Prevalence of Clinical and Isolated Subclinical Cardiovascular Disease in Older Adults With Glucose Disorders

The Cardiovascular Health Study

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OBJECTIVE — Clinical cardiovascular disease (CVD) is highly prevalent among people with diabetes. However, there is little information regarding the prevalence of subclinical CVD and its relation to clinical CVD in diabetes and in the glucose disorders that precede diabetes.

RESEARCH DESIGN AND METHODS — Participants in the Cardiovascular Health Study, aged ≥65 years (n = 5,888), underwent vascular and metabolic testing. Individuals with known disease in the coronary, cerebral, or peripheral circulations were considered to have clinical disease. Those without any clinical disease in whom CVD was detected by ultrasonography, electrocardiography, or ankle arm index in any of the three vascular beds were considered to have isolated subclinical disease.

RESULTS — Approximately 30% of the cohort had clinical disease, and ~60% of the remainder had isolated subclinical disease. In those with normal glucose status, isolated subclinical disease made up most of the total CVD. With increasing glucose severity, the proportion of total CVD that was clinical disease increased; 75% of men and 66% of women with normal fasting glucose status had either clinical or subclinical CVD. Among those with known diabetes, the prevalence was ~88% (odds ratio [OR] 2.46 for men and 4.22 for women, $P < 0.0001$). There were intermediate prevalences and ORs for those with impaired fasting glucose status and newly diagnosed diabetes.

CONCLUSIONS — Isolated subclinical CVD is common among older adults. Glucose disorders are associated with an increased prevalence of total CVD and an increased proportion of clinical disease relative to subclinical disease.

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Abbreviations: AAI, ankle-arm index; ADA, American Diabetes Association; BP, blood pressure; CBD, cerebrovascular disease; CHS, Cardiovascular Health Study; CVD, cardiovascular disease; ECG, electrocardiogram; IFG, impaired fasting glucose; OR, odds ratio; PAD, peripheral arterial disease; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The development of noninvasive cardiovascular technology has led to the appreciation that individuals without clinical cardiovascular disease (CVD) often have significant underlying subclinical CVD. Subclinical disease is a strong risk factor for clinical CVD (1–4). Knowledge of the prevalence of subclinical disease in asymptomatic patients is therefore of interest to the clinician for the purposes of risk stratification.

It is well documented that individuals with glucose disorders have a high prevalence of clinical coronary, cerebral, and peripheral arterial disease (5). Few studies, however, have looked at the prevalence of subclinical disease in these vascular beds or the overall burden of clinical and subclinical CVD among them. This issue is especially important in older adults, in whom glucose disorders have their highest prevalence and their greatest absolute impact on health.

In this study, we present prevalence data of simultaneous clinical and subclinical CVD in three vascular beds in a cohort of adults ≥65 years of age categorized by glucose status. All were members of the Cardiovascular Health Study (CHS), a longitudinal study to identify factors related to the onset and course of coronary heart disease and stroke in elderly individuals. We attempt to give an overview of the total burden of CVD in the elderly and how it is affected by glucose disorders. To our knowledge, such an approach has not previously been undertaken.

RESEARCH DESIGN AND METHODS

— Recruitment methods for CHS have been published previously (6). Individuals invited to participate in the study were selected from a random sample of Medicare eligibility lists. Potential participants were excluded if they were institutionalized, confined to a wheelchair in the home, or had severe illness that was expected to lead to early

death. Subjects were recruited in two phases. In the first phase, 5,201 eligible men and women (4,926 [94.7%] white, 245 [4.7%] African-American, 30 [0.6%] other) ≥65 years of age, agreed to participate. This cohort is called the original cohort. A second phase was later undertaken to provide additional representation of African-Americans. A total of 687 similarly aged members (678 [98.7%] African-Americans, 9 [1.3%] other) were recruited in a manner similar to the first phase.

Table 1—*Distribution of clinical CVD among CHS participants*

	Total	Sex	
		Male	Female
n	5,712	2,419	3,293
No clinical CVD*	3,946 (69.1)	1,525 (63.0)	2,421 (73.5)
Clinical CVD	1,766 (30.9)	894 (370)	872 (26.5)
Cardiac†	1,203 (68.1)	594 (66.4)	609 (69.8)
CBD	203 (11.5)	104 (11.6)	99 (11.4)
PAD	80 (4.5)	38 (4.3)	42 (4.8)
Cardiac and CBD	180 (10.2)	102 (11.4)	78 (8.9)
Cardiac and PAD	64 (3.6)	34 (3.8)	30 (3.4)
CBD and PAD	13 (0.7)	8 (0.9)	5 (0.6)
Cardiac, CBD, and PAD	23 (1.4)	14 (1.6)	9 (1.1)

Data are *n* (%). *Numbers in parentheses are percentages of total participants, male participants, or female participants; †numbers in parentheses are percentages of participants with clinical disease.

Baseline examination

After an overnight fast, venipuncture was performed at the start of the clinic visit. Plasma glucose levels were measured on a Kodak Ektachem 700 Analyzer (Ektachem Test Methodologies, Eastman Kodak, Rochester, NY) (7). Then, 12-lead electrocardiograms (ECGs) were obtained from all participants using a MAC PC-DT ECG recorder (Marquette Electronics, Milwaukee, WI) (8). These were interpreted using a Novacoder ECG measurement and classification system (9). Duplex ultrasonographs of the carotid arteries were also obtained and interpreted as described previously (10). Duplicate measurements of supine blood pressure (BP) in the right arm and both ankles were recorded to derive the ankle-arm index (AAI) (11). During the clinic visit, participants were questioned regarding prior health, and the answers were subsequently validated from clinical records and history.

The analyses performed for this study are based on the updated CHS database, which incorporates minor corrections through June 1999.

Disease categories

As previously reported (12), clinical CVD was defined as self-report (confirmed by medical record review) of the following: *1*) cardiac disease—myocardial infarction, symptoms of congestive heart failure, angina pectoris, use of nitroglycerin, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, insertion of a pacemaker, or known atrial fibrillation; *2*) cerebrovascular disease (CBD)—cerebrovascular accident or transient ischemic attack; *3*) peripheral arterial disease (PAD)—intermittent claudication or history of surgery for PAD.

Isolated subclinical CVD was defined as any of the following in the absence of any clinical cardiac disease, CBD, or PAD (12): *1*) cardiac—major ECG abnormalities, (Minnesota code [(13)] ventricular conduction defects, major Q/QS or ST-T wave abnormalities, left ventricular hypertrophy, atrial fibrillation, or first-degree atrioventricular block), Rose questionnaire positive response for angina pectoris in the absence of known angina pectoris, or use of nitroglycerin; *2*) CBD—increased common and/or internal carotid artery wall thickness (>80th percentile of each sex and race) or carotid artery stenosis >25%; *3*) PAD—AAI ≤0.9 mmHg or Rose questionnaire positive response for claudication in the absence of known claudication or surgery for PAD.

Glycemic categories

Each participant's glycemic category was based on the fasting glucose level. Self-report of a history of diabetes without concurrent use of hypoglycemic medication was not considered a defining criteria. Only subjects who had not drunk calorie-containing beverages or eaten within 9 h of blood collection were analyzed. This led to the exclusion of 94 participants (1.8%) in the original cohort. Of the remaining participants, 87 were using insulin, 278 were using oral hypoglycemic agents and 10 were using both. In the African-American cohort, 22 participants (3.2%) had not fasted before examination and were not included in the analysis. Of the remaining participants, 34 were using insulin, 73 were using oral hypoglycemic agents, and 1 was using both. A total of 60 participants from both cohorts did not have a fasting glucose level recorded and were also excluded. Classification was performed using the fasting American Diabetes Association (ADA) criteria (14). Subjects who met the criteria for diabetes but who were not taking diabetic medications were classified as having newly diagnosed diabetes. Those who were taking glucose-lowering agents were classified as having known diabetes.

Statistical analysis

Disease prevalences between men and women were compared using the Pearson χ^2 statistic. Further analyses were stratified by sex. Descriptive statistics were calculated for each glycemic category. Logistic regression was used to compute age- and race-adjusted odds ratios (ORs) comparing disease prevalences among normoglycemic subjects to those in the remaining glycemic categories. Age was categorized into 5-year intervals (65–69, 70–74, 75–79, 80–84, 85+), and race was categorized into white, African-American, and other. Polynomial contrasts were applied treating the glycemic category variables as ordered categorical variables. Wald tests on the linear contrasts were used to test for monotone trend in the log ORs across the glycemic categories. Wald tests were also computed on the quadratic contrasts to elucidate in which models the increase in log odds was greater than a linear trend. The Wald tests were derived from logistic-regression models and adjusted for age and race. Statistical calculations were performed using SPSS for Windows version 10.0.5 (SPSS, Chicago, IL).

Table 2—*Distribution of subclinical CVD in the absence of clinical disease among CHS participants*

	Total	Sex	
		Male	Female
n	3,946	1,525	2,421
No subclinical CVD*	1,551 (39.3)	541 (35.5)	1,010 (41.7)
Subclinical CVD	2,395 (60.7)	984 (64.5)	1,411 (58.3)
Cardiac†	387 (16.2)	154 (15.7)	229 (16.2)
CBD	1,249 (52.2)	502 (51.0)	747 (52.9)
PAD	74 (3.1)	30 (3.0)	45 (3.1)
Cardiac and CBD	387 (16.2)	187 (19.0)	200 (14.2)
Cardiac and PAD	32 (1.3)	18 (1.8)	14 (1.0)
CBD and PAD	192 (8.0)	57 (5.8)	135 (9.6)
Cardiac, CBD, and PAD	78 (3.3)	36 (3.7)	42 (3.0)

Data are *n* (%). *Numbers in parentheses are percentages of total participants, male participants, or female participants; †numbers in parentheses are percentages of participants with subclinical disease.

RESULTS — A total of 5,712 individuals participated in the cohort; 2,419 (42.3%) were men (2,083 white, 321 African-American, and 15 other). Mean age was 73.3 years. A total of 3,293 (57.7%) of the participants were women (2,729 white, 542 African-American, and 22 other). Mean age was 72.5 years. Among men, 66.4% were normoglycemic, 14.8% had impaired fasting glucose (IFG), and 18.8% had diabetes (8.9% newly diagnosed, 9.9% known). Among women, 73.2% were normoglycemic, 12.6% had IFG, and 14.2% had diabetes (6.9% newly diagnosed, 7.3% known).

A total of 1,698 members of the cohort (29.7%) had one or more forms of clinical CVD (Table 1). The most prevalent form was cardiac. It occurred mostly in isolation. Much less prevalent was CBD, half of which occurred as isolated disease, the rest together with cardiac and/or peripheral arterial disease. The least common form of disease was PAD, with most individuals having concomitant CVD elsewhere. Men had 10% higher prevalence of disease than women ($P < 0.0001$).

Of the 4,014 participants without clinical CVD, 2,437 (60.7%) had one or more forms of isolated subclinical CVD (Table 2). The most prevalent form was CBD, which was present in approximately half of participants. Subclinical cardiac disease was less common, and PAD was the least common. The prevalence in men was 6% greater than in women ($P < 0.0001$).

Table 3 shows the overall prevalences of clinical and isolated subclinical cardiac, cerebral, peripheral, and total CVD in the cohort categorized by glucose status (more detailed data of disease prevalence

Table 3—*Prevalences and ORs of clinical and isolated subclinical CVD categorized by glucose status and sex in the CHS cohort*

	Prevalence				OR†				
	Normoglycemia	IFG	Newly diagnosed diabetes	Known diabetes	Normoglycemia	IFG	Newly diagnosed diabetes	Known diabetes	Test of trend
Men									
Clinical									
Cardiac	28.8	27.6	35.8	44.1	1.00	0.95	1.41*	2.08*	<0.001
CBD	8.6	8.6	13.5	12.6	1.00	1.03	1.61*	1.52*	0.02
PAD	3.4	3.1	5.6	7.1	1.00	0.94	1.67	2.20*	0.002
Any clinical disease	34.5	34.0	44.7	51.3	1.00	1.00	1.56*	2.12*	<0.001
Subclinical									
Cardiac	23.7	29.5	34.5	29.3	1.00	1.42*	1.66*	1.35	0.14
CBD	49.7	53.2	57.1	56.0	1.00	1.18	1.32	1.45	0.06
PAD	7.5	7.6	16.0	21.6	1.00	1.06	2.29*	3.63*	<0.0001
Any subclinical disease	61.8	66.2	76.5	73.3	1.00	1.27	1.97*	1.85*	0.002
Women									
Clinical									
Cardiac	19.2	24.6	25.1	42.4	1.00	1.39*	1.41*	3.01*	<0.0001
CBD	5.2	4.3	7.0	12.7	1.00	0.82	1.32	2.22*	0.0001
PAD	2.2	2.4	3.5	6.5	1.00	1.10	1.60	3.00*	0.0004
Any clinical disease	23.6	27.5	30.4	49.8	1.00	1.25	1.40*	3.09*	<0.0001
Subclinical									
Cardiac	18.7	21.6	25.9	28.5	1.00	1.20	1.54*	1.43*	0.06
CBD	45.1	44.5	51.3	65.0	1.00	1.03	1.30	2.53*	<0.0001
PAD	8.7	9.6	8.2	26.8	1.00	1.20	0.87	3.49*	<0.0001
Any subclinical disease	56.4	56.8	66.5	78.9	1.00	1.06	1.55*	2.83*	<0.0001

Data are *n*. *Statistically significant ($P < 0.05$); †age- and race-adjusted.

Table 4—*Data for Table 3*

	Prevalence*				OR†				
	Normoglycemia	IFG	Newly diagnosed diabetes	Known diabetes	Normoglycemia	IFG	Newly diagnosed diabetes	Known diabetes	Test for trend
Men									
Clinical cardiac									
History of MI	14.75	13.19	22.79	25.21	1.00	0.88	1.73‡	2.06‡	<0.0001
History of CABG or PTCA	7.90	8.64	9.30	15.55	1.00	1.06	1.19	2.21‡	<0.001
History of angina pectoris or use of nitroglycerin	20.04	15.88	24.19	30.67	1.00	0.75	1.29	1.86‡	<0.0001
History of CHF	2.80	3.06	5.58	5.04	1.00	1.11	2.09‡	1.93‡	0.02
Atrial fibrillation or pacemaker insertion	5.04	4.18	6.98	6.72	1.00	0.85	1.49	1.55	0.05
Isolated subclinical cardiac									
Major ECG changes	22.32	28.27	33.61	28.45	1.00	1.45‡	1.74‡	1.41	0.094
Rose questionnaire angina pectoris without a history of angina pectoris	1.71	1.69	2.52	1.72	1.00	0.98	1.39	0.95	0.941
Abnormal ejection fraction	1.92	2.76	2.83	5.26	1.00	1.42	1.52	3.06‡	0.047
Abnormal wall motion	2.24	3.24	4.72	4.21	1.00	1.42	2.09	1.98	0.174
Isolated subclinical CBD									
Internal carolid thickness	14.06	17.30	18.49	16.38	1.00	1.34	1.36	1.25‡	0.43
Common carotid thickness	13.49	16.46	23.53	25.00	1.00	1.35	1.97‡	2.50‡	<0.0001
Carotid stenosis >25%	45.01	46.84	50.42	51.72	1.00	1.10	1.22	1.48	0.048
Isolated subclinical PAD									
AAI <0.9	7.12	7.17	15.97	20.69	1.00	1.05	2.42‡	3.62‡	<0.0001
Rose intermittent claudication	1.14	1.27	0.84	3.45	1.00	1.19	0.69	3.56‡	0.10
Women									
Clinical cardiac									
History of MI	7.02	9.64	13.66	19.59	1.00	1.43	2.15‡	2.99‡	<0.0001
History of CABG or PTCA	2.16	2.65	3.96	7.35	1.00	1.25	1.95	3.31‡	<0.0001
History of angina pectoris or use of nitroglycerin	14.75	16.63	18.50	31.84	1.00	1.16	1.31	2.59‡	<0.0001
History of CHF	1.79	1.93	3.52	7.76	1.00	1.10	1.95	4.25‡	<0.0001
Atrial fibrillation or pacemaker insertion	2.00	4.58	5.73	4.08	1.00	2.52‡	3.18‡	2.28‡	0.02
Isolated subclinical cardiac									
Major ECG changes	16.42	19.27	22.15	25.20	1.00	1.22	1.47	1.36	0.12
Rose questionnaire angina pectoris without a history of angina pectoris	2.88	2.99	3.80	4.07	1.00	1.07	1.32	1.65	0.27
Abnormal ejection fraction	0.24	1.16	0.70	1.19	1.00	5.04‡	3.00	6.24	0.17
Abnormal wall motion	0.97	1.93	1.40	4.76	1.00	2.06	1.46	5.50‡	0.014
Isolated subclinical CBD									
Internal carotid thickness	15.55	20.93	20.25	29.27	1.00	1.54‡	1.39	2.27‡	0.001
Common carotid thickness	15.50	17.61	15.19	31.71	1.00	1.24	0.98	2.54‡	0.0003
Cartoid stenosis >25%	38.66	39.20	46.20	55.28	1.00	1.08	1.40‡	2.31‡	<0.0001
Isolated subclinical PAD									
AAI <0.9	8.43	9.63	6.96	24.39	1.00	1.24	0.74	3.14‡	0.0004
Rose intermittent claudication	0.92	0.33	1.27	4.07	1.00	0.39	1.35	4.98‡	0.003

*Prevalence is crude without adjustment for age or sex; †age- and sex-adjusted; ‡statistically significant; 95% CIs do not include 1. CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

in each vascular bed according to glucose status appear in Table 4). Men and women with known diabetes had, respectively, two and three times greater odds of having clinical CVD compared with those with normal glucose status. Similar odds were present for isolated subclinical CVD. For each individual component of clinical and subclinical CVD, there was a trend for increasing prevalence with increasing glucose severity, other than subclinical cardiac and CBD in men. In addition, among women, any clinical disease, subclinical CBD, and subclinical PAD, showed evidence of an increase across categories in excess of a linear trend, as indicated by a statistically significant ($P < 0.05$) quadratic trend in the log ORs.

Figure 1 shows the prevalence of total CVD by glucose status. Isolated subclinical CVD prevalence here is presented as the percentage of the total population, including those with and without clinical disease ($n = 5,712$). Using this definition, 75% of men with normal glucose status had clinical or subclinical CVD. Among those with known diabetes, 87% had clin-

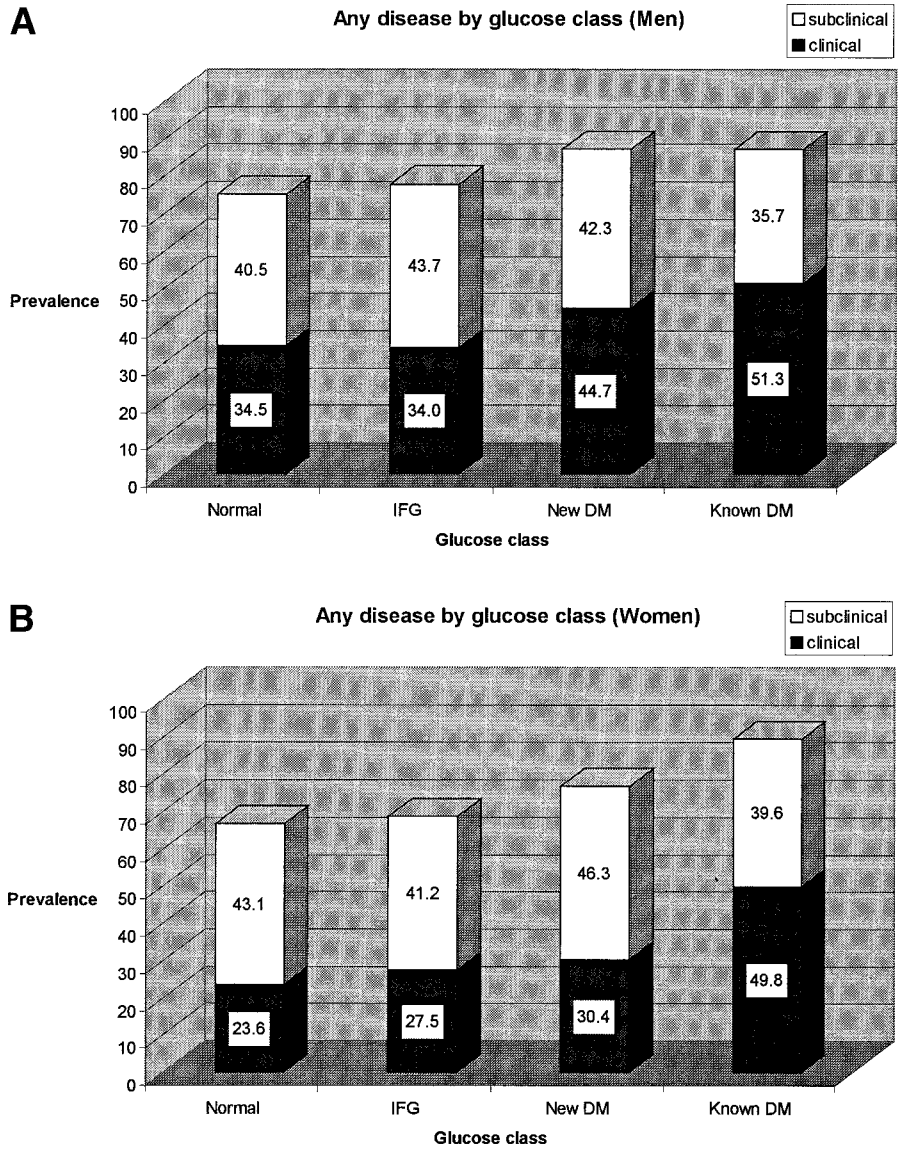

Figure 1—*Prevalence of total CVD by glucose status. DM, diabetes mellitus.*

ical or subclinical CVD (age- and race-adjusted OR 2.46, $P < 0.0001$). The proportion of total CVD that was clinical increased with worsening glucose severity. Among women, the prevalence of clinical or subclinical CVD was 66.7% in those with normal glucose status and 89.4% in those with known diabetes (age- and race-adjusted OR 4.22, $P < 0.0001$). Similar to men, the proportion among women of total CVD that was clinical relative to subclinical was higher with worsening glucose intolerance. Interestingly, 11.8% of the known diabetic male and female participants did not have either clinical or subclinical disease.

CONCLUSIONS — Unlike previous studies that have examined the prevalence of CVD in relation to glucose disorders, this study has arrived at an overall estimate of CVD prevalence based on a summation of clinical and subclinical disease parameters in three vascular beds. We found that ~30% of the cohort had clinical CVD in at least one vascular bed. Of those without clinical disease, ~60% had some form of isolated subclinical disease. The risk of having either clinical or isolated subclinical CVD was higher in the presence of a glucose disorder and increased with glucose severity. The increased risk was more pronounced in women than in men. Lastly, it was found that clinical CVD made up a larger proportion of the total CVD burden among those with glucose disorders than among those with normal fasting glucose status. Taken together, these results are consistent with the hypothesis that factors associated with glucose disorders promote atherosclerosis and also effect its progression to clinical disease.

By the criteria used in this study, clinical CVD was mostly cardiac, whereas isolated subclinical disease was mostly cerebrovascular (i.e., carotid disease). This latter finding, however, is a function of the tests used for measuring subclinical CVD. If duplex scanning of the femoral arteries or computed tomography scanning of the chest had been performed, it is likely that the prevalence of subclinical PAD and coronary artery disease would have been higher. Prior analysis of CHS has shown that subclinical carotid disease is closely related to prevalent and incident heart disease (3,15). Other studies have shown a significant inverse relationship between carotid wall disease and AAI (16). Carotid disease can therefore be considered a marker of subclinical atherosclerosis.

It should be noted that the increase in prevalence of CVD was not as large from normoglycemia to IFG as was the increase from IFG to newly diagnosed diabetes. This finding can be interpreted in two ways. One explanation is that prevalence of CVD increases mostly in the presence of elevated and sustained blood glucose levels. The alternative explanation is that the category of IFG does not capture a distinct subset of individuals with glucose disorders who have CVD. We, and others, have shown that IFG is much less sensitive than the World Health Organization (WHO) category of impaired glucose tolerance for capturing the prevalence of CVD (17,18).

Previous studies have shown that the odds of having clinical cardiac disease are higher for diabetic women than for diabetic men (19). In the present study, we found similar results. In addition, we extended these findings to include the stages of IFG and newly diagnosed diabetes. We have also shown that diabetic women have higher odds of having clinical and subclinical CBD and PAD than men. The lower absolute prevalence of CVD (both clinical and subclinical) among women with normal glucose sta-

tus as compared with men may explain the relatively larger increase in CVD prevalence among women with progressive glucose severity.

It is of interest that almost 12% of the known diabetic subjects in this cohort did not have evidence of either clinical or subclinical CVD. Preliminary analysis shows that they were less likely to be taking BP medications than those with CVD (53 vs. 69%, respectively; $P < 0.05$) (data not shown). Those without CVD, however, did not differ significantly from those with CVD with regard to fasting and 2-h glucose values; total, HDL, and LDL cholesterol levels; systolic and diastolic BP; current smoking; or inflammatory markers that are believed to be associated with atherosclerosis, such as fibrinogen, albumin, and C-reactive protein (data not shown). Further studies will be necessary to determine the protective mechanisms in this unique subgroup.

This study has several strengths. First, selection of participants was designed to obtain a representative sample of the U.S. population aged ≥65 years. As such, the results are generalizable. On the other hand, institutionalized individuals and those with serious illnesses, such as severe congestive heart failure and stroke, were excluded. Therefore, severe CVD complications associated with diabetes may be underrepresented. This would have the effect of making our results conservative estimates. Second, the tests for detecting subclinical CVD were noninvasive. Two of the tests (ECG and AAI) are office-based. The weaknesses of this study should also be noted. The classification of glucose disorders was based on one fasting glucose value and not on two values, as recommended by the ADA (14). Second, the fasting ADA criteria were used, as compared with prior studies that have used the WHO criteria (17). The fasting ADA criteria are not as sensitive as the WHO criteria for detecting clinical CVD in the elderly (17,18). Despite this, our results are similar to previous studies.

Recently, we have shown that subclinical CVD is the primary determinant of incident clinical CVD in individuals with glucose disorders (2). Considering the high prevalence of isolated subclinical CVD among participants with glucose disorders, efforts at CVD risk factor reduction in those without clinical CVD seem warranted.

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