

REVIEWER'S REPORT

Manuscript No.: JNHM-156

Title: The Inherited Scars: How Ancestral Trauma Echoes in the Mental Health of Descendants: A Narrative Review,

Recommendation:

Accept after minor revision.....

Rating	Excel.	Good	Fair	Poor
Originality		✓		
Techn. Quality		✓		
Clarity	✓			
Significance	✓			

Reviewer's ID: JPR- Bilqees Hamza

Detailed Reviewer's Report

This manuscript provides a comprehensive, rigorous narrative review synthesizing the complex biological, gestational, and psychosocial pathways through which ancestral adversity, depression, and anxiety shape descendant mental health. By integrating molecular epigenetics, developmental attachment models, the allostatic-load framework, and evidence-based interventions, the paper moves the field past simplistic biological determinism toward a actionable, modifiable risk model. The review is methodologically sound, follows SANRA guidelines, and features well-structured visual and tabular summaries. The manuscript is recommended for publication subject to minor revisions to refine specific theoretical nuances and address small textual edits.

The authors effectively bridge distinct disciplines, linking germline epigenetic marks (e.g., *NR3C1* and *FKBP5* methylation) and fetal HPA-axis programming with psychosocial mechanisms such as attachment quality and modeled affect dysregulation. Framing these converging lines of evidence through McEwen's allostatic load model and the American Academy of Pediatrics' toxic stress framework is a major strength. It correctly highlights that the availability of a

REVIEWER'S REPORT

buffering caregiver relationship is the pivotal moderator governing whether adversity leads to toxic biological embedding. Furthermore, detailing evidence-based, dyadic, and task-shared interventions—such as the Nurse-Family Partnership, Child-Parent Psychotherapy, Attachment and Biobehavioral Catch-up, and the Thinking Healthy Programme—gives the paper substantial practical value for preventive psychiatry and public health.

Several minor points should be addressed before publication:

First, while the distinction between intergenerational (F1) and transgenerational (F3) transmission is clearly noted, the section on third-generation Holocaust descendants could more clearly delineate the limits of current empirical evidence. While the Överkalix and Dutch Hunger Winter nutritional cohorts provide firm proof of multi-generational physiological inheritance in humans, psychiatric outcomes in F3 human descendants remain far more heterogeneous and prone to confounding by post-natal family culture and shared environment. Emphasizing this nuance in Section 4 will prevent reader misinterpretation.

Second, the discussion of preclinical reversibility in Section 2 and Section 6 should explicitly caution against over-extending rodent dietary or pharmacological models to human therapeutics. Although rodent studies demonstrate that methyl-donor supplementation can reverse *NR3C1* promoter hypermethylation and normalize stress reactivity, translating these systemic epigenetic modifications into targeted human psychiatric interventions is currently unestablished.

Third, the authors should review the text for minor typographical and reference formatting consistency. For instance, ensure that all inline citations follow a uniform ordering style when multiple references are grouped together. Additionally, verify that abbreviating conventions for gene targets (such as *NR3C1* and *FKBP5*) remain consistently italicized across both the main narrative and Table 1.

In summary, this review represents a significant contribution to the literature on intergenerational mental health, offering a balanced synthesis of vulnerability,

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REVIEWER'S REPORT

resilience, and actionable preventive strategy. Addressing these minor points will further strengthen the precision and clinical clarity of the paper.