Subclinical States of Glucose Intolerance and Risk of Death in the U.S.

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OBJECTIVE — Although clinically evident type 2 diabetes is a well-established cause of mortality, less is known about subclinical states of glucose intolerance.

RESEARCH DESIGN AND METHODS — Data from the Second National Health and Nutrition Examination Survey Mortality Study, a prospective study of adults, were analyzed. This analysis focused on a nationally representative sample of 3,174 adults aged 30–75 years who underwent an oral glucose tolerance test at baseline (1976–1980) and who were followed up for death through 1992.

RESULTS — Using 1985 World Health Organization criteria, adults were classified as having previously diagnosed diabetes ($n = 248$), undiagnosed diabetes ($n = 183$), impaired glucose tolerance (IGT) ($n = 480$), or normal glucose tolerance ($n = 2,263$). For these groups, cumulative all-cause mortality through age 70 was 41, 34, 27, and 20%, respectively ($P < 0.001$). Compared with those with normal glucose tolerance, the multivariate adjusted RR of all-cause mortality was greatest for adults with diagnosed diabetes (RR 2.11, 95% CI 1.56–2.84), followed by those with undiagnosed diabetes (1.77, 1.13–2.75) and those with IGT (1.42, 1.08–1.87; $P < 0.001$). A similar pattern of risk was observed for cardiovascular disease mortality.

CONCLUSIONS — In the U.S., there was a gradient of mortality associated with abnormal glucose tolerance ranging from a 40% greater risk in adults with IGT to a 110% greater risk in adults with clinically evident diabetes. These associations were independent of established cardiovascular disease risk factors.

D iabetes is a well-established risk factor for cardiovascular disease mortality, contributing to >700,000 deaths in the U.S. annually (1,2). However, less is known about the relationship between mortality and subclinical states of glucose intolerance, namely impaired glucose tolerance (IGT) and undiagnosed type 2 diabetes. Whereas previous studies have generally indicated increased mortality related to these states (3–14), they have been limited by nonstandard methods of glucose tolerance assessment (4,6–8), short follow-up (7,11), small numbers of events (10,11), suboptimal classification schemes (6,8,10,13), and samples atypical of the general U.S. population (3–14). Moreover, it remains unclear whether this excess mortality is conferred by glucose intolerance per se or rather by other known cardiovascular disease risk factors that commonly accompany diabetes, i.e., high blood pressure, dyslipidemia, and obesity (15,16). Many previous studies did not evaluate the relationship between subclinical states of glucose intolerance and death independent of these potential confounding factors (4,6,8,10,12). Establishing an independent association of IGT and undiagnosed diabetes with mortality in the general population would support the idea that improved screening programs and early intervention may help reduce diabetes-related mortality in the U.S.

Therefore, we conducted a prospective study with two objectives: *1*) to compare the mortality among individuals with diagnosed type 2 diabetes, undiagnosed diabetes, and IGT with individuals with normal glucose tolerance in the general U.S. population; and *2*) to determine whether excess mortality in adults with abnormal glucose tolerance was independent of other established cardiovascular disease risk factors.

RESEARCH DESIGN AND METHODS

Data were from the Second National Health and Nutrition Survey (NHANES II) Mortality Study, a prospective cohort study that passively followed participants >30 years of age who underwent a detailed examination in the NHANES II ($n = 9,250$). NHANES II was conducted between 1976 and 1980 by the National Center for Health Statistics. A stratified multistage sample design was used to produce a representative sample of the noninstitutionalized U.S. civilian population between the ages of 6 months and 74 years (17). The survey included a physical examination, laboratory tests, and questionnaires on health- and nutrition-related topics. The response rate for adults aged 20–74 years selected for the examination was 68% (18).

Participants
Among individuals aged 30–74 years, 4,664 were selected at random and asked to undergo an oral glucose tolerance test. Individuals were excluded from analysis if they attended the afternoon examination session ($n = 14$), had a 2-h oral glucose tolerance test duration <105 min or

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>135 min ($n = 2$), had a missing 2-h blood glucose value ($n = 1,402$), or reported race as "other" (i.e., neither Caucasian nor African-American) ($n = 62$). Participants who had type 1 diabetes, defined by age of diagnosis <30 years and current insulin use ($n = 10$), were also excluded from the analysis. Thus, the final sample for this analysis included 3,174 Caucasian or African-American adults whose glucose tolerance status was known. However, participants with missing values for blood pressure, HDL, education, smoking, or physical activity were excluded from the multivariate analysis ($n = 306$).

Baseline assessments

Participants' age, sex, race, years of education (less than high school and high school or greater), and personal health characteristics were obtained by interview. Smoking status was categorized as current, past, or never. Participants were asked to rate both their recreational and nonrecreational physical activity as "much," "moderate," or "little to no activity." Responses for both types of physical activity questions were summed and recorded according to the following classification: 1 (high in either recreational or nonrecreational and moderate in the other), 2 (moderate in both), 3 (moderate in one and low in the other), and 4 (low activity in both recreational and nonrecreational activity).

Physical examination included measuring height, weight, and blood pressure. BMI was calculated as kilograms per square meter for each participant (17). A physician recorded each participant's blood pressure twice in the sitting position. The average of the two blood pressure readings for each participant was used in this study. Laboratory measures including standard blood assays for total serum cholesterol, HDLs, triglycerides, creatinine, and plasma glucose levels were obtained after participants fasted overnight for 10–16 h (17). After a fasting blood sample was taken, participants ingested 75 g glucose (17). Subsequent blood samples were taken at 120 ± 15 min postchallenge.

Definitions

Glucose tolerance was classified according to 1985 World Health Organization (WHO) criteria (17). Participants were classified as having previously diagnosed diabetes if they answered "yes" to both of the following questions: "Do you have glucose diabetes?" and "Did a doctor tell you that you had it?" ($n = 248$). Participants were classified as having undiagnosed diabetes if fasting plasma glucose was ≥140 mg/dl or if 2-h plasma glucose was ≥200 mg/dl ($n = 183$) and classified as having IGT if fasting plasma glucose was <140 mg/dl ($n = 480$) and 2-h plasma glucose was between 140 and 199 mg/dl. All other participants were classified as having normal glucose tolerance ($n = 2,263$).

Participants were defined as having cardiovascular disease at baseline if they tested positive on a modified Rose angina questionnaire (17) or answered "yes" to any of the following questions from the medical history questionnaire: "Has a doctor ever told you that you had a heart attack?" or "Have you ever had a stroke? And did a doctor tell you this?" (17).

Outcomes

Mortality status was ascertained for the years 1976–1992 by searching the National Death Index and the Social Security Administration Death Master File (19). There was no censoring in this cohort; participants not found to be deceased by 31 December 1992 were assumed to be alive. Deaths were ascribed to cardiovascular disease if any of the following conditions were coded as underlying causes of death according to the ninth revision of the International Classification of Diseases: hypertensive heart disease (402.0–402.9), ischemic heart disease (410.0–414.9), cardiac arrest (427.5), unspecified heart failure (428.9), unspecified cardiovascular disease (429.2), cerebrovascular disease (430.0–438.9), and diseases of the arteries, arterioles, and capillaries (440.0–444.9).

Analysis

All analyses were weighted to the U.S. population at the midpoint of NHANES II (1 March 1978) using SUDAAN statistical software, version 6.4 (Research Triangle Park, NC), to account for the complex survey design and to provide nationally representative estimates (18,20).

Demographic characteristics and cardiovascular disease risk factors at baseline were compared for participants with diagnosed diabetes, undiagnosed diabetes, IGT, and normal glucose tolerance using analysis of variance or Pearson's χ^2 test. All tests of significance were two-tailed. No corrections were made for multiple comparisons.

Person-years analysis. The weighted number of person-years was summed separately for each glucose tolerance group. The weighted numbers of deaths due to all causes and to cardiovascular diseases were also summed for each group. Mortality was calculated for each group using these weighted sums. The Poisson distribution was used to calculate 95% CIs.

Life-table analysis. Cumulative mortality was determined using a life-table method. For each 5-year age-group, the weighted population, based on age at death or at the end of follow-up, was calculated along with the weighted number of deaths from all-cause mortality and cardiovascular disease mortality for each glucose tolerance group. A life table was developed, and the probability of mortality based on age was then calculated. Cumulative mortality was determined for all-cause and cardiovascular disease mortality and plotted as cumulative mortality curves by glucose tolerance group. Cumulative mortality curves were compared overall and by 5-year age intervals using log-rank tests.

Proportional hazards analysis. To determine whether differences in relative hazard between glucose tolerance groups could be explained by other variables, proportional hazard models were constructed including age, sex and race, education, behavioral risk factors (physical activity and smoking), and biological risk factors (BMI, systolic blood pressure, and HDL cholesterol). When participants with baseline cardiovascular disease were excluded from the analysis, there was no change in the direction or magnitude of the results. Therefore, the analysis includes participants with baseline cardiovascular disease. There were no significant first-order interactions between the glucose tolerance state and any covariate ($P > 0.05$). Graphs of the log-log plot of the relative hazards by time showed that the assumption of proportional hazards was met. To test for trend, glucose tolerance was treated as a single ordinal variable. Furthermore, because of potentially differing effects of glucose tolerance by age, all-cause mortality analyses were repeated after stratification at age 60 years. This cut point was selected due to the

Table 1—*Baseline characteristics of 3,174 adults aged 30–74 years in the NHANES II by glucose tolerance group*

	Normal glucose tolerance	Impaired glucose tolerance	Undiagnosed diabetes	Diagnosed diabetes
n	2,263	480	183	248
Age	47.9 ± 0.3	54.3 ± 0.7	58.3 ± 1.0	58.4 ± 0.7
Women	53.2	55.6	61.6	60.2
Caucasian	92.1	90.5	87.0	85.5
Education less than high school	33.5	41.5	53.7	51.7
Physical activity				
1 (high)	22.2	18.1	14.9	10.2
2	46.4	39.5	42.6	33.2
3	21.3	29.2	28.5	29.1
4 (low)	10.0	13.3	13.9	27.5
Smoking Status				
Current	36.4	27.8	29.6	22.9
Past	26.4	29.7	26.2	36.0
Never	37.2	42.5	44.2	41.1
BMI (kg/m^2)	25.3 ± 0.1	27.8 ± 0.3	29.8 ± 0.9	27.7 ± 0.4
Diastolic blood pressure (mmHg)	78.4 ± 0.6	83.8 ± 0.9	83.9 ± 0.9	83.4 ± 1.1
Systolic blood pressure (mmHg)	125.7 ± 0.8	138.5 ± 1.7	142.0 ± 1.7	143.4 ± 2.2
Total cholesterol (mg/dl)	219 ± 1.4	231 ± 3.0	238 ± 4.0	229 ± 3.4
HDL cholesterol (mg/dl)	50.9 ± 0.6	48.5 ± 1.2	47.7 ± 1.6	46.2 ± 1.5
Triglyercides (mg/dl)	129 ± 2.2	174 ± 7.7	216 ± 20.3	196 ± 6.3
History of heart attack	3.0	6.7	9.0	12.3
Angina	4.4	6.6	10.3	9.1
Cardiovascular disease	7.8	12.4	20.8	23.8

Data are % or means ± SD. *P* < 0.05 (tests null hypothesis of homogeneity across all four glucose tolerance groups, except for diastolic blood pressure).

oversampling of adults ≥60 years of age in the NHANES II. Age-stratified models were adjusted for all of the same risk factors as the unstratified models, including continuous age. Because of the small number of cardiovascular deaths in adults <60 years of age, stratified analyses were not performed for cardiovascular outcomes.

Analysis was repeated using the 1998 WHO criteria (21). Based on this criteria, participants were classified as having diagnosed diabetes (*n* = 248); undiagnosed diabetes if fasting plasma glucose was ≥126 mg/dl or if 2-h plasma glucose was ≥200 mg/dl (*n* = 206); IGT if fasting plasma glucose was <126 mg/dl and 2-h plasma glucose was ≥200 mg/dl (*n* = 464); or impaired fasting glucose if fasting glucose was ≥110 and <126 mg/dl and 2-h glucose was <140 mg/dl (*n* = 71). Because of the small number of participants with impaired fasting glucose and the small number of deaths in the group, we combined the impaired fasting glucose and the IGT groups into an abnormal glucose tolerance group. All other participants were classified as having normal glucose tolerance (*n* = 2,185).

RESULTS

Characteristics and risk factors at baseline
Table 1 summarizes the characteristics of the cohort by glucose tolerance group at baseline. The expected trends were observed across the groups from normal glucose tolerance to diagnosed diabetes. Specifically, compared with their counterparts with normal glucose tolerance, individuals with abnormal glucose tolerance were older and more likely to be female, less educated, and sedentary. They also had a greater adiposity, a lower HDL, a higher blood pressure and triglyceride level, and a stronger history of cardiovascular disease.

Death rates
There were 737 deaths (23%) during 42,130 person-years of follow-up. The all-cause death rate per 1,000 person-years was highest for the diagnosed diabetes group (40.9%), followed by the undiagnosed diabetes group (33.2%), the IGT group (20.8%), and the normal glucose tolerance group (10.6%) (*P* < 0.001) (Table 2). A similar gradient of death rates

was observed for cardiovascular disease death.

Cumulative mortality
Likewise, the cumulative all-cause mortality was strongly associated with the glucose tolerance group (Fig. 1*A*). The cumulative all-cause mortality at age 70 years was higher in those with diagnosed diabetes (41.2%), undiagnosed diabetes (33.9%), and IGT (26.7%) compared with those with normal glucose tolerance (20.3%) (overall log-rank *P* < 0.001). Again, a similar gradient of cumulative cardiovascular disease mortality was observed across glucose tolerance groups (Fig. 1*B*).

Adjusted RRs
We constructed proportional hazards models to determine whether the excess risk of mortality associated with abnormal glucose tolerance might be explained by the presence of established cardiovascular risk factors that commonly accompany diabetes. After simultaneous adjustment for age, sex, race, education, smoking, physical activity, BMI, systolic blood pressure, and HDL cholesterol, abnormal

Table 2—*All-cause and cardiovascular disease mortality by glucose tolerance group for 3,174 adults aged 30–74 years in the NHANES II*

	Normal glucose tolerance	Impaired glucose tolerance	Undiagnosed diabetes	Diagnosed diabetes
n	2,263	480	183	248
All-cause mortality				
Deaths (*n*)	408	137	70	122
Mortality per 1,000 person-years	10.6	20.8	33.2	40.9
Age-adjusted RR	1.00	1.37	1.76	2.26
95% CI	Reference	1.05–1.79	1.17–2.66	1.78–2.87
Multivariate adjusted RR*	1.00	1.42	1.77	2.11
95% CI	Reference	1.08–1.87	1.13–2.75	1.56–2.84
Cardiovascular disease mortality				
Deaths (*n*)	159	55	32	66
Mortality per 1,000 person-years	3.8	7.2	13.2	21.3
Age-adjusted RR	1.00	1.19	1.67	2.82
95% CI	Reference	0.87–1.63	0.98–2.84	1.96–4.06
Multivariate adjusted RR*	1.00	1.15	1.54	2.62
95% CI	Reference	0.81–1.62	0.85–2.79	1.81–3.78

*Adjusted for age (continuous), sex, race (Caucasian or African-American), education (less than high school or high school or greater), smoking (current, past, or never), physical activity (1-high to 4-low), HDLs, systolic blood pressure, and BMI (all continuous).

glucose tolerance remained strongly associated with all-cause mortality. Compared with their counterparts with normal glucose tolerance, RR of mortality was 1.42 times greater in those with IGT, 1.77 times greater in those with undiagnosed diabetes, and 2.11 times greater in those with diagnosed diabetes (Table 2). A similar gradient in adjusted risk was observed for cardiovascular disease mortality, although the individual RRs for those with IGT and undiagnosed diabetes were not statistically different from those with normal glucose tolerance (Table 2).

We repeated the analysis using the 1998 WHO criteria for undiagnosed diabetes and abnormal glucose tolerance. Similar trends were observed for both all-cause mortality and cardiovascular disease mortality. The RR of death from all cause, compared with participants with normal glucose tolerance, increased from 1.45 for abnormal glucose tolerance (95% CI 1.14–1.86) to 1.64 for undiagnosed diabetes (1.10–2.45) and to 2.42 for diagnosed diabetes (1.74–3.37) ($P < 0.05$). A similar trend was seen with the RR of death from all cause, compared with participants with normal glucose tolerance for cardiovascular disease mortality. For abnormal glucose tolerance, the RR was 1.19 (0.89–1.58), and for undiagnosed diabetes, the RRs were 1.39 (0.76–2.55) and 2.91 (1.94–4.35), respectively, compared with participants with normal glucose tolerance ($P < 0.05$).

We conducted subsidiary analyses after stratification by age in light of the known relationship of abnormal glucose tolerance with age. These stratified analyses revealed an attenuated pattern of risk in individuals ≥60 vs. <60 years of age. Specifically, the RR of all-cause mortality compared with participants with normal glucose tolerance were as follows: IGT 1.68 (95% CI 0.90–3.15) for participants ≥60 years vs. 1.10 (0.85–2.73) for participants <60 years; undiagnosed diabetes 2.35 (1.02–5.49) for participants ≥60 years vs. 1.35 (0.83–2.20) for participants <60 years; and diagnosed diabetes 2.38 (0.95–6.00) for participants ≥60 years vs. 2.00 (1.46–2.73) for participants <60 years. However, this apparent attenuation of age with glucose tolerance was not statistically significant ($P = 0.24$).

CONCLUSIONS — These data suggest that in the U.S., subclinical states of glucose intolerance are associated with a 42–77% greater risk for all-cause mortality and a 15–54% greater risk for cardiovascular disease mortality. These associations are independent of established cardiovascular disease risk factors that commonly accompany abnormal glucose tolerance. Strengths of this study include a large nationally representative sample, 12–16 years of follow-up, use of standard definitions of glucose tolerance, and a specific focus on the subclinical states of

glucose intolerance that would be the object of screening programs.

Nonetheless, there were three limitations of this study. First, there was nonresponse in NHANES II at each stage of the survey. In particular, for adults aged 20–74 years, only 68.0% of the participants selected for the survey in the oral glucose tolerance test subsample completed the examination (18). Previous analysis showed that respondents and nonrespondents did not differ significantly in demographic or health-related characteristics (18,22). The respondents and nonrespondents also did not differ by mortality experience: all-cause mortality per 1,000 person-years was 17.3 (95% CI 16.1–18.7) for respondents and 18.0 for nonrespondents (16.1–20.2). Second, because mortality follow-up was passive, misclassification of vital status was possible. Previous studies indicate that deaths may be underascertained in African-Americans (19). In as far as African-Americans were overrepresented in the abnormal glucose tolerance groups, this may have produced an underestimate of the mortality risk. Finally, glucose tolerance status was only assessed at baseline, and it is likely that many participants in the IGT group developed diabetes. Recent evidence from several U.S. cohort studies suggests a conversion rate from IGT to diabetes ranging from 3.5 per 100 person-years to 5.7 per 100 person-years (23). However, only 6.7% of the IGT

A

B
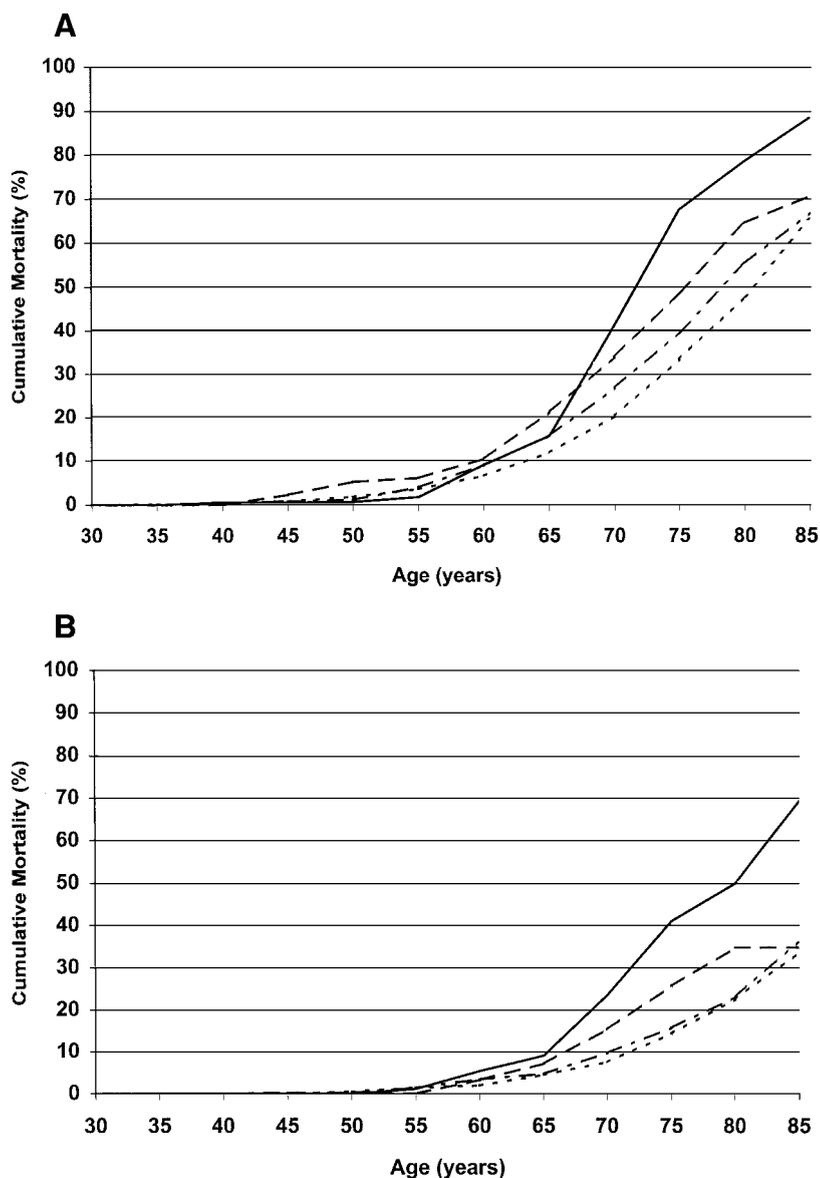
Figure 1—A) *Cumulative all-cause mortality in 3,174 adults aged 30–74 years in NHANES II by glucose tolerance group at baseline.* B) *Cumulative cardiovascular disease mortality in 3,174 adults aged 30–74 years in NHANES II by glucose tolerance group at baseline. Cumulative mortality was calculated using a life-table approach after weighting to the U.S. population in 1978. ——, mortality in adults with diagnosed diabetes at baseline; – – – –, mortality in adults with undiagnosed diabetes at baseline; – - – - –, mortality in adults with IGT at baseline; - - - -, mortality in adults with normal glucose tolerance at baseline. Overall log-rank test* $P < 0.001$.

group who died had diabetes coded on death certificates. This cannot fully explain the increased risk of mortality.

Since 1990, at least 12 epidemiological studies have related glucose tolerance to mortality (3–14); of these studies, 9 had follow-up periods >5 years (3–11,14). All nine studies showed increased risk of death among individuals with abnormal glucose tolerance, but all had important limitations. Three studies were limited to employed, primarily Caucasian, men (4,7,10). Four studies used

nonstandard glucose tolerance tests (4,6–8), the results of which cannot be directly compared with WHO standards. Although the Seven Counties Finnish Study and the Paris Prospective Study used a 75-g standard, neither evaluated individuals with undiagnosed diabetes separately; instead, individuals were pooled into a single diabetes category to compensate for small numbers of incident cases (4,10). Finally, only three studies reported >10 years of follow-up (4,8). However, all 12 studies did show a con-

sistent gradient of mortality across categories of worsening glucose intolerance. Recent studies have also shown an increased risk of death by elevated 2-h glucose levels compared with elevated fasting glucose levels (3,9,11,14). A previous study using nationally representative data from the U.S. found an increased risk of mortality for adults with type 2 diabetes, but lacked information on subclinical states (24).

Our results suggest that IGT and undiagnosed diabetes are independent pre-

dictors of all-cause and cardiovascular disease mortality. There are several possible explanations for this finding (25,26). First, the subclinical states may be markers for greater or more prolonged exposure to established cardiovascular disease risk factors (such as high blood pressure), beyond what is captured by measurements of these risk factors at a single point in time, as in this study. Second, the subclinical states may be mainly important insofar as they predict the development of clinically evident (i.e., more severe) diabetes. Finally, hyperglycemia or hyperinsulinemia may directly confer risk. Elucidation of the exact causal pathway may lead to improvements in treatment. Nonetheless, even without such information on mechanism, subclinical states appear to convey important prognostic information that would otherwise be overlooked during routine clinical assessment of adiposity, blood pressure, and lipids.

Thus, subclinical states of glucose intolerance may represent logical targets for mass screening programs aimed at reducing diabetes-related mortality in the U.S. However, identification of prognostically valuable subclinical states alone is not sufficient justification for mass screening. One must also demonstrate that treatments applied at the subclinical stage are more effective (and perhaps more cost-effective) than treatments applied after diabetes clinically manifests (27,28). Unfortunately, data on the treatment of subclinical states of glucose intolerance are sparse. The U.K. Prospective Diabetes Study (UKPDS) demonstrated that more aggressive glycemic control of adults with newly diagnosed type 2 diabetes produced reductions in microvascular complications, but these individuals had clinically manifested diabetes. In other words, UKPDS recruitment relied on physician referral of patients, not screening of asymptotic individuals (29). With regard to IGT, one small treatment trial has been completed (30), and several larger trials are currently being undertaken, including the Diabetes Prevention Program (31), but these trials are not powered to study the effects of early intervention on diabetic complications or death. Nonetheless, the main implication of our study is that improvement in the detection and treatment of undiagnosed diabetes and IGT should reduce mortality in the general U.S. population. The deter-

mination of effective treatments depends on the results of ongoing trials and advances in our understanding of the pathogenesis of cardiovascular disease and other diabetes-related complications that lead to premature death.

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