



# Excess Risk of Dying From Infectious Causes in Those With Type 1 and Type 2 Diabetes

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## OBJECTIVE

To investigate infection-related mortality in individuals with type 1 and type 2 diabetes.

## RESEARCH DESIGN AND METHODS

A total of 1,108,982 individuals with diabetes who were registered with the Australian Diabetes register between 2000 and 2010 were linked to the National Death Index. Mortality outcomes were defined as infection-related<sub>A-B</sub> death (ICD codes A99–B99), pneumonia (J12–J189), septicemia (A40 and A41), and osteomyelitis (M86).

## RESULTS

During a median follow-up of 6.7 years, there were 2,891, 2,158, 1,248, and 147 deaths from infection-related<sub>A-B</sub> causes, pneumonia, septicemia, or osteomyelitis, respectively. Crude mortality rates from infections<sub>A-B</sub> were 0.147 and 0.431 per 1,000 person-years in type 1 and type 2 diabetes, respectively. Standardized mortality ratios (SMRs) were higher in type 1 and type 2 diabetes for all outcomes after adjustment for age and sex. For infection-related<sub>A-B</sub> mortality, SMRs were 4.42 (95% CI 3.68–5.34) and 1.47 (1.42–1.53) for type 1 and type 2 diabetes ( $P < 0.001$ ), respectively. For pneumonia in type 1 diabetes, SMRs were approximately 5 and 6 in males and females, respectively, while the excess risk was ~20% for type 2 (both sexes). For septicemia, SMRs were approximately 10 and 2 for type 1 and type 2 diabetes, respectively, and similar by sex. For osteomyelitis in type 1 diabetes, SMRs were 16 and 58 in males and females, respectively, and ~3 for type 2 diabetes (both sexes).

## CONCLUSIONS

Although death owing to infection is rare, we confirm that patients with diabetes have an increased mortality from a range of infections, compared with the general population, and that the increased risk appears to be greater for type 1 than type 2 diabetes.

Individuals with type 1 and type 2 diabetes are widely considered to be more prone to infections than those without diabetes (1). Evidence to support this hypothesis can be traced back as far as 1915 when Lichty noted a range of acute infections in patients with diabetes who subsequently died (2). Several decades later, two well-cited studies showed that bacteremia and bacteriuria are more common in adult women with diabetes versus those without (1,3). The factors thought to explain the excess risk of infections in these women were microvascular complications such as

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neuropathies (3,4). Diabetes has also been associated with tuberculosis in several studies (5–8) and has been shown to be a risk factor for severe gram-positive infections (9,10), hospital-acquired post-operative infections (11,12), and urinary tract infections (3).

The underlying pathology for an increased risk of infections among people with diabetes is not fully elucidated and is probably multifactorial. However, there are some data to suggest that it could, in part, relate to a compromised immune system. Short- and long-term hyperglycemia may disturb immune functions such as neutrophil bactericidal function (13), cellular immunity (14), and complement activation (15). These defects in the immune system, along with vascular insufficiency, render patients with diabetes at higher risk for a variety of severe or invasive infections compared with those without diabetes (16). It was also shown in a previous study (with a small number of deaths) that the excess risk of infection-related deaths was only present in those with established cardiovascular disease (17). Diabetes is associated with a high prevalence of adverse prognostic factors for the outcomes of severe infections mainly because diabetes is associated with age and other comorbidities (1).

While there is a reasonably good understanding of the biological link between diabetes and infection, there are few data quantifying the excess risk of acquiring an infection or dying from infections associated with diabetes. A small retrospective cohort study from the U.S. with only 36 deaths suggested that the risk of death owing to infection is doubled in individuals with diabetes compared with those without and is largely driven by cardiovascular disease-related complications (17). Similarly, using an administrative data set from Canada, Shah and Hux (18) reported that diabetes was associated with a doubling of risk of incident infectious disease. Neither of these studies examined the relationship between diabetes and specific infections. Currently, there are limited data quantifying risk of infection by diabetes type, by age, or over time or by specific infection.

Given the potentially serious nature of infection, better information regarding the risk of infection-related death in diabetes would help define the public

health burden and enhance our understanding of the mechanisms involved. Thus, the objective of this study was to examine the excess risk of death from several infectious causes in those with type 1 and type 2 diabetes compared with the general population and to see if this excess risk differs by age and over time.

## RESEARCH DESIGN AND METHODS

### Study Population

This analysis used data from individuals registered with the National Diabetes Services Scheme (NDSS), an Australian government initiative established in 1987 to deliver diabetes-related products at subsidized prices and provide information and support services to people with diabetes. Registration of patients is free and is completed by a medical practitioner or credentialed diabetes nurse educator. The NDSS captures 80–90% of all Australians with known diabetes (19) with almost 100% coverage of type 1 diabetes and up to 90% coverage of type 2 diabetes (D.J.M., J.E.S., unpublished data).

### Definition of Diabetes

We included all individuals with type 1 diabetes or type 2 diabetes who were on the NDSS between 2000 and 2010. The year 2000 was chosen as the start date, as this followed a unification of state-based registries. Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were recorded as type 1 on the NDSS registry, were registered at <45 years of age, and were taking insulin. Registration date was used as a proxy for diagnosis date, as a large proportion of registrants (59.1% for type 1 diabetes and 36.1% for type 2 diabetes) were missing date of diagnosis, many of whom registered in the early years of the operation of NDSS and had diabetes for a number of years. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss without misclassifying significant numbers of people with type 2 diabetes as having type 1 diabetes (20). Additionally, registrants who were recorded as type 2 on the registry were diagnosed before the age of 30 years and taking insulin within 1 year of diagnosis date were reclassified as having

type 1 diabetes. All others were classified as having type 2 diabetes (20).

### Mortality Ascertainment

For ascertainment of vital status and cause of death (COD), diabetes registrants were matched to the National Death Index (NDI). The NDI was established in 1983 and has been shown to have sensitivity and specificity for the identification of death of 93.7% and 100%, respectively (21). The NDSS was linked to the NDI from the period of 1987 up to and including 31 December 2010. NDI data beyond this date were not available at the time of linkage. Linkage was performed by the Australian Institute of Health and Welfare (AIHW) using the general framework of Fellegi and Sunter (22). First name, second name, last name, sex, and date of birth were used to conduct the linkage. The record linkage methodology assigns each compared pair of records a record pair comparison weight. Based on clerical review of a sample of these links, it is expected that links with weightings of “low,” “medium,” and “high” correspond to a link accuracy (positive predictive value) of 96.75%, 98.97%, and 99.90%, respectively. For this study, we chose a medium cutoff point with a predictive value of 98.97%, as this has shown to be a reliable cutoff in other studies (23). Sensitivity analyses were also conducted using the high and low cutoffs.

Death certification in Australia follows internationally recognized death certification procedures. The COD section on the death certificate consists of two parts. Part I is for reporting the chain of events leading directly to death, with the immediate COD (the final disease, injury, or complication directly causing death) on line a and the underlying COD (the disease or injury that initiated the chain of morbid events that led directly and inevitably to death) on the lowest line. Part II is for reporting all other significant diseases, conditions, or injuries that contributed to death but which did not result in the underlying cause of death given in Part I. Text on the death certificate is coded according to ICD-10 (24).

Cause of death was initially classified according to the underlying COD codes as follows: infection-related<sub>A,B</sub>, A00–B99 (infections and parasitic disease);

pneumonia, J12–J189; septicemia, A40 and A41 (subsets of A00–B99); and osteomyelitis, M86. We excluded, from the NDSS cohort, all deaths that had an ICD-10 code anywhere on the death certificate pertaining to cystic fibrosis (E84).

In a secondary analysis, deaths with an underlying COD corresponding to “diabetes without complications” (E10.9, E11.9, E12.9, E13.9, and E14.9) where an infection-related<sub>A-B</sub> death (A00–B99) ICD-10 code also appeared on the first line of part 1 of the death certificate and was the disease or condition that led to the final death event were reclassified as an infection-related death. These recoded deaths are thought to reflect infectious disease-related death, as it is unlikely that people die of “uncomplicated diabetes” rather than that the infection occurred as a consequence of diabetes. “Uncomplicated diabetes” deaths for which a pneumonia, septicemia, or osteomyelitis code appeared in line a, part 1, of the death certificate were also recoded as being the result of the relevant infection.

**Data Analysis**

All analyses were conducted in Stata MP12, version 12.0 (StataCorp, College Station, TX). Participant characteristics were compared using Pearson  $\chi^2$  tests and Mann-Whitney *U* test for proportions and medians, respectively. A *P* value <0.05 was considered significant. For infection-related<sub>A-B</sub> mortality (primary outcome), individuals were followed from 1 January 2000, or registration date if thereafter, to 31 December 2010 or date of death—whichever occurred first. For deaths owing to septicemia, pneumonia, or osteomyelitis, individuals

were followed from 2000 to 31 December 2007 or the death date, as national data for specific infections beyond this date were not available at the time of analysis. For calculation of standardized mortality ratios (SMRs), observed deaths among registrants on the NDSS were compared with expected deaths of the same sex, 5-year age-group, and calendar year in the Australian general population. 95% CIs for SMRs were estimated using a Poisson distribution. SMRs for type 1 and type 2 diabetes were compared in Poisson models with and without the adjustment for age-group and sex. Trends of SMRs over age-group and time (year) were tested by inclusion of age-group or year as a continuous variable in the Poisson model. National mortality data were obtained from the AIHW. The Alfred Health Human Research Ethics Committee and the AIHW Human Research Ethics Committee approved this study.

**RESULTS**

**Participant Characteristics**

This study included 1,108,982 (53.6% male) registrants with type 1 diabetes (*n* = 85,144 [7.7%]) or type 2 diabetes (*n* = 1,023,838 [92.3%]), with a median follow-up of 6.7 years (11.0 for type 1 diabetes, 6.3 for type 2 diabetes) and 7,700,086 (752,298 type 1 diabetes, 6,435,718 type 2 diabetes) person-years (PY) of follow-up. The median (25th, 75th percentile) baseline age of participants registered on the NDSS between 2000 and 2010 was 58.8 years (48.9, 67.9) and 59.4 years (47.5, 69.9) in males and females, respectively. By diabetes type, the median age at baseline was 60.4 years (51.2, 69.7) and 26.9 years (14.6, 36.2), for

type 2 diabetes and type 1 diabetes, respectively.

Table 1 compares participants’ baseline characteristics by sex and diabetes type, according to vital status. In total, there were 2,891 (109 type 1 diabetes, 2,782 type 2 diabetes), 2,158 (41 type 1 diabetes, 2,117 type 2 diabetes), 1,248 (39 type 1 diabetes, 1,209 type 2 diabetes), and 147 (8 type 1 diabetes, 139 type 2 diabetes) deaths from infection-related<sub>A-B</sub> causes, pneumonia, septicemia, and osteomyelitis, respectively. Those who died of infection-related<sub>A-B</sub> or other causes were older at baseline than those who survived. Among those with type 2 diabetes, compared with death from other causes, infection-related<sub>A-B</sub> mortality was higher among those on insulin but not among those not on insulin. Crude mortality rates from infection-related<sub>A-B</sub> were 0.147 per 1,000 PY and 0.431 per 1,000 PY in type 1 diabetes and type 2 diabetes, respectively.

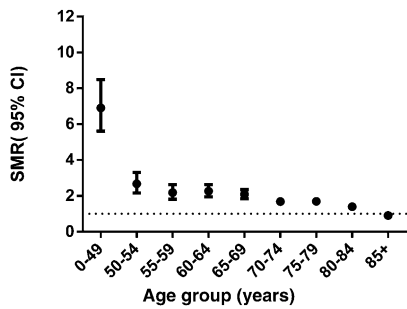
The SMR for death from infection-related<sub>A-B</sub> causes was higher in type 1 diabetes compared with type 2 diabetes (4.42 [95% CI 3.68–5.34] vs. 1.47 [1.42–1.53], *P* = 0.005). This difference remained significant after accounting for age and sex. In type 1 diabetes, females and males had a comparable risk of death from infection-related<sub>A-B</sub> (5.20 [3.77–7.18] vs. 4.11 [3.26–5.18], *P* = 0.243). In type 2 diabetes, the SMRs for death from infection-related<sub>A-B</sub> causes in males and females were also similar (1.53 [1.45–1.61] vs. 1.42 [1.36–1.50], *P* = 0.087).

Figure 1 shows SMRs for infection-related<sub>A-B</sub> deaths by age-group in type 2 diabetes. The SMRs for type 2 diabetes decreased with increasing age (*P* < 0.001).

**Table 1—Baseline characteristics of NDSS registrants according to diabetes type and vital status outcome**

	Males			Females		
	Alive	Death from other causes	Infection death	Alive	Death from other causes	Infection death
Type 1 diabetes						
<i>N</i> (%)	41,364 (8.5)	3,079 (2.9)	72 (4.5)	38,712 (9.0)	1,880 (2.3)	37 (2.9)
Age (years)	26.1 (14.3, 36.1)	39.0 (30.9, 43.4)	41.1 (35.2, 43.6)	26.1 (13.7, 34.7)	38.0 (29.6, 43.3)	38.8 (33.2, 41.6)
Type 2 diabetes						
<i>N</i> (%)	446,143 (91.5)	102,606 (95.5)	1,530 (97.1)	393,139 (91.0)	79,169 (97.1)	1,252 (97.7)
Age (years)	58.1 (49.9, 66.3)	68.9 (60.8, 76.0)	68.0 (58.9, 75.7)	58.8 (49.1, 68.1)	72.0 (63.7, 79.1)	70.8 (62.4, 78.4)
Insulin use	123,197 (27.6)	40,045 (39.0)	653 (42.7)	103,256 (26.3)	31,421 (39.7)	591 (47.2)
No insulin use	322,946 (72.4)	62,561 (61.0)	877 (57.3)	289,882 (73.4)	47,753 (60.3)	661 (52.8)

Data are median (25th, 75th percentile) or *n* (%) unless otherwise indicated. Differences across groups (within both sexes) are significant (*P* < 0.001).



**Figure 1**—SMRs and 95% CIs for infection-related<sub>A-B</sub> mortality according to age-group in type 2 diabetes.

The SMRs for infection-related<sub>A-B</sub> deaths in type 1 diabetes and type 2 diabetes combined, by age-group and sex, are shown in Supplementary Fig. 1. In general, SMRs varied between 1 and 5, with high SMRs peaking at ages 35–40 and 45–49 years for males and females, respectively, with wide CIs. The magnitude of the SMR decreased with increasing age ( $P < 0.001$ ) (Supplementary Fig. 1). Patterns were generally similar for males and females.

From 2000 to 2010, there was a 25% and 13% reduction in SMRs for type 2 diabetes in males and females, respectively. These decreasing trends over time in both sexes were significant (Supplementary Fig. 2). For type 1 diabetes, the SMRs over time were higher than type 2 diabetes, with no discernible trend from 2000 to 2010 (Supplementary Fig. 3).

After recoding relevant “uncomplicated diabetes” deaths to infection-related deaths, an extra 570 (542 type 2 diabetes and 28 type 1 diabetes) deaths among the total group were

reclassified as infection-related<sub>A-B</sub> mortality. The subsequent SMRs were as follows: 5.56 (95% CI 4.70–6.57) and 1.76 (1.70–1.82),  $P < 0.001$ , in type 1 diabetes and type 2 diabetes, respectively. In type 1 diabetes, males and females had a similar excess risk of death from infectious disease<sub>A-B</sub> (6.47 [95% CI 4.80–8.64] vs. 5.19 [4.23–6.38],  $P = 0.255$ ). In type 2 diabetes, the SMR for death from infection was significantly lower in males than in females (1.67 [1.59–1.75] vs. 1.88 [1.79 – 1.98],  $P = 0.001$ ).

The SMRs for death from pneumonia, septicemia, and osteomyelitis are shown in Table 2. For death from pneumonia, SMRs for type 1 and type 2 diabetes were 5.77 (95% CI 4.25–7.83) and 1.22 (1.17–1.27),  $P < 0.001$ , respectively. The difference between SMRs for type 1 and type 2 diabetes remained significant after accounting for age and sex. The SMRs for pneumonia death for type 1 diabetes were similarly elevated in both males and females with a five- to sixfold increase in risk compared with the general population ( $P = 0.503$ ) (males vs. females). For type 2 diabetes, the SMRs for pneumonia death were similar in males and females with an excess risk of around 20% ( $P = 0.502$ ) (males vs. females). For death from septicemia, a subset of the primary outcome, SMRs for type 1 and type 2 were 9.86 (7.20–13.50) and 1.87 (1.76–1.97),  $P < 0.001$ , respectively. The difference between the SMRs for type 1 and type 2 diabetes remained significant after accounting for age and sex. The SMRs were similar in males and females ( $P = 0.941$ ) (males vs. females). For type 2 diabetes, there

was a doubling of risk, which was similar in males and females ( $P = 0.266$ ) (males vs. females). We could only attribute ~25% of these deaths to any single initiating infection (e.g., urinary tract infection, pneumonia).

For death from osteomyelitis, SMRs for type 1 and type 2 were 29.56 (95% CI 14.71–59.1) and 3.28 (2.78–3.88),  $P < 0.001$ , respectively. The difference between the SMRs for type 1 and type 2 diabetes remained significant after accounting for age and sex. The SMRs in type 1 diabetes were high in males and extremely high in females; 16 and 58, respectively, but with wide CIs. For type 2 diabetes and osteomyelitis, SMRs for males and females were similar to each other, at ~3–4 ( $P = 0.362$ ) (males vs. females).

Among the 147 osteomyelitis deaths, 61% had a sepsis code and a further 13% had a pneumonia code as consequences of osteomyelitis on the death certificate.

Recoding of uncomplicated diabetes-related deaths to septicemia or pneumonia deaths resulted in an extra 365 and 859 deaths for septicemia and pneumonia outcomes, respectively, and thus higher SMRs were computed. For pneumonia-related deaths, in type 1 diabetes, the SMRs were 8.68 (95% CI 6.34–11.87) and 6.12 (3.75–9.99) in males and females, respectively ( $P = 0.279$ ) (males vs. females). In type 2 diabetes, the SMRs were similar in males and females (1.72 [95% CI 1.62–1.81] vs. 1.67 [1.59–1.76],  $P = 0.396$ ). SMRs for septicemia for type 1 diabetes were 15.76 (95% CI 11.47–21.66) and 12.95 (8.36–20.07) in type 1 diabetes for males and females, respectively ( $P = 0.232$ ). For

**Table 2**—SMRs (95% CI) for pneumonia-, septicemia-, and osteomyelitis-related mortality in diabetes by sex and diabetes type

	Males				Females			
	Deaths		SMR	95% CI	Deaths		SMR	95% CI
	Observed	Expected			Observed	Expected		
Type 1 diabetes								
Pneumonia	28	5	6.23	4.3–9.0	13	3	5.0	2.9–8.6
Septicemia	24	2	10.0	6.7–14.9	15	2	9.7	5.9–16.1
Osteomyelitis	3	0*	16.3	5.2–50.4	5	0*	58	24.1–139.3
Type 2 diabetes								
Pneumonia	1,128	913	1.2	1.2–1.3	989	824	1.2	1.1–1.3
Septicemia	646	356	1.8	1.7–2.0	563	291	1.9	1.8–2.1
Osteomyelitis	90	16	3.5	2.9–4.3	49	17	2.9	2.2–3.9

\*Rounded to whole number.

type 2 diabetes, the SMR was higher in females than males (2.61 [95% CI 2.43 – 2.80] vs. 2.23 [2.08–2.39],  $P = 0.002$ ). There were no deaths in the NDSS cohort with an “uncomplicated diabetes” COD and an osteomyelitis COD in line a, part 1, of the death certificate, and thus no recoding was performed for this outcome.

There were very few deaths due to tuberculosis ( $n = 24$ ), endocarditis ( $n = 69$ ), or pyelonephritis ( $n = 10$ ) in the NDSS cohort, and thus SMRs were not computed.

Sensitivity analyses using NDI cutoffs with linkage rates of 99.9% and 96.75% did not change the overall pattern of results (data not shown).

## CONCLUSIONS

In a large population-based Australian diabetes registry, individuals with diabetes had a greater risk of dying from infections compared with the general population. The excess mortality owing to infection from septicemia was five times greater in individuals with type 1 diabetes than in those with type 2 diabetes, with no evidence to suggest a greater effect among women as previously suggested. In absolute terms, however, the actual number of deaths due to infection among individuals with diabetes is very low, with some evidence to suggest a small decline in those with type 2 diabetes over the past decade.

A key strength of this analysis was the ability to look at specific types of common infection, namely, septicemia, pneumonia, and osteomyelitis, which were all associated with excess mortality in individuals with diabetes. The magnitude of the excess mortality risk for these specific types of infections was comparable with those for all infections: for example, for pneumonia-related death the SMRs were approximately 1.2 for type 2 diabetes and 5–6 for type 1 diabetes, comparable with estimates from a previous study (25). However, upon recoding deaths from “uncomplicated diabetes” (as an underlying cause but with an infection-related cause of death) to an infection-related death, the SMRs were even larger. Other studies that have explored the relationship between pneumonia death and diabetes are conflicting, with some showing a link and others not (25–29). A possible reason for the disparate results may be the use of high-risk clinic-based

samples (27), cohorts of hospitalized patients (26,29), and lack of adjustment for confounding (28).

We further explored the contributory causes of deaths for septicemia and osteomyelitis deaths. We showed that for the septicemia deaths, we could only attribute infection to a specific initiating site in ~25% of these deaths. For osteomyelitis, we found that 61% of these deaths also had a sepsis code and a further 13% also had a pneumonia code on the death certificate, implying that disseminated sepsis and pneumonia were the final paths to death in these cases.

While it is accepted that diabetes increases the risk of infection, supported mainly by *in vitro* data, analyses like these are sparse. There are several reasons why those with diabetes may be more likely to die of infectious causes. Hyperglycemia may compromise immune function (16), complement activation (14), and antioxidant systems (16). This, along with vascular insufficiency commonly observed in diabetes, increases the risk of infection (16). Furthermore, foot ulceration, due to peripheral neuropathy or peripheral arterial disease, provides a portal of entry for micro-organisms, leading to osteomyelitis.

Patients with diabetes have a higher case fatality from infections than those without diabetes (17,30), which is both due to altered host immunity and due to having a higher prevalence of comorbidities, which places them at increased risk of death. For example, in the U.S., individuals with diabetes are at increased risk of dying from infections, but this is chiefly driven by those with congestive heart failure (17).

Other studies have also shown that diabetes is associated with infection-related deaths. A study conducted in Brazil has shown a sixfold excess risk of infection-related mortality in those with type 2 diabetes compared with the general population, which is higher than what is reported here (31). In that study, the definition of infection-related death was more inclusive than was used here, which potentially may explain the discrepant findings. Secrest et al. (32), using the Allegheny County childhood-onset diabetes registry, reported a very high SMR (41) for infectious causes in individuals with type 1 diabetes over 30 years, which was attributed to the presence of micro- and microvascular

complications. It is likely that a period effect explains some of the difference in findings between Secrest and our study: the Allegheny County study recruited individuals in the 1960s and 1970s (when the management of individuals with type 1 diabetes is likely to have been less intensive than current practice) and followed them for between 28 and 43 years. In comparison, in our study the mean duration of diabetes is only 9 years and the mortality was followed from 2000 to 2010.

After recoding relevant “uncomplicated diabetes” deaths where an infectious disease code also appeared in part 1 of the death certificate, we showed that the SMRs increased in magnitude but the overall patterns by diabetes type, sex, and age were unchanged. In the calculation of SMRs for this analysis, the national population data were used without similar recoding. We believe this is justified, as the proportion of deaths this recoding relates to in the total population would be very small and thus it is unlikely to have an impact on national rates. This finding suggests that mortality risks calculated using only underlying COD may be underestimations of the true infectious-disease mortality in diabetes.

## Strengths and Limitations

The main strengths of this study are that it is population-based with a large sample size, long follow-up time, and the ability to distinguish between type 1 diabetes and type 2 diabetes. There are several limitations, however, that should be acknowledged. Firstly, the NDSS is an administrative database, and there are inherent problems with using administrative databases for research purposes (33). Namely, for our study, precise information about type of diabetes for all registrants was not available. The classification of diabetes can be challenging, and misclassification can occur. However, the proportions of type 1 diabetes to type 2 diabetes in this study (7.6% vs. 92.4%) are similar to proportions of known diabetes in Australia. Further, the proportion of individuals with type 2 diabetes who were also on insulin is consistent with other studies (34).

Other potential limitations relate to the validity of the NDSS. There are no published data on the completeness of the NDSS. However, data from the Fremantle

Diabetes Study Phase II (35), a contemporary, community-based cohort study of people with diabetes, show that 88% of 1,732 participants were registered on the NDSS (W.A. Davis, personal communication). In a pilot study from the national AusDiab study, 80, 90, and 100% of those on diet, oral medication, and insulin reported being on the NDSS, respectively (unpublished data).

It should be noted that a possible reason for increased SMRs of infection-related deaths in diabetes is diagnostic bias. Given that diabetes is associated with infection, doctors may be more likely to assign an infectious disease-related COD in someone with than without diabetes, potentially leading to an overestimation of the association. However, since severe infection is usually associated with typical clinical and laboratory findings, the influence of this bias is likely to be small.

While we were able to examine many infectious causes of death, we were limited by the availability of general population data. Further, in our data set, some causes of infectious death were not so common, such as death from endocarditis or tuberculosis. Furthermore, our classification of pneumonia did not include pneumonia death due to influenza, as the national data do not include these codes in the classification. It is likely that this omission did not affect the results, since only six deaths due to influenza pneumonia were present in our cohort.

Our findings are limited by a lack of covariates in the data set such as smoking and body size, which may explain some of the excess risk of death from infections. While the prevalence of community-acquired pneumonia is higher in smokers, those with diabetes generally have a lower prevalence of smoking. In terms of obesity, increased body mass was not shown to have an effect on infection-related mortality in U.S. diabetes patients (17). Thus, we argue that the lack of some of these variables (at least smoking and BMI) would not materially influence the associations that we report.

Further, the lack of HbA<sub>1c</sub> and other markers of diabetes care may make extrapolation of our data to other populations difficult. However, standards of diabetes care in Australia are not too dissimilar to those seen in other

developed countries. For example, the proportions of adults with diabetes in Australia who were not meeting HbA<sub>1c</sub>, blood pressure, and lipid treatment goals were similar to, or a little better than, those in the U.S. (36,37).

Other limitations relate to sample size. Even though we have a large population, upon stratification by sex and diabetes type, the number of deaths became small and resulted in large CIs and uncertainty in some of the SMRs.

### Summary

This prospective study of more than one million people with diabetes provides evidence that individuals with type 1 and type 2 diabetes are more likely to die of infection-related death, in particular death due to pneumonia, septicemia, and osteomyelitis, compared with the general population. These data show that infection in those with diabetes is an important cause of mortality. Research should focus on understanding the risk of developing severe infections in people with diabetes, the case fatality rate, and management strategies that reduce both the incidence and the case fatality rate.

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