10-Year Follow-up of Subclinical Cardiovascular Disease and Risk of Coronary Heart Disease in the Cardiovascular Health Study

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Background: The incidence of coronary heart disease (CHD) is very high among individuals 65 years or older.

Methods: We evaluated the relationships between measurements of subclinical disease at baseline (1989-1990) and at the third-year follow-up examination (1992-1993) and subsequent incidence of cardiovascular disease and total mortality as of June 2001. Approximately 61% of the participants without clinical cardiovascular disease at baseline had subclinical disease based on our previously described criteria from the Cardiovascular Health Study.

Results: The incidence of CHD was substantially increased for participants with subclinical disease compared with those who had no subclinical disease: 30.5 per 1000 person-years with and 16.3 per 1000 person-years without for white individuals, and 31.2 per 1000 person-years with and 12.5 per 1000 person-years without for black individuals. The risk persisted over the entire follow-up period. Incidence rates were higher for men than for women with or without subclinical disease, but there was little difference in rates for black individuals and white individuals.

Conclusions: In multivariable models, subclinical disease at baseline remained a significant predictor of CHD in both men and women; the hazard ratios (95% confidence intervals) of their relative risks were 1.64 (1.30-2.06) and 1.49 (1.21-1.84), respectively. The presence of subclinical disease substantially increased the risk of subsequent CHD for participants with hypertension, diabetes mellitus, or elevated C-reactive protein. In summary, subclinical disease is very prevalent among older individuals, is independently associated with risk of CHD even over a 10-year follow-up period, and substantially increases the risk of CHD among participants with hypertension or diabetes mellitus.

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THE INCIDENCE OF CORONARY heart disease (CHD) is very high among individuals aged 65 years or older. In the Cardiovascular Health Study (CHS), the incidence was 39.6 per 1000 person-years in men (95% confidence interval [CI], 36.4-43.1) and 22.3 per 1000 person-years in women (95% CI, 20.4-24.2) 65 years or older at entry into the study.[1]

In 1994, we reported[2] an index for classifying subclinical cardiovascular disease (CVD) in older individuals in the CHS that combined the subclinical measurements. The measurements included ankle-brachial blood pressure (BP), carotid artery stenosis and wall thickness, abnormalities in electrocardiographic and echocardiographic findings, and positive responses to the Rose angina and claudication questionnaire from participants without clinical evidence of angina or claudication. This index of subclinical vascular disease, based on measurements of several vascular beds, was a better predictor of the risk of developing short-term clinical CVD than the measurements of either traditional risk factors or of subclinical vascular abnormalities in a single vascular bed.[2-4]

In cross-sectional analyses, the prevalence of subclinical disease increased dramatically with age and was generally higher in men than in women. At baseline examination in 1989-1990, 1612 (31%) of 5201 CHS participants had clinical CVD, 1935 (37.2%) had subclinical CVD, and 1644 (31.6%) had neither subclinical nor clinical CVD. The prevalence of subclinical disease compared with the absence of subclinical disease was related to traditional risk factors for CVD, including lipoprotein levels, glucose-insulin levels, inflammatory markers, body mass index (calculated as weight in kilograms divided by the square of height in meters), and systolic and diastolic BP in both men and women.[2]

In this study, we followed the CHS cohort through June 2001 to test whether (1) subclinical disease continues to predict clinical events over a period of 10 years, (2) the classification of subclinical disease changed

Table 1. Disease Status at Baseline and Associated Incidence Rates of Cardiovascular Disease Events and Mortality by Race and Sex

Characteristic	1826 Individuals With Clinical Disease*		2454 Individuals With Subclinical Disease		1499 Individuals With No Subclinical Disease		HR (95% CI)†
	Events, No.	Rate per 1000 Person-Years	Events, No.	Rate per 1000 Person-Years	Events, No.	Rate per 1000 Person-Years	
Women							
White*	707		1170		867		
CHD			264	24.7	124	14.2	1.61 (1.30-2.01)
MI			125	11.2	48	5.3	2.00 (1.43-2.80)
Angina			202	18.9	104	11.9	1.55 (1.22-1.97)
Death due to CHD	107	16.6	86	7.4	24	2.6	2.23 (1.40-3.35)
Total mortality	345	53.4	439	37.8	186	20.0	1.56 (1.31-1.86)
Stroke			168	15.1	68	7.5	1.72 (1.29-2.29)
Black*	191		244		129		
CHD			53	29.2	10	9.2	2.90 (1.47-5.74)
MI			22	11.5	4	3.7	2.89 (0.99-8.45)
Angina			43	23.7	7	6.5	3.30 (1.48-7.39)
Death due to CHD	21	14.7	17	8.6	3	2.7	2.99 (0.87-10.32)
Total mortality	70	49.1	63	31.7	18	16.2	1.71 (1.01-2.91)
Stroke			35	18.7	7	6.4	2.55 (1.12-5.79)
Men							
White*	799		891		445		
CHD			309	45.2	98	23.1	1.87 (1.48-2.35)
MI			148	19.8	56	12.6	1.49 (1.09-2.04)
Angina			241	35.1	82	19.3	1.82 (1.41-2.34)
Death due to CHD	214	34.3	101	12.5	20	4.3	2.36 (1.45-3.83)
Total mortality	532	85.3	444	55.0	116	24.8	1.82 (1.48-2.24)
Stroke			117	15.2	35	7.7	1.83 (1.25-2.69)
Black*	129		149		58		
CHD			38	39.1	8	16.9	2.01 (0.99-4.38)
MI			20	19.8	3	6.1	2.80 (0.82-9.60)
Angina			26	26.6	6	12.6	1.92 (0.78-4.76)
Death due to CHD	22	25.4	14	13.0	2	4.0	2.36 (0.51-10.84)
Total mortality	71	82.0	65	60.5	11	21.9	2.56 (1.33-4.92)
Stroke			11	10.6	5	10.4	0.78 (0.25-2.39)

Abbreviations: CI, confidence interval; CHD; coronary heart disease; HR, hazard ratio; MI, myocardial infarction.
*Total number in group.
†For subclinical disease vs no disease; age-adjusted.

between the original examination in 1989-1990 and the second evaluation in 1992-1993, (3) the prediction of CVD is enhanced by measuring subclinical disease at more than 1 point in time, (4) subclinical disease is an independent predictor after inclusion of other risk factors and inflammatory markers, and (5) racial differences exist in the association of subclinical disease to CVD events.

Finally, we determined whether the use of subclinical measurements alone or in combination with the presence of diabetes mellitus and hypertension or C-reactive protein (CRP) can help to identify populations of older individuals who are at very high risk for CHD and who may be candidates for aggressive pharmacological therapies to reduce that risk.

METHODS

The CHS is a population-based study of risk factors for CVD in older adults sponsored by the National Heart, Lung, and Blood Institute (Bethesda, Md).[5] The original cohort of 5201 participants was enrolled in 1989-1990, and a second cohort of 687 predominantly black participants was enrolled in 1992-1993. Of the combined cohort of 5888 individuals, 57.6% were women and 15.7% were black. The average age at enrollment was 72.8±5.6 years. Baseline examination included a detailed medical history, list of current medications, blood studies, BP, electrocardiogram, ultrasonography of the carotid arteries, and an echocardiogram in 1989-1990.[6-8] A composite measurement of subclinical CVD was defined as having any 1 of the following: (1) major abnormalities in electrocardiographic findings based on the Minnesota Code, (2) an ankle-arm–systolic BP ratio of 0.9 or less, (3) a percentage of stenosis of the internal carotid artery (based on ultrasonographic findings) of more than 25% or intimal medial thickness of the internal or common carotid artery higher than the 80th percentile of the CHS distribution, (4) abnormalities in echocardiographic findings, (5) abnormality in wall motion, (6) low ejection fraction, or (7) positive findings for Rose angina or claudication without clinical history of angina or claudication.[2] (The definition of clinical disease has been published.[1])

Participants were queried twice per year for new diagnoses, hospitalizations, and medical procedures. Individuals were examined annually in the clinic through 1998-1999. After 1998-1999, only telephone follow-up was continued. To enhance the complete ascertainment of events, Health Care Finance Administration records were also obtained for unreported hospitalizations. All clinical CVD events in the study were reviewed

by an adjudication committee. Adjudicated events occurring through June 30, 2001, were available, which allowed for a maximum of 12 years of follow-up in the original cohort and 9 years in the cohort added in 1992-1993.

The echocardiogram was not repeated at the time of the second evaluation of subclinical disease in 1992-1993 and, therefore, was not available for most of the black cohort.[9] We have excluded the echocardiographic findings from the subclinical disease criteria at both the first (1989-1990) and second (1992-1993) examination for consistency in this article. The exclusion of the echocardiographic findings from the criteria of subclinical disease has very little effect on the estimate of subclinical disease prevalence.[2]

Incidence rates of CVD events by subclinical disease status were calculated by dividing the number of events by the total person-years at risk. Hazard ratios (HRs) of the relative risk of events associated with the presence of subclinical disease at baseline were estimated from Cox proportional hazards models. To determine whether associations of subclinical disease with cardiovascular events remained after adjustment for traditional risk factors for CVD, multivariable Cox models (separately for men and women) were developed for total mortality, CHD, myocardial infarction (MI), and stroke. All models were adjusted for age and race. Other risk factors were evaluated for significance in 2 stages and retained in the model if significant at $P<.05$. The first-stage risk factors included overweight, history of smoking, diabetes mellitus status, systolic blood pressure, and use of antihypertension medications. The second stage included renal insufficiency, defined as creatinine levels higher than 1.3 mg/dL (99.1 µmol/L) in women and higher than 1.5 mg/dL (114.7 µmol/L) in men; and high levels of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, triglyceride, CRP, and fibrinogen; and high white blood cell count. All risk factors were measured at the baseline examination. Interactions between subclinical disease and each risk factor were tested and included in the model if significant. Participants with clinical disease at baseline were excluded from the analyses. Participants who died or were lost to follow-up were censored at the time of death or date of last information.

Participants from the original cohort who did not have CVD at baseline and who had measures of subclinical disease at baseline and 3 years later were assigned to 1 of 4 groups based on their subclinical disease status at each time point. Incidence rates of events occurring after the third follow-up visit were calculated separately for women and men who did not have clinical CVD at the 1992-1993 follow-up visit. In models combining men and women, Cox proportional hazards models were used to check for interactions between disease status and sex for each outcome, after adjustment for age and race. All analyses were performed using statistical software by SPSS (version 13; SPSS Inc, Chicago, Ill) or Stata (version 8; Stata Corp, College Station, Tex).

RESULTS

Of the 5888 CHS participants, 109 (1.9%) without clinical CVD were missing 1 or more components of subclinical disease status and could not be classified. Of the remaining 5779 participants, 1499 (26.0%) had no subclinical or clinical CVD at baseline, 2454 (42.5%) had subclinical disease, and 1826 (31.6%) had clinical disease (**Table 1**). The prevalence of both clinical and subclinical CVD increased with age. The prevalence of being disease free, (ie, having no subclinical or clinical disease) was greater in women than in men (996 [30.1%] vs 503 [20.4%]) and higher in white individuals than in black individuals (1312 [26.9%] vs 187 [20.8%]). Among the participants without clinical CVD at baseline, 62% had subclinical disease.

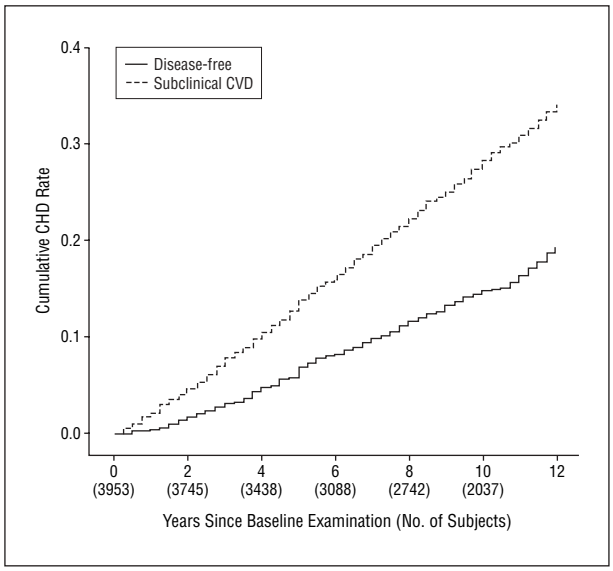

Figure. Incidence of coronary heart disease (CHD) by presence or absence of subclinical disease at baseline by time since baseline examination.

The incidence rates of CHD, MI, angina, death by CHD, stroke, and total mortality are shown in Table 1 by the presence or absence of subclinical disease. The HRs were substantially elevated for participants with subclinical disease compared with those with no subclinical disease in all race and sex groups. Incidence rates were higher for men than women with or without subclinical disease. Of the observed differences in HRs of subclinical disease between black and white individuals or between men and women (Table 1), only 1 was marginally statistically significant: $P=.046$ for a difference in association of subclinical disease to angina between black and white women. The HR was twice as high in black women as in white women (3.30 vs 1.55). The increased risk of clinical CVD associated with subclinical CVD persisted over the entire 10 years of follow-up, with no evidence of attenuation over time (**Figure**).

A total of 3023 individuals were evaluated both at baseline and again in 1992-1993, excluding participants who had clinical disease at the 1989-1990 examination and those recruited in 1992-1993. Of the 495 participants who were not evaluated in 1992-1993, 127 (26%) were deceased, 175 (35.4%) had a home visit or telephone interview, 57 (11.5%) had a clinic visit but were missing 1 or more components of subclinical disease, and 134 (27.1%) had no clinic visit that year. Among the participants with no subclinical disease at the baseline examination, 405 (33.7%) had subclinical CVD at the follow-up examination approximately 3 years later, and 124 (10.3%) had clinical CVD. Of those who had subclinical disease, 264 (14.5%) had reverted to having no disease, 1242 (68.2%) still had subclinical disease, and 316 (17.3%) had developed clinical CVD. Of the 264 who apparently reverted to having no subclinical disease, for 176 (66.7%) this was owing to a change in the maximum percentage of improved stenosis, which was graded as 25% to 49% at baseline and as 1% to 24% at follow-up.

Table 2. Incidence Rates of Events Occurring After Third Follow-up (1992-1993) and Through June 30, 2001*

Characteristic	No Disease		Subclinical Disease	
	No. of Events	Rate Per 1000 Person-Years	No. of Events	Rate Per 1000 Person-Years
No Disease at Baseline				
Women, No.	465		251	
CHD	46	12.7 (9.5-17.0)	34	18.2 (13.0-25.4)
MI	15	4.0 (2.4-6.7)	14	7.3 (4.3-12.3)
Angina	40	11.0 (8.1-15.1)	23	12.3 (8.2-18.5)
Death due to CHD	7	1.8 (0.9-3.9)	12	6.1 (3.4-10.7)
Total mortality	80	21.1 (17.0-26.3)	47	23.8 (17.9-31.6)
Stroke	23	6.2 (4.1-9.3)	22	11.5 (7.6-17.6)
Men, No.	207		154	
CHD	26	16.4 (11.2-24.1)	37	35.3 (25.5-48.7)
MI	15	9.3 (5.6-15.3)	20	17.7 (11.4-27.4)
Angina	19	12.0 (7.6-18.8)	33	31.4 (22.3-44.2)
Death due to CHD	8	4.8 (2.4-9.6)	6	5.1 (2.3-11.3)
Total mortality	39	23.3 (17.0-31.9)	41	34.8 (25.6-47.2)
Stroke	11	6.7 (3.7-12.1)	16	14.0 (8.6-22.8)
Subclinical Disease at Baseline				
Women, No.	180		716	
CHD	32	24.4 (17.3-34.6)	139	28.5 (24.1-33.6)
MI	14	10.3 (6.1-17.3)	74	14.6 (11.6-18.3)
Angina	25	19.1 (12.9-28.3)	109	22.3 (18.5-26.9)
Death due to CHD	9	6.4 (3.4-12.4)	45	8.5 (6.3-11.4)
Total mortality	48	34.4 (25.9-45.6)	233	44.0 (38.7-50.1)
Stroke	22	16.2 (10.7-24.6)	86	17.0 (13.7-20.9)
Men, No.	84		526	
CHD	15	25.0 (15.1-41.5)	148	45.6 (38.8-53.6)
MI	8	12.9 (6.5-25.8)	72	20.8 (16.5-26.2)
Angina	12	19.8 (11.2-34.9)	119	36.6 (30.6-43.8)
Death due to CHD	3	4.6 (1.5-14.3)	44	11.9 (8.9-16.0)
Total mortality	27	41.4 (28.4-60.4)	224	60.6 (53.2-69.1)
Stroke	2	3.1 (0.8-12.5)	56	15.7 (12.1-20.4)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
*Based on status at baseline and third follow-up among participants with no clinical disease at either time. Original cohort only.

The sex-specific incidence rates of CHD, MI, angina, death due to CHD, stroke, and total mortality are shown in **Table 2** according to subclinical disease status at baseline and follow-up, among original cohort participants with no clinical CVD as of the 1992-1993 visit. The incidence of CVD and total mortality was highest for participants who had subclinical disease at both time periods, lowest for those with no subclinical disease at both times, and intermediate for those with subclinical disease at only 1 time point. The CHD rates, as shown in Table 2, vary from 12.7 per 1000 person-years for women and 16.4 per 1000 person-years for men with no subclinical disease at both time periods to 28.5 per 1000 person-years for women and 45.6 per 1000 person-years for men who had subclinical disease at both time periods.

We repeated the analysis excluding participants with carotid stenosis of 25% to 50% as the only criteria for subclinical disease. None of the rates were significantly different than those shown in Table 2.

Distribution of risk factors for men and women at baseline by presence or absence of subclinical disease at both time periods and whether there was an incident CHD event after 1992-1993 (ie, the second evaluation for subclinical disease) are shown in **Table 3** and **Table 4**. Men who had incident CHD and subclinical disease at both times (the highest risk group) had a much higher prevalence of diabetes mellitus and impaired fasting glucose; hypertension; lower high-density lipoprotein levels; and higher levels of triglycerides, fibrinogen, and CRP (Table 3).

Women who had subclinical disease at both times and had incident CHD were older and had higher systolic BP than those who had no subclinical disease and no incident CHD (Table 4).

Subclinical disease remained a significant predictor in the multivariable Cox proportional hazards models of the risk of CHD, as shown in **Table 5**, modeled separately for men and women. Age, presence of diabetes mellitus, measurements of inflammation, renal insufficiency, CRP or white blood cell count, and subclinical disease were the primary determinants of the risk of CHD. There was only a weak and inconsistent relationship between subclinical disease and level of lipids. For women, the HR of subclinical disease for CHD was only slightly reduced by the inclusion of these risk factors, from 1.61 (CI,1.30-2.01) (Table 1) to 1.49 (95% CI, 1.21-1.84) and for men, from 1.87 (95% CI, 1.48-2.35) to 1.64 (95% CI,1.30-2.06). Renal insufficiency, defined as a creati-

Table 3. Distribution of Baseline Risk Factors Among Men*

Risk Factor	No Incident CHD†			Incident CHD†		
	No Subclinical (n = 181)	Subclinical (n = 378)	*P* Value‡	No Subclinical (n = 26)	Subclinical (n = 148)	*P* Value‡
Black race, %	3.3	2.6		3.8	2.7	
Age, y	70.3 (3.7)	73.4 (5.6)	$P<.001$	72.5 (4.3)	73.3 (5.4)	
History of smoking, %						
Never	40.4	33.9	$.001\leq P<.01$	26.9	32.4	
Former	56.4	52.9		65.4	58.1	
Current	3.3	13.2		7.7	9.5	
Weight, kg	174 (26)	174 (25)		169 (26)	177 (27)	
Diabetes (as defined by ADA criteria[10]), %						
Reference range, <110 mg/mL	82.9	71.5	$.01\leq P<.05$	92.3	58.1	$.001\leq P<.01$
IFG, 110-126 mg/mL	10.5	15.2		3.8	20.3	
Diabetes mellitus, >126 mg/mL	6.6	13.3		3.8	21.6	
Hypertension§	38.7	54.4	$P<.001$	46.2	62.2	
Diastolic BP, mm Hg	73.5 (11.0)	71.1 (10.7)*	$.01\leq P<.05$	73.7 (11.5)	72.2 (11.5)	
Systolic BP, mm Hg	129[11]	137[12]	$P<.001$	138[13]	141[14]	
Renal insufficiency,‖%	3.9	7.4		0	8.1	
Creatinine, mg/dL	1.15 (0.21)	1.18 (0.25)		1.14 (0.21)	1.20 (0.26)	
LDL cholesterol, mg/dL	122 (30)	122 (32)		124 (31)	129 (33)	
HDL cholesterol, mg/dL	49.3 (12.3)	49.5 (13.1)		52.4 (12.3)	47.2 (11.6)	$.01\leq P<.05$
Triglycerides, mg/dL	126 (54)	132 (62)		120 (54)	144 (72)	
Fibrinogen, mg/dL	301 (64)	310 (65)		294 (65)	323 (66)	$.01\leq P<.05$
CRP, mg/dL	2.06 (3.08)	2.90 (5.17)	$.01\leq P<.05$	1.76 (1.64)	4.38 (10.7)	$.01\leq P<.05$
White blood cell count, $10^3/\mu L$	59100 (1.48)	62700 (1.48)	$.001\leq P<.01$	62600 (1.67)	62000 (1.54)	

Abbreviations: ADA, American Diabetes Association; BP, blood pressure; CHD, coronary heart disease; CRP, C-reactive protein; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.05551; creatinine to micromoles per liter, multiply by 76.25; cholesterol to millimoles per liter, multiply by 0.02586; triglycerides to millimoles per liter, multiply by 0.1129.

*Based on absence of subclinical disease at baseline (1988-1989) and follow-up (1992-1993) and by incident coronary heart disease after follow-up visit; original cohort only.

†Values are given as mean (SD) unless otherwise specified.

‡*P* values compare the groups defined by subclinical disease status.

§A history of hypertension and receiving antihypertension drug therapy, or blood pressure higher than 140/90 mm Hg.

‖Creatinine level 1.3 mg/dL (99.1 µmol/L) or higher in women or 1.5 mg/dL (114.7 µmol/L) or higher in men.

nine level of 1.3 mg/dL (99.1 µmol/L) or higher for women, was a strong risk factor for CHD (Table 5). The prevalence of a creatinine level of 1.3 mg/dL (99.1 µmol/L) or higher for women is very low, however: 5.8% for those with subclinical disease and incident CHD (Table 4). For other end points, risk factor–adjusted HRs from Cox models for women were 1.40 (95% CI, 1.17-1.66) for total mortality, 1.71 (95% CI, 1.23-2.38) for MI, and 1.65 (95% CI, 1.26-2.18) for stroke; for men, HRs were 1.73 (95% CI, 1.39-2.14) for total mortality, 1.35 (95% CI, 0.98-1.86) for MI, and 1.38 (95% CI, 0.95-2.01) for stroke.

We evaluated further the relationship between hypertension or diabetes mellitus at baseline and subclinical disease on the risk of CHD in men and women. Only 22% of women had neither hypertension nor subclinical disease; 19%, hypertension only; 22%, subclinical disease only; and 37%, both hypertension and subclinical disease. Nineteen percent of men had neither hypertension nor subclinical disease; 13%, hypertension only; 27%, subclinical disease only; and 41%, both hypertension and subclinical disease. The risk of CHD (**Table 6**) was substantially higher for men and women with both subclinical disease and hypertension. The rates were lowest for those who had neither hypertension nor subclinical disease, especially for women. Note also that 55% of all of the CHD events occurred among women with both subclinical disease and hypertension, and 51% occurred among the men with both subclinical disease and hypertension.

Very few individuals with diabetes mellitus did not have subclinical disease: only 75 (26%) of 287 women and 52 (21%) of 242 men.[4] Participants with diabetes mellitus and subclinical disease had very high incidence of CHD, whereas participants with diabetes mellitus without subclinical disease had a moderate to no increased risk of CHD (Table 6). Much of the increased risk of CHD among participants with diabetes mellitus and those with hypertension was due to both their higher prevalence of subclinical disease, as previously reported,[15] and their substantially increased risk of CHD given the presence of subclinical disease by either hypertension or diabetes mellitus.

COMMENT

The results of this study have important implications for both further research and application of CVD prevention programs among elderly individuals. First, the results of this study expand our previous findings to 10 or more years of follow-up. Subclinical disease is a strong independent predictor in black individuals as well as in

Table 4. Distribution of Baseline Risk Factors Among Women*

Risk Factor	No Incident CHD			Incident CHD		
	No Subclinical (n = 419)	Subclinical (n = 577)	*P* Value†	No Subclinical (n = 46)	Subclinical (n = 139)	*P* Value†
Black race, %	4.1	5.9	NS	0	5.0	NS
Age, y	70.1 (4.1)	72.4 (5.3)	<.001	71.1 (4.5)	73.8 (5.2)	<.001
History of smoking, %						
Never	63.2	51.1	<.001	54.3	56.1	NS
Former	27.4	32.6	NS	34.8	32.4	NS
Current	9.3	16.3	NS	10.9	11.5	NS
Weight, kg	145 (28)	147 (29)	NS	156 (43)	156 (43)	NS
Diabetes mellitus (as defined by ADA criteria[10]), %						
Reference range, <110 mg/mL	83.9	77.7	.001≤*P*<.01	69.6	65.5	NS
IFG, 110-126 mg/mL	10.6	11.1	NS	21.7	15.8	NS
Diabetes mellitus, >126 mg/mL	5.5	11.1	NS	8.7	18.7	NS
Hypertension‡	34.3	58.4	<.001	60.9	71.2	NS
Diastolic BP, mm Hg	69.5 (10.1)	69.0 (10.8)	NS	71.5 (11.3)	69.5 (11.3)	NS
Systolic BP, mm Hg	127 (17)	137 (22)	.001≤*P*<.01	132 (19)	142 (22)	.001≤*P*<.01
Renal insufficiency, %§	1.7	2.6	NS	0	5.8	NS
Creatinine, mg/dL	0.89 (0.18)	0.90 (0.20)	NS	0.94 (0.18)	0.93 (0.26)	NS
LDL cholesterol, mg/dL	128 (33)	138 (36)	<.001	136 (44)	137 (33)	NS
HDL cholesterol, mg/dL	61.9 (15.4)	59.2 (15.8)	.001≤*P*<.01	59.8 (16.7)	55.7 (13.2)	NS
Triglycerides, mg/dL	130 (61)	139 (67)	.01≤*P*<.05	152 (64)	158 (89)	NS
Fibrinogen, mg/dL	308 (56)	320 (60)	<.001	313 (59)	330 (63)	NS
CRP, mg/dL	2.31 (2.71)	2.91 (4.20)	.001≤*P*<.01	3.07 (4.17)	3.49 (4.66)	NS
White blood count, $10^3/\mu L^3$	57400 (1.47)	61200 (1.68)	<.001	61000 (1.16)	65100 (1.68)	NS

Abbreviations: ADA, American Diabetes Association; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein; NS, not significant.

SI conversion factors: See Table 3.

*Values in table are means (SD) unless otherwise specified.

†*P* values compare the groups defined by subclinical disease status.

‡A history of hypertension and on antihypertension medications, or blood pressure higher than 140/90 mm Hg.

§Defined as a creatinine level of 1.3 mg/dL (99.1 µmol/L) or higher in women or of 1.5 mg/dL (114.7 µmol/L) or higher in men.

white individuals.[16,17] The CHD rates are similar for black and white individuals but are substantially higher for men than for women. Subclinical disease remained a strong independent risk factor for CHD and total mortality even when including risk factors in multivariable models. Similarly, the addition of the inflammatory markers such as CRP had little effect on the independent prediction of subclinical disease, especially for women.[18]

The measurements of subclinical disease are an imprecise estimate of the true extent of vascular disease.[19,20] The classification of subclinical disease within an individual was fairly consistent over 3 years. A small number of individuals reverted from having subclinical disease to having no subclinical disease. There is variability in all of the measurements of subclinical disease, and the criteria for existence of an abnormality (ie, cutoff points) are arbitrary. The risk of CHD increases with the number of positive measurements within the subclinical disease categories. The use of a composite index of subclinical disease increases the likelihood of identifying a higher percentage of individuals at higher risk for clinical disease. This may be increasingly important as effective therapies are recommended for higher-risk individuals.

The risk factors, including high levels of lipoproteins, BP, history of smoking, and presence of diabetes mellitus are determinants of subclinical disease. The length of time of exposure to these risk factors, their severity, and the host susceptibility (ie, genetic factors) determine the extent of subclinical disease.

We have previously reported in the CHS that levels of low-density lipoprotein cholesterol among CHS participants were not a strong predictor of the risk of clinical coronary artery disease among participants with or without subclinical disease.[21] High-density lipoprotein cholesterol was not a significant risk factor in adjusted models that included subclinical disease. Only 3.2% of women and 5.1% of men were using lipid-lowering drug therapy at baseline. Subsequent treatment with lipid-lowering drug therapy could have an impact on lipid level and risk of CHD. Both diabetes mellitus and hypertension have been associated with increased risk of CHD within the CHS.[15] History of smoking was a determinant of total mortality but weakly related to CVD in the CHS.[22]

Cushman et al[18] evaluated the joint relationship between CRP, subclinical disease, and incidence rates of CHD in the CHS. For both men and women, the risk of CHD was substantially higher for those with subclinical disease compared with those with no subclinical disease at every level of CRP. The relationship of CRP level with subclinical disease is similar to that for BP and diabetes mellitus in that the combination of high CRP level and subclinical disease is associated with a substantially increased risk and that subclinical disease in the absence of an elevated CRP level is still associated with substantially increased risk for CVD.

Table 5. Cox Models for Risk of Incident Coronary Heart Disease

Risk Factor	Men, HR (95% CI)	Women, HR (95% CI)
Age, 5-y increments	1.19 (1.09-1.30)	1.25 (1.14-1.37)
Diabetes mellitus (as defined by ADA criteria[10]), %		
Reference range, <110 mg/mL	1.0	1.0
IFG, 110-126 mg/mL	1.29 (0.99-1.67)	1.18 (0.89-1.56)
Diabetes mellitus, >126 mg/mL	1.63 (1.27-2.09)	1.51 (1.15-1.97)
Systolic blood pressure, per SD unit (21 mm Hg)	1.16 (1.06-1.28)	1.18 (1.07-1.29)
LDL-C, per SD unit (35 mg/dL)	1.14 (1.03-1.26)	–
Triglycerides, per SD unit (74 mg/dL)	1.14 (1.01-1.27)	1.10 (1.02-1.19)
CRP, mg/dL		
<1	1.00	1.00
1-3	1.03 (0.82-1.30)	0.96 (0.75-1.23)
>3	1.37 (1.06-1.78)	1.29 (0.99-1.67)
White blood cell count, per SD unit (1.9×10^3/μL)	NS	10900 (1.02-1.18)
Renal insufficiency*	NS	1.57 (1.03-2.38)
Subclinical disease		
Not receiving lipid-lowering drug therapy	1.70 (1.35-2.15)	1.60 (1.29-2.00)
Receiving lipid-lowering drug therapy	0.50 (0.15-1.63)	0.46 (0.20-1.06)

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IFG, impaired fasting glucose level; LDL-C, low-density lipoprotein cholesterol; NS, not significant.

SI conversion factors: See Table 3.

*Defined as a creatinine level of 1.3 mg/dL (99.1 μmol/L) or higher in women or of 1.5 mg/dL (114.7 μmol/L) or higher in men.

Table 6. Incidence of Coronary Heart Disease by History of Hypertension or Diabetes Mellitus and Presence of Subclinical Disease at Baseline

		Women			Men		
Disease	Subclinical Disease	No. of Events/ No. at Risk	Incidence per 1000 Person-Years	HR*	No. of Events/ No. at Risk	Incidence per 1000 Person-Years	HR*
			Hypertension				
No	No	57/530	10.6 (8.2-13.8)	1.00	58/298	21.0 (16.2-27.1)	1.00
Yes	No	77/464	17.3 (13.8-21.6)	1.57	48/205	24.6 (18.5-32.7)	1.15
No	Yes	91/525	18.5 (15.1-22.8)	1.64	13/412	33.7 (28.1-40.6)	1.53
Yes	Yes	226/888	29.8 (26.0-33.8)	2.54	234/627	52.6 (46.2-59.8)	2.30
			Diabetes Mellitus				
No	No	120/911	13.3 (11.1-15.9)	1.0	96/451	22.6 (18.5-27.6)	1.00
Yes	No	13/75	19.1 (11.1-32.9)	1.45	10/52	21.6 (11.6-40.2)	0.97
No	Yes	247/1187	22.9 (20.1-25.9)	1.60	261/839	39.9 (35.3-45.0)	1.68
Yes	Yes	68/212	42.6 (33.6-54.1)	3.11	84/190	68.7 (55.4-85.0)	3.00

*Age-adjusted hazard ratio.

In D'Agostino et al[23] it was reported that the Framingham Risk Score was not a good predictor of CHD within this older population. The prevalence of subclinical disease increased with the Framingham Risk Score (ie, subclinical disease). The Framingham Risk Score, independent of subclinical disease, was a predictor of the risk of CHD. However, only 18% of deaths due to CHD among women occurred in the high-risk category of the Framingham score (>20% risk) and 46% in the lowest risk groups. The lowest-risk stratum in women was still a relatively high-risk category: about a 14% risk in the 65- to 74-year-old age group over a 10-year period and a higher than 20% risk in the 75- to 84-year-old age group. Results for men were similar: 35% of deaths due to CHD were in the highest-risk group. There were much fewer men in the low-risk stratum.[11]

Most older men are at very high risk for CVD, and measurement of subclinical disease should probably be used only to identify a smaller group of men who have no subclinical disease and are at lower risk.

The situation for women is quite different. At least 30% to 40% of women are at lower risk for CHD because they do not have subclinical disease. In the CHS, 74% of the women with diabetes mellitus had subclinical disease. Some of the older women without diabetes mellitus can be identified because they will have very high levels of key risk factors, especially hypertension, low high-density lipoprotein cholesterol, and large numbers of low-density lipoprotein particles.[24] The lower prevalence of subclinical disease and risk for women compared with men in this older age group may account for the apparent lack of benefit to women of lipid-lowering drugs in several of the recent clinical trials with older individuals,[12,14] especially in the absence of subclinical or clinical disease or diabetes mellitus.[13,25]

The primary limitation of this study is the absence of measurements of coronary calcium and some of the other newer measurements of subclinical disease, the relatively small sample size of black participants, and the absence of exercise tests to measure fitness.

In conclusion, this study has extended the results of the CHS to 10 years of follow-up and has clearly documented the high prevalence and risk associated with subclinical disease for older individuals. We have further showed relatively good consistency of measurements of subclinical disease over time and that the risk for CVD for both men and women with no subclinical disease at 2 time points 3 years apart is lower than for those with subclinical disease at either time point. The subclinical measurements are more widely available now than in 1989-1990. Very effective therapies to prevent clinical CHD are also now available. These results from the CHS suggest that better use of subclinical measurements and effective therapies could substantially reduce the incidence of and mortality due to CVD in the elderly population.

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