OBJECTIVE — Birth weight is a risk factor for both diabetes and mortality. Diabetes is a risk factor for mortality. Whether the excess mortality observed for diabetes varies with birth weight is unclear.

RESULTS — Of the diabetic case subjects, 16% (27 of 171) died vs. 7% (25 of 342) of control subjects (P = 0.004). The difference was less for normal-birth-weight (NBW) (2,948–3,856 g) individuals (12% [12 of 102] vs. 8% [20 of 246], P = 0.31) than for abnormal-birth-weight individuals (low birth weight [LBW] 20% [8 of 39] vs. 2% [1 of 46], P = 0.01; high birth weight [HBW] 23% [7 of 30] vs. 8% [4 of 50], P = 0.16), as confirmed with age- and sex-adjusted Cox proportional hazards (diabetes-associated hazard ratio 1.4 [95% CI 0.69–2.90] for NBW vs. 4.8 [1.7–13.3] for abnormal birth weight, test for interaction P = 0.056). The observed diabetes deaths were greater than expected, based on mortality for the general population (27 vs. 13.3, P < 0.001), with 70% of excess deaths occurring among LBW (8 vs. 2.2, P < 0.001) and HBW (7 vs. 3.1, P = 0.03) individuals.

CONCLUSIONS — The excess mortality observed for diabetes appears disproportionately concentrated among abnormal-birth-weight individuals, thus identifying a subset of at-risk diabetic individuals and reinforcing the importance of NBW deliveries.

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Diabetes is a prevalent disease with serious adverse consequences. Several studies have reported an association between diabetes and abnormal birth weight (1–11), and abnormal birth weight has been implicated as a risk factor for mortality in studies of the general population (12–15). Whether birth weight is predictive of diabetes-associated mortality is unclear. The question is important because the risk of death for people with diabetes is approximately twofold that for their nondiabetic peers (16). If abnormal birth weight is a risk factor, it could help identify high-risk diabetic individuals. Because birth weight is modifiable, the risk of death associated with diabetes could be reduced in the future. A rare opportunity to investigate the association between birth weight and diabetes-related mortality is afforded with access to the complete detailed medical records from birth until migration or death of all individuals born in Rochester, Minnesota, since 1922.
Birth weight, diabetes, and mortality

The vast majority of members of the REP diabetes incidence cohort were born before 1922 and/or moved into the area after birth. Only 171 were born locally in-hospital after 1922 (i.e., for whom we had access to recorded weights at birth) as singleton, term infants and met the criteria for type 2 diabetes. For each of the 171 case subjects, we identified two nondiabetic Rochester residents of the same sex and birth year who met the same birth characteristics among diabetic case subjects and who were seen by a REP provider in the year (±2) that the case subject first met the criteria for diabetes.

**Determination of vital status**

Vital status as of 31 December 2000 and date of last follow-up were determined after review of medical records, State of Minnesota death tapes, the Social Security Death Index, and telephone and mail follow-up. Confirmation that individuals were alive as of 31 December 2000 or had died (with date of death) before that date was available for 95% of control subjects and 99% of case subjects. Follow-up for remaining individuals was censored at the date vital status was last known.

**Statistical analyses**

Analyses were conducted using SAS version 8.02 (SAS Institute, Cary, NC), with statistical significance set at $P < 0.05$. Univariate descriptive statistics were used to compare case subjects and control subjects for baseline characteristics. In keeping with our previous publication (11), low birth weight (LBW) was defined as 2,948 g (<6.5 lb), normal birth weight (NBW) as 2,948–<3,856 g (6.5–<8.5 lb), and high birth weight (HBW) as ≥3,856 g (8.5 lb). Within each category, differences in mortality between case subjects and control subjects were tested using the Kaplan-Meier product limit method and a two-sample log-rank test. Cox proportional hazards modeling was used to assess the contribution of diabetes to mortality, for each birth weight category separately (adjusting for sex, age, and birth year) and for all categories combined (adjusting for sex, age, birth year, and birth weight category). To assess whether the effect of diabetes differed as a function of birth weight, we tested for an interaction between case status and birth weight category, considered both as a three-level (low versus normal and high versus normal) and a two-level (normal versus abnormal) variable.

We additionally tested whether diabetes-associated mortality differed as a function of birth weight category by comparing observed mortality for diabetic case subjects with that expected, based on sex/age/calendar year stratified rates for the white West North Central U.S. population. This approach validated the representativeness of the control cohort and provided an independent assessment of the role of birth weight in diabetes-associated mortality. Within each category, differences between observed and expected mortality were tested using the Kaplan-Meier product limit method and a one-sample log-rank test. We then examined the effect of birth weight on the relative risk of mortality after adjusting for age, sex, and birth year. Relative mortality was analyzed by creating a new time variable that took into account the actuarial life-table survival distribution for each individual. This variable was defined as $-\log[S(T)],$ where $S(T)$ is the actuarial life-table probability of survival for each individual up until his or her date of last follow-up. Under the assumption that each individual’s survival follows the expected actuarial life-table distributions, this variable has a negative exponential distribution with parameter 1.0, independent of the individual’s age, sex, and year he or she met the criteria for diabetes. The departure of the individual’s actual survival from expected is reflected in the departure of this “survival time” from the predicted negative exponential distribution. This transformed censored survival time was then subjected to ordinary Cox regression to determine how “relative survival” was related to birth weight, as well as to age, sex, and birth year. Within this framework, we analyzed birth weight as a continuous variable, considered both as a linear and a nonlinear function. The latter was based on several different models: 1) a quadratic function (two parameters), 2) a wedge-shaped function (linear, then flat), with the initial slope and change point estimated from the data (two parameters), and 3) a wedge-shaped function with two lines, neither of which was required to be flat (three parameters). In each case, it was the overall model $\chi^2$ that was assessed, relative to its degrees of freedom.

**RESULTS** — Comparison of characteristics among diabetic case subjects and nondiabetic control subjects (Table 1) revealed significant differences in the distribution of birth weight categories, with a greater proportion of both LBW and HBW case subjects compared with control subjects.

**Mortality among diabetic case subjects versus nondiabetic control subjects**

Median follow-up from baseline through 31 December 2000 was 10.0 years (11.6 ± 7.4 years [mean ± SD]; range 0–38 years). The proportion of deaths among case subjects was more than twice that for control subjects (27 of 171 [16%] vs. 25 of 342 [7%], two-sample log-rank $P = 0.004$). The difference was less apparent for NBW individuals (12 of 102 [12%] vs. 20 of 246 [8%], $P = 0.31$) than for HBW individuals (7 of 30 [23%] vs. 4 of 50 [8%], $P = 0.16$) and LBW individuals (8 of 39 [20%] vs. 1 of 46 [2%], $P = 0.01$). In models adjusted for age, sex, and birth year, the diabetes-associated hazard of death was 1.39 (95% CI 0.67–2.86, $P = 0.38$) for NBW individuals,
CONCLUSIONS—Previous studies have found that abnormal-birth-weight infants are at increased risk of developing type 2 diabetes (1–11). However, because the majority of adults who develop diabetes are normal weight at birth, (2,5,10,11) the population-attributable risk of diabetes due to abnormal birth weight is probably small (26). By contrast, findings from the present study suggest that the population-attributable risk of diabetes-associated mortality due to abnormal birth weight may be large. Our finding that diabetic case subjects had an overall risk of death approximately twice that for nondiabetic control subjects is consistent with numerous observations (16). We additionally observed that the risk of death associated with diabetes varied as a function of birth weight. Although abnormal-birth-weight individuals accounted for a minority of diabetic case subjects, they accounted for the majority of excess deaths associated with diabetes.

There are few opportunities to investigate the association between birth weight and mortality in persons with adult-onset diabetes. REP resources afford access to the detailed medical records for a geographically defined population, including all local birth certificates and laboratory glucose values, for more than 7 decades. Identification of all individuals who were born locally and who met the criteria for adult-onset diabetes before emigration or death thus minimizes the potential for selective survival that is
problematic with studies identifying older individuals with and without prevalent diabetes. Selection bias is also minimized because REP diabetes incidence case subjects include all individuals irrespective of sex, diabetes treatment, and/or ability to participate. Additional opportunities afforded by the REP include 1) recorded birth weights (avoiding recall bias), 2) exclusion of preterm births, 3) relatively long follow-up, and 4) essentially complete information on vital status.

The few investigations of the association between birth weight and mortality have focused on the population generally; most found significant inverse associations between birth weight and the likelihood of death due to cardiovascular disease (12–15). The extent to which people with diabetes accounted for these observations is not known. Eriksson et al. (4) followed 1,319 Swedish men from age 20 years in 1933 to age 85 years and found no effect of weight as recorded at birth on cardiovascular disease mortality. This is consistent with our finding of no significant effect of birth weight on mortality when both diabetic case subjects and control subjects were included together in the model (Table 2). In contrast to our findings, however, Eriksson et al. (4) found no significant effect of birth weight on mortality for individuals either with or without diabetes. Eriksson et al. identified diabetes from 1933 forward using hospital discharge or death certificate diagnoses. The problems with identifying diabetes from death certificates are well recognized. The limitations decreased over time (24,27). REP studies reveal that the proportion of diabetic decedents with any mention of diabetes on their death certificate averaged 34% for 1945–1970 and 49% for 1970–1994 (20,24,28). The likelihood that any individual is hospitalized and the likelihood that diabetic individuals receive a clinical diagnosis of diabetes has also increased markedly since the 1930s (21,29). If, as our findings suggest, abnormal-birth-weight diabetic individuals are at increased risk of death, such individuals in the study by Eriksson et al. (4) would have died earlier in the course of follow-up and may have been differentially misclassified as nondiabetic.

The present study defined diabetes based on review of medical records (in-
cluding all glucose values); standardized glycemic criteria were applied throughout the study period. To minimize differences in detection over time, we used NDDG criteria rather than the more sensitive American Diabetes Association criteria (30). Thus, nondiabetic control subjects may have included individuals who never met NDDG criteria but who did meet American Diabetes Association criteria for diabetes. Control subjects may have also included individuals who would have met NDDG criteria if tested but who never received a diagnosis of diabetes or a diabetes-like condition while a local resident. The generalizability of our study findings to nonwhite individuals also cannot be assessed because the Rochester population during the period under investigation was >95% white.

The direction of our findings was consistent across all analyses. However, few comparisons reached conventional statistical significance of $P < 0.05$. Thus, caution is needed in interpreting the study findings, and the importance of replicating findings elsewhere is emphasized. If replicated, the findings have important implications for both research and clinical practice. They reinforce the need to decrease LBW deliveries and maintain tight control of glucose during pregnancy. They suggest that monitoring and treatment of diabetes complications may be especially important in the subgroup of diabetic patients whose weight at birth was outside the normal range.

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