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Systematic review

LIPID METABOLISM IN ALZHEIMER DISEASE: A SYSTEMATIC REVIEW OF GENOME-WIDE ASSOCIATION STUDIES

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ABSTRACT

Background: Alzheimer disease is a polygenic disorder involving lipid transport, cholesterol homeostasis and microglial biology. This review aimed to synthesize genome-wide association study evidence on lipid-metabolism pathways and distinguish replicated associations from mechanistic hypotheses.

Methods: Searches of PubMed/MEDLINE, Scopus and Web of Science were run from inception through February 2026. Selection followed the eligibility criteria described in the Methods within a PRISMA 2020-informed structure. Risk of bias and certainty were not formally assessed. Findings were synthesized narratively, because cohorts, phenotypes, analytic pipelines and pathway definitions differed substantially.

Results: Fifty-two studies met the eligibility criteria, and five large association studies are summarized in Table 2 as the principal evidence base. Recurrent signals involved APOE, ABCA7, CLU, BIN1, PICALM, TREM2, CR1 and SORL1. Lipid transport and efflux, cholesterol and phospholipid homeostasis, endosomal trafficking and microglial immune signaling formed interconnected biological themes. Many associated variants were non-coding, and evidence for causality was uneven.

Conclusions: Genetic association evidence supports a relationship between lipid regulation and Alzheimer disease susceptibility, but does not establish causal genes or therapeutic efficacy. Functional validation and multi-ancestry studies are required before translation into individualized risk prediction or treatment.

Keywords: Alzheimer Disease; Genome-Wide Association Study; Lipid Metabolism; Apolipoproteins E; Microglia.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a substantial heritable component and a complex polygenic architecture. Genetic risk is distributed across loci involved in lipid transport, endosomal trafficking, innate immunity, synaptic biology and protein clearance rather than being determined by a single pathogenic gene (1,2). Large genome-wide association studies (GWAS) have therefore become an important way to identify susceptibility loci and to prioritize biological pathways for functional investigation (3,4,5,6,7).

Lipid homeostasis is particularly relevant to AD because cholesterol and phospholipids are required for neuronal membranes, synaptic vesicle cycling and myelin maintenance. Lipid-mediated signaling also influences amyloid precursor protein processing, intracellular trafficking and inflammatory responses (8,9). APOE, ABCA7 and CLU have direct or closely related roles in lipid transport and efflux, whereas BIN1, PICALM, SORL1 and TREM2 connect lipid biology with endocytosis, microglial activation and amyloid clearance (4,5,6,7).

At the same time, GWAS associations are not equivalent to causal mechanisms. Linkage disequilibrium, non-coding regulatory variants, ancestry imbalance and differences in phenotype definition can complicate the assignment of a lead variant to a specific gene or pathway. A systematic synthesis is therefore needed to distinguish replicated statistical signals from biological interpretations that still require experimental validation.

The objective of this systematic review was to synthesize human GWAS and GWAS meta-analysis evidence on the genetic regulation of lipid-metabolism pathways in AD, summarize recurrent loci and interconnected biological processes, and identify limitations that constrain clinical translation.

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METHODS

Protocol and registration

The review was not prospectively registered and no public protocol was deposited; eligibility and synthesis decisions are therefore reported as applied. Registration status is stated in the closing declarations.

Information sources and search strategy

The review follows a PRISMA 2020-informed reporting structure (10). Searches of PubMed/MEDLINE, Scopus and Web of Science were run from inception through February 2026. Search concepts covered Alzheimer's disease, genome-wide association studies and lipid-related biology, including cholesterol, lipoproteins, phospholipids, lipid transport, lipid metabolism, APOE and ABCA7. Reference lists were also screened. Strategies are reported at concept level; executed strings, per-source exports and a day-specific final search date are not included in the supplementary material, and PRISMA-S identifies the search details that full reproducibility would require (11). Table S1 maps reporting completeness.

Eligibility criteria

Eligible studies were human GWAS, GWAS meta-analyses or integrative genetic studies that evaluated AD or clinically relevant AD-related phenotypes and reported susceptibility loci, mapped genes or pathway-level results relevant to lipid biology. Studies were excluded when they were animal or in vitro experiments, narrative reviews, editorials, unrelated to AD, or did not provide interpretable genetic-locus or pathway information. Duplicate reports of the same analysis were consolidated where possible.

Study selection and data extraction

Records were screened by title and abstract and then by full-text assessment. Extracted items included publication year, study design, cohort size, population, phenotype definition, lead loci or genes, functional annotation, lipid-related pathways and principal interpretation. Screening and extraction were carried out by the review team, with disagreements resolved by discussion. Overlapping cohort reports were considered together where identifiable; sample sizes are not added across reports, because the cohorts of large consortium studies partly overlap.

Author contact and missing data

No contact with primary-study authors was undertaken and no unpublished data were sought. Information not reported in a publication was coded as not reported; individual participant data and missing effect estimates were not reconstructed. Partial cohort overlap between large consortium studies limits the interpretation of independent replication.

Risk of bias and applicability

No formal study-level risk-of-bias assessment was performed. Methodological limitations are considered descriptively, including phenotype ascertainment, ancestry representation, cohort overlap, imputation quality, population structure, gene mapping and pathway annotation. These observations do not constitute validated risk-of-bias categories.

Reporting bias and certainty of evidence

Reporting bias and outcome-specific certainty were not formally assessed. Narrative conclusions distinguish replicated associations from mechanistic hypotheses and do not imply a formal certainty rating.

Synthesis and interpretation

The primary synthesis was narrative. Findings were organized by recurrent loci, lipid-related biological processes and their connections with endosomal trafficking and microglial immunity. A pooled quantitative estimate was not calculated because the studies differed in cohort composition, phenotype ascertainment, variant prioritization, analytic pipelines and definitions of lipid-related pathways. Statistical associations were therefore interpreted as evidence of statistical association and gene or pathway prioritization, not as proof of causality or treatment efficacy. The Synthesis without meta-analysis (SWiM) guideline addresses intervention-effect reviews and is cited only as a reporting reference for transparent grouping, not as a genetic-association appraisal tool (12).

RESULTS

Study selection

The selection flow comprised 3,248 records: 1,284 from PubMed, 1,236 from Scopus and 728 from Web of Science. After removal of 842 duplicates, 2,406 records were screened and 2,256 excluded. Of the 150 reports sought, 12 were not retrieved and 138 were assessed; 86 were excluded, leaving 52 included studies. Table 2 presents the principal genome-wide association studies and meta-analyses on which the synthesis is based; contextual and mechanistic references cited in the Discussion are not counted as additional eligible studies. No quantitative meta-analysis was performed (Figure 1).

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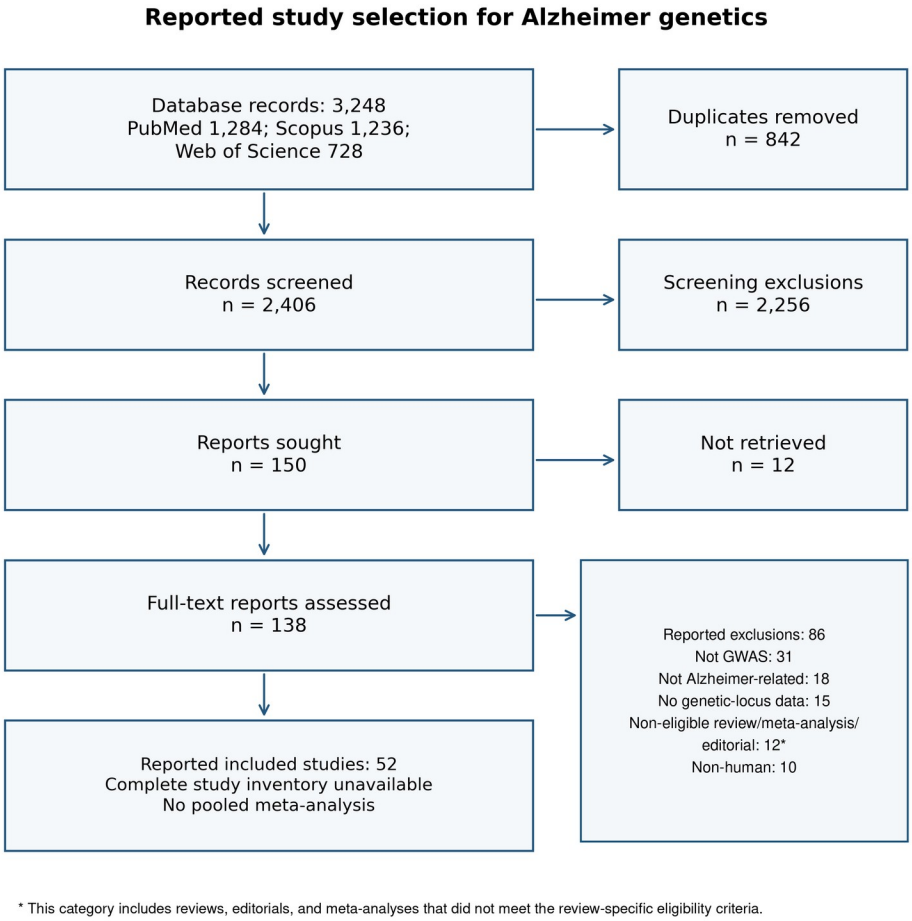


Figure 1. PRISMA 2020 study-selection flow.

Table 1. Recurrent AD-associated loci and their relationship to lipid biology

Gene	Representative variant	Chr	Principal function	Relationship to lipid biology
APOE	rs429358 / rs7412	19	Lipoprotein transport and cholesterol distribution	Direct; strongest common genetic risk signal
ABCA7	rs3764650	19	Lipid efflux and phagocytosis	Direct; linked to membrane lipid handling and clearance
CLU	rs11136000	8	Lipid transport and chaperone activity	Direct; linked to extracellular lipid and amyloid biology
BIN1	rs6733839	2	Endocytosis and membrane dynamics	Indirect; connects membrane remodeling with trafficking
PICALM	rs3851179	11	Clathrin-mediated endocytosis	Indirect; relevant to vesicle and APP trafficking
TREM2	rs75932628	6	Microglial activation and phagocytosis	Linked immune-lipid pathway; affects lipid sensing
CR1	rs6656401	1	Complement regulation	Linked immune pathway with potential effects on clearance
SORL1	rs11218343	11	APP and endosomal trafficking	Linked to lipid-dependent membrane trafficking
CD33	rs3865444	19	Microglial immune regulation	Linked to inflammatory and lipid-handling states
MS4A6A	rs610932	11	Microglial signaling	Linked immune-lipid and phagocytic processes
EPHA1	rs11767557	7	Cell signaling	Indirect; pathway-level relationship remains uncertain
HLA-DRB1	rs9271192	6	Antigen presentation	Indirect; reflects immune context rather than a lipid-specific effect

Abbreviations: APP, amyloid precursor protein; Chr., chromosome; GWAS, genome-wide association study.

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Recurrent loci and pathway-level evidence

The reviewed evidence consistently supported a polygenic architecture. APOE remained the most prominent common risk locus, while ABCA7, CLU, BIN1, PICALM, TREM2, CR1 and SORL1 were repeatedly implicated across large-scale analyses. These loci do not represent a single linear pathway: they span lipoprotein transport, phagocytosis, endocytosis, complement signaling, microglial activation and amyloid precursor protein trafficking. Table 1 summarizes representative loci and their relationships to lipid biology.

The exact number of associated loci varied by cohort size, phenotype definition and analytic design. Larger meta-analyses expanded the catalog of risk regions and increased the number of loci that could be functionally prioritized, but the presence of a lead variant did not by itself establish the causal gene. Many signals were located in non-coding regions, making gene assignment dependent on expression quantitative trait loci, chromatin accessibility, colocalization or other integrative evidence (4,5,6,7).

Table 2. Representative GWAS and meta-analysis evidence relevant to lipid-metabolism pathways in Alzheimer's disease

Study	Design and sample	Key loci / genes	Main lipid-related interpretation
Lambert et al. (3) (2013)	GWAS meta-analysis; 74,046 individuals	CLU, ABCA7, CR1 and additional loci	Established multiple susceptibility loci and linked AD risk to lipid processing and immune biology.
Kunkle et al. (4) (2019)	Diagnosed-AD meta-analysis; approximately 94,000 individuals	APOE, BIN1, CLU, ABCA7, PICALM and others	Supported the roles of amyloid, tau, immunity and lipid processing in AD risk.
Jansen et al. (5) (2019)	GWAS meta-analysis; approximately 455,000 individuals	APOE, CR1, TREM2, ABCA7 and additional loci	Identified functional pathways linking genetic risk with immune and lipid-related processes.
Wightman et al. (7) (2021)	GWAS; 1,126,563 individuals	Previously known and newly prioritized risk regions	Expanded the locus catalog and reinforced microglial, immune and protein-catabolism pathways.
Bellenguez et al. (6) (2022)	Two-stage GWAS; 111,326 clinically diagnosed/proxy cases and 677,663 controls (788,989 total)	ABCA7, APOE, PLCG2 and additional loci	Highlighted microglial biology and interactions between lipid handling and innate immunity.

Abbreviations: AD, Alzheimer's disease; GWAS, genome-wide association study.

Lipid transport, cholesterol homeostasis and membrane biology

The strongest mechanistic theme was the relationship between AD risk and lipid transport. APOE participates in the distribution of cholesterol and other lipids in the central nervous system, while ABCA7 contributes to lipid efflux and phagocytic function. CLU has chaperone and lipid-transport functions that intersect with extracellular amyloid biology. Together, these signals support the view that altered lipid handling may affect neuronal membranes, endosomal trafficking and the clearance of extracellular material, although the direction and magnitude of these effects are context-dependent (4,6,9).

Endosomal trafficking and microglial pathways

Several loci that are not lipid-specific in annotation nevertheless converge on lipid-dependent cellular processes. BIN1 and PICALM influence membrane curvature, clathrin-mediated endocytosis and vesicle trafficking. SORL1 participates in amyloid precursor protein sorting, while TREM2, CD33 and MS4A6A are associated with microglial activation and phagocytic states (15,16). These pathways provide a biological bridge between lipid metabolism, membrane remodeling, immune signaling and amyloid clearance.

Microglia require tightly regulated lipid uptake, storage and export to respond to myelin debris, apoptotic material and amyloid-associated structures. Disruption of this balance may promote a disease-associated inflammatory state, but the available genetic evidence cannot determine whether altered lipid metabolism is an initiating event, a consequence of neurodegeneration or a process that amplifies pathology. This distinction is important when translating pathway associations into therapeutic targets (7,9,17,18,19,20,21).

Cross-trait architecture and population considerations

APOE illustrates the distinction between a biological pathway and a clinical risk association. Its alleles influence age-related susceptibility to Alzheimer disease, but this does not establish that a peripheral lipid measurement mediates the genetic association. Family-based gene-dose evidence and population-based age-at-onset evidence should be interpreted within their respective designs (22,23).

Generalizability remains a major limitation. Many large GWAS have been conducted predominantly in populations of European ancestry, and the effect sizes, linkage disequilibrium structure and allele frequencies may differ across populations. Multi-ancestry studies and ancestry-aware fine-mapping are needed to determine whether the same variants, genes and lipid-related pathways operate consistently across populations.

Methodological limitations of the evidence

The included studies varied in phenotype ascertainment, case-control composition, cohort

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overlap, imputation quality, variant prioritization and pathway databases. Some reports focused on diagnosed AD, whereas others used proxy phenotypes, family history or biomarker-defined traits. These differences limit direct comparison of locus counts and make a pooled quantitative estimate inappropriate. In addition, pathway enrichment can be sensitive to the choice of gene-mapping method and reference annotation. The STrengthening the REporting of Genetic Association Studies (STREGA) extension provides relevant reporting considerations for genotyping, population stratification and relatedness; it does not replace a study-level risk-of-bias assessment (24).

The review is limited by coverage of three databases and by prioritization of English-language reporting. Search strategies are reported at concept level rather than as executed strings, and exclusions are reported by category rather than by citation. Table 2 presents the principal studies underpinning the synthesis rather than an exhaustive included-study table. No formal risk-of-bias or evidence-certainty ratings were assigned. Genetic association also requires functional validation before causal or clinical claims can be made.

DISCUSSION

This systematic review indicates that lipid biology is not a peripheral theme in AD genetics. Across large GWAS and meta-analyses, recurrent signals converge on cholesterol transport, lipid efflux, membrane remodeling, endosomal trafficking and microglial immune function. APOE, ABCA7 and CLU provide the most direct links to lipid handling, whereas BIN1, PICALM, SORL1 and TREM2 illustrate how lipid-dependent cellular functions intersect with amyloid processing and innate immunity.

The findings should nevertheless be interpreted with appropriate caution. A locus can be robustly associated with AD while the causal gene, cell type and direction of biological effect remain uncertain. Non-coding variants may regulate several transcripts in a context-dependent manner, and a pathway enriched in statistical signals may reflect correlated genes rather than a single modifiable process. The most defensible conclusion is therefore that lipid homeostasis is a biologically supported and clinically promising area for further investigation, not that a specific lipid-targeted intervention has already been validated.

Foundational studies placed CLU and PICALM among the common-variant susceptibility loci and subsequently expanded the signal to ABCA7 and immune-related regions, including MS4A and CD33 (25,26,27). Rare-variant studies of TREM2 provide complementary evidence linking innate immune biology to disease susceptibility (28,29). Integrative fine-mapping further illustrates how association signals can be prioritized using functional evidence without equating the lead variant with a proven causal gene (30). These studies provide biological context for the loci discussed above.

Future studies should combine multi-ancestry GWAS with fine-mapping, single-cell transcriptomics, epigenomic profiling, lipidomics and experimental perturbation. Longitudinal designs should test whether genetic risk modifies lipid-related biomarkers, microglial states, amyloid or tau progression, and response to treatment. Such integrative work is necessary before genetic information can be used to provide individualized risk prediction or to select a lipid-directed therapy.

CONCLUSIONS

The accumulated GWAS evidence supports a central relationship between genetic regulation of lipid metabolism and AD susceptibility. Recurrent loci implicate cholesterol transport, lipid efflux, membrane trafficking and microglial immune biology. However, most associations remain probabilistic and require functional confirmation, particularly in populations that are underrepresented in current datasets. The next stage of translation should prioritize causal gene mapping, multi-ancestry validation and experimentally tested links between lipid homeostasis and clinically meaningful AD outcomes. Figure 2 summarizes these proposed relationships without implying causality.

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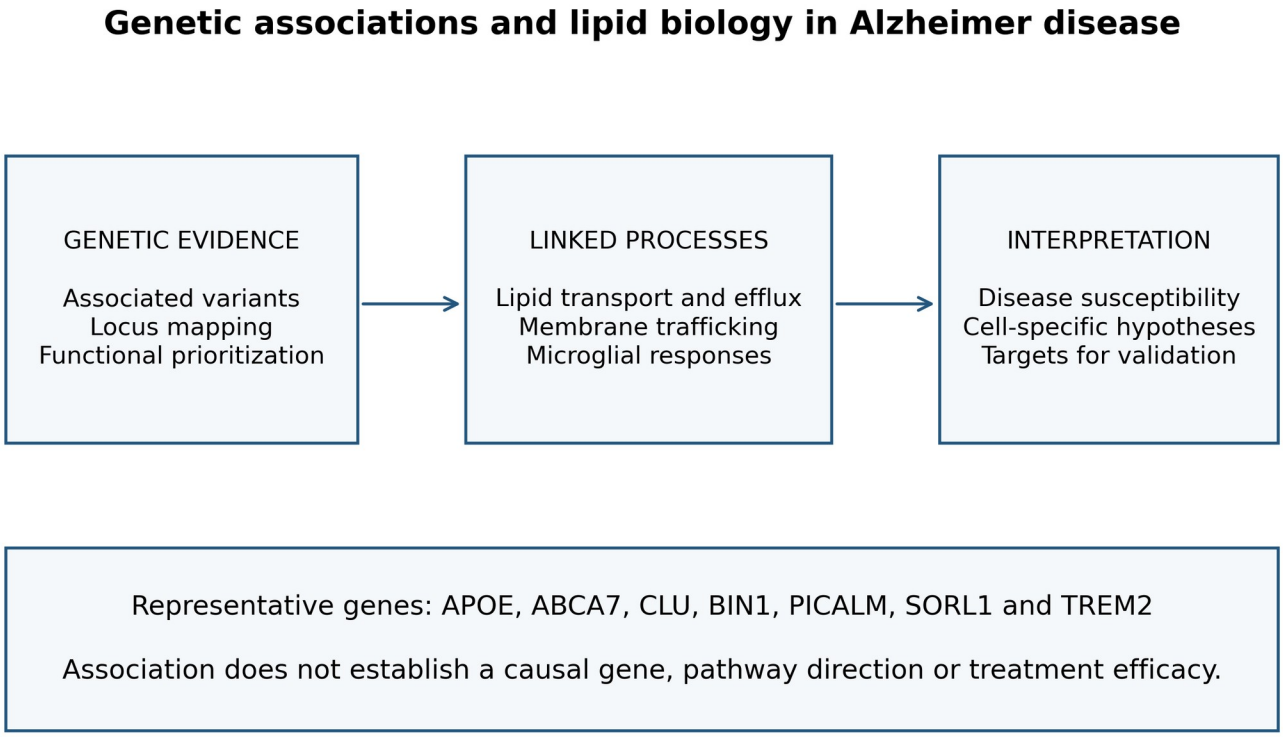


Figure 2. Conceptual links between genetic associations, lipid biology and Alzheimer disease. Arrows indicate proposed relationships, not proven causation. Representative genes are discussed in the text.

DECLARATIONS

Author contributions: ZK: Conceptualization, Methodology, Investigation, Formal analysis, and Writing – original draft. AT: Data curation, Investigation, and Writing – review and editing. ZT: Formal analysis, Visualization, and Writing – review and editing. AK: Validation, Data curation, and Writing – review and editing. DT: Project administration, Supervision, and Writing – review and editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Conflicts of interest: None of the authors report relationships that could be perceived as influencing the work reported here.

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Data availability statement: The review synthesizes published aggregate results from the cited genome-wide association studies and meta-analyses; no new or individual-level genotype data were generated or analyzed. The complete included-study inventory, the executed search strategies, per-source exports and the individual screening, exclusion and extraction records are not included in the supplementary material.

AI use statement: ChatGPT (OpenAI) assisted with language editing, internal consistency checks, citation placement and formatting only. It was not used for searching, screening, data extraction or appraisal, and no formal risk-of-bias assessment was produced with it. The authors are responsible for verifying the revised content and these declarations.

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Table S1. PRISMA 2020 reporting checklist

Item	Topic	Location and reporting status
1	Title	Title identifies a systematic review.
2	Abstract	Four-part Abstract; limitations and undocumented registration stated; funding unknown.
3	Rationale	Introduction.
4	Objectives	Introduction, final paragraph.
5	Eligibility criteria	Methods – Eligibility criteria.
6	Information sources	Methods – Information sources. Month only; source-specific final dates missing.
7	Search strategy	Table S1; strategies reported at concept level.
8	Selection process	Methods – Study selection. Reviewer number and independence undocumented.
9	Data collection process	Methods – Study selection and data extraction.
10a	Data items - outcomes	Methods – Extraction and synthesis; loci and pathway findings.
10b	Data items - other variables	Methods – Extraction; Tables 1 and 2.
11	Risk of bias assessment	Methods – Risk of bias: appraised narratively; no study-level ratings assigned.
12	Effect measures	No pooled estimate; association and mechanistic evidence distinguished.
13a	Synthesis methods	Methods – Synthesis; recurrent loci and pathway themes.
13b	Synthesis methods	Methods – Missing data and overlap. No imputation; samples not added.
13c	Synthesis methods	Tables 1 and 2; Figures 1 and 2.
13d	Synthesis methods	Methods – Synthesis. Narrative synthesis; no pooled meta-analysis.
13e	Synthesis methods	Results – Population considerations and methodological limitations.
13f	Synthesis methods	Not applicable: no meta-analysis was performed.
14	Reporting bias assessment	Methods – Reporting bias: discussed narratively.
15	Certainty assessment	Methods – Certainty: discussed narratively.
16a	Study selection	Results – Study selection; Figure 1.
16b	Study selection	Figure 1: exclusions reported by category.
17	Study characteristics	Table 2 contains five representative reports, not a complete inventory.
18	Risk of bias in studies	Not applicable: no study-level ratings assigned.
19	Results of individual studies	Tables 1 and 2; narrative results.
20a	Results of syntheses	Narrative pathway sections; methodological limitations.
20b	Results of syntheses	Not applicable: no statistical synthesis.
20c	Results of syntheses	Narrative discussion of ancestry, phenotype and analytic differences.
20d	Results of syntheses	Not applicable: no meta-analysis was performed.
21	Reporting biases	Limitations: reporting bias discussed narratively.
22	Certainty of evidence	Discussion: narrative certainty statement.
23a	Interpretation	Discussion.
23b	Limitations of evidence	Results – Methodological limitations; Discussion.
23c	Limitations of review processes	Methods caveats and methodological limitations.
23d	Implications	Discussion; Conclusions.
24a	Registration	Closing declarations – Registration and protocol.
24b	Protocol	Closing declarations – Registration and protocol.
24c	Amendments	Closing declarations – Registration and protocol.
25	Support	Closing Funding declaration.
26	Competing interests	Conflicts of interest declaration.
27	Availability of data, code and materials	Data availability declaration; Table S1.

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