INPLASY

Immunometabolic and lipid dysregulation in autism spectrum disorder: a systematic review and multivariate/multilevel meta-analysis of peripheral lipids, insulin resistance and inflammatory markers

INPLASY202620085

doi: 10.37766/inplasy2026.2.0085

Received: 27 February 2026

Published: 27 February 2026

Hu, JQ; Jiang, ZM.

Corresponding author:
Zhimei Jiang

mynard93@163.com

Author Affiliation:
School of Basic Medical Sciences, Jiamusi University.

ADMINISTRATIVE INFORMATION

Support - Innovation Team Project of the Department of Education of Heilongjiang Province (2024-KYYWF-0611); "Dongji" Academic Team Project of Jiamusi University (DJXSTD202413).

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202620085

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 February 2026 and was last updated on 27 February 2026.

INTRODUCTION

Review question / Objective Primary objective: To systematically review and quantitatively synthesize evidence on peripheral immunometabolic and lipid dysregulation in individuals with autism spectrum disorder (ASD) compared with neurotypical/healthy controls.

PICOS:
P (Population): Individuals of any age diagnosed with ASD using established diagnostic criteria (DSM/ICD) and/or validated instruments (e.g., ADOS, ADI-R, CARS), with peripheral blood sampling.
I/E (Exposure/Index measures): Peripheral (serum/plasma/whole blood/RBC membrane) biomarkers within four prespecified domains: (1) Lipids: TC, TG, LDL-C, HDL-C, non-HDL-C or lipid ratios (if reported), fatty acid profiles (e.g., omega-3/omega-6, EPA/DHA/AA) and lipid oxidation markers (if available); (2) Insulin resistance: fasting insulin, fasting glucose, HOMA-IR (and related indices if available); (3) Inflammation/immune markers: CRP/hs-CRP and cytokines (IL-6, TNF-α, IL-1β, IL-17, IL-10; other cytokines recorded if reported); (4) Adipokines: leptin and adiponectin (others recorded if reported).
C (Comparator): Neurotypical/healthy controls (community controls, matched controls, or sibling controls).
O (Outcomes): Between-group differences in biomarker levels (primary effect size: Hedges' g/SMD), plus an integrated "immunometabolic fingerprint" across marker domains.
S (Study design): Observational studies (case-control, cross-sectional, cohort) and controlled trials' baseline data that provide ASD–control comparisons.

Secondary objectives: (i) account for within-study dependence from multiple correlated biomarkers/subgroups using multilevel and/or robust variance

estimation methods; (ii) explore heterogeneity and potential moderators (age, sex, BMI/obesity, psychotropic medication, fasting status, specimen type, assay platform, and key comorbidities where available); and (iii) assess robustness and potential small-study effects using prespecified sensitivity analyses.

Rationale ASD is a neurodevelopmental condition characterized by difficulties in social communication/interaction and restricted or repetitive behaviors, with substantial clinical heterogeneity and frequent co-occurring medical conditions. Increasing evidence links ASD to systemic immune activation and metabolic alterations that may interact with neurodevelopment via immune–metabolic signaling, adipokine pathways, and lipid-mediated inflammation.

Multiple peripheral inflammatory markers (e.g., IL-6, TNF-α, IL-1β) have been repeatedly investigated in ASD, and prior meta-analyses suggest group-level differences but with notable heterogeneity related to age, sex, geography, and methodological variability. In parallel, cardiometabolic risks (including dyslipidemia and diabetes) appear elevated in ASD in population-based syntheses, while mechanistic and clinical studies report altered lipid fractions, fatty acid composition, and adipokines (e.g., leptin), again with inconsistent findings across studies. Importantly, many ASD biomarker studies report panels of lipids, cytokines, and/or metabolic indices within the same sample. These outcomes are biologically correlated (e.g., lipids and inflammation are often co-reported), which creates statistical dependence across effect sizes within a study.

Conventional meta-analyses that extract one "representative" outcome per study or treat multiple outcomes as independent can (i) discard information, (ii) inflate precision, and/or (iii) increase the risk of selective outcome emphasis. Therefore, an integrated synthesis that prespecifies biomarker domains and appropriately models within-study dependence is needed to map an interpretable immunometabolic "fingerprint" in ASD.

This review will provide: (1) a comprehensive, domain-structured evidence map of peripheral lipids, insulin resistance indices, inflammatory markers, and adipokines in ASD; (2) quantitative pooled estimates using multilevel and/or robust variance approaches to handle multiple outcomes per study; (3) moderator analyses to identify clinical and methodological sources of heterogeneity (e.g., BMI/obesity, medication, fasting, specimen type); and (4) a pathway-organized visualization of the ASD immunometabolic profile to inform mechanistic hypotheses and stratified clinical research.

Condition being studied Autism spectrum disorder (ASD) is a neurodevelopmental condition that affects how individuals interact with others, communicate, learn, and behave. Core clinical features include persistent difficulties in social communication and social interaction, alongside restricted and repetitive patterns of behaviors or interests. ASD is a lifelong condition with variable manifestations and support needs across development, and it frequently co-occurs with medical and psychiatric conditions (e.g., gastrointestinal symptoms, epilepsy, sleep problems, obesity, and psychotropic medication exposure).

In this review, ASD is the index condition. The focus is on peripheral (blood-based) immunometabolic and lipid biomarkers, including standard lipid fractions (TC, TG, LDL-C, HDL-C), insulin resistance indices (fasting glucose/insulin, HOMA-IR), inflammatory markers (CRP and cytokines), and adipokines (leptin, adiponectin). The aim is to characterize whether individuals with ASD show a reproducible peripheral biomarker pattern compared with neurotypical/healthy controls, and to identify factors that may explain heterogeneity across studies (e.g., age, sex, BMI, medication, fasting status, assay methods).

METHODS

Search strategy Databases: We will search PubMed/MEDLINE, Embase, Web of Science Core Collection, Scopus (if available), and PsycINFO. For Chinese-language literature, we will search CNKI, Wanfang, and VIP. Trial registries/grey literature will be searched in ClinicalTrials.gov and WHO ICTRP (or equivalent registry portals). Reference lists of eligible studies and relevant reviews will be hand-searched, and forward citation tracking will be conducted (e.g., via Web of Science/Google Scholar).

Time frame: From database inception to 27 February 2026 (final search date). No restrictions by publication status. Human studies only.

Core concepts: (A) ASD terms AND (B) peripheral blood terms AND (C) biomarker terms (lipids/insulin resistance/inflammation/adipokines). Search strings will be adapted to each database using

controlled vocabulary (e.g., MeSH/Emtree) plus free text.

Example PubMed search (to be adapted):
(autis* OR "autism spectrum disorder" OR ASD OR Asperger* OR "pervasive developmental disorder")
AND (serum OR plasma OR blood OR peripheral OR "red blood cell*" OR RBC)
AND (cholesterol OR "total cholesterol" OR triglyceride* OR HDL OR "high density lipoprotein" OR LDL OR "low density lipoprotein" OR "lipid profile" OR lipid* OR "fatty acid*" OR PUFA OR omega-3 OR omega-6 OR EPA OR DHA OR arachidonic OR "oxidized LDL" OR oxLDL OR malondialdehyde OR MDA
OR insulin OR glucose OR "insulin resistance" OR HOMA OR "HOMA-IR" OR "homeostasis model assessment" OR HbA1c
OR CRP OR "C-reactive protein" OR cytokine* OR interleukin* OR IL-6 OR TNF OR "tumor necrosis factor" OR IL-1β OR IL-17 OR IL-10
OR adiponectin OR leptin OR adipokine*)

Chinese keywords (to be adapted):
(自闭症 OR 孤独症 OR 自闭症谱系障碍 OR ASD)
AND (血清 OR 血浆 OR 外周血)
AND (总胆固醇 OR 甘油三酯 OR 高密度脂蛋白 OR 低密度脂蛋白 OR 脂肪酸 OR ω-3 OR ω-6
OR 胰岛素 OR 空腹血糖 OR 胰岛素抵抗 OR HOMA-IR
OR C反应蛋白 OR CRP OR 细胞因子 OR 白细胞介素 OR IL-6 OR TNF-α OR IL-1β OR IL-17 OR IL-10
OR 瘦素 OR leptin OR 脂联素 OR adiponectin)

Screening: Two reviewers will independently screen titles/abstracts and then full texts. Disagreements will be resolved by discussion or a third reviewer. The search and selection process will be reported using a PRISMA flow diagram.

Participant or population Individuals with a clinical diagnosis of autism spectrum disorder (ASD) of any age and sex, diagnosed using DSM/ICD criteria and/or validated diagnostic instruments (e.g., ADOS, ADI-R, CARS). Participants must have peripheral blood-based measurement(s) of at least one prespecified biomarker. Studies including ASD with common comorbidities will be eligible; comorbidities (e.g., epilepsy, GI symptoms), BMI/obesity, and medication use will be extracted where reported for moderator analyses.

Intervention Not applicable. This review primarily includes observational studies comparing biomarker levels between ASD and control groups. If controlled intervention trials are retrieved, only baseline (pre-intervention) ASD–control comparisons will be extracted; the intervention effects are not the focus of this review.

Comparator Neurotypical/healthy control participants, including community controls, matched controls, or sibling controls without ASD. Control group characteristics (age, sex, BMI/obesity, fasting status, specimen type) will be extracted. Studies without an appropriate control group will not contribute to the primary ASD–control meta-analyses but may be summarized narratively if relevant.

Study designs to be included Observational studies (case-control, cross-sectional, cohort) and controlled trials' baseline data providing ASD–control comparisons of peripheral immunometabolic/lipid biomarkers.

Eligibility criteria Inclusion criteria:

1) Human studies with ASD and a non-ASD control group; 2) peripheral blood-based measurement(s) of at least one prespecified biomarker; 3) sufficient quantitative data to compute an effect size (mean/SD, SE, CI, or convertible statistics) or data obtainable from authors; 4) clear ASD diagnostic ascertainment (DSM/ICD or validated instruments).

Exclusion criteria:
1) Animal/in vitro studies; 2) studies reporting only central biomarkers (CSF/brain tissue) without peripheral measures; 3) prenatal/maternal/cord-blood biomarker studies not measuring biomarkers in individuals with ASD; 4) reviews, editorials, case reports/series without a comparator; 5) duplicate/overlapping samples (the most complete dataset will be retained).

Information sources Electronic databases: PubMed/MEDLINE, Embase, Web of Science Core Collection, Scopus (if available), PsycINFO; Chinese databases: CNKI, Wanfang, VIP.

Trial registries/grey literature: ClinicalTrials.gov and WHO ICTRP (or equivalent). Additional sources will include hand-searching reference lists of included studies and relevant reviews, forward citation searching (e.g., Web of Science/Google Scholar), and contacting corresponding authors for missing or clarifying data (e.g., SDs, subgroup breakdowns, fasting status, assay details).

Main outcome(s) Primary outcomes are between-group differences (ASD vs controls) in peripheral biomarker levels within prespecified domains:

1) Lipids: TC, TG, LDL-C, HDL-C (and non-HDL-C/ratios if available);
2) Insulin resistance: fasting glucose, fasting insulin, HOMA-IR (or equivalent indices);
3) Inflammation/immune markers: CRP/hs-CRP, IL-6, TNF-α, IL-1β, IL-17, IL-10;
4) Adipokines: leptin and adiponectin.

Primary effect size: standardized mean difference (Hedges' g) with 95% confidence interval. For trials, baseline measurements will be used. When multiple measures/timepoints are reported, the fasting/predefined baseline timepoint will be prioritized; alternative selections will be evaluated in sensitivity analyses.

Additional outcome(s)
Secondary outcomes include:
1) Domain-level pooled effects (e.g., lipid domain, insulin resistance domain, inflammation domain, adipokine domain) and an integrated "immunometabolic fingerprint" visualization organized by biological pathways;
2) Heterogeneity metrics and variance components (between-study and within-study) and identification of influential studies/outliers;
3) Moderator effects from meta-regression/subgroup analyses (e.g., age, sex, BMI/obesity, psychotropic medication, fasting status, specimen type, assay platform, comorbidities);
4) Evidence mapping and narrative synthesis for biomarkers with insufficient studies for meta-analysis (e.g., specific fatty acids or lipid oxidation markers).

Data management Records will be exported from each database to reference-management software (e.g., EndNote/Zotero) for de-duplication, then imported into a screening platform (e.g., Rayyan/Covidence) for title/abstract and full-text screening. A standardized extraction form (pilot-tested) will be used to collect study characteristics, participant characteristics, assay details (specimen type, fasting status, platform), and quantitative biomarker data.

Data will be stored in a version-controlled spreadsheet (e.g., Excel/Google Sheets) and analyzed in R (metafor and related packages). A data dictionary will define prespecified biomarker domains, coding rules for moderators, unit conversions, and handling of multiple outcomes/subgroups per study.

Quality assessment / Risk of bias analysis Two reviewers will independently assess methodological quality/risk of bias of included studies. For case-control and cohort studies, the Newcastle–Ottawa Scale (NOS) will be used. For cross-sectional studies, an appropriate Joanna Briggs Institute (JBI) checklist will be applied. Disagreements will be resolved by consensus or a third reviewer.

In addition, we will extract key biomarker-measurement reporting items (e.g., fasting status, specimen type, assay platform, handling of values below detection limits, and adjustment for key confounders such as BMI and medication) to support interpretation of heterogeneity. Risk-of-bias/quality ratings will be explored as moderators and used in sensitivity analyses (e.g., excluding high-risk studies).

Strategy of data synthesis We will conduct quantitative synthesis when ≥3 studies report the same biomarker with ASD–control comparisons. Effect sizes will be computed as Hedges' g from means/SDs or converted statistics (SE, CI, p-values). Units will be harmonized where appropriate (e.g., lipid units), but SMD will be the primary metric to accommodate different assay scales (especially for cytokines).

Given that many studies report multiple correlated biomarkers and/or multiple subgroups, dependence will be handled using multilevel (three-level) random-effects meta-analysis models with study-level clustering. Robust variance estimation (RVE) with small-sample corrections will be used as a complementary approach when dependence structures are complex (e.g., multiple outcomes sharing the same control group) or when model assumptions require robustness. Where feasible and justified by the data structure, multivariate meta-analysis will be considered within domains (e.g., lipid panel or cytokine panel); if within-study correlations are not available, sensitivity analyses will be performed across plausible correlation assumptions or the analysis will default to multilevel/RVE approaches.

Heterogeneity will be assessed using variance components, I^2-type statistics, and prediction intervals where appropriate. Prespecified meta-regressions/subgroup analyses will be conducted to examine moderators. For biomarkers with insufficient data, a narrative synthesis and evidence map will be provided. Results will be presented using forest plots and a pathway-organized "fingerprint" figure summarizing pooled effects across domains.

Subgroup analysis Where data permit (typically ≥5–10 studies per biomarker/domain), subgroup

analyses and/or meta-regressions will be conducted for:
1) Age group: children, adolescents, adults (or continuous mean age);
2) Sex distribution (male %);
3) BMI/obesity status (mean BMI, BMI z-score, or obesity prevalence; and whether BMI-adjusted estimates were reported);
4) Psychotropic medication exposure (especially antipsychotics; any psychotropic use vs none/unknown);
5) Fasting status (fasting vs non-fasting/unclear);
6) Specimen type (serum vs plasma; RBC membrane for fatty acids if applicable);
7) Assay platform (single-plex ELISA vs multiplex panels/other methods);
8) Study design (case-control vs cross-sectional vs cohort; clinical vs community samples);
9) Key comorbidities if consistently reported (e.g., epilepsy, GI symptoms) and ASD severity/IQ when available.

Sensitivity analysis

Planned sensitivity analyses include:
1) Excluding studies at high risk of bias (NOS/JBI) and re-estimating pooled effects;
2) Restricting to fasting samples, and/or to serum-only or plasma-only studies (as appropriate);
3) Excluding studies with imputed/converted mean–SD values (e.g., from medians/IQRs) to test robustness;
4) Leave-one-out and influence diagnostics to assess whether conclusions are driven by single studies or outliers;
5) Comparing alternative synthesis methods: multilevel random-effects vs RVE; and (when feasible) multivariate vs multilevel approaches;
6) Using alternative effect size choices for highly skewed biomarkers (e.g., log ratio of means) where data allow;
7) Testing different assumptions for within-study correlations in any multivariate models;
8) Small-study/publication bias assessments when enough studies are available (e.g., funnel plot/Egger), plus robustness checks using PET–PEESE and/or selection-model approaches as feasible.

Language restriction No language restrictions. English and Chinese studies will be included; other languages will be screened and translated where feasible.

Country(ies) involved China.

Keywords Autism Spectrum Disorder; Immunometabolism; Lipid Metabolism; Insulin Resistance; Multilevel Meta-analysis.

Contributions of each author

Author 1 - Jiaquan Hu.
Author 2 - Zhimei Jiang.