

Peer Review

Review of: "Does Sugar Control Arrest Complications in Type 2 Diabetes? Examining the Rigour in Statistical Methods and Causal Inference in Clinical Trials."

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Major Scientific Concerns

1. Overgeneralization of Conclusions

The manuscript concludes:

"There is no support for the belief that glucose normalisation reduces complications or mortality."

This statement is **too definitive** considering:

Established microvascular benefit evidence in multiple trials.

Long-term legacy effects reported in follow-up studies.

Current guideline consensus integrating multi-factorial risk reduction rather than exclusive glucocentric therapy.

Suggested Correction:

Change:

"There is no support..."

To:

"The available evidence suggests that the clinical benefits of intensive glucose normalization in T2DM are modest, heterogeneous, and potentially context-dependent."

2. Selective Interpretation of Evidence

The manuscript emphasizes statistical limitations but does not equally discuss:

Robust mechanistic evidence linking chronic hyperglycemia with:

Advanced glycation end-products

Oxidative stress pathways

Microvascular damage mechanisms

Ignoring biological plausibility weakens causal debate.

3. Simulation Model Limitations

While informative, the simulation model:

Relies on theoretical assumptions

Lacks empirical validation

Does not incorporate patient-level covariates

Cannot replace pooled individual patient data meta-analysis

The manuscript occasionally treats simulation outputs as confirmatory rather than exploratory.

4. Incomplete Consideration of Multifactorial Treatment Context

Modern T2DM management targets:

Cardiovascular risk factors

Renal protection

Metabolic syndrome components

The manuscript critiques glucose lowering in isolation, which may misrepresent real-world treatment frameworks.

Declarations

Potential competing interests: No potential competing interests to declare.