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Abstract

Diabetes mellitus and angina pectoris are important conditions in older persons. The utility of pre-diabetes mellitus, diabetes mellitus and other risk factors as predictors of incident angina pectoris among older adults has not been characterized. We examined incident angina pectoris rates by sex and diabetes mellitus status in 4511 adults aged ≥ 65 years without coronary heart disease at baseline from the Cardiovascular Health Study. Cox regression examined predictors of incident angina pectoris, including pre-diabetes mellitus or diabetes mellitus adjusted for sociodemographic characteristics and other risk factors, over 12.2 ± 6.9 years of follow-up. Overall, 39.1% of participants had pre-diabetes mellitus, 14.0% had diabetes mellitus and 532 (11.8%) had incident angina pectoris. Incident angina pectoris rates per 1000 person-years in those with neither condition, pre-diabetes mellitus, and diabetes mellitus were 7.9, 9.0 and 12.3 in women and 10.3, 11.2 and 14.5 in men, respectively. Pre-diabetes mellitus and diabetes mellitus were not independently associated with incident AP; however, key predictors of AP were male sex, low-density lipoprotein-cholesterol, triglycerides, systolic blood pressure, antihypertensive medication and difficulty performing at least one instrumental activity of daily living (all $p < 0.05$ to $p < 0.01$). In our cohort of older adult participants, while the incidence of AP is greater in those with diabetes mellitus, neither diabetes mellitus nor pre-diabetes mellitus independently predicted incident angina pectoris.

Keywords

Angina pectoris, diabetes, older age, sex differences

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among adults in the United States and is increasing in prevalence worldwide.¹ While diabetes mellitus (DM) has been characterized as a coronary heart disease (CHD) ‘risk equivalent’,^{2,3} a large meta-analysis shows this may not be the case, because patients with DM without prior myocardial infarction (MI) have a 43% lower risk of CHD events compared to patients without DM and with clinically evident CHD or prior MI.⁴ Symptomatic angina pectoris (AP) can be a debilitating consequence of CHD⁵ in patients with and without DM alike, and is often the initial presenting symptom.^{6,7} Demographically, in patients with DM, AP has been reported to be more prevalent in women than men.^{8,9} The relationship between type 2 DM, documented stable CHD, and AP symptoms in relation to all-cause and CVD mortality has been previously investigated using the results of the Bypass Angioplasty Revascularization Investigation 2

Diabetes (BARI 2D) trial. In patients with DM and stable CHD, a similar risk of all-cause mortality and CVD death has been demonstrated over 5 years of follow up in those

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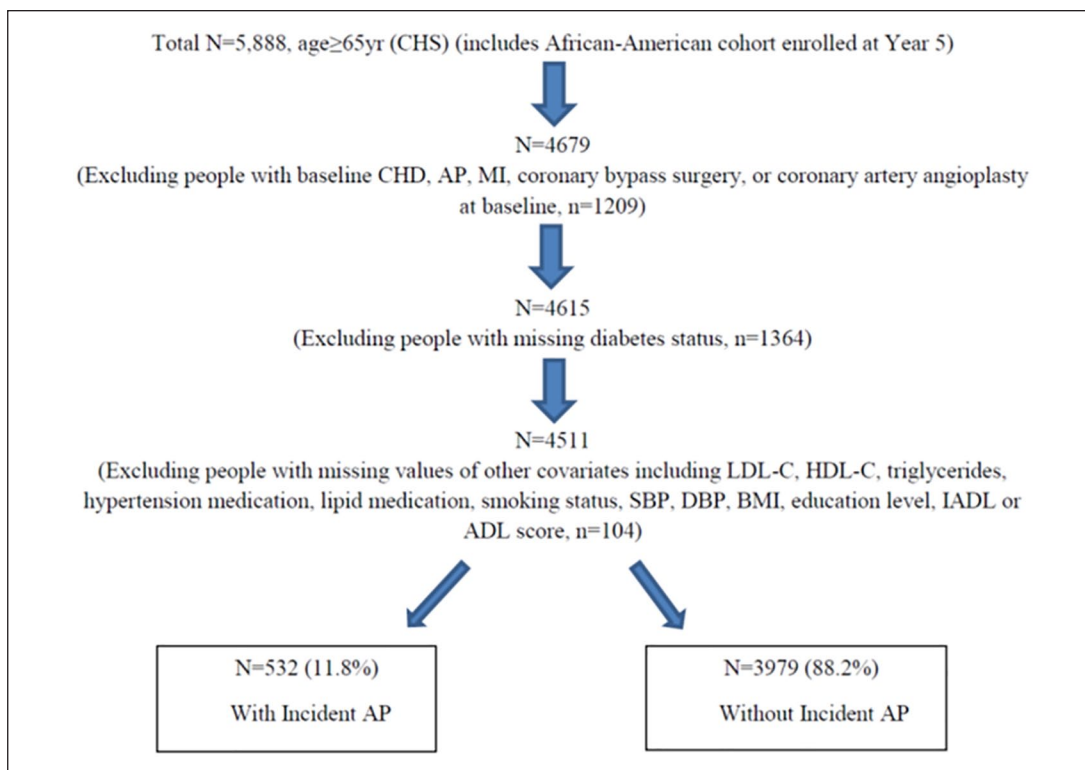


Figure 1. Flow diagram showing derivation of study sample.

ADL: activities of daily living; AP: angina pectoris; BMI: body mass index; CHD: coronary heart disease; CHS: Cardiovascular Health Study; DBP: diastolic blood pressure; DM: diabetes mellitus; HDL-C: high density lipoprotein cholesterol; IADL: instrumental activities of daily living; LDL-C: low density lipoprotein cholesterol; pre-DM: pre-diabetes mellitus; SBP: systolic blood pressure.

with asymptomatic CHD compared to those with symptomatic CHD (i.e. AP or angina-equivalent symptoms, such as dyspnea on exertion) at baseline.¹⁰ In addition, impaired glucose tolerance (pre-DM) and increased serum creatinine have also been described as important factors that predict increased CV events in younger patients with stable angina.¹¹ Not examined, however, is the temporal relationship between pre-DM, DM and incident AP, as well as other factors that predict incident AP in older adults. Early population studies have sought to estimate the incidence and prognosis of AP in the general population among adults without previously known CHD;^{7,12} however, prior studies have been performed primarily in younger patient groups.^{7,8,10,12} The Cardiovascular Health Study (CHS) is a population-based observational study of adults aged 65 years and older, designed to evaluate the risk factors associated with CVD incidence, morbidity and mortality. In this study, we aimed to examine the factors, including potential sex differences, associated with the development of incident AP among older adults without prior CHD, and to examine whether DM (and to a lesser extent pre-DM) is an independent predictor of incident AP in this population.

Methods

The CHS is a prospective, population-based observational study of CVD in older adults. Detailed CHS design and

methodology have been published.¹³ 5201 participants were enrolled in the initial recruitment during 1989–1990, and 3 years later, 687 African-American participants were enrolled for a total combined cohort of 5888 participants. Participants were recruited from four US regions: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland and Pittsburgh, Pennsylvania, and sampled using Health Care Financing Administration Medicare eligibility data. Consent was obtained at the time of the initial examination. Extensive history and physical examination and fasting laboratory studies were performed at baseline, and participants were followed over time with semi-annual contacts, including telephone calls and scheduled clinic visits. Specifically, the current analysis was derived from 4511 participants without known CHD at baseline (1989–1990 in the original cohort and 1992–1993 in the African-American cohort) but with known DM status and complete covariates for analysis. A flow diagram showing the derivation of the study sample is shown in Figure 1.

Adults with prevalent CHD at baseline, including prior MI, AP, coronary bypass surgery or coronary artery angioplasty, were excluded. CHS criteria for AP required a physician diagnosis along with current medical therapy for AP (nitrates, beta-blockers or calcium-channel blockers), or one of the following: coronary artery bypass surgery, $\geq 70\%$ luminal diameter blockage of a coronary artery, or ST depression > 1 mm on

exercise stress testing with a positive medical history using the Rose questionnaire.¹³ Time to incident AP was defined as the adjudicated first occurrence of AP during follow up after the baseline examination (1989–1990 for the original cohort and 1992–1993 for the African-American cohort) through the end of 2004, with a mean follow-up time of 12.2 ± 6.9 years.

DM was defined as having a fasting plasma glucose level ≥ 126 mg/dL, use of either oral hypoglycemic medications or insulin, or both in combination. Pre-DM was defined as having a fasting plasma glucose level between 100 and 125 mg/dL without use of oral hypoglycemic medication or insulin. Those with neither condition were defined as non-DM. The average of two systolic blood pressure (SBP) and diastolic blood pressure (DBP) measures were taken. Serum total cholesterol, high density lipoprotein-cholesterol (HDL-C) and triglycerides were measured as previously described¹³ with low density lipoprotein-cholesterol (LDL-C) calculated by the Friedewald equation. Physical functioning was assessed by the number of reported blocks walked in the week prior to the 1992–1993 examination and by self-reported exercise intensity level. Exercise intensity level was categorized as low, moderate or high intensity versus no reported exercise activity. The modified Mini-Mental State (3MS) exam was used to assess cognitive function (maximum score of 100). The 3MS has been validated in prior studies defining cognitive impairment as a score less than 77.¹⁴ Additional assessment of physical, cognitive and sensory input functioning was performed using the modified version of the Health Interview Survey Supplement on Aging questionnaire,^{13,15} which evaluated self-reported difficulty with any task of Instrumental Activities of Daily Living (IADL) and Activities of Daily Living (ADL).¹⁶ Education level was categorically defined as those with no prior schooling, high school or vocational school graduate, college graduate, and graduate or professional studies completion.

CVD outcomes, including MI, AP, congestive heart failure, claudication as a result of peripheral artery disease, stroke and transient ischemic attack were ascertained through June 2014 for the overall CHS study. During follow up, suspected CVD events and the cause of all non-stroke fatalities were reviewed and adjudicated by a 5-member cardiovascular events committee.^{13,17} Persons who were concurrently classified as having MI at the time of AP were censored. The current investigation was limited to examining the incidence of AP in persons free of AP at baseline, and the predictors of the development of AP.

The bivariate association of pre-DM and DM, as well as other potential risk factors, with incident AP was examined using the Student's *t*-test and Chi-square test of proportions for continuous and categorical predictors, respectively. Incident AP event rates per 1000 person-years were calculated by sex and DM status. Kaplan Meier

curves were used to describe the cumulative incidence and time to incident AP by DM status and sex. Cox proportional hazards regression was used to determine the hazard ratios (HRs) for the risk of incident AP according to presence of pre-DM or DM, compared to neither condition. Participants who developed incident non-fatal MI or coronary death during the follow up period were censored in the analysis.

Models were adjusted for age, sex, race, smoking status, HDL-C, LDL-C, triglyceride levels, body mass index (BMI), SBP and DBP, any antihypertensive use, use of a lipid-lowering medication, aspirin use, difficulty with more than one IADL or ADL, cognitive function, exercise intensity level, and education level. Secondary analyses were done stratified by sex and DM status and interaction terms with sex as an effect modifier in the relationship of pre-DM and DM as predictors of incident AP. SAS version 9.3 was used for all statistical analysis.¹⁸ An α level of <0.05 was deemed to be statistically significant.

Results

Table 1 shows baseline characteristics of the entire cohort and among participants with and without AP. Of the 4511 older adults without CHD at baseline in our study sample, the mean age was 72.6 ± 5.5 years, with 60.4% women and 15.3% African-Americans. In total, 11.7% of women and 12.0% of men had incident AP. Overall, 39.1% had pre-DM, 14.0% had DM, 40.3% were former smokers, 12.4% current smokers, 43.9% had completed a high school education, and 82.5% reported engaging in either low- or moderate-intensity level exercise activity at baseline. In the overall cohort, 29.3% of participants reported aspirin use at baseline, while 40.3% and 4.5% reported use of antihypertensive and lipid medications, respectively. Those with incident AP, as compared to those without AP, were slightly younger (72.5 vs 72.6 years, $p < 0.05$), more likely to be on antihypertensive medication (47.6% vs 39.4%, $p < 0.001$), have difficulty with one or more IADLs (27.1% vs 21.6%) or ADLs (6.8% vs 4.0%) (both $p < 0.01$), and have higher BMI, waist circumference, SBP, total and LDL-C, lower HDL-C, and higher triglycerides.

Among those with incident AP, those with DM (compared to pre-DM and no DM) were less likely to be White, had higher BMI and waist circumference, higher systolic BP, lower HDL-C and higher triglycerides (Table 2). Incident AP event rates generally increased across DM status categories and were greater in men than in women. Overall, incident AP event rates per 1000 person-years were 8.6, 9.9 and 13.2 in those with no-DM, pre-DM and DM, respectively. In those with no DM, pre-DM, and DM, incident AP event rates were 7.9, 9.0 and 12.3 in women and 10.3, 11.2 and 14.5 in men, per 1000 person-years, respectively (Figure 2).

Table 1. Demographic and risk factor characteristics among participants with and without incident angina.

	All participants (n=4511)	Incident AP (n=532)	No AP (n=3979)	p value
Age, years	72.6 ± 5.5	72.5 ± 5.0	72.6 ± 5.6	0.0499
Sex				
Women	2723 (60.4)	318 (59.8)	2405 (60.4)	0.7674
Men	1788 (39.6)	214 (40.2)	1574 (39.6)	
Ethnicity				
White	3795 (84.1)	451 (84.8)	3344 (84.0)	0.7208
African American	689 (15.3)	80 (15.0)	609 (15.3)	
American Indian/Alaskan Native	11 (0.2)	0 (0)	11 (0.3)	
Asian/Pacific Islander	2 (0.1)	0 (0)	2 (0.1)	
Other	14 (0.3)	1 (0.2)	13 (0.3)	
Body mass index, kg/m ²	26.6 ± 4.7	27.3 ± 4.7	26.5 ± 4.7	0.0002
Waist circumference, cm	93.9 ± 13.2	96.0 ± 12.6	93.7 ± 13.3	0.0002
Diabetes status				
No diabetes	2116 (46.9)	237 (44.6)	1879 (47.2)	0.4832
Pre-diabetes	1764 (39.1)	215 (40.4)	1549 (38.9)	
Diabetes mellitus	631 (14.0)	80 (15.0)	551 (13.9)	
Systolic blood pressure, mm Hg	136.4 ± 21.5	138.6 ± 21.7	136.1 ± 21.5	0.0129
Diastolic blood pressure, mm Hg	71.1 ± 11.3	71.2 ± 11.1	71.1 ± 11.3	0.8370
Total cholesterol, mg/dL	211.7 ± 38.7	216.5 ± 39.2	211.1 ± 38.6	0.0026
HDL, mg/dL	55.5 ± 15.7	53.8 ± 15.4	55.8 ± 15.7	0.0064
LDL, mg/dL	129.6 ± 35.6	133.5 ± 37.9	129.1 ± 35.2	0.0108
Triglyceride, mg/dL	132.9 ± 59.3	145.8 ± 64.3	131.1 ± 58.3	<0.0001
Aspirin use	1323 (29.3)	167 (31.4)	1156 (29.1)	0.2658
Antihypertensive meds	1819 (40.3)	253 (47.6)	1566 (39.4)	0.0003
Lipid meds	204 (4.5)	27 (5.1)	177 (4.5)	0.5134
Smoking status				
Current smoker	558 (12.4)	58 (10.9)	500 (12.6)	0.2103
Former smoker	1818 (40.3)	232 (43.6)	1586 (39.9)	
Physical activity (blocks walked in the prior week)	39.4 ± 54.1	36.5 ± 48.0	39.8 ± 54.9	0.1348
Difficulty with IADLs (≥1)	1002 (22.2)	144 (27.1)	858 (21.6)	0.0041
Difficulty with ADLs (≥1)	196 (4.3)	36 (6.8)	160 (4.0)	0.0035
Modified mini-mental state (3MS) exam (maximum score of 100)	89.9 ± 8.9	90.4 ± 8.1	89.9 ± 9.0	0.1287
Exercise intensity level				
No exercise	360 (8.0)	43 (8.1)	317 (8.0)	0.9504
Low intensity	2154 (47.8)	248 (46.6)	1906 (47.9)	
Moderate intensity	1567 (34.7)	188 (35.3)	1379 (34.6)	
High intensity	430 (9.5)	53 (10.0)	377 (9.5)	
Education level				
<High school	2531 (56.1)	299 (56.2)	2232 (56.1)	0.5015
Vocational school	389 (8.6)	51 (9.6)	338 (8.5)	
College graduate	1135 (25.2)	137 (25.7)	998 (25.1)	
Graduate or professional	456 (10.1)	45 (8.5)	411 (10.3)	

AP: angina pectoris; HDL: high density lipoprotein; LDL: low density lipoprotein; IADL: instrumental activities of daily living; ADL: activities of daily living.

Data presented as mean ± SD, n (%).

For those with no DM, pre-DM or DM, women had lower AP event rates than did men. In fully adjusted multi-variable Cox regression analysis, only male sex (HR=1.40, 95% CI=1.11–1.78), LDL-C, triglycerides, SBP, antihypertensive medication use, and difficulty with at least one

IADL were independently associated with an increased likelihood of incident AP; in men, only HDL-C (inversely), LDL-C, and difficulty with at least one IADL, and in women, only triglycerides, SBP, antihypertensive medication use, difficulty with at least one IADL and difficulty

Table 2. Demographic and risk factor characteristics among participants with and without incident angina by diabetes status.

	Incident angina (n = 532)				No angina (n = 3979)				p value					
	No DM (n = 237)		Pre-DM (n = 215)		DM (n = 80)		No DM (n = 1879)			Pre-DM (n = 1549)		DM (n = 551)		
	n	(%)	n	(%)	n	(%)	n	(%)		n	(%)	n	(%)	
Age, years														
65–74	159	(67.1)	151	(70.2)	61	(76.3)	0.4485	1299	(69.1)	1059	(68.4)	357	(64.8)	
75–84	75	(31.6)	60	(27.9)	19	(23.7)		502	(26.7)	440	(28.4)	174	(31.6)	
≥85	3	(1.3)	4	(1.9)	0	(0)		78	(4.2)	50	(3.2)	20	(3.6)	
Sex							0.0570	1263	(67.2)	854	(55.1)	288	(52.3)	
Women	155	(65.4)	120	(55.8)	43	(53.7)		616	(32.8)	695	(44.9)	263	(47.7)	
Men	82	(34.6)	95	(44.2)	37	(46.3)		1593	(84.8)	1347	(87.0)	404	(73.3)	
Ethnicity							0.0007	286	(15.2)	202	(13.0)	147	(26.7)	
White	199	(84.0)	194	(90.2)	58	(72.5)		25.3 ± 4.3	90.0 ± 12.7	95.7 ± 12.8	100.8 ± 12.6	28.7 ± 5.0		
Other	38	(16.0)	21	(9.8)	22	(27.5)	<0.0001	90.0 ± 12.7	133.3 ± 21.2	137.6 ± 21.2	141.7 ± 21.6	<0.0001		
Body mass index, kg/m ²	26.2 ± 4.3		27.9 ± 4.9		29.2 ± 4.6		70.1 ± 11.1	72.0 ± 12.0	72.0 ± 12.0	72.0 ± 12.0	72.0 ± 12.0	<0.0001		
Waist circumference, cm	92.7 ± 11.7		97.5 ± 12.3		101.6 ± 13.2		212.2 ± 37.3	211.7 ± 38.4	211.7 ± 38.4	205.5 ± 43.0	48.8 ± 12.7	<0.0001		
Systolic blood pressure, mm Hg	136.7 ± 22.1		138.7 ± 21.0		143.7 ± 21.9		59.3 ± 16.3	54.0 ± 14.9	54.0 ± 14.9	125.6 ± 38.6	125.6 ± 38.6	0.0181		
Diastolic blood pressure, mm Hg	71.0 ± 11.4		71.0 ± 10.6		72.3 ± 11.1		129.0 ± 34.5	135.8 ± 57.1	135.8 ± 57.1	155.7 ± 71.7	155.7 ± 71.7	<0.0001		
Total cholesterol, mg/dL	215.9 ± 38.1		218.5 ± 40.3		212.6 ± 39.9		120.1 ± 52.0	120.1 ± 52.0	120.1 ± 52.0	205.5 ± 43.0	205.5 ± 43.0	0.0012		
HDL, mg/dL	57.7 ± 17.3		51.3 ± 13.0		48.7 ± 12.4		535	(28.5)	454	(29.3)	167	(30.3)	0.6778	
LDL, mg/dL	131.2 ± 38.3		137.4 ± 37.9		130.1 ± 36.2		589	(31.4)	664	(42.9)	313	(56.8)	<0.0001	
Triglyceride, mg/dL	135.0 ± 62.0		149.1 ± 62.5		169.2 ± 69.5		82	(4.4)	67	(4.3)	28	(5.1)	0.7384	
Aspirin use	65	(27.4)	74	(34.4)	28	(35.0)	0.2092	192	(12.4)	192	(12.4)	59	(10.7)	0.0016
Antihypertensive meds	104	(43.9)	103	(47.9)	46	(57.5)	0.1072	690	(36.7)	670	(43.3)	226	(41.0)	
Lipid meds	8	(3.4)	12	(5.6)	7	(8.8)	0.1512	41.2 ± 55.5	39.5 ± 21.0	309	(20.0)	154	(28.0)	0.0003
Smoking status							69	(3.7)	57	(3.7)	34	(6.2)	0.0217	
Current smoker	24	(10.1)	24	(11.2)	10	(12.5)	0.9491	90.3 ± 9.1	90.3 ± 9.1	90.1 ± 8.5	87.8 ± 9.7	87.8 ± 9.7	<0.0001	
Former smoker	105	(44.3)	95	(44.2)	32	(40.0)		123	(6.6)	129	(8.3)	65	(11.8)	<0.0001
Physical activity (blocks walked in the prior week)	34.0 ± 41.2		39.8 ± 56.6		34.7 ± 41.2		870	(46.3)	756	(48.8)	280	(50.8)		
Difficulty with IADLs (≥ 1)	68	(28.7)	58	(27.0)	18	(22.5)	0.4130	674	(35.9)	530	(34.2)	175	(31.8)	
Difficulty with ADLs (≥ 1)	13	(5.5)	13	(6.1)	10	(12.5)	0.5590	212	(11.2)	134	(8.7)	31	(5.6)	
Modified mini-mental state (3MS) exam (maximum score of 100)	90.7 ± 8.2		90.5 ± 8.6		89.5 ± 6.4		984	(52.4)	889	(57.4)	359	(65.2)	<0.0001	
Exercise intensity level							175	(9.3)	121	(7.8)	42	(7.6)		
No exercise	20	(8.4)	18	(8.4)	5	(6.2)	0.4243	510	(27.1)	377	(24.3)	111	(20.2)	
Low intensity	104	(43.9)	111	(51.6)	33	(41.3)		210	(11.2)	162	(10.5)	39	(7.0)	
Moderate intensity	91	(38.4)	64	(29.8)	33	(41.2)		984	(52.4)	889	(57.4)	359	(65.2)	<0.0001
High intensity	22	(9.3)	22	(10.2)	9	(11.3)		175	(9.3)	121	(7.8)	42	(7.6)	
Education level							510	(27.1)	377	(24.3)	111	(20.2)		
≤High school	125	(52.7)	122	(56.7)	52	(65.0)	0.1738	162	(10.5)	162	(10.5)	39	(7.0)	
Vocational school	28	(11.8)	16	(7.4)	7	(8.8)		984	(52.4)	889	(57.4)	359	(65.2)	<0.0001
College graduate	68	(28.7)	53	(24.7)	16	(20.0)		175	(9.3)	121	(7.8)	42	(7.6)	
Professional	16	(6.8)	24	(11.2)	5	(6.2)		510	(27.1)	377	(24.3)	111	(20.2)	

DM: diabetes mellitus; pre-DM: pre-diabetes; HDL: high density lipoprotein; LDL: low density lipoprotein; IADL: instrumental activities of daily living; ADL: activities of daily living. Data presented as mean ± SD or n (%).

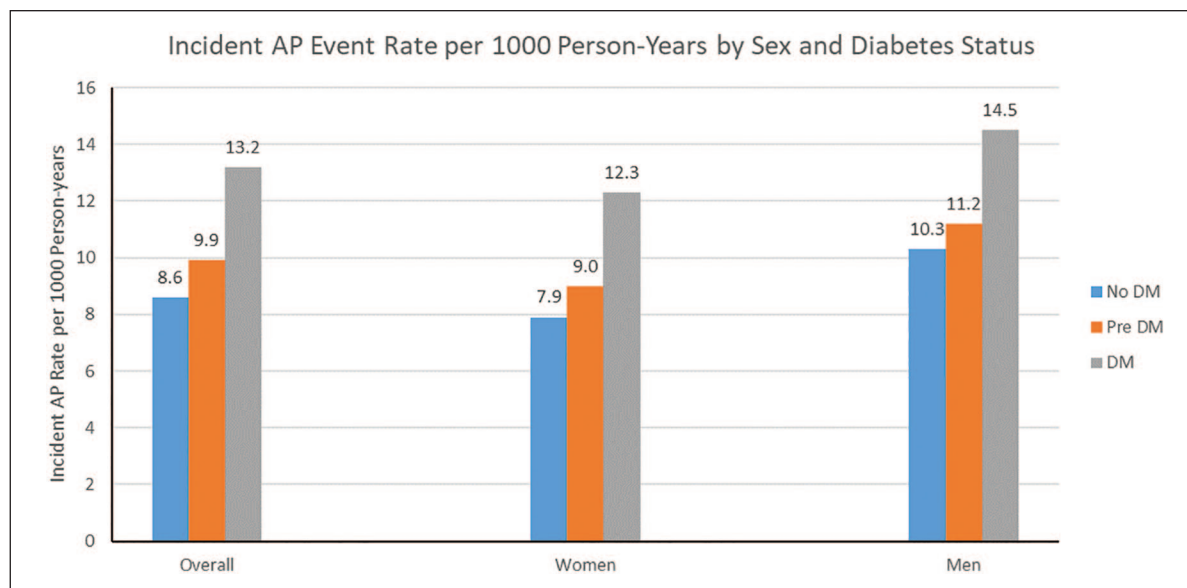


Figure 2. Incident AP event rates overall in the entire cohort and by sex and DM status. Overall, incident AP event rates per 1000 person-years were 8.6, 9.9 and 13.2 in those with no-DM, pre-DM and DM, respectively. In those with neither, pre-DM or DM, incident AP event rates were 7.9, 9.0 and 12.3 in women and 10.3, 11.2 and 14.5 in men, per 1000 person-years, respectively. AP: angina pectoris; DM: diabetes mellitus; pre-DM: pre-diabetes.

with at least one ADL were independently associated with incident AP (Table 3).

Kaplan Meier curves of time to incident angina by DM status among men and women are shown in Figures 3 to 5. A significant difference was seen in time to incident AP overall and among men and women, respectively, stratified by DM status. In the overall sample, there was significantly greater incident AP across disease groups ($p < 0.01$) (Figure 3); however, these differences across DM status groups did not reach significance in sex-stratified analyses (Figures 4 and 5).

Discussion

In this study, approximately 12% of community dwelling older adults, who were free of CHD at baseline, developed AP over 12.2 years of follow-up. While the incidence of AP was greater in persons with DM, after adjustment for age and other risk factors, important predictors of AP were limited to male sex, higher LDL-C, triglycerides, SBP, antihypertensive medication, and difficulty with at least one IADL.

Prior studies have found AP to be more prevalent in women, as compared to men, particularly among younger patients and those with DM.^{8,9} However, in the general population of US adults over age 40 years, AP prevalence has ranged from between 8% and 11% for men, and 5%–9% for women over the age of 65 years.¹⁹ Our study further shows incidence rates of AP to be consistently higher in older men compared to older women among those with

pre-DM, DM, or neither condition, with adjusted risks showing men overall to be 40% more likely to develop incident AP than women. The lower incidence rates of AP among women may reflect a sex-specific difference in AP symptom recognition, reporting, and evaluation,^{6,20} or may reflect sex-specific differences in the development of atherosclerosis.

Our findings further demonstrate a disparity in sex-specific AP incidence among older adults during long-term follow up. Furthermore, the difference between known AP prevalence and incidence is noteworthy. A retrospective study from the National Health and Nutrition Examination Survey (NHANES) from 1998 to 2012 reported a decline in the prevalence of AP in US adults, particularly in individuals aged ≥ 65 years (decline from 9.4% in 2001–2004 to 5.1% in 2009–2012 among women; and from 11.0% in 2001–2004 to 7.8% in 2009–2012 among men).¹⁹ NHANES data on AP prevalence were derived from Rose Questionnaires of AP symptoms and self-reported survey information, which can lead to an underestimation of AP prevalence. Our study, with physician-adjudicated criteria for incident AP from the CHS, offers unique insight into the incidence of AP in older adults over longer term follow up not reflected in prior studies.

Although incident AP event rates were greater with more profound glucometabolic derangement, neither DM nor pre-DM were independent predictors of AP in our study after adjustment for age, sex and risk factors. This suggests that those with DM or pre-DM who did not experience AP, therefore possibly being inadequately treated

Table 3. Multivariable Cox regression of predictors of incident angina.

	Overall	Men	Women
Age	1.16 (0.94–1.51)	1.23 (0.89–1.69)	1.14 (0.86–1.51)
Sex			
Men (Ref=Women)	1.40 (1.11–1.78)**	–	–
Race			
White	Ref	Ref	Ref
Other	0.88 (0.55–1.42)	1.11 (0.51–2.43)	0.77 (0.42–1.41)
Diabetic status			
Normal glycaemic	Ref	Ref	Ref
Pre-DM	0.99 (0.80–1.23)	1.02 (0.73–1.44)	1.03 (0.78–1.35)
DM	1.09 (0.79–1.49)	1.37 (0.85–2.23)	1.04 (0.68–1.60)
Smoking status			
Never	Ref	Ref	Ref
Former	1.14 (0.92–1.40)	1.28 (0.92–1.79)	1.05 (0.79–1.38)
Current	1.15 (0.82–1.61)	1.16 (0.64–2.10)	1.13 (0.75–1.72)
HDL-C	0.97 (0.86–1.10)	0.75 (0.59–0.97)*	1.05 (0.91–1.22)
LDL-C	1.13 (1.02–1.24)*	1.39 (1.19–1.63)**	1.02 (0.90–1.15)
Triglycerides	1.16 (1.05–1.28)**	1.11 (0.95–1.31)	1.16 (1.02–1.32)*
BMI	1.07 (0.96–1.19)	0.94 (0.76–1.16)	1.11 (0.98–1.26)
Systolic blood pressure	1.09 (1.03–1.15)**	1.03 (0.94–1.11)	1.12 (1.04–1.20)**
Diastolic blood pressure	0.92 (0.83–1.02)	0.99 (0.85–1.18)	0.88 (0.77–1.00)
Antihypertensive medication use	1.32 (1.08–1.61)**	1.05 (0.76–1.46)	1.53 (1.18–1.99)**
Lipid medication use	1.10 (0.71–1.69)	0.87 (0.38–1.98)	1.16 (0.70–1.94)
Aspirin use	1.04 (0.85–1.28)	1.13 (0.82–1.55)	1.01 (0.77–1.33)
IADLs			
No difficulty with IADLs	Ref	Ref	Ref
Difficulty with IADLs (≥ 1)	1.48 (1.17–1.87)**	1.60 (1.05–2.43)*	1.42 (1.07–1.89)*
ADLs			
No difficulty with ADLs	Ref	Ref	Ref
Difficulty with ADLs (≥ 1)	1.20 (0.77–1.88)	0.32 (0.08–1.35)	1.65 (1.01–2.68)*
Cognitive function (modified mini-mental state exam score)	0.98 (0.87–1.12)	0.98 (0.80–1.19)	0.99 (0.83–1.17)
Exercise intensity level			
No exercise	Ref	Ref	Ref
Low intensity	0.93 (0.64–1.35)	0.95 (0.80–1.19)	0.91 (0.58–1.44)
Moderate intensity	0.94 (0.64–1.38)	0.93 (0.47–1.82)	0.93 (0.58–1.51)
High intensity	1.03 (0.65–1.62)	0.84 (0.39–1.82)	1.20 (0.68–2.11)
Education level			
\leq High school	Ref	Ref	Ref
Vocational school	0.99 (0.71–1.38)	1.11 (0.65–1.88)	0.93 (0.60–1.43)
College graduate	0.99 (0.78–1.25)	0.99 (0.68–1.44)	1.02 (0.76–1.38)
Graduate or professional	0.83 (0.58–1.19)	0.96 (0.58–1.58)	0.78 (0.46–1.33)

pre-DM: pre-diabetes; DM: diabetes mellitus; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; BMI: body mass index; IADL: instrumental activities of daily living; ADL: activities of daily living.

Values presented are hazard ratios (HRs) with 95% confidence limits in parenthesis. HRs for age, systolic blood pressure and diastolic blood pressure expressed per 10 years and 10 mmHg, respectively. All other continuous variables expressed per standard deviation.

* $p < 0.05$.

** $p < 0.01$.

due to the absence of AP, could be at higher risk of worse prognosis, especially women. While it was beyond the scope of our study to investigate this, it may in part explain the worse cardiovascular prognosis in those with DM, especially among women.²¹ A recent study from the Duke Databank for Cardiovascular Diseases reported that, in a comparatively younger patient population (median age

64 years),²² prevalent AP was associated with a similar risk of CV hospitalization, revascularization, and all-cause mortality, regardless of DM status. The authors concluded that there was insufficient evidence to support an association between different clinical outcomes in patients with AP based solely on DM status.²² Moreover, Zellweger and colleagues²³ have shown the extent of objective evidence

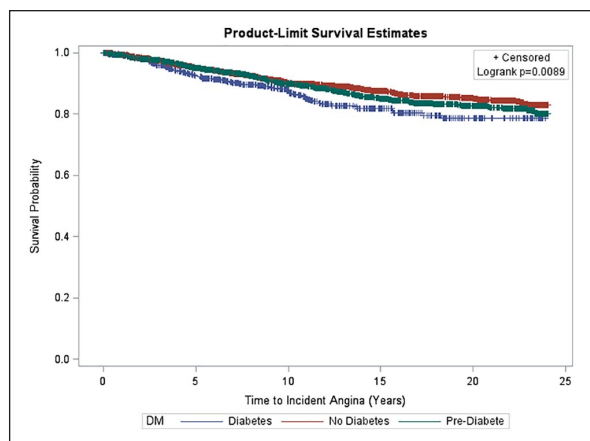


Figure 3. Survival curve of time to incident angina by diabetes status. Kaplan Meier curves depicting time to incident AP by DM status categories overall. Mean time to incident AP overall was 12.2 ± 6.9 years. A significant difference was seen in time to incident AP overall with the lowest survival probability seen in people with DM ($p=0.0089$).

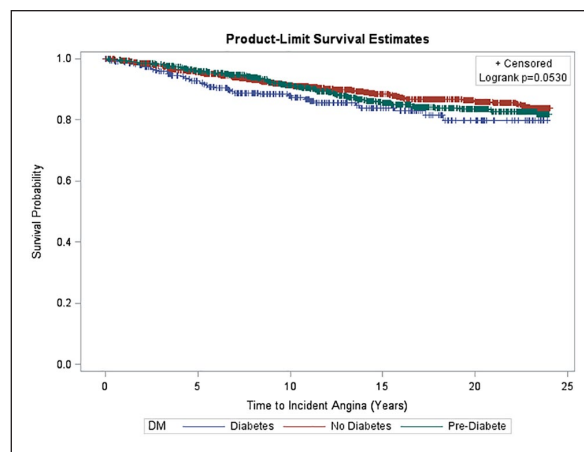


Figure 5. Survival curve of time to incident angina by diabetes status. Kaplan Meier curves depicting time to incident AP by DM status categories among older women. Mean time to incident AP was 13.3 ± 6.9 years. No significant difference was seen in time to incident AP among DM categories ($p=0.0530$).

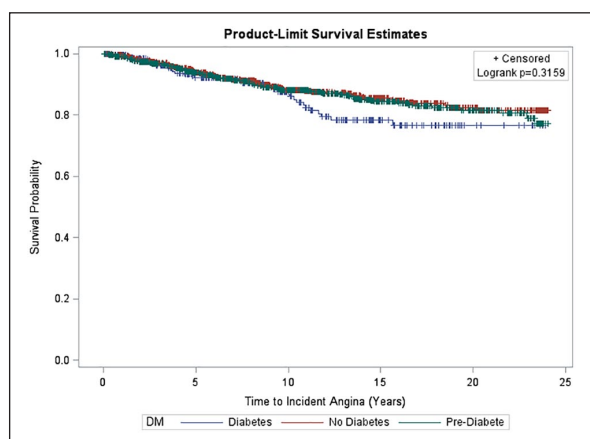


Figure 4. Survival curve of time to incident angina by diabetes status. Kaplan Meier curves depicting time to incident AP by DM status categories among older men. Mean time to incident AP was 10.6 ± 6.7 years in men. No significant difference was seen in time to incident AP among DM categories ($p=0.3159$).

of coronary disease as well as MI or cardiac death were similar in those with and without AP. However, data from the Rancho Bernardo study among older adults showed that women with AP and DM had a 3–4 times higher risk of CHD mortality, independent of other CVD risk factors, than women with DM but no AP.²⁴ This sex-specific difference in CHD mortality among those with DM with AP versus DM without AP was not seen in men.²⁴ Although the incidence of AP was found to be lower among older women compared to men in our study, studies have shown that women tend to have a poorer prognosis and higher morbidity once AP develops.⁶ Despite the limitation in assessing duration of DM and pre-DM among the cohort in

our study, on univariate and multivariate analysis (including controlling for fasting plasma glucose levels, oral hypoglycemic agents, and insulin use), there was no independent association between DM and incident AP in either men or women in our sample.

The association between global cognitive function and CVD has been previously examined.^{25–27} Prior findings have suggested that decreased cognitive function may lead to an increased risk of CVD and CVD death,^{26,27} likely given the overlap of risk factors related to CVD and vascular-disease-mediated cognitive decline.²⁸ In a recent analysis from the Women’s Health Initiative Memory Study (WHIMS),²⁷ the link between cognitive impairment and incident CVD was examined in older post-menopausal women who were free of cardiovascular disease at baseline. The 3MS score was used as the measure of cognitive function at baseline and prospectively, with higher scores indicating better cognitive function.²⁷ Our results are consistent with these findings: Cognitive function, similarly measured by the 3MS score, was not an independent predictor of incident AP among older men or women in the CHS cohort. Interestingly, when stratified by DM status, those with AP and DM were less likely to be college graduates as compared to those without AP and with DM. Further investigation regarding the association between cognitive function and incident AP in a more ethnically diverse cohort of patients with lower cognitive function scores and education level at baseline may reveal an association between lower cognitive function and incident AP not captured by our specific cohort of predominantly White older adults.

Prior reports have assessed the association between AP and physical activity,⁸ showing that community-based adults with AP have significantly more limitations in

physical functioning compared to those without AP, with worse limitations in physical activity observed in adults with AP who also have DM. In our cohort of older adults, we further assessed the impact of baseline physical functioning, by determining specific exercise intensity levels, on the development of incident AP. In our study, we showed that in women, those with difficulty with at least one ADL had a 65% greater risk of developing AP. We found that levels of baseline exercise intensity were not independently associated with development of AP. The possibility that more intense physical activity could have precipitated angina in some persons cannot be excluded.

Strengths of our study include the large sample size, the prospective study design of the Cardiovascular Health Study with long term follow up, and the availability of well-characterized and standardized CVD and socio-demographic risk factors. Notably, all self-reported CHD was verified by medical records and baseline EKG findings, and CHS criteria for adjudicated baseline and incident AP also included physician diagnosis along with a positive medical history obtained using the Rose questionnaire, AP medical therapy, or the development of an ischemic end point such as coronary artery bypass surgery, $\geq 70\%$ blockage of a coronary artery, or ST depression > 1 mm on exercise stress testing.^{13,28} The Rose questionnaire has previously been validated as a tool for use in AP determination in epidemiological studies.^{19,20} In addition, participants who developed incident non-fatal MI and coronary death were censored in the analysis, thus reducing the likelihood of misclassification and validating the results of our cohort vis-a-vis participants with incident AP. Our study is one of the few that provide further insight into the predictors of incident AP in older community-dwelling adults, while uniquely assessing the impact of DM and pre-DM, along with sex differences, as independent risk factors in this special population over a long-term follow up period.

There are several limitations of our study. First, the Cardiovascular Health Study was comprised of White and African-American participants, but a limited number of participants of other ethnicities, which may limit the generalizability of our findings among more diverse populations. Also, since subjects did not routinely receive ischemic testing or coronary angiography at baseline or in conjunction with the development of AP, we cannot exclude the possibility of significant coronary disease or ischaemia being present in some included persons at baseline. Furthermore, although atherosclerotic obstructive disease of the epicardial coronary arteries is the most common cause of AP, other causes may include coronary artery spasm or endothelial dysfunction. In addition, duration of DM and pre-DM could not be ascertained at baseline; thus, potential variations in disease severity could not be controlled for within our multivariate analysis. Further investigation that combines a temporal assessment of the relationship of incident

DM, and pre-DM, to the development of incident AP, with extension to subsequent cardiovascular mortality, would enhance the findings of our study.

Our results show that while persons with DM have a greater incidence of AP, this is largely explained by other CHD risk factors – in particular, male sex, higher LDL-C, triglycerides, SBP, antihypertensive medication, and difficulty with at least one IADL. Moreover, there are sex-specific differences in predictors of incident AP risk in older adults which may be considerations for sex-specific strategies aimed at preventing AP in these individuals.

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