Risk of Cardiovascular and All-Cause Mortality in Individuals With Diabetes Mellitus, Impaired Fasting Glucose, and Impaired Glucose Tolerance

The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab)

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Background—Diabetes mellitus increases the risk of cardiovascular disease (CVD) and all-cause mortality. The relationship between milder elevations of blood glucose and mortality is less clear. This study investigated whether impaired fasting glucose and impaired glucose tolerance, as well as diabetes mellitus, increase the risk of all-cause and CVD mortality.

Methods and Results—In 1999 to 2000, glucose tolerance status was determined in 10,428 participants of the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). After a median follow-up of 5.2 years, 298 deaths occurred (88 CVD deaths). Compared with those with normal glucose tolerance, the adjusted all-cause mortality hazard ratios (HRs) and 95% confidence intervals (CIs) for known diabetes mellitus and newly diagnosed diabetes mellitus were 2.3 (1.6 to 3.2) and 1.3 (0.9 to 2.0), respectively. The risk of death was also increased in those with impaired fasting glucose (HR 1.6, 95% CI 1.0 to 2.4) and impaired glucose tolerance (HR 1.5, 95% CI 1.1 to 2.0). Sixty-five percent of all those who died of CVD had known diabetes mellitus, newly diagnosed diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance at baseline. Known diabetes mellitus (HR 2.6, 95% CI 1.4 to 4.7) and impaired fasting glucose (HR 2.5, 95% CI 1.2 to 5.1) were independent predictors for CVD mortality after adjustment for age, sex, and other traditional CVD risk factors, but impaired glucose tolerance was not (HR 1.2, 95% CI 0.7 to 2.2).

Conclusions—This study emphasizes the strong association between abnormal glucose metabolism and mortality, and it suggests that this condition contributes to a large number of CVD deaths in the general population. CVD prevention may be warranted in people with all categories of abnormal glucose metabolism. (Circulation. 2007;116:151-157.)

Key Words: epidemiology ■ diabetes mellitus ■ mortality ■ risk factors ■ cardiovascular diseases ■ risk factors

It is well established that diabetes mellitus increases the risk of all-cause and cardiovascular disease (CVD) mortality and that this relationship is independent of traditional cardiovascular risk factors. Recognition is now growing that even nondiabetic levels of hyperglycemia, as observed in impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), may also be associated with an elevated risk of CVD and premature mortality.

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Evidence for the relationships between IFG, IGT, and all-cause and CVD mortality is primarily derived from a series of large meta-analyses, however, several reasons exist to be cautious about interpreting these findings. First, the component studies used different blood sample types (eg, whole blood and plasma) and different glucose assays. Second, some studies did not fully adjust for concomitant CVD risk factors. Third, these analyses may have limited relevance to contemporary populations, because baseline data were collected up to 20 years ago. The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) is a recently conducted national, population-based study of 11,247 adults that provides an opportunity to investigate the contribution of different categories of abnormal glucose metabolism to the risk of all-cause and CVD mortality.

Methods

Baseline measurements for the AusDiab survey were collected in 1999 to 2000 on 11,247 noninstitutionalized people aged ≥25 years.
Methods and response rates have been described previously. Briefly, people were recruited from 42 randomly selected urban and nonurban Census Collector Districts, 6 in each of the states and the Northern Territory of Australia. Of the 20,347 eligible people who completed a household interview, 11,247 (55.3%) attended a biomedical examination. Compared with nonresponders, responders to the biomedical examination were equally likely to report "ever having been told they had diabetes" (6.2% [95% confidence interval CI 5.2% to 7.1%] versus 6.4% [95% CI 5.7% to 7.1%]) but were more likely to have "suspected they had diabetes" (0.5% [95% CI 0.4% to 0.7%] versus 1.5% [95% CI 1.3% to 1.7%]).

Involving Humans, Monash University, and for matching to the NDI, the Standing Committee on Ethics in Research Committee and the Standing Committee on Ethics in Research.

whereby the Cox proportional hazards regression was used to estimate unadjusted and adjusted all-cause and CVD mortality hazard ratios (HRs) and 95% confidence intervals (CIs) for KDM, NDM, IGT, and IFG compared with NGT. Stratified analyses according to sex were conducted for all-cause mortality but not CVD mortality because of the smaller number of CVD deaths. Deaths due to non-CVD causes are a competing risk for CVD mortality, and therefore we also investigated the risk (HR and 95% CI) of non-CVD mortality for the groups with different abnormalities of glucose tolerance compared with NGT. Variables significant in univariate analysis at the 25% level were entered into the multivariate model. In addition, other variables known to be confounders were included in the model. Multicollinearity between covariates was examined by calculating the mean and individual covariate variance inflation factors. None of the individual covariate variance inflation factors were greater than 2, and the mean variance inflation factors for all covariates included in the all-cause and CVD mortality models were 1.25 and 1.22, respectively. For all-cause mortality, we controlled for age, sex, previous CVD (angina, coronary heart disease, or stroke), smoking, including (current or ex-smokers), hypertension (blood pressure ≥140/90 mm Hg or antihypertensive medication use), waist circumference, lipid-lowering medication use, and total cholesterol-high-density lipoprotein cholesterol ratio. For CVD mortality, we controlled for the same covariates, except diastolic blood pressure was included rather than hypertension because it showed a stronger relationship with CVD mortality. For non-CVD mortality, we controlled for age, sex, smoking, waist/hip ratio, and previous CVD.

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All-Cause and CVD Mortality

Over a median follow-up of 5.2 years, 298 deaths occurred (180 in males), which represents an all-cause mortality rate of 5.5 per 1000 person-years. Of those who had KDM, 11.8% had died within the follow-up period. By comparison, 6.2% who had NDM, 5.2% who had IGT, 3.9% who had IFG, and 1.7% who had NGT at baseline had died. For women, the proportions of those deceased were 9.8%, 5.6%, 4.2%, 3.2%, and 1.1%, and for men, the proportions were 13.4%, 6.9%, 6.6%, 4.3%, and 2.5% for KDM, NDM, IGT, IFG, and NGT, respectively. Figure 1 shows the unadjusted all-cause mortality HR (95% CI) for IFG, IGT, NDM, and KDM compared with NGT according to baseline age. In those aged 25 to 44 years, no deaths occurred among those with NDM or KDM, and although the risk of death was elevated in IFG and IGT,

Statistical Analysis

To test differences in means and proportions for baseline characteristics between the NGT, IFG, IGT, NDM, and KDM groups, 1-way ANOVA or Kruskal-Wallis tests and χ² analyses were used, respectively. The follow-up period for all-cause mortality was up to the date of death or December 12, 2004. Incidence of all-cause mortality and CVD mortality was plotted with one minus Kaplan-Meier failure function. Cox proportional hazards regression was used to estimate unadjusted and adjusted all-cause and CVD mortality hazard ratios (HRs) and 95% confidence intervals (CIs) for KDM, NDM, IGT, and IFG compared with NGT. Stratified analyses according to sex were conducted for all-cause mortality but not CVD mortality because of the smaller number of CVD deaths. Deaths due to non-CVD causes are a competing risk for CVD mortality, and therefore we also investigated the risk (HR and 95% CI) of non-CVD mortality for the groups with different abnormalities of glucose tolerance compared with NGT. Variables significant in univariate analysis at the 25% level were entered into the multivariate model. In addition, other variables known to be confounders were included in the model. Multicollinearity between covariates was examined by calculating the mean and individual covariate variance inflation factors. None of the individual covariate variance inflation factors were greater than 2, and the mean variance inflation factors for all covariates included in the all-cause and CVD mortality models were 1.25 and 1.22, respectively. For all-cause mortality, we controlled for age, sex, previous CVD (angina, coronary heart disease, or stroke), smoking (including current or ex-smokers), hypertension (blood pressure ≥140/90 mm Hg or antihypertensive medication use), waist circumference, lipid-lowering medication use, and total cholesterol-high-density lipoprotein cholesterol ratio. For CVD mortality, we controlled for the same covariates, except diastolic blood pressure was included rather than hypertension because it showed a stronger relationship with CVD mortality. For non-CVD mortality, we controlled for age, sex, smoking, waist/hip ratio, and previous CVD.

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the CIs were wide owing to the small number of deaths in this age group. In those aged 45 to 65 years, the risk of all-cause mortality increased steadily across the glucose tolerance categories. In people aged ≥65 years, the pattern was less consistent, but the risk of death was highest in those with KDM (HR 2.6, 95% CI 1.8 to 3.7). Similar patterns remained after adjustment for sex and previous CVD at baseline (data not shown).

Cause-specific mortality was available for 260 of the 298 deaths over a median follow-up period of 4.7 years. Eighty-eight deaths (33.8%) were due to CVD (58.0% of CVD deaths were due to coronary heart disease, 30.7% to cerebrovascular disease, and 11.4% to other CVD). Sixty-five percent (57/88) of all CVD deaths occurred in people with abnormal glucose metabolism at baseline.

The unadjusted cumulative incidence of all-cause mortality (Figure 2A) and CVD mortality (Figure 2B) for NGT, IFG, IGT, NDM, and KDM is outlined in Figure 2. Table 2 shows the adjusted HR (95% CI) for IFG, IGT, NDM, and KDM compared with NGT. The risk of total and CVD mortality was increased for all categories of abnormal glucose metabolism, although this was not significant for NDM for all-cause and CVD mortality or for IGT for CVD mortality. When stratified by sex, the risk of all-cause mortality for IFG, IGT, NDM, and KDM compared with NGT was similar for men and women (data not shown). However, because stratification by sex decreased the statistical power for the analyses, for women, only IGT (HR=1.7, 95% CI 1.1 to 2.8) and KDM (HR=2.5, 95% CI 1.4 to 4.3) and for men, only KDM (HR=2.1, 95% CI 1.3 to 3.2) remained significant predictors of all-cause mortality after controlling for other covariates.

**Noncardiovascular Mortality**

Of the 260 participants for whom cause-specific mortality data were available, 172 (66.2%) were classified as non-CVD deaths, of which 102 (59.3%) were attributed to malignant neoplasm (ICD-10 codes C00–C97). Compared with NGT, the HRs (95% CIs) for non-CVD mortality were 2.3 (1.5 to 3.6) for KDM, 1.0 (0.5 to 1.9) for NDM, 1.6 (1.1 to 2.3) for IGT, and 1.3 (0.7 to 2.3) for IFG, after adjustment for age and sex. These associations remained unchanged after the inclusion of smoking, waist:hip ratio, and previous CVD in the model.

**Discussion**

The primary findings from this large, national, population-based cohort study indicate that after adjustment for the traditional CVD risk factors, the 5-year mortality from all causes was significantly greater for KDM, IFG, and IGT than for NGT. Persons with KDM had a mortality risk that was more than 2 times greater than those with NGT, and those with IGT and IFG had a 50% to 60% greater mortality risk. The risk of CVD mortality was also significantly greater for those with KDM and IFG, but not IGT, compared with NGT. Finally, the importance of abnormal glucose metabolism to the risk of CVD mortality is supported by the present finding that 65% of all CVD deaths occurred in people with KDM, NDM, IFG, or IGT at baseline.

Experimental studies have long indicated that abnormal glucose metabolism increases the likelihood of macrovascular disease because it disrupts normal endothelial function, accelerates atherosclerotic plaque formation, and contributes to plaque rupture and subsequent thrombosis. In addition, the risk attributed to other CVD risk factors such as hypertension and dyslipidemia may be compounded by the presence of abnormal glucose metabolism.

There have been many studies that have demonstrated that diabetes mellitus is an important risk factor for both all-cause and CVD mortality. The present finding of a strong
association between KDM and mortality is consistent with these data. However, we did not find a significant association between NDM and all-cause or CVD mortality, although after adjustment for known risk factors, NDM was associated with a 30% increased risk (HR 1.3, 95% CI 0.9 to 2.0) for all-cause mortality, and an 80% increased risk (HR 1.8, 95% CI 0.9 to 3.6) for CVD mortality. This may have been due to the relatively small number of deaths among those in the NDM group (n=1100527) over the 5-year follow-up period. Even though risk is greater in those who have been diagnosed with diabetes mellitus for a longer period of time, other longer-term studies have reported that people identified with NDM are also at significantly greater risk for both all-cause and CVD mortality.8,9,20

Fewer studies have investigated the impact of IGT and IFG on all-cause and CVD mortality,2,8,20–23 with most of the evidence derived from large meta-analyses that combined results from a number of diverse populations (occupation- and population-based samples).9,10,13 The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) and DECODA (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia) meta-analyses reported that IGT, not IFG, was a strong predictor of all-cause mortality and CVD mortality. The differences between the present study data and the DECODE and DECODA analyses could reflect different study methods. The DECODE and DECODA meta-analyses compared the IFG group with people without IFG, whereas the comparison group in the present study consisted of people who had both “normal” FPG (≤6.1 mmol/L) and 2-hour PG (>7.8 mmol/L) values, which allowed better discrimination of mortality risk between those with IFG and NGT. Furthermore, these meta-analyses relied on different blood glucose samples (eg, whole blood and plasma) and analyzed the glucose measurements with different assays. This meant that glucose values obtained from whole blood had to be manipulated statistically before the results were pooled with the plasma glucose results. Consequently, this could have influenced the precision of the results reported in the studies. The AusDiab study used a single assay to analyze all plasma glucose samples, and analyses were performed in a central laboratory according to standardized criteria.

In contrast with the findings from DECODE,9 DECODA,10 and Coutinho et al13 that showed a significant positive

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**Figure 1.** Unadjusted all-cause mortality HRs (95% CIs) for IFG, IGT, NDM, and KDM compared with NGT according to baseline age groups: the AusDiab study. A, 25 to 44 years; B, 45 to 54 years; C, ≥65 years.

**Figure 2.** Unadjusted cumulative incidence of all-cause mortality (A) and CVD mortality (B) according to glucose metabolism categories: the AusDiab study.

The present study now adds to these observations. We showed that not only is IGT associated with all-cause mortality, but IFG appears also to be an independent predictor of all-cause mortality and CVD mortality. The differences between the present study data and the DECODE and DECODA analyses could reflect different study methods. The DECODE and DECODA meta-analyses compared the IFG group with people without IFG, whereas the comparison group in the present study consisted of people who had both “normal” FPG (<6.1 mmol/L) and 2-hour PG (<7.8 mmol/L) values, which allowed better discrimination of mortality risk between those with IFG and NGT. Furthermore, these meta-analyses relied on different blood glucose samples (eg, whole blood and plasma) and analyzed the glucose measurements with different assays. This meant that glucose values obtained from whole blood had to be manipulated statistically before the results were pooled with the plasma glucose results. Consequently, this could have influenced the precision of the results reported in the studies. The AusDiab study used a single assay to analyze all plasma glucose samples, and analyses were performed in a central laboratory according to standardized criteria.

In contrast with the findings from DECODE,9 DECODA,10 and Coutinho et al13 that showed a significant positive
TABLE 2. HRs (95% CIs) for All-Cause and CVD Mortality According to Categories of Abnormal Glucose Metabolism: the AusDiab Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Mortality Risk, HR (95% CI)</th>
<th>Age and Sex Adjusted</th>
<th>Multivariate Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>IFG</td>
<td>1.6 (1.0–2.5)</td>
<td>1.6 (1.0–2.4)</td>
<td></td>
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<tr>
<td>IGT</td>
<td>1.4 (1.1–2.0)</td>
<td>1.5 (1.1–2.0)</td>
<td></td>
</tr>
<tr>
<td>NDM</td>
<td>1.4 (0.9–2.1)</td>
<td>1.3 (0.9–2.0)</td>
<td></td>
</tr>
<tr>
<td>KDM</td>
<td>2.5 (1.8–3.5)</td>
<td>2.3 (1.6–3.2)</td>
<td></td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>IFG</td>
<td>2.9 (1.4–5.9)</td>
<td>2.5 (1.2–5.1)</td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>1.3 (0.7–2.3)</td>
<td>1.2 (0.7–2.2)</td>
<td></td>
</tr>
<tr>
<td>NDM</td>
<td>2.2 (1.1–4.4)</td>
<td>1.8 (0.9–3.6)</td>
<td></td>
</tr>
<tr>
<td>KDM</td>
<td>3.4 (1.9–6.0)</td>
<td>2.6 (1.4–4.7)</td>
<td></td>
</tr>
</tbody>
</table>

*For all-cause mortality, adjusted for age, sex, previously reported CVD, smoking (current or ex-smoker), hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medication), waist circumference (cm), lipid-lowering medication use, and total cholesterol:high-density lipoprotein cholesterol ratio. For CVD mortality, adjusted for age, sex, previously reported CVD, smoking (current or ex-smoker), diastolic blood pressure (mm Hg), waist circumference (cm), lipid-lowering medication use, and total cholesterol:high-density lipoprotein cholesterol ratio.

relationship between IGT and CVD mortality, we found that IGT was only a significant predictor for all-cause mortality, not for CVD mortality. This may be largely explained by our observation that IGT was significantly associated with non-CVD mortality. Although our ability to investigate the specific non-CVD causes of death was limited by inadequate sample size, it is possible to infer that in the present study cohort, IGT may increase the risk of cancer mortality, because the underlying cause for the majority (59.3%) of non-CVD deaths was attributable to malignant neoplasm. This concurs with the findings reported by other studies. Other explanations include the possibility that the effects of IGT on CVD mortality may be mediated by the clustering of hypertension, dyslipidemia, and hyperglycemia rather than by hyperglycemia per se, although the age- and sex-adjusted CVD mortality rates also were not higher in participants with IGT. Misclassification of IGT status due to a single oral glucose tolerance test may also have led to attenuation of an association of IGT and CVD mortality.

Previous data suggest that a significant proportion of the population with IFG or IGT develops diabetes mellitus. Hence, when one interprets findings from studies that have used a longer follow-up period, it is difficult to determine whether it is actually the prediabetes status (ie, IFG or IGT) or the development of diabetes mellitus among those with these disturbances of glucose metabolism that is directly associated with the risk of mortality. The increased risk of mortality for IGT and IFG after only a relatively short period of follow-up in the present study suggests that conversion to diabetes mellitus was not a major pathway to death and that IFG and IGT are genuine risk factors for mortality and not just precursors of diabetes mellitus. These findings are consistent with the presence of a continuous relationship between increasing blood glucose and increased risk of CVD and all-cause mortality.

Several studies have shown that abnormal glucose metabolism is present in approximately two thirds of patients with acute myocardial infarction or coronary artery disease. However, it is difficult to generalize some of these results to the wider community because they are derived from clinical and hospital-based populations and are subject to survivor bias. Furthermore, the cross-sectional nature of the studies limits conclusions about causality. The present study extends this previous work, because our longitudinal, population-based data showed that 65% of all CVD deaths occurred in those with diabetes mellitus, IFG, or IGT at baseline. This figure of 65% is far higher than the prevalence observed in the general population aged ≥25 years (reported to be 24%) and is also higher than the prevalence of abnormal glucose metabolism (reported to be 53%) seen in Australian adults aged ≥75 years. This suggests that the public health benefits of targeting CVD prevention toward those with “prediabetes” and diabetes mellitus would be significant.

The findings of the present study need to be considered within the context of its limitations. The differences between responders and nonresponders indicate that the cohort may not have been fully representative of Australian adults; however, these differences are unlikely to affect the strength of the relationships between glucose tolerance categories and mortality. The present study has relied on the results of a single oral glucose tolerance test to determine the participants’ glucose metabolism status, and therefore, misclassification may have occurred. The use of self-reported CVD as a covariate may also represent some measurement error; however, studies conducted in community-based populations have found self-reported myocardial infarction, stroke, and ischemic heart disease to be moderately to highly accurate in determining disease status. Furthermore, to account for CVD event measurement error, other covariates associated with CVD, such as age, sex, hypertension, lipids, lipid-lowering medication use, and waist circumference, were also included in the multivariate models. Misclassification of death status and cause of death was also possible, because these outcomes were determined through matching the cohort to the NDI, which is derived from death certificate data. However, a previous study has shown that the ascertainment of vital status and CVD deaths through the NDI is robust, with sensitivity and specificity for the identification of deaths being 93.7% and 100%, respectively, and sensitivity and specificity for CVD deaths being 92.5% and 89.6%, respectively. Inadequate statistical power as a result of the shorter follow-up period has also limited our ability to conduct further stratified analyses at this time, although it is planned that this will be explored after a longer follow-up period.

In summary, this large, contemporary, population-based cohort study provides further data on the relationship between abnormal glucose metabolism and CVD and all-cause mortality. These findings suggest that strategies to prevent premature mortality, particularly CVD death, need to be

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targeted not only to people with diabetes mellitus but also toward people with milder forms of abnormal glucose metabolism.

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Disclosures
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References
The findings from this large, national, population-based cohort study indicate that 5-year mortality from all causes is significantly greater for people with previously known diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance than for those with normal glucose tolerance. Persons with known diabetes mellitus had a mortality risk that was more than 2 times greater than for those with normal glucose tolerance, and those with impaired glucose tolerance and impaired fasting glucose had a 50% to 60% greater mortality risk, even after adjustment for age, sex, and other traditional cardiovascular disease risk factors, such as hypertension and hyperlipidemia. The risk of cardiovascular disease mortality was also significantly greater for those with known diabetes mellitus or impaired fasting glucose, but not for those with impaired glucose tolerance, compared to those with normal glucose tolerance. Furthermore, 65% of all cardiovascular disease deaths in the entire population occurred in people who had known diabetes mellitus, newly diagnosed diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance at baseline. These findings suggest that a large number of cardiovascular disease deaths occur in people with abnormal glucose metabolism and that strategies to prevent premature mortality and particularly cardiovascular disease death need to be targeted not only to people with diabetes but also to people with milder forms of abnormal glucose metabolism.
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