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Association of carotid atherosclerosis and stiffness with abdominal aortic aneurysm: the Atherosclerosis Risk in Communities (ARIC) Study

Lu Yao^a, Aaron R. Folsom^a, Alvaro Alonso^b, Pamela L. Lutsey^a, James S. Pankow^a, Weihua Guan^c, Susan Cheng^d, Frank A. Lederle^e, and Weihong Tang^a

^aDivision of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, U.S.A

^bDepartment of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, U.S.A

^cDivision of Biostatistics, University of Minnesota, Minneapolis, Minnesota, U.S.A

^dCardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts, U.S.A

^eCenter for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, Minnesota, U.S.A

Abstract

Background and aims—Individuals with atherosclerosis and stiffness often have increased abdominal aortic diameters, but prospective evidence linking them to the risk of abdominal aortic aneurysm (AAA) is limited.

Methods—We prospectively examined the relationship of carotid atherosclerosis and stiffness with future risk of AAA in ARIC. At Visits 1 (1987–89) or 2 (1990–1992), we assessed carotid atherosclerosis (represented by greater carotid intima-media thickness [cIMT] or presence of atherosclerotic plaque) and lower carotid distensibility (reflected by a higher carotid Beta Index). We identified incident, clinical AAAs during follow-up through 2011 using hospital discharge codes, Medicare outpatient diagnoses, or death certificates.

Results—Participants' mean age at baseline was 54.2 years (SD 5.8), 45% were male and 73% white. During a median of 22.5 years of follow-up, 542 clinical AAAs were ascertained. After multivariable adjustment, the presence of carotid atherosclerotic plaque at baseline was associated

Correspondence to: Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 S 2nd St, Suite 300, Minneapolis, Minnesota 55454, U.S.A. tang0097@umn.edu Weihong Tang.

CONFLICT OF INTEREST

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

AUTHOR CONTRIBUTIONS

LY conducted statistical analysis and wrote the draft. ARF, AA, PLL, JSP, WG, SC, and FAL critically reviewed the manuscript. WT supervised the project and reviewed the manuscript.

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with 1.31 (95% CI: 1.10–1.57; $p=0.003$) times higher risk of clinical AAA. Greater cIMT and Beta Index were also associated with clinical AAA with a dose-response across quartiles (p trend for both: 0.006; hazard ratios [95% CI] for the highest vs. lowest quartiles: 1.55 [1.13–2.11] and 1.68 [1.16–2.43], respectively). The associations of cIMT and Beta Index with AAA were independent of each other.

Conclusions—This prospective population-based study found that indices of greater carotid atherosclerosis and lower carotid distensibility are markers of increased AAA risk.

Keywords

Atherosclerosis; abdominal aortic aneurysm; carotid distensibility; carotid plaque; carotid intima-media thickness

INTRODUCTION

Abdominal aortic aneurysms (AAA) affect about 1% to 2% of the general population aged 50 years in the US [1, 2]. According to the most recent estimates, AAA rupture causes about 2,446 deaths annually in the US [3]. Thus, AAA is an important public health concern.

There is a debate about whether atherosclerosis is a cause of AAA [4]. Prospective cohort studies have suggested that traditional risk factors for atherosclerotic disease, including smoking, hypertension, dyslipidemia, advanced age, male gender, and some inflammatory and hemostasis biomarkers, are associated with a higher risk of AAA [1, 4–9]. In addition, angiotensin-2, endothelin-1, and measures of oxidative stress, which are involved in the development of atherosclerotic diseases, are associated positively with the risk of AAA [10–12]. In contrast, some risk factors for atherosclerosis, such as type 2 diabetes, may decrease the risk of AAA [13]. Pathologically, atherosclerosis is widespread throughout the vasculature [14], while aortic aneurysms occur only in specific locations of the body such as the abdominal aorta. Moreover, atherosclerosis primarily forms in the intima while AAA primarily affects the media and adventitia [14]. The most recently released guideline by the US Preventive Service Task Force stated that atherosclerosis was a risk factor for AAA [15]; however, literature reviews included in this guideline to support the statement were based on cross-sectional data for abdominal diameter among patients free of AAA [15, 16].

Current knowledge gaps regarding the determinants of AAA are due to limited evidence. Epidemiologic data on atherosclerosis and AAA are sparse; only one population-based study, to date, has examined the relation between subclinical markers of atherosclerosis and maximal abdominal aortic diameter [17]. Data on the relation between arterial stiffness and AAA are also limited [18, 19]. To better understand the possible relationship of generalized measures of atherosclerosis and arterial stiffness with AAA occurrence, we analyzed data collected from a large population-based cohort study with over 20 years of follow-up. We hypothesized that greater baseline carotid intima-media thickness (cIMT) and carotid plaque, and reduced carotid artery distensibility are associated with higher incidence of AAA.

MATERIALS AND METHODS

The ARIC Study

The ARIC study was designed to investigate risk factors for atherosclerosis and its clinical sequelae [20]. The ARIC investigators recruited a population-based cohort comprising 15,792 men and women aged 45–64 from four communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and suburban Minneapolis, MN) in 1987–1989 (Visit 1). ARIC conducted follow-up examinations in 1990–92 (Visit 2), 1993–95 (Visit 3), 1996–98 (Visit 4), and 2011–13 (Visit 5). ARIC administered a telephone interview annually or semiannually to ask about any interim hospitalizations or deaths and these records were sought to identify cardiovascular events including AAAs. To identify additional hospitalizations or deaths, ARIC also conducted surveillance of local hospital discharge lists for cohort members. For each hospitalization identified, all International Classification of Disease (ICD) - 9 - CM discharge and procedure codes were recorded, and for deaths, the ICD-9 or ICD-10 codes for the underlying cause were recorded. Additionally, ARIC linked participant identifiers with Medicare data from the Centers for Medicare and Medicaid Services (CMS), since 1991, to find any missing hospital or outpatient events for participants over 65 years.

Ascertainment of clinical AAA

Participants reporting prior AAA surgery or aortic angioplasty at baseline were excluded from all analyses. Clinical AAAs were ascertained since the baseline examination through 2011, defined as either a hospital discharge diagnosis from any sources or two Medicare outpatient claims that occurred at least one week apart, with ICD-9-CM codes of 441.3 (ruptured AAA) or 441.4 (AAA without mention of rupture), or procedure codes of 38.44 (AAA resection and replacement) or 39.71 (AAA endovascular repair) or a listed cause of death coded as ICD-9 441.3 or 441.4, or ICD-10 code I71.3 (ruptured AAA) or I71.4 (AAA without mention of rupture) [9]. Both symptomatic and asymptomatic AAAs that were medically documented were included. Thoracic, thoracoabdominal, or aortic aneurysms at unspecified locations were not deemed to be AAA events in this study.

Risk factor assessment

At Visits 1 and 2, ARIC measured cIMT bilaterally in the extracranial carotid arteries, namely in the common carotid artery (1 cm proximal to the dilatation of the carotid bulb), the carotid bifurcation (1 cm proximal to the flow divider), and the internal carotid artery (1 cm distal to the flow divider). In each 1-cm section, there were up to 11 measurements (along the far wall) at 1-mm intervals [21]. For each visit, the mean cIMT was calculated by averaging all measures (far wall) from the six carotid sites (Supplemental Fig. 1). A previous study reported that in ARIC between-reader reliability coefficients for cIMT ranged from 0.78 to 0.93 and coefficients of variation ranged from 13.1% to 18.3% [22]. ARIC ultrasound readers recorded the presence of atherosclerotic plaque at any of the 6 segments, defined as wall thickness more than 1.5 mm or the presence of lumen encroachment, irregular intimal surface, and/or image characteristics indicative of structural heterogeneity of the arterial wall.

In the carotid ultrasound examination at Visit 2, the carotid arterial systolic and diastolic arterial diameters were measured with an ultrasonic echo-tracking radiofrequency device (Autrec 4881-AWT, Winston-Salem, NC) [23]. A diameter change was calculated to represent change in arterial diameter between systole and diastole from the left common carotid artery during cardiac cycles. Concurrently, two brachial blood pressures were measured with an automated oscillometric device (1846SX Dinamap, Critikon, Inc., Tampa, FL), and the mean of the two blood pressure measures was used in calculating arterial stiffness indices. Based on the ultrasound and blood pressure measures, Beta Index was generated as a stress-strain ratio representing carotid artery distensibility [23]. Beta Index was calculated as $\log(\text{systolic blood pressure}/\text{diastolic blood pressure})/(\text{arterial diameter change}/\text{diastolic arterial diameter})$. A higher Beta Index indicates less carotid distensibility.

In home interview and clinical examinations at Visits 1 and 2, standardized questionnaires were used to obtain information on demographics, lifestyle risk factors including smoking history, medication use, and medical history. Smoking status was categorized as never, former (more than 100 cigarettes in the past), or current smoker at each visit [24]. Smoking pack-years were calculated among the current and former smoker groups, based on the number of cigarettes per day and duration of smoking. Height was measured without shoes to the nearest centimeter at Visit 1. Weight was measured in a scrub suit to the nearest pound using a beam balance scale at Visits 1 and 2. Body mass index was calculated by dividing weight (in kilograms) from the corresponding Visit by height (in meters) squared from Visit 1. At both visits, systolic and diastolic fifth phase blood pressures were measured three times after a 5-minute rest in the right arm of seated participants by certified technicians using random zero sphygmomanometers. The mean of the last two measurements was used in analysis. Prevalent hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medications. Blood specimens were collected into vacuum tubes, centrifuged at 3000g for 10 minutes at 4°C, and then stored at -70°C until analysis within a few weeks. Serum glucose was assessed by the hexokinase method [25]. Prevalent diabetes mellitus was defined as a fasting glucose ≥ 126 mg/dL, a nonfasting glucose ≥ 200 mg/dL, and/or a history of or treatment for diabetes. Plasma total cholesterol was measured by enzymatic methods [26]. HDL cholesterol was measured after dextran-magnesium precipitation [27]. At Visit 1, white blood cells were counted with Coulter counters [8], and fibrinogen was measured by the thrombin-time titration method with reagents and calibration materials (Fibriquik) obtained from General Diagnostics (Organon-Technika Co) [28].

Statistical analyses

We included ARIC participants who had carotid ultrasound measures at ARIC Study Visits 1 or 2 ($n = 15,671$), all of whom were then followed for clinical AAA status. For the analysis of cIMT and plaque, we excluded 55 participants who were in race groups other than white or black or blacks in Minneapolis or Washington County, 11 who had prior AAA surgery, and 30 with uncertain AAA status during follow-up. We further excluded 1,002 participants without measurement of cIMT, leaving a final sample size of 14,573. For the analysis of Beta Index which was measured at Visit 2 only, we excluded from 14,348 participants of baseline population 91 who were in race groups other than white or black or blacks in

Minneapolis or Washington County, 22 who had AAA surgery or AAA prior to Visit 2, 24 with uncertain AAA status during follow-up, and 3,921 without carotid Beta Index, leaving a final sample of 10,290 participants.

Carotid plaque (yes/no) measured at Visit 1 and Beta Index measured at Visit 2 were analyzed. For cIMT analyses, if the measurement was available only at Visit 1, or if a participant had an AAA between Visits 1 and 2, then the Visit 1 measure of cIMT was used. Otherwise, the average cIMT value of both Visits 1 and 2 (three years apart) was used in the analysis to reduce random error in the measurement. In both situations, Visit 1 was baseline for the analysis of cIMT. Both cIMT and Beta Index were categorized into quartiles in the analysis.

We plotted Kaplan-Meier curves to depict the unadjusted association of cIMT and Beta Index with clinical AAA risk. We used Cox regression models to calculate hazard ratios (and 95% confidence intervals) of incident clinical AAA according to presence/absence of carotid plaque or across quartiles of cIMT and Beta Index. Follow-up time was calculated from Visit 1 for carotid plaque analysis and cIMT analysis while from Visit 2 for carotid distensibility analysis. A trend test across quartiles was calculated using the ordinal number for quartiles as a continuous variable in the Cox models. The basic models to test our hypotheses were adjusted for age, sex, race, and ARIC field center. The additional models (i.e., fully adjusted models) were further adjusted for baseline height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes. In addition, interactions by sex or race were explored.

Sensitivity analysis—Given that there was no ultrasound examination available to identify prevalent AAAs at baseline, to address the possibility of reverse causality, we performed a secondary analysis by excluding AAAs who were ascertained during the first 10 years of follow-up. Since Medicare outpatient claims have unknown validity in the diagnosis of AAA, we also performed a sensitivity analysis by excluding outpatient AAAs which were not verified by hospitalization records, death records, or the ultrasound exam. Additional sensitivity analyses included further adjustment for Visit 1 fibrinogen or white blood cell count, which were associated with AAA in ARIC [8]. We performed another sensitivity analyses by further adjusting for body mass index, waist circumference, diastolic blood pressure, alcohol intake, and plasma triglycerides in the fully adjusted models. Moreover, we conducted the following analyses to account for competing risk of atherosclerotic cardiovascular disease and death: a) excluded prevalent coronary heart disease, stroke, and myocardial infarction at baseline; b) used a cause-specific Cox regression model where each participant was classified as either an AAA event, censored, or a cardiovascular disease event, whichever occurred first; the time to the first event—either an AAA or another cardiovascular event—was considered the failure time; c) repeated analysis b) using death instead of cardiovascular event [29, 30]. Finally, we included cIMT and Beta Index simultaneously in the fully-adjusted models to evaluate the independence of these two indices in their associations with AAA. SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA) was used in all analyses.

RESULTS

Baseline description

At Visit 1 in 1987–1989, the mean age of this ARIC sample (N=14,573) at risk of AAA was 54.2 years (SD 5.8); 45% were male and 73% were white. Approximately 34.2% of participants had carotid plaque. As shown in Table 1, on average, participants in the higher quartiles of cIMT were older, more often male, non-white, current/former smokers, hypertensive, diabetic, had carotid plaque, had lower levels of high-density lipoprotein cholesterol, and had higher levels of weight, body mass index, total cholesterol, systolic/diastolic blood pressure, fibrinogen, white blood cell count, and Beta Index (all p for trend < 0.0001). The pattern of risk factor associations with Beta Index at Visit 2 was similar to that for cIMT with the exception that white blood cell count was not associated with Beta Index and smoking was inversely associated with Beta Index (Supplemental Table 1).

Carotid atherosclerosis in relation to AAA

During a median of 22.5 years of follow-up through 2011, 542 clinical AAAs were ascertained. Similar to the pattern observed on Kaplan-Meier curves (Supplemental Fig. 2A), participants in the highest quartile of cIMT (>0.82 mm) had 2.71-fold increased risk of incident clinical AAA [95% CI: 2.01, 3.67], compared to the lowest quartile, after adjustment for age, sex, race, and ARIC field center (p for trend <0.0001) (Table 2). With further adjustment for other risk factors (model 2), a linear relationship remained (p for trend: 0.006; hazard ratio [95% CI] for the highest vs. lowest quartiles of cIMT: 1.55 [1.13, 2.11]). Participants who had a carotid plaque had 1.31 (95% CI: 1.10, 1.57; p : 0.003) times higher risk of incident clinical AAA than those without a plaque in the fully adjusted model (Table 3).

Carotid artery distensibility in relation to AAA

Consistent with the pattern shown on the Kaplan-Meier curves (Supplemental Fig. 2B), there was a positive association between Beta Index quartiles and clinical AAA in the fully adjusted model (p for trend 0.006); participants in the highest quartile of the Beta Index (>13.05), indicating less carotid distensibility, had 1.68 (95% CI: 1.16, 2.43) times higher risk of incident clinical AAA compared to those in the lowest quartile (Table 4).

The above associations for all of the three carotid measures did not differ significantly by sex or race (all p for interactions > 0.05, data not shown).

Sensitivity analyses

The associations of AAA with cIMT, carotid plaque, and Beta Index were similar in our sensitivity analysis after excluding AAAs occurring in the first 10 years of follow-up. For example, in the fully adjusted model, the hazard ratio of incident clinical AAA for carotid plaque presence vs. absence was 1.38 (95% CI: 1.13, 1.68, p : 0.002); the hazard ratio (95% CI) of incident clinical AAAs for the highest vs. lowest quartile of cIMT was 1.47 (1.05, 2.05) and p for trend was 0.03; the hazard ratio (95% CI) of incident clinical AAAs for the highest vs. lowest quartile of Beta Index was 1.49 [1.01, 2.20], and p for trend was 0.04. Results remained consistent after removing 101 Medicare outpatient AAAs who were not

verified by hospitalization/death records or ultrasound exam; additionally adjusting for white blood cell count, fibrinogen, waist circumference, body mass index, diastolic blood pressure, triglycerides, or alcohol intake did not materially change the associations of any of the three carotid measures with AAA risk (data not shown). In the competing risk analyses, consistent results were observed after accounting for the competing risk of cardiovascular events or death; the associations became slightly stronger after excluding prevalent cardiovascular disease at baseline (data not shown). Furthermore, in the fully adjusted model, the associations of cIMT and Beta Index with AAA risk remained significant with mutual adjustment for each other (Supplemental Table 2).

DISCUSSION

This population-based prospective study showed that carotid atherosclerosis as represented by greater cIMT or presence of plaque and carotid stiffness as represented by reduced carotid artery distensibility were associated with higher risk of clinically detected, incident AAA. Our findings indicate that persons with carotid atherosclerosis or ‘stiff’ carotid arteries are at a higher risk for AAA than those without these conditions. This information might be useful in consideration of a prediction model to identify high risk individuals for AAA screening.

Although an atherosclerosis-AAA association has not been directly documented in previous epidemiological studies, a dose-response relationship between atherosclerosis as reflected by carotid total plaque area and maximal abdominal aortic diameter was reported in a cross-sectional survey including Norwegians aged 55 to 74 years with and without AAA [31]. A follow-up study of 2,019 persons in that sample showed that one-standard-deviation increase in carotid plaque area was associated with 0.12 mm concurrent growth in average infrarenal aortic diameter over 6–7 years (including 130 AAAs) [17]. In contrast, our study prospectively examined the association between baseline carotid ultrasound and a large number of incident AAAs ascertained over two decades. Our findings suggest that subclinical carotid atherosclerosis is a risk marker for clinical AAA. Although any biological link is indirect, because we assessed atherosclerosis in the carotids, not the abdominal aorta, it is well known that atherosclerosis is typically widespread throughout the vasculature [14]. Therefore, the association observed in our study likely reflects a relation between general atherosclerosis and AAA occurrence.

With regard to our findings that AAA is more likely to occur in the presence of subclinical atherosclerosis, data from animal studies have shown that aortic aneurysms often form after prolonged exposure to atherogenic conditions reflected by aortic atherosclerotic plaque [32]. Atherosclerotic plaques in the aortic wall include matrix fibers, and the expansion of plaques may simultaneously dilate and weaken aortic walls that support mural tension, potentially leading to aneurysmal enlargement [32]. Studies have demonstrated that atherosclerosis, although initially occurring in the intima, promotes the dilation or shrinkage of the tunica media and adventitia; this in turn aggravates luminal obstruction and promotes vascular remodeling via a disturbance in the synthesis and degradation of matrix proteins [33, 34]. In addition, atherosclerotic plaques may be associated with later arterial dilation [35]. On the other hand, atherosclerosis clearly is not necessary for AAA formation. AAA can form with

toxic exposure to smoking, or for instance, with hypertension, Marfan's syndrome, Chlamydia pneumoniae infection, or syphilis [36]. Thus, a link between atherosclerosis and AAA is largely supported by physiological data but further pathological and epidemiological evidence is warranted to establish a causal relationship.

On the other hand, it may be that both atherosclerosis and AAA are the result of common risk factors or a common genetic predisposition (pleiotropy), and there is no direct pathophysiological connection of atherosclerosis with AAA. We adjusted for many AAA risk factors, but residual confounding may be present from measurement error in those risk factors or from failure to adjust for unrecognized or unmeasured AAA risk factors.

Concerning arterial stiffness and AAA, in vivo studies have shown a greater stiffness of dilated or aneurysmal aortic walls in AAAs [37, 38]. As the pathogenesis of AAA is related to an alteration in systemic connective tissue metabolism, change in wall stiffness may occur in the rest of the vascular system, such as the carotid arteries, of AAA patients [39]. So far, only a small cross-sectional, hospital-based study reported that patients with AAA had a higher carotid artery Beta Index than did those without AAA [18]. In addition, carotid stiffness has been positively associated with abdominal aortic diameters both in AAAs and non-AAAs [40, 41]. To our knowledge, our study is the first investigation showing that greater carotid stiffness is prospectively associated with higher risk of AAA in the general population. Findings from our study as well as the previous studies suggest that carotid stiffness index is a risk marker of AAA.

The inverse association between smoking (collected in 1990–92 at Visit 2) and Beta Index, suggesting that smoking is associated with more distensible carotid arteries, was unexpected. A possible explanation is that some participants who had a more severe cardiovascular risk factor profile at Visit 1 may have stopped smoking around the Visit 2 exam. For example, we noticed that participants with prevalent hypertension smoked less compared to those without hypertension in ARIC Visit 2 (ever smoker 57% vs. 60%; p for difference <0.001); a similar pattern was also observed for prevalent diabetes (ever smoker 56% vs. 59%; p for difference <0.001). Future research is warranted to clarify this issue.

The strengths of our study include the prospective design, high quality measurements of exposures and outcomes, and a large sample size with a large number of incident AAAs. Nonetheless, the following limitations should be acknowledged when interpreting our results. First, misclassification may have occurred. Misclassification in the carotid ultrasound measures would likely have been non-differential with respect to AAA status given the prospective design of our study. Misclassification in the AAA outcomes would also likely have been non-differential, since staff who ascertained AAAs in ARIC were blinded to the exposure status. Non-differential misclassifications most likely would have diluted the estimates of association between AAA and exposures. Second, as noted above and as in other observational studies, residual confounding cannot be eliminated. Third, the clinical AAAs were ascertained based on ICD codes, and thus included both symptomatic and medically documented, asymptomatic AAAs. Finally, since there was no baseline ultrasound exam for AAA, we cannot verify that atherosclerosis and carotid stiffness always preceded incident AAA. However, participants who had AAAs through ARIC Visit 5 were

likely free of AAA when they were aged 45–64 years at baseline considering the low prevalence of AAAs in that age group (about 1.8% in men and 0.2% in women) [42]. Our sensitivity analysis excluding clinical AAAs ascertained within 10 years of baseline showed similar results to our main analysis.

In conclusion, this large, population-based cohort study, with more than 20 years of follow-up, showed that carotid atherosclerosis and stiffness were associated positively with future risk of AAA, independent of traditional risk factors for atherosclerosis and AAA. The association likely reflects the underlying link between general atherosclerosis, arterial stiffness, and AAA or the impact of risk factors common to AAA and these conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

Findings of this report were based on a large, population-based cohort study with more than 20 years of follow-up.

Carotid atherosclerosis was associated with increased risk of clinical abdominal aortic aneurysms (AAA)

Low carotid distensibility was also associated with increased risk of clinical AAA

Table 1
Baseline characteristics by quartiles of carotid intima-media thickness (cIMT), ARIC, 1987–89

Characteristics ^a	cIMT quartile				p for trend
	1 N=3643	2 N=3643	3 N=3644	4 N=3643	
cIMT median, mm	0.59	0.67	0.76	0.93	
cIMT range, mm	0.37 – 0.63	0.64 – 0.71	0.72 – 0.82	0.83 – 2.26	
Carotid plaque, %	431 (11.8)	746 (20.5)	1279 (35.1)	2532 (69.5)	<0.0001
Age, years	51.6 (5.2)	53.4 (5.5)	54.8 (5.6)	57.0 (5.3)	<0.0001
Male, %	965 (26.5)	1395 (38.3)	1864 (51.2)	2297 (63.1)	<0.0001
White, %	2878 (79.0)	2642 (72.5)	2612 (71.7)	2705 (74.3)	<0.0001
Height, cm	166.3 (8.7)	167.8 (9.2)	169.5 (9.4)	170.5 (9.2)	<0.0001
Weight, kg	72.5 (15.5)	77.7 (15.8)	80.9 (16.5)	81.4 (16.2)	<0.0001
Body mass index, kg/m ²	26.2 (5.0)	27.5 (5.1)	28.1 (5.2)	28.0 (4.9)	<0.0001
Smoking status					<0.0001
Current smoker, %	833 (22.9)	881 (24.2)	930 (25.6)	1185 (32.5)	
Former smoker, %	970 (26.7)	1090 (30.0)	1221 (33.5)	1415 (38.9)	
Never smoker, %	1837 (50.4)	1669 (45.8)	1490 (40.9)	1042 (28.6)	
Pack-years among smokers	21.6 (17.6)	24.6 (19.9)	28.8 (22.7)	34.9 (24.3)	<0.0001
Total cholesterol, mg/dL	205.5 (40.2)	213.3 (40.7)	217.1 (41.3)	222.2 (42.7)	<0.0001
High-density lipoprotein cholesterol, mg/dL	56.8 (17.7)	53.3 (17.9)	49.9 (16.1)	47.2 (15.4)	<0.0001
Lipid lowering medication, %	73 (2.0)	87 (2.4)	105 (2.9)	150 (4.2)	<0.0001
Systolic blood pressure, mmHg	114.7 (16.7)	119.2 (17.1)	122.7 (18.0)	127.6 (20.5)	<0.0001
Hypertensive medication use, %	751 (20.6)	1018 (28.0)	1160 (31.8)	1411 (38.8)	<0.0001
Diabetes, %	190 (5.3)	345 (9.6)	440 (12.2)	650 (18.0)	<0.0001
Fibrinogen, mg/dL	292.9 (58.4)	298.8 (63.4)	302.5 (64.4)	316.3 (71.1)	<0.0001
White blood cell count, 1000 cells/mm ³	5.9 (1.9)	6.0 (1.9)	6.1 (1.9)	6.5 (2.1)	<0.0001
Beta Index ^b	10.0 (3.7)	10.8 (4.1)	11.5 (4.6)	12.7 (5.6)	<0.0001

^aMean (SD) for continuous variables or N (%) for categorical variables;

^bBeta index was measured in 1990–1992.

Table 2

Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT), ARIC, 1987–2011

cIMT	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p for trend
Quartile range, mm	0.37 – 0.63	0.64 – 0.71	0.72 – 0.82	0.83 – 2.26	
N at risk	3643	3644	3644	3644	
No. events	59	95	139	249	
Incidence rate ^a	0.76 (0.59, 0.98)	1.26 (1.03, 1.55)	1.92 (1.63, 2.27)	3.90 (3.45, 4.42)	
HR (95% CI)					
Model 1 ^b	1	1.32 (0.96, 1.84)	1.62 (1.18, 2.21)	2.71 (2.01, 3.67)	<0.0001
Model 2 ^c	1	1.11 (0.80, 1.54)	1.15 (0.84, 1.59)	1.55 (1.13, 2.11)	0.006

CI: confidence interval; HR: hazard ratio;

^aCrude incidence rate per 1000 person-years;^bModel 1: Adjusted for age, sex, race, and ARIC center;^cModel 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3
Risk of clinical abdominal aortic aneurysm in relation to presence vs. absence of carotid plaque, ARIC, 1987–2011

Plaque (y/n)	Absence	Presence	p value
N at risk	9596	4989	
No. events	259	283	
Incidence rate ^a	1.31 (1.16, 1.48)	3.11 (2.77, 3.49)	
HR (95% CI)			
Model 1 ^b	1	1.82 (1.53, 2.17)	<0.0001
Model 2 ^c	1	1.31 (1.10, 1.57)	0.003

^aCrude incidence rate per 1000 person-years;

^bModel 1: Adjusted for age, sex, race, and ARIC center;

^cModel 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 4

Risk of clinical abdominal aortic aneurysm in relation to quartiles of Beta Index of the carotid artery, ARIC, 1990–2011

Beta Index ^a	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p for trend
Quartile range	2.83 – 8.17	8.18 – 10.28	10.29 – 13.05	13.06 – 44.49	
N at risk	2572	2573	2573	2572	
No. events	50	89	102	111	
Incidence rate ^b	1.05 (0.79, 1.38)	1.91 (1.55, 2.35)	2.25 (1.85, 2.73)	2.55 (2.12, 3.07)	
HR (95% CI)					
Model 1 ^c	1	1.58 (1.11, 2.24)	1.68 (1.19, 2.38)	1.72 (1.21, 2.44)	0.003
Model 2 ^d	1	1.61 (1.12, 2.31)	1.62 (1.12, 2.33)	1.68 (1.16, 2.43)	0.006

CI: confidence interval; HR: hazard ratio;

^aHigher level of the Beta Index indicates less carotid artery distensibility;

^bCrude incidence rate per 1000 person-years;

^cModel 1: Adjusted for age, sex, race, and ARIC center;

^dModel 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 2.