Fasting and 2-Hour Postchallenge Serum Glucose Measures and Risk of Incident Cardiovascular Events in the Elderly

The Cardiovascular Health Study

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Background: The contributions of fasting and 2-hour postchallenge glucose level to cardiovascular events remain ill-defined, especially for nondiabetic adults. This study examined the relative predictive power of fasting and 2-hour glucose level on cardiovascular event risk.

Methods: A total of 4014 community-dwelling adults 65 years or older who participated in the baseline visit of the Cardiovascular Health Study and who were without treated diabetes or previous myocardial infarction or stroke were eligible for analyses. Participants with treated diabetes at baseline were excluded. Incident myocardial infarction or stroke, or coronary death, was the outcome of interest. Age-, sex-, and race-adjusted proportional hazards regression models described individual and joint associations between baseline measures of fasting and 2-hour postchallenge glucose level and event risk.

Results: There were 764 incident cardiovascular events during 8.5 years of follow-up. Fasting glucose level of 115 mg/dL (6.4 mmol/L) or more was associated with an increased cardiovascular risk (hazard ratio [HR], 1.66 [95% confidence interval (CI), 1.39-1.98]) in adjusted analyses compared with fasting glucose level less than 115 mg/dL. Two-hour glucose level was associated with a linear risk (HR, 1.02 [95% CI, 1.00-1.04] per 10 mg/dL [0.6 mmol/L]) that included an additional increase in risk for 2-hour glucose level of 154 mg/dL (8.5 mmol/L) or more (HR, 1.29 [95% CI, 1.04-1.59]) in adjusted analyses. In joint fasting and 2-hour glucose models, only 2-hour glucose level remained predictive of event risk.

Conclusions: Two-hour glucose level was better than fasting glucose level alone at identifying older adults at increased risk of major incident cardiovascular events.

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IN 1997, THE American Diabetes Association (ADA) revised diabetes diagnostic criteria by lowering the fasting plasma glucose threshold and by recommending against the routine use of glucose challenge testing, especially as it concerns epidemiologic studies.[1] The change was justified primarily by epidemiologic data indicating that the new criteria would identify roughly the same number of people with microvascular complications as the previous criteria, without the burden of glucose challenge testing. These revised criteria have prompted the research community to examine the effects of the diagnostic change on the identification of persons at risk for cardiovascular disease (CVD), the primary complication of glucose disorders in old age, and all-cause mortality.[2,3] Findings indicate that the current ADA criteria do not maximize the identification of persons at risk for these major health outcomes. Nonetheless, the individual and joint associations of fasting and 2-hour glucose measures with cardiovascular morbidity and mortality remain ill-defined, especially for those who do not meet 1997 ADA diabetes criteria.

In this study, we examined the relative predictive power of fasting and 2-hour postchallenge glucose level on fatal and nonfatal myocardial infarction and stroke and on cardiovascular mortality among a cohort of older adults, none of whom had treated diabetes at study entry.

RESULTS

There were 386 participants (7% of the original cohort) with pharmacologically treated diabetes at baseline and 585 (11% of the original cohort) with a baseline history of myocardial infarction or stroke who were not eligible for these analyses. From among the 4230 remaining participants, 184 participants (4%) who were missing fasting or 2-hour glucose measures and 32

SUBJECTS AND METHODS

SETTING AND DESIGN

The Cardiovascular Health Study (CHS) is a population-based, prospective cohort study of risk factors for CVD in the elderly.[4] Participants were recruited from 4 US communities (Washington County, Maryland; Pittsburgh [Allegheny County], Pa; Forsyth County, North Carolina; and Sacramento County, California) on the basis of a randomly generated sampling frame from Health Care Financing Administration files. Annual examinations began in June 1989 and ended in June 1999.

SUBJECTS

The CHS cohort consisted of 5201 community-dwelling adults 65 years and older who participated in the baseline clinic visit in 1989 to 1990 (original cohort) and an additional 687 African American adults 65 years or older who were recruited in 1992 to 1993 (new cohort). Baseline postchallenge glucose testing was not done in the new cohort, so these participants were not included in this report. Approximately 57% of eligible participants participated in the study. Nonparticipants were more likely to be older and less educated and to have more self-reported CVD and hypertension.[5] All study participants gave informed consent for their participation according to guidelines of the appropriate institutional review boards.

This study excluded participants with missing fasting or 2-hour glucose measures (see "Measures") and those who reported using insulin or an oral hypoglycemic agent at the baseline medication inventory.[6] Self-reported history of diabetes was not a criterion for exclusion, although 28% of participants with self-reported diabetes and not using antidiabetic medication opted not to undergo glucose challenge testing. The study population was further restricted to participants who did not have a baseline history of myocardial infarction or stroke, to investigate the risk of incident cardiovascular events.[7] We did not exclude participants with a history of other clinical or subclinical cardiovascular conditions, since we were interested in the primary prevention of major coronary and cerebrovascular atherosclerotic or thrombotic events, namely, myocardial infarction and stroke.

MEASURES

At the baseline examination, venipuncture was performed on study participants under 12-hour fasting conditions early during the study visit. Serum glucose was measured (Kodak Ektachem 700 Analyzer; Eastman Kodak Corp, Rochester, NY).[8] After the fasting venipuncture, 75 g of glucose was given orally to consenting nondiabetic participants. A second venipuncture was performed 2 hours after the glucose challenge.

Covariate baseline measures included demographic characteristics (age, sex, race [white vs other], and self-reported health [good, very good, or excellent vs fair or poor]), cardiovascular risk factors (body mass index [weight in kilograms divided by the square of height in meters], current smoker, currently treated hypertension, sitting diastolic and systolic blood pressure, and low-density lipoprotein cholesterol level), clinical CVD (history of angina, coronary revascularization, congestive heart failure, or transient ischemic attacks; electrocardiogram-identified atrial fibrillation), and subclinical CVD (no clinical CVD, ankle-arm index ≤0.9, maximum internal or common carotid wall thickness >80th percentile [≥2.06 and ≥1.16 mm, respectively], carotid stenosis >25%, major electrocardiogram abnormalities [ventricular conduction defect, major Q-wave abnormalities, left ventricular hypertrophy, isolated ST-T–wave abnormalities, atrial fibrillation, and

(1%) who were fasting less than 8 hours were excluded. These exclusions yielded 4014 participants for analysis (95% of eligible participants). During a median follow-up of 8.5 years, there were 359 incident myocardial infarctions (9%), of which 12% were fatal; 348 incident CBD events (9%), of which 12% were fatal; and 117 CAD deaths (3%). There were 60 participants who had both incident CAD and CBD events during follow-up. Thus, there were a total of 764 incident CVD events (19%), of which 27% were fatal, among the 4014 study participants. The date of the first occurring event was used for combined end points.

Table 1 depicts characteristics of the study population according to fasting glucose values. As expected, CVD risk factors including male sex, hypertension, higher systolic blood pressure and body mass index, and lower high-density lipoprotein cholesterol levels were generally more prevalent across categories of increasing fasting glucose levels. Smoking and low-density lipoprotein cholesterol risk factors were not associated with fasting glucose levels. The prevalence of clinical CVD did not differ according to baseline glucose measures, whereas subclinical CVD in the absence of clinical disease was increasingly more common among those with higher fasting glucose level. Noteworthy is that more than half of the cohort had clinical or subclinical CVD at study entry.

INDEPENDENT CONTRIBUTIONS OF FASTING AND 2-HOUR GLUCOSE LEVELS

Figure 1 presents the unadjusted incident CVD event rates per 1000 person-years for each decile of fasting and 2-hour glucose levels independently. For fasting and 2-hour glucose measures, the event rate appeared to increase rapidly in the top 2 and 4 deciles, respectively. Nearly identical associations were seen for CHD-specific and CBD-specific rates (**Figure 2**) and sex-specific rates (**Figure 3**). When data were stratified by prevalent CVD (clinical and subclinical), the data depicted a similar increase in event rates in the upper deciles, but only among subjects with CVD; among those without CVD, rates across glucose deciles were variable but did not suggest a trend (**Figure 4**).

Exploratory analyses of age-, sex-, and race-adjusted fasting glucose data demonstrated that a simple

atrioventricular block], abnormal ejection fraction or wall motion on echocardiogram [qualitatively assessed], or positive findings on Rose Questionnaire for angina or claudication[9]). These covariates were selected to adjust for potential confounding of the glycemia–CVD event risk association in selected analyses.

An incident coronary artery disease (CAD) event was defined as first nonfatal or fatal myocardial infarction or CAD death; an incident cerebrovascular disease (CBD) event was defined as first nonfatal or fatal stroke of any type.[10] A combined end point for an incident cardiovascular event was based on the first occurrence of either CAD or CBD.[4] Data on adjudicated events through June 1998 are presented in this report. These analyses were based on the updated CHS database as of June 1999, which incorporated minor corrections to baseline examination data.

ANALYSIS

Descriptive summaries of participant characteristics were derived for the 3 categories of fasting glucose level described in the revised ADA diabetes criteria[1]: normal, 109 mg/dL (6.0 mmol/L) or less; impaired fasting glucose, 110 to 125 mg/dL (6.1-6.9 mmol/L); and diabetes, 126 mg/dL (7.0 mmol/L) or more.

Unadjusted cardiovascular event rates per 1000 person-years were calculated independently for each decile of fasting and 2-hour glucose level. Exploratory statistical testing compared threshold (single step), linear, linear plus quadratic, and linear plus threshold (linear model with jump in risk at specified cutoff point) models to determine which model best fit the data. For proportional hazards modeling, failure time was the date of the incident fatal or nonfatal CVD event. All surviving participants were censored on June 30, 1998, the last day of follow-up for these analyses, or on the date of their last contact with the study

if they were unavailable for follow-up. Survival time was the difference in days between date of enrollment and either failure or censoring date.

Multivariate proportional hazards regression was used to determine the individual and joint contributions of fasting and 2-hour glucose levels to cardiovascular risk. Quintile and continuous measures of glucose were used, and hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated for each quintile. Models were adjusted for age, sex, and race and were further adjusted for potential confounders to determine their effect on the glycemia-CVD relationship.

Unadjusted CVD event rates are presented across strata of fasting glucose level according to 2-hour glucose level categories recommended by World Health Organization criteria: normal, 139 mg/dL (7.7 mmol/L) or less; impaired glucose tolerance, 140 to 199 mg/dL (7.8-11.0 mmol/L); and diabetic, 200 mg/dL (11.1 mmol/L) or more. Age-, sex-, and race-adjusted hazard ratios for 2-hour glucose level categories were estimated by means of proportional hazards regression. Population attributable risk percentages were used to estimate the percentage of incident events that could be explained by impaired glucose tolerance or diabetic-level, 2-hour glucose concentration among participants with normal fasting and impaired fasting levels.[11] Percentages were calculated for each 2-hour glucose level category on the basis of estimated hazard ratios from models that adjusted for potential confounders listed above.

Isolated postchallenge hyperglycemia was defined as fasting glucose measures of 125 mg/dL (6.9 mmol/L) or less and 2-hour glucose measures of 200 mg/dL (11.1 mmol/L) or more. Age-, sex-, and race-adjusted hazard ratios were calculated for isolated postchallenge hyperglycemia compared with 2-hour glucose values of 139 mg/dL (7.7 mmol/L) or less and fasting glucose values of 125 mg/dL (6.9 mmol/L) or less.

threshold model where the risk of an incident CVD event increased at the 85th percentile of fasting glucose level (≥115 mg/dL [≥6.4 mmol/L]) was the best fitting model. This stepped increase was associated with a 66% increase in CVD event risk (HR, 1.66; 95% CI, 1.39-1.98) compared with those with baseline fasting glucose level less than 115 mg/dL. For CAD and CBD outcomes, this corresponded to a 62% and 84% increase in risk, respectively. No interactions were detected between a fasting glucose threshold and either sex or CVD for all cardiovascular events.

For 2-hour glucose level, age-, sex-, and race-adjusted analyses demonstrated that a combined linear and threshold model fit the data best. In this model, there was a 2% increase in risk of an incident CVD event for every 10-mg/dL (0.6-mmol/L) increase in 2-hour glucose level (HR, 1.02; 95% CI, 1.00-1.04) plus an additional 29% increase in risk for all values above the 65th percentile (≥154 mg/dL [≥8.5 mmol/L]) (HR, 1.29; 95% CI, 1.04-1.59). This held true for CAD and CBD outcomes where there was a 2% linear increase in addition to a 28% (CAD) and 42% (CBD) increase in event risk for 2-hour glucose values of 154 mg/dL (8.5 mmol/L) or more. No interactions were

detected between linear and threshold 2-hour glucose levels and either sex or CVD for all events.

JOINT CONTRIBUTIONS OF FASTING AND 2-HOUR GLUCOSE LEVELS

Table 2 presents relative risks for quintiles of fasting (top rows) and 2-hour (bottom rows) glucose levels in 3 models. For fasting glucose, adding a continuous measure of 2-hour glucose to the age-, sex-, and race-adjusted model produced a better fitting model (P<.001) and largely removed the association between fasting glucose level and incident CVD event risk. Additional adjustments for smoking, blood pressure, hypertension treatment, low-density lipoprotein cholesterol level, body mass index, self-reported health, and clinical and subclinical CVD had trivial effects on the fasting glucose level–CVD association. Concerning 2-hour glucose level, adding a continuous measure of fasting glucose to the age-, sex-, and race-adjusted model did not produce a better fitting model (P=.40) and did not change the association between 2-hour glucose level and CVD event risk. Adjusting further for known CVD risk factors slightly diminished the predictive power of 2-hour

Table 1. Baseline Characteristics, Cardiovascular Health Study, 1989 to 1990*

	Fasting Serum Glucose		
	Normal (≤109 mg/dL) (n = 3137)	Impaired (110-125 mg/dL) (n = 592)	Diabetic (≥126 mg/dL) (n = 285)
Age, y	73.2	72.8	73.5
Sex, % male	38	47†	45‡
Race, % white	96	95	92†
Current smoker, %	12	11	10
Self-reported good, very good, or excellent health, %	82	83	73†
Treated hypertension, %	29	44†	44†
Prevalent clinical cardiovascular disease, %	14	17	17
Angina history	10	10	9
Coronary revascularization history	3	5‡	4
Congestive heart failure history	2	2	4
ECG atrial fibrillation	2	3	4†
Transient ischemic attack history	1	2	2
Prevalent subclinical cardiovascular disease, %	43	47‡	54†
Any cardiovascular disease, %	56	63†	71†
Self-reported diabetes history, %	1	3†	15†
Systolic blood pressure, mm Hg	135	137†	139†
Diastolic blood pressure, mm Hg	70	72†	71
BMI, kg/m²	25.7	28.2†	28.6†
Total cholesterol, mg/dL	213	212	212
LDL cholesterol, mg/dL	131	132	130
HDL cholesterol, mg/dL	57	50†	48†
Triglycerides, mg/dL	131	155†	176†
Fasting serum glucose, mg/dL	97	115†	155†
2-h Serum glucose			
Mean, mg/dL	131	168†	253†
≤139 mg/dL, %	63	30†	10†
140-169 mg/dL, %	21	24	8
170-199 mg/dL, %	10	21	8
≥200 mg/dL, %	6	25	74

*To convert glucose level to millimoles per liter, multiply by 0.0555; cholesterol, by 0.0259; and triglycerides, by 0.0113. ECG indicates electrocardiogram; BMI, body mass index; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.
†$P ≤ .01$ compared with the normal glucose group.
‡$P ≤ .05$ compared with the normal glucose group.

glucose level. When analyses excluded participants with diabetic-level fasting glucose values, risk estimates changed by no more than 5% in any stratum.

ANALYSES STRATIFIED BY FASTING GLUCOSE LEVEL

Table 3 presents the number of incident CVD events, unadjusted event rates, and age-, race-, and sex- (where appropriate) adjusted hazard ratios for each 2-hour glucose category according to fasting glucose strata. Among participants with normal fasting glucose levels, the CVD event rate increased with each stratum of 2-hour glucose. This observation generally held true for event types and sex and prevalent CVD strata, although the numbers of person-years and events were limited in the top 2-hour glucose strata for men and for those without CVD. In exploratory analyses, a threshold model where cardiovascular risk increased 34% for 2-hour glucose values of 154 mg/dL (8.5 mmol/L) or more fit the data best (HR, 1.34; 95% CI, 1.12-1.61). This model did not vary by event type, nor was an interaction with sex and with prevalent CVD observed. Among participants with impaired fasting glucose level, the event rate increased for each stratum of 2-hour glucose level. These findings generally held true for

event type, sex, and prevalent CVD strata, although events were limited in the top 2-hour glucose stratum for those without CVD. Exploratory analyses showed that a threshold increase in CVD event risk of 83% for 2-hour glucose values of 161 mg/dL (8.9 mmol/L) or more fit the data best (HR, 1.83; 95% CI, 1.29-2.60). This model did not vary by event type or by sex or prevalent CVD strata, although person-years and events were sparse in some strata. The diabetic stratum of fasting glucose level is not presented in Table 3 since, among this stratum, 73% of the person-years and 72% of the events were in the 2-hour glucose stratum of 200 mg/dL (11.1 mmol/L) or more. This resulted in too few person-years (n = 518) and events (n = 21) in the remaining 2-hour glucose strata to calculate meaningful rates and age-, sex-, and race-adjusted relative rates.

Among the 3137 participants with normal fasting glucose levels, there were 548 incident CVD events (17%), of which 5% were attributable to 2-hour glucose levels of 140 mg/dL (7.8 mmol/L) or more and 1% were attributable to 2-hour glucose levels of 200 mg/dL (11.1 mmol/L) or more in adjusted models according to population attributable risk estimates. Among the 592 participants with impaired fasting glucose, there were 141 incident CVD events (24%), of which 24% were attributable to 2-hour glucose levels of 140 mg/dL (7.8 mmol/L) or
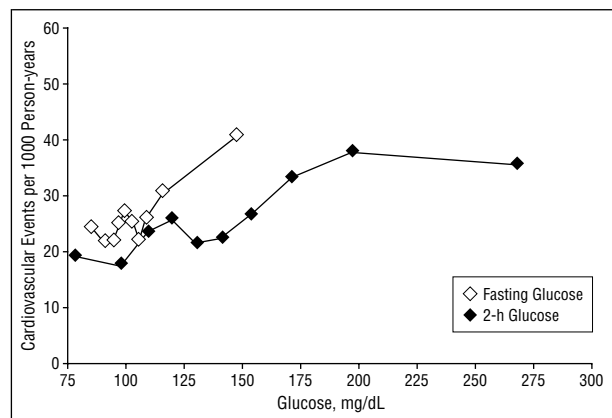
Figure 1. Cardiovascular event rates per 1000 person-years according to deciles of fasting and 2-hour glucose level, Cardiovascular Health Study, 1989 to 1998. To convert glucose level to millimoles per liter, multiply by 0.0555.
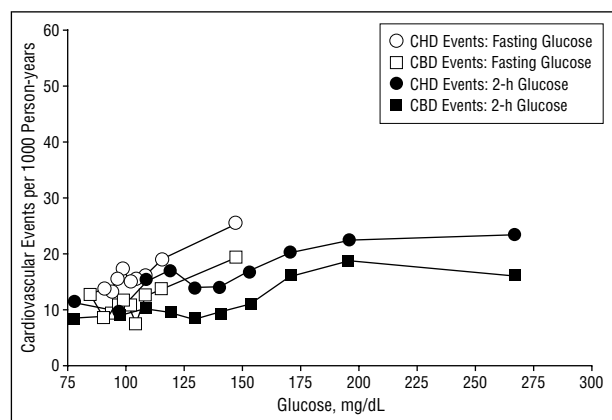

Figure 3. Cardiovascular event rates per 1000 person-years according to deciles of fasting and 2-hour glucose level stratified by sex, Cardiovascular Health Study, 1989 to 1998. To convert glucose level to millimoles per liter, multiply by 0.0555.

Figure 2. Coronary (CHD) and cerebrovascular (CBD) event rates per 1000 person-years according to deciles of fasting and 2-hour glucose level, Cardiovascular Health Study, 1989 to 1998. To convert glucose level to millimoles per liter, multiply by 0.0555.

Figure 4. Cardiovascular event rates per 1000 person-years according to deciles of fasting and 2-hour glucose level stratified by the prevalence of clinical or subclinical cardiovascular disease (CVD), Cardiovascular Health Study, 1989 to 1998. To convert glucose level to millimoles per liter, multiply by 0.0555.

more and 12% were attributable to levels of 200 mg/dL (11.1 mmol/L) or more in adjusted models.

Participants with isolated postchallenge hyperglycemia accounted for 329 (8%) of the 4014 participants at baseline. In age-, sex-, and race-adjusted multivariate modeling, isolated postchallenge hyperglycemia was associated with a 53% increase in CVD event risk relative to participants with 2-hour glucose values of 139 mg/dL (7.7 mmol/L) or less (HR, 1.53; 95% CI, 1.22-1.92). Similar results were found for CHD (HR, 1.55; 95% CI, 1.16-2.05) and CBD (HR, 1.65; 95% CI, 1.20-2.27), for women (HR, 1.67; 95% CI, 1.26-2.26) and men (HR, 1.34; 95% CI, 0.94-1.91), and for participants with CVD (HR, 1.59; 95% CI, 1.25-2.02). Isolated postchallenge hyperglycemia was not associated with increased event risk for participants without CVD (HR, 0.78; 95% CI, 0.40-1.54).

COMMENT

In this study of older adults without treated diabetes at study entry, both fasting and 2-hour glucose levels were individually associated with an increased risk of incident CVD events, but only 2-hour glucose values were predicti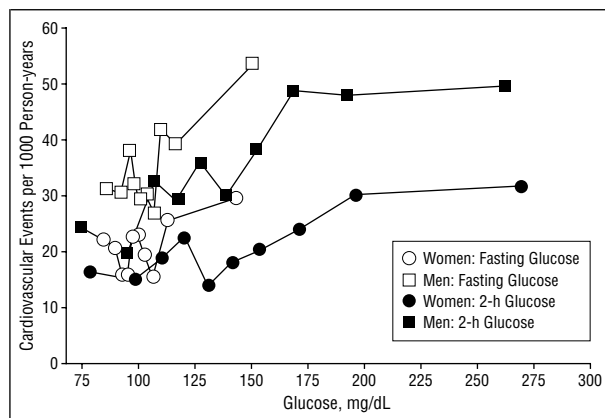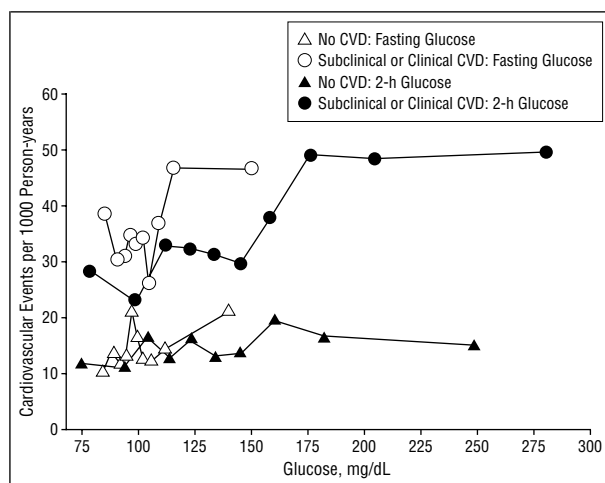ve of CVD events in models that included both glycemia measures. Among participants with normal and impaired fasting glucose levels, impaired glucose tolerance and diabetic-level 2-hour glucose values were associated with an increased risk of CVD events. These relationships were similar for CHD and CBD outcomes, did not vary by sex, and were similar for participants with prevalent clinical or subclinical CVD at study entry. Among study participants without prevalent CVD, evidence of a glycemia-CVD association was limited.

These prospective data provide evidence that an elevated 2-hour glucose level is a useful risk factor for identifying older adults who are at increased risk of a CVD event, which occurred in 20% of the study participants after 8.5 years of follow-up. Besides predicting CVD events independent of fasting glucose level, 2-hour glucose measurement contributed additional risk information beyond fasting glucose information for participants with normal and impaired fasting glucose levels. Among participants with normal fasting glucose levels, above-normal 2-hour glucose values accounted for 1 of 20 incident CVD events, and among those with impaired fasting

Table 2. Adjusted Relative Hazards of Incident Cardiovascular Events Among Nondiabetic and Untreated Diabetic Participants, Cardiovascular Health Study, 1989 to 1998*

	Hazard Ratio (95% Confidence Interval)		
	Age, Sex, and Race Adjusted	Age, Sex, Race, and 2-h Glucose Adjusted	Age, Sex, Race, 2-h Glucose, and Covariate† Adjusted
Fasting glucose quintiles, mg/dL			
≤92	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
93-97	0.92 (0.73-1.16)	0.90 (0.71-1.14)	0.91 (0.72-1.15)
98-103	1.04 (0.83-1.29)	0.99 (0.79-1.24)	0.98 (0.78-1.23)
104-111	0.92 (0.73-1.17)	0.85 (0.67-1.08)	0.79 (0.62-1.01)
≥112	1.42 (1.14-1.76)	1.11 (0.86-1.43)	1.09 (0.84-1.41)
	Age, Sex, and Race Adjusted	Age, Sex, Race, and Fasting Glucose Adjusted	Age, Sex, Race, Fasting Glucose and Covariate† Adjusted
2-h Glucose quintiles, mg/dL			
≤103	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
104-124	1.36 (1.07-1.73)	1.32 (1.06-1.72)	1.30 (1.02-1.65)
125-146	1.17 (0.91-1.50)	1.16 (0.90-1.49)	1.07 (0.83-1.38)
147-181	1.54 (1.22-1.95)	1.52 (1.20-1.93)	1.38 (1.09-1.76)
≥182	1.90 (1.51-2.39)	1.83 (1.43-2.34)	1.58 (1.23-2.02)

*To convert glucose level to millimoles per liter, multiply by 0.0555.
†Covariates: current smoking status; diastolic and systolic blood pressure; treated hypertension; low-density lipoprotein cholesterol; body mass index; and self-reported health of good, very good, or excellent.

glucose levels, above-normal 2-hour glucose levels accounted for 1 of 4 events. If hyperglycemia is causally related to CVD events, these statistics represent the number of CVD events that could have been avoided in the cohort if this risk factor was removed. Epidemiologic evidence supporting causality of hyperglycemia to CVD events, however, is limited.[12]

Data from several prospective studies in nondiabetic adults have yielded inconsistent findings on the relationship between hyperglycemia and CVD risk in nondiabetic adults. The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study Group recently published an article on the association between fasting and 2-hour glucose levels and various mortality outcomes and concluded that 2-hour glucose level was a better predictor of CVD, CHD, and all-cause mortality than fasting glucose.[13] Compared with participants with normal 2-hour glucose levels, impaired glucose tolerance and diabetic-level 2-hour glucose values were associated with a 34% and 55% increase in risk, respectively. The findings are similar to findings in this report for incident CVD. The Rancho Bernardo follow-up cohort reported no significant associations between fasting or 2-hour glucose and either CHD or cardiovascular mortality in men or in women when the highest quintile of glucose measurement was compared with the lowest.[14] Although the Rancho Bernardo findings were null for fasting and 2-hour glucose measures, there was a significant threshold association (HR, 2.6) between the highest quintiles of glycosylated hemoglobin and the lowest in women. There was no association in men. The dissimilar findings from the CHS and Rancho Bernardo data are not explained by the focus on fatal events, since our findings did not change when analyses were restricted to fatal events. Framingham Heart Study analysts found a sex difference in their data from nondiabetic participants 45 to 84 years of age attending the 1969 to 1970 biennial examination. The authors reported a graded effect of casual glucose level on fatal and nonfatal cardiovascular risk in women, but not in men, after 2 years of follow-up.[15] In the original Rancho Bernardo cohort of nondiabetic participants, authors found a linear relationship between fasting glucose level and CHD death in men and a threshold effect (≥110 mg/dL [≥6.1 mmol/L]) in women.[16] Other findings from cohorts of nondiabetic middle-aged adults, mainly men, are heterogeneous and suggest various associations, including flat, J-shaped, linear, and threshold relationships for various glucose measures and cardiovascular outcomes.[17-22]

Risk estimates for isolated postchallenge hyperglycemia are more homogeneous across studies. Findings from the follow-up cohort of the Rancho Bernardo study indicated that women with isolated postchallenge hyperglycemia had a 160% increased risk of cardiovascular mortality, while men had no increased risk when compared with nondiabetic participants.[23] Recent data from the DECODE study demonstrated a 60% increased risk of death among both sexes with isolated postchallenge hyperglycemia when compared with nondiabetic subjects.[24] In general, CHS data tend to support the previous findings that isolated postchallenge hyperglycemia is a cardiovascular risk factor and that this risk may be higher in women than in men.

The primary strengths of this study include population-based sampling, standardized glucose measurements to assess glycemia, extensive CVD risk factor measurements, and complete follow-up for morbid and fatal events. Several limitations merit discussion, however. First, only 1 measure each of fasting and 2-hour glucose was available at baseline. This method is standard for most epidemiologic studies in which populations and not individuals are studied. According to ADA clinical practice guidelines, a diagnosis of diabetes requires a confir-

Table 3. Cardiovascular Event Rates per 1000 Person-Years and Age- and Sex-Adjusted Relative Hazard Estimates According to Baseline Fasting and 2-Hour Serum Glucose Levels, Cardiovascular Health Study, 1989 to 1998*

| | Fasting Serum Glucose | | | | | | | |
| | Normal (≤109 mg/dL) | | | | Impaired (110-125 mg/dL) | | | |
2-h Glucose, mg/dL	Events	Person-Years†	Rates‡	HR (95% CI)§	Events	Person-Years†	Rates‡	HR (95% CI)§
All events								
≤139	315	14 912	21.1	1.00 (Reference)	34	1294	26.3	1.00 (Reference)
140-199	193	6931	27.8	1.24 (1.03-1.48)	60	1908	31.5	1.34 (0.89-2.05)
≥200	40	1294	30.9	1.32 (0.95-1.84)	47	961	48.9	1.98 (1.26-3.12)
Total	**548**	**23 138**	23.7		**141**	**4163**	33.9	
CHD events								
≤139	198	15 180	13.0	1.00 (Reference)	24	1316	18.2	1.00 (Reference)
140-199	125	7122	15.9	1.27 (1.02-1.59)	32	1989	16.1	1.06 (0.62-1.82)
≥200	27	1341	20.1	1.45 (0.97-2.17)	28	1024	27.3	1.75 (0.99-3.08)
Total	**350**	**23 643**	14.8		**84**	**4330**	19.4	
Stroke events								
≤139	137	15 332	8.9	1.00 (Reference)	13	1350	9.6	1.00 (Reference)
140-199	85	7123	11.9	1.22 (0.93-1.60)	34	1978	17.2	1.76 (0.92-3.39)
≥200	19	1356	14.0	1.34 (0.83-2.18)	25	1000	25.0	2.42 (1.21-4.81)
Total	**241**	**23 811**	10.1		**72**	**4328**	16.6	
Men								
≤139	155	5482	28.3	1.00 (Reference)	25	820	30.5	1.00 (Reference)
140-199	97	2470	39.3	1.34 (1.04-1.72)	34	743	45.8	1.54 (0.92-2.58)
≥200	13	402	32.4	1.05 (0.60-1.85)	21	316	66.4	1.82 (1.02-3.27)
Total	**265**	**8354**	31.7		**80**	**1880**	42.6	
Women								
≤139	160	9432	17.0	1.00 (Reference)	9	474	19.0	1.00 (Reference)
140-199	96	4462	21.5	1.13 (0.87-1.45)	26	1165	22.3	1.10 (0.52-2.37)
≥200	27	892	30.3	1.48 (0.99-2.23)	26	645	40.3	1.95 (0.91-4.20)
Total	**283**	**14 785**	19.1		**61**	**2283**	26.7	
No CVD								
≤139	94	7378	12.7	1.00 (Reference)	10	552	18.1	1.00 (Reference)
140-199	48	3021	15.9	1.22 (0.86-2.73)	15	812	18.5	1.27 (0.55-2.89)
≥200	6	428	14.0	0.92 (0.40-2.11)	3	335	9.0	0.62 (0.16-2.39)
Total	**148**	**10 827**	13.7		**28**	**1699**	16.5	
CVD								
≤139	221	7536	29.3	1.00 (Reference)	24	742	32.4	1.00 (Reference)
140-199	145	3910	37.1	1.19 (0.96-1.47)	45	1096	45.1	1.34 (0.81-2.23)
≥200	34	866	39.3	1.33 (0.92-1.91)	44	626	70.3	2.18 (1.31-3.64)
Total	**400**	**12 312**	32.5		**113**	**2464**	45.9	

*To convert glucose level to millimoles per liter, multiply by 0.0555. CHD indicates coronary heart disease; CVD, cardiovascular disease.
†Because of rounding, totals may not sum exactly.
‡Event rate per 1000 person-years.
§Age-, race-, and sex- (where appropriate) adjusted hazard ratios (HR) and 95% confidence intervals (CI) calculated by means of proportional hazards regression.

mation of elevated glucose measures on a subsequent day.[1] Since an elevated glucose measure was not confirmed by a second measure, we cannot be certain that any glucose classification was correct and not the result of random fluctuations in glycemia. Second, nearly 43% of people originally contacted to participate in the CHS refused participation.[5] Those who participated tended to be healthier than those who refused participation, and this fact may limit the generalizability of the findings. Third, in some analytic strata, there were too few events and person-years to produce sufficiently narrow confidence limits to draw meaningful conclusions. Fourth, the cohort averaged 73 years of age at entry, so data and results cannot be generalized to younger populations. Last, although this study is primarily observational, information from the annual clinic visits was shared with participants' physicians and may have influenced the care received by the participants after the baseline examination.[25]

CONCLUSIONS

Numerous cardiovascular risk factors have been identified during the past 50 years of modern epidemiologic research, and the role of glycemia is just now being defined. Any clinical or policy implications that may arise from this study must be balanced with issues of patient burden and cost as they relate to modifiable risk factors that affect health outcomes in older adults.

Our findings indicate that both fasting and 2-hour postchallenge glucose levels were associated with an increased risk of major incident coronary and cerebrovascular events in older adults. Furthermore, 2-hour glucose level was better able to identify those at risk than

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fasting glucose level alone. Although a 2-hour measure of glycemia is burdensome in routine clinical practice, it may serve a role in identifying older adults at increased risk of incident cardiovascular events.

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