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The triglyceride-glucose index and cardiovascular disease outcomes in the Prospective Urban Rural Epidemiology (PURE) study in 22 low-, middle-, and high-income countries

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In the *The Lancet Healthy Longevity*, Patricio Lopez-Jaramillo and colleagues present results from the groundbreaking Prospective Urban Rural Epidemiology (PURE) cohort on the association between insulin resistance and cardiovascular (CVD) outcomes. The PURE study is well-known from prior publications. This study uses PURE to introduce a novel cardiometabolic risk factor, the triglyceride-glucose (TyG) index.

The TyG index is a surrogate marker for insulin resistance, often considered the key pathophysiologic abnormality in diabetes and pre-diabetes. It is calculated as the natural log of fasting triglycerides multiplied by fasting plasma glucose and therefore is practical to measure in primary care settings with laboratory capacity. This PURE analysis included 141,243 individuals aged 35–70 years who were followed up for a median of 12.9 years in 22 low-, middle-, and high-income countries. The composite primary outcome was major CVD events (nonfatal myocardial infarction or stroke) or CVD death. In adjusted models, individuals in the highest compared to lowest TyG tertile had an approximately 20% greater incidence of the composite outcome. Moreover, there was heterogeneity in the size of this association by country income group; a larger association was seen in low-

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and middle-income countries (LMICs), while in high-income countries no association was observed. These findings are promising, but before regular use becomes the norm, more knowledge is required for TyG's role in conducting causal inference, describing inequity, predicting clinical risk, and implementing the marker in clinical practice.

From a causal perspective, one challenge is disentangling the biological role of insulin resistance versus the known risk factors of elevated glucose and elevated triglycerides on CVD risk.[1,2] In other words, how much of the explanatory power of the TyG-index is *not* mediated via a pathway of insulin resistance? In a sensitivity analysis, the authors reported that the TyG-index had a greater hazard ratio for incident CVD than tertiles of glucose or triglycerides in separate models. The authors hypothesize that the higher hazard ratios for the TyG index on CVD observed in LMICs compared to high-income countries might be driven by differences in early life nutritional and environmental exposures, a manifestation of the "double burden of malnutrition."[3] Indeed, evidence from longstanding nutrition trials has emerged supporting the adult metabolic consequences of early-life malnutrition.[4] As the authors note, the higher vulnerability of LMIC populations to the presence of insulin resistance in this study might also plausibly be explained by differential health care access. Further research is needed to elucidate potential causal pathways between insulin resistance, early-life nutrition, receipt of health care services, and CVD.

From a descriptive perspective, PURE again illuminates considerable inequities in outcomes of cardiometabolic diseases. Prior PURE reports have shown a higher risk of mortality and CVD events among individuals with diabetes who live in countries at lower levels of economic development.[5] PURE also has provided pivotal evidence of the massive inequities in access to affordable treatment for diabetes and CVD in LMICs compared to high-income countries.[6] As noted above, an important equity-related finding in the present study is the sizeable association between TyG index and CVD outcomes in LMICs, while there was no association in high-income countries. This gap is most likely due to more patients in high-income countries receiving risk-reducing medicines such as blood pressure drugs and statins.

From a prognosis perspective, while this study was not designed as a risk prediction analysis, it is interesting to consider the implications of leveraging the TyG index to enhance CVD risk prediction. A future study using PURE data might quantify the additional discriminative power gained by including TyG versus other commonly recommended models such as the 2019 revised World Health Organization CVD risk prediction tool[7] or the INTERHEART Modifiable Risk Score.[8] Prior studies have tended to show modest improvements in model performance when laboratory-based measurements are added to non-laboratory models relying on inputs such as age, sex, smoking status, blood pressure, and body mass index.[7,9]

Finally, from an implementation perspective, the authors conclude that the TyG index is suitable for use in routine clinical practice. We see two important challenges: (1) to demonstrate that the diagnosis of insulin resistance via the TyG index would meaningfully change clinical decision-making and (2) to build on ongoing efforts to improve access to laboratory measurements in primary care settings in many LMICs.[10] Research exploring

novel risk-prediction variables in diverse global populations is important. At the same time, the PURE collaborators likely would agree that the top priority is to improve the scandalously low implementation of evidence-based CVD care in LMICs and among marginalized populations in high-income countries.

In summary, this study illustrates the association of a simple surrogate measure of insulin resistance, the TyG index, with CVD outcomes, and how this association differs by countries' level of economic development. It marks a valuable step in a long path to clinical utility. Future causal, descriptive, prognostic, and implementation research will help to better understand how insulin resistance influences cardiometabolic outcomes worldwide.

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