

Review of: "A Novel Approach: The Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE) as an Alternative to HOMA-IR for Predicting Insulin Resistance"

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Potential competing interests: No potential competing interests to declare.

In their manuscript titled "A Novel Approach: The Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE) as an Alternative to HOMA-IR for Predicting Insulin Resistance," Maher M. Akl and Amr Ahmed propose a new equation for assessing insulin sensitivity. Their equation is based on body mass index (BMI), C-reactive protein (CRP) concentration, and the concentration of interleukin-6 (IL-6).

This project addresses a question of high and growing importance. However, fundamental shortcomings in both the analysis and reporting preclude acceptance in its current form.

First of all, the equation seems to be quite arbitrary. What is the justification for multiplying the biomarkers by the constant factors a, b, and c (thereby implying a linear relationship)? And what is the justification for adding the three terms? Are there any physiological reasons for this form of equation? A non-linear (e.g., non-competitive or Michaelis-Menten-based) relationship seems to be more realistic.

Second, the authors provide no information about the validity of their equation. Does it indicate insulin resistance at all? Based on populations with sufficient sample size, the results should be correlated with established markers of insulin resistance (or insulin sensitivity, which would be suitable as well), e.g., HOMA-IR and QUICKI or, preferably, better parameters like the Matsuda index and SPINA-GR. Additionally, they should be correlated to integrated biomarkers, e.g., the M value from glucose clamp investigations and/or SPINA-DI.

Third, no information on the re-test reliability of their index is reported. The index should be repeatedly calculated in individuals based on parameters obtained with a sufficient time interval, e.g., one month. The repeatability should be reported as a correlation coefficient or with the ergodicity coefficient e .

Fourth, the reader learns nothing about the diagnostic utility. The authors should select subjects with and without a meaningful diagnosis (e.g., with and without diabetes mellitus, prediabetes, or metabolic syndrome) and report the sensitivity, specificity, and likelihood ratios for positive and negative test results.

Both reliability and diagnostic utility should be compared to established biomarkers, including HOMA-IR, QUICKI, and SPINA-GR.

The usefulness of the new equation can only be assumed if it is based on physiological assumptions and if validity, reliability, and diagnostic utility can be verified.

In the Methodology section, the authors write that “the inclusion of BMI, CRP, and IL-6 as predictive variables was based on extensive literature review”, but they don’t describe the methods of review. The authors should completely describe the used search terms and provide a flow diagram as demanded by the PRISMA statement.

Likewise, they write that “data on BMI, CRP, IL-6, and insulin resistance sensitivity were collected from a diverse cohort of participants spanning various demographic and clinical characteristics”, but they don’t provide any information on the sources of the data. The cohort(s) should be thoroughly described. Which institutional review board approved the study protocol? Was the study performed according to the Declaration of Helsinki?

Likewise, the “rigorous validation procedures” should be completely described so that the study can be reproduced. The results of the validation process should be reported.

After all, it remains completely obscure why the Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE) represents a “significant advancement” in metabolic research.