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Effects of Isolated Post-challenge Hyperglycemia on Mortality in American Indians: The Strong Heart Study

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PURPOSE: To assess the effects of isolated post-challenge hyperglycemia (IPH) on risk of cardiovascular disease (CVD), cancer, and all-cause mortality in American Indians using longitudinal data from the Strong Heart Study.

METHODS: Of 4549 American Indian women and men aged 45 to 74 years participating in the Strong Heart Study, 4304 had fasting blood measurements or oral glucose tolerance test (OGTT) data to ascertain diabetes status. At baseline and follow-up, a personal interview was conducted, and physical examinations and laboratory tests were performed. Fasting blood samples were drawn for measurement of glucose, fibrinogen, insulin, lipids, lipoproteins, creatinine, and hemoglobin A1c (HbA1c). A 75-g OGTT was performed. Five diabetes categories were defined: (i) known diabetes, (ii) newly diagnosed diabetes (fasting glucose $\geq$126 mg/dL and no history of diabetes or diabetes medication; ADA-new diabetes), (iii) IPH, (iv) impaired fasting glucose ($\geq$110 $-$ $<$126 mg/dL; IFG), and (v) normal fasting glucose ($<$110 mg/dL; NFG). Surveillance was initiated to determine CVD, cancer, and all-cause mortality over 9 years.

RESULTS: IPH had a worse CVD risk factor profile than NFG, but IPH was associated with a better CVD risk factor profile than known diabetes or ADA-new diabetes. At follow-up, individuals with IFG had no increased risk for CVD or all-cause mortality, whereas those with ADA-new or known diabetes had significantly increased risk (RR = 1.70 and 1.40 for ADA-new diabetes, and RR = 2.87 and 2.19 for known diabetes, respectively). Those with IPH had nonsignificant elevations in risk for CVD (RR = 1.54) and all-cause (RR = 1.27) mortality. Cancer mortality was not increased in those with IFG, IPH, ADA-new diabetes, or known diabetes compared to those with NFG.

CONCLUSIONS: Among American Indians 45 to 74 years of age, IPH is associated with nonsignificant elevations in total and CVD mortality. The magnitude of mortality risk associated with IPH is intermediate between diabetes and IFG. Because those with IPH are at high risk for diabetes, American Indians with IPH should be targeted for diabetes prevention.

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KEY WORDS: Diabetes Mellitus, Cardiovascular Diseases, Neoplasms, Indians, North American.

INTRODUCTION

In 1997, the American Diabetes Association (ADA) Expert Committee On the Diagnosis and Classification of Diabetes Mellitus recommended that the threshold for diagnosis of diabetes should be lowered from a fasting plasma glucose (FPG) level of 140 mg/dL to 126 mg/dL (7.8 to 7.0 mmol/L) (1, 2) and that the oral glucose tolerance test (OGTT) should no longer be used in epidemiological studies. Studies that have employed glucose tolerance testing have identified a considerable number of individuals with isolated post-challenge hyperglycemia (IPH), i.e., those who are nondiabetic by ADA criteria (FPG $<$ 126 mg/dL ($<$7.0 mmol/L)) but who have a 2-hour glucose $\geq$200 mg/dL ($\geq$11.0 mmol/L).

Epidemiological studies have reported varied prevalences of IPH in cohorts of different ages, and those studies generally showed that the prevalence of IPH increases with age (3–6). The Third National Health and Nutrition Examination Survey (NHANES III) recently showed that prevalence of both diabetes and IPH increased with age, and age-specific diabetes/IPH ratio decreased from 5.49 in the 40 to 44 age group to 0.77 in the 70 to 74 age group (6). Some studies reported that postprandial glucose levels in-

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Selected Abbreviations and Acronyms

ADA = American Diabetes Association
ANOVA = analysis of variance
BMI = body mass index
CI = confidence interval
CVD = cardiovascular disease
DBP = diastolic blood pressure
FPG = fasting plasma glucose
HR = hazard ratio
HbA1c = hemoglobin A1c
HDL = high-density lipoprotein
ICD-9 = International Classification of Diseases, Ninth Revision
IGT = impaired glucose tolerance
IPH = isolated post-challenge hyperglycemia
IHS = Indian Health Service
RR = relative risk
SAS = statistical analysis software by SAS Institute, Cary, NC
SBP = systolic blood pressure
SD = standard deviation

crease with age (approximately 0.83 mmol/L per decade) at a rate almost ten-fold greater than fasting glucose levels (0.06 to 0.11 mmol/L per decade) (7–10). It is not clear whether IPH reflects age-associated change in glucose homeostasis that is clinically insignificant, on one end of the continuum of metabolic dysfunction leading from glucose intolerance to diabetes, or whether it is a pathologic disorder whose risk for morbidity and mortality is smaller in diabetes.

It is well established that type 2 diabetes is an independent risk factor for cardiovascular disease (CVD). Individuals with diabetes, as well as those with impaired glucose tolerance (IGT), have been reported to be at increased risk of CVD and all-cause mortality (11–17). A possible link between diabetes and cancer has also been proposed for many years (18), and one recent study reported that people with IPH had higher rates of all-cause and cancer mortality than did those with diabetes diagnosed by ADA criteria (19). The purpose of this study is to assess the effects of IPH on risk of CVD, cancer, and all-cause mortality using longitudinal data from the Strong Heart Study.

RESEARCH DESIGN AND METHODS

The Strong Heart Study was initiated in 1988 to study CVD and its risk factors in American Indians. The study design, survey methods, and laboratory techniques of the study have been described elsewhere (20, 21). Briefly, the population at the time of the baseline examinations (1989 to 1992) included 4549 American Indian resident tribal members aged 45 to 74 years in three geographic areas: Arizona, Oklahoma, and South and North Dakota. Participation rates of all age-eligible tribal members were 72% in the Arizona center, 62% in the Oklahoma center, and 55% in the South/North Dakota center (22). Non-respondents did not differ significantly from respondents in age, body mass index (BMI), or frequency of self-reported diabetes. Respondents were more often female and nonsmokers and had a slightly higher self-reported frequency of hypertension and obesity than did nonrespondents (21–23). Informed consent was obtained from all participants.

The baseline clinical examination consisted of a personal interview, a physical examination, and laboratory tests. Survey methods and procedures in the follow-up examinations were similar to those used in the baseline eaminations. The personal interview assessed demographic information, education, marital status, family health history, personal medical history, and American Indian heritage. Lifestyle factors were assessed by self-report, and included current physical activity (hours of physical activity in the past week), smoking (current, former, and never), and alcohol intake (type of alcoholic beverages consumed, frequency of alcohol consumption, and average quantity consumed per day and per week). The physical examination included weight, height, and waist and hip circumferences; these measurements were taken with participants wearing light clothing and having removed their shoes. Blood pressure measurements were taken; examination of the heart, lungs, and pulses was conducted; and a 12-lead electrocardiogram was taken. Fasting blood samples were drawn in the morning after at least a 12-hour overnight fast. Fasting glucose, fibrinogen, insulin, lipids, lipoproteins, creatinine, and hemoglobin A1c (HbA1c) were measured from these samples. A 75 gram OGTT was performed on all participants, except for diabetic persons treated with insulin or oral hypoglycemic agents or participants with a fasting glucose ⩾225 mg/dL (⩾12.5 mmol/L) as determined by an Accu Check II (Baxter Healthcare Corporation, Grand Prairie, TX) (22). Laboratory methods were published previously (20, 21).

Of the 4549 Strong Heart Study participants at baseline, 245 participants either refused the OGTT or otherwise had no blood measurements available, leaving 4304 examined participants whose diabetes status could be determined. For all participants, five mutually exclusive diabetes categories were defined:

1. Known diabetes —Participant was taking insulin or a hypoglycemic agent and had two prior measurements of elevated glucose in his or her medical record, *OR* was on renal dialysis *OR* had had a kidney transplant *OR* had a FPG ⩾126 mg/dL (⩾7.0 mmol/L) or a 2-h glucose ⩾ 200mg/dL (⩾11.1 mmol/L) and a history of diabetes by questionnaire
2. ADA-new diabetes — Participant had diabetes defined by ADA criteria, i.e., a FPG ⩾126 mg/dL (⩾7.0 mmol/L) and no mention of a history of diabetes or diabetes medication by questionnaire.

3. Isolated post-challenge hyperglycemia (IPH) — Participant had a FPG <126 mg/dL (<7.0 mmol/L) and 2-h glucose ⩾ 200 mg/dL (⩾11.1 mmol/L) and no mention of a history of diabetes or diabetes medication by questionnaire
4. Impaired fasting glucose (IFG) — Participant had a FPG ⩾110 (6.1 mmol/L) and <126 mg/dL (<7.0 mmol/L)
5. Normal fasting glucose (NFG) — Participant had a FPG <110 mg/dL (<6.1 mmol/L)

From the baseline examinations conducted between 1989 and 1992, surveillance was initiated to determine CVD, cancer, and all-cause mortality until December 31, 1998. Deceased participants were identified by each field center from tribal records, Bureau of Indian Affairs, Indian Health Service (IHS) hospital, state departments of health, and/or the National Death Index. Copies of death certificates were obtained from state departments of health. Cause of death was defined as underlying cause of death and was coded by the central nosologist according to the International Classification of Diseases, Ninth Revision (ICD-9) (24). In addition to the review of death certificates, hospital records and autopsy reports, if available, were also used in the final classification of cause of death. Criteria for CVD and non-CVD death and procedures used for review and adjudication were reported previously (25).

Data were analyzed using SAS version 8.1. Differences in baseline characteristics between glucose status groups were assessed using ANOVA for each of the continuous variables, and the chi square test for categorical variables. A Cox proportional hazards model was performed to determine the relative risks (RR) for CVD, cancer, and all-cause mortality in those with IPH, ADA-new diabetes, known diabetes, and IFG compared with NFG. This method models follow-up time between baseline and either an event, death, or censoring, in relation to independent variables of interest. In the cause-specific mortality model, an individual who died from CVD at 4 years after enrollment in the study is considered censored at 4 years. The model was adjusted for age, sex, BMI, physical activity, and study center; subsequent models were adjusted for smoking status, alcohol intake status, hypertension, fasting insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. All-cause and CVD mortality cumulative hazard curves for IPH, ADA-new diabetes, known diabetes, and IFG and NFG by follow-up year were constructed after adjustment for sex and age (26). Because their distributions were skewed, insulin and triglycerides were log-transformed.

RESULTS

Baseline characteristics of the 4304 study participants are shown by glycemic status in Table 1. At baseline, 154 participants were categorized as having IPH, 362 had ADA-new diabetes, 1698 had known diabetes, 1626 had NFG, and 464 had IFG. In general, compared with their NFG counterparts, participants with ADA-new and known diabetes had worse CVD risk-factor profiles, but individuals with IPH had risk factors that were intermediate between the nondiabetic and diabetic groups. In participants with IPH, systolic blood pressure (SBP) and 2-hour plasma glucose were higher than in those with NFG. In addition, in participants with IPH, age, BMI, waist circumference, HbA1c, and triglycerides were all significantly higher than in those with NFG. Compared with those with diabetes, participants with IPH had higher HDL cholesterol and lower HbA1c.

During an average follow-up of 9 years, 888 deaths occurred. Of these, 271 (30.5%) were attributed to CVD, and 153 (17.2%) were from cancer. Compared with individuals with NFG, and after adjusting for age, sex, physical activity, BMI, and study center, individuals with IFG had no elevation in CVD or total mortality (Table 2). Participants with ADA-new and known diabetes at baseline, however, had a significantly higher risk of all-cause and CVD mortality. Cancer mortality was not increased in any of the glycemic categories compared with NFG. Additional adjustment for smoking, alcohol consumption, hypertension, insulin, total and HDL cholesterol, and triglycerides yielded no changes in these relationships. Compared with IFG, IPH had a higher RR for CVD (RR = 1.54, 95% CI 0.71–3.36) and all-cause mortality (RR = 1.27, 95% CI 0.84–1.91) but these increases were not statistically significant.

Cumulative hazard analyses illustrated the trends in all-cause and CVD mortality (Fig. 1 and Fig. 2). Nondiabetic participants had lower all-cause and CVD mortality than did participants with ADA-new or known diabetes over the 9-year follow-up period. Individuals with known diabetes at baseline had the worst survival profile. Those with IPH had a slightly lower CVD mortality rate than did nondiabetic participants during the first 5 years of follow-up; after 5 years, the rate was slightly higher than in nondiabetic participants but still lower than in those with ADA-new or known diabetes. Those with IFG had all-cause and CVD mortality trends similar to those with NFG, and no difference in cancer incidence.

CONCLUSIONS

The Strong Heart Study is a population-based study of CVD and its risk factors in American Indians. This population has a high prevalence of diabetes, which greatly increases its risk of CVD (27). Since the baseline examination, the cohort has been under continued surveillance, and medical records of all participants were reviewed to ascertain CVD events or determine cause of death.

TABLE 1. Baseline characteristics by glycemic status: The Strong Heart Study

Characteristics	NFG	IFG	IPH	ADA-new diabetes	Known diabetes
N	1626	464	154	362	1698
Age (y)	55 ± 8	56 ± 8	57 ± 9[a]	57 ± 8[a]	57 ± 8[a]
Sex (%)	55	56	57[a]	57	57[a]
Parental diabetes (%)	37	42	42	43	55[a]
Body mass index (kg/m^2)	29 ± 6	32 ± 6[a]	32 ± 6[a]	33 ± 7[a]	32 ± 6[a]
Waist circumference (cm)	100 ± 14	107 ± 14[a]	108 ± 14[a]	110 ± 14[a]	109 ±144[a]
HbA1c (%)	5.0 ± 0.6	5.3 ± 0.6[a]	5.6 ± 0.7[a,c]	6.8 ± 2.1[a]	8.9 ± 2.3[a]
Indian heritage (%)	0.8 ± 0.3	0.8 ± 0.3	0.9 ± 0.2[a]	0.9 ± 0.2[a]	0.9 ± 0.2[a]
Current smoker (%)	42	36	32	34[a]	25[a]
Current drinker (%)	49	45	40	44	33[a]
Systolic blood pressure (mmHg)	124 ± 18	126 ± 18	132 ± 19[a,b]	129 ± 17[a]	132 ± 21[a]
Diastolic blood pressure (mmHg)	76 ± 10	77 ± 10	78 ± 10	77 ± 10	77 ± 10[a]
Reported physical activity (%)	31	28[a]	20[a]	22	10[a]
High school graduate (%)	59	58	48	55	44[a]
Fasting plasma glucose (mg/dL)	97 ± 8	116 ± 5[a]	111 ± 11[a,c]	167 ± 57[a]	217 ± 80[a]
2h-plasma glucose (mg/dL)	117 ± 34	137 ± 32[a]	230 ± 28[a,b]	240 ± 103[a]	309 ± 107[a]
Insulin (μU/mL)*	11 (10–11)	16 (15–17)[a]	19 (17–21)[a,b]	22 (21–24)[a]	21 (20–22)[a]
Total cholesterol (mg/dL)	193 ± 37	194 ± 38	187 ± 36	194 ± 41	190 ± 45
HDL cholesterol (mg/dL)	48 ± 15	46 ± 13[a]	47 ± 13[c]	43 ± 11[a]	43 ± 12[a]
Triglycerides (mg/dL)*	104 (101–107)	124 (118–130)[a]	127 (117–136)[a]	139 (131–147)[a]	147 (143–151)[a]
Fibrinogen (mg/dL)	283 ± 67	285 ± 71	294 ± 75	300 ± 72[a]	329 ± 8[a]

Data are means ± SD, or %.
*Geometric mean values and 95% confidence interval.
[a]significant difference ($P < 0.05$) between IPH and NFG, new diabetes and NFG, or known diabetes and NFG.
[b]significant difference ($P < 0.05$) between IPH and IFG.
[c]significant difference ($P < 0.05$) between IPH and new diabetes.

The Strong Heart Study is an ideal population in which to study type 2 diabetes, and results obtained in this group are generalizable to the population at large. Although the Strong Heart Study population is a distinct ethnic group with unique anthropometric and metabolic characteristics, diabetes has never been shown to have unique physiology in American Indians, and the role of diabetes in CVD is similar across ethnic groups. Further, the current ADA and World Health Organization definitions of diabetes are largely based on data collected in American Indian communities. The fact that these fundamental clinical practice guidelines are based on data from American Indians indicates that these data are generalizable to other populations.

In this study, we assessed the effects of IPH and diabetes on CVD, cancer, and all-cause mortality in 4304 American Indians aged 45 to 74 years. Although participants with ADA-new diabetes by FPG and known diabetes had significantly increased risk of all-cause and CVD mortality, those with IPH had a small and nonsignificant increase in risk of all-cause or CVD mortality.

TABLE 2. Relative risk for CVD, cancer and all-cause mortality by baseline glycemic status: The Strong Heart Study

Mortality Risk	IFG	IPH	ADA-new diabetes	Known diabetes
CVD				
RR[a]	0.72 (0.40–1.30)	1.32 (0.62–2.84)	1.65 (1.01–2.71)	2.75 (1.99–3.80)
RR[b]	0.75 (0.41–1.36)	1.54 (0.71–3.36)	1.70 (1.02–2.84)	2.87 (2.04–4.04)
Cancer				
RR[a]	0.92 (0.51–1.64)	0.72 (0.26–2.04)	1.09 (0.59–1.99)	1.22 (0.82–1.82)
RR[b]	0.93 (0.52–1.67)	0.76 (0.27–2.17)	1.21 (0.63–2.31)	1.37 (0.90–2.10)
All-cause				
RR[a]	0.80 (0.59–1.08)	1.25 (0.83–1.88)	1.37 (1.04–1.81)	2.22 (1.87–2.64)
RR[b]	0.83 (0.61–1.12)	1.27 (0.84–1.91)	1.40 (1.04–1.88)	2.19 (1.82–2.64)

Data are hazard ratios (95% CIs), with NFG as referent group.
[a]Adjusted for age, sex, BMI, reported physical activity, and study center.
[b]Adjusted for 1 and smoking, alcohol consumption, hypertension, insulin, total cholesterol, HDL cholesterol, and triglycerides.

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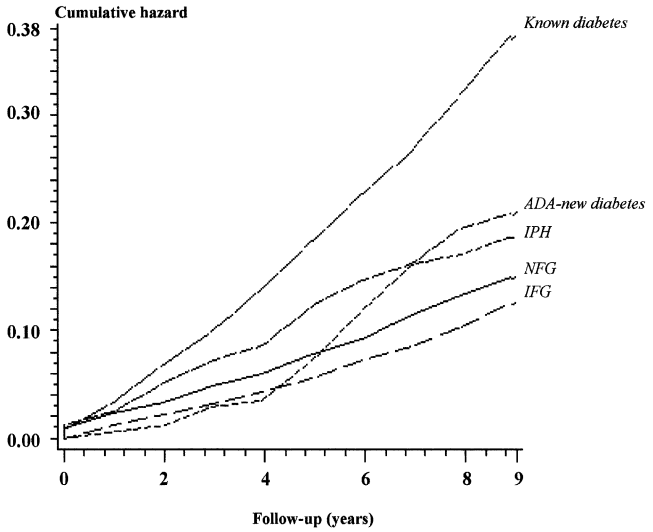

FIGURE 1. All-cause mortality cumulative hazard by diabetes status: The Strong Heart Study.

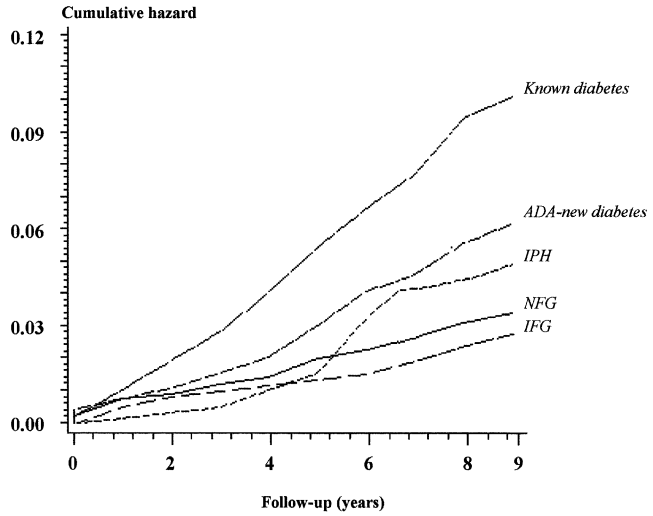

FIGURE 2. CVD mortality cumulative hazard by diabetes status: The Strong Heart Study.

These results are not in agreement with three recent reports from other prospective studies that assessed the consequences of IPH in different cohorts (4, 5, 19). The Rancho Bernardo Study followed for 7 years a group of 769 men and 1089 women aged 50 to 89 years who had no history of diabetes or myocardial infarction and no fasting hyperglycemia at baseline (4). In this study, women with IPH had a significantly increased risk of fatal CVD compared with nondiabetic women (hazard ratio [HR] = 2.6), but men with IPH did not have increased risk (HR = 0.7). The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study included 11 population-based European studies totaling 4415 men and 2526 women aged 60 to 79 years, with followup ranging from 4 to 10 years (5). Compared with nondiabetic subjects, the HR for all-cause mortality was significantly higher in people with IPH (RR = 1.6), and RR was similar to those with fasting hyperglycemia (RR = 1.8) and known diabetes (RR = 1.9). The Paris Prospective Study involved a cohort of 6881 nondiabetic white men aged 44 to 55 years who were followed for 20 years to describe the characteristics and prognosis of diabetes by FPG, IPH, and IGT (19). At follow-up, all-cause and cancer death rates were higher in men with IPH than in men with diabetes diagnosed by FPG (55% versus 44%, $P < 0.01$ and 31% versus 17%, $P < 0.01$, respectively), but were not significantly different for coronary cause.

The fact that significantly increased CVD, cancer, or all-cause mortality was not observed in those with IPH in this study may be due to the duration of IPH. In this population, there is a high rate of diabetes and a very rapid conversion from IGT to diabetes and rapid decline in glycemia. Therefore, although CVD risk factors were worse in IPH, individuals may not remain in the category of IPH long enough for mortality to increase. In contrast, elderly whites may remain in the IPH category for long periods of time, thus allowing the impact of the metabolic changes that accompany IPH to become evident. In another longitudinal analysis that compared different cohorts from baseline with Strong Heart Study data, 140 individuals with IPH, of 3356 eligible participants, had an approximately seven-fold higher incidence of diabetes (68/140) by ADA criteria than did nondiabetic individuals over an average five-year follow-up. Those with IFG and IGT had an approximately four-fold higher incidence of diabetes by ADA criteria than did nondiabetic individuals (28).

In this study, the baseline prevalence of IPH in American Indians from the Strong Heart Study cohort was 3.6%, which accounts for 30.3% among those with newly diagnosed diabetes. There are conflicting reports from epidemiological studies of IPH prevalence. Our results for IPH prevalence are consistent with those of NHANES III, which reported a 3.27% prevalence of IPH and a 4.73% prevalence of newly diagnosed diabetes in 40- to 74-year-old US adults (6). Prevalence of IPH in 65- to 80-year-old men and women in the Cardiovascular Health Study was 8.4% in the total cohort and 52% among newly screened diabetic individuals (3). IPH accounted for 60% of newly screened diabetic men and women aged 50 to 89 years in the Rancho Bernardo Study (4) and IPH accounted for 35% of newly screened diabetic individuals aged 60 to 79 years in the large DECODE study (5). Of 6881 nondiabetic men aged 44 to 55 years from the Paris Prospective Study, 1% had IPH and 33% had diabetes defined by FPG (19).

Cancer is the second leading cause of death in American Indians (25), but risk of cancer mortality was not elevated in those with IPH or diabetes in this study. A study that in-

cluded 1135 incident cases of diabetes with a follow-up of more than 9800 person-years showed that overall risk of cancer did not differ significantly between the diabetic group and the background population (29). However, in a recent report from the Paris Prospective Study, in which cancer death rates were higher in those with IPH than in those with diabetes by FPG, the authors concluded that the most likely explanation for the high cancer rates is that men with IPH are heavy consumers of alcohol (49 g of pure alcohol on average per day) (19). Another large study reported increased overall risk of cancer among 51,008 subjects with diabetes in a Swedish cohort (30). More analyses are needed on the effects of hyperglycemia on cancer risk.

At least two issues must be considered. First, the current study is established on the basis that hyperglycemia is associated with increasing CVD risk and all-cause mortality in diabetic and nondiabetic individuals (11–17). A review of 12 prospective studies convincingly indicates that hyperglycemia plays an important role in cardiovascular complications in type 2 diabetes (11). A meta-analysis of 20 studies containing 95,763 nondiabetic participants over 12.4 years demonstrated that the rise in plasma glucose associated with increased cardiovascular risk extends below the diabetic range of glycemia (12). In the UKPDS, however, intensive glucose control had limited effect on the prevention of cardiovascular complications ($P = 0.052$) in type 2 diabetes (31). Although UKPDS prospective data show a significant effect of hyperglycemia on CVD risk, lowering HbA1c by 1% had only a small effect on decreasing microvascular events. As with UKPDS, our data show that CVD risk increases with severity of glycemia. More intervention strategies with various treatment goals need to be tried before there is a clear picture of the effect of glucose lowering on CVD risk.

The second issue is the limitations imposed by our relatively small cohort, in which only 50 of 1744 (2.9%) men and 104 of 2560 (4.1%) women were classified as having IPH. Authors of other studies, however, also have had difficulty in identifying large numbers of people with IPH (4, 5, 19).

In conclusion, the results of our analysis indicate that individuals with IPH have a small, but statistically insignificant increase in total or CVD mortality—less than those with diabetes but more than those with IFG (who had no increased CVD risk). This finding implies that IPH simply represents a stage in the continuum of the deterioration of glucose homeostasis that leads to frank diabetes. In populations such as American Indians, which have a high prevalence of diabetes, this "downhill" slope is a rapid phenomenon with early age of onset of diabetes, thus effects on CVD are not seen. In other groups, in whom diabetes onset takes longer, it is plausible that these conditions, with their associated alterations in CVD risk factors, are associated with more marked increases in disease rates. Like those of other studies, our results showed that individuals with diabetes, even those newly diagnosed on the basis of fasting hyperglycemia, had a significantly increased risk of CVD mortality. Therefore, regardless of its prognostic value, IPH (and even IGT or IFG), when recognized, must receive immediate preventive attention because of its known associated high risk for the development of diabetes.

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