

ORIGINAL INVESTIGATIONS

Population-Based Risk Factors for Ascending, Arch, Descending, and Abdominal Aortic Dilations for 60-74-Year-Old Individuals



Lasse M. Obel, MD,^{a,b,c} Axel C. Diederichsen, MD, PhD,^{a,d} Flemming H. Steffensen, MD, PhD,^e Lars Frost, MD, PhD, DMSc,^f Jess Lambrechtsen, MD, PhD,^g Martin Busk, MD, PhD,^e Grazina Urbonaviciene, MD, PhD,^f Kenneth Egstrup, MD, DMSc,^g Marek Karon, MD,^h Lars M. Rasmussen, DMSc,^{a,i} Oke Gerke, MSc, PhD,^{c,j} Anders S. Bovling, MD,^{a,b,c} Jes S. Lindholt, MD, PhD, DMSc^{a,b}

ABSTRACT

BACKGROUND Aortic dilations (ectasias and aneurysms) may occur on any segment of the aorta. Pathogenesis varies between locations, suggesting that etiology and risk factors may differ. Despite this discrepancy, guidelines recommend screening of the whole aorta if 1 segmental dilation is discovered.

OBJECTIVES The purpose of this study was to determine the most dominant predictors for dilations at the ascending, arch, descending, and abdominal part of the aorta, and to establish comprehensive risk factor profiles for each aortic segment.

METHODS Individuals aged 60-74 years were randomly selected to participate in DANCAVAS I+II (Danish Cardiovascular Multicenter Screening Trials). Participants underwent cardiovascular risk assessments, including blood samples, blood pressure readings, medical records, and noncontrast computed tomography scans. Adjusted odds ratios for potential risk factors of dilations were estimated by multivariate logistic analyses.

RESULTS The study population consisted of 14,989 participants (14,235 men, 754 women) with an average age of 68 ± 4 years. The highest adjusted odd ratios for having any aortic dilation were observed when coexisting aortic dilations were present. Other noteworthy predictors included coexisting iliac dilations, hypertension, increasing body surface area, male sex, familial disposition, and atrial fibrillation, which were present in various combinations for the different aortic parts. Smoking and acute myocardial infarction were inversely associated with ascending and abdominal dilations. Diabetes was a shared protective factor.

CONCLUSIONS Risk factors differ for aortic dilations between locations. The most dominant predictor for having a dilation at any aortic segment is the presence of an aortic dilation elsewhere. This supports current guidelines when recommending a full screening of the aorta if a focal aortic dilation is discovered. (J Am Coll Cardiol 2021;78:201-11)

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From the ^aElitry Research Centre CIMA, Odense University Hospital, Odense, Denmark; ^bDepartment of Cardiothoracic and Vascular Surgery, Odense University Hospital, Odense, Denmark; ^cDepartment of Clinical Research, University of Southern Denmark, Odense, Denmark; ^dDepartment of Cardiology, Odense University Hospital, Odense, Denmark; ^eDepartment of Cardiology, Vejle Hospital, Vejle, Denmark; ^fDepartment of Cardiology, Diagnostic Centre, Regional Hospital Silkeborg, Silkeborg, Denmark; ^gDepartment of Cardiology, Odense University Hospital, Svendborg, Denmark; ^hDepartment of Medicine, Nykøbing Falster Hospital, Nykøbing Falster, Denmark; ⁱDepartment of Clinical Biochemistry, Odense University Hospital, Odense, Denmark; and the ^jDepartment of Nuclear Medicine, Odense University Hospital, Odense, Denmark.

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ABBREVIATIONS AND ACRONYMS

AFLI	= atrial fibrillation
AMI	= acute myocardial infarction
AP	= anterior-posterior
AUC	= area under the curve
BSA	= body surface area
CT	= computed tomography
CVD	= cardiovascular disease
OR	= odds ratio
ROC	= receiver operating characteristic curve

An aortic aneurysm is a potentially lethal condition, because it may lead to rupture or dissection (1). Aortic dilations (ectasias and aneurysms) can occur on any aortic level and are typically symptom free, for which reason they are often identified coincidentally in patients undergoing imaging for other purposes. Subsequently, some countries have implemented screening programs for abdominal aortic aneurysms. Due to the lower thoracic aneurysm mortality, general population-based screening of such is hardly cost-effective, and a more targeted screening of individuals who are at high risk seems more likely to be beneficial (2-4).

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PATHOLOGY. The pathology of aortic dilations differs with the location. Ascending aortic dilations are considered to be caused by inflammatory cystic medial degeneration, whereas descending and abdominal dilations are associated with arteriosclerotic lesions (5,6). Pathogenesis of dilations on the aortic arch, however, is uncertain. Despite these discrepancies and lack of evidence regarding coexisting aortic dilations, guidelines recommend screening of the whole aorta if 1 segmental dilation is discovered (1).

RISK FACTORS. Well-recognized risk factors for abdominal dilations include male sex, smoking, hypertension, previous history of cardiovascular disease (CVD), familial disposition, and increasing age (1). Risk factors for thoracic dilations in younger patients include genetic syndromes and inflammatory diseases, but risk factors among the elderly are not well described (1). Because the pathology differs between segments, it is possible that they have different risk factors.

DEFINITIONS OF NORMATIVE SIZES AND DILATIONS. The aortic size varies according to location, body surface area (BSA), sex, and age, and several studies have sought to establish normal reference diameters for the different aortic segments (7-9). However, lack of international well-recognized definitions for aortic dilations are still persistent (1). In general, ectatic and aneurysmal aortas are defined as having a $\geq 25\%$ and $\geq 50\%$ increase from individually normal diameters, respectively (10). Nevertheless, these relative cutoff points can be applied only when a patient's normal reference diameter is known, which rarely is the case.

Consequently, the aims for this study were as follows:

1. To develop prediction formulas on the basis of sex, age, and strongest body-size correlating factor to the aortic diameters, providing individual references for normal ascending, arch, descending, and abdominal aortic diameters, respectively;
2. To report prevalence of dilations ($\geq 25\%$) and aneurysms ($\geq 50\%$) for all aortic segments, using the prediction formulas; and
3. To identify the individually most dominant predictors for aortic dilations by establishing detailed cardiovascular risk factor profiles for each aortic segment.

METHODS

The material stems from 2 comprehensive Danish population-based screening trials, DANCAVAS I and II (Danish Cardiovascular Multicenter Screening Trials), which included approximately 78,000 participants aged 60-74 years from the national civil registry (11). Participants had to have residence in certain communities in the regions of Southern and Central Denmark; otherwise, there were no exclusion criteria. The populations were randomized 1:2 (DANCAVAS I) or 1:5 (DANCAVAS II) to be invited to cardiovascular screening or participate as control subjects. Examinations were performed from 2014 to 2018 with screening sites at Odense University Hospital, Svendborg Hospital, Vejle Hospital, Nykøbing Falster Hospital, and Silkeborg Hospital. The trials were approved by the Regional Scientific Ethical Committee of Southern Denmark (S-20140028, 2014).

Both men and women were invited at the beginning of the DANCAVAS I trial, but a pilot study concluded that women were not likely to benefit cost-effectively from screening for CVD (12). Consequently, only men were recruited from May 2015.

A total of 15,006 individuals attended screening. In this study, participants with missing registered personal data ($n = 1$), missing measurements of height or weight ($n = 11$), or missing measurements of the ascending, arch, descending, or abdominal aortic diameters ($n = 5$) were excluded, leading to a study-population of 14,989 participants (14,235 men and 754 women).

DATA COLLECTION. Categorical information regarding medical history including risk factors for CVD was collected through questionnaires and interview. Participants were categorized according to self-reported prior acute myocardial infarction (AMI), stroke, use of platelet inhibitors, anticoagulant therapy, statin therapy, and use of beta-agonists for chronic obstructive pulmonary disease. Smoking status was registered

as current, former, and never smoker. Familial disposition to an aneurysm was defined as a first-degree relative diagnosed with an aneurysm. Height and weight were measured, and blood pressure measurements on arms and legs were taken. Body mass index was calculated. Body surface area (BSA) was calculated using DuBois and DuBois's formula (13).

SUBGROUP DEVELOPMENT. Participants already diagnosed with systematic arterial hypertension by a physician, receiving antihypertensive treatment, or having a systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg during the screening session were categorized as having hypertension. Peripheral arterial disease was defined as an ankle-brachial index ≤ 0.9 or ≥ 1.4 . Blood samples were taken for determination of hemoglobin, creatinine, triglyceride, cholesterol, and HbA1c levels. Participants were categorized as diabetic if they had been diagnosed prior to the screening by a physician, if they received antidiabetic treatment, or if HbA1c ≥ 48 mmol/L at screening. Anemia was defined according to the WHO criteria as hemoglobin levels < 8.1 mmol/L for men and < 7.5 mmol/L for women, respectively (14). The estimated glomerular filtration rates were calculated according to the Chronic Kidney Disease Epidemiology Collaboration equations for men and women, respectively (15). An estimated glomerular filtration rate < 60 mL/min/m² was defined as chronic kidney disease. Participants with a documented history of atrial fibrillation (AFLI) prior to the screening, or if found during the computed tomography (CT) scan, were categorized as AFLI.

CT IMAGING PROTOCOL. For thoracic and abdominal aortic dimension assessment, an electrocardiogram-gated noncontrast CT scan was performed from the jaw to the groin using slice thicknesses of 0.5-0.6 mm. Philips Brilliance was used at Nykøbing Falster Hospital, Siemens Somatom Definition Flash/Force at Odense University Hospital and Vejle Hospital, while GE Revolution and Toshiba Aquilion One scanners were used at Svendborg Hospital and Silkeborg Hospital, respectively. When measuring the aortic diameter, a reconstructed scan using slice thicknesses of 5 mm was applied for optimal visualization of the aortic wall.

All aortic segments including the iliac arteries were evaluated and assessed for dilations. If a dilation was found, the diameter was measured as the maximal size of the dilation. If no dilation appeared, the aortic dimensions were measured at 5 predetermined levels: the anterior-posterior (AP) ascending aortic diameter was measured at the first perpendicular circular level above the sinotubular junction, and the

AP descending aortic diameter was measured on the corresponding level. The diameter of the aortic arch was measured perpendicular where aorta passes trachea, and the AP abdominal aortic diameter just above the bifurcation. The measurements were performed from the exterior-to-exterior surfaces of the aortic wall according to guidelines (16). Experienced radiographers performed all measurements.

DEFINITION OF THORACIC AND ABDOMINAL AORTIC DILATIONS. A dilated aorta was in this study defined as an observed diameter $\geq 25\%$ of the individual expected normal aortic diameter, and a fully-grown aneurysm was defined as a $\geq 50\%$ increase. For determination of the individual expected normal aortic diameters, prediction formulas on the basis of sex, age, and body-size correlating factor with the highest correlation to the aortic diameters were created for all aortic segments, respectively. A dilated iliac artery was defined as an AP diameter ≥ 20 mm.

The prevalence of dilations and risk factors from multivariate logistic analyses are equally reported using absolute cutoff points to define thoracic and abdominal aortic dilations (Supplemental Tables 1 and 2). The definitions used for a dilated aorta in the Supplemental Appendix were set at 40, 35, 30, and 25 mm for ascending, arch, descending, and abdominal dilations, respectively (1,9,17). We chose 40 mm as upper limit of normal for the ascending aorta because guidelines state that the healthy aorta does not usually exceed 40 mm in diameter, and 25 mm for the abdominal aorta because 50% of men with an abdominal diameter between 25-29 mm develop an abdominal aortic aneurysm within 5 years (1,18).

STATISTICS. Distribution of data was assessed visually through probability plots and followed normal distributions. Comparison of differences between sexes were analyzed with chi-square tests for dichotomous data and Student's *t*-test for continuous data, respectively.

For determination of which body-size related factors to be included in the prediction formulas for calculation of normal aortic diameters, correlations between the aortic diameters and the physiological factors of age, height, weight, body mass index, and BSA were assessed through the Pearson's *r*, respectively. Possible interactions between variables were evaluated with likelihood ratio tests, and Akaike Information Criteria model selection was used to distinguish between prediction models including BSA versus height and weight.

Through multivariate linear regression analyses based upon age, sex, and strongest body-size related factor, formulas for normal diameters of the

ascending, arch, descending, and abdominal aorta were created, respectively. The formulas were based upon data from participants with presumed normal aortic diameters (ascending diameter <40 mm [n = 11,411], arch diameter <35 mm [n = 13,919], descending diameter <30 mm [n = 11,264], and abdominal diameter <25 mm [n = 13,764], respectively).

To evaluate the final prediction formulas performances, standardized residual analyses were derived including probability plots and histograms for evaluation of distribution patterns. Scatterplots with predicted aortic diameters and standardized residuals were created for evaluation of variance. By dividing the observed aortic diameters with the estimated normal aortic diameters, indexes were created. Indexes ≥ 1.25 and ≥ 1.50 were defined as dilated and aneurysmal, respectively (8,19). Proportions of agreement between dilations defined by the size-index and absolute diameters were calculated.

For identification of potential categorical risk factors associated with aortic dilations, univariate logistic regression analyses were used. Numerical risk factors were analyzed by Student's *t*-test. An alpha level of 10% was determined as indicator for a potential risk factor. Potential risk factors discovered in the univariate analyses were entered into multivariate logistic analyses estimating adjusted odds ratios (OR) of the independent risk factors for being associated with ascending, arch, descending, and abdominal aortic dilations. Discrimination of the multivariate logistic regressions were evaluated from area under the curves (AUC) extracted from receiver operating characteristic curves (ROC). Cross-validated AUC were performed by dividing the total study-population into 10 subgroups. Bootstrap bias corrected 95% CIs for each cross-validated AUC were calculated. Finally, Brier scores are reported for each multivariate logistic regression. All analyses were performed with STATA/IC 16.1 (StataCorp LLC, College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. The study population consisted of 14,989 participants (14,235 men, 754 women) with an average age of 68 ± 4 years. As can be seen in Table 1, male participants were significantly different from female participants in all parameters besides previous events of stroke, peripheral arterial disease, familial aneurysmal cases, diastolic blood pressure, triglyceride levels, and HbA1c levels.

PREDICTION FORMULAS FOR EXPECTED AORTIC NORMAL DIAMETERS. Correlations assessed by

Pearson's *r* between the aortic diameters and physiological factors are displayed in Table 2. Age correlated modestly but significantly with all aortic segments, and BSA had the strongest correlation of them all. No significant interactions were found among sex, age, and BSA for either the thoracic or the abdominal aortic diameters, and BSA had a lower Akaike Information Criteria score compared with height and weight.

Thus, sex, age, and BSA were used in the final prediction formulas for each aortic segment:

$$\text{Ascending aorta}_{\text{Estimated}} = 20.99 + (\text{age} \times 0.10) + (\text{BSA} \times 3.37) + 1.32 \text{ (if male)}$$

$$\text{Aortic arch}_{\text{Estimated}} = 14.57 + (\text{age} \times 0.09) + (\text{BSA} \times 3.95) + 1.14 \text{ (if male)}$$

$$\text{Descending aorta}_{\text{Estimated}} = 14.86 + (\text{age} \times 0.08) + (\text{BSA} \times 2.65) + 1.67 \text{ (if male)}$$

$$\text{Abdominal aorta}_{\text{Estimated}} = 7.02 + (\text{age} \times 0.06) + (\text{BSA} \times 3.17) + 2.05 \text{ (if male)}$$

All tested variables had *P* values <0.001. Adjusted *R*² values were 0.09, 0.12, 0.17, and 0.13, respectively. Standardized residuals from the prediction formulas for ascending, arch, descending, and abdominal aortic diameters were 0.6 ± 1.5 , 0.2 ± 1.2 , 0.6 ± 1.6 , and 0.4 ± 2.1 , respectively. Residuals from the thoracic aortic equations displayed normal distribution, and variance between residuals and predicted diameters appeared acceptably homogeneous. Residuals from the abdominal aortic equation showed little deviation from normal distribution, but some divergence was observed between residuals and predicted diameters. Proportions of agreement between dilations defined by the size-index and absolute diameters were high (Supplemental Table 3).

AORTIC DIAMETERS AND DILATIONS. Normal values. The overall ascending, arch, descending, and abdominal aortic diameters from the CT scans were 37.3, 30.6, 28.3, and 20.3 mm, respectively (Table 3). Male participants were significantly 2.5-4.0 mm larger on each aortic segment compared with women. **Prevalence of aortic dilations and aneurysms.** The prevalence estimates of aortic dilations in men were 4.0%, 0.9%, 2.3%, and 9.4% and in women were 2.1%, 0.3%, 1.1%, and 3.9% for the ascending, arch, descending, and abdominal aorta, respectively. The prevalence estimates of aortic aneurysms in men were 0.1%, <0.1%, 0.1%, and 3.7% and in women were 0.1%, 0.0%, 0.1%, and 0.4% for the ascending, arch, descending, and abdominal aorta, respectively (Table 3).

The prevalence of aortic dilation was significantly higher in men than women for all aortic segments,

TABLE 1 Descriptive Baseline Characteristics Stratified by Sex From a Randomized Danish Study Population of 14,989 Individuals Aged 60-74 Years

	N	Total (N = 14,989)	Men (n = 14,235)	Women (n = 754)	P Value
Smoking	14,928				<0.001
Current		16.0 (15.4-16.6)	16.1 (15.5-16.7)	13.1 (11.0-15.8)	
Former		50.0 (49.2-50.8)	50.8 (50.0-51.6)	35.2 (31.8-38.6)	
Never		34.0 (33.2-34.8)	33.1 (32.3-33.9)	51.7 (48.1-55.2)	
Diabetes	14,989	12.6 (12.1-13.2)	12.9 (12.3-13.4)	8.5 (6.7-10.7)	<0.001
Hypertension	14,989	52.3 (51.5-53.1)	52.1 (51.2-52.9)	57.7 (54.1-61.2)	<0.001
Stroke	14,989	6.4 (6.0-6.8)	6.3 (5.9-6.7)	8.0 (6.2-10.1)	0.07
AMI	14,989	5.8 (5.4-6.2)	6.0 (5.6-6.4)	1.6 (0.9-2.7)	<0.001
PAD	14,907	9.6 (9.2-10.1)	9.5 (9.1-10.0)	11.1 (9.0-13.6)	0.16
Familial disposition	14,853	4.4 (4.1-4.8)	4.4 (4.1-4.7)	5.6 (4.2-7.5)	0.12
AFLI	14,989	8.1 (7.7-8.6)	8.2 (7.8-8.7)	6.0 (4.5-7.9)	0.028
Platelet inhibitors	14,989	21.2 (20.5-21.8)	21.5 (20.8-22.1)	15.7 (13.2-18.4)	<0.001
Anticoagulant therapy	14,989	6.8 (6.4-7.2)	7.0 (6.5-7.4)	3.5 (2.4-5.0)	<0.001
Beta-agonist therapy	14,989	2.6 (2.4-2.9)	2.5 (2.2-2.7)	5.4 (4.0-7.3)	<0.001
Statin therapy	14,989	33.1 (32.4-33.9)	32.9 (32.2-33.7)	36.5 (33.1-40.0)	0.043
Anemia	14,989	6.1 (5.7-6.5)	6.2 (5.8-6.6)	4.4 (3.1-6.1)	0.046
CKD	14,989	10.0 (9.5-10.5)	9.7 (9.2-10.2)	16.1 (13.6-18.8)	<0.001
Age, y	14,989	67.8 ± 3.8	67.8 ± 3.8	68.7 ± 3.5	<0.001
Height, m	14,989	1.8 ± 0.1	1.8 ± 0.1	1.6 ± 0.1	<0.001
Weight, kg	14,989	87.6 ± 15.3	88.4 ± 14.9	71.9 ± 13.7	<0.001
BMI, kg/m ²	14,989	28.1 ± 4.4	28.1 ± 4.4	26.7 ± 5.1	<0.001
BSA, m ²	14,989	2.0 ± 0.2	2.1 ± 0.2	1.8 ± 0.2	<0.001
Systolic BP, mm Hg	14,893	149.3 ± 18.7	149.0 ± 18.6	154.5 ± 20.4	<0.001
Diastolic BP, mm Hg	14,890	82.5 ± 9.9	82.4 ± 9.9	82.8 ± 9.3	0.28
Triglyceride, mmol/L	14,864	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.0	0.07
Cholesterol, mmol/L	14,872	5.0 ± 1.1	5.0 ± 1.1	5.6 ± 1.1	<0.001
HbA1c, mmol/mol	14,849	39.2 ± 7.7	39.2 ± 7.8	38.9 ± 4.9	0.17

Values are % (95% CI) or mean ± SD, unless otherwise indicated. P values <0.05 are in **bold**, indicating significant differences between men and women.
 AFLI = atrial fibrillation; AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; BSA = body surface area; CKD = chronic kidney disease; PAD = peripheral artery disease.

apart from the aortic arch, whereas prevalence of aneurysms was only significantly higher in men in the abdominal part.

The prevalence of aortic dilations and aneurysms defined by absolute diameters are presented in Supplemental Table 1.

PREDICTORS FOR AORTIC DILATIONS. Univariate regressions. Detailed unadjusted OR and mean

differences from univariate regression analyses between potential predictors and dilations for each aortic segment are presented in Table 4.

Multivariate logistic regressions. Adjusted OR for potential predictors identified in Table 4 are presented in Table 5. The highest adjusted OR observed for dilations at any aortic segments were coexisting aortic dilations (Central Illustration). Also,

TABLE 2 Correlations Between Aortic Diameters and Physiological Parameters

	Ascending Aorta		Aortic Arch		Descending Aorta		Abdominal Aorta	
	Pearson's r	P Value	Pearson's r	P Value	Pearson's r	P Value	Pearson's r	P Value
Age	0.12	<0.001	0.12	<0.001	0.16	<0.001	0.11	<0.001
Weight	0.26	<0.001	0.29	<0.001	0.30	<0.001	0.17	<0.001
Height	0.22	<0.001	0.26	<0.001	0.24	<0.001	0.17	<0.001
BMI	0.17	<0.001	0.19	<0.001	0.21	<0.001	0.11	<0.001
BSA	0.28	<0.001	0.32	<0.001	0.32	<0.001	0.20	<0.001

Correlations with Pearson's r between thoracic and abdominal aortic diameters and physiological factors, respectively. Variables in **bold** were implemented in the prediction formulas for calculation of individual expected normal diameter. P values test for linear correlation between the aortic diameter and the physiological factor.
 Abbreviations as in Table 1.

TABLE 3 Aortic Dimensions From Noncontrast CT Scans and Prevalence of Ascending, Arch, Descending, and Abdominal Aortic Dilations and Aneurysms

	Total (N = 14,989)	Men (n = 14,235)	Women (n = 754)	P Value
Ascending aorta, mm	37.3 ± 4.1	37.5 ± 4.1	34.1 ± 3.6	<0.001
Aortic arch, mm	30.6 ± 3.0	30.7 ± 2.9	28.1 ± 2.6	<0.001
Descending aorta, mm	28.3 ± 2.8	28.5 ± 2.7	25.2 ± 2.4	<0.001
Abdominal aorta, mm	20.3 ± 4.7	20.5 ± 4.8	16.6 ± 2.2	<0.001
Thoracic aortic dilations ^a				
Ascending aorta	3.9 (3.6-4.2)	4.0 (3.6-4.3)	2.1 (1.3-3.4)	0.011
Aortic arch	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.3 (0.1-1.0)	0.06
Descending aorta	2.2 (2.0-2.5)	2.3 (2.0-2.5)	1.1 (0.5-2.1)	0.029
Infrarenal dilations ^{a,b}				
Abdominal aorta	9.2 (8.7-9.6)	9.4 (9.0-9.9)	3.9 (2.6-5.5)	<0.001
Iliac arteries	1.9 (1.7-2.2)	2.0 (1.8-2.2)	0.3 (0.1-1.0)	0.001
Thoracic aortic aneurysms ^c				
Ascending aorta	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.0-0.7)	0.92
Aortic arch	<0.1 (0.0-0.1)	<0.1 (0.0-0.1)	0.0 (0.0-0.0)	0.61
Descending aorta	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.0-0.7)	0.92
Infrarenal aortic aneurysms ^c				
Abdominal aorta	3.6 (3.3-3.9)	3.7 (3.4-4.1)	0.4 (0.1-1.2)	<0.001

Values are mean ± SD or % (95% CI). P values <0.05 are in **bold**, indicating significant differences between men and women. ^aAscending, arch, descending, and abdominal aortic dilations are defined as a ≥25% increase in observed diameter compared with individual calculated normal diameter. ^bIliac artery dilations are defined as an AP diameter ≥20 mm. ^cAscending, arch, descending, and abdominal aortic aneurysms are defined as a ≥50% increase in observed diameter compared with individual calculated normal diameter. The prevalence of aortic dilations and aneurysm defined by absolute aortic diameters are represented in Supplemental Table 1.
AP = anterior-posterior.

hypertension and increasing BSA were positively associated with all aortic segments, whereas various risk factors and combinations of these were found for individual segments. Hence, coexisting iliac dilations were positively associated with all aortic segments except for the ascending aorta. Familial disposition was positively associated with ascending and abdominal dilations. AFLI was positively associated with ascending and descending aortic dilations. Male sex, smoking, AMI, and peripheral arterial disease were positively associated with abdominal dilations.

On the other hand, diabetes was negatively associated with all aortic segments. Smoking and AMI were negatively associated with ascending aortic dilations.

In summary, significant shared risk factors for all aortic dilations were the presence of concomitant dilations, hypertension, and increasing BSA. AFLI was a significant shared risk factor for ascending and descending dilations, while familial disposition was a significant shared risk factor for ascending and abdominal dilations. AMI as well as former and especially current smoking increased the risk for abdominal dilations significantly while decreasing the risk for ascending dilations. Diabetes was a significant protective factor for all thoracic segments.

The ROC-AUC and cross-validated ROC-AUC from the final models were moderately strong, ranging from 0.69-0.80 and 0.68-0.78, respectively, and the Brier scores ranged from 0.01-0.07 (Table 6).

Using absolute cutoff points for aortic dilations presented little influence on results except for the following: male sex and increasing age were significant risk factors for all aortic segments, current smoking increased risk significantly for descending dilations, and familial disposition lost association with ascending dilations (Supplemental Table 2).

DISCUSSION

MAIN FINDINGS. In this large, population-based, cross-sectional study including randomly selected participants aged 60-74 years, we sought to identify the most dominant predictors for having an aortic dilation at any aortic segment. This study found that the most dominant predictor for having an aortic dilation, regardless of location, is the presence of a coexisting aortic dilation (Central Illustration). This supports current cardiovascular guidelines; when a focal aortic dilation has been discovered, it is important to screen the whole aorta for dilations (1). Additionally, the iliac arteries should be scanned when an aortic arch, descending, or abdominal aortic dilation is discovered. Other noteworthy predictors to be considered were hypertension, increasing BSA, male sex, familial disposition, AFLI, smoking, and AMI, which were present in various combinations for different parts of the aorta. Finally, this study provides prediction formulas for calculating individual expected normal thoracic and abdominal aortic diameters from noncontrast CT scans.

RISK FACTORS. All traditional CVD risk factors were evaluated. Data from The DANCAVAS trials are well-characterized, and several variables were considered counterparts. Thus, most continuous variables to be found in Table 1, such as blood pressure, HbA1c levels, and creatinine levels, were converted and/or implemented in the dichotomy equivalents of hypertension, diabetes, and chronic kidney disease, respectively. Furthermore, use of anticoagulants, statins, and platelet inhibitors were not evaluated as potential risk factors to avoid potential misleading collinearity with AFLI and comorbidities associated with arteriosclerotic lesions in the multiple logistic regressions.

The highest adjusted OR for thoracic aortic dilations was observed when a dilated ascending or descending aorta occurred. In these cases, the risk of having a coexisting aortic arch dilation was increased by a factor of 6-8. This is most likely caused by the

TABLE 4 Univariate Models of Potential Associated Risk Factors for Thoracic and Abdominal Aortic Dilations

	Ascending Aortic Dilation		Aortic Arch Dilation		Descending Aortic Dilation		Abdominal Aortic Dilation	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Male	1.9 (1.1-3.1)	0.013	3.5 (0.9-14.2)	0.078	2.2 (1.1-4.4)	0.033	2.6 (1.8-3.8)	<0.001
Smoking								
Former	0.8 (0.7-0.9)	0.010	0.9 (0.6-1.3)	0.58	1.1 (0.9-1.5)	0.28	2.3 (2.0-2.6)	<0.001
Current	0.8 (0.6-1.0)	0.034	0.9 (0.5-1.5)	0.59	1.4 (1.1-2.0)	0.022	4.2 (3.5-4.9)	<0.001
Diabetes	0.7 (0.5-0.9)	0.005	0.5 (0.3-0.9)	0.043	0.7 (0.5-1.0)	0.075	1.2 (1.0-1.4)	0.054
Hypertension	1.8 (1.5-2.1)	<0.001	1.7 (1.2-2.84)	0.004	1.5 (1.2-1.9)	<0.001	1.4 (1.2-1.6)	<0.001
Stroke	1.3 (1.0-1.8)	0.056	1.2 (0.6-2.3)	0.61	1.4 (0.9-2.0)	0.12	1.6 (1.3-1.9)	<0.001
AMI	0.7 (0.5-1.1)	0.089	0.8 (0.3-1.7)	0.52	1.1 (0.7-1.7)	0.82	2.7 (2.3-3.2)	<0.001
PAD	1.0 (0.7-1.3)	0.89	1.2 (0.7-2.1)	0.51	1.1 (0.7-1.5)	0.77	2.1 (1.8-2.4)	<0.001
Familial disposition	1.6 (1.1-2.2)	0.010	1.4 (0.7-2.8)	0.39	1.0 (0.6-1.7)	0.91	1.8 (1.4-2.3)	<0.001
Atrial fibrillation	2.2 (1.7-2.8)	<0.001	1.4 (0.8-2.5)	0.19	1.9 (1.4-2.6)	<0.001	1.3 (1.1-1.6)	0.008
Beta-agonist therapy	1.0 (0.6-1.7)	0.98	0.6 (0.1-2.3)	0.42	0.8 (0.4-1.7)	0.57	1.5 (1.1-2.0)	0.008
Anemia	0.9 (0.7-1.3)	0.72	1.5 (0.8-2.8)	0.16	1.4 (0.9-2.1)	0.11	1.4 (1.2-1.8)	0.001
CKD	1.1 (0.9-1.5)	0.32	1.4 (0.8-2.3)	0.19	1.1 (0.7-1.5)	0.72	1.4 (1.2-1.6)	<0.001
Ascending aortic dilation	[outcome]	–	13.1 (9.0-19.0)	<0.001	5.8 (4.3-7.8)	<0.001	2.1 (1.7-2.6)	<0.001
Aortic arch dilation	13.1 (9.0-19.0)	<0.001	[outcome]	–	12.7 (8.3-19.6)	<0.001	3.3 (2.2-4.9)	<0.001
Descending aortic dilation	5.8 (4.3-7.8)	<0.001	12.7 (8.3-19.6)	<0.001	[outcome]	–	5.1 (4.0-6.4)	<0.001
Abdominal aortic dilation	2.3 (1.9-2.9)	<0.001	3.6 (2.5-5.3)	<0.001	5.5 (4.4-6.9)	<0.001	[outcome]	–
Iliac dilation	2.0 (1.2-3.1)	<0.001	4.9 (2.6-9.2)	<0.001	4.7 (3.1-7.2)	<0.001	12.4 (9.8-15.8)	<0.001
Dilated vs Nondilated								
	Mean		Mean		Mean		Mean	
	Difference (95% CI)	P Value	Difference (95% CI)	P Value	Difference (95% CI)	P Value	Difference (95% CI)	P Value
Age, y	0.5 (0.1-0.8)	0.004	0.7 (0.1-1.4)	0.025	1.0 (0.6-1.5)	<0.001	1.3 (1.1-1.5)	<0.001
BSA, m ²	0.04 (0.03-0.06)	<0.001	0.05 (0.02-0.08)	<0.001	0.04 (0.02-0.06)	<0.001	0.02 (0.01-0.03)	<0.001

Unadjusted odds ratios from univariate logistic regressions for categorical variables and Student's t-test for continues variables. P values <0.10 are in **bold** and indicate potential association. Aortic dilations are defined in this table as a ≥25% increase in diameter compared with individual calculated expected normal diameter. Iliac dilations are defined by an anterior-posterior diameter ≥20 mm.
 Abbreviations as in [Table 1](#).

association between aortic arch aneurysms and adjacent aneurysms of the ascending or descending aorta (1). When a focal dilation at the descending or abdominal aorta was present, the risk of having a coexisting dilation at the opposite site was increased by a factor of 4. We assumed this to be explained by the common pathology for descending and abdominal aneurysms (1,6). When an abdominal aortic dilation was exposed, the risk of having a coexisting dilation on the common iliac arteries was increased by a factor of 10. This emphasizes the importance of screening the iliac arteries, particularly when an abdominal aortic dilation is found.

Male sex was positively and significantly associated with dilations on all aortic segments by univariate analysis, but lost significance in the multivariate analyses for the thoracic aortic sites—perhaps caused by lack of power, as positive associations persisted, supported by the significant association when using absolute cutoff points as criterion for dilations (Supplemental Table 2).

Hypertension was positively associated with dilations on all aortic segments and was continuously

reduced going from the ascending to the abdominal part. This may be caused by higher blood pressures in the first part of the aorta and hypertension causing accelerated cystic media degeneration in the ascending arterial wall (20). Hence, controlling blood pressure in patients with aortic dilations may be a central component in reducing aortic growth rate.

Family medical history of first-degree relative(s) with aortic aneurysms was positively associated with dilations on both the ascending and abdominal aortic site, supporting the concept that underlying genetic variants play a role in the development of aortic dilations (1,21-23). Screening for aortic dilations in family members should be warranted.

AFLI increased the risk of both ascending and descending dilations, supporting that several molecular mechanisms in the development of ascending dilations and AFLI are shared (24). Patients with both conditions simultaneously may benefit from more frequent surveillance regarding aortic growth.

This study confirms that smoking is an important risk factor for abdominal aortic dilations—especially among current smokers. It is therefore strongly

TABLE 5 Multivariate Models of Associated Risk Factors for Thoracic and Abdominal Aortic Dilations

	Ascending Aortic Dilatation		Aortic Arch Dilatation		Descending Aortic Dilatation		Abdominal Aortic Dilatation		P Value ^b
	OR (95% CI)	P Value ^a	OR (95% CI)	P Value ^a	OR (95% CI)	P Value ^a	OR (95% CI)	P Value ^a	
Male	1.5 (0.9-2.6)	0.12	1.9 (0.5-8.0)	0.38	1.4 (0.7-2.9)	0.40	1.8 (1.2-2.7)	0.003	0.91
Smoking									<0.001
Former	0.7 (0.6-0.9)	0.001	—	—	1.1 (0.8-1.4)	0.71	2.0 (1.7-2.4)	<0.001	
Current	0.7 (0.6-1.0)	0.028	—	—	1.3 (0.9-1.8)	0.12	4.2 (3.5-5.1)	<0.001	
Diabetes	0.5 (0.4-0.7)	<0.001	0.4 (0.2-0.9)	0.022	0.6 (0.4-0.9)	0.016	0.9 (0.7-1.1)	0.21	0.015
Hypertension	1.7 (1.4-2.0)	<0.001	1.5 (1.0-2.2)	0.043	1.3 (1.0-1.7)	0.021	1.2 (1.0-1.3)	0.026	0.013
Stroke	1.2 (0.9-1.7)	0.25	—	—	—	—	1.2 (1.0-1.5)	0.08	0.98
AMI	0.6 (0.4-0.9)	0.013	—	—	—	—	2.3 (1.9-2.8)	<0.001	<0.001
PAD	—	—	—	—	—	—	1.5 (1.3-1.8)	<0.001	—
Familial disposition	1.6 (1.1-2.2)	0.013	—	—	—	—	1.9 (1.5-2.4)	<0.001	0.36
Atrial fibrillation	1.9 (1.5-2.5)	<0.001	—	—	1.5 (1.1-2.2)	0.013	1.0 (0.8-1.2)	0.63	0.001
Beta-agonist therapy	—	—	—	—	—	—	1.3 (1.0-1.8)	0.09	—
Anemia	—	—	—	—	—	—	1.2 (0.9-1.5)	0.16	—
CKD	—	—	—	—	—	—	1.1 (0.9-1.3)	0.47	—
Ascending aortic dilatation	[outcome]	—	8.8 (6.0-13.1)	<0.001	3.4 (2.4-4.8)	<0.001	1.8 (1.4-2.3)	<0.001	<0.001
Aortic arch dilatation	8.4 (5.6-12.6)	<0.001	[outcome]	—	6.2 (3.8-10.1)	<0.001	1.9 (1.2-3.0)	0.008	0.001
Descending aortic dilatation	3.3 (2.3-4.6)	<0.001	6.1 (3.7-9.9)	<0.001	[outcome]	—	3.7 (2.8-4.8)	<0.001	0.22
Abdominal aortic dilatation	1.7 (1.3-2.2)	<0.001	1.8 (1.1-2.8)	0.012	3.6 (2.8-4.8)	<0.001	[outcome]	—	0.004
Iliac dilatation	1.0 (0.6-1.7)	0.91	2.2 (1.1-4.5)	0.031	1.9 (1.2-3.0)	0.007	9.9 (7.6-12.9)	<0.001	<0.001
Age, y	1.02 (1.0-1.0)	0.12	1.02 (1.0-1.1)	0.36	1.05 (1.0-1.1)	0.005	1.09 (1.1-1.1)	<0.001	<0.001
BSA, m ²	2.3 (1.4-3.8)	0.001	4.0 (1.5-11.0)	0.007	2.2 (1.2-4.4)	0.017	2.0 (1.4-2.8)	<0.001	0.57

Adjusted odds ratios from multivariate logistic regressions. P values <0.05 are in **bold**. A dash indicates that the variable was not a potential risk factor from univariate testing and thus not included in the multivariate regression analyses. Aortic dilations are in this table defined as $\geq 25\%$ increase in observed diameter compared with individual calculated expected normal diameter. Iliac dilations are defined by an AP diameter ≥ 20 mm. ^aP value for adjusted odds ratio between aortic dilatation and risk factor. ^bP value comparing adjusted odds ratios across aortic segments. For multivariate logistic regressions using absolute diameters as criterion for dilations, please see [Supplemental Table 2](#).

Abbreviations as in [Table 1](#).

advisable for patients with abdominal dilations to discontinue cigarette smoking, because risk reduces 50%. Surprisingly, smoking seems to reduce the risk of ascending aortic dilations. Because ascending aortic dilations are associated with several inflammatory conditions, the protective effect might be explained by the anti-inflammatory response from nicotine in cigarettes (25). However, this needs further investigation. Peripheral arterial disease was not associated with ascending aortic dilations, supporting previous findings that ascending aortic dilations may protect against systematic arteriosclerosis (26). This may also rationalize the reduced cases of ascending aortic dilations among patients with previous events of AMI.

Diabetes had a mutual protective effect for aortic dilations at all aortic segments, although insignificant in the abdominal part. The negative correlation between aortic aneurysms and diabetes is well described, but explorations of the underlying biological mechanisms are still lacking (27,28).

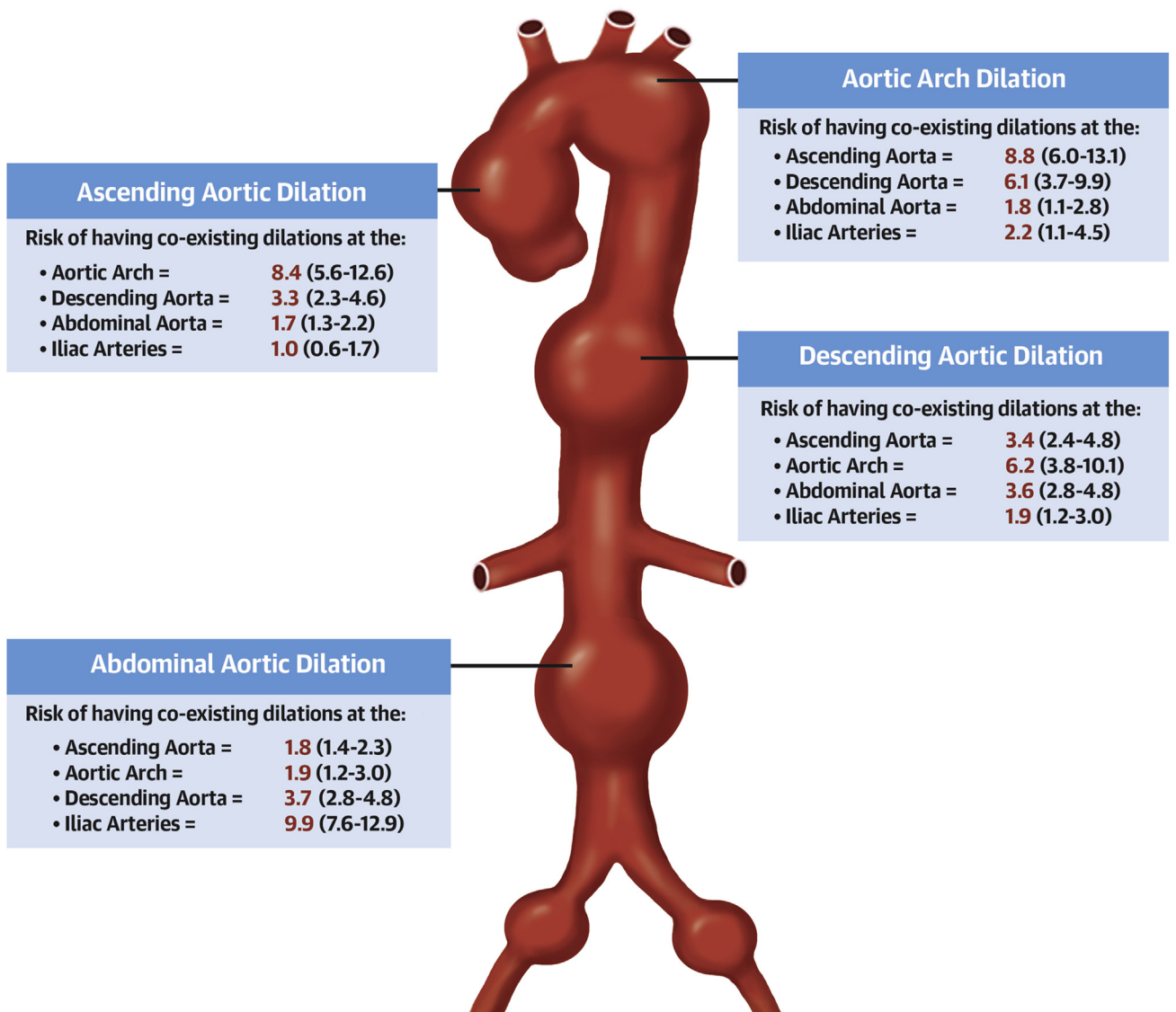
AORTIC DIMENSIONS. As expected, male participants had significantly larger aortic diameters on all aortic segments compared with women. It is well-known that sex, increasing BSA, and age influence

the aortic size. This may suggest that aortic dilations should be evaluated using relative cutoff points based upon these specific factors, rather than absolute cutoff points as current cardiology guidelines suggest (1). This is equally reflected by the overwhelmingly high prevalence of thoracic dilations using the conventional cutoff values of “normal” at 40 and 30 mm for the ascending and descending aorta, respectively ([Supplemental Table 1](#)).

The overall prevalence estimates confirmed that ascending aortic dilations are the most common lesion for thoracic aortic dilations (6), with nearly 4 times and double estimates, respectively, of the arch and descending aorta. The highest prevalence of aortic dilations was observed in the abdominal aorta for both men and women. The prevalence of aortic dilations was significantly higher in men than women with a factor 2 on all aortic segments, despite the aortic arch ([Table 3](#)). The prevalence of aortic aneurysms was only significantly higher in men compared to women in the abdominal segment, which is most likely caused by lack of power.

STUDY LIMITATIONS AND STRENGTHS. As any other cross-sectional study seeking to evaluate potential risk factors for a given disease, it is important to

CENTRAL ILLUSTRATION Adjusted Odds Ratios for Having a Coexisting Aortic Dilation



Obel, L.M. et al. J Am Coll Cardiol. 2021;78(3):201-11.

Having an aortic dilation is the most important risk factor for having a coexisting aortic dilation elsewhere according to this study. Adjusted odds ratios (ORs) from multivariate logistic regression analyses are presented for each aortic site with corresponding 95% confidence intervals. Adjusted ORs from all investigated risk factors are presented in [Table 5](#).

TABLE 6 Postregression Evaluations of the Multivariate Logistic Regression Performances

	Ascending Aortic Dilations	Aortic Arch Dilations	Descending Aortic Dilations	Abdominal Aortic Dilations
ROC-AUC (95% CI)	0.69 (0.66-0.71)	0.80 (0.76-0.84)	0.73 (0.70-0.76)	0.74 (0.73-0.75)
cvROC-AUC (BBC 95% CI)	0.68 (0.65-0.70)	0.78 (0.74-0.84)	0.72 (0.69-0.75)	0.74 (0.72-0.75)
Brier scores	0.04	0.01	0.02	0.07

Discrimination tests for the multivariate logistic regressions used in [Table 5](#). The cross-validated ROC-AUC were estimated by dividing the total study-population into 10 subgroups.

AUC = area under the curve; BBC = bootstrap bias corrected; CI = confidence interval; cvROC = cross-validated receiver-operating characteristic; ROC = receiver operating characteristic curve.

remember that only associations will be identified as it is not possible to demonstrate that the associations are causal. Nevertheless, this study computes adjusted OR from a very well-characterized study population, minimizing the risk of missing unmeasured confounders that could account for the observed differences among dilations and the investigated variables.

The strengths lie in the general population-based setup in various Danish areas that are geographically and thus socioeconomically different, keeping the risk of selection bias to a minimum. The standardized protocols of the various measurements combined with large numbers guarantee high internal validity, which should have gained substantial power for the multivariate logistic analyses. Nevertheless, the low prevalence of dilations on the aortic arch and descending aorta could explain some insignificant findings.

As only men were recruited after the pilot phase of the DANCAVAS study, there is a rather large difference in numbers between men and women. Although the inclusion of >750 women is more than in most other studies, comparative analyses of sex-specific risk factors would be meaningless, as prevalence of thoracic aortic dilations was quite low in women.

A very important limitation is the lack of internationally clear definitions, particularly for thoracic aortic dilations. Consequently, we chose to use relative cutoff points at an observed +25% enlargement of the calculated normal diameters. Based upon the statistical post-regression evaluations, we find it reasonable to use the formulas for predictions of normal aortic diameters. However, we are not able to validate the formulas because the regressions used to define expected aortic diameters and the classifications of aortic dilations are derived upon the same data set; we plan to do so when follow-up data is available from the trials. An important observation is that risk factors found using the relative size index (Table 5) and absolute cutoff points (Supplemental Table 2) varied little. Proportions of agreements between dilations defined by the relative size index versus absolute measures were equally high, especially for participants with large aortic diameters (Supplemental Table 3). This may justify the use of relative size indexes as criterion for dilation.

Further limitations to be considered include the lack of aortic root assessment, because evaluations of diameters at this aortic level from noncontrast CT scans are associated with inaccurate measurements (6). Thus, the reported prevalence of ascending aortic dilations might be underestimated. Additionally, as

localized aortic arch dilations are rare, the high adjusted ORs for coexisting ascending and descending dilations are most likely reflections of the anatomic continuity of dilations from either thoracic neighboring part.

A statistical limitation is the inherent overlap across segments making interaction testing difficult, ie, participants with concomitant aortic dilations appear more than once in the multivariate logistic regressions. For an overview of distribution patterns for coexisting dilations, please see Supplemental Table 4.

CONCLUSIONS

First, our findings support current guidelines for aortic diseases in recommending a full screen of the aorta when a focal aortic dilation is discovered (1), as we noted the most essential risk factor for any aortic segment is the presence of an aortic dilation elsewhere, including the iliac arteries.

Not surprisingly, the different aortic sites shared several risk factors, including hypertension, increasing BSA, AFLI, and familial disposition, which were present in various combinations for different parts of the aorta. Diabetes was a mutual protective factor for all thoracic aortic sites. Other risk factors appeared diversely associated to different segments, eg, smoking and AMI increased risk for abdominal dilations remarkably, while they reduced risk for ascending dilations.

Finally, this study provides clinically applicable prediction formulas for calculating expected normal ascending, arch, descending, and abdominal aortic diameters, respectively, when measured on non-contrast CT scans. Although further validation is needed, it will be possible to evaluate aortas using an individualized size assessment to help distinguish between patients with healthy upper-normal biological variations from those who potentially may have started a pathological aortic dilation.

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ADDRESS FOR CORRESPONDENCE: Dr Lasse Mollegaard Obel, Department of Cardiothoracic and Vascular Surgery, Odense University Hospital, Søndre Boulevard 29, 5000 Odense C, Denmark. E-mail: Lasse.Mollegaard.Obel@rsyd.dk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Risk factors for aortic dilation differ across various aortic segments, but generally applicable factors include coexisting dilation in other aortic segments, coexisting iliac dilations, hypertension, large BSA, male sex, family history of aortic aneurysm, and atrial fibrillation.

TRANSLATIONAL OUTLOOK: Further research is needed to integrate and validate segment-specific genetic and clinical factors predictive of aortic dilation as the basis for the development of strategies for prevention of dissection and rupture.

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APPENDIX For supplemental tables, please see the online version of this paper.