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Central and Peripheral Molecular Biomarkers in Self-harm and Suicidality: A Systematic Review

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Zhang, S; Ji, WD; Liu, BW; Shi, JM; Yi, C; Luo, PW; Chen, RS.

Corresponding author:
Runsen Chen

runsenchen@tsinghua.edu.cn

Author Affiliation:
Vanke School of Public Health, Tsinghua University.

ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670044

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 July 2026 and was last updated on 15 July 2026.

INTRODUCTION

Review question / Objective (1)To summarize the epigenomic and transcriptomic profiles of self-harm and suicidality across central and peripheral biospecimens.
(2)To synthesize evidence on converging biological alterations between central and peripheral systems associated with self-harm and suicidality.
(3)To investigate the shared and distinct molecular signatures of self-harm and suicidality across different psychiatric disorders and behavioral phenotypes (e.g., non-suicidal self-injury (NSSI), self-harm, suicidal ideation, suicide plan, suicide attempt, and suicide death).
(4)To cross-reference identified differentially expressed genes (DEGs) and differentially methylated genes (DMGs) with genome-wide association study (GWAS) data to highlight genetically supported molecular targets.

Rationale To date, biomarker-driven diagnostic tools and treatments for self-harm and suicide remain lacking. Although studies utilizing postmortem brain tissue have identified extensive epigenomic and transcriptomic alterations, no research has yet integrated these findings to evaluate their convergence with peripheral signatures. Given the inaccessibility of living brain tissue, more easily obtainable peripheral biomarkers hold significant potential for predicting and diagnosing suicidal ideation and behaviors. Furthermore, the shared and distinct suicide-associated biological processes across psychiatric diagnoses and diverse suicide phenotypes remain largely uncharacterized. Elucidating this heterogeneity is essential for developing precise predictive models and targeted interventions. Overall, by systematically reviewing and integrating epigenetic and gene expression evidence from central and peripheral biospecimens, this review aims to identify convergent molecular signatures and potential peripheral biomarkers t.

Condition being studied To systematically map biological alterations across the spectrum of self-harm and suicidality, this review focuses on all

related behavioral phenotypes, such as NSSI, self-harm, suicidal ideation, suicide plan, suicide attempt, and suicide death.

METHODS

Search strategy A systematic literature search will be conducted in four major electronic databases: PubMed, Embase, Web of Science, and PsycINFO. To ensure comprehensive coverage, supplementary searches will be performed using Google Scholar, alongside manual backward citation tracking of the reference lists of included studies and relevant reviews. The search strategy will integrate two core conceptual domains: biological processes and self-harm/suicide, linked via the Boolean operator 'AND'. Controlled vocabulary terms (e.g., Medical Subject Headings [MeSH] in PubMed, APA Thesaurus terms in PsycINFO) will be applied where appropriate.

(1)Terms related to biological processes: (epigen* OR methylat* OR methylome OR methylation OR "DNA methylation" OR histon* OR "histone modification" OR "histone methylation" OR "gene modification" OR acetylat* OR acetylation) OR ("gene expression" OR "expressed genes" OR "expression profiling" OR transcript* OR RNA OR RNA-seq OR RNAseq OR "RNA sequencing" OR mRNA OR "messenger RNA" OR "no.

Participant or population This review focuses on individuals with self-harm or suicidal phenotypes from both clinical and general populations. We imposed no demographic or clinical restrictions (e.g., age, sex, or psychiatric diagnosis). These variables will be systematically coded during data extraction to inform subgroup analyses and stratified reporting, where appropriate.

Intervention Not applicable. We will not evaluate the therapeutic or preventive efficacy of intervention strategies. Instead, we aim to integrate the epigenetic and transcriptomic mechanisms underlying suicide to identify biomarkers with diagnostic or therapeutic potential.

Comparator Given that the suicide phenotypes investigated across studies may differ, the choice of comparator may vary accordingly. Generally, the control or comparison group comprises individuals without self-harm or suicidal phenotypes.

Study designs to be included Eligible studies must be original research articles. Non-primary literature (e.g., reviews, editorials, case reports, and commentaries) and qualitative studies will be excluded. To ensure comprehensive coverage of the existing literature, we will not restrict study design, allowing for the inclusion of case-control, cohort, cross-sectional, and other relevant study types.

Eligibility criteria Inclusion criteria: Studies were deemed eligible for inclusion if they met all of the following criteria:
(1)Published in a peer-reviewed journal prior to July 20, 2026.
(2)Written in English.
(3)Original empirical research.
(4)Investigated epigenetic or transcriptomic mechanisms underlying self-harm and suicidal phenotypes.
(5)Provided an accessible list of reported DEGs or DMGs.

Exclusion criteria
Studies were excluded from the review if they met any of the following criteria:
(1)Lacked epigenetic or transcriptomic data related to self-harm and suicidality.
(2)Employed a purely qualitative research design.
(3)Non-primary literature (e.g., reviews, editorials, commentaries).
(4)Full text unavailable.
Involved animal subjects (e.g., mice) rather than human participants.

Information sources A systematic search will be performed across PubMed, Embase, Web of Science (Core Collection), and PsycINFO. To guarantee a comprehensive review, the primary search will be supplemented by Google Scholar and a manual screening of reference lists from all included studies and relevant reviews. Studies with unavailable full texts will be excluded.

Main outcome(s) The primary outcomes of this review are epigenetic and transcriptomic alterations associated with self-harm and suicide phenotypes. Specifically, we aim to identify biological dysregulation at the regional and cell-type-specific levels within the central and peripheral biospecimens, comparing individuals with self-harm and suicidal phenotypes to their controls. A critical objective is to determine whether these multi-omic alterations converge across central and peripheral systems. To achieve this, DEGs and DMGs will serve as our primary markers of interest.

Additional outcome(s) None.

Data management We will use Covidence (Veritas Health Innovation) as our primary tool to manage study records. This platform supports efficient

deduplication, organization, screening, and data extraction throughout the review process.

Quality assessment / Risk of bias analysis To evaluate the methodological quality of the included studies, we will primarily utilize the Newcastle-Ottawa Scale (NOS), which is specifically designed for assessing case-control and cohort studies. Furthermore, we will complement the NOS with the Q-Genie tool to capture quality metrics specific to genomic research. Given our focus on transcriptomic and epigenetic markers, we will apply a modified version of the Q-Genie scale. This adapted tool excludes genotyping-specific domains, replacing them with analogous criteria tailored for sample processing, platform quality control, normalization procedures, and appropriate correction for multiple testing.

Strategy of data synthesis This review will employ a multi-omics data integration and reanalysis strategy. First, transcriptomic (DEGs) and methylomic (DMGs) data from both central and peripheral biospecimens will be systematically extracted and evaluated. Subsequently, comprehensive gene annotation will be performed by querying public database APIs (e.g., Ensembl), followed by Gene Ontology (GO) enrichment analysis using clusterProfiler to identify dysregulated biological pathways at both the transcriptional and epigenetic levels. At the molecular network level, protein-protein interaction (PPI) networks will be constructed using the STRING database to screen for hub genes mediating key pathological mechanisms based on node centrality. Finally, a comparative analysis of central and peripheral data will be conducted to identify shared dysregulated signatures, which will then be integrated with genome-wide association study (GWAS) databases (such as the NHGRI-EBI GWAS Catalog).

Subgroup analysis Given the heterogeneity of suicidality, analyses will be stratified by:
(1) Self-harm and suicidality phenotype: such as NSSI, self-harm, suicidal ideation, suicide plan, suicide attempt and suicide death.
(2) Psychiatric diagnosis: major depressive disorder, schizophrenia spectrum disorders, bipolar disorder, other psychiatric or non-psychiatric populations
(3) Tissue type: such as postmortem brain regions, cerebrospinal fluid, peripheral blood and saliva; single-cell / bulk.
(4) Demographic characteristics: such as age groups and sex.

Where data permit, we will further explore severity-dependent molecular trajectories across the self-harm and suicidality continuum.

Sensitivity analysis Sensitivity analyses will be conducted by:
(1) Excluding studies rated as low methodological quality (e.g., NOS score < 5).
(2) Restricting analyses to studies using RNA-seq technology (excluding microarray).
(3) Restricting analyses to studies that controlled for key confounders (e.g., postmortem interval, medication status, pH).

Language restriction English only.

Country(ies) involved China.

Other relevant information None

Keywords Self-harm; NSSI; Suicide; Suicidal ideation; Suicide plan; Suicide attempt; Suicide death; Epigenetics; Transcriptomics; Biomarkers; Central and peripheral; Multi-omics; Systematic review.

Dissemination plans The results of this study will be published in a peer-reviewed academic journal.

Contributions of each author
Author 1 - Shan Zhang - Conceptualisation; Data Collection; Data Synthesis; Visualisation; Drafting Original Manuscript; Editing Manuscript.
Email: shan_zhangmt@163.com
Author 2 - Weidong ji - Conceptualisation; Data Collection; Data Synthesis; Drafting Original Manuscript; Editing Manuscript.
Email: jiwd@tsinghua.edu.cn
Author 3 - Bowen Liu - Data Collection; Data Synthesis; Drafting Original Manuscript; Editing Manuscript.
Email: liu-bw25@mails.tsinghua.edu.cn
Author 4 - Jiamei Shi - Data Collection; Visualisation; Editing Manuscript.
Email: sjm25@mails.tsinghua.edu.cn
Author 5 - Cheng Yi - Data Collection; Visualisation; Editing Manuscript.
Email: yic24@mails.tsinghua.edu.cn
Author 6 - Peiwen Luo - Data Collection; Visualisation; Editing Manuscript.
Email: luopeiwen287@163.com
Author 7 - Runsen Chen - Conceptualisation; Editing Manuscript; Supervision.
Email: runsenchen@tsinghua.edu.cn