Progress in the Estimation of Mortality due to Diabetes

In this issue, Roglic et al. (1) provide new estimates of the proportion of deaths worldwide attributable to diabetes. Their result is about three times as high as a prior estimate from the World Health Organization in 2002. The World Health Organization estimate was based on the underlying cause of death listed on death certificates and likely underestimated the contribution of this disorder to mortality, as underrecording of diabetes on death certificates has been demonstrated in several studies (2–4).

Further issues make use of death certificates to assess cause of mortality problematic. Recording of diabetes is likely to be inconsistent due to the lack of a standardized method for death certificate coding. Contrast this situation with a clinical research study that applied specific criteria to assign a cause of death. Such rigor would never be possible in the "real" world because of educational and practice differences regionally and nationally, as well as the current emphasis on the judgment of an individual physician in assigning cause of death. The idea of having a clinician assign cause of death seems sound, but the lack of standardization will lead to uncertainty about the meaning and inclusiveness of causes listed on death certificates.

Causal interpretations and competing causes of mortality also must be considered in interpreting and estimating causes of death. Diabetes may lead to the immediate cause of death by, for example, causing cardiovascular disease but remain unlisted on the death certificate since it was one or more steps removed from the terminal event. Conversely, the presence of diabetes in the deceased does not necessarily mean that diabetes contributed to mortality, as might be the case if death occurred due to non–hypoglycemia-related trauma, drowning, or another condition that is not likely to occur more frequently in a person with diabetes. A more subtle and similar issue would also apply to conditions that may be caused by diabetes, such as cardiovascular disease, but also may occur in individuals without diabetes. Therefore, it is not the case that all people with diabetes who die of cardiovascular disease experienced their fatal cardiovascular event because diabetes was involved in the causal sequence leading to death.

Given the inaccuracy of relying on death certificate data to estimate disease-specific mortality, what alternative approaches exist to address this problem? Epidemiologic data may be used to estimate the number or proportion of deaths attributable to a particular underlying cause. The calculations used in these instances are fairly straightforward and simple (5). In general, if the incidence of death in persons with diabetes (I_D) exceeds that in persons without diabetes (I_N), then the proportion of deaths attributable to diabetes is $(I_D - I_N)/I_D$. If I_D = 4/100 and I_N = 2/100, then the proportion of deaths associated with diabetes is (0.04–0.02)/0.04 = 50%. The numerator subtracts out the baseline death rate from the overall diabetes death rate, and this difference represents the excess death rate due to diabetes, which, when divided by the overall death rate in diabetic individuals, yields the proportion of all deaths in people with diabetes attributable to this disorder. This result multiplied by the number of individuals with diabetes who die will yield the number of diabetic deceased people whose death was attributable to this disorder. I want to note now for a later purpose in this editorial that dividing each term in the formula above by I_N yields the following result: (RR − 1)/RR, where RR is the relative risk of death in diabetic versus nondiabetic individuals. It is therefore possible to estimate the proportion of deaths due to diabetes or another disease without knowing either I_D or I_N.

Other issues must be considered before concluding that these calculations provide the number of subjects whose deaths were caused by diabetes. Diabetes may have served as a marker for other conditions that increase the risk of death, such as hypertension, dyslipidemia, obesity, and even smoking (6,7). Therefore, an adjustment must be made for factors that are associated with diabetes that may be related to an alteration in risk of death. Failure to perform this adjustment would lead to bias in the estimate of death due to diabetes, since the adverse effects of dyslipidemia and hypertension would be mixed together with the diabetes effect. An important distinction must be made between factors associated with diabetes and factors caused by diabetes. For example, diabetes increases the risk of cardiovascular disease and therefore will be found more frequently in people with cardiovascular disease. One might be tempted to adjust for cardiovascular disease in order to better estimate the proportion of deaths attributable to diabetes, but this would falsely bias this estimate downward, assuming an increase in the risk of death due to diabetes. This is because the development of cardiovascular disease is in the causal pathway, leading from diabetes to higher risk of death, whereas, for example, hypertension is not, as this is a correlate of diabetes and not caused by it. Therefore, the process of estimating proportion of deaths due to a disease using epidemiologic methods involves judgments regarding adjustment for factors associated with diabetes. Thus, death certificate coding and epidemiologic methods both rely on expert judgment; in the former case, expert opinion is needed to directly assign a cause of death, and in the latter case, it is needed to eliminate other potential causal explanations for the estimated fraction of deaths associated with diabetes or some other condition of interest.

Roglic et al. developed a model of mortality attributable to diabetes based on estimates of age- and sex-specific diabetes prevalence, RR of death for people with diabetes, all-cause mortality rates, and population structure. They used DisMod II, a free downloadable software program, to input these variables into a model that estimated the proportion of

deaths attributable to diabetes (8). DisMod II uses complex mathematical modeling, including differential equations, to estimate several different epidemiologic parameters. The inner workings of DisMod II will remain beyond the understanding of most readers of *Diabetes Care*, and it would have been preferable for these authors to base their analyses on models that are equally accurate but less sophisticated. Roglic et al. also performed an analysis of attributable mortality using the simpler methods to which I refer above. The standard methods yielded mortality estimates that are very similar to those derived from the DisMod II program, and thus in my mind are to be preferred as the methodology for future investigations of mortality attributable to diabetes.

Regarding adjustment of important factors associated with diabetes and mortality, Roglic et al. did consider the important confounding effects of age and sex but did not consider other previously mentioned diabetes-associated factors such as obesity, hypertension, dyslipidemia, and smoking. Such information is not available on a global level to my knowledge, and thus such adjustments might not have been possible even if the authors had considered them. Such adjustments may lead to important findings, as shown by a recent study of excess deaths in the U.S. associated with overweight and obesity that reported lower numbers than its predecessors (9). The authors attributed their findings in part to effective adjustment of their estimates for factors associated with excess body weight and mortality. There are data, though, that indirectly suggest that adjustments for potential confounding factors of the association between diabetes and mortality may not yield results that differ greatly from the unadjusted estimates. Adjustment for BMI and smoking of the RR of coronary heart disease death in relation to diabetes in the Nurses Health Study did not result in appreciable changes (10). Similarly, adjustment for BMI, smoking, serum cholesterol, systolic blood pressure, and coronary heart disease at baseline had little effect on the increase in mortality associated with diabetes in a cohort of >7,000 men followed for up to 16 years (11). As shown above, the proportion of deaths attributable to a given condition can be expressed as a function of RR only. The minimal change in RR after adjustment for these confounding factors in these two studies suggests that if Roglic et al. had performed a similar adjustment in their analyses, similar results would have occurred. An important next step to confirm or refute this suspicion would be a similar study in a population in which sufficient information exists to perform complete adjustments for potential confounding variables.

Roglic et al. have shown us an important direction for the assessment of deaths attributable to diabetes in their use of epidemiologic data, thereby avoiding the chronic deficiencies of death certificate coding. However, their results represent only the start, and better data and more thorough analyses should soon enhance our understanding of the worldwide impact of diabetes on mortality.

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