

Peer Review

Review of: "Theory of the Leaky Intestine: Sex Differences in Intestinal Parasitic Infections, Cytoskeletal Wall Dysfunctions, and Hypertension"

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Njemanze et al. present an ambitious and highly integrative study proposing a unifying “**Theory of the Leaky Intestine**” linking intestinal parasitic infections (IPIs), cytoskeletal wall dysfunction, altered permeability, and systemic outcomes such as hypertension and metabolic dysregulation, with an emphasis on sex differences. The work combines parasitological diagnostics, high-frequency ultrasound duodenography/colonography, biochemical measurements, and regression modeling to explore structural–functional correlations in a clinical cohort.

Major Concerns

Causal Inference vs. Association

The central thesis—that IPIs cause cytoskeletal dysfunction leading to a “leaky gut,” autonomic imbalance, and hypertension—extends well beyond the cross-sectional data presented. The study demonstrates associations (wall thickness ↔ sodium, DBP), but mechanistic steps (e.g., sodium channel inactivation, SGLT1/GLUT2 dysregulation, sympathetic activation) remain hypothetical and unmeasured.

Definition and Measurement of “Leaky Gut”

Increased wall thickness is interpreted as evidence of increased permeability; however, permeability was not directly measured (e.g., lactulose–mannitol test, zonulin levels, tight junction protein assays). Thickening may reflect inflammation, edema, or fibrosis rather than increased permeability per se. The term “leaky gut syndrome,” while discussed critically in literature, should be framed cautiously and anchored to established permeability markers.

Confounding Variables

Patients with IPIs had significantly higher BMI. Obesity itself is independently associated with intestinal barrier dysfunction, sodium handling changes, hypertension, and microbiome alterations. Multivariate regression controlling for BMI, age, and diabetes status would strengthen conclusions.

Regression Effect Size

Although statistically significant, the predictive power of DSCTHICK for DBP and sodium is relatively small ($R^2 < 0.1$). This suggests modest explanatory capacity and limits clinical generalizability.

Declarations

Potential competing interests: No potential competing interests to declare.