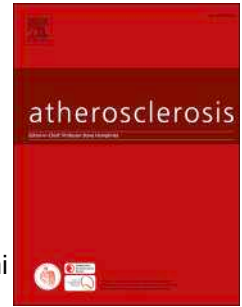


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Symptomatic and asymptomatic peripheral artery disease and the risk of abdominal aortic aneurysm: The Atherosclerosis Risk in Communities (ARIC) study

Caitlin W. Hicks, Ada Al-Qunaibet, Ning Ding, Lucia Kwak, Aaron R. Folsom, Hirofumi Tanaka, Thomas Mosley, Lynne E. Wagenknecht, Weihong Tang, Gerardo Heiss, Kunihiro Matsushita



PII: S0021-9150(21)01277-6

DOI: <https://doi.org/10.1016/j.atherosclerosis.2021.08.016>

Reference: ATH 16704

To appear in: *Atherosclerosis*

Received Date: 24 December 2020

Revised Date: 1 July 2021

Accepted Date: 10 August 2021

Please cite this article as: Hicks CW, Al-Qunaibet A, Ding N, Kwak L, Folsom AR, Tanaka H, Mosley T, Wagenknecht LE, Tang W, Heiss G, Matsushita K, Symptomatic and asymptomatic peripheral artery disease and the risk of abdominal aortic aneurysm: The Atherosclerosis Risk in Communities (ARIC) study, *Atherosclerosis* (2021), doi: <https://doi.org/10.1016/j.atherosclerosis.2021.08.016>.

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**Author Contributions**

CWH, AAQ, ND, and KM designed and conceptualized study and analyzed the data. CWH, AAQ, ND, LK, ARF, HT, TM, LEW, WT, GH, and KM interpreted the data. CWH, AAQ, ND, and KM drafted the manuscript for intellectual content. LK, ARF, HT, TM, LEW, WT, and GH revised the manuscript for intellectual content. All authors gave approval for submission of the final manuscript.

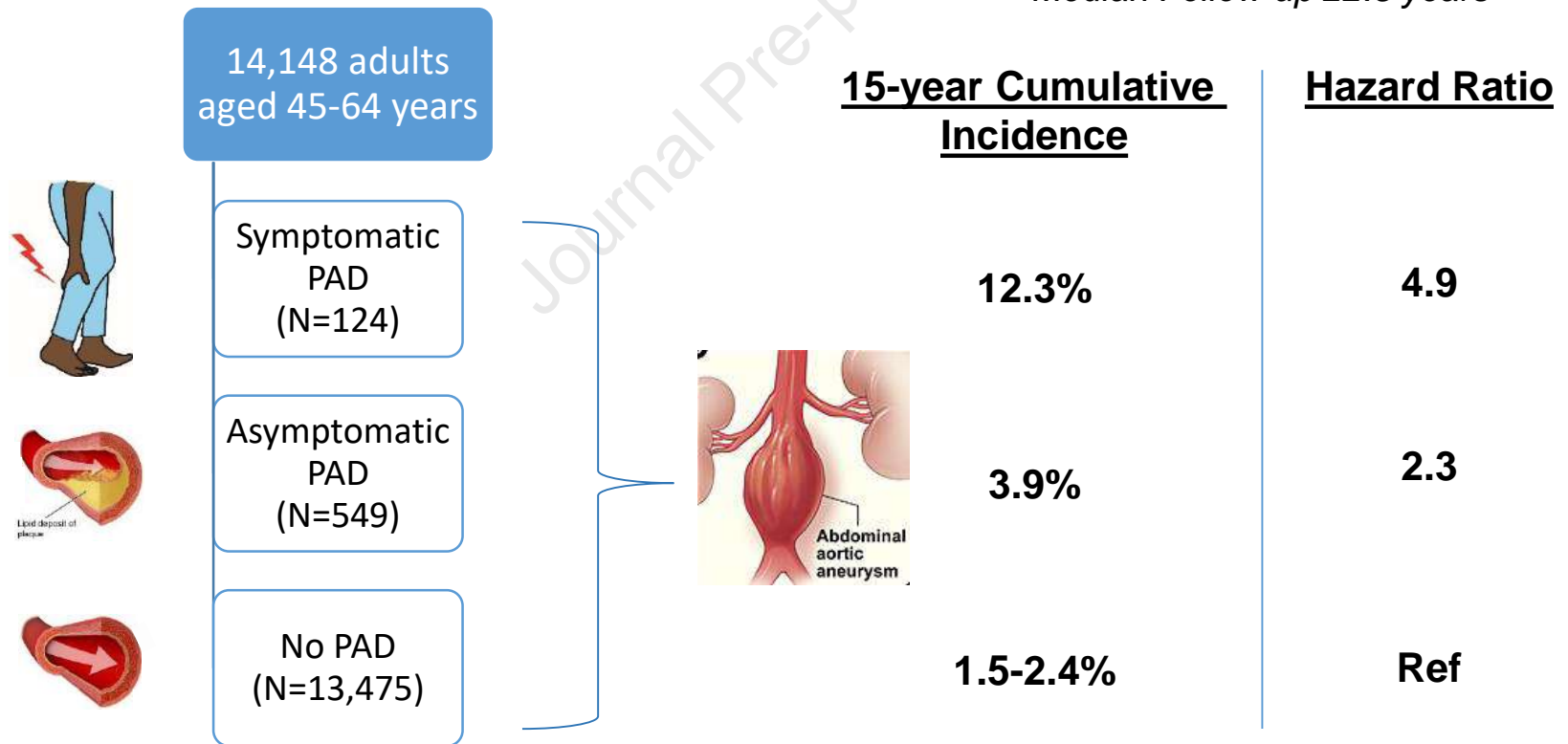
# Symptomatic and Asymptomatic Peripheral Artery Disease (PAD) is Associated with Increased Risk of Abdominal Aortic Aneurysm (AAA)

## Study Population



## Risk of AAA

*Median Follow-up 22.5 years*



**Symptomatic and asymptomatic peripheral artery disease and the risk of abdominal aortic aneurysm: The Atherosclerosis Risk in Communities (ARIC) Study**

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**Abstract**

*Background and aims:* Symptomatic peripheral artery disease (PAD) is a risk factor for abdominal aortic aneurysm (AAA). However, data on the association of asymptomatic PAD with AAA are limited. We explored the association of symptomatic and asymptomatic PAD with AAA.

*Methods:* We primarily assessed a prospective association of symptomatic (based on clinical history) and asymptomatic (ankle-brachial index  $\leq 0.9$ ) PAD at baseline (1987-89 [ages 45-64 years]) with incident AAA in a biracial community-based cohort, the Atherosclerosis Risk in Communities Study. We secondarily investigated a cross-sectional association of PAD with ultrasound-based AAA (diameter  $\geq 3.0$  cm) (2011-13 [ages 67-91 years]).

*Results:* Of 14,148 participants (55.1% female, 25.5% black, 0.8% with symptomatic PAD) in our prospective analysis (median follow-up 22.5 years), 530 (3.7%) developed incident AAA. Symptomatic PAD had a higher hazard ratio (HR) of incident AAA [4.91 (95%CI 2.88-8.37)], as did asymptomatic PAD with ABI  $\leq 0.9$  [2.33 (1.55-3.51)], compared to the reference ABI  $> 1.1-1.2$  in demographically-adjusted models. Crude 15-year cumulative incidence of AAA in these three groups were 12.3%, 3.9%, and 1.5%, respectively. The associations remained significant after accounting for other potential confounders [corresponding HR 2.96 (95%CI 1.73-5.07) and 1.52 (95%CI 1.00-2.30), respectively]. The cross-sectional analysis demonstrated similar patterns with ultrasound-based AAA [odds ratio 2.46 (95%CI 1.26-4.81) for symptomatic PAD and 3.98 (1.96-8.08) for asymptomatic PAD in a demographically-adjusted model].

*Conclusions:* Our prospective and cross-sectional data show elevated risk of AAA in both symptomatic and asymptomatic PAD. Our data support the current recommendation of AAA

screening in symptomatic PAD patients and suggest the potential extension to asymptomatic PAD patients as well.

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## 1. Introduction

Abdominal aortic aneurysms (AAA) affect between 3.9% and 7.2% of men and between 1.0% and 1.3% of women based on population-based studies <sup>1</sup>. The main risk conveyed by AAA is rupture, with high fatality rates ranging between 75-90% <sup>1</sup>. The majority of AAA are asymptomatic until rupture, which highlights the importance of screening. A one-time screening for AAA has been previously shown to significantly reduce AAA-specific mortality <sup>2,3</sup>. In the largest randomized trial to date, AAA screening of men aged 65-74 years reduced AAA-related death by 42% over 13 years <sup>3</sup>.

The US Preventive Services Task Force (USPSTF) currently recommends a one-time ultrasound screening for AAA in men ages 65 to 75 years of age who have a history of smoking <sup>4</sup>. This recommendation is made based on the observation that men with a smoking history have an estimated AAA prevalence of 6-7% <sup>5,6</sup>, compared to a prevalence of only 2% in men who never smoked <sup>5</sup>. However, peripheral artery disease (PAD) has been shown to be a risk factor for AAA independent from smoking. In a meta-analysis by Cornuz et al. investigating risk factors associated with AAA detected by screening, PAD was associated with a 2.5-times higher odds of AAA than no PAD <sup>7</sup>. A more recent meta-analysis by Li et al. similarly demonstrated that intermittent claudication was associated with a 3-times higher odds of AAA in the general population <sup>8</sup>.

Based on these observations, the American Heart Association (AHA) guidelines recommend a screening duplex ultrasound for AAA for patients with symptomatic PAD <sup>9</sup>. However, there are limited epidemiological data on the association of asymptomatic PAD with AAA. This is a critical knowledge gap since many persons with PAD are asymptomatic <sup>10</sup>. To address this question, we conducted a prospective and cross-sectional investigation of the

association of symptomatic and asymptomatic PAD with AAA in the Atherosclerosis Risk in Communities (ARIC) study.

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## 2. Patients and methods

### 2.1 Study population

The ARIC study is a prospective study of adults aged 45 and 64 years at intake in 1987-89, from four U.S. communities (Washington County, Maryland; suburban Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Carolina). The current study included two analyses: our primary analysis, which was a prospective analysis with incident AAA (based on a clinical diagnosis) as the outcome; and a secondary analysis, which was a cross-sectional analysis with ultrasound-based AAA (diameter  $\geq 3.0$  cm).

For our primary analysis from all ARIC participants at visit 1 (1987-1989) (n=15,792), we excluded individuals whose race/ethnicity was other than white or black (n=48), those who had AAA surgery prior to visit 1 (n=11) or AAA surgery without an AAA diagnosis code (n=2), those who had missing baseline ankle brachial index (ABI) (n=583), and those who were missing other variables of interest (n=1,286) (specific variables listed in Supplemental Table 1). The final sample for the prospective analysis was 14,148 participants.

For our secondary analysis, we used data from visit 5 of the ARIC study cohort (2011-2013). Of 6,538 participants at visit 5, we excluded participants whose race/ethnicity was other than white or black (n=18), those who had missing aortic diameter variables (proximal, mid, or distal diameter) (n=903), those who had missing ABI values (n=335), and those who were missing other covariates of interest (n=618), leaving a final study sample for the cross-sectional analysis of 4,664 participants.

The study was approved by the Institutional Review Board at each participating institution. Written informed consent was provided by the participants for each examination.

## 2.2 Symptomatic and asymptomatic PAD

For our prospective analysis, symptomatic PAD was defined based on the presence of intermittent claudication or a history of prior lower extremity revascularization at visit 1. The presence of intermittent claudication was defined by a standardized, interviewer-administered questionnaire as participant-reported leg pain that started during walking and went away within 10 minutes after rest. Prior lower extremity revascularization was identified based on self-report.

For our secondary analysis, symptomatic PAD was based on self-reported leg pain symptoms, prior lower extremity revascularization, and/or a hospital diagnosis of critical limb ischemia at or prior to visit 5. Leg pain was defined as present when participants answered yes to the questions “any leg pain due to blockage of arteries” or “any medication use for leg pain while walking, or claudication” in semi-annual follow-up interviews prior to visit 5. Prior lower extremity revascularization and critical limb ischemia were defined based on ICD9-CM codes for leg artery revascularization (440.3x, 38.18, 39.25, 39.29, 39.5x), atherosclerosis of native arteries of the extremities with rest pain (440.22), atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); or any diagnosis of PAD (440.20; 440.21; 440.29; 440.3; 440.4) with coexisting codes of leg amputation (84.1x), lower extremity ulcer (707.1x), or gangrene (785.4) <sup>11</sup>.

Asymptomatic PAD was based on the value of the ABI, the ratio of a participant’s systolic blood pressure at the ankle compared to that at the brachial artery. At visit 1, ABI was measured by an oscillometric device that automatically obtains repeated blood pressure measurements (Dinamap Model 1846 SX). The ankle systolic blood pressure was measured four times in a randomly selected leg, and the last non-missing value was used as the numerator to calculate ABI. The brachial systolic blood pressure was measured twice in the right arm, and the first non-missing value was used as the denominator to calculate ABI. Using this method, the reliability for

ABI has been shown to be 0.61 (95% CI 0.50-0.70)<sup>12</sup>. For visit 5, the ABI was measured using another oscillometric device, VP-1000 Plus (Omron Co., Ltd., Kyoto, Japan), following a standardized protocol. This device employs a double cuff technology where one cuff inflates while the other detects oscillation. The participant was in the supine position with both arms resting along his/her side. Size-appropriate blood pressure cuffs were placed on both arms and ankles. Blood pressure was measured simultaneously in the four limbs at least twice at an approximately 5-minute interval. The VP-1000 Plus estimates ABI for each lower extremity as  $ABI = \text{ankle systolic blood pressure} / (\text{higher of left and right arm systolic blood pressure})$ . In general, the lower ABI value for each individual was used. However, when the higher ABI value was greater than 1.3 and the lower ABI value was between 1.0 and 1.3, the higher value was used<sup>13</sup>. The ABI measurements using oscillometric devices have previously shown to be highly correlated with manual methods, with a correlation coefficient of 0.95<sup>14</sup>.

### 2.3 Covariates

Details about collection and definitions of covariates are described in Supplemental data.

### 2.4 Incident abdominal aortic aneurysm for the primary analysis

The ARIC Study identified participants with incident clinical AAA based on annual follow-up telephone calls, detailed medical records, and surveillance of local hospital records as previously described<sup>15,16</sup>. In addition, the ARIC study identified participants who developed a clinically diagnosed AAA based on linkage with data from the Centers for Medicare and Medicaid Services (CMS). Clinical AAA was defined as a hospitalization from any source or two CMS outpatient claims documented  $\geq 7$  days apart with ICD-9 diagnosis codes of 441.3 (abdominal aneurysm, ruptured), 441.4 (abdominal aneurysm without mention of rupture), 38.44 (resection of

vessel with replacement, aorta, abdominal) or 39.71 (endovascular implantation of other graft in abdominal aorta) or deaths with the ICD-9 or 10 codes of 441.3, 441.4, I71.3 (abdominal aortic aneurysm, ruptured) or I71.4 (abdominal aortic aneurysm, without rupture). Any AAA diagnoses based on a procedure code had to be verified by diagnosis codes as well.

### *2.5 Ultrasound-based abdominal aortic aneurysms for secondary analysis*

Abdominal aorta diameters were measured by high resolution, real time duplex ultrasound (Philips IE33) at ARIC visit 5 (2011-2013). To ensure data quality, the certified technologists and radiologists were trained to follow standardized scanning and reading protocols. Transverse and anterior-posterior diameters were measured at three standardized levels of the abdominal aorta. The images were taken at the following anatomical positions: proximal aorta below the superior mesenteric artery, proximal infrarenal aorta 2 cm below the renal arteries, distal infrarenal aorta 1 cm superior to the aortic bifurcation, and the point of maximal abdominal aortic dilatation if it was not at the level of proximal or distal infrarenal aorta. Participants with a history of previous AAA repair or previous aortic bypass surgery for occlusive atherosclerotic disease were not scanned. In this study we focused on maximum abdominal aorta diameter reported as a binary variable according to the presence ( $\geq 3.0$  cm) or absence ( $< 3.0$  cm) of an AAA.

### *2.6 Statistical analysis*

For the primary analysis, we compared baseline characteristics across categories of symptomatic PAD, asymptomatic PAD ( $ABI \leq 0.9$ ) and five other ABI categories ( $>0.9-1.0$ ,  $>1.0-1.1$ ,  $>1.1-1.2$ ,  $>1.2-1.3$ , and  $>1.3$ ). We then examined the association of these categories with incident AAA. We created three Cox proportional hazards models. Model 1 adjusted for age, sex, race, center, and education level. Model 2 additionally adjusted for baseline smoking status (never,

former, and current), alcohol use, diabetes, anti-hypertensive medication use, systolic blood pressure, body mass index, total and HDL cholesterol levels, prevalent coronary heart disease (CHD), heart failure (HF), and stroke. Model 3 was similar to Model 2, but adjusted for baseline smoking in pack-years rather than smoking status. The ABI category of >1.1-1.2 was considered as the reference group, as recommended<sup>17</sup> and because this category was the largest in our study population. Finally, among individuals without symptomatic PAD, we then characterized the strength and shape of association between the full spectrum of ABI and incidence rate of AAA (per 1,000 person-years) by modeling ABI as linear splines and accounting for age, sex, race, and center.

For the secondary (cross-sectional) analysis of ABI with AAA as measured by abdominal ultrasound at ARIC visit 5, we compared participant visit 5 characteristics across the same categories as the primary analysis (i.e., symptomatic PAD, asymptomatic PAD [ABI ≤0.9] and other ABI categories). We then quantified the associations of these categories with the presence of AAA on duplex ultrasound, which we defined as maximum abdominal aortic diameter ≥3 cm. Multivariable logistic regression models were run, with the same three models of progressive adjustment for potential confounders from ARIC visit 5 as the primary analysis described above.

We performed an additional analysis to assess the association of PAD and AAA with incident cardiovascular events in our prospective cohort using unadjusted Cox proportional hazards models.

All statistical tests for both analyses are 2-sided with a nominal significance level of  $P < 0.05$ . All analyses were performed using Stata, version 14.0 (StataCorp LP, College Station, TX).

### 3. Results

#### 3.1 Primary prospective analysis: PAD status and incident AAA

As shown in Table 1, the mean age at baseline of the 14,148 ARIC participants included in the primary analysis was 54.1 (SD 5.7) years, 3,608 (25.5%) were black, 7,795 (55.1%) were female, 1,641 (11.6%) had diabetes, and 4,287 (30.3%) were on anti-hypertensive medications. More than half of the participants (n=8,079, 57.1%) were current or former smokers. Symptomatic PAD was present in 124 participants (0.9%). The median ABI at visit 1 among those without symptomatic PAD was 1.13, with 549 (3.9%) participants having an ABI  $\leq$ 0.9.

Over a median of 22.5 years of follow-up, 530 (3.7%) participants developed incident AAA (crude incidence rate of 1.9 per 1,000 person-years. According to ICD codes, 30.7% of the incident AAA cases went on to undergo rupture or repair. There was a strong association of symptomatic PAD with incident AAA on Kaplan Meier survival analysis (Figure 1), with 15-year cumulative incidence of 12.3% of AAA among those with symptomatic PAD. Asymptomatic PAD with ABI  $\leq$ 0.9 also showed a higher cumulative incidence compared to other ABI categories (15-year cumulative incidence of 3.9% vs. 1.5%-2.4%, respectively).

These associations were statistically significant after adjustment for demographic variables [HR 4.91 (95% CI 2.88-8.37) for symptomatic PAD and HR 2.33 (95% CI 1.55-3.51) for asymptomatic PAD vs. ABI >1.1-1.2 (Model 1 in Table 2)]. We observed a slight attenuation in Model 2 but both associations remained statistically significant [HR 2.96 (95% CI 1.73-5.07) and HR 1.52 (95% CI 1.00-2.30), respectively]. The borderline low ABI category of >0.9-1.0 demonstrated a significant association with incident AAA only in Model 1 [HR 1.51 (95% CI 1.12-2.03)]. The associations were consistent when we adjusted for smoking pack-years (Model 3 in Table 2). The association of PAD with AAA was similar for women and men (p-value for interaction=0.78) and for black vs. white participants (p-value for interaction=0.28).

Among individuals without symptomatic PAD, we then characterized the continuous association between ABI and incidence rate of AAA (per 1,000 person-years) across the range of ABI values, after accounting for demographic variables. There was no evident risk gradient in the range of ABI >1.1-1.4 (Figure 2), but we observed a monotonically increasing incidence rate of AAA below 1.1.

### *3.2 Secondary cross-sectional analysis: PAD status and prevalent AAA*

The mean age of participants who underwent abdominal aortic duplex at exam visit 5 was 75.4 (SD 5.1) years (Supplemental Table 2). There were 517 participants (11.1%) with symptomatic PAD. The median ABI at visit 5 among those participants without symptomatic PAD was 1.13, with 260 (6.3%) participants having an ABI  $\leq$ 0.9. The overall means (and SDs) for the proximal, mid, and distal anterior-posterior abdominal aortic diameters were 2.0 (0.3) cm, 1.9 (0.4) cm, and 1.8 (0.4) cm respectively (Supplemental Table 2). The overall mean maximum abdominal aortic diameter was 2.1 (SD 0.4) cm. There were 106 (2.3%) participants with an AAA based on ultrasound measurements (maximum abdominal aortic diameter  $\geq$ 3.0 cm).

On multivariable logistic regression analysis (Table 3), compared with ABI >1.1-1.2, participants with asymptomatic PAD and ABI  $\leq$ 0.9 had a statistically increased prevalence of AAA based on Model 1 [OR 3.98 (95% CI 1.96-8.08)]. This association was slightly attenuated but remained significant in Model 2 [OR 2.20 (95% CI 1.03-4.70)]. Again, the adjustment for smoking pack-years did not materially alter the result (Model 3 in Table 3). Symptomatic PAD, compared with no PAD, was significantly associated with AAA only based on Model 1 [OR 2.46 (95% CI 1.26-4.81)]. Although ABI 0.9-1.0 did not reach statistical significance, ABI 1.0-1.1 demonstrated significantly higher odds of AAA compared to ABI >1.1-1.2 in all three Models, as did ABI >1.3 in Model 3 (Table 3).

### 3.3 Analysis of PAD status, prevalent AAA, and incident cardiovascular events

We performed an additional analysis to assess the association of PAD and AAA with incident cardiovascular events in our prospective cohort. There was a statistically significant association of PAD without AAA with incident cardiovascular events [HR 1.64 (95% CI 1.22-2.20)]. The group of PAD with AAA demonstrated HR of 2.28 (95% CI 0.57, 9.19) but this estimate is imprecise due to lack of power (Supplemental Table 3).

## 4. Discussion

We confirmed a strong positive association of symptomatic PAD with AAA in a prospective population-based analysis. In cross-sectional analysis, the association of symptomatic PAD with subclinical AAA was statistically significant only in a limited model adjusting for demographics. We also found a significant and robust positive association of asymptomatic PAD (i.e.  $ABI \leq 0.9$ ) with AAA in both prospective and cross-sectional analyses. The majority of these associations persisted after the adjustment for potential confounders, suggesting an independent relationship between lower extremity atherosclerotic disease and AAA in both symptomatic and asymptomatic individuals. We also observed a modest association between borderline low ABI of  $>0.9-1.0$  and incident AAA when adjusted for demographic variables.

Our finding that the association of PAD with incident AAA was strongest among individuals with symptomatic PAD is consistent with previous studies on the topic, although those studies were all cross-sectional. Barba et al. performed a screening abdominal ultrasound on 1,190 consecutive patients with chronic lower extremity ischemia between 1999 and 2004<sup>18</sup>. They found that the overall prevalence of AAA was 13%, which was nearly twice that of the general population<sup>1</sup>. Galland et al. similarly performed abdominal ultrasound on 242 patients with symptomatic PAD and found that AAA was present in 14% of patients<sup>19</sup>. Notably, the prevalence

of AAA was similar despite whether the patient had claudication, rest pain, or gangrene<sup>19</sup>. Our findings, together with those of others, support symptomatic PAD as a high risk condition for AAA as noted in the AHA guidelines<sup>9</sup>.

The weaker association of symptomatic PAD with AAA in our cross-sectional analysis compared to our prospective analysis deserves discussion. The reasons for this discrepancy could be three-fold. First, unlike visit 1, ARIC visit 5 did not collect detailed information about leg symptoms, and thus we relied on data obtained prior to visit 5 during semi-annual phone interviews and hospitalization data, which might result in misclassification. Second, visit 5 participants who had a history of previous aortic bypass surgery for occlusive atherosclerotic disease did not undergo an aortic duplex. It is thus possible that our cross-sectional estimates were biased toward null since we may have missed some AAA cases in those participants with symptomatic PAD and previous aortic bypass surgery. Third, the power of our cross-sectional analysis was low, with only 106 participants identified as having an AAA on duplex.

Probably the most novel finding of our study was the significant association of asymptomatic PAD with incident and prevalent AAA. Although previous meta-analyses have demonstrated an increased risk of AAA among patients with symptomatic PAD<sup>7,8</sup>, the association of asymptomatic PAD with AAA is less well established. Based on a longitudinal analysis of 4,734 adults >65 years of age, Newman et al. reported that an ABI  $\leq 0.9$  was associated with twice the risk of AAA compared to ABI  $> 0.9$  (24% vs. 12%)<sup>20</sup> but they did not separate AAA risk based on symptomatic vs. asymptomatic PAD. Sultan et al. found an increased risk of an AAA among patients with both asymptomatic PAD and asymptomatic carotid artery stenosis, but the specific risk of AAA among patients with asymptomatic PAD alone was not reported<sup>21</sup>. Thus, to our best of knowledge, our study is the first to report a significant association of asymptomatic PAD with both incident and prevalent AAA.

Notably, we also found a weak association of borderline low ABI (>0.9-1.0) with increased incident AAA after adjustment of sociodemographic variables. Based on our linear spline analysis, the incidence of AAA increased substantially for all ABI levels <1.1. The association of ABI >0.9-1.0 with incident AAA was attenuated after adjustment for confounding variables, but the presence of this association reinforces the notion that a borderline low ABI of >0.9-1.0 represents a category at elevated risk of cardiovascular events, including AAA <sup>9,22</sup>.

Currently the AHA <sup>9</sup>, but not the US Preventive Services Task Force <sup>23</sup> or the Society for Vascular Surgery <sup>24</sup>, recommends a screening duplex ultrasound for AAA for patients with symptomatic PAD. Screening for AAA in patients with asymptomatic PAD is not currently recommended by any professional guidelines because, “there are no data on AAA screening in patients with asymptomatic PAD” <sup>9</sup>. Our data generally support the current recommendation of AAA screening in symptomatic PAD patients, and suggest the potential to expand screening to asymptomatic PAD patients as well. Although the US Preventive Services Task Force only recommends AAA screening in men aged 65-75 years with smoking history <sup>23</sup>, a 2007 Cochrane review of four randomized controlled trials of population screening for AAA found a significant reduction in AAA-related mortality for men aged 65 to 79 years regardless of smoking status compared to those who were not screened <sup>25</sup>. Two more recent randomized controlled trials performed in Denmark <sup>2</sup> and England <sup>3</sup> confirmed a similar mortality benefit of screening for AAA. The screening of AAA in persons with PAD may have additional benefits beyond aortic repair, such as intensifying preventive therapies. Although there were too few events to fully analyze the association of PAD and AAA with incident cardiovascular events in this study, the point estimate of HR >2 suggests an elevated risk for patients with both PAD and AAA. This concept needs to be explored in future studies. Of note, although the concept is slightly different, the Viborg vascular (VIVA) screening trial demonstrated significantly reduced mortality by a

comprehensive screening of AAA, PAD, and elevated blood pressure in older men <sup>26</sup>. Although the cost-effectiveness of expanding AAA screening should be evaluated in future studies, our data support the notion that AAA screening in asymptomatic PAD patients may be useful.

Limitations of our study include identification of AAA based only on hospital diagnostic codes in our longitudinal analysis, the use of slightly different ABI measurement protocols at visit 1 compared to visit 5, and a lack of longitudinal ultrasound data to track the progression of AAA among affected individuals. Our use of a variety of approaches to identify participants with incident AAA based annual follow-up telephone calls, detailed medical records, and surveillance of local hospital records, as well as linkage with CMS outpatient claims <sup>15, 16</sup> mitigate the majority of these concerns. In addition, we were able to do a single ultrasound screening in approximately 60% of living ARIC participants in 2011-2013 that detected relatively few silent AAAs. Although this would not address asymptomatic AAA missed in those who had died or were not screened, our overall AAA incidence of 1.9% per 1,000 person-years is within the range of that reported by other population based studies <sup>1</sup>. Finally, as true in any observations studies, we cannot deny the possibility of residual confounding (e.g., smoking variables in our study might not completely capture smoking exposure).

#### **4.1 Conclusions**

Based on population-based ARIC data, we found a statistically significant positive association of symptomatic PAD with incident AAA. We also found a significant association of asymptomatic PAD ( $ABI \leq 0.9$ ) with incident and prevalent AAA. Our data support the current recommendation of AAA screening in symptomatic PAD patients and suggest the potential extension to those with asymptomatic PAD as well.

**Declaration of competing interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Financial support**

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). Dr. Hicks was supported by NIH/NIDDK grant K23DK124515. Dr. Matsushita was supported by NIH/NHLBI grant R21HL133694.

**Author contributions**

CWH, AAQ, ND, and KM designed and conceptualized study and analyzed the data. CWH, AAQ, ND, LK, ARF, HT, TM, LEW, WT, GH, and KM interpreted the data. CWH, AAQ, ND, and KM drafted the manuscript for intellectual content. LK, ARF, HT, TM, LEW, WT, and GH revised the manuscript for intellectual content. All authors gave approval for submission of the final manuscript.

**Acknowledgements**

The authors thank the staff and participants of the ARIC study for their important contributions.

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**Table 1. Baseline characteristics of ARIC participants by ABI category, 1987-1989**

	Overall	Symptomatic PAD	Asymptomatic ABI category					
			<0.9	>0.9-1.0	>1.0-1.1	>1.1-1.2	>1.2-1.3	>1.3
Number	14,148	124	549	1,786	3,324	4,154	2,817	1,394
Age	54.1 (5.7)	56.6 (5.5)	55.5 (5.9)	54.0 (5.8)	53.7 (5.6)	54.1 (5.8)	54.1 (5.7)	54.9 (5.7)
Black	25.5	21.8	30.8	25.9	26.6	26.6	23.9	20.7
Female	55.1	42.7	68.7	71.5	63.5	52.1	44.3	40.7
Center								
Forsyth County, NC	26	21.8	20.2	20.2	21.9	26.4	31.3	34
Jackson, MS	22.1	16.9	26.8	21.4	22.9	23.4	20.8	17.9
Minneapolis, MN	26.4	33.1	20.8	31.1	29.1	26.3	24.4	19.7
Washington County, MD	25.6	28.2	32.2	27.2	26.1	23.9	23.4	28.4
Education level								
Basic	22.9	31.5	33.5	25.5	23.8	22.7	19.7	19.7
Intermediate	41.2	46	41	42.2	42.1	41.5	39.2	40.6
Advanced	35.9	22.6	25.5	32.3	34.1	35.7	41	39.7
Smoking status								
Current	25.6	44.4	39.2	28.6	27.4	23.1	24	21
Former	32.1	39.5	25.7	28.8	30.1	34	34.4	32.9
Never	42.3	16.1	35.2	42.7	42.5	42.9	41.6	46.1
Pack-years of smoking	16.0 (21.8)	36.1 (28.1)	23.8 (27.2)	16.5 (22.9)	16.0 (21.4)	15.4 (21.1)	15.4 (21.0)	14.1 (20.4)
Drinking status								
Current	56.3	62.1	49.5	54.9	55.5	57.1	58.4	56.2
Former	18.7	22.6	21.5	18.7	18	18.8	19	18.4
Never	24.9	15.3	29	26.4	26.5	24.1	22.6	25.3
Body mass index, kg/m <sup>2</sup>	27.6 (5.3)	28.1 (5.1)	27.9 (6.1)	28.2 (6.1)	27.6 (5.5)	27.4 (5.0)	27.4 (4.8)	28.0 (5.3)
Systolic blood pressure, mmHg	120.9 (18.6)	125.7 (22.7)	124.5 (21.1)	122.3 (19.6)	121.7 (19.5)	120.9 (18.2)	119.2 (17.1)	119.0 (16.5)
Total cholesterol, mmol/L	5.6 (1.1)	5.8 (1.2)	5.8 (1.2)	5.6 (1.1)	5.6 (1.1)	5.5 (1.1)	5.5 (1.0)	5.5 (1.1)

HDL cholesterol, mmol/L	1.3 (0.4)	1.2 (0.4)	1.3 (0.5)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Anti-hypertensive use	30.3	52.4	43.5	33	32.1	28.9	26	28
Diabetes	11.6	19.4	17.5	12.3	12.2	11.1	10.1	11.1
Prevalent stroke	1.8	5.6	2.4	1.9	1.6	1.9	1.7	1.4
Prevalent heart failure	4.6	9.7	10.4	5.7	5	3.9	3.4	3.7
Prevalent coronary heart disease	4.9	23.4	8.9	5	4.3	4.5	4.2	5.2

All data presented as mean (SD) or %

**Table 2. Hazard ratios (95% CI) for the association of symptomatic PAD and ABI category with incident AAA, ARIC, 1987-2011**

Model	Symptomatic PAD	Asymptomatic ABI category					
		ABI <0.9	ABI >0.9-1.0	ABI >1.0-1.1	ABI >1.1-1.2	ABI >1.2-1.3	ABI >1.3
1	4.91 (2.88, 8.37)	2.33 (1.55, 3.51)	1.51 (1.12, 2.03)	1.13 (0.88, 1.45)	Referent	1.10 (0.86, 1.41)	1.04 (0.77, 1.42)
2	2.96 (1.73, 5.07)	1.52 (1.00, 2.30)	1.27 (0.94, 1.71)	1.04 (0.81, 1.35)	Referent	1.14 (0.89, 1.46)	1.27 (0.94, 1.73)
3	3.08 (1.79, 5.29)	1.53 (1.01, 2.32)	1.26 (0.94, 1.70)	1.04 (0.80, 1.34)	Referent	1.14 (0.89, 1.46)	1.28 (0.94, 1.73)

Model 1: Adjusted for age, sex, race, center, and education level

Model 2: Further adjusted for smoking status, drinking status, diabetes, systolic blood pressure, antihypertensive medication use, BMI, total and HDL cholesterol levels, prevalent HF, prevalent CHD, and prevalent stroke

Model 3: Model 1 further adjusted for pack-years of smoking (instead of smoking status), drinking status, diabetes, systolic blood pressure, antihypertensive medication use, BMI, total and HDL cholesterol levels, prevalent HF, prevalent CHD, and prevalent stroke

**Table 3. Odds ratio (95% CI) for the association of symptomatic PAD and ABI category with AAA as defined by maximum abdominal aortic diameter  $\geq 3.0$  cm based on abdominal ultrasound, ARIC, 2011-2013**

Model	Symptomatic PAD	Asymptomatic ABI category					
		ABI <0.9	ABI >0.9-1.0	ABI >1.0-1.1	ABI >1.1-1.2	ABI >1.2-1.3	ABI >1.3
1	2.46 (1.26, 4.81)	3.98 (1.96, 8.08)	2.06 (0.90, 4.71)	2.34 (1.29, 4.24)	Referent	0.72 (0.33, 1.58)	1.54 (0.78, 3.06)
2	1.79 (0.90, 3.55)	2.20 (1.03, 4.70)	1.43 (0.61, 3.32)	1.96 (1.07, 3.61)	Referent	0.84 (0.38, 1.85)	1.68 (0.84, 3.37)
3	1.95 (0.98, 3.89)	2.30 (1.09, 4.85)	1.29 (0.54, 3.08)	2.15 (1.16, 3.99)	Referent	0.91 (0.41, 2.04)	2.13 (1.05, 4.33)

Model 1: Adjusted for age, sex, race, center, and education level

Model 2: Further adjusted for smoking status, drinking status, diabetes, systolic blood pressure, antihypertensive medication use, BMI, total and HDL cholesterol levels, prevalent HF, prevalent CHD, and prevalent stroke

Model 3: Model 1 further adjusted for pack-years of smoking (instead of smoking status), drinking status, diabetes, systolic blood pressure, antihypertensive medication use, BMI, total and HDL cholesterol levels, prevalent HF, prevalent CHD, and prevalent stroke

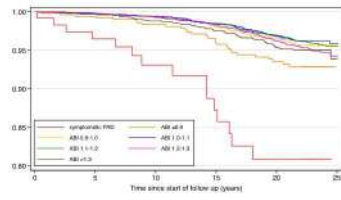
## Figure Legends

**Figure 1.** Kaplan Meier analysis assessing the association of symptomatic PAD and asymptomatic ABI category with incident AAA.

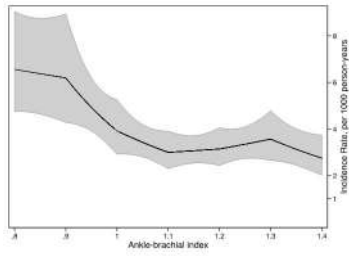
There was a significant association of symptomatic PAD with incident AAA. There was also a weaker but statistically significant association of  $ABI \leq 0.9$  with incident AAA among participants without symptomatic PAD. PAD = peripheral artery disease; ABI = ankle brachial index; IC = intermittent claudication; LER = lower extremity revascularization.

**Figure 2.** Incidence rate of AAA according to ABI among participants without symptomatic PAD, ARIC, 1987-2011.

A linear spline model adjusting for age, sex, race, and center demonstrated no evident risk gradient for incident AAA in the range of ABI 1.1-1.4, but a monotonically increasing incidence rate of AAA below 1.1.



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## Highlights

- Both symptomatic and asymptomatic peripheral artery disease (PAD) are independently associated with a higher hazard ratio of incident clinical abdominal aortic aneurysm based on 22.5 years of follow-up
- Symptomatic and asymptomatic PAD are also associated with ultrasound-based AAA based on cross-sectional analysis
- Our data support the current recommendation of AAA screening in symptomatic PAD patients
- AAA screening may be appropriate for asymptomatic PAD patients as well

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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