor-1, GH: Growth hormone, GHD: Growth hormone deficiency, SGA: Small for gestational age

Pubertal stage, sex, and IGF-1 status are important modifiers of amino-acid profiles and must be accounted for when interpreting AA signatures in children.

Conditions altering the IGF-1 axis (growth hormone deficiency, IGF-1 deficiency, small-for-gestational-age status) are associated with distinct amino-acid fingerprints, supporting a mechanistic link between growth endocrinology and AA metabolism.

Table V. Management and intervention studies: how amino-acid patterns shift with treatment and their importance for this review

Ref	First author (Year)	Intervention/design	Population	Key AA-related findings	Clinical takeaway
(48)	Hampl (2023)	Pediatric obesity guideline	Children/adolescents	Lifestyle-first; pharmacotherapy/ surgery for selected cases	AA biomarkers not routine yet; focus remains on weight/IR management
(49)	Rigamonti (2023)	Short-term body weight reduction program (prospective)	Adolescents with obesity	Program altered metabolomic profile toward improved cardiometabolic pathways	Supports metabolomics as response-tracking tool in structured programs
(50)	Becetti (2023)	Sleeve gastrectomy vs non-surgical (12 months)	Youth 13-24 yrs	Post-surgery BCAA reductions associated with improved IR	Bariatric surgery may normalize BCAA burden alongside IR improvement
(20)	Hellmuth (2016)	Longitudinal observational (weight/IR trajectory)	Obese children	Tyrosine alterations associated with IR preceded broader BCAA changes	Early AA markers may help identify high-risk trajectories
(51)	Glynn (2015)	Aerobic + resistance training (exercise intervention; context)	Overweight adults *[Adult; mechanistic context only]*	Exercise improved IS; glycine conjugation pathways implicated	Mechanistic insight: AA handling changes may mediate IS improvements
(52)	Lee (2021)	Exercise training (context)	Dysglycemic men *[Adult; mechanistic context only]*	IS improved with enhanced tissue BCAA catabolism despite stable plasma BCAA	Plasma BCAA may not fully reflect tissue catabolism changes
(53)	Lim (2024)	Weight-loss RCT secondary analysis (context)	Prediabetes adults *[Adult; mechanistic context only]*	Low glycine strengthened BCAA-IR association; concurrent assessment improved interpretation	Supports combined glycine + BCAA measurement for IR phenotyping

AA: Amino acid(s), BCAA: Branched-chain amino acid(s), IR: Insulin resistance, IS: Insulin sensitivity, RCT: Randomized controlled trial

Pediatric weight-loss interventions, particularly bariatric surgery, are associated with measurable reductions in BCAA levels alongside improved insulin resistance.

Adult mechanistic studies suggest amino-acid catabolism can shift with exercise training before changes are detectable in plasma BCAA, underscoring the need for pediatric-specific intervention trials.

Table VI. Quality assessment summary table (Cochrane-aligned)

Evidence cluster	Studies included from Tables I-V (Ref no.)	Typical study designs	Key bias concerns (ROBINS-I/RoB 2 domains)	Overall certainty (narrative)
Pediatric obesity AA signatures (Table I)	(14-26)	Mostly cross-sectional and cohort; some longitudinal and phenotype-stratified cohorts	Confounding (puberty stage, diet/protein source, ethnicity, adiposity distribution); selection bias (clinic-based cohorts); measurement variability (fasting status, assay/platform/batch effects); multiple testing/selective reporting in high-dimensional metabolomics	Moderate (directional consistency across cohorts; heterogeneity and residual confounding remain)
Pediatric dysglycemia/ diabetes AA signatures (Table II)	(8,19,24,26-31)	Case-control and cohort (often small); some studies with gold-standard physiology/phenotyping; diabetes subtype comparisons	Phenotype misclassification (definitions of dysglycemia; T1D vs T2D overlap); treatment effects and disease duration; puberty confounding; small samples/selection bias; reverse causality (cross-sectional designs)	Low-moderate (signals emerging; strongest where detailed phenotyping is present; heterogeneity remains)
Pediatric NAFLD/ MASLD AA signatures (Table III)	(32-41)	Case-control/cohort with imaging (MRI/MRS/US) ± metabolic phenotyping; prediction models/indices	Outcome ascertainment heterogeneity (US vs MRI vs MRS vs biopsy); confounding by obesity/IR/lifestyle; selection toward tertiary/ severe obesity cohorts; model overfitting and limited external validation for indices/ML models	Moderate (repeatability of BCAA/glutamate-related patterns; broader validation still needed)

Table VI. Continued

Evidence cluster	Studies included from Tables I-V (Ref no.)	Typical study designs	Key bias concerns (ROBINS-I/RoB 2 domains)	Overall certainty (narrative)
IGF-1/ development modifiers (Table IV)	(42-47)	Large population cohorts plus special endocrine/ perinatal states	Developmental confounding (age, sex, puberty staging); generalizability limits for rare endocrine states; assay/platform differences; within-person variability across growth	Low-moderate (strong evidence that puberty/ sex/adiposity modify AA distributions; fewer disease-state datasets directly linking AA patterns to IGF-1 outcomes)
Intervention effects (Table V)	Pediatric interventions/ guideline: (20,48-50); adult mechanistic context: (51-53)	Prospective lifestyle programs and surgery cohorts; guideline framing; adult mechanistic trials for interpretation	Non-randomized designs (selection bias), adherence/co-interventions; short follow-up for lifestyle; small samples; outcome changes may lag metabolite shifts	Low-moderate (clear biologic shifts when metabolic state improves substantially—especially surgery; limited pediatric randomized metabolomics evidence)

RoB 2: Cochrane risk of bias tool version 2, ROBINS-I: Risk of bias in non-randomized studies of interventions, AA: Amino acid(s), IR: Insulin resistance, NAFLD: Non-alcoholic fatty liver disease, MASLD: Metabolic dysfunction-associated steatotic liver disease, IGF-1: Insulin-like growth factor-1, MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, US: Ultrasound

Most included pediatric evidence derives from cross-sectional or case-control designs, supporting moderate (and in some clusters low-to-moderate) certainty for the amino-acid signatures described.

Longitudinal and interventional pediatric studies remain comparatively scarce, representing the key evidence gap for future confirmatory research.

Algorithm Text (Figure 2)

The algorithm summarizes a stepwise clinical-research pathway for children and adolescents with overweight/ obesity or metabolic risk. Baseline phenotyping includes anthropometrics and pubertal staging, followed by standard metabolic evaluation (fasting glucose/HbA1c ± OGTT when indicated, fasting insulin/HOMA-IR, lipids, and liver enzymes). IGF-1 (standard deviation score, SDS) is incorporated when growth or pubertal concerns are present to contextualize developmental endocrine influences on metabolite patterns. Amino-acid (AA) profiling (fasting, standardized sampling; targeted AA panel ± acylcarnitines) is positioned as an adjunct tool for advanced risk stratification in metabolically unhealthy obesity, rising insulin resistance, dysglycemia risk, or suspected NAFLD/MASLD. Interpretation is anchored to phenotype (normal glycemia vs dysglycemia vs NAFLD suspicion) to guide escalation of guideline-based management and liver imaging when indicated. Follow-up at 3-6 months prioritizes clinical outcomes (BMI-z/ waist, glycemia, HOMA-IR/insulin sensitivity markers, liver enzymes, lipids); repeat AA profiling, when used, should be performed under identical conditions and interpreted alongside metabolic improvement. Throughout this pathway, AA profiling is intended strictly as an adjunct to standard clinical, biochemical, and imaging assessment rather than as a replacement for it; the algorithm reflects a proposed research-informed framework, and prospective validation in diverse pediatric populations is required before broader clinical implementation.

Graphic Abstract (Figure 3)

Provides graphical synthesis of this composite amino-acid signature—BCAA/AAA elevation with glycine reduction and glutamine–glutamate imbalance—and summarizes how these candidate biomarker signatures intersect with standard clinical phenotyping, puberty/IGF-1 context, and downstream risk for prediabetes/T2D and NAFLD/MASLD across the pediatric evidence base described in Tables I-V.

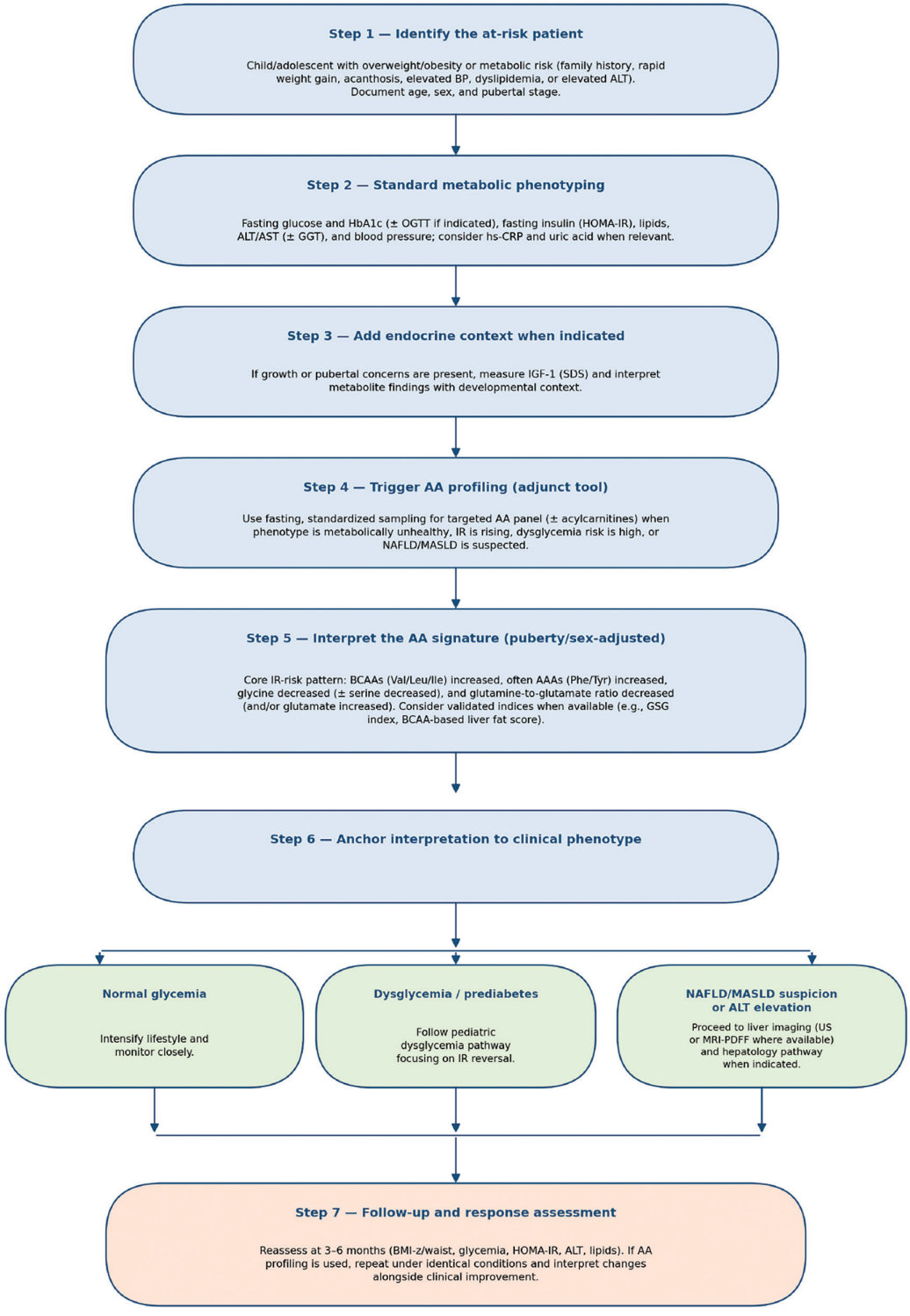

Figure 2. Algorithmic framework for interpreting amino-acid pattern signatures across pediatric obesity, dysglycemia, and fatty liver disease, incorporating insulin resistance and IGF-1 context. This algorithm is intended as an adjunct to, not a replacement for, standard clinical assessment; amino-acid profiling requires further prospective validation before broader clinical implementation.

Figure 2. Algorithmic framework for interpreting amino-acid pattern signatures across pediatric obesity, dysglycemia, and fatty liver disease, incorporating insulin resistance and IGF-1 context. This algorithm is intended as an adjunct to, not a replacement for, standard clinical assessment; amino-acid profiling requires further prospective validation before broader clinical implementation

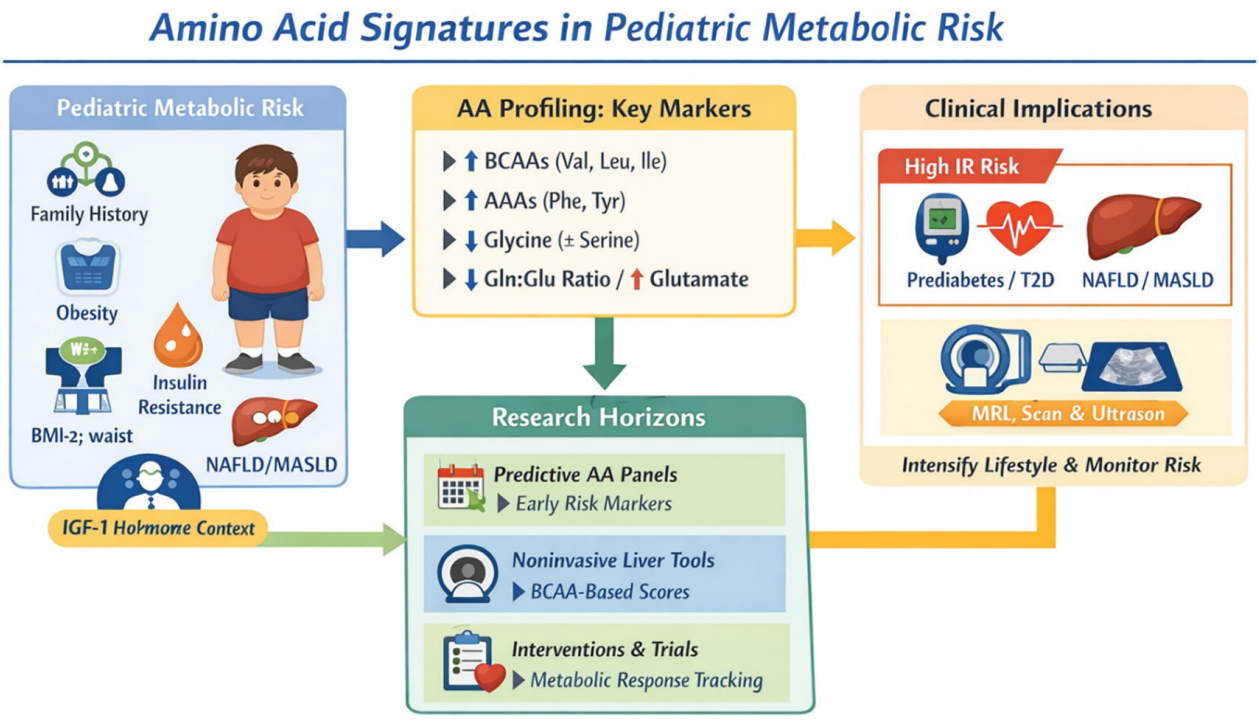

Figure 3. Amino acid signatures in pediatric metabolic risk: linking obesity to insulin resistance, dysglycemia, and fatty liver disease. This graphical abstract summarizes the key amino-acid pattern associated with pediatric metabolic risk (candidate biomarker signatures: BCAA/AAA elevation with glycine reduction and glutamine-glutamate imbalance) and shows how these signatures integrate with standard clinical phenotyping in order to identify children at higher risk of prediabetes/T2D and NAFLD/MASLD, while emphasizing puberty/IGF-1 context and the need for prospective validation before these candidate signatures can inform intervention trials

Discussion

Across pediatric studies, the most reproducible amino-acid (AA) fingerprint linked to metabolic risk is an increase in branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs), frequently accompanied by higher glutamate and lower glycine/serine, with substantial modulation by age, pubertal stage, sex, and adiposity distribution (9-13,42,43). These patterns are clinically meaningful rather than purely descriptive as multiple pediatric cohorts show associations with insulin resistance (IR) and cardiometabolic risk clustering, indicating that AA profiles can serve as integrated readouts of disrupted nutrient handling in pediatric obesity (14-16,19,24).

Mechanistic interpretations converge on altered BCAA catabolism and downstream metabolic 'spillover.' Elevated circulating BCAAs may reflect reduced activity or regulation of catabolic enzymes and altered tissue partitioning, while BCAA-derived intermediates can mirror mitochondrial substrate overload and incomplete oxidation (2-5,13). In parallel, recurring reductions in glycine/serine may reflect constrained one-carbon and antioxidant capacity and limited acyl-group buffering, while glutamine-glutamate imbalance may indicate altered transamination and hepatic nitrogen flux (6,7). Evidence synthesis supports the concept that composite AA panels (BCAA/AAA elevation with glycine reduction and glutamine-glutamate imbalance) are among the most consistent metabolite features associated with prediabetes/diabetes risk, providing an interpretive scaffold relevant to youth as pediatric data mature (8).

A key pediatric nuance is that metabolic risk is not uniform within obesity, and AA signatures appear most informative when aligned to phenotype rather than BMI alone. Metabolomic comparisons across adolescent overweight/obesity phenotypes indicate that AA differences cluster with 'metabolically at-risk' profiles (e.g., adverse glycemia and lipid patterns) rather than with adiposity per se (23). Similarly, metabolomic differences between metabolically healthy obesity and metabolically unhealthy obesity are driven primarily by abnormal glucose homeostasis and related metabolic disturbances, supporting AA profiling as a potential adjunct to phenotype anchoring (26).

Longitudinal pediatric findings add strength by moving beyond cross-sectional discrimination toward prediction. Baseline BCAA elevations have been associated with future

insulin resistance in children and adolescents, supporting their potential as early-risk markers (14). Longitudinal metabolomic profiling also suggests that certain signals, particularly tyrosine, may track IR trajectories and could change earlier than broader BCAA disturbances in some pediatric obesity cohorts (20). In addition, AA-based signatures in school-age children have predicted future hypertriglyceridemia, reinforcing the concept that AA patterns can act as early 'stress integrators' across metabolic pathways (22). Collectively, these studies argue that the most clinically relevant next step is prospective validation of AA signatures for dysglycemia and progression to fatty liver disease.

For dysglycemia and pediatric diabetes phenotypes, the evidence is evolving and heterogeneous, reflecting developmental physiology, pubertal insulin resistance, differing diabetes subtypes, and treatment effects. Clamp-based pediatric studies indicate that AA-β-cell relationships can differ from adult paradigms and may reflect compensatory physiology early in the disease trajectory (27). Youth-onset Type 2 diabetes has also shown distinct AA/acylcarnitine patterns compared with obesity alone, suggesting that pediatric T2D metabolomic features cannot be assumed to mirror adult profiles (28). More recent youth-focused targeted profiling supports a 'risk-like' AA pattern (higher BCAA/AAA and lysine with lower glycine and glutamine-glutamate signals) in youth with or at risk of Type 2 diabetes, consistent with impaired insulin sensitivity and potential β-cell stress (29). Prospective modeling in youth cohorts further indicates that metabolite panels including AAs can predict dysglycemia, with sex-specific signals which underscore the need for developmentally stratified interpretation (30). Finally, targeted AA signatures distinguishing pediatric diabetes types suggest potential future utility for phenotype refinement in research and specialized clinical settings (31).

Pediatric NAFLD/MASLD shows particularly strong convergence of AA disturbances across untargeted pathway analyses, targeted metabolite panels, and prediction tools. Studies in obese adolescents demonstrate AA pathway disruption in NAFLD, including BCAA-related signatures and broader perturbations which align with hepatic fat and insulin resistance phenotypes (33-35). In youth with severe obesity, a BCAA-based metabolic score has been proposed to predict liver fat, offering a practical approach to non-invasive risk stratification which may be especially valuable where imaging access is constrained (36). Complementary approaches such as the glutamate-serine-glycine (GSG) index further highlight the recurring role of glutamate and glycine/serine biology in pediatric fatty liver phenotypes (37). In biopsy-proven pediatric NAFLD, models incorporating valine, tyrosine, glutamate, and glycine have achieved strong discrimination, but require external validation and pragmatic evaluation before clinical translation (38). Current pediatric NAFLD guidelines emphasize early identification and risk stratification but acknowledge the need for better non-invasive biomarkers, providing a clear translational rationale for continued AA biomarker development (32).

Dietary AA composition is a plausible contributor to circulating AA signatures and liver-fat risk, but causal evidence in children remains limited and confounded by total energy intake, protein source, and dietary pattern quality. Observational pediatric work suggests that higher dietary BCAA intake, particularly leucine, is associated with NAFLD odds in overweight/obese youth, but these findings require cautious interpretation and prospective validation (39). Mechanistic context from progressive NAFLD studies supports BCAA pathway remodeling across disease severity and highlights intersections with hepatic inflammation and lipid handling (40). Recent syntheses also emphasize that essential AAs can influence metabolic liver disease biology through nutrient signaling pathways, but pediatric interventional trials specifically targeting AA composition while preserving growth needs remain a priority (41).

The IGF-1 axis adds an endocrine-growth lens to AA interpretation in pediatrics. Large healthy pediatric cohorts demonstrate that whole-blood AAs and acylcarnitines vary systematically with age, sex, BMI, and pubertal stage, and can associate with IGF-1 levels and growth-related phenotypes, reinforcing the need for puberty- and sex-aware reference frameworks (42,43). Mechanistic possibility is supported by metabolomic analyses linking circulating IGF-1 and IGF-1/IGFBP-3 ratios to AA-related metabolites (44). Moreover, endocrine states characterized by altered IGF-1 or GH biology provide direct evidence that hormonal status can shape AA metabolism: long-term IGF-1 deficiency shows abnormal plasma AA metabolism which is partially reversible with IGF-1 therapy, and GH deficiency cohorts demonstrate distinct metabolomic fingerprints with IGF-1-related correlations (45,46). Early-life metabolomic data in growth-restricted infants further support the concept that AA availability and handling relate to linear growth trajectories, strengthening the rationale to integrate IGF-1 context when interpreting AA risk panels across pediatric ages (47).

From a clinical perspective, current pediatric guidelines for obesity, NAFLD, and youth-onset Type 2 diabetes remain anchored in lifestyle intervention, weight management, and cardiometabolic risk control, with imaging/laboratory assessment for NAFLD rather than AA biomarkers (32,48,54,55). This is appropriate given the present heterogeneity in platforms, the lack of standardized pediatric cutoffs, and limited evidence that AA-informed stratification improves outcomes. Nevertheless, AA profiling is positioned for near-term research-to-practice transition in three areas: identifying metabolically higher-risk obesity phenotypes, enriching screening for NAFLD risk when imaging is limited, and monitoring metabolic response in intensive programs or post-surgical settings.

Intervention evidence supports partial 'reversibility' of AA disturbances when metabolic states improve meaningfully. In adolescents with obesity, short-term structured weight-reduction programs can shift metabolomic profiles toward more favorable cardiometabolic patterns, supporting metabolomics as a potential response-tracking tool (49). In youth undergoing sleeve gastrectomy, reductions in BCAAs have been reported in parallel with improvements in insulin resistance, suggesting that major weight loss and metabolic remodeling can normalize at least part of the BCAA-related signature (50). Longitudinal observational data also indicate that specific AAs such as tyrosine track insulin resistance trajectories in children, highlighting candidate markers for monitoring high-risk courses (20). Mechanistic adult intervention studies provide context that improved insulin sensitivity may be mediated by enhanced handling of BCAA-derived acyl groups and glycine conjugation and that tissue BCAA catabolism can improve even when plasma BCAA changes are modest, concepts which may guide pediatric trial design without being assumed as directly generalizable to children (51-53).

Key research gaps now center on standardization and validation. Pediatric studies need harmonized sampling (fasting status, timing relative to puberty), consistent reporting of pubertal stages and body composition, and cross-platform analytic comparability, as highlighted by pediatric metabolomics syntheses (9,10). Longitudinal cohorts are needed in order to test whether AA signatures add predictive value beyond established clinical risk factors for incident dysglycemia and NAFLD progression, and to define whether AA-informed phenotyping can guide interventions without compromising growth and nutritional adequacy. Finally, pragmatic studies should evaluate whether incorporating AA panels into clinical pathways improves risk stratification, patient engagement, or response monitoring compared with guideline-based care alone (32,48,54,55).

Overall, pediatric literature supports AA signatures as biologically coherent, developmentally modulated candidate biomarkers aligned with insulin resistance, dysglycemia risk, and fatty liver burden. This field is now positioned to move from association to action by establishing pediatric reference frameworks, validating prediction tools in diverse populations, and embedding AA profiling into interventional trials designed around clinically meaningful endpoints and growth-safe nutrition.

Conclusion

Pediatric and adolescent metabolic disorders, namely obesity, dysglycemia/diabetes risk, and NAFLD/MASLD, share partially overlapping amino-acid fingerprints, most commonly involving elevated BCAAs and AAAs, glutamate-related shifts, and reduced glycine/serine in higher-risk phenotypes. These patterns align with insulin resistance biology and can associate with liver fat burden and adverse cardiometabolic trajectories. However, AA signatures are strongly influenced by age, sex, puberty, and IGF-1/GH axis status, mandating pediatric-specific interpretive frameworks. While the current clinical management remains guideline-based, AA profiling is poised to become a valuable adjunct for research-grade risk stratification and response monitoring once standardized, validated, and tested for incremental clinical utility.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., H.Z., F.A., N.A., S.A., N.H., S.E., Concept: A.S., H.Z., F.A., N.A., Design: A.S., H.Z., Data Collection or Processing: A.S., H.Z., N.A., S.A., N.H., S.E., Analysis or Interpretation: A.S., F.A., Literature Search: A.S., F.A., N.A., S.A., Writing: A.S., H.Z., N.H., S.E.

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References

1. Ling ZN, Jiang YF, Ru JN, Lu JH, Ding B, Wu J. Amino acid metabolism in health and disease. Sig Transduct Target Ther. 2023; 8:345.
2. White PJ, McGarrah RW, Herman MA, Bain JR, Shah SH, Newgard CB. Insulin action, type 2 diabetes, and branched-chain amino acids: A two-way street. Mol Metab. 2021; 52:101261.

3. Lynch CJ, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance. Nat Rev Endocrinol. 2014; 10:723-36.

4. De Bandt JP, Coumoul X, Barouki R. Branched-chain amino acids and insulin resistance, from protein supply to diet-induced obesity. Nutrients. 2022; 15:68.

5. Yoon MS. The emerging role of branched-chain amino acids in insulin resistance and metabolism. Nutrients. 2016; 8:405.

6. Adeva-Andany M, Souto-Adeva G, Ameneiros-Rodríguez E, Fernández-Fernández C, Donapetry-García C, Domínguez-Montero A. Insulin resistance and glycine metabolism in humans. Amino Acids. 2018; 50:11-27.

7. Alves A, Bassot A, Bulteau AL, Pirola L, Morio B. Glycine metabolism and its alterations in obesity and metabolic diseases. Nutrients. 2019; 11:1356.

8. Guasch-Ferré M, Hruby A, Toledo E, et al. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. Diabetes Care. 2016; 39:833-46.

9. Handakas E, Lau CH, Alfano R, et al. A systematic review of metabolomic studies of childhood obesity: state of the evidence for metabolic determinants and consequences. Obes Rev. 2022; 23(Suppl 1):e13384.

10. De Spiegeleer M, De Paepe E, Van Meulebroek L, Gies I, De Schepper J, Vanhaecke L. Paediatric obesity: a systematic review and pathway mapping of metabolic alterations underlying early disease processes. Mol Med. 2021; 27:145.

11. Polidori N, Grasso EA, Chiarelli F, Giannini C. Amino acid-related metabolic signature in obese children and adolescents. Nutrients. 2022; 14:1454.

12. Zamosteanu D, Filip N, Trandafir LM, et al. Current data on the role of amino acids in the management of obesity in children and adolescents. Int J Mol Sci. 2025; 26:7129.

13. Dimou A, Tsimihodimos V, Bairaktari E. The critical role of the branched chain amino acids (BCAAs) catabolism-regulating enzymes, branched-chain aminotransferase (BCAT) and branched-chain α-keto acid dehydrogenase (BCKD), in human pathophysiology. Int J Mol Sci. 2022; 23:4022.

14. McCormack SE, Shaham O, McCarthy MA, et al. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. Pediatr Obes. 2013; 8:52-61.

15. Butte NF, Liu Y, Zakeri IF, et al. Global metabolomic profiling targeting childhood obesity in the Hispanic population. Am J Clin Nutr. 2015; 102:256-67.

16. Mangge H, Zelzer S, Prüller F, et al. Branched-chain amino acids are associated with cardiometabolic risk profiles found already in lean, overweight and obese young. J Nutr Biochem. 2016; 32:123-7.

17. Mastrangelo A, Martos-Moreno GÁ, García A, et al. Insulin resistance in prepubertal obese children correlates with sex-dependent early onset metabolomic alterations. Int J Obes (Lond). 2016; 40:1494-502.

18. Martos-Moreno GÁ, Mastrangelo A, Barrios V, et al. Metabolomics allows the discrimination of the pathophysiological relevance of hyperinsulinism in obese prepubertal children. Int J Obes (Lond). 2017; 41:1473-80.

19. Suzuki Y, Kido J, Matsumoto S, Shimizu K, Nakamura K. Associations among amino acid, lipid, and glucose metabolic profiles in childhood obesity. BMC Pediatr. 2019; 19:273.

20. Hellmuth C, Kirchberg FF, Lass N, et al. Tyrosine is associated with insulin resistance in longitudinal metabolomic profiling of obese children. J Diabetes Res. 2016; 2016:2108909.

21. Bugajska J, Berska J, Wójcik M, Sztefko K. Amino acid profile in overweight and obese prepubertal children - can simple biochemical tests help in the early prevention of associated comorbidities?. Front Endocrinol (Lausanne). 2023; 14:1274011.

22. Moran-Ramos S, Ocampo-Medina E, Gutierrez-Aguilar R, et al. An amino acid signature associated with obesity predicts 2-year risk of hypertriglyceridemia in school-age children. Sci Rep. 2017; 7:5607.

23. Perng W, Rifas-Shiman SL, Sordillo J, Hivert MF, Oken E. Metabolomic profiles of overweight/obesity phenotypes during adolescence: a cross-sectional study in project viva. Obesity (Silver Spring). 2020; 28:379-87.

24. Short KR, Chadwick JQ, Teague AM, et al. Effect of obesity and exercise training on plasma amino acids and amino metabolites in American Indian adolescents. J Clin Endocrinol Metab. 2019; 104:3249-61.

25. McCann JR, Bihlmeyer NA, Roche K, et al. The pediatric obesity microbiome and metabolism study (POMMS): methods, baseline data, and early insights. Obesity (Silver Spring). 2021; 29:569-78.

26. Ng DZW, Shie YH, Piyasanka SR, et al. Metabolome alterations in pediatric metabolically unhealthy obesity are primarily linked to abnormal glucose homeostasis. Sci Rep. 2025; 15:23934.

27. Michaliszyn SF, Sjaarda LA, Mihalik SJ, et al. Metabolomic profiling of amino acids and β-cell function relative to insulin sensitivity in youth. J Clin Endocrinol Metab. 2012; 97:E2119-2124.

28. Mihalik SJ, Michaliszyn SF, de las Heras J, et al. Metabolomic profiling of fatty acid and amino acid metabolism in youth with obesity and type 2 diabetes: evidence for enhanced mitochondrial oxidation. Diabetes Care. 2012; 35:605-11.

29. Bacha F, El-Ayash H, Mohamad M, et al. Distinct amino acid profile characterizes youth with or at risk for type 2 diabetes. Diabetes. 2024; 73:628-36.

30. Perng W, Hivert MF, Michelotti G, Oken E, Dabelea D. Metabolomic predictors of dysglycemia in two U.S. youth cohorts. Metabolites. 2022; 12:404.

31. Tosur M, Hsu JW, Deen S, et al. Plasma amino acid signatures define types of pediatric diabetes. Clin Nutr ESPEN. 2023; 57:21-8.

32. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr. 2017; 64:319-34.

33. Jin R, Banton S, Tran VT, et al. Amino acid metabolism is altered in adolescents with nonalcoholic fatty liver disease-an untargeted, high resolution metabolomics study. J Pediatr. 2016; 172:14-9.e5.

34. Goffredo M, Santoro N, Tricò D, et al. A branched-chain amino acid-related metabolic signature characterizes obese adolescents with non-alcoholic fatty liver disease. Nutrients. 2017; 9:642.

35. Tricò D, Caprio S, Rosaria Umano G, et al. Metabolic features of nonalcoholic fatty liver (NAFL) in obese adolescents: findings from a multiethnic cohort. Hepatology. 2018; 68:1376-90.

36. Lischka J, Schanzer A, Hojreh A, et al. A branched-chain amino acid-based metabolic score can predict liver fat in children and adolescents with severe obesity. Pediatr Obes. 2021; 16:e12739.

37. Leonetti S, Herzog RI, Caprio S, Santoro N, Tricò D. Glutamate-serine-glycine index: a novel potential biomarker in pediatric non-alcoholic fatty liver disease. Children (Basel). 2020; 7:270.

38. Chae W, Lee KJ, Huh KY, Moon JS, Ko JS, Cho JY. Association of metabolic signatures with nonalcoholic fatty liver disease in pediatric population. Metabolites. 2022; 12:881.

39. Nikparast A, Razavi M, Sohouli MH, et al. The association between dietary intake of branched-chain amino acids and the odds of nonalcoholic fatty liver disease among overweight and obese children and adolescents. J Diabetes Metab Disord. 2024; 24:19.

40. Lake AD, Novak P, Shipkova P, et al. Branched chain amino acid metabolism profiles in progressive human nonalcoholic fatty liver disease. Amino Acids. 2015; 47:603-15.

41. Deng Y, Hu M, Huang S, Fu N. Molecular mechanism and therapeutic significance of essential amino acids in metabolically associated fatty liver disease. J Nutr Biochem. 2024; 126:109581.

42. Jensch R, Baber R, Körner A, et al. Association of whole blood amino acid and acylcarnitine metabolome with anthropometry and IGF-I serum levels in healthy children and adolescents in Germany. Metabolites. 2024; 14:489.

43. Hirschel J, Vogel M, Baber R, et al. Relation of whole blood amino acid and acylcarnitine metabolome to age, sex, BMI, puberty, and metabolic markers in children and adolescents. Metabolites. 2020; 10:149.

44. Knacke H, Pietzner M, Do KT, et al. Metabolic fingerprints of circulating IGF-1 and the IGF-1/IGFBP-3 ratio: a multifluid metabolomics study. J Clin Endocrinol Metab. 2016; 101:4730-42.

45. Barazani C, Werner H, Laron Z. Changes in plasma amino acids metabolites, caused by long-term IGF-I deficiency, are reversed by IGF-I treatment - a pilot study. Growth Horm IGF Res. 2020; 52:101312.

46. Aggelaki EA, Giannakopoulos A, Georgiopoulou PD, et al. Unveiling the metabolomic profile of growth hormone deficiency children using NMR spectroscopy. Metabolomics. 2025; 21:25.

47. Inoue M, Sekiguchi K, Kishimoto S, Maeda T, Ihara K. Umbilical cord serum metabolomics identifies amino acid alterations associated with impaired linear growth in small for gestational age infants. Sci Rep. 2025; 15:27378.

48. Hampl SE, Hassink SG, Skinner AC, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediatrics. 2023; 151:e2022060640.

49. Rigamonti AE, Frigerio G, Caroli D, et al. A metabolomics-based investigation of the effects of a short-term body weight reduction program in a cohort of adolescents with obesity: a prospective interventional clinical study. Nutrients. 2023; 15:529.

50. Becetti I, Lauze M, Lee H, Bredella MA, Misra M, Singhal V. Changes in branched-chain amino acids one year after sleeve gastrectomy in youth with obesity and their association with changes in insulin resistance. Nutrients. 2023; 15:3801.

51. Glynn EL, Piner LW, Huffman KM, et al. Impact of combined resistance and aerobic exercise training on branched-chain amino acid turnover, glycine metabolism and insulin sensitivity in overweight humans. Diabetologia. 2015; 58:2324-35.

52. Lee S, Gulseth HL, Langleite TM, et al. Branched-chain amino acid metabolism, insulin sensitivity and liver fat response to exercise training in sedentary dysglycaemic and normoglycaemic men. Diabetologia. 2021; 64:410-23.

53. Lim JJ, Prodhan UK, Silvestre MP, et al. Low serum glycine strengthens the association between branched-chain amino acids and impaired insulin sensitivity assessed before and after weight loss in a population with pre-diabetes: the PREVIEW_NZ cohort. Clin Nutr. 2024; 43:17-25.

54. Shah AS, Zeitler PS, Wong J, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. Pediatr Diabetes. 2022; 23:872-902.

55. American Diabetes Association Professional Practice Committee. 14. Children and Adolescents: Standards of Care in Diabetes-2025. Diabetes Care. 2025; 48(1 Suppl 1):S283-305.

56. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372:n71.

57. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366:l4898.

58. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016; 355:i4919.