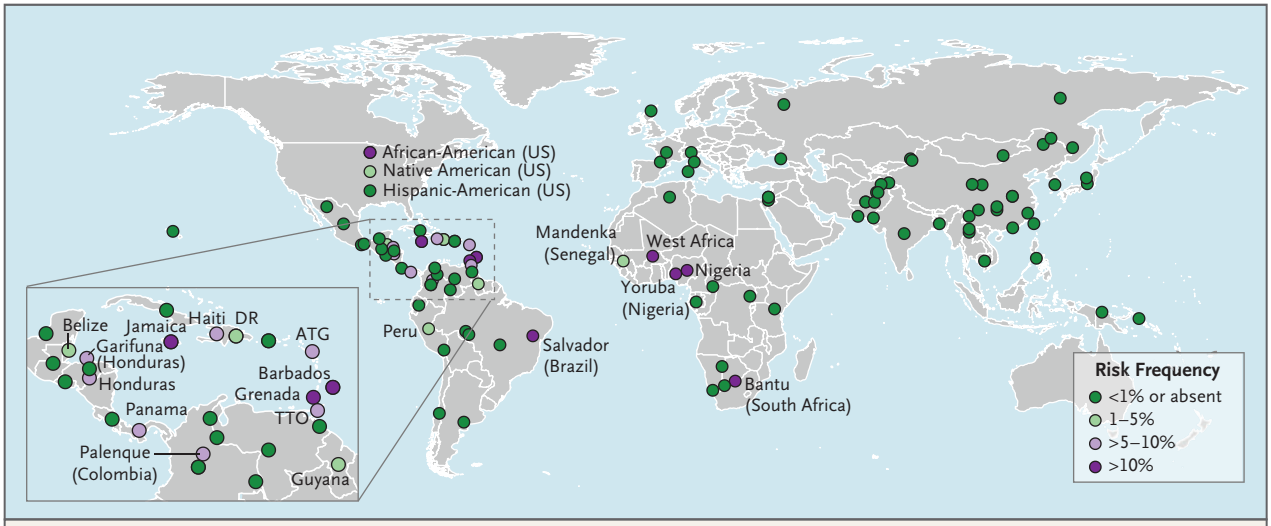

Figure 1. *APOL1* G1 and G2 Risk Alleles in 111 Global Reference Populations.

We inferred risk-allele status using the two G1 alleles (rs60910145 and rs73885319) and the proxy single-nucleotide polymorphism commonly typed for G2 (rs12106505) on *APOL1*. Only populations with a risk allele status of 1% or higher are labeled (with the exception of Hispanic Americans). Where possible, precise geographic region or ethnic group labels are used on the map; otherwise, populations are labeled according to country or general geographic region. A more detailed map is available at http://APOL1.org. ATG denotes Antigua, DR Dominican Republic, and TTO Trinidad and Tobago.

fied as being of African descent. Such persons may also be at significant risk for kidney disease, early-onset hypertension, and cardiovascular disease, which is important in the consideration of genetic testing, population management, clinical trials, and health policy decisions.

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Smoking and Other Risk Factors in Type 2 Diabetes

TO THE EDITOR: Hu et al. (Aug. 16 issue)[1] conclude in their study that the survival benefit after smoking cessation was not affected by weight gain. In contrast, as presented the data support a different interpretation — patients with moderate weight gain (5.1 to 10.0 kg) had lower cardiovascular mortality and all-cause mortality, as compared with current smokers, than did those without weight gain (hazard ratio for death from cardiovascular causes, 0.25 [95% confidence in-

terval {CI}, 0.15 to 0.42] vs. 0.69 [95% CI, 0.54 to 0.88]; hazard ratio for death from any cause, 0.46 [95% CI, 0.38 to 0.55] vs. 0.81 [95% CI, 0.73 to 0.90]). These results could indicate that moderate weight gain after smoking cessation is indeed favorable and heralds better prognosis than does no weight gain.

Moreover, patients were excluded from the mortality analysis if they had cancer or cardiovascular disease. Doing so diminishes the applicability of the findings in real-world settings, in which coexisting conditions are quite common. Sick patients rarely gain weight, and including these patients in the analysis would have further magnified the difference in outcome among the weight groups and made the favorable outcomes associated with weight gain even more prominent. We therefore suggest that the authors provide additional mortality analyses that include patients with cardiovascular disease and those with cancer.

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1. Hu Y, Zong G, Liu G, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. N Engl J Med 2018;379:623-32.

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TO THE EDITOR: Hu and colleagues discuss whether weight gain after smoking cessation attenuates the health benefits of quitting. One of the primary outcomes indicated that the temporary increase in the risk of type 2 diabetes was directly proportional to weight gain, and the risk was not increased among quitters who did not gain weight (P<0.001 for interaction). Since a prospective trial showed that a higher body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) was associated with the onset of diabetes,[1] we wonder whether the BMI differed substantially before the trial between quitters with weight gain and those without weight gain.

The research of Hu and colleagues is of substantial importance. In future studies, statistical analysis of the BMI of participants before they engage in smoking cessation could be considered, because there may be important intervention factors that might have bearing on outcomes.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Rawshani et al. (Aug. 16 issue)[1] note that lipid-lowering medication use, smoking, physical activity, and other factors are important in predicting death from any cause. It is tempting to attribute the unexpected relationship between the use of lipid-lowering medication and death to confounding by indication. However, Figure 2 of their article shows that lipid-lowering medication was not important in predicting acute myocardial infarction or heart failure and was marginally important in predicting stroke, which indicates that confounding by indication was probably not involved in this association, since confounding by indication would probably be obvious in these outcomes.

It is also tempting to dismiss this finding because randomized, controlled trials[2] have shown that statins lower the risk of cardiovascular outcomes and mortality. However, randomized, controlled trials commonly select patients with high cardiovascular risks, with few noncardiac coex-

isting conditions, and without polypharmacy and monitor patients in a sophisticated manner that is not amenable to regular practice. Moreover, high withdrawal rates (up to 33% in some trials) and contamination in trial groups can minimize the reported incidence of adverse events.[3] Thus, the study by Rawshani et al. underscores the importance of observational studies to confirm the findings of randomized, controlled trials as they apply in wider populations.

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No potential conflict of interest relevant to this letter was reported.

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3. Mansi IA. Statins in primary prevention: uncertainties and gaps in randomized trial data. Am J Cardiovasc Drugs 2016;16:407-18.

DOI: 10.1056/NEJMc1812842

TO THE EDITOR: Rawshani et al. conclude that persons with type 2 diabetes and five risk-factor variables that were controlled to target ranges have little to no excess risk of death or cardiovascular outcomes, as compared with the general population. An important limitation of their study is not discussed — namely, that risk-factor data were not available for the control group. That limitation has two implications.

First, as compared with the other four risk-factor variables, the effect of the glycated hemoglobin level is overestimated. The glycated hemoglobin level — but not blood pressure, the low-density lipoprotein (LDL) cholesterol level, or smoking status — can be assumed to be in the normal range for the large majority of persons in the general population control group, who had not received a diagnosis of diabetes.

Second, several risk-factor variables are likely to be outside the target ranges for a substantial number of persons in the general population control group. Therefore, the major conclusion should not be interpreted as the presence of type 2 diabetes having no effect on mortality or cardiovascular outcomes as long as the five specified risk factors are being controlled to the target ranges.

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Dr. Kannt reports being an employee of Sanofi. No other potential conflict of interest relevant to this letter was reported.

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MR. HU AND COLLEAGUES REPLY: As Anker et al. suggest, persons with chronic diseases are more likely to lose weight unintentionally and also have higher mortality than those without chronic disease. Including persons with chronic diseases in studies that examine adiposity and mortality would probably distort true associations of interest.[1] This issue is even more problematic for our analysis regarding smoking cessation, for which "ill quitter effects" have been long recognized.[2] For these reasons, we excluded patients who had cancer or cardiovascular disease at baseline and stopped updating the smoking status and body weight if these conditions developed in participants during follow-up, in order to alleviate the ill quitter effects. Anker et al. also suggest that weight gain after smoking cessation might have favorable effects on mortality. We did not specifically test that hypothesis. Detailed analyses will be useful in examining the relationship between body-weight changes and subsequent mortality among persons who have never smoked, those who quit smoking recently, and those who continue to smoke.

In response to Fan et al.: we calculated that, at the time of quitting, BMI was slightly lower among quitters who gained weight than among those without weight gain (median BMI, 23.4 and 24.3, respectively). Adjustment for BMI at smoking cessation only strengthened the positive associations with diabetes for the weight-gain categories, which indicates that our primary findings were not due to confounding by BMI at quitting. Further analyses will be useful in accounting for weight changes and BMI history among persons who continue to smoke and those who never smoked in order to elucidate the complex relationships among smoking status, weight change, and health consequences.

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Since publication of their article, Dr. Sun reports receiving ad hoc consulting fees from Emavant Solutions. No further potential conflict of interest relevant to this letter was reported.

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DR. AIDIN RAWSHANI AND COLLEAGUES REPLY: We concur with Mansi that the indication for statins may influence the association between ongoing use of lipid-lowering medications and the outcomes. It is likely that persons with ongoing use of lipid-lowering medications at baseline have high cardiovascular risk and mortality. Our study highlights the strong relationship between the LDL cholesterol level and the risk of atherothrombotic events. Nevertheless, confounding by indication, reverse causation, and residual confounding will always be important caveats of observational studies.

In response to Kannt: the absence of information on risk factors for matched controls could be considered to be a limitation. However, we believe that the results are easier to interpret and extrapolate by ignoring specific subgroups (according to risk-factor control) in the general population. After all, we are examining the excess risk conveyed by diabetes and wish to use the general population as the comparator. So, regardless of the characteristics of the general population, our study highlights the excess risk associated with type 2 diabetes. Thus, in the study, we occasionally compared patients who had type 2 diabetes with an average-risk, matched control.

Our results are based on a nationwide sample of persons with type 2 diabetes and matched controls. We found that contemporary risk-factor control was highly efficient, although young patients with type 2 diabetes have an elevated risk of most outcomes, even with all the risk factors within target ranges. We also found that the excess risk among patients with type 2 diabetes was gradually attenuated with age.

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Restrictive versus Liberal Transfusion for Cardiac Surgery

TO THE EDITOR: The findings reported by Mazer et al. (Sept. 27 issue)[1] in the Transfusion Requirements in Cardiac Surgery (TRICS) trial lend further support to the purported harms of blood transfusion in patients undergoing cardiac surgery. These include tissue ischemia,[2] increased red-cell aggregation,[3] and the accumulation of toxic microparticles and proinflammatory cytokines, all of which may elevate the patient's risk of future cardiovascular events.

However, the distinction between elective and emergency cardiac surgery remains important; the latter is known to carry an increased risk of severe postoperative bleeding.[4] Unfortunately, the proportion of patients undergoing emergency surgery in this trial was too small to serve as the basis for meaningful subgroup analysis, but the risks associated with emergency cardiac surgery should be an important consideration in future trials.

Improvements in clinical indicators of red-cell transfusion can also be made. Although the hemoglobin level has been widely used as the objective marker for anemia and tissue hypoxia, the key indicator of tissue oxygenation is cardiac output. Near-infrared spectroscopy may offer a noninvasive means of measuring the oxygenation of cerebral tissue. This approach is also superior