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Invited Commentary

Random Plasma Glucose Levels and Cardiovascular Risk

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The first global report on diabetes published by the World Health Organization in April 2016[1] spotlighted the increasing public health problem of diabetes. The global diabetic population quadrupled from 108 million in 1980 to 422 million in 2014. China has the largest population of people living with diabetes, estimated at nearly 100 million as of 2013 and projected to grow to more than 142 million by 2035.[2] Cardiovascular disease is a well-known serious complication of diabetes.[3] Data from 4 European cohorts showed that isolated increases in the fasting or 2-hour postload plasma glucose level, even at levels below traditional cutoffs for diabetes, had a significant effect on cardiovascular risk.[4,5] However, important gaps in knowledge remain regarding the association of random plasma glucose (RPG) levels with cardiovascular risk and the validity of these observations in non-European cohorts.

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The study in this issue of *JAMA Cardiology* by Bragg and colleagues[6] addressed this gap using a large sample of nearly half a million Chinese adults aged 30 to 79 years from the China Kadoorie Biobank with a mean follow-up of 7 years. All participants with a history of self-reported diabetes, ischemic heart disease, stroke, or transient ischemic attack were excluded. They found a modest (approximately 10% for 1 mmol/L [18 mg/dL]) but statistically significant positive association between RPG levels and the risk for major occlusive vascular disease and ischemic stroke in the normal range of glucose levels as low as 4.3 mmol/L (77 mg/dL). For cardiovascular death, major coronary events, and intracerebral hemorrhage, increased risk was observed at levels as low as 5.8 mmol/L (104 mg/dL) compared with the reference group (<4.3 mmol/L [77 mg/dL]).

The study by Bragg and colleagues[6] has several major strengths. The sample size was large enough to enable finer categorizations of blood glucose levels, stratified analyses, and detection of modestly increased risks. The study population was diverse in terms of age groups (30-79 years), residence (5 urban and 5 rural areas), and geographic locations (from 10 provinces spanning from Northeastern, Eastern, and Southwestern to Southern China). For ascertainment of end points, the study team leveraged the existing Disease Surveillance Points system, residential, health, and insurance records, and established registries with supplementation by verbal autopsy for deaths without recent medical attention and by actively collecting information through local sources. Validation by computed tomographic scan or magnetic resonance imaging for more than 90% of stroke events was a particular strength. Besides one-time measurement of baseline glucose levels, the authors attempted to correct for regression dilution bias by estimating usual glucose levels through application of a calculated regression dilution ratio to avoid underestimations of risk associations, although the underlying data for the estimations were derived from a repeated survey of only 5% of the sample conducted a mean of 2.6 years after the baseline survey, thus confounded by the effect of aging. The authors also conducted a series of sensitivity analyses that enhanced the credibility of the results.

Several noteworthy issues warrant consideration. First, the main measure used in this study was RPG level instead of fasting or postload glucose level, making it one of the few and the largest studies on random glucose levels to date. Use of this measure represents a weakness and strength. Random glucose levels, compared with the other 2 measures, have larger intraindividual and interindividual variations owing to well-recognized influences from sampling time (the length of time since the last meal). On the other hand, random sampling is easier to collect in large population-based studies, which is the case for the China Kadoorie Biobank. Similarly, the use of SureStep Plus—a commercially available, handheld glucose meter—although less accurate than validated laboratory results, has the advantages of lower costs, higher feasibility, and closer proximity to the choice of real-world patient self-monitoring devices. More important, the speculation that "nonfasting glucose levels may be more relevant to cardiovascular risks, because people spend more time in a nonfasting state"[5] is plausible and worth further investigation. The authors reported fasting (sampling) time–adjusted plasma glucose levels in eFigure 5 in the Supplement; however, detailed subgroup analyses by strata of sampling time instead of adjustment only are

warranted to examine its influence on the association of interest. Future research could also benefit from repeated measures of RPG levels, comparisons between random glucose levels and ambulatory (continuous) glucose profiling,[7] and direct comparisons with traditional fasting and postload glucose and hemoglobin A_{1c} levels.

Second, the relationship between random glucose levels and cardiovascular outcomes appeared to be significant, continuous, and linear. However, risks remained modest (5%-30%) until glucose levels reached 11.1 mmol/L (200 mg/dL), which is high enough to diagnose diabetes if 2-hour postload glucose levels were used. Furthermore, the incremental improvements in predictive power from adding glucose to multivariable models were minimal, suggesting that no value would be added for including this variable in risk prediction models. It remains unclear how these findings may affect ethnicity-specific thresholds for the detection of prediabetes or diabetes.

Third, the China Kadoorie Biobank cohort had a fairly low response rate of about 30%, but loss to follow-up rate was also extremely low (0.5%). The lower rate of loss to follow-up is particularly important for longitudinal studies on risk associations (whereas response rate particularly affects cross-sectional prevalence studies). Nevertheless, medical insurance coverage was not nearly universal during the early phases of follow-up (2004-2009) and may result in underreporting of events. In addition, registry- and claims-based data on causes of death or medical diagnosis may not be as reliable as other methods. Hence, sensitivity analyses with all-cause mortality or hospitalizations for any reasons as the outcomes may be worth conducting. The large sample size also permits—not available in the study—finer classifications of outcomes into nonoverlapping categories such as nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, coronary or cerebrovascular deaths, and noncardiovascular deaths.

Fourth, although smoking, alcohol intake, physical activity, and systolic blood pressure were adjusted for in the models, other important risk factors such as dyslipidemia, unhealthy diet (with a high glycemic load, in particular), overweight and obesity, renal function (albuminuria), and any concurrent cardiovascular treatment were not available. Adjustment for these variables led to the loss of significance in cardiovascular risks associated with plasma glucose levels in some previous studies.[8] These risk factors often coexist with higher levels of glucose and may mediate the relationship between glucose and cardiovascular disease, thus providing clues to potential mechanisms of the observed findings.

What are the implications of the study for the prevention and management of diabetes and cardiovascular disease—2 major noncommunicable diseases? From a public health perspective, even modest increases in risks translate into large health, social, and economic burdens. Therefore, results from this study, if confirmed by future research, suggest the potential in measuring RPG levels—more practical to achieve than fasting or postload glucose levels—for screening, early detection, and prevention of diabetes and cardiovascular disease. However, much more work is needed to establish the clinical utility of these data. Using RPG levels for screening or early detection is only beneficial if therapy reduces the onset of diabetes or improves outcomes in patients. These issues have not been addressed in any study to date. This study enriches our understanding of risks associated with RPG levels. It provides a timely reminder of the importance of cardiovascular risk in diabetes and demonstrates that blood glucose levels are a continuous cardiovascular risk factor extending well into the normal range, where cutoffs are necessarily arbitrary.

ARTICLE INFORMATION

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