Unnatural Deaths in a National Cohort of People Diagnosed With Diabetes

DOI: 10.2337/dc14-0005

OBJECTIVE
To examine risk of unnatural death among people diagnosed with diabetes irrespective of disease type.

RESEARCH DESIGN AND METHODS
We conducted a matched cohort study of the entire Swedish population using interlinked national registers. From the National Diabetes Register we identified 252,191 people diagnosed with diabetes (type 1 or 2) during 1996–2009. Each cohort member was matched for age, sex, and county of birth to five unaffected individuals randomly sampled from the Total Population Register. Mortality was examined with complete ascertainment, and risk ratios RRs for all unnatural deaths and for specific causes (suicide, accident, homicide, and iatrogenic effects) were estimated using conditional fixed-effects Poisson regression.

RESULTS
Risk of any unnatural death was elevated versus the general population: 77.3 versus 32.1 per 10,000 (RR 2.2 [95% CI 2.1–2.4]), and these deaths occurred at a younger age in the diabetes cohort. Risk was increased for suicide (RR 3.4 [95% CI 3.0–3.8]), accident (RR 2.0 [95% CI 1.9–2.1]), homicide (RR 3.1 [95% CI 1.6–6.1]), and iatrogenic effects (RR 2.4 [95% CI 1.9–3.2]). It was greatly elevated for fatal poisoning from a variety of agents, including psychotropic drugs and “other and unspecified medication,” as well as narcotics, alcohol, and carbon monoxide. Almost 9% of all fatal poisoning cases in the diabetes cohort were identified as overdoses of insulin or oral hypoglycemic drugs.

CONCLUSIONS
Various causes of unnatural death, in particular deliberate and accidental poisonings, occur more frequently among diabetic patients. Before preventive strategies can be implemented, a deeper understanding of the risk factors and causal mechanisms explaining the marked elevations in risk is needed.

Diabetes is a severe and enduring progressive disease with a high and increasing prevalence. The World Health Organization estimates an increase in the worldwide prevalence of type 1 or 2 diabetes from 2.8% to 4.4% between 2000 and 2030 (1). The Centers for Disease Control and Prevention predicts that one in three U.S. adults could have the disease by 2050 should current trends continue (2). Much of this increase is attributable to non-insulin-dependent type 2 diabetes, caused by sharp rises in the prevalence of obesity in many countries (3). Diabetes has been linked with serious and debilitating metabolic (4), neurologic (5), renal (6), ophthalmic (7),
and circulatory complications (8), as well as with lower-limb amputation (9) and comorbid mental illness (10). It is, therefore, unsurprising that premature death occurs more frequently in this population (11–16).

Research into mortality risk in diabetes has focused on natural deaths because of their higher incidence. Thus, little is known about the risk of unnatural death, although a Swedish study showed that around two-thirds of premature deaths among diabetic patients diagnosed at a younger age were associated with social or mental dysfunction or substance misuse (15). Some studies have reported moderate elevations in risk for any type of unnatural death (11), suicide (12–15), and accidental death (12,13). Larger relative risks of three to four have been reported for suicide attempts and suicidal ideation (17). Much of the evidence for these adverse outcomes relates to childhood-onset (type 1) diabetes (14–17). Unnatural death among all people diagnosed with diabetes requires more thorough examination because type 2 diabetes predominates, accounting for approximately 90–95% of all diabetes cases in the U.S. population (2).

Comprehensive epidemiologic studies have not yet been conducted across the full range of unnatural causes of death in a population-based cohort of all people diagnosed with both types of diabetes, and these are needed to inform preventive initiatives. We estimated risk across broad categories of unnatural death (suicide, accident, homicide, iatrogenic effects) and conducted a detailed examination of more precise causes of death, focusing particularly on deliberate and accidental poisoning. We hypothesized elevated risk among diabetic patients versus the general population for each unnatural cause. We examined the distribution of age at death from unnatural causes and stratified relative risk among those first registered with a diabetes diagnosis at an age younger than 40 years versus those older than 40 years, as a proxy measure for type 1 versus type 2 disease. We acknowledge that some of the patients in the younger age category may not have type 1 diabetes, especially those aged 30–39 years at registration. However, we felt that a time lag between disease onset, diagnosis, and registration might exist in some cases, so we selected <40 years of age as the cutoff to maximize sensitivity in delineating the type 1 group. We also investigated the frequency of fatal insulin poisonings (18) in the diabetes cohort per se and categorized them by specific cause: deliberate self-poisoning, accidental poisoning, or poisoning of unknown intent. Prescribed insulin is necessary for many people diagnosed with diabetes, and this group of patients therefore has continual access to a potentially lethal substance. Assuming that we would indeed observe increased risk of unnatural death among diabetic patients, we wished to establish how much of the excess risk could be attributed to this readily accessible means.

**RESEARCH DESIGN AND METHODS**

**Interlinking Multiple National Registers**

After gaining the necessary ethical and data protection approvals from the relevant Swedish authorities, we extracted data from the following national administrative registers:

- National Diabetes Register, Västra Götaland Regional Register Centre, Gothenburg
- National Patient Register, National Board of Health and Welfare
- Cause of Death Register, National Board of Health and Welfare
- Migration Register, Statistics Sweden
- Total Population Register, Statistics Sweden

These sources were interlinked with almost total completeness using the unique civil registration number that is assigned to each Swedish citizen.

**Ascertaining Diabetes Cases**

The cohort consisted of 252,191 individuals who had been registered between 1 January 1996 and 31 December 2009 and diagnosed with diabetes according to the National Diabetes Register. This was set up in 1996 as a response to recently implemented European-wide and national initiatives to monitor quality of care (19). Its purpose was to capture all diabetes diagnoses in the population, including disease types 1 and 2, and across primary and secondary treatment settings. Cases of diabetes were reported to the National Diabetes Register by the patient’s physician following first diagnosis. If the initial diagnosis was made during a hospital consultation or treatment episode, the primary care physician would routinely be informed of it. Registration is not mandatory, but by 2006 almost 80% of primary health care centers in the nation were reporting their cases annually (20). We used the National Patient Register to capture information on comorbid disease. This records inpatient and outpatient treatment for both somatic and psychiatric illnesses, including the few privately funded health care providers. Before 1987 not all county councils reported their data to the register, but registration has been comprehensive since it was made compulsory in that year (21). Only 1% of all hospital discharges recorded in this register have missing civil registration numbers (22). We did not consider diabetes diagnoses made in the National Patient Register unless the patient also had a diagnosis in the National Diabetes Register. Each cohort member was matched by age (birth year), sex, and county of birth to five individuals without a registered diagnosis of diabetes sampled at random from the Total Population Register. Matching on age according to calendar year of birth took account of both age and period effects by design.

**Definitions for Unnatural Causes of Death**

Deaths by specific cause were ascertained for the diabetes cohort and their matched comparison subjects until 31 December 2009. This information was obtained from the Cause of Death Register and classified according to the International Classification of Diseases, 9th revision (ICD-9), in 1996 (23) and the 10th revision (ICD-10) from 1997 onward (24). Data for this register have been collected systematically since 1952, with ascertainment of >99% since 1961 (25). To reduce false-negative misclassification (26), and consistent with most recent Swedish studies, our definition of suicide included unnatural deaths of undetermined cause. Supplementary Table 1 outlines the standard ICD-10 coding ranges that we used to delineate specific causes of unnatural death: suicide, accident, homicide, and iatrogenic effects. The latter category included adverse reactions to prescribed medication.
and complications induced by surgery or other procedures. More than 90% of these deaths in both the diabetes cohort and general population group were health care interventions other than prescribed medication. A small number of unnatural deaths (n = 3 in the diabetes cohort; n = 6 in the comparison group) were classified by cause during 1996 using ICD-9 codes. These were assigned to their appropriate ICD-10 categories.

Covariates
From the National Patient Register we identified the following comorbid physical and mental illness diagnoses: ischemic heart disease (ICD-9 codes 410, 411 B; ICD-10 codes I20-I22); stroke (ICD-9 codes 430–436; ICD-10 codes I60-I64); psychotic disorders (ICD-9 codes 291–292, 295, 296x, 297, 298; ICD-10 codes F20-F25, F28-F29, F32.3, x.5 in F10–F19); affective disorders (ICD-9 codes 296A, 296B-296E, 296W, 300E, 311; ICD-10 codes F30-F39 [excluding 32.3]); anxiety disorders (ICD-9 codes 300 [excluding 300E], 307B, 307F; ICD-10 codes F40-F42, F44-F45, F48, F50); alcohol and drug misuse disorders (ICD-9 codes 303, 304, 305A, 305x; ICD-10 codes F10 [excluding F10.5], F11–F19 [excluding x.5]); and all psychiatric diagnoses (ICD-9 codes 290–319; ICD-10 codes F00-F99).

From the Total Population Register we extracted variables denoting county of birth and point of exit from the educational system. The latter was a seven-item categorical variable ranging from lower secondary school (with <9 years of education completed) to doctoral-level study. This variable was missing for 3.5% of the diabetes cohort and 4.1% of the general population group. We applied a missing data code to these subjects to enable their inclusion in the multiple regression models.

Statistical Analyses
Analyses were conducted using Stata software version 12 (StataCorp LP, College Station, TX). We estimated the absolute risk for any unnatural death and for specific causes per 10,000 and the risk ratio (RR) and its 95% CI for the diabetes cohort versus the age- and sex-matched general population comparison group. These effects were generated using univariate and multiple conditional fixed-effects Poisson regression, an approach recommended for analyzing matched cohort data (27); the matching variables were adjusted for as covariates (28). These models were fitted at the level of the individual person, that is, exposure status, covariates, and outcome events all were measured at the individual level. We did not calculate person-years as a risk denominator in this matched cohort study because equal follow-up times are assumed in this design. Therefore risks for cause-specific unnatural death were calculated per 10,000 people. We also calculated the excess risk (i.e., risk difference) between the two populations. We fitted interaction terms to assess differences between sex-specific RRs, and we formally applied standard Pearson χ² tests to test these interactions. We assessed variation by age of death between groups using the non-parametric Mann-Whitney U test. In the analysis of large cohorts, even small relative and excess risk can be statistically significant. Therefore we carefully considered the precision of the observed relative risk estimates, the absolute risks, and the number of cause-specific mortality events in the diabetes cohort when cautiously interpreting our findings.

RESULTS
Descriptive Profile of the Diabetes Cohort versus the General Population
More than half of the diabetes cohort was male (n = 139,668, 55.4%), and the median age at registration in the National Diabetes Register was 69.3 years (interquartile range, 59.2–78.7). Table 1 presents information on the demographics and prevalence of comorbidities in the diabetes cohort versus the general population. All characteristics examined were more prevalent in the diabetes cohort (P < 0.001). The greatest percentage differences in prevalence between the diabetes cohort and general population were for ischemic heart disease, stroke, mental illness treated in secondary care, and educational level attained.

RRs for Specific Causes of Unnatural Death
The effect estimates are presented in Table 2. Risk of any unnatural death was increased compared with the general population: 77.3 vs. 32.1 per 10,000 (RR 2.2 [95% CI 2.1–2.4]; excess risk 45.2 per 10,000). Relative risk for suicide (RR 3.4 [95% CI 3.0–3.8]) was substantially greater than for accidental death (RR 2.0 [95% CI 1.9–2.1]), whereas the excess risk was larger for accidental death (28.6 per 10,000) than for suicide (14.0 per 10,000). We assessed effect modification by sex for the two most commonly occurring causes of unnatural death. The male RR was significantly greater with accidental death [men: RR 2.2 [95% CI 2.0–2.4]; women: RR 1.7 [95% CI 1.5–1.9]; P < 0.001, interaction test], but there was no evidence of effect modification by sex with suicide (P = 0.34, interaction test). We examined broad categories of suicide method and mode of accidental death. The most marked risk elevations were for suicidal and accidental poisoning; transportation accidents also had a greatly increased risk. Risks for “violent suicide”

Table 1—Demographics and comorbidity in the diabetes cohort vs. the age- and sex-matched general population comparison group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetes cohort (n = 252,191)</th>
<th>General population (n = 1,260,214)</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born outside Sweden</td>
<td>37,799 (15.0)</td>
<td>180,390 (14.3)</td>
<td>0.7 (0.5–0.8)</td>
</tr>
<tr>
<td>Lower educational attainment*</td>
<td>89,739 (36.6)</td>
<td>375,195 (30.8)</td>
<td>5.8 (5.6–6.0)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>62,650 (24.8)</td>
<td>155,348 (12.3)</td>
<td>12.5 (12.3–12.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>36,618 (14.5)</td>
<td>100,988 (8.0)</td>
<td>6.5 (6.4–6.7)</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>7,139 (2.8)</td>
<td>21,825 (1.7)</td>
<td>1.1 (1.0–1.2)</td>
</tr>
<tr>
<td>Affective disorders</td>
<td>18,006 (7.1)</td>
<td>61,197 (4.9)</td>
<td>2.3 (2.2–2.4)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>11,166 (4.4)</td>
<td>38,551 (3.1)</td>
<td>1.4 (1.3–1.5)</td>
</tr>
<tr>
<td>Alcohol/drug disorders</td>
<td>14,258 (5.7)</td>
<td>42,603 (3.4)</td>
<td>2.3 (2.2–2.4)</td>
</tr>
<tr>
<td>Any mental illness</td>
<td>50,057 (19.8)</td>
<td>179,381 (14.2)</td>
<td>5.6 (5.4–5.8)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified. *Lower level of educational attainment was defined as leaving the education system during lower secondary school, with <9 years of education completed.
(i.e., methods other than self-poisoning), accidental fall, and “other and unspecified accident” were higher in the diabetes cohort than in the general population but with much smaller RRs compared with the aforementioned categories. Risks of homicide and fatal iatrogenic effects also were significantly increased.

Figure 1 illustrates relative risk for suicide and accidental death, adjusted for hospital-treated mental illness and alcohol- or drug-related disorder, educational level attained, and being an immigrant. These adjustments did not greatly attenuate the RRs for either cause, although the apparent confounding effect was considerably greater for suicide, with mental illness having the strongest influence. The multiple regression models indicated an almost threefold independent elevation in suicide risk and an independent doubling of risk for accidental death.

We examined age at registration in the National Diabetes Register (i.e., age, sex, and county of birth) as a proxy for type 1 versus type 2 diabetes. A minority of all the cases (15,127 of 252,191 [6.0%]) were registered at an age younger than 40 years. We fitted statistical interaction terms for the two most common cause-specific mortality outcomes: suicide and accidental death. For both causes there was a much greater relative risk of death among the patients registered with a diabetes diagnosis at an age younger than 40 years. These results are tabulated in Supplementary Table 2.

### Distribution of Age at Death by Cause

The median age (64 years) of patients with diabetes who died by suicide was

### Table 2—RRs for unnatural death by cause in the diabetes cohort vs. the general population

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Diabetes cohort (n = 252,191)</th>
<th>General population (n = 1,260,214)</th>
<th>Excess risk (per 10,000)</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All unnatural causes</td>
<td>1,949 (77.3)</td>
<td>4,046 (32.1)</td>
<td>45.2</td>
<td>2.23 (2.12–2.36)</td>
</tr>
<tr>
<td>Suicide</td>
<td>482 (19.1)</td>
<td>644 (5.1)</td>
<td>14.0</td>
<td>3.36 (2.99–3.79)</td>
</tr>
<tr>
<td>Deliberate self-poisoning</td>
<td>187 (7.4)</td>
<td>146 (1.2)</td>
<td>6.3</td>
<td>5.77 (4.65–7.18)</td>
</tr>
<tr>
<td>Violent method†</td>
<td>295 (11.7)</td>
<td>498 (4.0)</td>
<td>7.7</td>
<td>2.66 (2.30–3.07)</td>
</tr>
<tr>
<td>Accident</td>
<td>1,366 (54.2)</td>
<td>3,216 (25.5)</td>
<td>28.6</td>
<td>1.98 (1.86–2.11)</td>
</tr>
<tr>
<td>Accidental poisoning</td>
<td>80 (3.2)</td>
<td>95 (0.8)</td>
<td>2.4</td>
<td>3.82 (2.83–5.15)</td>
</tr>
<tr>
<td>Transportation accident</td>
<td>179 (7.1)</td>
<td>219 (1.7)</td>
<td>5.4</td>
<td>3.73 (3.06–4.55)</td>
</tr>
<tr>
<td>Accidental fall</td>
<td>472 (18.7)</td>
<td>1,005 (8.0)</td>
<td>10.7</td>
<td>2.16 (1.94–2.42)</td>
</tr>
<tr>
<td>Other or unspecified accident</td>
<td>635 (25.2)</td>
<td>1,897 (15.1)</td>
<td>10.1</td>
<td>1.59 (1.45–1.74)</td>
</tr>
<tr>
<td>Homicide</td>
<td>14 (0.6)</td>
<td>20 (0.2)</td>
<td>0.4</td>
<td>3.08 (1.55–6.11)</td>
</tr>
<tr>
<td>Iatrogenic effects</td>
<td>87 (3.4)</td>
<td>166 (1.3)</td>
<td>2.1</td>
<td>2.44 (1.88–3.17)</td>
</tr>
</tbody>
</table>

*Rrs are adjusted for the matching variables: age, sex, and county of birth. †Violent suicide includes any method other than self-poisoning. In both the diabetes cohort and the general population, the most common violent methods were (in descending rank order) hanging, suffocation, and strangulation; shooting; drowning; and jumping from a height.

### Figure 1—RRs and 95% CIs for suicide and accidental death adjusted for mental illness treated with secondary care and sociodemographics

The RRs presented here were estimated via conditional fixed-effects Poisson regression, comparing risk of cause-specific mortality in the diabetes cohort versus the age- and sex-matched general population comparison group. Adjustment for mental illness included all psychiatric episodes treated at secondary care level (including alcohol/drug misuse disorders); adjustment for sociodemographics included county of birth and educational level attained.
RRs by Type of Poisoning Agent

The large RRs observed for deliberate and accidental poisoning prompted us to examine risk by specific poisoning agent. To maximize precision and to preclude reporting small numbers of event, we combined all poisonings, irrespective of whether the fatal episode was deemed to be suicidal or accidental. Significant elevations in risk were observed for each agent except analgesics, antipyretics, and antirheumatics (Table 3). For alcohol, psychotropic medication, and narcotic drugs, risks were three to five times higher among the diabetic patients than in the general population, and the elevation in risk was even greater for carbon monoxide and other gases and for “ unspecified drugs and medication.” A much larger proportion of all fatal poisonings in the diabetes cohort were classified in this miscellaneous category (105 of 267, 39.3%) versus the general population (57 of 241, 23.7%; P < 0.001). People registered with a diabetes diagnosis at an age younger than 40 years were overrepresented among these cases of poisoning by unspecified drugs or medication (19 of 105, 18.1%). We did not present relative risk for all other poisonings in the table because there was only one such death in the general population; risk was, however, significantly higher in the diabetes cohort (P < 0.001).

In Supplementary Table 3 we report relative risk for poisoning from unspecified drugs and medication by postmortem verdict: definite suicide, accidental death, or undetermined intent. Risk was markedly increased for all three verdicts, but especially so for definite suicide. In addition to the single ICD code denoting the underlying cause of death, we also examined all the contributory causes among the 105 cases of poisoning by unspecified drugs and medication in the diabetes cohort. Of the 64 definite suicide verdicts in this category, 19 (30%) were poisonings with insulin or oral hypoglycemic drugs (ICD-10 code T38.3). Among the unspecified drugs and medication cases, insulin or oral hypoglycemic drug poisonings were much less common for the other two postmortem verdicts: accidental death (3 of 21) and undetermined intent (1 of 20). Thus, 8.6% (23 of 267) of all the fatal poisonings in the diabetes cohort were identified as being overdoses with medication of this sort.

CONCLUSIONS
Summary of Main Findings

We report findings from the first comprehensive national epidemiologic study of unnatural death in diabetes. These deaths occurred more frequently and at a younger age than in the general population. Especially high relative risk was observed among members of the diabetes cohort who were registered with the disease at an age younger than 40 years, which we considered a useful proxy for type 1 versus type 2 disease. We observed a more than doubled risk for any unnatural death: 0.77% in the diabetes cohort versus 0.32% in the general population. Risk also was increased for each broad cause examined: suicide, accident, homicide, and iatrogenic effects. These strong associations persisted after adjusting for mental illness and educational level. Detailed cause-specific analyses revealed that risk of fatal poisoning was greatly increased across multiple pathways, including by psychotropic drugs, narcotics, alcohol, and carbon monoxide. The highest RR and number of deaths observed was for unspecified drugs and medication, and a sizeable proportion of these cases were overdoses with insulin or oral hypoglycemic drugs. The relative risk for death by transportation accident was also high.

Interpretation

Compared with previously published evidence (11–16), we found larger and more precise RRs for unnatural mortality across a broader range of specific causes. Our findings indicate that people with diabetes are particularly prone to dying deliberately or accidentally by poisoning using a range of agents, including medication prescribed for comorbid somatic and psychiatric illnesses as well as for diabetes (including insulin), illegal or illicitly taken drugs, alcohol, and car exhaust fumes. The highly

Table 3—RRs for deliberate or accidental fatal self-poisoning by specific type of agent

<table>
<thead>
<tr>
<th>Poisoning agent</th>
<th>Diabetes cohort (n = 252,191)</th>
<th>General population (n = 1,260,214)</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics, antipyretics, and antirheumatics</td>
<td>7</td>
<td>15</td>
<td>1.91 (0.76–4.76)</td>
</tr>
<tr>
<td>Psychotropic medication</td>
<td>60</td>
<td>70</td>
<td>3.88 (2.74–5.48)</td>
</tr>
<tr>
<td>Narcotic drugs</td>
<td>24</td>
<td>23</td>
<td>4.64 (2.61–8.24)</td>
</tr>
<tr>
<td>Unspecified drugs and medication</td>
<td>105</td>
<td>57</td>
<td>8.33 (6.03–11.51)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>46</td>
<td>61</td>
<td>3.40 (2.31–5.00)</td>
</tr>
<tr>
<td>Carbon monoxide and other gases</td>
<td>18</td>
<td>12</td>
<td>6.63 (3.18–13.79)</td>
</tr>
<tr>
<td>All other poisonings†</td>
<td>5</td>
<td>1</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*RRs were adjusted for the matching variables: age, sex, and birth county. †Includes solvents, pesticides, and other drugs acting on the autonomic nervous system. Please note that relative risk is not presented for this category because there was only one such death in the general population; risk was, however, significantly higher in the diabetes cohort (P < 0.001).
increased risks across multiple forms of fatal poisoning, regardless of whether a verdict of suicide or accident was returned, presents a major challenge for developing effective preventive approaches.

The generalizability of these findings from the Swedish national population should be considered. Recent estimates suggest that the prevalence of diabetes in Sweden (6.4%) is broadly similar to that in several other European nations, including France (7.5%), the Netherlands (7.5%), the U.K. (6.6%), and Belgium (6.4%) (29). Sweden does, however, have a relatively low prevalence of diabetes compared with the U.S., (10.9%) and some other nations such as Germany (11.9%), Mexico (11.8%), Spain (10.8%), Canada (10.2%), Australia (10.0%), and the Russian Federation (10.0%) (29). Thus, our findings may not generalize completely to these countries with a higher prevalence of diabetes. Comparison between national rates of unnatural mortality is problematic because of classification differences, although international estimates generated during the early 2000s suggest that Sweden and the U.S. have national suicide rates that are not markedly different (13.2 and 11.0 per 100,000, respectively) (30).

Our multiple regression models assumed a confounding role for mental illness and alcohol or drug misuse disorders, although theoretically these variables could also act as potential mediators acting directly on the causal pathway between being diagnosed with diabetes and unnatural death. We did not explore this possibility in part because we had no empirical basis for assuming the existence of such a causal pathway and also because the observed effect of adjusting for these factors as potential confounders was small indeed. Thus, any overadjustment incurred would have been of a trivial order of magnitude.

We specifically aimed to quantify the frequency of deliberate versus accidental fatal insulin overdoses among diabetes patients. We used ICD-10 code T38.3 to identify such cases as accurately as possible, although this code identifies other types of medication (oral hypoglycemic drugs) as well as insulin. We found that less than a tenth of all fatal poisonings—in the diabetes cohort were coded for this medication type. This could be an underestimate if T38.3 was not coded consistently and completely as a contributory cause of death. Our findings do, however, seem to confirm two things that were highlighted in a recent evidence synthesis for clinicians (31). First, they reiterate the rarity of fatal insulin poisonings. In 2005 the American Association of Poison Control Centers reported that just 0.16% of the 2.42 million inquiries they received pertained to insulin overdoses (32). Second, they indicate that the great majority of fatal insulin overdoses are suicides as opposed to accidents, consistent with a retrospective outcome study showing that 90% of 160 insulin overdoses reported to a regional poison control unit were of suicidal intent (33). Although the number of suicide cases we observed was low, representing only a small proportion of all unnatural deaths in this national cohort, careful vigilance for depressive symptoms and reported suicidal ideation is indicated. If clinicians have concerns that a patient with diabetes has become depressed or suicidal, one possibility might be to discuss the patient’s insulin medication and its potential lethality in an overdose with relatives or caregivers. Another could be to consider how administration of insulin might be supervised in these particular patients. Suicide prevention initiatives in this population will need to be broadly based, given that only 39% of all suicides were self-poisonings and that 55% of these cases did not involve insulin or other types of medication specifically used to treat diabetes.

Road traffic accidents (34) and falls among elderly people (35) are additional important concerns for patients with diabetes. The increased rate of death by transportation accident could to some extent be due to unconsciousness caused by hypoglycemia and ketoacidosis (36) or restricted vision from diabetic retinopathy (7). Less than 1% of all the unnatural deaths in the diabetes cohort were homicides; nonetheless, risk for this extremely rare outcome was significantly increased. Clearly the overwhelming majority of people diagnosed with diabetes are not at greater risk of being killed by someone else; however, it seems there may be very small high-risk subgroups with increased risk of becoming a homicide victim. We should reemphasize here that relative risk was imprecise and based on a very small number of events in this national cohort.

Strengths and Limitations

Examining this large population-based cohort of people diagnosed with both main types of diabetes provided an abundance of statistical power to examine the full range of rare unnatural causes of death. Our study cohort was not restricted to people with diabetes diagnosed and treated in secondary care. Complete linkage to national mortality records meant that we achieved near-complete follow-up details, and we could estimate relative risk versus a sex- and age-matched comparison cohort that was representatively sampled from the general population. The scale of the registry data sets enabled us to accurately match diabetes-exposed to diabetes-unexposed subjects for age according to birth year.

However, while our cohort design was ideally suited to examining multiple cause-specific mortality outcomes, it was somewhat limited as a tool for identifying the determinants of adverse outcome. We plan to conduct detailed nested case-control studies in the future to determine risk factor profiles for suicide and accidental death in diabetes. The cohort study we reported here did not consider the full array of comorbid physical illnesses and conditions that may be linked with elevated suicide risk. In addition, the National Diabetes Register did not capture all cases of the disease in the population. Thus, as mentioned earlier in Research Design and Methods, around four-fifths of primary care centers in Sweden were reporting their cases to the Register by 2006 (20). Unfortunately we do not know the characteristics of the unreported cases. However, this register provides a unique opportunity to study the great majority of diagnosed diabetes cases in a national population. A further limitation of studying administrative registers is that some potentially important risk factors and covariates may be unavailable for examination because they have not been collected in the source registers.

Finally, our analyses did not take into account competing risk for natural causes of death or unnatural causes
other than the specific one being examined. We opted not to take this approach because we had little basis for making the standard assumption of independence between competing causes of death (37), and comorbid clinical depression could be the common underlying mechanism for both natural and unnatural mortality in diabetes.

Implications
The increasing burden of diabetes worldwide and poor mental health experienced by some of these patients provide a strong rationale for examining the risk of unnatural death among people diagnosed with diabetes. Treatment has improved greatly in recent decades; multidisciplinary clinical teams now provide support to patients for multiple aspects of the condition (38). Mental health assessment and liaison psychiatry intervention (39) are indicated for diabetic patients with heightened levels of psychological distress, and those who experience mental illness must receive optimal treatment for their diabetes (40). Preventive measures should focus on restricting means of self-poisoning, especially in relation to safe prescribing and medication monitoring.

Acknowledgments. The authors are grateful to Christina Norby, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, for her work in constructing the study cohort using the interlinked national registry datasets. Funding. Support for this study was provided by Södertörn-Königska Foundation, Sweden. Duality of Interest. No potential conflicts of interest relevant to this article were reported. The funder played no role in the design or conduct of the study or in the decision to submit the manuscript for publication.

Author Contributions. R.T.W., P.L., and B.R. conceived of and designed the study. R.T.W., P.L., M.D., N.K., J.F.L., and B.R. analyzed and interpreted the data, critically revised the article, and approved the final article. R.T.W. and B.R. wrote the article. R.T.W. and P.L. provided statistical expertise. P.L. collected and assembled data and provided administrative, technical, and logistic support. M.D. and B.R. obtained funding. R.T.W. and B.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was presented orally at the European Congress of Epidemiology (EuroEpi) 2013, Aarhus, Denmark, 11–14 August 2013, and was published as an abstract in the European Journal of Epidemiology 2013;28(Suppl1):563–564. This study also was presented at the 27th World Congress of the International Association for Suicide Prevention, Oslo, Norway, 24–28 September 2013.

References
20. Adolffson ET, Rosenblad A. Reporting systems, reporting rates and completeness of data reported from primary healthcare to a Swedish quality register—the National Diabetes Register. Int J Med Inform 2011;80:663–668