Long-Term Trends in Childhood Diabetes Mortality: 1968–1998

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OBJECTIVE — In the context of recent improvements in type 1 diabetes therapy, to describe longitudinal trends in mortality attributable to childhood diabetes and to investigate socioeconomic and health services correlates of mortality.

RESEARCH DESIGN AND METHODS — We extracted mortality data for 1968–1998 from National Center for Health Statistics files and covariates from the Bureau of Health Professions Area Resource File. Analytical techniques included linear and Poisson regression and standard descriptive statistics.

RESULTS — Childhood (defined as 0–19 years of age) age-adjusted mortality from diabetes declined from 9.5 (1968) to 3.0 (1984) deaths per 10 million but remained relatively constant subsequently. All-cause childhood mortality, however, continued to decline. Older children experienced higher mortality rates, as did those living in counties with higher levels of unemployment.

CONCLUSIONS — Despite recent improvements in therapy, diabetes-related mortality among children has not declined for 14 years. This finding may be partially attributable to sociodemographic factors influencing access to care, but the remaining mortality may defy available treatment methods. Reducing childhood diabetes mortality rates below the current apparent plateau may require new prevention and/or treatment strategies.

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Before the introduction of insulin therapy in 1922, therapeutic diets low in carbohydrates, coupled with buffer supplementation but accompanied by wasting and worsening acidosis, could only briefly delay mortality among children with type 1 diabetes. These dreadful circumstances improved with the introduction of insulin, allowing most children to reach maturity. Mortality rates fell dramatically, but microvascular and neuropathic complications appeared among 15- to 20-year survivors. Recent research has demonstrated that achievement of near-normal blood glucose levels delays onset and progression of these morbidities (1).

New treatment methods reduce chronic complications and should translate into improved long-term mortality; diabetes-related mortality during childhood also might be expected to fall in response to improved access to health care and new therapies, such as self-monitoring of blood glucose levels and more physiological insulin regimens. Population- and registry-based studies suggest that mortality among diabetic children and young adults exceeds that in the general population, both in the U.S. and other developed countries (2–6). Two studies from the U.K. indicate standardized mortality ratios of 2.3 and 5.4 among children with diabetes (7,8). A recent international study showed up to 10-fold geographic variation in mortality among individuals with youth-onset diabetes, with the lowest mortality rates in Western Europe and Canada (9). These studies do not reflect trends and some investigations that suggest improving mortality have not focused on children (4). One examination of longitudinal trends in a small region claimed that childhood mortality might even be rising (10).

We initiated the present study to assess population-wide trends in diabetes-related mortality among U.S. children because, apparently, long-term nationwide trends have not been examined previously. We compared these trends with those for childhood all-cause and infectious disease mortality. Additionally, we hypothesized that socioeconomic factors and access to tertiary-care pediatric services might influence rates of childhood diabetes mortality.

RESEARCH DESIGN AND METHODS

— We used the Compressed Mortality File (CMF) for the years 1968–1992, multiple-cause-of-death (MCOD) files for 1993–1995, and the Centers for Disease Control and Prevention (CDC) Wonder Web site for 1996–1998 (11–13). These files derive from all individual death certificates, recorded by state vital statistics agencies, validated and compiled by the National Center for Health Statistics, and aggregated on a county level. We used five age categories to represent the childhood population: 0–364 days, 1–4 years, 5–9 years, 10–14 years, and 15–19 years. The CMF includes population estimates for 1968–1992; we obtained estimates for 1993–1998 from Census Bureau files (14). Because the MCOD and CDC Wonder files exclude identifiers for deaths in counties with 100,000 people, we restricted covariate analysis to the 1968–1992 interval. Temporal changes in county definitions for Alaska, Hawaii, and Virginia led to exclusion of these states, after which 3,074 counties remained. We used the Area Resource File for examined covariates (15).

For the 1968–1978 interval, we used

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Abbreviations: CDC, Centers for Disease Control and Prevention; CMF, Compressed Mortality File; DKA, diabetic ketoacidosis; DRG, diagnosis-related group; MCOD, multiple-cause-of-death; PICU, pediatric intensive care unit.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ICD-8 code 250, and for 1979–1998 ICD-9 codes 250.0–250.3 (no childhood deaths attributable to ICD-9 codes 250.4–250.9 were recorded) to capture mortality attributable to diabetes (16,17). These mortality files provide the principal cause of death, hence the numerator for our rate calculations is the number of deaths with diabetes coded as the principal cause of death, not the total number of deaths among children with diabetes. For example, a child who died from insulin-induced hypoglycemia or from ketoacidosis would be included, whereas one with diabetes who died from motor vehicle trauma would not. All-cause mortality calculations used the same files, but included all ICD codes.

Because preliminary analysis suggested two distinct segments of mortality trends, we used piecewise linear regression to model individual segments, initially using visual inspection, then subsequently fitting each segment optimally. This approach permits identification of separate trend analyses for each time period. We also examined regression models fit using the logarithm of the mortality rate; exponentially changing curves may mimic two linear components. After reviewing the age-adjusted mortality trends, we decided to examine the relation of selected covariates to mortality for the 1979–1992 interval because these age-adjusted mortality rates remained relatively constant and the ICD codes did not change. We reasoned that mortality during the rapid decline from 1968 to 1978 might reflect mediators different from those subsequently.

We generated a binary variable to represent the reported presence of pediatric residents and/or pediatric intensive care unit (PICU) beds in each county as indexes of access to sophisticated regional medical care. Those counties without a PICU or pediatric residency were coded 0, and all other counties were coded as 1. We examined several county-level socioeconomic variables—per-capita income, median housing value, and unemployment rate—and found that the latter fit these data best. The relations among the access to care, socioeconomic variables, and mortality rates were modeled using Poisson regression. While very similar conceptually to other regression methods, such as linear (ordinary least squares) regression, the Poisson method gives more valid results during the analysis of events, with low rates or counts.

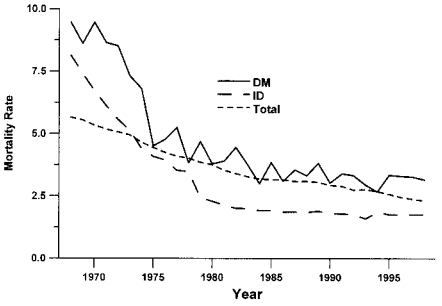

Figure 1—*Age-adjusted childhood diabetes (DM), infectious disease (ID), and all-cause (Total) mortality rates: 1968–1998 (deaths/10 million, deaths/100,000, and deaths/10,000, respectively)*

We calculated age-adjusted mortality rates using direct standardization with a 1980 U.S. population reference (18). Denominators in all age-adjusted mortality rates therefore reflect the total population, not the 0- to 19-year age-group. Linear and Poisson regression analyses were performed using the *regress* and *poisson* commands, respectively, in the Stata statistical package, Version 5 (Stata College Station, TX).

RESULTS — Between 1968 and 1984, childhood age-adjusted diabetes mortality declined more than threefold (1968–1984), from 9.5–3.0 deaths per 10 million per year (Fig. 1). Except for minor fluctuations, it remained relatively constant after 1984. Piecewise linear regression confirms this visual impression with a slope of −0.42 deaths per 10 million per year for 1968–1984 (adjusted $R^2 = 0.9$) but only −0.02 deaths per 10 million per year for 1984–1998 (adjusted $R^2 = 0.0$). From 1968 to 1998, the total number of childhood deaths attributable to diabetes declined slightly more than twofold—from 164 to 71. Approximately two-thirds of this reduction occurred among the 5- to 9-year and 10- to 14-year age-groups. Deaths among the 15- to 19-year age-group declined between 1968 and 1977 and then climbed, reaching its highest post-1977 total in 1998—only slightly below the 1968 high value for the study period (Fig. 2).

Examination of age-group–specific mortality rates revealed substantive improvement among the children younger than 15 years of age, while the 15- to 19-year age-group experienced a far more modest decline (Fig. 3). Although the risk of dying from diabetes increased with age, this difference does not adjust for the age-dependent increasing prevalence of diabetes. It therefore represents the population-wide risk of dying from diabetes, not the case-fatality ratio, or the risk of dying among children with diabetes. Children living in counties with higher unemployment rates experienced higher diabetes mortality, increasing 2.5% per 1% increase in unemployment ($P = 0.0005$; 95% CI 1.02–1.06). Counties with either a PICU or a pediatric residency program experienced a 14% lower mortality rate ($P = 0.06$).

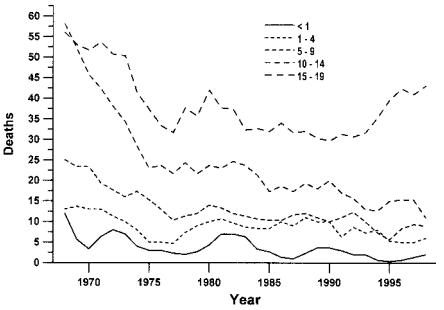

Figure 2—*Deaths attributable to diabetes, by age-group: 1968–1998. Three-year moving average.*

All-cause age-adjusted mortality fell at a relatively constant rate, declining ~2.5-fold throughout the 1968–1998 interval (Fig. 1). Younger children experienced a more rapid, threefold decline (from 21.8 deaths/1,000 to 7.2 deaths/1,000), however, compared with a nearly 40% reduction in the 15- to 19-year age-group (1.1 deaths/1,000 vs. 0.71 deaths/1,000). Total childhood deaths in the study interval fell from 126,510 in 1968 to 55,201 in 1998. The proportion of childhood deaths attributable to diabetes

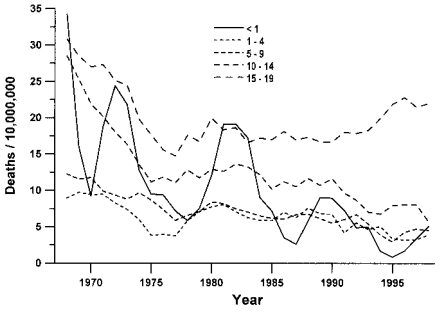

Figure 3—*Childhood diabetes mortality rates, by age-group: 1968–1998. Three-year moving average.*

remained unchanged at 0.13%, but the proportion dropped among the younger children while increasing in the oldest ones.

CONCLUSIONS — The data presented here indicate that diabetes-related mortality in children has not changed substantively since the mid-1980s. During this same time interval, all-cause age-adjusted U.S. childhood mortality rates consistently declined ~2.2% each year. The observed plateau in diabetes mortality therefore does not conform to recent historic trends in the overall rate of childhood mortality. The diabetes experience parallels infectious disease mortality, however, which declined 7% per year until 1985, then stabilized (19) (Fig. 1). Thus, the lack of further decline in mortality is not specific to diabetes. The apparent diabetes mortality plateau persisted despite the coincident introduction of major new treatment methods, including self-monitoring of blood glucose levels, more physiological insulin regimens, human insulins, and HbA_{1c} measurement.

Not surprisingly, the risk of diabetes mortality correlated strongly with unemployment, a measure of social stratification, increasing ~2.5% for each 1% increase in county-level unemployment rate. Socioeconomic factors also likely mediated observed differences in reports of ethnic disparity in mortality among diabetic children (20,21). Social stratification clearly influences the morbidity and mortality risks for a variety of diseases and has a major impact on all-cause childhood mortality (22,23). Less is known about the influence of these social factors on childhood diabetes mortality, although analyses that include patients of all ages with type 1 diabetes suggest similar effects (24). We initially examined several socioeconomic covariates, but even the application of the very stringent Bonferroni correction for multiple comparisons leaves the *P* value for the association between unemployment and mortality in a highly significant range (18).

The limitations of this study include the possibility of temporal changes in coding practices, the potential for errors in the recorded cause of death on death certificates, and the relatively small number of deaths observed, particularly in the latter portion of the study period. Although we appeared to use three separate files, each one derives from the same data sources at the National Center for Health Statistics; the observations should therefore be unaffected. The transition from ICD-8 to ICD-9 took place in 1979 and was associated with an ~22% increase in age-adjusted mortality rate—well within 1 SD for the year-to-year variability of this rate for 1968–1980 (14 ± 9.7%). It does not appear to have influenced the rate of decline, which remained fairly constant until 1985, approximately the time during which the diagnosis-related group (DRG) system was implemented. While DRGs may have changed hospital diagnostic coding practices, this type of impact should have resulted in an abrupt increase or decrease in mortality rates; explaining a decade-long plateau through this mechanism becomes problematic. As noted earlier, the all-cause mortality rates continued to fall throughout the apparent plateau in diabetes mortality, further reducing the likelihood of a coding artifact. The plot of a constantly declining rate may appear to plateau when examined on a linear axis, but demonstrates a straight-line geometry on a semilogarithmic plot. The data for the 1984–1998 segment exhibit a slope of essentially zero (no matter which mathematical transformation is chosen), substantially different from the 1968–1984 interval.

In addition to systematic changes in coding practice, errors in death certificate data entry may have influenced the validity of this study. Nondifferential misclassification of the principal variable of interest leads, in the vast majority of situations, to a reduction in effect measure–to–incidence rate ratio in the case of our covariate analysis. Death certificate coding errors would almost certainly have diluted rather than enhanced the associations with covariates that we identified (18). Therefore, the observed associations between diabetes mortality and access to care and unemployment underestimate the true strengths of these associations in some relation to the level of misclassification. Death certificate miscoding would have an uncertain impact on the calculated mortality rates, however, leading to higher or lower levels depending on whether the errors consistently under- or overreported the number of deaths in ICD categories 250.0–250.9.

Death certificate data in general provide reasonable accuracy, even when far more complex diagnoses are considered (25). We are unaware of any studies examining the validity of death certificate coding for childhood diabetes, although investigations of adult mortality suggest underreporting of diabetes as a cause of death (26,27). The alleged underreporting reflected situations such as when a death certificate listed a principal cause of death—myocardial infarction, for example—but failed to mention the presumed (but not proven) contributing factor of type 1 or type 2 diabetes. Because children die with acute, rather than chronic, complications of diabetes, we doubt that coding errors of this variety occur with any substantive frequency or that any significant alteration in mortality rates resulted.

These types of errors, even if present, have the potential to influence the observed mortality rates, but should not alter the rate trends. Therefore, for any given year, the calculated age-adjusted mortality rate may have been slightly higher or lower than the true rate, but the magnitude of this error should have been relatively small and reasonably constant from year to year. The shape of the mortality curve from 1968 through 1998 would not be changed substantively by these sorts of death certificate errors; the observed plateau almost certainly represents a valid observation.

The design of the present study, within the limitations noted above, avoids some potential difficulties of earlier investigations, which examined childhood diabetes case fatality ratios from small cohorts, or occasionally a small regional population. These types of studies, while useful, may not properly reflect population trends because the cohorts do not represent the entire population. Smaller cohort-based analyses frequently cannot examine as wide a range of covariates because of the homogeneity of their patient populations.

Investigations of type 1 diabetes deaths before age 30 or before 20 years' duration of diabetes showed that one-third to one-half died of acute complications—notably diabetic ketoacidosis (DKA) and hypoglycemia (28–30). A retrospective analysis of 55 deaths in children showed that 64% were caused by ketoacidosis (31). In another recent series of 116 deaths among children, DKA caused 69 (59%) and hypoglycemia caused 7 (7). Ketoacidosis accounted for 83% of the deaths attributable to diabetes in the latter series. A substantial fraction of deaths occurs at onset of the disease (31,32), suggesting that delayed diagnosis may contribute to excess mortality. A

recent study by Glaser et al. (33) reinforces earlier observations that deaths among hospitalized children with DKA generally result from cerebral edema. The children who died from DKA-associated cerebral edema had lower partial pressures of carbon dioxide and higher levels of serum urea nitrogen—implying, perhaps, that severity and/or chronicity of DKA influences outcome. An equally disturbing trend is the apparent recent increase in the occurrence of the "dead in bed" syndrome (4,5,32). Partly because some of these patients had histories of frequent hypoglycemia, including nocturnal episodes (32), hypoglycemia is suspected as a possible cause of the syndrome. In summary, existing reports suggest that acute complications cause most diabetes-related deaths in children—with ketoacidosis accountable for the majority.

The relation between mortality rate and sociodemographic variables, as well as measures of availability of specialized care, suggests that some of the present, apparently stable, mortality might be preventable. The recent literature on specific causes of mortality in diabetic youth also suggests that a large fraction of current deaths are related to acute diabetes complications and are therefore theoretically preventable. The demonstration by Vanelli et al. (34) that a regional education program was able to reduce the occurrence of DKA dramatically is an example that may be relevant to this problem in the U.S. In conclusion, diabetes mortality in U.S. children appeared to plateau for the period 1984–1998; further reductions in mortality may depend on overcoming the obstacles to earlier treatment of uncontrolled diabetes and/or prevention of ketoacidosis and hypoglycemia.

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