

The Burden of Mortality Attributable to Diabetes

Realistic estimates for the year 2000

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OBJECTIVE — To estimate the global number of excess deaths due to diabetes in the year 2000.

RESEARCH DESIGN AND METHODS — We used a computerized generic formal disease model (DisMod II), used by the World Health Organization to assess disease burden through modeling the relationships between incidence, prevalence, and disease-specific mortality. Baseline input data included population structure, age- and sex-specific estimates of diabetes prevalence, and available published estimates of relative risk of death for people with diabetes compared with people without diabetes. The results were validated with population-based observations and independent estimates of relative risk of death.

RESULTS — The excess global mortality attributable to diabetes in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths. Excess mortality attributable to diabetes accounted for 2–3% of deaths in poorest countries and over 8% in the U.S., Canada, and the Middle East. In people 35–64 years old, 6–27% of deaths were attributable to diabetes.

CONCLUSIONS — These are the first global estimates of mortality attributable to diabetes. Globally, diabetes is likely to be the fifth leading cause of death.

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D iabetes is a serious illness with multiple complications and premature mortality, accounting for at least 10% of total health care expenditure in many countries (1). However, routinely

reported statistics based on death certification seriously underestimate mortality from diabetes (2), because individuals with diabetes most often die of cardiovascular and renal disease and not from a

cause uniquely related to diabetes, such as ketoacidosis or hypoglycemia (3).

Most international mortality statistics, including those published by the World Health Organization (WHO), are based solely on the “underlying cause of death” as recorded on the death certificate, even in the presence of other information. Complex methods have been developed for estimating cause-specific mortality for some conditions (AIDS, tuberculosis) but not for diabetes (4).

Based on routine statistics, recent World Health Reports estimated mortality from diabetes in the world as 987,000 deaths for the year 2002 (5), which was 1.7% of total world mortality. There were estimated to be at least 170 million people with diabetes in the world in the year 2000 (6); therefore, mortality attributable to diabetes could be expected to be much higher, since diabetes is a serious and chronic condition. The aim of this study was to provide a more realistic estimate of the number of deaths attributable to diabetes.

RESEARCH DESIGN AND METHODS

Model and data

To estimate the number of deaths attributable to diabetes in the year 2000, we used a software program, DisMod II, developed for the Global Burden of Disease 2000 study (7,8) and routinely used by WHO for disease estimates. The DisMod II disease model is that of a multistate life table that describes a single disease. There are two causes of death, from the disease and from “all other” causes, that are assumed to be independent. There are four transition hazards: incidence, remission, case fatality, and the “all other mortality” hazard. These transition hazards are age specific, but DisMod II assumes them to be constant within a 1-year age interval. The analytical solution to these equations enables the calculation of the number of people in each of the three states (healthy, diseased, and dead) at age x as a function

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Abbreviations: DECODA, Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Asia; DECODE, Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Europe; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 2320.

Table 1—Studies used to estimate age-specific RR of dying in individuals with diabetes compared with individuals without diabetes

	Sex	Number of deaths	RR at age 20–39 years	RR at age 40–59 years	RR at age 60–79 years
Sweden	M	2,074	3.4	3.7	1.5
South Wales	M*	1,649	5.2	2.8	1.3
U.S. NHANES	M†	486	4.9	2.0	1.4
U.K.	M‡	3,399	3.75	2.51	1.52
Combined	M	7,653	4.05	2.86	1.46
Sweden	F	2,074	10.6	4.0	1.9
South Wales	F*	1,649	5.4	3.3	2.4
U.S. NHANES	F†	486	3.2	2.7	1.6
U.K.	F‡	3,399	5.51	3.50	2.48
Combined	F	7,653	6.72	3.54	2.25

*RR for age 25–34 years is proxy for RR age 20–39 years; average of RRs age 35–44 years, age 45–54 years, and age 55–64 years is proxy for RR age 40–59 years. †RR for age 25.44 years is proxy for RR age 20–39 years; RR for age 45–64 years is proxy for 40–59 years; RR for age 65–74 is proxy for RR age 60–79 years. ‡RR for age <40 years is proxy for age 20–39 years; average of RRs <50 years and 50–64 years is proxy for RR 40–59 years; RR 65–74 years is proxy for RR 60–79 years. NHANES, National Health and Nutrition Examination Survey.

of the number of people in those states at the previous age and of the three hazards at that age. Setting initial conditions for age 0 then allows the computation of the numbers of people in the three states from the lowest age up. From these numbers, the other rates, such as prevalence and mortality, are calculated. The above equations assume that three hazard transitions (incidence, remission, and case fatality) are available as input variables. When this is not the case, and input variables like prevalence are available instead, DisMod II combines the analytical solution with a loss function and minimizes that loss function to find values of the hazards that minimize the difference between the input and output variables. Of six disease-specific input variables (incidence, remission, case fatality/relative risk [RR] for total mortality, prevalence, duration, and mortality), three are needed, together with population size and total mortality, to calculate the others in the model. Input data for this study included population structure and all-cause mortality rates, age- and sex-specific diabetes prevalence, remission (equal to zero), and available published estimates of RR of death for people with diabetes.

Regional country groupings developed by the World Health Organization were used (available at http://www.who.int/whr/2004/annex/topic/en/annex_member_en.pdf). They are based on the geo-political grouping of countries into six regions (AFR, African Region; AMR,

Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, Southeast Asia Region; WPR, Western Pacific Region). These six regions are further divided into 17 subregions (5), on the basis of mortality rates in children <5 years old and in males 15–59 years old (A, very low child, very low adult; B, low child, low adult; C, low child, high adult; D, high child, high adult; E, high child, very high adult).

Estimates for prevalence and the number of people with diabetes were those from a recent WHO study (6), in which population-based, age- and sex-specific diabetes prevalences from 40 countries were applied to the United Nations population estimates for every country to get the number of people with diabetes in the year 2000 (online appendix [available at <http://care.diabetesjournals.org>]).

We searched the literature for measures of RR of death for people with diabetes, compared with people without diabetes. Only a few cohort studies were found to be representative of the diagnosed diabetic population, provide the RR of all-cause mortality for individuals with diabetes by sex and age-group (9–11), or provide the number of deaths among individuals with diabetes and individuals without diabetes in the case of follow-up of population-based samples (12). Data from these studies were combined and weighted by the total number of deaths in each study to provide com-

bined RRs (Table 1). Based on a recent U.K. study, the RR of dying in the age-group 0–19 years was assumed to be 1.8 for males and 3.1 for females (13). In people >80 years old, the RR of dying was assumed to be 1.

Validation

In 1994, a population-based cohort of 4,842 individuals with diagnosed diabetes was identified in South Tees, U.K., and followed up annually for mortality until 1999 (14). The number of deaths attributable to diabetes in 1995–1999 in this cohort was calculated as the actual observed number of deaths that occurred in the cohort, reduced by the number of deaths that would have occurred if South Tees' death rates in people without diagnosed diabetes operated in the diabetes cohort. This directly calculated number of excess deaths attributable to diabetes was compared with the number of excess deaths calculated by DisMod II.

To validate the DisMod II method, separate calculations of the number of deaths due to diabetes were performed according to the formula proposed by Miettinen for estimating the proportion of a disease or event caused by a given exposure (15):

$$EF = P(RR - 1) / (P(RR - 1) + 1)$$

where EF indicates the fraction of total mortality that is attributable to diabetes (the “etiologic fraction”), *P* indicates the proportion of the population with diabetes, and RR indicates the ratio of the mortality rate among individuals with diabetes to that among individuals without diabetes in age-groups 0–19, 20–39, 40–59, 60–79, and 80+ years. To estimate the number of deaths attributable to diabetes, the calculated “etiologic fractions” for each region were applied to the total number of deaths from the corresponding region for the year 2000 (16). Again, diabetes prevalence rates were obtained from the recent WHO publication (6), and the RRs of dying were those used in DisMod II.

To further validate the assumption that the available few published RRs of death were suitable proxy for unavailable information, we also used previously unpublished age-specific but otherwise unadjusted RRs of death in people with diabetes from the DECODE (Diabetes Epidemiology, Collaborative Analysis of

Table 2—Estimated number of deaths attributable to diabetes (thousands) and percentage of total deaths by age and WHO region

	Number of deaths attributable to diabetes				Percentage of all-cause deaths			
	0–34 years (M/F)	35–64 years (M/F)	≥65 years (M/F)	All (M/F)	0–34 years (M/F)	35–64 years (M/F)	≥65 years (M/F)	All (M/F)
AFRO D	7.1/11.0	46.7/37.8	12.1/19.6	65.9/68.4	0.4/0.6	8.7/9.1	3.1/4.8	2.4/2.6
AFR E	12.9/21.2	55.0/48.6	8.6/13.9	76.6/83.7	0.6/0.9	6.2/7.2	2.3/3.4	2.1/2.5
All AFR	20.0/32.2	101.7/86.4	20.7/33.5	142.5/152.1	0.5/0.8	7.1/7.9	2.7/4.1	2.2/2.5
AMR A	0.5/0.4	53.4/38.8	62.2/73.3	116.1/112.5	0.6/1.0	15.7/18.7	6.9/6.7	8.7/8.3
AMR B	1.1/1.0	41.8/50.0	21.1/59.8	64.0/110.8	0.3/0.4	8.7/17.4	3.3/9.7	4.0/9.4
AMR D	0.7/0.5	8.5/8.9	4.0/6.4	13.3/15.8	0.5/0.5	11.4/16.2	4.4/7.6	4.4/6.5
All AMR	2.3/1.9	103.7/97.7	87.3/139.5	193.3/239.1	0.4/0.5	11.6/17.8	5.4/7.7	6.0/8.6
EMR B	0.9/1.2	1.6/2.0	9.9/16.2	26.5/37.6	0.7/1.1	13.8/27.3	6.7/12.4	6.6/11.9
EMR D	1.0/1.3	20.6/18.2	10.9/13.8	32.5/33.3	0.4/0.6	15.8/18.5	6.5/8.2	5.8/6.8
All EMR	1.9/2.5	21.6/20.2	21.8/30.0	59.0/70.9	0.5/0.8	14.8/22.3	6.6/10.0	6.1/8.8
EUR A	0.7/0.3	40.6/18.2	85.9/76.1	127.2/94.6	0.8/0.8	8.9/8.1	5.8/4.3	6.3/4.7
EUR B1	1.3/0.9	38.4/24.4	26.8/35.0	66.5/60.3	1.2/1.2	14.1/18.3	6.0/7.1	8.0/8.6
EUR B2	0.3/0.2	7.0/6.6	4.3/6.6	11.5/13.5	0.3/0.3	9.6/14.6	5.3/6.4	4.9/6.4
EUR C	2.5/0.8	69.2/35.4	48.2/45.9	120.0/82.2	1.2/1.0	8.3/10.1	5.9/3.4	6.5/4.6
All EUR	4.8/2.2	155.2/84.6	165.2/163.3	352.2/250.6	1.0/0.9	9.5/11.3	5.8/4.4	6.6/5.1
SEAR B	6.9/4.8	69.2/60.2	34.1/44.0	110.2/108.9	1.3/1.3	14.0/17.3	6.4/8.4	7.0/8.7
SEAR D	22.2/28.3	253.6/254.1	107.9/147.5	384.7/429.9	0.7/0.9	12.5/18.4	4.8/8.1	5.1/6.6
All SEAR	29.1/33.1	322.8/314.3	142.0/191.5	494.9/538.8	0.8/0.9	12.7/18.2	5.1/8.2	5.4/6.9
WPR A	0.1/0.1	17.1/8.5	23.1/18.8	40.4/27.4	0.4/0.6	11.9/13.0	5.2/4.3	6.6/5.4
WPR B1	2.4/2.2	90.9/84.0	61.8/112.9	155.1/199.1	0.2/0.2	5.8/9.1	2.3/4.8	3.0/4.8
WPR B2	0.4/1.2	8.8/9.9	3.6/6.0	12.8/17.1	0.1/0.5	5.1/7.9	1.5/2.6	1.8/2.9
WPR B3	0.1/0.3	1.7/1.9	0.4/0.6	2.2/2.8	0.5/2.0	17.5/23.5	6.0/11.3	6.1/9.3
All WPR	3.0/3.8	118.5/104.3	88.9/138.3	210.5/246.4	0.2/0.3	6.4/9.2	3.0/5.1	3.4/4.8

AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, Southeast Asia Region; WPR, Western Pacific Region.

Diagnostic Criteria in Europe) and DECODA (Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Asia) studies to calculate the number of deaths attributable to diabetes in people older than 39 years (J.T., personal communication). The DECODE study examined 22 adult European cohorts for diabetes, and >27,000 people were followed up for mortality for an average of 11 years (17).

The DECODA study followed five cohorts of Japanese and Indian origin (18). We used the RR of deaths in 3,482 Asian Indians living in Mauritius and Fiji to recalculate the number of deaths for Southeast Asia and compared it with the number of deaths derived using published RRs of dying from studies conducted in Europe and the U.S. The unadjusted RR of death for diabetic patients, compared with people without diabetes in the DECODA study populations of Asian Indian origin, was 5.76 for men and 3.28 for women in the age-group 30–39 years; 8.16 for men and 1.77 for women in the age-group 40–49 years;

4.07 for men and 3.13 for women in the age-group 50–59 years; 2.44 for men and 1.87 for women in the age-group 60–69; and 2.02 for men and 2.32 for women in the age-group 70–89. The RR above the age of 89 was assumed to be equal to 1.

To get a range of numbers of deaths attributable to diabetes, we calculated the number of deaths using the RRs from each of the four studies. For both men and women, the lowest number of deaths was obtained by using RRs from the National Health and Nutrition Examination Survey (NHANES) (12). South Wales RRs gave the highest number of deaths in men (10), and the U.K. study RRs gave the highest number of deaths in women (11). Therefore, age- and sex-specific RRs of death from these three studies were applied to each region to get a range based on published results.

RESULTS— The numbers of excess deaths due to diabetes and the percentage of total mortality in each WHO region are presented in Table 2. Global excess mortality attributable to diabetes is estimated

at 2.9 million deaths (1.4 million men and 1.5 million women), which is equivalent to 5.2% of world all-cause mortality in the year 2000: 1 million deaths in developed countries and 1.9 million deaths in developing countries. The percentage of excess deaths was lowest (2.4%) in the poorest African countries and in Cambodia, Laos, Myanmar, and Vietnam (WPR B2) and highest in the Middle East (9% in the Arabian Peninsula) and North America (8.5% in the Region of the Americas). In countries with a high prevalence of diabetes in younger age-groups (Southeast Asia Region, SEAR D; Arabian Peninsula, Eastern Mediterranean Region, EMR B; and Western Pacific Region, WPR B3), the percentage of excess deaths peaked at 50–54 years of age. In the rest of the world, the percentage of excess deaths due to diabetes was highest in people aged 55–59 years.

Overall, 7.5 million people with diabetes are estimated to have died in the year 2000. This includes 4.6 million people with diabetes assumed to have died from causes other than diabetes, plus the excess 2.9 million that died because of

Table 3—Number of excess deaths attributable to diabetes in individuals ≥ 40 years old by source of RR of death (thousands)

	Number of deaths calculated with published RRs (Miettinen's formula)	Number of deaths calculated with published RRs (DisMod II)	Number of deaths calculated with DECODE study RRs* (DisMod II)
AFR D	104	103	79
AFR E	106	103	75
AMR A	216	226	237
AMR B	167	169	151
AMR D	27	27	22
EMR B	60	60	52
EMR D	62	61	51
EUR A	200	220	251
EUR B1	124	122	108
EUR B2	24	24	21
EUR C	194	195	169
SEAR B	196	197	164
SEAR D	723	721	587
WPR A	63	67	72
WPR B1	343	354	313
WPR B2	27	27	22
WPR B3	4	4	3
World	2,640	2,680	2,380

AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, Southeast Asia Region; WPR, Western Pacific Region.

diabetes. In individuals with diabetes younger than 35 years, 75% of all deaths were attributable to diabetes; in individuals with diabetes aged 35–64 years, 59% of deaths were attributable to diabetes; while in individuals with diabetes and older than 64 years, 29% of all deaths were attributable to diabetes.

Validation

The number of directly calculated deaths attributable to diabetes in South Tees was systematically 5–32% higher for each year than that calculated by the model (76 vs. 72 in 1995, 94 vs. 64 in 1996, 87 vs. 63 in 1997, 86 vs. 58 in 1998, and 88 vs. 66 in 1999).

Using the method of Miettinen, the estimated total number of excess deaths was comparable to the DisMod II results (Table 3).

Table 3 also compares the excess diabetes deaths in individuals aged ≥ 40 years calculated with RRs of death from the published studies and those calculated with unpublished RRs from the DECODE study. In developed regions, the DECODE study RRs of death yielded a number of excess deaths that was 4–15% higher than the number of excess deaths calculated with published RRs. In developing regions, the DECODE study RRs yielded estimates 10–28% lower. The total world number of deaths in this age-group differed by 11%. Applying the RR of death from the Asian Indian DECODA cohort to the SEAR D region yielded 1 million deaths attributable to diabetes, which is almost double that estimated using RRs derived from European populations.

The range for the overall number of deaths is 1.9–3.7 million when the lowest and highest published RRs of death were used for the calculations (Fig. 1).

CONCLUSIONS — The DisMod II method yielded an estimate of excess global mortality attributable to diabetes that is three times higher than estimates given in available international statistical reports mostly based on death certificates. The number of excess deaths attributable to diabetes is similar in magnitude to numbers reported for HIV/AIDS in the year 2000 (16). The higher proportion of

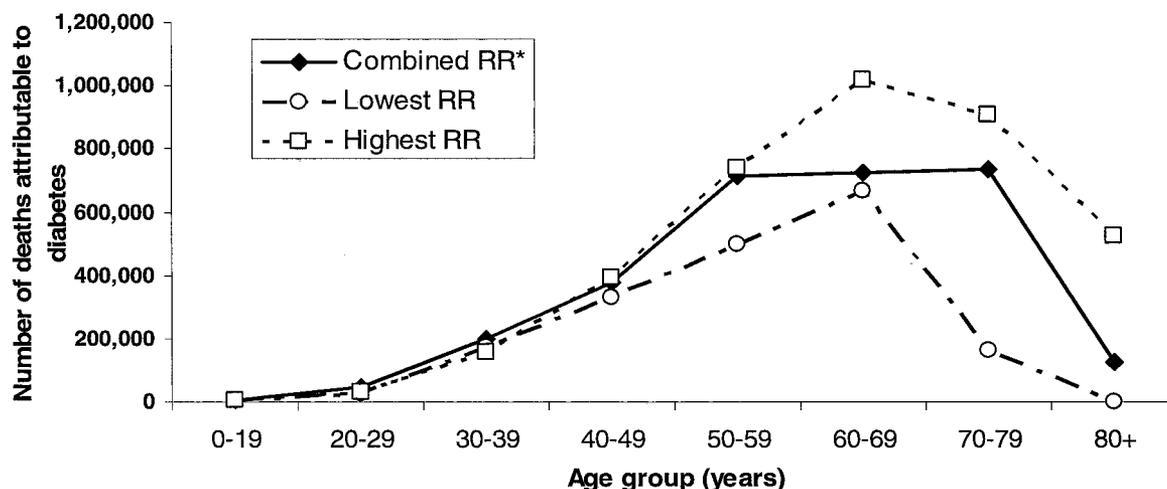


Figure 1—Variation in the number of deaths attributable to diabetes according to lowest and highest RR of death. *See Table 1 and RESEARCH DESIGN AND METHODS for the derivation of the combined RR.

excess deaths in females compared with males is explained by females' lower background mortality levels. There is a larger increase in the absolute risks of dying in women compared with men with diabetes in almost all age-groups. Validation using the South Tees population data indicates that the estimated number of deaths is probably conservative for developed countries, possibly because in reality the RR of death in individuals >80 years is higher than the value of 1 assumed for this study because of the lack of data. Diabetes is often perceived as a disease of affluent countries. This study suggests that in most developing countries, almost one in ten deaths in economically productive individuals aged 35–64 years can be attributed to diabetes.

The RRs of death obtained in developed countries may have overestimated the number of deaths among individuals with diabetes in developing countries because of higher competing mortality risks in developing countries. However, in Mauritius and Brazil, the risks were about three times higher in individuals with known diabetes than in the general population (19,20), but these studies were not used in our calculations because RRs were not presented by age-group. DECODA study data indicate that Indians with diabetes in Mauritius had a higher RR of dying than individuals with diabetes in Europe and the U.S. This is consistent with the sparse information from low-income countries indicating a poor prognosis for individuals with diabetes, largely due to infection and acute metabolic complications (21,22). The number of deaths attributable to diabetes in SEAR D, affected by the size of the RRs selected for the calculations, can substantially alter global numbers because of the large population size and high diabetes prevalence in the region. Although the RR of death may not be the same for Indians living in India and those living in Mauritius and Fiji, the RRs from the DECODA study were judged to be the most appropriate for validation.

The sensitivity analysis with the lowest and highest published RRs of death shows that the global number of deaths attributable to diabetes could be as low as 1.9 million. This is still double the number in available reports. No sensitivity analysis was performed for the WHO estimates of diabetes prevalence used for these calculations (6), and we have not

speculated on the possible range. However, subsequent studies have shown that the WHO study probably underestimated the prevalence of diabetes (23), and, consequently, these mortality estimates are likely to be conservative.

The prevalence estimates of diabetes used include both diagnosed and undiagnosed diabetes, whereas the RRs of death were derived from individuals with diagnosed diabetes. The proportion of undiagnosed diabetes varies and is often higher than 50% (24). The RR of death may not be the same for diagnosed and undiagnosed diabetes, but data from the DECODE study show that the difference is relatively small (17). Moreover, people with impaired glucose tolerance have a 40% increased mortality, regardless whether they progress to diabetes or not (25,26). Because impaired glucose tolerance is a common condition affecting 15–40% of adults (27,28) and is an independent predictor of mortality, the impact of hyperglycemia on mortality is larger than that associated with diabetes alone.

Our aim was to provide more realistic estimates of diabetes-attributable mortality than currently exist. The results suggest that mortality attributable to diabetes is likely to be considerably higher than previous global estimates based on death certificates. This moves diabetes from the eighth to the fifth place in cause of death ranking, after communicable diseases, cardiovascular disease, cancer, and injuries. The number of deaths related to hyperglycemia would have been even higher if mortality attributable to impaired glucose tolerance was taken into account (1,25). Even in the poorest countries, at least one in twenty adult (35–64 years of age) deaths is diabetes related, and in most countries, the proportion is substantially higher. These figures illustrate the considerable burden diabetes currently imposes on poor countries, a burden that will inevitably increase with the estimated doubling of the population with diabetes in the next 25 years (6).

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