The Evolving Genetic Landscape of Metabolic Syndrome: A Bibliometric Analysis and Systematic Evidence Map toward Precision Prevention and Health-System Resilience

Anggelia Puspasari[1]*, Citra Maharani[1], Rosdiana Mus[2], Rina Nofri Enis[3], Rita Halim[4], Tengku Arief Buana Perkasa[1], Afifah Amatullah[5], Amelia Dwi Fitri[6], and Nyimas Natasha Ayu Shafira[6]

[1] Department of Medical Biology and Biochemistry, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi, Indonesia
[2] Department of Biochemistry, Faculty of Medicine, Universitas Pattimura, Maluku, Indonesia
[3] Department of Anatomy, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi, Indonesia
[4] Department of Nutrition, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi, Indonesia
[5] Department of Internal Medicine, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi, Indonesia
[6] Department of Medical Education, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi, Indonesia

*Coressponding Authors: anggelia.puspasari@unja.ac.id

Abstract

Genetic research on metabolic syndrome (MetS) has expanded from candidate variants toward genome-wide, interaction-based, polygenic, and predictive approaches, yet the coherence and transferability of direct variant-level evidence remain uncertain. To characterize the temporal, thematic, methodological, and geographic development of MetS genetic research and systematically map direct evidence in adults. Scopus and PubMed searches produced 1,453 deduplicated records. Title-abstract screening retained 506 records, 488 full texts were assessed, and file-level and article-level verification yielded 487 unique articles for bibliometric profiling. A nested evidence map included 246 original adult human studies reporting direct inherited variant-MetS associations; 15 additional articles were retained as contextual evidence. Publication output increased from seven articles in 1996-2004 to 151 in 2020-2024 and peaked in 2024 with 43 articles. Candidate-gene or single-variant research remained the largest bibliometric category (238/487; 48.9%), although genome-wide, interaction, Mendelian-randomization, prediction, and omics approaches increased. Direct evidence was concentrated in Asia (150/246; 61.0%), particularly China, South Korea, and Iran. APOA5, ADIPOQ, FTO, LPL, and CETP were the most recurrent genes; FTO rs9939609 and APOA5 rs662799 were the most frequently investigated variants. Among 95 studies with structured result coding, mixed or conditional findings predominated. **Conclusion:** MetS genetic research is expanding and diversifying, but replication, cross-population validation, standardized outcome definitions, and clinical translation lag behind publication growth. Locally validated, ancestry-aware genetic evidence integrated with modifiable exposures may support equitable precision prevention and health-system resilience, but current findings do not justify routine genotype-guided care.

Keywords: metabolic syndrome; genetic variation; bibliometric analysis; evidence mapping; health-system resilience

© 2026 The Author(s). Published with license by LPPM Universitas Jambi. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0 International). This license enables reusers to distribute, remix, adapt, and build upon the material in any medium or format, so long as attribution is given to the creator.

Cite This Article
The Evolving Genetic Landscape of Metabolic Syndrome: A Bibliometric Analysis and Systematic Evidence Map toward Precision Prevention and Health-System Resilience. Proceedings Academic Universitas Jambi, 2(3): e12345. DOI: 10.22437/proca.v2i3.59974

Editor
Hansein Arif Wijaya

Article info
Received: August 04, 2026 . Revised: August 26, 2026 . Accepted: September 01, 2026

© 2026 The Author(s). Published with license by LPPM Universitas Jambi. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0 International). This license enables reusers to distribute, remix, adapt, and build upon the material in any medium or format, so long as attribution is given to the creator.

INTRODUCTION

Metabolic syndrome (MetS) is a clustering of abdominal obesity, dysglycemia, elevated blood pressure, hypertriglyceridemia, and low high-density lipoprotein cholesterol that substantially increases the risk of type 2 diabetes and cardiovascular disease. Although diagnostic thresholds differ across organizations and populations, the harmonized definition established a clinically useful syndrome-level construct for research and surveillance [1]. The increasing global burden of obesity, sedentary behavior, and population aging has made MetS an important challenge for noncommunicable disease prevention [2].

MetS is also genetically complex. Its components are correlated but biologically heterogeneous, and inherited susceptibility can act through lipid handling, adipogenesis, appetite regulation, insulin signaling, inflammation, vascular function, and interactions with environmental exposures. Early research therefore concentrated on biologically plausible candidate genes, including APOA5, ADIPOQ, FTO, LPL, PPARG, and TCF7L2. Subsequent genome-wide association studies broadened discovery beyond predefined pathways and showed particularly strong contributions from lipid-related loci, while also questioning whether a single common genetic architecture explains the clustering of all MetS components [3-4].

The field has continued to diversify. Gene-diet and gene-lifestyle studies have evaluated whether modifiable exposures alter genetic effects, as illustrated by interactions involving circadian, lipid, and fatty-acid metabolism pathways [5-6]. More recent research has added polygenic risk scores, machine learning, multi-omics, and Mendelian-randomization approaches. These developments create a broad and rapidly changing literature, but they do not necessarily produce directly comparable evidence for variant-level associations with syndrome-defined MetS.

Bibliometric analysis is useful for describing the growth, intellectual structure, sources, contributors, and thematic evolution of a research field [7]. However, bibliometric frequency alone cannot distinguish direct human association evidence from reviews, animal studies, studies of individual metabolic traits, causal summary-data analyses, or prediction-oriented reports. A systematic evidence map complements bibliometric profiling by applying explicit eligibility criteria and displaying where evidence is concentrated, inconsistent, or absent [8].

This study therefore used a nested design. First, we profiled the complete verified full-text literature to characterize how MetS genetic research has evolved. Second, we systematically mapped adult human studies that directly evaluated inherited variants against syndrome-level MetS. The objectives were to quantify publication and citation trends; describe shifts from candidate variants to genome-wide, interaction-based, and predictive approaches; map the geographic distribution of direct evidence; identify recurrent genes and SNPs; summarize the direction of findings where structured results were available; and discuss implications for equitable precision prevention and health-system resilience.

METHODS

Study design and reporting framework

A combined bibliometric analysis and systematic evidence map was conducted. The bibliometric component used the entire verified full-text corpus, whereas the evidence map was nested within that corpus and restricted to studies that provided direct adult human evidence on inherited genetic variation and syndrome-level MetS. The workflow was informed by the PRISMA 2020 framework for transparent study selection and by evidence-mapping principles that emphasize structured description

of the available literature rather than automatic pooling of heterogeneous estimates [8-9].

The unit of analysis for bibliometric profiling was the unique article. For the evidence map, the unit remained the article, although an article could investigate multiple genes, SNPs, genetic models, subgroups, or cohorts. Consequently, gene and SNP frequencies represent the number of articles in which a target was identified, not the number of independent cohorts or effect estimates.

Data sources and search concepts

Records were retrieved from Scopus and PubMed. The searches combined three concept blocks: (1) metabolic syndrome or metabolic syndrome X; (2) single-nucleotide polymorphisms, genetic polymorphisms, genetic variants, genotypes, alleles, haplotypes, candidate genes, genome-wide association, or related inherited-variation terminology; and (3) association, susceptibility, risk, odds ratio, genotype, or allele terminology. Search fields covered titles, abstracts, and indexed keywords as supported by each database. The database exports were combined, normalized, and deduplicated before screening. The final corpus contained publications indexed from 1996 through 2026; 2026 was an incomplete publication year at the time of analysis.

No language restriction was applied at the broad retrieval stage. Screening prioritized original human research relevant to the MetS-genetic landscape. Full-text files were obtained from available database links, publisher sites, institutional access, and open-access sources. The bibliographic metadata were reconciled against the locally stored PDF collection using titles, digital object identifiers, filenames, and file-level SHA-256 hashes.

Screening and article-level audit

The deduplicated master corpus contained 1,453 records. Title and abstract screening retained 506 records that were potentially relevant to inherited genetic variation and MetS. A total of 488 full-text records were represented in the verified retrieval collection. Eighteen focused records were not represented because full-text retrieval or final eligibility could not be confirmed at the time of analysis. File-level verification identified 488 distinct PDF hashes; subsequent article-level review found one duplicated article record and one article stored in two PDF versions, leaving 487 unique articles for bibliometric profiling.

All 487 unique articles were classified as direct evidence, contextual evidence, or excluded from the direct evidence map. Direct evidence required an original human study; an adult population; syndrome-level MetS as the analyzed outcome; an inherited genetic exposure such as an SNP, polymorphism, haplotype, or genome-wide variant; a direct comparison between the genetic exposure and MetS status, risk, or incidence; and an interpretable result. Contextual evidence included methodologically or biologically informative reports, such as selected prediction, polygenic, interaction, or mechanistic studies, that did not satisfy all criteria for direct variant-level mapping but informed interpretation of the field.

Articles were excluded from direct evidence mapping when they used special clinical or restricted populations without a generalizable MetS comparison, did not assess an eligible inherited point variant, were Mendelian-randomization or summary-data causal studies without a primary SNP-MetS analysis in an adult sample, lacked an interpretable direct association, analyzed only individual components or biomarkers rather than syndrome-level MetS, used animal or preclinical designs, or were reviews or meta-analyses.

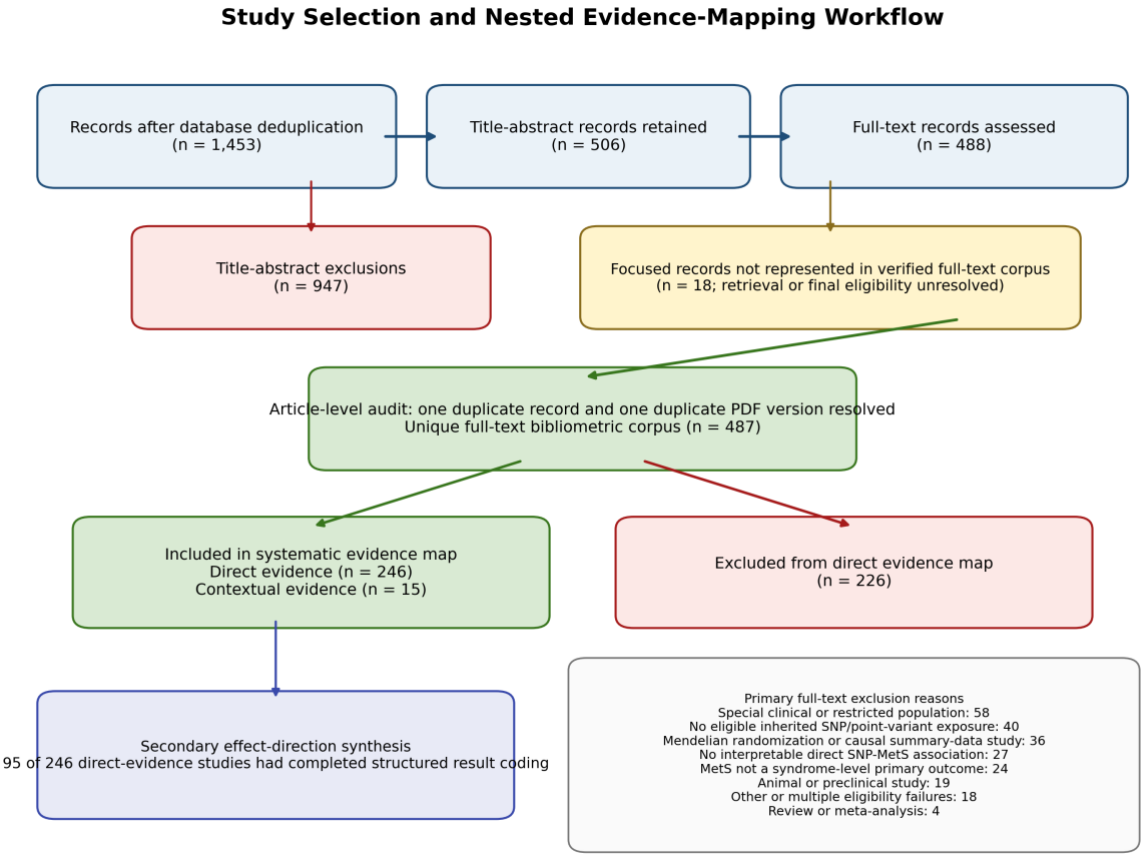

Figure 1. Study selection and nested evidence-mapping workflow. Exclusion categories represent the primary reason assigned at full-text assessment; the 95-study subset was used only for effect-direction synthesis, not as the complete evidence map

Bibliometric variables and analysis

Bibliometric variables included publication year, journal, authorship, Scopus citation count, study setting, author keywords, indexed keywords, and methodological approach. Annual production was summarized for the entire period and grouped into six publication periods. Citation indicators included total citations, mean and median citations, and the corpus h-index among records with available Scopus citation data. Citation counts were used as exported and were not normalized for publication age or field.

Research approaches were classified using transparent rule-based text coding of titles, abstracts, keywords, and available methodological fields. Categories included candidate gene or single-variant research, gene-environment or clinical interaction, genome-wide or exome-wide research, Mendelian randomization or causal inference, prediction or polygenic-risk-score or machine-learning studies, multi-omics or molecular profiling, heritability or family or linkage studies, reviews and meta-analyses, preclinical studies, and other or unclear approaches. The categories were mutually exclusive for the broad bibliometric profile. Thematic profiling used overlapping keyword rules; therefore, one article could contribute to several biological or methodological themes.

Evidence-map coding and synthesis

For the 246 direct-evidence articles, we coded study setting and continent, study design, genetic approach, recurrent gene targets, recurrent rs-numbered variants, and the availability of interpretable results. Study design was standardized as cohort or prospective or longitudinal, case-control, cross-sectional, genome-wide discovery, prediction or modeling, intervention or genetic subgroup, or observational or unspecified. Countries were grouped into geographic regions based on the reported study setting.

Gene targets were identified from titles, author keywords, and curated gene and variant fields. SNPs were counted using rs identifiers reported in those fields. This strategy reduced the risk of counting genes mentioned only as background in an abstract, but it may underestimate genes that were insufficiently represented in the structured metadata.

A secondary effect-direction synthesis was conducted for the 95 direct-evidence articles with completed structured result coding. Findings were classified as risk, protective, null, mixed or conditional, significant with direction not yet unambiguously coded, or model or prediction only. Mixed or conditional findings included effects that differed by genetic model, subgroup, population, lifestyle exposure, diagnostic definition, or SNP within the same article. The remaining 151 direct-evidence studies stayed in the evidence map but were not assigned an effect direction because variant-level alleles, models, estimates, or conclusions had not been extracted uniformly. No pooled meta-analysis was undertaken because comparable effect estimates, genetic models, and MetS definitions were not yet sufficiently harmonized.

RESULTS

Growth and bibliometric profile of the field

The verified bibliometric corpus comprised 487 unique full-text articles published between 1996 and 2026. Output increased from seven articles in 1996-2004 to 47 in 2005-2009, 118 in 2010-2014, 122 in 2015-2019, and 151 in 2020-2024. Publication activity peaked in 2024 with 43 articles. Forty articles were identified for 2025-2026; 2026 was incomplete at the time of analysis.

The corpus represented 201 journals or source titles and 3,198 unique author names. PLoS ONE was the most frequent identified source with 40 articles, followed by Diabetology and Metabolic Syndrome with 24, Scientific Reports with 21, Diabetologia with 13, and Frontiers in Endocrinology with 12. Citation information was available for 425 records. These articles accumulated 9,303 Scopus citations, with a mean of 21.9, median of 12, maximum of 212, and corpus h-index of 48.

The most highly cited direct-evidence article was the genome-wide study by Kristiansson et al. (2012), which highlighted a strong lipid-gene contribution but limited evidence for a single genetic basis underlying the full clustering of MetS traits [3]. Other highly cited direct studies included IL6 promoter variants in Danish adults, the genome-wide study of Indian Asian men, FTO rs9939609 in a multi-ethnic non-Caucasian sample, APOA5 variants in Caucasians, and genome-wide analyses in Korean and Han Chinese populations [10-12,4].

Table 1. Main bibliometric indicators of the 487-article corpus.

Indicator	Result	Interpretation
Publication period	1996-2026	2026 was an incomplete publication year
Peak annual output	43 articles in 2024	Highest observed annual production
Output in 2020-2024	151 articles	31.0% of the full-text corpus
Identified journals/sources	201	Includes 23 records with unknown source metadata
Unique author names	3,198	Name variants may remain despite normalization
Records with Scopus citation data	425	87.3% of the corpus
Total Scopus citations	9,303	Not normalized for publication age
Mean; median citations	21.9; 12	Right-skewed citation distribution
Corpus h-index	48	Calculated among records with citation data
Top identified sources	PLoS ONE (40); Diabetology and Metabolic Syndrome (24); Scientific Reports (21)	Most frequent publication venues

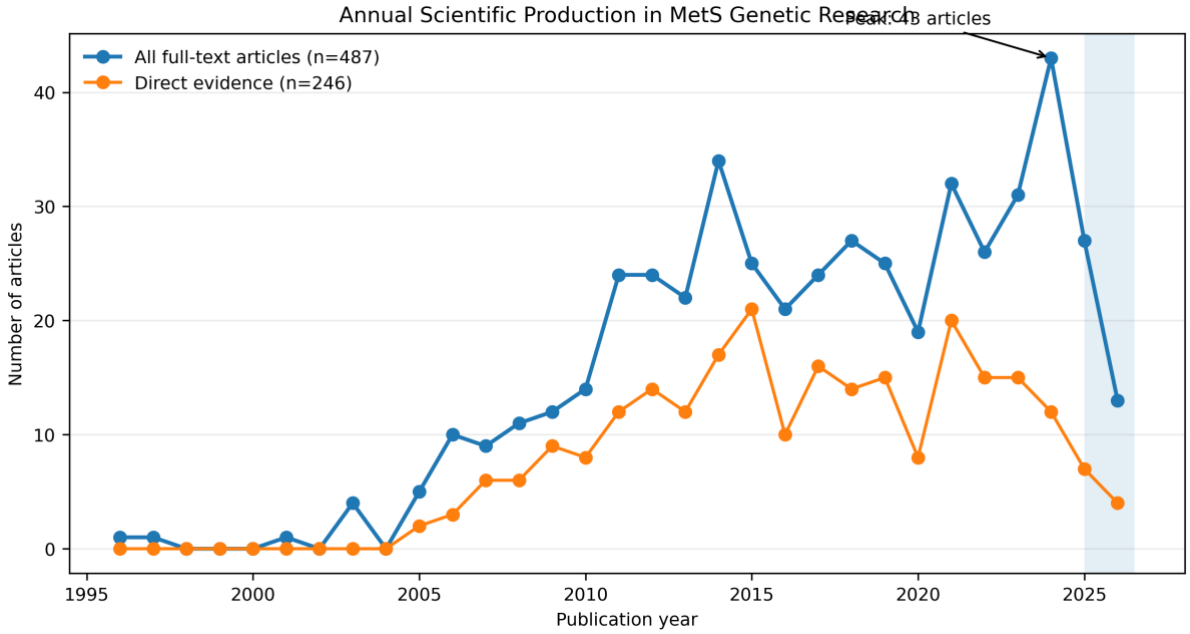

Figure 2. Annual scientific production in MetS genetic research. The shaded final interval indicates the incomplete 2025-2026 period

Evolution from candidate variants to integrated approaches

Candidate-gene or single-variant studies were the largest methodological category, accounting for 238 of 487 articles (48.9%). Genome-wide or exome-wide approaches accounted for 60 articles (12.3%), gene-environment or clinical-interaction studies for 53 (10.9%), Mendelian-randomization studies for 40 (8.2%), and prediction, polygenic-risk-score, or machine-learning studies for 26 (5.3%). Reviews, preclinical studies, omics research, heritability studies, and other designs made up the remaining corpus.

Candidate-variant research dominated the earlier literature, whereas genome-wide analysis and interaction studies became increasingly visible after 2010. Mendelian-randomization and prediction-oriented research emerged primarily after 2020. Many recent records were retained in the bibliometric profile or contextual synthesis rather than the direct evidence map because they did not provide directly interpretable SNP-MetS associations.

Thematic coding showed that glucose and insulin or type 2 diabetes, lipid and lipoprotein metabolism, and obesity or adiposity each appeared in more than 300 articles. Population and ethnic diversity, blood pressure and vascular biology, and lifestyle were also frequent themes. Gene-environment interaction, genome-wide discovery, Mendelian randomization, multi-omics, and polygenic prediction increased in later periods.

Table 2. Research approaches in the full bibliometric corpus.

Research approach	Articles, n	Proportion, %
Candidate gene/single variant	238	48.9
GWAS/exome/genome-wide	60	12.3
Gene-environment/clinical interaction	53	10.9
Mendelian randomization/causal inference	40	8.2
Prediction/PRS/GRS/ML	26	5.3
Review/meta-analysis	22	4.5
Preclinical/animal	18	3.7
Omics/molecular profiling	13	2.7
Other/unclear	11	2.3
Heritability/family/linkage	6	1.2

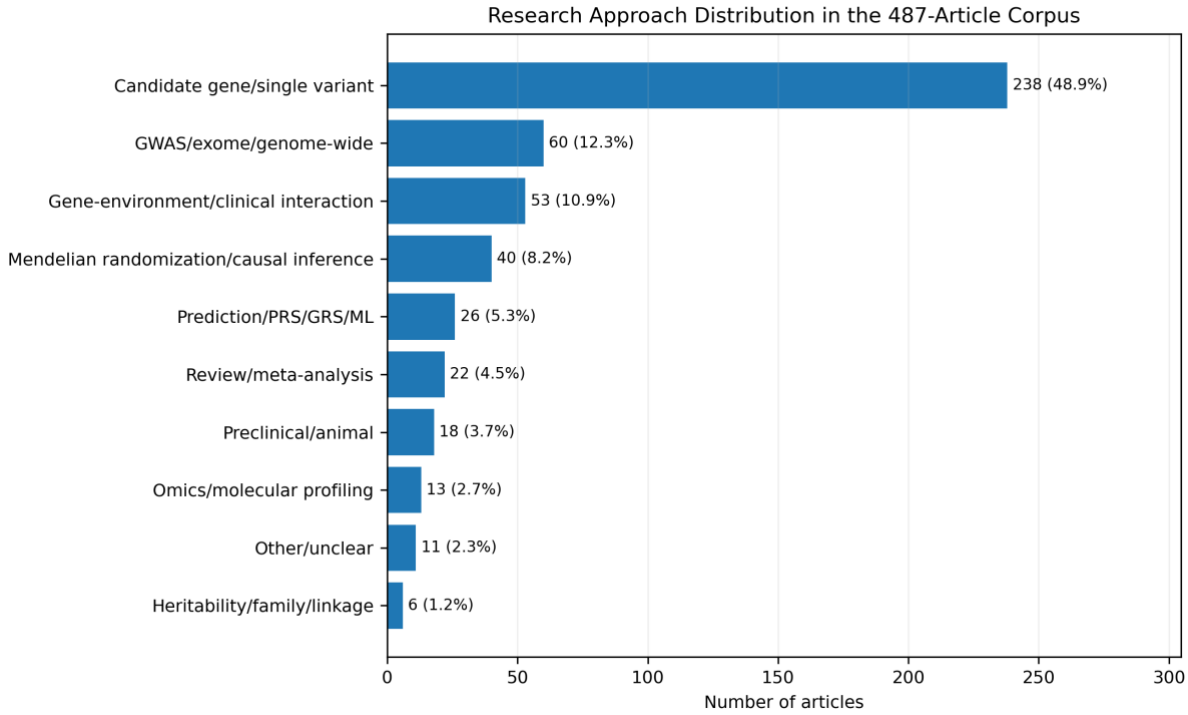

Figure 3. Distribution of research approaches in the complete bibliometric corpus. Categories were mutually exclusive and assigned by rule-based coding of titles, abstracts, keywords, and available methodological fields

Structure and geographic concentration of direct evidence

The systematic evidence map included 246 direct-evidence articles and 15 contextual articles. Within direct evidence, candidate or single-variant studies remained dominant (125/246; 50.8%). Gene-environment or clinical-interaction studies represented 46 articles (18.7%), multi-variant or haplotype studies 36 (14.6%), genome-wide or exome-wide studies 13 (5.3%), prediction or polygenic-risk-score or machine-learning studies 9 (3.7%), and model or mediation or subgroup studies 7 (2.8%); 10 articles could not be classified confidently.

Study designs included 52 cohort, prospective, or longitudinal studies (21.1%), 43 case-control studies, 25 cross-sectional studies, 19 genome-wide discovery studies, 8 prediction or modeling studies, and 3 intervention or genetic-subgroup studies. Ninety-six articles were observational but insufficiently specified in the structured fields.

Direct evidence was geographically concentrated. Asia contributed 150 of 246 articles (61.0%), followed by Europe with 35 (14.2%), North America with 15 (6.1%), Latin America or the Caribbean with 15 (6.1%), Africa with 13 (5.3%), multi-region studies with 6 (2.4%), and Oceania with only 1 (0.4%); 11 settings were unclear. China contributed 43 direct-evidence articles, South Korea 31 after normalization of country labels, Iran 23, Taiwan 14, the United States 13, Egypt 8, and Japan 7. Indonesia contributed three direct-evidence articles.

Table 3. Characteristics of the 246 direct-evidence articles.

Domain	Category	n	%
Genetic approach	Candidate/single variant	125	50.8
Genetic approach	Gene-environment/clinical interaction	46	18.7
Genetic approach	Multi-variant/haplotype	36	14.6
Genetic approach	GWAS/exome-wide	13	5.3
Genetic approach	Prediction/GRS/PRS/ML	9	3.7
Genetic approach	Model/mediation/subgroup	7	2.8
Genetic approach	Unclear/not coded	10	4.1
Study design	Cohort/prospective/longitudinal	52	21.1
Study design	Case-control	43	17.5
Study design	Cross-sectional	25	10.2
Study design	Genome-wide/discovery	19	7.7
Study design	Prediction/modeling	8	3.3
Study design	Intervention/genetic subgroup	3	1.2
Study design	Observational/unspecified	96	39.0
Region	Asia	150	61.0
Region	Europe	35	14.2
Region	North America	15	6.1
Region	Latin America/Caribbean	15	6.1
Region	Africa	13	5.3
Region	Oceania	1	0.4
Region	Multi-region	6	2.4
Region	Unclear	11	4.5

Recurrent genes, variants, and consistency of findings

The direct evidence map remained strongly centered on lipid metabolism, adiposity, and insulin-related pathways. APOA5 was identified as a target in 25 articles, followed by ADIPOQ in 17, FTO in 16, LPL in 11, CETP in 8, TCF7L2 and APOC3 in 7 each, and ACE and APOE in 6 each. The most recurrent individual variants were FTO rs9939609 and APOA5 rs662799, each reported in 12 articles, followed by APOA5 rs651821 and ADIPOQ rs1501299, each in 8, and TCF7L2 rs7903146 in 5.

The gene-by-continent heatmap showed that recurrent genes were not represented evenly across regions. APOA5 had 20 Asian and 4 European target articles, with minimal representation elsewhere. FTO was more geographically distributed, including Asian, European, North American, and African studies, while most other genes remained heavily concentrated in Asia.

Of the 246 direct-evidence studies, 95 had sufficiently structured variant-level results for effect-direction classification. Mixed or conditional findings were the largest category (31 studies), followed by statistically significant findings whose direction was not yet unambiguously coded (22), risk associations (19), null findings (12), protective associations (7), and model or prediction-only findings (4).

Table 4. Most recurrent genes and SNPs in the direct evidence map.

Gene	Articles, n	SNP (mapped gene)	Articles, n
APOA5	25	rs9939609 (FTO)	12
ADIPOQ	17	rs662799 (APOA5)	12
FTO	16	rs651821 (APOA5)	8
LPL	11	rs1501299 (ADIPOQ)	8
CETP	8	rs7903146 (TCF7L2)	5
TCF7L2	7	rs1801282 (PPARG)	4
APOC3	7	rs780094 (GCKR)	4
ACE	6	rs7799039 (LEP)	4
APOE	6	rs780093 (GCKR)	3
CAV1	5	rs266729 (ADIPOQ)	3

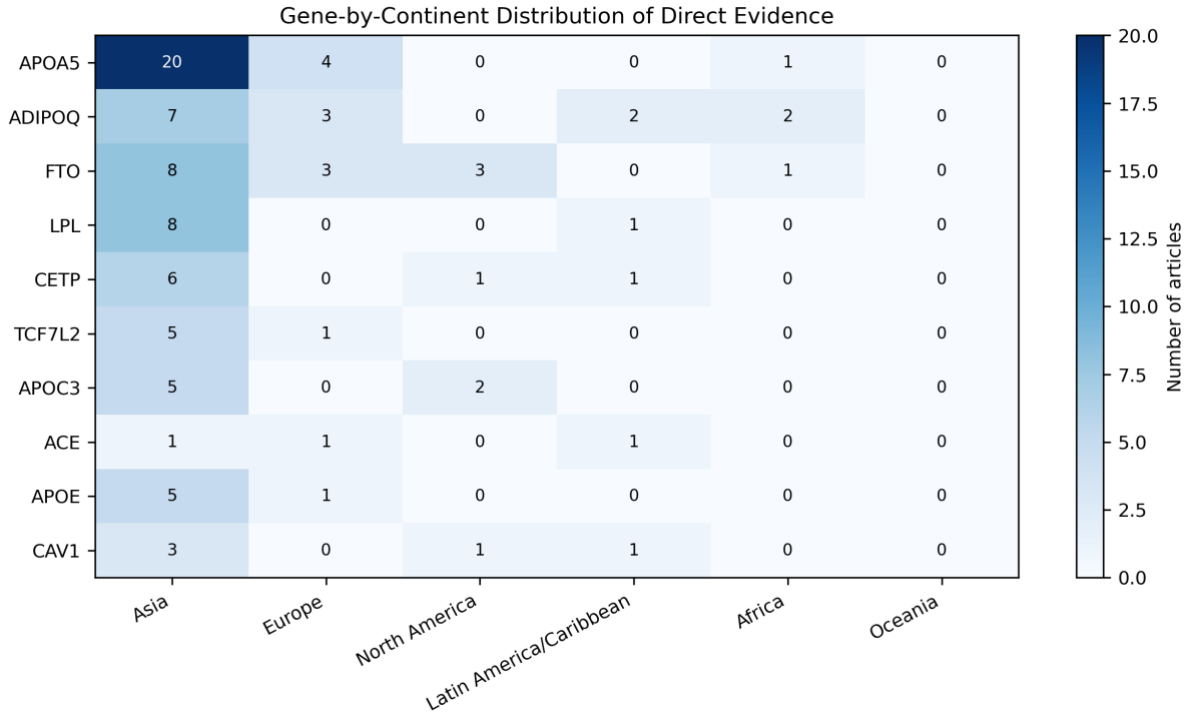

Figure 4. Gene-by-continent distribution of direct evidence. Darker cells indicate a greater number of articles targeting the gene in the reported study region. Counts represent articles, not independent cohorts

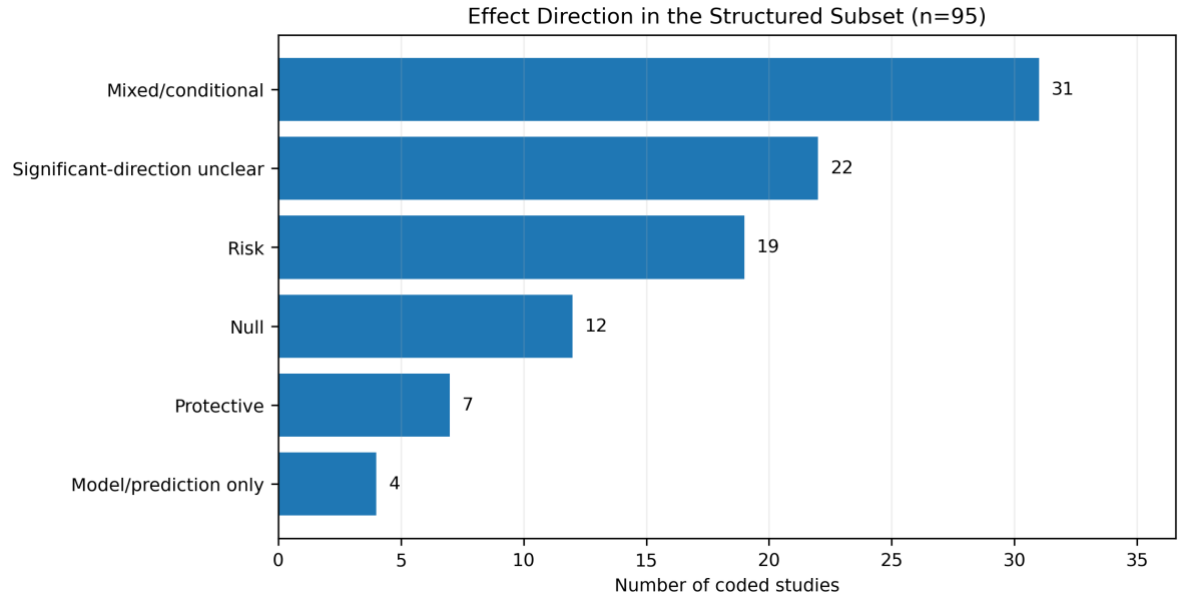

Figure 5. Effect direction among 95 direct-evidence studies with completed structured result coding. The complete systematic evidence map included 246 studies; the remaining 151 were retained in the map but were not assigned a direction because variant-level results were not uniformly extracted

DISCUSSION

The publication trajectory indicates sustained expansion rather than a short-lived peak, with particularly rapid methodological diversification after 2020. The shift from candidate-variant studies toward genome-scale discovery, gene-environment analysis, causal inference, and multivariable risk modeling demonstrates increasing methodological breadth. However, newer methodological sophistication did not automatically translate into direct, clinically interpretable SNP-MetS associations. Overall, the intellectual development of the field reflects a transition from candidate loci within lipid and adiposity pathways toward multi-level approaches that incorporate ancestry, exposures, and prediction. The citation profile also reinforces the centrality of lipid pathways and the importance of population-specific discovery, although citation indicators should be interpreted as measures of visibility rather than methodological quality because they favor older publications and were not normalized by year.

Alongside this methodological evolution, the evidence base remains constrained by study design and geographic concentration. The limited proportion of clearly prospective research is important because cross-sectional and case-control associations cannot establish whether genetic information improves prediction of incident MetS beyond conventional clinical factors. The large group of observational studies with incompletely specified designs further limits assessment of methodological maturity and comparability. The dominance of Asian studies is scientifically valuable because allele frequencies, linkage disequilibrium, diet, body-composition patterns, and MetS thresholds may differ from those in European-ancestry populations. Nevertheless, concentration within a limited set of East and West Asian settings means that "Asian evidence" should not be treated as homogeneous, while the sparse representation of Southeast Asia, Africa, Latin America, and Oceania remains a major barrier to globally equitable genetic risk prediction.

At the biological level, the recurrent genetic targets are coherent with the major pathophysiological pathways of MetS. APOA5, LPL, CETP, APOC3, APOE, and GCKR

participate in triglyceride-rich lipoprotein or cholesterol metabolism; FTO and MC4R relate to adiposity and energy balance; ADIPOQ and PPARG influence adipocyte function and insulin sensitivity; and TCF7L2 contributes to glucose regulation. The recurrent investigation of APOA5 is consistent with earlier association and genome-wide evidence emphasizing lipid loci in MetS [3,11]. FTO rs9939609 has also been studied across ethnically diverse populations, although its relationship with syndrome-level MetS can be attenuated or modified by adiposity and population context [10]. Despite this biological coherence, the gene-by-continent pattern indicates that recurrent targets have not been replicated uniformly across populations. Consequently, high article frequency should not be interpreted as universally replicated evidence, particularly when most studies of a gene are concentrated in a single region.

The predominance of mixed or conditional results further reflects variation in genetic models, alleles, populations, sex and age strata, diagnostic definitions, lifestyle exposures, and covariate adjustment. This heterogeneity explains why pooling studies by gene name alone would be misleading. A defensible meta-analysis should instead be conducted for a specific SNP, effect allele, genetic contrast, and sufficiently comparable MetS definition.

These scientific limitations have direct implications for precision prevention and health-system resilience. Health-system resilience refers to the capacity to maintain essential functions, adapt, and improve in the face of shocks and long-term pressure [13]. MetS contributes to the chronic burden of diabetes, cardiovascular disease, and kidney disease, which can reduce system capacity even in the absence of an acute emergency. Genetic evidence may therefore contribute through earlier identification of susceptible groups, targeted prevention, and more efficient surveillance. However, the present study did not directly measure resilience, and these implications depend on successful clinical translation [14-17].

Within this context, the evidence map suggests four prerequisites for responsible translation. First, risk markers and polygenic models must be validated locally and across ancestries, because a model developed in one East Asian, European, or Middle Eastern population cannot be assumed to perform equally in Indonesian or other underrepresented populations [18-19]. Second, genetic information should be integrated with modifiable exposures and routine clinical measurements rather than treated as deterministic; waist circumference, blood pressure, glucose, triglycerides, HDL cholesterol, diet, and physical activity remain actionable and inexpensive [20-21]. Third, prediction studies must demonstrate incremental discrimination, calibration, and clinical usefulness beyond these conventional variables. Fourth, implementation should avoid widening inequity through costly testing or risk models that underperform in populations absent from discovery datasets [22-23].

These priorities align with the broader goal of climate-resilient and adaptive health systems, which require equitable surveillance, prevention, and service planning under changing demographic and environmental pressures. In this context, the immediate contribution of MetS genetics is not routine genotype-guided care, but the development of locally validated evidence that can identify high-risk subgroups, clarify modifiable gene-environment pathways, and guide precision prevention without diverting resources from proven population-level interventions [21,24-25].

The study itself has several strengths. The layered corpus design allowed the 1,453-record search universe, 506-record focused set, 487-article verified bibliometric corpus, and 246-study direct evidence map to serve different analytical purposes rather than being combined indiscriminately. The PDF collection was audited using file

hashes and article-level metadata, preventing duplicate files or records from inflating publication counts. The analysis also separated direct association evidence from contextual methodological developments, allowing the evolution of the field to be described without presenting Mendelian-randomization, animal, or prediction studies as equivalent to primary adult SNP-MetS associations.

These strengths should be considered alongside several limitations. The bibliometric corpus was assembled from Scopus and PubMed and may not capture all regional databases or non-indexed literature, and 18 focused records were not represented in the verified full-text corpus. Citation data were unavailable for 62 articles and were not normalized for publication age. Country coding represented study setting rather than complete author-affiliation collaboration, so formal international co-authorship networks were not inferred. Rule-based approach and thematic coding may misclassify incompletely reported studies, while article-based gene and SNP counts may combine repeated cohorts. Most importantly, structured effect-direction coding was complete for only 95 of 246 direct-evidence articles. A formal study-level risk-of-bias appraisal and harmonized extraction of alleles, genetic models, effect estimates, MetS definitions, and covariates are therefore still required before SNP-specific meta-analysis.

CONCLUSIONS

The genetic literature on metabolic syndrome has grown substantially and evolved from candidate-gene studies toward genome-wide discovery, gene-environment analysis, causal inference, polygenic prediction, machine learning, and omics. Nevertheless, the direct evidence base remains dominated by candidate or single-variant studies, is concentrated in Asian populations, and is methodologically heterogeneous. APOA5, ADIPOQ, FTO, LPL, and CETP are the most recurrent genes, while FTO rs9939609 and APOA5 rs662799 are the most frequently investigated individual variants. Mixed and conditional findings are more common than simple, consistently replicated effects in the structured subset.

Future research should prioritize harmonized MetS definitions, complete and standardized genetic reporting, multi-ethnic and especially Southeast Asian replication, prospective designs, gene-environment integration, and evaluation of incremental clinical utility. Such evidence may eventually support equitable precision prevention and strengthen long-term health-system preparedness for cardiometabolic disease. At present, however, the literature supports locally validated research and targeted prevention rather than routine genotype-guided care.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FUNDING

This research was funded by Research Institutions and Community Service and the Faculty of Medicine and Health Sciences at the Universitas Jambi through Applied Research Funding Scheme 2026.

DECLARATION OF ARTIFICIAL INTELLIGENCE (AI) USE

AI-assisted techniques such us ChatGPT and Rayyan AI were applied for data cleaning, feature selection, and transformation to prepare the dataset for analysis. AI were also

used for language refinement (improving the grammar, sentence structure, and readability of the manuscript) and content summarization (assisting in summarizing the findings and conclusions concisely). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

REFERENCES

[1]. Alberti, K. G. M. M., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J.-C., James, W. P. T., Loria, C. M., & Smith, S. C., Jr. (2009). Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 120(16), 1640-1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.

[2]. Saklayen, M. G. (2018). The global epidemic of the metabolic syndrome. Current Hypertension Reports, 20, 12. https://doi.org/10.1007/s11906-018-0812-z.

[3]. Kristiansson, K., Perola, M., Tikkanen, E., Kettunen, J., Surakka, I., Havulinna, A. S., Stančáková, A., Barnes, C., Widen, E., Kajantie, E., Eriksson, J. G., Viikari, J., Kähönen, M., Lehtimäki, T., Raitakari, O. T., Hartikainen, A.-L., Ruokonen, A., Pouta, A., Jula, A., … Salomaa, V. (2012). Genome-wide screen for metabolic syndrome susceptibility loci reveals strong lipid gene contribution but no evidence for common genetic basis for clustering of metabolic syndrome traits. Circulation: Cardiovascular Genetics, 5(2), 242-249. https://doi.org/10.1161/CIRCGENETICS.111.961482.

[4]. Zabaneh, D., & Balding, D. J. (2010). A genome-wide association study of the metabolic syndrome in Indian Asian men. PLOS ONE, 5(8), e11961. https://doi.org/10.1371/journal.pone.0011961.

[5]. Garaulet, M., Lee, Y.-C., Shen, J., Parnell, L. D., Arnett, D. K., Tsai, M. Y., Lai, C.-Q., & Ordovas, J. M. (2009). CLOCK genetic variation and metabolic syndrome risk: Modulation by monounsaturated fatty acids. The American Journal of Clinical Nutrition, 90(6), 1466-1475. https://doi.org/10.3945/ajcn.2009.27536.

[6]. Lin, E., Kuo, P.-H., Liu, Y.-L., Yang, A. C., Kao, C.-F., & Tsai, S.-J. (2016). Association and interaction of APOA5, BUD13, CETP, LIPA and health-related behavior with metabolic syndrome in a Taiwanese population. Scientific Reports, 6, 36830. https://doi.org/10.1038/srep36830.

[7]. Aria, M., & Cuccurullo, C. (2017). bibliometrix: An R-tool for comprehensive science mapping analysis. Journal of Informetrics, 11(4), 959-975. https://doi.org/10.1016/j.joi.2017.08.007.

[8]. Miake-Lye, I. M., Hempel, S., Shanman, R., & Shekelle, P. G. (2016). What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Systematic Reviews, 5, 28. https://doi.org/10.1186/s13643-016-0204-x.

[9]. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71.

[10]. Al-Attar, S. A., Pollex, R. L., Ban, M. R., Young, T. K., Bjerregaard, P., Anand, S. S., Yusuf, S., Zinman, B., Harris, S. B., Hanley, A. J. G., Connelly, P. W., Huff, M. W., & Hegele, R. A. (2008). Association between the FTO rs9939609 polymorphism and the metabolic syndrome in a non-Caucasian multi-ethnic sample. Cardiovascular Diabetology, 7, 5. https://doi.org/10.1186/1475-2840-7-5.

[11]. Grallert, H., Sedlmeier, E.-M., Huth, C., Kolz, M., Heid, I. M., Meisinger, C., Herder, C., Strassburger, K., Gehringer, A., Haak, M., Giani, G., Kronenberg, F., Wichmann, H.-E., Adamski, J., Paulweber, B., Illig, T., & Rathmann, W. (2007). APOA5 variants and metabolic syndrome in Caucasians. Journal of Lipid Research, 48(12), 2614-2621. https://doi.org/10.1194/jlr.M700011-JLR200.

[12]. Oh, S.-W., Lee, J.-E., Shin, E., Kwon, H., Choe, E. K., Choi, S.-Y., Rhee, H., & Choi, S. H. (2020). Genome-wide association study of metabolic syndrome in Korean populations. PLOS ONE, 15(1), e0227357. https://doi.org/10.1371/journal.pone.0227357.

[13]. Kruk, M. E., Myers, M., Varpilah, S. T., & Dahn, B. T. (2015). What is a resilient health system? Lessons from Ebola. The Lancet, 385(9980), 1910-1912. https://doi.org/10.1016/S0140-6736(15)60755-3.

[14]. Zavaleta MM. Metabolic syndrome, genetic susceptibility, and risk of chronic obstructive pulmonary disease: The UK Biobank Study. Diabetes Obesity and Metabolism 2023;26:482–494. https://doi.org/10.1111/dom.15334..

[15]. Shenai A, Savitha G. METABOLIC SYNDROME - AN EMERGING RISK FACTOR FOR CHRONIC KIDNEY DISEASE. Asian Journal of Pharmaceutical and Clinical Research 2018;11:212. https://doi.org/10.22159/ajpcr.2018.v11i6.24658..

[16]. Puspasari A, Maharani C, Halim R, Aurora WID, Shafira NNA, Fitri AD, et al. Integrating genetic susceptibility into obesity risk prediction: Evidence from Jambi Malays with low-to- moderate physical activity. Proceedings Academic Universitas Jambi 2025;1:790–9.

[17]. Chen Z, Lv D, Huang X, Xu Q, Fan J, Zhou D, et al. Association of Smoking, Smoking Cessation, and Genetic Susceptibility With Chronic Kidney Disease Risk. Kidney Medicine 2026;8:101408. https://doi.org/10.1016/j.xkme.2026.101408.

[18]. Márquez-Luna C, Loh P, Price AL. Multiethnic polygenic risk scores improve risk prediction in diverse populations. Genetic Epidemiology 2017;41:811–823. https://doi.org/10.1002/gepi.22083.

[19]. Lennon NJ, Kottyan LC, Kachulis C, Abul-Husn NS, Arias J, Belbin GM, et al. Selection, optimization, and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse populations 2023. https://doi.org/10.1101/2023.05.25.23290535.

[20]. Son KY, Son H, Chae J, Hwang J, Jang S-S, Yun JM, et al. Genetic association of APOA5 and APOE with metabolic syndrome and their interaction with health-related behavior in Korean men. Lipids in Health and Disease 2015;14. https://doi.org/10.1186/s12944-015-0111-5.

[21]. Povel, C. M., Boer, J. M. A., Onland-Moret, N. C., Dollé, M. E. T., Feskens, E. J. M., & van der Schouw, Y. T. (2012). Single nucleotide polymorphisms involved in insulin resistance, weight regulation, lipid metabolism and inflammation in relation to metabolic syndrome: An epidemiological study. Cardiovascular Diabetology, 11, 133. https://doi.org/10.1186/1475-2840-11-133.

[22]. Selma-Soriano E, Valero-Hervás DM, Boix F, Planelles D, Vera B, Vayá MJ, et al. Value of Genetically Rare Cord Blood Units Beyond Conventional Quality Metrics. Hla 2026;108. https://doi.org/10.1111/tan.70817.
[23]. Wang Y, Zhang L, Niu M, Li R, Tu R, Liu X, et al. Genetic Risk Score Increased Discriminant Efficiency of Predictive Models for Type 2 Diabetes Mellitus Using Machine Learning: Cohort Study. Frontiers in Public Health 2021;9. https://doi.org/10.3389/fpubh.2021.606711.
[24]. Williams JR, Lorenzo D, Salerno JP, Yeh VM, Mitrani VB, Kripalani S. Current Applications of Precision Medicine: A Bibliometric Analysis. Personalized Medicine 2019;16:351–359. https://doi.org/10.2217/pme-2018-0089.
[25]. World Health Organization. (2023). Operational framework for building climate resilient and low carbon health systems. World Health Organization.