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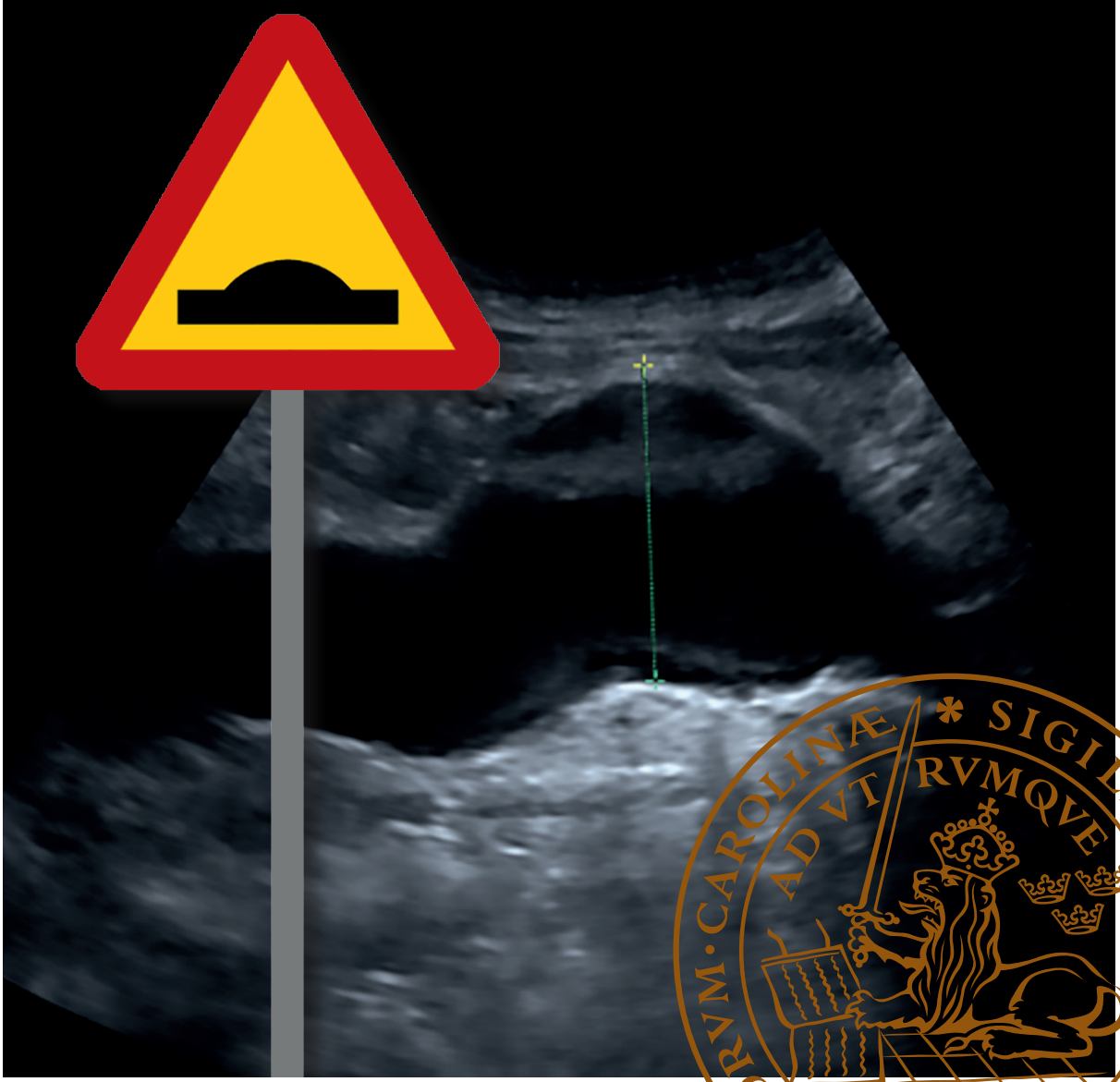

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If anywhere we have appeared dogmatic, we hope this may serve to stimulate discussion, since, in the end, real development depends on an exchange of views.
(J M G Wilson, 1913–2006 and C G Jungner, 1914–1982)

If you can meet with Triumph and Disaster
And treat those two impostors just the same;
(R Kipling, 1865 – 1936)

Diagnostic aspects of abdominal aortic aneurysm disease in men with reference to population-based screening

Joachim Starck

LUND
UNIVERSITY

DOCTORAL DISSERTATION
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Title and subtitle: Diagnostic aspects of abdominal aortic aneurysm disease in men with reference to population-based screening. Possibilities for refinement of ultrasound screening for abdominal aortic aneurysm in 65-year-old men.

Abstract:

Introduction Abdominal aortic aneurysm (AAA) mainly affects elderly men, grows slowly, and carries high mortality if left untreated, as rupture risk increases with larger diameters. AAA is well suited for screening due to its slow progression, long latent phase, reliable diagnostics, and established treatments. The primary aim of this thesis was to assess whether absolute infrarenal aortic diameter (IAD) or IAD relative to body surface area (BSA) better predicts aneurysm growth toward rupture-prone sizes, using the criterion IAD ≥ 1.5 times the expected diameter. A secondary aim was to evaluate whether screening can be simplified using more affordable, mobile ultrasound devices without compromising diagnostic accuracy.

Methods Data from the AAA screening program for men in Malmö, from 2010 to 2017 was used in Study I and II; first to assess the relationship between IAD and BSA and then to assess the relationship between AAA growth and BSA. In Studies III and IV, men with an IAD of 25–29 mm at screening were re-examined; Study III assessed growth in relation to expected IAD (Study I definition), and Study IV compared handheld and standard ultrasound regarding bias, repeatability, and diagnostic accuracy.

Results In Study I, correlation between BSA and IAD in 14,883 men supported using IAD ≥ 1.5 times expected for AAA diagnosis, increasing detection rate by 30 %. In Study II, AAA in 301 men had a mean growth rate of 1.6 mm/year, with no correlation to BSA. In Study III, 270 men with IAD 25–29 from screening were re-examined and those with an IAD ≥ 1.5 times expected grew 0.5 mm/year more compared to controls, but time to reach 40 mm differed by less than half a year. In Study IV, 230 men were examined, with a wider repeatability interval for handheld ultrasound but comparable accuracy to standard ultrasound for detecting AAA.

Conclusion IAD correlates with BSA, allowing for individualisation of AAA diameter criteria, whereas AAA growth does not. Adjusting the diagnostic threshold for AAA based on BSA, rather than a fixed diameter, may improve the identification of aneurysms likely to reach rupture-prone sizes during screening. Handheld ultrasound devices are feasible for use in AAA screening.

Key words: Human; Male sex; Screening; Aortic Aneurysm, abdominal; Growth rate; Ultrasound

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In loving memory of my late mother, Birgitta Starck, whose approach to work and life continued to be a great inspiration for this thesis.

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Summaries of key facts

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Disclosures

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The author was appointed registry custodian for Swedvasc, the Swedish national quality register for vascular surgery, from which data were requested for this thesis.

During the preparation of this work, the author used ChatGPT, an artificial intelligence language model developed by OpenAI, to check spelling and improve readability, and OpenEvidence, a free AI-powered medical search engine, for literature searches. After using these tools, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Abstract

Introduction

Abdominal aortic aneurysm (AAA) mainly affects elderly men, grows slowly, and carries high mortality if left untreated, as rupture risk increases with larger diameters. AAA is well suited for screening due to its slow progression, long latent phase, reliable diagnostics, and established treatments. The primary aim of this thesis was to assess whether absolute infrarenal aortic diameter (IAD) or IAD relative to body surface area (BSA) better predicts aneurysm growth toward rupture-prone sizes, using the criterion IAD ≥ 1.5 times the expected diameter. A secondary aim was to evaluate whether screening can be simplified using more affordable, mobile ultrasound devices without compromising diagnostic accuracy.

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Sammanfattning på Svenska

Ett bukaortaaneurysm (BAA), ett bråck på kroppspulsådern i buken, som brister är ett livshotande tillstånd med hög dödlighet utan akut operation. BAA växer långsamt, vanligtvis 1 till 2 mm per år. Mindre BAA är ofarliga och risken för bristning ökar först vid diametrar över 5,5 till 6 cm, då en förebyggande operation rekommenderas. Normalt är bukaortan cirka 2 cm i diameter hos 65-åriga män, men om den överstiger 3 cm klassas det som ett BAA, vilket förekommer hos cirka 1% av män i denna ålder och mer sällan hos kvinnor varför screening idag endast erbjuds män. Diagnosen ställs oftast med ultraljudsundersökning, en billig och icke invasiv metod med hög tillförlitlighet.

Aortascreening erbjuds 65-åriga män där de med en aortadiameter på 3 cm och större följs upp medan övriga avslutas från vidare kontroller. Här är evidensen stark. Vissa regioner följer även upp de på 2,5 till 3 cm. Evidensen för detta är begränsad då endast ett mindre antal växer. Att kunna särskilja dem i den här gruppen som riskerar tillväxt skulle vara mycket värdefullt.

Då förekomsten av BAA sjunkit har vissa riktlinjer föreslagit en mer riktad screening, där man i stället kallar personer med riskfaktorer som rökning, högt blodtryck eller ärftlighet. Dessa grupper har dock ofta lägre benägenhet att komma på undersökning. Mobila undersökningar med enklare utrustning skulle kunna underlätta sådan uppsökande screening med mindre resursåtgång.

Avhandlingens primära syfte var att undersöka om det är den absoluta kärldiametern eller dess värde i förhållande till kroppsstorlek som är bäst på att förutsäga utveckling mot behandlingskrävande BAA i syfte att identifiera de med en diameter på 2,5 till 3 cm som löper risk att växa till behandlingskrävande BAA.

Ett andra syfte var att undersöka om mätningen av aortadiameter, som vid BAA-screening, kan utföras med billigare och portabla ultraljudsapparater utan att kompromissa med den diagnostiska tillförlitligheten.

Data från Malmöregionens screeningprogram för BAA mellan 2010 och 2017 användes för att undersöka om aortadiameter och aneurysmtillväxt hänger ihop med kroppsstorlek. Aortadiametern visade en tydlig samvariation med kroppsstorleken, men aneurysmtillväxten gjorde det inte. Män med aortadiameter 25–29 mm följdes upp efter cirka tio år. De som hade aortor ≥ 1,5 gånger förväntat växte snabbare än övriga, men skillnaden i tid till att nå över 40 mm i diameter var mindre än ett år. Ultraljudsapparater i fickformat hade något större mätvariation, men ändå likvärdig noggrannhet jämfört med standardutrustning för att upptäcka BAA.

Aortadiametern i förhållande till kroppsstorleken, snarare än diametermåttet i sig, tycks ha betydelse för när en vidgning kan räknas som sjuklig. Små och enkla ultraljudsapparater skulle också kunna fungera vid screening för pulsåderbråck.

List of Original papers

This thesis is based on the following papers, which are referred to in the text as Study I–IV, using Roman numerals.

I. **J STARCK**, H L AALTONEN, K BJÖRSES, F LUNDGREN, A GOTTSÄTER, B SONESSON, J HOLST. *A significant correlation between body surface area and infrarenal aortic diameter is detected in a large screening population with possibly clinical implications.* Int Angiol. 2019 Oct;38(5):395-401

II. **J STARCK**, F LUNDGREN, H PÄRSSON, A GOTTSÄTER, J HOLST. *Body surface area does not affect growth rates of abdominal aortic aneurysms diagnosed in a male screening cohort.* Int Angiol. 2023 Feb;42(1):65-72

III. **J STARCK**, S BRUNKWALL, F LUNDGREN, H PÄRSSON, A GOTTSÄTER, J HOLST. *Predictors of aneurysm progression in men with small infrarenal aortic diameters at screening.* J Vasc Surg. 2025 Jun;81(6):1309-1318

IV. **J STARCK**, S BRUNKWALL, A GOTTSÄTER, J HOLST. *Evaluation of Point Of Care Ultrasound (POCUS) in screening for Abdominal Aortic Aneurysm in men: a comparative, cohort study.* Ultrasound Med Biol 51 (2025) 1840−1845

Introduction

Abdominal Aortic Aneurysm (AAA) screening in elderly men is well suited due to the relatively high prevalence of the condition in this population, alongside its significant health impact, straightforward detection methods, a long latent phase with a well-documented natural history, well-established treatment options with favourable outcomes, and potential for substantial health economic benefits. It requires only a single examination and not, as for most cancer screening programs, repeated examinations. However, the precise definition of an AAA remains a topic of debate. The widely accepted definition of an arterial aneurysm is a focal and persistent dilation of 1.5 times or more compared to the expected normal diameter of the artery in question. This typically means an infrarenal aortic diameter of ≥30 mm. However, some dilations, but not all, in the range of 25-29 mm also tend to enlarge over time, suggesting that it is not the absolute diameter alone that drives the growth mechanism.

The underlying pathology involves structural weakening of the aortic wall driven by a chronic inflammatory response, exacerbated by cardiovascular risk factors. In this process, vascular smooth muscle cells adopt a macrophage-like phenotype and secrete proteolytic enzymes that degrade key elastic components of the extracellular matrix. While such remodelling is also a feature of physiological ageing—manifesting as gradual aortic dilatation—once the aortic diameter exceeds a critical threshold, biomechanical forces begin to dominate. In accordance with Laplace's law, this facilitates further expansion and substantially increases the risk of rupture if left untreated.

This thesis focuses on the pivotal threshold where these biomechanical properties start to dominate and the abdominal aorta begins to exhibit substantial and rather predictable growth. It also considers diagnostic options and tools. The results presented here can contribute to the ongoing discussion about when a dilated abdominal aorta should be classified as an AAA and what methods can be used for detecting it.

Abbreviations & definitions

AAA	Abdominal Aortic Aneurysm. Includes pararenal, juxtarenal and infrarenal aneurysms. Defined as an infrarenal aortic diameter ≥ 30 mm.
BMI	Body Mass Index expressed in kg/m^2. Calculated as $BMI\ (kg/m^2) = Weight(kg)/Height(m)^2$
BSA	Body Surface Area expressed in m^2. Calculated with the DuBois and DuBois formula: $BSA\ (m^2)\ =\ 0.007184\ x\ Height\ (cm)^{0.725}\ x\ Weight\ (kg)^{0.425}$
IAD	Infrarenal Aortic Diameter
INI	Inner-to-inner (US measurement)
LELE	Leading-edge-to-leading-edge (US measurement)
OTO	Outer-to-outer (US measurement)
POCUS	Point-of-Care Ultrasound, a bedside, focused use of ultrasound, usually by healthcare professionals other than radiologists or sonographers, aimed at detecting positive findings rather than excluding disease.
US	Standard, cart-based ultrasonography

Square brackets [ ] within quotations are used to indicate clarifications, explanatory comments, or additions made by the author.

Background

Abdominal Aortic Aneurysm (AAA)

Abdominal aortic aneurysm (AAA) is defined as a permanent dilation of the abdominal aorta, typically ≥30 mm in diameter, representing a 1.5-fold increase from the normal infrarenal diameter in 65-year-old men (approximately 20 mm). Most AAAs expand slowly, about 1–2 mm/year, but larger diameters are associated with greater rupture risk, and a threshold of ≥ 55 mm is commonly used to guide prophylactic repair.

The infrarenal aorta is especially prone to aneurysmal degeneration due to its distinct vessel wall composition. The disease process reflects an accelerated form of age-related medial degeneration, driven by cardiovascular risk factors shared with atherosclerosis but pathophysiologically distinct. Progressive dilation increases wall tension, further weakening the vessel wall and promoting expansion.

Major risk factors include male sex, age, smoking, hypertension, obesity, cardiovascular disease, and genetic predisposition, whereas diabetes appears protective. Smoking is the strongest modifiable risk factor, and cessation reduces both growth and rupture risk. No medical therapy prevents progression; prophylactic surgical repair remains the only effective treatment, with approach determined by aneurysm size, growth rate, anatomy, and patient life expectancy.

Overview

The mean infrarenal aortic diameter (IAD) in 65-year-old men is 19–20 mm [1] and an abdominal aortic aneurysm (AAA) is clinically defined for men as an IAD measuring 30 mm or more [2]. This diagnostic criterion for AAA is based on the definition of an arterial aneurysm as a permanent, localized dilation of an artery including all vascular wall layers, by 1.5 times the expected normal diameter [3].

The AAA criterion of IAD ≥ 30 mm is commonly used and has been shown to predict progression to AAA requiring treatment within 10 years with a sensitivity of 68 %. However, specificity is low, as only a small proportion of aneurysms

expand to ≥ 55 mm [4]. Also, over half of men with an IAD of 25 to 29 mm at screening exceed the 30 mm threshold within five years, and 10 to 30 % reach 55 mm (the recommended diameter for prophylactic intervention) within 10 years [5, 6].

The aorta as an organ

The aorta is the largest artery in the body and should be considered an organ of its own [7]. It originates from the left ventricle of the heart and the aortic valve, carrying oxygenated, arterial blood from the pulmonary circulation to the systemic circulation. It is sectioned into the root, the ascending aorta, the aortic arch, the descending aorta, and ends with the abdominal aorta that splits up in two iliac arteries at the level of the umbilicus [8].

Like all arteries, the aorta consists of three layers. The innermost layer, the intima, is composed of endothelial cells in direct contact with the bloodstream. The middle layer, the media, contains vascular smooth muscle cells (VSMCs) embedded in an extracellular matrix (ECM) composed of elastin, collagen (types I and III), and proteoglycans. The outermost layer, the adventitia, is composed of fibroblasts, interstitial collagen, nerve fibres, and vasa vasorum, with its density decreasing along the length of the aorta [9].

VSMCs are the predominant cell population of the vessel, originating from at least seven unique and non-overlapping sources in vertebrate embryos [10], and interact with the ECM to maintain aortic homeostasis [11]. This diversity reflects the complex embryonic development of the aorta, which forms through the fusion of isolated vascular islands into paired aortae and several aortic arches that connect the aortic sac to the dorsal aorta, ultimately forming and uniting the different segments into a single vessel known as the aorta [12, 13].

The elastin fibres in the aortic media, together with associated microfibrils and proteoglycans [14-16] allow the aorta to expand and recoil during cardiac cycles [17], a phenomenon known as the *Windkessel* effect [18]. This involves the aorta stretching, primarily in diameter but also in length during systole and recoiling during diastole, helping to maintain blood pressure. In contrast, the collagen fibres in the media and adventitia provide tensile strength, allowing the wall to withstand pulse waves [19].

With ageing, elastin fibres gradually fragment and lose elasticity due to fatigue from continuous cyclic loading and low-grade chronic inflammation [20-22]. This structural remodelling, with a reduced elastin-to-collagen ratio in the ECM and also the deregulated behaviour of VSMCs [23], leads to gradual aortic dilation, tortuosity, and wall thickening in the intima and media [24]. This process should not be considered as pathologic although it increases the susceptibility to aortic disease [25] and is accelerated by cardiovascular risk factors [26].

Pathophysiology of AAA

An abdominal aortic aneurysm (AAA) is a pathological dilation of the abdominal aorta involving all layers of the vessel wall. While it shares risk factors with other cardiovascular diseases, it is considered a distinct clinical entity and should be differentiated from aortic dissection [8].

With age, structural remodelling of the aorta increases susceptibility to aortic disease. This includes a reduced elastin-to-collagen ratio in the ECM and the deregulation[1] of VSMCs, both of which are key contributors to aneurysmal development [25]. The healthy infrarenal aorta, in particular, has a lower density of elastic fibres and a higher proportion of collagen compared to the thoracic aorta, making it especially susceptible to aneurysmal disease [26-28]. Additionally, VSMCs in the infrarenal aorta appear especially prone to deregulation [29, 30]. Together, these features could help explain the high prevalence of abdominal aortic aneurysm (AAA) compared to aneurysmal disease in other segments of the vascular tree [31].

The deregulation of VSMCs is characterized by phenotypic[2] switching with transition from smooth muscle cells into diverse cell types, including macrophage-like, T-cell-like, fibroblast-like, and mesenchymal-like cells. These VSMC-derived cells, especially the macrophage-like phenotypes, express high levels of chemokines, proteinases, and proinflammatory mediators, contributing to ECM degradation, chronic inflammation, and loss of aortic wall integrity [23, 32]. VSMC phenotype switching to mesenchymal stem cell-like states can also differentiate to osteoblasts (bone producing), chondrocytes (cartilage producing), adipocytes (fatty tissue), and macrophages, leading to ectopic calcification, ossification, and increased cellular heterogeneity within the aortic wall. From functioning as contractile elements linked with the ECM, capable of harbouring the pulse wave, VSMCs transform into solitary synthetic cells that degrade the ECM [33]. Deregulation and phenotypic switching of VSMCs are considered to play a greater and more causative role than VSMC apoptosis in the initiation and progression of AAA according to recent and comprehensive molecular and translational studies [23, 29, 30, 33-35].

[1] **Deregulation** can be described as the disturbance or loss of normal regulatory control over essential cellular processes such as growth, division, differentiation, apoptosis (programmed cell death), and signalling. This can occur in various biological contexts and is a key concept in understanding diseases such as cancer, autoimmune conditions, and, as in this case, degenerative disorders.

[2] **Phenotype** is the observable physical, biochemical, and behavioural characteristics of an organism or a cell, resulting from the interaction of its genetic makeup (**genotype**) with the environment.

The phenotypic switching of VSMCs, particularly in the context of altered vessel geometry and hemodynamic changes such as vessel widening, is driven by multiple interrelated factors:

- **Low and oscillatory shear stress**. Vessel widening alters local blood flow, creating regions of disturbed shear stress that initiate endothelial dysfunction [36-38].
- **Endothelial dysfunction**. This leads to the upregulation of adhesion molecules and cytokines, promoting leukocyte recruitment and local inflammation [39-42].
- **Inflammation and oxidative stress**. These factors further drive the transition of VSMCs from a contractile phenotype that is structurally integrated with the extracellular matrix, forming a flexible, contractile unit, to synthetic, proinflammatory, or even macrophage-like states characterized by increased proliferation, migration, and secretion of proteinases such as matrix metalloproteinases (MMPs)[3], which degrade the ECM [29, 30, 32].
- **ECM degradation**, particularly the breakdown of elastin, leads to a loss of vessel wall elasticity leaving the structural integrity dependent on collagen which is much stiffer. This results in reduced compliance, predisposing to further dilation and mechanical failure. Also, the breakdown products of the extracellular matrix itself promote VSMC phenotypic switching [43-45].
- **Dysregulated growth factor signaling**. Abnormal signaling (primarily originating from endothelial cells) involving key factors such as transforming growth factor beta (TGF-β), which maintains VSMC integrity, and platelet-derived growth factor BB (PDGF-BB)[4], which promotes VSMC migration, proliferation, and phenotypic switching, contributes to the inflammatory process [33, 46, 47].
- **Genetic factors**. Mutations or variants affecting ECM proteins, signaling pathways, or the VSMC contractile apparatus can predispose to cell-

[3] **Matrix metalloproteinases (MMPs)** are zinc-dependent enzymes that remodel the extracellular matrix (ECM) by degrading proteins such as collagen and elastin. Under physiological conditions, their activity is balanced by tissue inhibitors of metalloproteinases (TIMPs), supporting vascular development, repair, and homeostasis. In aneurysm disease, excessive MMP activity drives ECM degradation, loss of wall integrity, and smooth muscle cell phenotypic switching, thereby promoting vascular weakening.

[4] **Platelet-derived growth factor-BB (PDGF-BB)** is one of three biologically active isoforms of PDGF, which forms disulfide-linked dimers of A and B polypeptide chains (AA, AB, BB). The "BB" designation denotes a homodimer of two B chains, with distinct receptor-binding and biological effects. In vascular biology, PDGF-BB promotes smooth muscle cell migration, proliferation, and phenotypic switching, and modulates vessel wall inflammation.

dedifferentiation, increasing susceptibility to aneurysm formation and progression [23, 48, 49].

- **Epigenetic mechanisms**. Heritable changes in gene expression, modify VSMC behaviour in response to environmental cues such as disturbed shear stress, inflammation, and oxidative stress. These epigenetic changes promote VSMC transitions to synthetic, proinflammatory, or macrophage-like phenotypes that secrete proteases, contributing to ECM degradation and aortic wall weakening [29, 50].
- **ECM breakdown products and sustained signaling**. These factors reinforce phenotypic switching and maintain the non-contractile VSMC states [23, 29, 30].

Together, these processes establish a self-perpetuating cycle that promotes aneurysm progression in the context of altered vessel geometry and hemodynamic stress, with no single determining factor initiating the process [30, 51].

Risk factors and markers for AAA

At the cellular and vascular level, deregulation such as VSMC phenotypic switching, endothelial dysfunction, and ECM remodelling are central to AAA pathogenesis in both sexes, but sex hormones modulate these processes differently. In men, androgens and androgen receptor signalling promote VSMC phenotypic modulation, inflammation, and ECM degradation, increasing susceptibility to AAA. In women, premenopausal oestrogen confers protection by stabilizing VSMC phenotype, reducing inflammation, and preserving ECM integrity; loss of oestrogen after menopause leads to increased ECM degradation, VSMC apoptosis, and higher matrix metalloproteinase activity, contributing to more rapid aneurysm growth and higher rupture risk. Biomechanical studies have also shown that female aortas have lower tensile strength, which may further increase rupture risk [52-56].

Tobacco smoking and AAA

The strongest modifiable risk factor for aneurysm expansion and rupture is smoking, with a clear dose-response relationship between smoking exposure and both AAA growth and rupture risk [57]. A review by Lederle et al. 2003 of ten studies including more than three million participants indicate that the association between smoking and aortic aneurysm is substantially stronger than the association between smoking and coronary or cerebral vascular disease [58].

Chronic cigarette smoking accelerates aortic remodelling by promoting wall thickening, increased collagen deposition, and reduced elastic fibre function. This leads to decreased aortic distensibility and increased vulnerability to atherosclerotic changes, partly through enhanced MMP activity by activating signalling pathways

in VSMCs. Additionally, smoking increases the recruitment and activation of inflammatory cells, including macrophages and lymphocytes, as well as upregulation of genes involved in inflammation, which further amplify proteolytic and inflammatory processes with the aneurysm wall [59, 60]. Experimental data show that smoking induces region-dependent increases in aortic wall thickness and impairs mechanical function, compounding the effects of ageing and further increasing the risk of aortic disease [26, 61]. Nicotine itself, independent of smoking, promotes AAA development in experimental models by driving vascular smooth muscle cell phenotypic switching, protease activity, and extracellular matrix degradation, with sex-hormone–modulated effects. While human data mainly implicate smoking, the risk from non-smoking nicotine use (e.g., vaping, smokeless tobacco, nicotine replacement) remains uncertain, as large-scale epidemiologic studies are lacking [62].

As smoking cessation is associated with a reduction in both AAA growth rate and rupture risk, the causal and reversible nature of these mechanisms is supported [63].

Hypertension and AAA

Epidemiologic data demonstrate that hypertension increases the risk of developing AAA by 66% compared to normotensive individuals, and both systolic and diastolic blood pressure are positively associated with AAA risk and growth. Notably, every 20 mmHg increase in systolic blood pressure and every 10 mmHg increase in diastolic blood pressure are associated with a 14 % and 28 % increase in AAA risk respectively, with a particularly strong nonlinear association for diastolic blood pressure above 80 mmHg [64]. Elevated diastolic blood pressure seems also to be independently associated with faster AAA expansion rates [65].

While endothelial dysfunction, due to elevated blood pressure, amplifies the inflammatory and proteolytic environment in AAA, the mechanical stress is the initiating event that triggers downstream biological responses, including the upregulation of pro-inflammatory cytokines, activation of MMPs, and recruitment of inflammatory cells [66, 67].

Elevated blood pressure also induces endothelial dysfunction as increased wall tension impairs nitric oxide production which elevates oxidative stress contributing to a pro-inflammatory environment that fosters leukocyte recruitment, MMP activation, and further ECM breakdown [68].

Obesity and AAA

Obesity is not explicitly designated as a risk factor for AAA in current guidelines, but epidemiological and observational studies as have suggested that BMI is positively correlated to the risk of developing AAA [69-73]. Obesity has also been associated with faster outward proximal aortic remodelling that, together with arterial hypertension would account for a 0.6 to 0.8 mm greater diameter at the

ascending aorta [74]. This has been attributed to hyperlipidemia, and high-fat diets, which promote inflammation, oxidative/nitrosative stress, mitochondrial dysfunction, endothelial apoptosis, and macromolecular damage. These processes contribute to vascular wall senescence (age-related loss of normal cell function) and thereby increase cardiovascular risk and disease, including AAA [75].

Diabetes and AAA

Extensive epidemiologic and meta-analytic data consistently demonstrate an inverse association between diabetes and AAA prevalence and incidence, with diabetes conferring a lower risk of developing AAA compared to non-diabetic individuals. This negative association persists across diverse populations and study designs, and is more pronounced with longer diabetes duration and higher glycaemic burden [76, 77]. Diabetes mellitus is also associated with a slower rate of aneurysmal growth, despite accelerating other forms of vascular disease [78]. This is attributed to diabetes-induced increases in ECM stability due to enhanced cross-linking of collagen and elastin fibres by advanced glycation end-products, which make these proteins more resistant to enzymatic degradation [79-81]. Additionally, research suggests that altered metal ion homeostasis in diabetes reduces the activity of MMPs, further limiting the proteolytic degradation involved in aneurysm pathogenesis [82]. There is also evidence suggesting that metformin, a commonly used drug in type 2 diabetes mellitus, may inhibit AAA growth, possibly through broad anti-inflammatory effects, as indicated by large systematic reviews and meta-analyses, although this has not yet been confirmed in a randomised contol trial (RCT) [78, 83-86].

Alcohol intake and AAA

High alcohol intake is associated with increased risk of AAA development, while moderate intake does not appear to increase risk. The effect on AAA progression is less clear, but high alcohol intake may indirectly contribute via its hypertensive effects [87].

Cardiovascular disease and AAA

The prevalence of AAA is significantly higher among patients with coronary artery disease (CAD) compared to those without CAD, with odds ratios ranging from approximately 2.4 to 3.5. Among men with CAD, AAA prevalence has been reported between 8 % and 12 %. Similarly, both symptomatic and asymptomatic PAD are independently associated with increased risk of incident AAA, with hazard ratios of 1.5–3.0 in prospective cohort studies [88-90].

Other cardiovascular comorbidities (such as coronary artery disease, dyslipidaemia, and peripheral artery disease) are associated with increased AAA risk although occlusive atherosclerotic disease is a different entity. Physical inactivity and elevated CRP are also associated with increased AAA risk, particularly in women

and younger individuals [78, 91] Although AAA and occlusive atherosclerotic disease share common risk factors and often coexist, their underlying pathophysiology is distinct. AAA is characterized by medial degeneration and chronic inflammation rather than the intimal plaque formation typical of occlusive atherosclerosis [92].

Genetic factors and AAA

Genetic factors, which may serve as targets for future therapeutic interventions, are also highly relevant in the contemporary debate on targeted AAA screening. Emerging modelling studies suggest that polygenic risk scores (PRS), which aggregate the effects of a large number of single nucleotide variants across the genome, may enhance risk prediction. The most recent and comprehensive PRS for AAA includes up to 911,440 single nucleotide variants associated with AAA risk, along with variants linked to related cardiovascular traits to improve predictive performance. Stratified screening based on PRS could improve cost-effectiveness and allow for more efficient targeting of high-risk individuals, potentially justifying earlier or more frequent screening, also in selected women. However, these approaches are not yet incorporated into clinical guidelines, as further validation is needed [93, 94].

Epidemiology of AAA – sex differences

AAA is significantly more common in men than in women, with a four- to six-fold higher prevalence. This sex disparity is consistent across age groups, though the incidence in women rises with age and tends to present later in life. Prevalence for AAA in general population cohorts aged 40–95 years in Europe are 4.0 % in men and 0.7% in women [95]. AAA in women is also typically smaller at detection and rarely progresses to rupture or requires intervention [96, 97]. Smaller baseline aortic diameters, potential protective effects of estradiol, and lower smoking prevalence contribute to this pattern, although smoking appears more deleterious in women than in men. These factors, however, cannot fully explain the sex gap, and intrinsic processes such as vascular wall biology and genetic regulation are likely involved, but evidence remains limited and further studies are needed [97].

Although population-based studies demonstrate that male sex is a strong independent risk factor for AAA, women are more likely to experience rupture at smaller diameters and have higher perioperative morbidity and mortality after both elective and emergency repair. These differences are likely related to aortic wall structure, a higher prevalence of cardiovascular risk factors such as hypertension and chronic kidney disease, and smaller body size [98-100]. Up to 30 % of ruptures in women occur at diameters below 55 mm, compared to 8 % in men at the same threshold. Indexing aneurysm size to body surface area or using the aortic size index has been shown to better predict rupture risk in women than relying on absolute

diameter alone [53, 56, 101]. Risk factors such as smoking, physical inactivity, and elevated C-reactive protein (CRP)[5] have a greater impact on AAA risk in women than in men, with smoking conferring a higher population attributable fraction and relative risk in women [52, 100].

Meanwhile, the prevalence of abdominal aortic aneurysm (AAA) in men aged 65 years in Europe has declined over the last decades from 4 to 5 % [102] in the late 20th century to 1.3 to 1.5 % in recent years as seen in population-based screening studies [63]. Over the past four years a mean prevalence of 1.0 % or lower has been noted in four Swedish counties, with the lowest prevalence down to 0.5 % observed in Uppsala [103]. This trend is attributed to reductions in smoking rates and improved cardiovascular risk management, making hypertension now the predominant global risk factor for AAA disease instead of smoking [8, 104-107].

Aneurysmal progression

In its natural course, AAA expands slowly over several years, typically by 1 to 2 mm per year [108] compared to about 1 mm per 10 years for a normal diameter aorta in adults [109].

The most important factor impacting growth and rupture risk of AAA is maximum aneurysm diameter as larger aneurysms expand faster and have a higher risk of rupture [78]. The maximum vessel diameter has a significant impact on both the growth rate and rupture risk of AAAs because increasing diameter directly increases wall tension according to the law of Laplace[6].

Law of Laplace: **wall tension** (T) is proportional to the product of **transmural pressure** (P) and **vessel radius** (r), divided by **wall thickness** (h).

$$T = \frac{P \cdot r}{h}$$

[5] **C-reactive protein (CRP)** is an acute-phase protein produced by the liver in response to inflammation, widely used as a biomarker of systemic inflammation, cardiovascular risk, and infection. Beyond being a marker, CRP may also contribute directly to pathology, as its monomeric form is deposited in aneurysmal tissue and associated with upregulation of inflammatory and proteolytic pathways.

[6] Pierre-Simon Laplace (1749–1827). French mathematician and physicist whose work laid foundations in many fields, including Bayesian statistics, celestial mechanics, and mathematical physics. His law of spherical and cylindrical pressures, formulated in the early 19th century, arose from studies of fluid mechanics and capillarity.

As the aneurysm enlarges, wall tension rises, predisposing the vessel to further expansion and ultimately rupture if wall strength is exceeded [110, 111]. Biomechanical studies and clinical data confirm that larger AAAs are associated with higher peak wall stress and a greater likelihood of local wall failure, especially in regions of maximal diameter or asymmetry [112]. Histopathologically, larger aneurysms also exhibit greater elastin degradation, increased intraluminal thrombus formation, and reduced wall strength, further compounding rupture risk as diameter increases [113].

There is no evidence from the four major RCTs of AAA screening (MASS, Viborg County, Chichester, and Western Australia) that a specific threshold or "tipping point" in infrarenal aortic diameter triggers accelerated aortic growth or subsequent development of a rupture-prone AAA [57, 114]. Meta-analyses and cohort studies likewise do not support the existence of a discrete diameter threshold; rather, they indicate a continuous, diameter-dependent increase in both aortic growth and rupture risk. For instance, the risk of rupture in men is estimated to rise by a factor of 1.9 for every 5 mm increase in baseline diameter, illustrating a gradual, not abrupt, change [8, 115]. While recent cohort data suggest that men with subaneurysmal diameters (25–29 mm) are at increased long-term risk of developing clinically significant AAAs, current evidence supports a continuous progression of risk rather than a sharply defined threshold for accelerated growth [6, 116].

The risk of rupture increases significantly once the aneurysm expands beyond 55–60 mm, resulting in life-threatening internal bleeding [117]. The most robust and validated predictor of rupture is aneurysm diameter [118], and there is broad consensus that it is safe to delay preventive intervention until the aneurysm reaches a diameter of ≥ 55 mm in men (class 1 recommendation, evidence grade A, ESC/ESVS) [2, 8]. Preventive intervention using open or endovascular techniques is well established and has demonstrated favourable outcomes [2].

Treatment – Lifestyle

Robust evidence from clinical guidelines, cohort studies, and meta-analyses supports that **smoking cessation** reduces the prevalence, growth rate, and rupture risk of AAA [8, 63, 119-121].

Smoking cessation has been found to nearly halve the relative risk of AAA for every ten years of cessation, and after 25 years, the risk approaches that of never-smokers. This dose-response relationship is consistent across diverse populations and independent of other cardiovascular risk factors, underscoring the causal and potentially reversible impact of tobacco smoking on AAA [63].

Smoking cessation is strongly associated with slower AAA expansion and a reduced risk of rupture, following a clear dose-response pattern. Prospective cohort data show that the risk of AAA rupture is highest in current smokers and declines

progressively with increasing duration of abstinence [57]. Greater cumulative smoking exposure correlates with faster aneurysm growth and increased rupture risk, while longer durations of abstinence gradually reduce this risk, approaching that of never-smokers. Supporting this, data from a Markov cohort simulation model show that intensive smoking cessation interventions in patients with small AAAs could reduce rupture substantially over ten years and also decrease the need for elective AAA repair [120, 121].

A longer duration of smoking cessation prior to AAA surgery reduces, but does not fully normalise, complication rates to the level seen in never-smokers. The greatest reduction in perioperative risk is observed with at least 8 weeks of abstinence, although a residual excess risk remains compared to never-smokers [122, 123].

Physical activity also seems to be associated with a dose-response relationship with lower prevalence of abdominal aortic aneurysm (AAA), although the effect is less pronounced than that of smoking cessation [124, 125]. Randomised trials and meta-analyses of exercise interventions in patients with small AAAs have confirmed that exercise training is generally safe, improves functional capacity, and does not accelerate aneurysm growth, although current evidence remains inconclusive regarding its long-term impact on aneurysm progression [126-128].

Dietary patterns rich in fruits, vegetables, nuts, and fiber are associated with lower AAA incidence, with fruit intake especially protective [129, 130]. DASH-style[7] and anti-inflammatory diets [131] likewise correlate with reduced risk. Higher intakes of vitamins C, E, D, riboflavin, and folate are linked to lower risk, particularly in older adults [132-134]. However, evidence from RCTs is lacking, and supplementation has not been shown to slow AAA progression or improve outcomes [135].

Treatment – Medical

There is currently no medical (non-surgical) treatment that has been convincingly shown in a RCT to limit the growth or reduce the risk of rupture of abdominal aortic aneurysms (AAA). Although observational data have suggested potential benefits of statins, blood pressure control, and metformin, these findings have not been confirmed in prospective trials and are not endorsed by current clinical guidelines. Multiple RCTs and meta-analyses of these and other agents have failed to demonstrate a convincing reduction in AAA growth or rupture risk in humans [83, 91, 135-138].

[7] The Dietary Approaches to Stop Hypertension (DASH) diet was developed by the U.S. National Heart, Lung, and Blood Institute in the 1990s to lower blood pressure. It emphasizes fruits, vegetables, whole grains, low-fat dairy, nuts, and legumes, and has since been widely studied as a cardioprotective dietary pattern.

Nevertheless, statin and antiplatelet therapy are recommended for patients with AAA, based on their high baseline cardiovascular risk and in accordance with current guidelines on the management of AAA [135, 139, 140].

Treatment – Surgical

Prophylactic surgical repair remains the only proven intervention to prevent rupture in patients with large or symptomatic AAA, given the lack of effective medical therapies other than smoking cessation to reduce AAA prevalence, growth, or rupture risk [135, 140].

Indications for elective repair in men include an IAD ≥ 55 mm, although a higher threshold has been debated [141]. Also, rapid aneurysm growth (> 10 mm/year) or symptomatic AAA – most commonly pain in the abdomen, back, or flank – warrant repair regardless of size [2, 91, 142, 143].

Ruptured AAA (rAAA) is a surgical emergency requiring immediate open or endovascular intervention to prevent death. Without repair, rAAA is almost universally fatal due to exsanguination. Both open aneurysm repair (OAR) and emergency endovascular aneurysm repair (EVAR) are established life-saving procedures, although perioperative mortality remains high, typically 25–50 % at 30 days [144-147]. Long-term survival among hospital survivors is poor, with mortality rates approaching 60 % at seven years, often following difficult and protracted rehabilitation [148].

Timing for prophylactic surgery is based on balancing rupture risk against perioperative risk and life expectancy. Elective repair is not recommended for patients with a life expectancy less than 2 to 3 years, as the risks outweigh the benefits. For patients with a life expectancy more than 10 to 15 years, OAR is preferred if operative risk is acceptable. For those with a life expectancy of 3 to 15 years and suitable anatomy, EVAR is preferred due to lower perioperative mortality [2, 140, 149].

Post-operatively there is strong evidence and guideline support for continuing long-term (lifelong) surveillance after EVAR, while allowing for discontinuation of routine surveillance after OAR in most patients once early postoperative recovery is complete [91, 150-153]. This approach is endorsed by both the Society for Vascular Surgery and the European Society for Vascular Surgery, and is supported by contemporary outcome data and cost-effectiveness analyses [2, 150].

General concepts in screening

Screening is the systematic application of a test to identify individuals at risk of a specific disorder, before symptoms appear. Initially used in early 20th-century military and public health settings, screening aimed to detect infectious diseases like syphilis and tuberculosis, or physical or psychological impairments affecting fitness for service.

A major development came with a World Health Organisation (WHO) report authored by Wilson and Jungner 1968, which set out ten principles to guide screening programs. These emphasise the importance of targeting serious, treatable conditions, using reliable tests, and considering ethical, economic, and organizational factors.

Their framework still underpins screening today, with growing attention to test performance, overdiagnosis, psychological consequences, and equitable access. While screening can save lives, it also carries risks which makes thoughtful, evidence-based implementation essential.

Definition

The WHO states in *Screening programmes: a short guide (2020, p. ii)* [154]:

> "The purpose of screening is to identify people in an apparently healthy population who are at higher risk of a health problem or a condition, so that an early treatment or intervention can be offered and thereby reduce the incidence and/or mortality of the health problem or condition within the population."

The Commission on Chronic Illness (CCI) Conference on Preventive Aspects of Chronic Disease, held in 1951, defined screening as

> "[…] the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment." (Commission on Chronic Illness, 1957)

Note that, in most cases, a screening test is not intended to be diagnostic but rather to identify individuals at high risk of having the condition. The aim is to minimize harms such as unnecessary procedures, psychological distress, and overtreatment, while ensuring that true cases are accurately identified and managed, since definitive diagnostic tests often involve invasive procedures [155, 156].

Origins and evolution

Medical screening originated in the early 20th century, with its first systematic applications in military and infectious disease settings. Early milestones included psychiatric evaluations of U.S. Army recruits and mass serological testing for syphilis, both of which demonstrated the feasibility and value of detecting disease in asymptomatic individuals. The concept expanded during the interwar and post-World War II periods to encompass school health examinations and, later, chronic disease screening in civilian populations, including diabetes, cervical cancer (via the Pap test[8]), and breast cancer (via mammography) [157, 158]. Chest radiography emerged as a population-based screening method for tuberculosis between the 1940s and 1970s. However, its use in detecting occupational diseases such as silicosis dates back to the earlier than that, when chest radiography became a key tool in occupational health surveillance for pneumoconiosis[9]. This was, in effect, an early form of screening [159]. In the mid-20th century, mass miniature chest radiography campaigns were launched to detect pulmonary tuberculosis among asymptomatic adults, with major efforts in the 1950s, most notably the 1957 Glasgow campaign, which screened over 700,000 adults in five weeks. These initiatives, driven by the need to reduce transmission and morbidity, contributed to substantial and sustained reductions in tuberculosis case notifications through early case finding [160, 161].

Much screening practice evolved in the USA during the 1950's in the form of multiple screening programmes defined as "the application of two or more screening tests in combination to large groups of people" [162]. These programs demonstrate high ambitions for screening as a concept, as the CCI in 1957 considered that multiple screenings might profitably be carried out for several diseases, both communicable and non-communicable diseases including cancer like:

- pulmonary tuberculosis and syphilis
- visual defects (including chronic glaucoma), diabetes, hypertensive disease, and ischaemic heart disease
- cancers of skin, mouth, breast, cervix and rectum

Advances in medical technology, such as blood tests, radiology, and cytology, made it increasingly possible to detect diseases early, even in asymptomatic individuals.

[8] **Pap test** (Papanicolaou test) is a screening procedure for cervical cancer in which cells collected from the cervix are examined microscopically to detect precancerous or cancerous changes, developed by Dr. Georgios Papanicolaou in the 1940s.

[9] **Pneumoconiosis** is a group of occupational lung diseases caused by the inhalation of mineral dust—such as coal dust, silica, or asbestos—leading to chronic inflammation, fibrosis, and impaired lung function. It commonly affects miners, construction workers, and others exposed to airborne particulate matter over long periods.

As interest in mass screening grew, particularly in high-income countries, so too did concerns about its effectiveness, ethical justification, and resource implications [157].

Wilson & Jungner criteria for screening

To address these issues, the WHO commissioned J.M.G. Wilson[10] and C.G. Jungner[11] to establish a rational, evidence-based framework to guide decisions about which diseases should be targeted for screening and under what circumstances such programs would be justified and effective. The guidelines for the work were:

- Evaluating the principles underlying disease screening.
- Provide practical guidance for governments and public health authorities.
- Establish a systematic framework for assessing whether a condition is appropriate for screening.

The result was the 1968 monograph, *Principles and Practice of Screening for Disease* [163], published by the WHO's Public Health Papers series. This report reflects a broad understanding of screening as shaped by ethical, economic, global, and sociological considerations. It acknowledges that factors such as health system capacity and socioeconomic conditions influence the feasibility and design of screening programs. Sociological aspects—such as the level of education and awareness, access to medical care, and general living standards—are central to assessing the population at risk. The report also highlights that the goals and challenges of early disease detection differ significantly between high-income and low-income settings, requiring context-sensitive approaches [163]. As WJ states in the report:

> The central idea of early disease detection [i.e., screening] is far from simple though sometimes it may appear deceptively easy (Wilson & Jungner, WHO 1968, p. 30).

The Wilson & Jungner ten principles of Screening

The report articulated ten criteria that have since become the foundational reference for evaluating screening programs globally. These criteria were designed to ensure that screening would be implemented only when it was likely to do more good than harm, considering factors such as the importance of the health problem, the availability of effective treatment, the characteristics of the screening test, and the balance of costs and benefits [164-167].

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[10] **James M. G. Wilson** (1913–2006), Principal Medical Officer at the UK Ministry of Health.

[11] **Carl Gunnar Jungner** (1914–1982), Chief of Clinical Chemistry at Sahlgrenska Hospital, Gothenburg.

The following seeks to elaborate and unify the text accompanying the Wilson & Jungner (WJ) ten principles [157, 163]:

I. *The condition sought should be an important health problem.*

An important health problem may be defined by high prevalence, by severe individual consequences, or by a combination of both, reflecting significant health or social impact at the population and/or individual level. Screening programs are most effective when targeting populations with a high burden of undiagnosed disease, but the rationale is also strengthened when the undetected condition carries significant health consequences for the individual if left untreated [168].

II. *There should be an accepted treatment for patients with recognized disease.*

a. Does treatment at the pre-symptomatic borderline stage of a disease affect its course and prognosis?

b. Does treatment of the developed clinical condition at an earlier stage than normal affect its course and prognosis?

III. *Facilities for diagnosis and treatment should be available.*

This principle has a clear bearing on the socio-economic context in which the screening takes place. In planning to detect some condition, or group of conditions, in a population it is a prerequisite that persons found in need of treatment should be able to obtain it. In general, the larger the scheme the more this proviso assumes importance. In developing countries, the challenge of providing effective treatment and care for conditions detected through mass screening must be considered, since medical services may be very limited.

IV. *There should be a recognizable latent or early symptomatic stage.*

In order usefully to detect and treat disease at an early stage there must clearly be a reasonable period in the natural history of the condition during which symptoms are either not present or at any rate not clamant.

V. *There should be a suitable test or examination.*

The screening test (which of its nature should be easy and quick to perform) should aim to maximize sensitivity to identify as many potential cases as possible, accepting a lower specificity, which are then resolved by more specific confirmatory diagnostic testing [169]. This could be debated, as false positive screening tests could have as large consequences for the individual as false negative tests [170].

VI. *The test should be acceptable to the population.*

A test or series of tests must be acceptable to the target population, which is assumed to be healthy. The perceived prevalence of disease and community awareness, particularly the question ‘What do I gain from screening?’, strongly influence acceptance and, consequently, compliance.

VII. *The natural history of the condition, including development from latent to declared disease, should be adequately understood.*

a. What changes should be regarded as pathological and what should be considered physiological variations?

b. Are early pathological changes progressive?

c. Is there an effective treatment that can be shown either to halt or to reverse the early pathological changes?

This principle must remain under continuous scrutiny in all screening programs, as research developments provide new insights into disease diagnostics, progression, and treatment.

VIII. *There should be an agreed policy on whom to treat as patients.*

This principle stresses the careful management of borderline cases, individuals with unclear screening results, reflecting principles V and VIIa. To prevent harm and confusion, clear policies and follow-up plans are essential to avoid unnecessary labelling or segregation of screening participants with borderline results.

IX. *The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.*

The health economic benefit from screening depends on reducing morbidity and prolonging productivity for the disease in question, which may vary at both individual and community levels depending on the specific context, and requires RCTs to establish cost-efficiency.

X. *Case-finding should be a continuing process and not a "once and for all" project.*

As one-time projects and campaigns were often the practice when the principles were formulated, WJ advocated for ongoing programs integrated into routine care to improve coverage and efficiency, since single-occasion screenings miss future cases and often reach only low-risk individuals.

The Wilson and Jungner Criteria 50, years later

All in all, the WJ principles remain relevant, particularly regarding disease characteristics, test performance, and the availability of treatment. Contemporary frameworks place increasing emphasis on program- and system-level

considerations, ethical and equity issues, and the need for robust evidence on effectiveness and harm-benefit balance [164, 167, 171, 172].

Measuring test performance

Sensitivity and specificity

Ideally, a screening test would perfectly distinguish between individuals with and without the condition (AAA screening comes close to this ideal, as will be discussed later). In practice, however, this level of accuracy is rarely achievable. As noted in the commentaries on the fifth principle of the WJ criteria, screening tests may be allowed a greater margin of error and lower validity than diagnostic tests in order to be feasible for testing whole populations.

The classical approach to screening emphasizes high **sensitivity**, the ability of a test to correctly identify individuals with the condition as positive. High sensitivity minimizes false negatives, ensuring that few affected individuals are missed in the initial screening.

This often comes at the expense of lower **specificity**, the ability of a test to correctly identify individuals without the condition as negative. Reduced specificity leads to more false positives, meaning some healthy individuals will receive an abnormal or positive test result, which must later be clarified by confirmatory diagnostic testing with higher specificity [171, 173-175].

Test result contingency table

	Condition present	**Condition absent**
Test positive	True positive (TP)	False positive (FP)
Test negative	False negative (FN)	True negative (TN)

A positive test result with disease present is a true positive (TP), while with disease absent it is a false positive (FP). Conversely, a negative test result with disease present is a false negative (FN), and with disease absent it is a true negative (TN).

For screening tests, the specific point or cut-off that distinguishes a positive from a negative result, such as a laboratory value, an imaging score, or, in the case of AAA, the diameter of the infrarenal aorta, is called the **threshold value**. This value determines which individuals are classified as likely having the disease and should proceed to confirmatory diagnostic testing or follow-up measurements. Setting the threshold value directly affects the sensitivity and specificity of the screening test: lowering the threshold increases sensitivity (identifying more true positives, but also more false positives), while raising it increases specificity (reducing false positives but potentially missing true cases) [173, 176, 177].

Sensitivity – the ability of a test to correctly identify individuals with the condition as positive.

$$Sensitivity = \frac{TP}{TP + FN}$$

Specificity – the ability of a test to correctly identify individuals without the condition as negative.

$$Specificity = \frac{TN}{TN + FP}$$

Threshold value – the specific point or cut-off on a continuous test measurement that determines whether the result is classified as positive or negative.

The threshold value in screening programs is determined by analysing the trade-off between sensitivity and specificity across different cutoffs, often using Receiver Operating Characteristic[12] curve analysis and modelling. The goal is to balance accurate case detection with minimizing false positives and managing resource use. Thresholds are validated through population studies assessing real-world outcomes and may be tailored by demographic factors to improve efficiency [178-183].

Positive and negative predictive value

Even with a test of high sensitivity and specificity, when applied to a population with low disease prevalence, that is, a large proportion without the condition, the absolute number of false positives can exceed the number of true positives [184] (see Figure 1 as example). This underscores the importance of considering disease prevalence when interpreting two additional measures: **positive predictive value (PPV)** – the likelihood of having the condition given an abnormal result – and **negative predictive value (NPV)** – the likelihood of not having the condition given a normal result.

[12] **Receiver Operating Characteristic (ROC)** is a graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied. It displays the trade-off between sensitivity (true positive rate) and 1-specificity (false positive rate). The area under the ROC curve provides a single measure of overall test accuracy, with values closer to 1 indicating better performance. The name ROC comes from its original use in radar signal detection during World War II, where it helped operators (receivers) decide whether a signal was present or not. The term "operating characteristic" refers to the performance of the receiver system in distinguishing signals from noise.

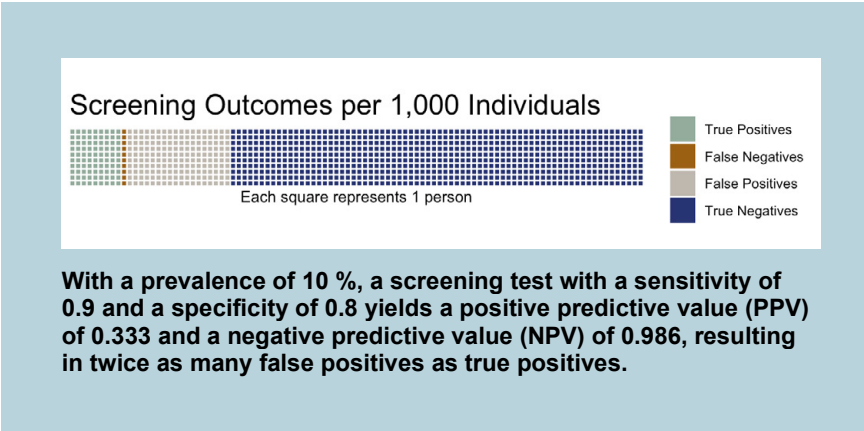

Figure 1.
Green (True Positives): 90 people with the condition correctly identified. **Brown (False Negatives):** 10 people with the condition missed by the test. **Grey (False Positives):** 180 healthy people incorrectly flagged. **Blue (True Negatives):** 720 healthy people correctly identified.

Using the same type of screening test in different populations yields different results depending on disease prevalence. In low-prevalence groups, false positives are more common than true positives because there are many more healthy individuals who can receive a false positive result, even though test specificity is high.

Positive Predictive Value (PPV) – the probability of having the condition given a positive test result.

$$PPV = \frac{TP}{TP + FP}$$

Negative Predictive Value (NPV) – the probability of not having the condition given a negative test result.

$$NPV = \frac{TN}{TN + FN}$$

This has been consistently observed in multiple large studies and systematic reviews, where even with improved imaging modalities the PPV remains modest and the absolute number of false positives may exceed true positives, as exemplified by population-based breast cancer screening [185-187].

Sensitivity and **specificity** measure a test's accuracy independent of disease prevalence, whereas **positive** and **negative predictive values** describe how likely test results are to be correct in practice, which depends directly on prevalence.

Evaluating screening effectiveness: NNS, NNI, a population-level benefit

Number needed to screen (NNS) refers to the number of individuals who must undergo a screening procedure to prevent one adverse health outcome—most commonly disease-specific mortality. NNS depends on the absolute risk reduction (ARR) provided by the screening programme, defined as the difference in event rates between those who are screened and those who are not [188, 189].

NNS was introduced and defined in the late 1990's [188, 190] to provide a methodology for comparing different screening strategies. The interpretation of NNS is inherently context-sensitive, as it depends on the prevalence of undiagnosed disease in the target population, the design and performance of the screening programme (including test sensitivity, specificity, frequency, and follow-up), as well as compliance rates and post-screening treatment uptake[13] [191, 192]. Despite being a key indicator of programme effectiveness, NNS must be interpreted in conjunction with compliance or adherence to the screening program, disease severity, and its potential clinical and social impact on individuals [188].

For example, in Sweden, screening 100,000 newborns for PKU prevents approximately 7–11 cases of severe PKU-related intellectual disability, corresponding to a NNS of about 9,000–14,000 per case prevented, considered favourable for a rare but serious condition [193-195].

[13] **Post-screening treatment uptake** refers to the proportion of individuals with a positive screening result who proceed to complete the recommended diagnostic evaluation and, if indicated, initiate and adhere to appropriate treatment.

Number needed to screen (NNS) is calculated as the inverted **absolute risk reduction** (ARR)

$$\text{NNS} = \frac{1}{ARR}$$

where ARR is calculated as the event rate (adverse outcome) in the control group minus the event rate in the screened group. A positive ARR indicates fewer adverse outcomes with screening.

$$ARR = Event\ rate_{control} - Event\ rate_{screened}$$

In contrast, cancer screening programs such as mammography for breast cancer or fecal occult blood testing for colorectal cancer in average-risk populations have much lower NNS values. For instance, the NNS to prevent one breast cancer death with mammography in women aged 50–59 is 700 to 2000 [196, 197], and for colorectal cancer with fecal occult blood testing, the NNS is about 250 to 1,250 over five years [188, 196, 197]. For AAA screening the figures are somewhere between 300–700 [198, 199].

Example: NNS in AAA screening (MASS trial; 10-year follow-up, 2009)

If the rupture rate in the non-screened cohort is **0.87%** and **0.46%** in the screened cohort, the **absolute risk reduction (*ARR*)** is:

$$ARR = 0.87\% - 0.46\% = 0.41\% = 0.0041$$

This yields:

$$NNS = \frac{1}{ARR} = 1/0.0041 \approx 244$$

Number Needed to Screen (***NNS***) is thus **244 individuals** who must undergo screening to prevent **one adverse health outcome**, in this case, **one AAA-related death** (MASS trial; 10-year follow-up, 2009).

To account for compliance, the figure *number needed to invite* (NNI) can be used instead of the NNS. The NNI reflects the fact that not everyone invited will attend or participate in screening [196, 200].

Perhaps the NNS, in conjunction with the attendance rate, best reflects the efficacy of a screening program, as it allows one to easily identify where the potential for improvement lies [189, 197].

To assess the population health impact of screening programs, the concept of *gain* is used. Gain represents the absolute benefit, such as increased life expectancy or

reduced mortality due to screening, often measured in quality-adjusted life years[14] (QALYs). It provides a direct measure for comparative effectiveness and health economic evaluations. Maximizing gain involves minimizing NNI and NNS to achieve meaningful benefits. Additionally, considering the costs of delayed diagnoses is important for a comprehensive evaluation. This is especially true in AAA screening, where emergency surgery follows a life-threatening complication that not only poses serious risks to the individual but also is costly [201-203].

Harms of Screening

> "All screening programs do harm; some do good as well, and, of these, some do more good than harm at reasonable cost" (Gray, Patnick, & Blanks, 2008).

This opening statement of an article by Gray, Patnick, and Blanks, responds to a 2008 pledge by British politicians to expand NHS screening services in the UK.

This perspective is reinforced by several systematic reviews of screening interventions, which consistently demonstrate that all screening programs expose individuals to potential harms. These harms include *overdiagnosis*, *overtreatment*, *false positives* and *negatives*, and *procedure-related complications*, often resulting from further diagnostic investigations triggered by initial screening findings [155, 204-208].

There are examples of screening programs that have been discontinued due to a lack of benefit or evidence of net harm. For instance, melanoma and type 2 diabetes screening in asymptomatic adults have been halted after trials demonstrated no mortality benefit and raised concerns about overdiagnosis, unnecessary treatment, and psychological harm [209-211].

Major health authorities, including the The Swedish Board of Health and Welfare, the United States Preventive Services Task Force and the WHO, explicitly acknowledge these harms in their guidance, emphasizing that such risks are inherent to all screening strategies and that the overall benefit varies by condition, population, and screening modality [154, 155, 212].

Overdiagnosis

In a general screening context, overdiagnosis is defined as the detection of a finding that, if left undetected, would not cause symptoms or harm to a patient during their

[14] **Quality-adjusted life years (QALYs)** measures benefits of medical interventions by combining both the **quantity** and **quality** of life. One QALY equals one year of life in perfect health; years lived in less-than-perfect health are weighted accordingly.

Weinstein, M. C., Torrance, G., & McGuire, A. (2009). QALYs: The basics. *Value in Health*, *12*(Suppl 1), S5–S9. https://doi.org/10.1111/j.1524-4733.2009.00515.x

lifetime [213]. This means that the detected finding would either remain asymptomatic and non-progressive, the patient would die of other causes before the disease became clinically relevant. Overdiagnosis is distinct from false positives, misclassification, or overtreatment, though it can lead to unnecessary interventions, psychological distress, and financial burden. It is recognized as a harm of screening for both cancer and noncancer conditions, and is driven by factors such as expanded disease definitions, increased use of sensitive diagnostic technologies, and screening in low-risk populations [214].

Overtreatment

Overtreatment is defined as the initiation of treatment for a disease detected through screening that would not have negatively affected the patient's health during their lifetime. It is often a consequence of overdiagnosis depending on the disease being screened for. Individuals who receive early treatment contribute to overtreatment rates, which likely mirror those of overdiagnosis, although reliable estimates are difficult to obtain [215].

False positive

A false positive screening test is defined as a test result that incorrectly suggests disease, leading to unnecessary follow-up procedures such as imaging or biopsy, without resulting in a diagnosis [173]. This can cause both somatic and psychological harm, with no benefit to the person screened—most often mild, but occasionally severe [156, 216].

False negative

False negative results may provide participants with a false sense of health, potentially leading to delayed diagnosis and risking a loss of public trust and confidence in the screening program, consequences that can be as significant as the direct clinical harms, however, the direct psychological impact on individual participants is less well documented [217, 218].

Cost-effectiveness

Cost-effectiveness analyses and QALY modelling, further support that only a subset of screening programs deliver more benefit than harm at a reasonable cost, and that this balance is highly sensitive to disease prevalence, test performance, and the burden of harms [211, 219]. Screening programmes usually require considerable investment in equipment, personnel and information technology resulting in reallocation of resources to the screening programme and away from symptomatic care, delaying care for people with symptoms and potentially leading to greater as populations with less access to care or lower health literacy may be less likely to

benefit from screening while still experiencing the *opportunity costs*[15] of diverted resources [220-222].

Understanding harms of screening

Since benefits are intended and harms are unintended, professionals developing and delivering screening programs, as well as the public undergoing screening, may have less awareness or understanding of the potential harms involved [154, 223, 224].

The characteristics of screening programmes, when acting together, tend to lead to harms being more significant than often appreciated.

- Most screened individuals do not have the condition, meaning that more people may be exposed to the potential harms of screening than those who can benefit from it [155, 225].
- All screening tests yield false positives and false negatives, as no test is 100% sensitive or specific and even with high sensitivity and specificity, low disease prevalence reduces the PPV, increasing the likelihood that false positives will outnumber true positives.
- Early detection carries the risk of overdiagnosis, identifying conditions that would never have caused harm during the individual's lifetime.
- Receiving a diagnosis, especially if unnecessary or uncertain, can cause psychological distress, anxiety, and a diminished sense of well-being, even in the absence of symptoms or disease progression.

This imbalance is recognized as a barrier to informed decision-making and is a key reason why shared decision-making and improved communication about both benefits and harms are emphasized in contemporary recommendations [222].

[15] **Opportunity costs** are the benefits lost when resources are used for one purpose instead of the next best alternative. In healthcare, investing in screening means fewer resources for other needs, such as treating symptomatic patients.

Screening for AAA

Screening for AAA serves two main purposes: identifying individuals at risk of aneurysm progression and those at risk of rupture, as elective surgery differs fundamentally from rupture and possible emergency repair.

Randomised controlled trials have shown that one-time ultrasound screening for AAA in men reduces AAA-related mortality and emergency surgery, and may even lower all-cause mortality, while being highly cost-effective. However, limited observational data from contemporary settings suggest smaller benefits, likely due to lower AAA prevalence and increased background detection compared to the era in which the RCTs were conducted.

Current evidence does not indicate significant or lasting negative effects on health-related quality of life from AAA surveillance. While screening continues to be supported for select populations, evolving risk profiles and healthcare contexts may warrant reconsideration of current strategies, with potential value in exploring more targeted, risk-based approaches.

The four major RCTs for AAA screening

Overview

Four major RCTs: Viborg (Denmark) [226], Chichester (UK, which also included women) [227], Western Australia [228], and MASS (UK) [229], form the foundation of current evidence for AAA screening in men.

These studies were driven by the high mortality of rAAA (70–95 %), including among those undergoing emergency surgery (30–70 %); the feasibility of non-invasive detection using ultrasound, validated for IAD measurement [230, 231]; and the potential for elective repair to prevent rupture, with significantly lower mortality (4–8 %) at the time for the RCTs and even lower in contemporary studies (1–2 %) [140, 226-229, 232].

The rationale to focus on screening for AAA in men was based on the substantially higher prevalence and mortality from AAA in men compared to women, as well as the greater potential for mortality reduction and cost-effectiveness in this population [114, 226-229, 232].

Study populations

Conducted between 1988 and 1999, these trials collectively included over 130,000 participants, primarily men aged 64 to 83, with MASS being the largest, enrolling over 67,000 men. The prevalence of AAA (IAD ≥ 30 mm) ranged from 4.0 % to 7.6 % in men with much lower prevalence in women (1.3 %). AAA growth rates were estimated to range between 2 and 4 mm per year, with larger aneurysms tending to grow faster and risk of rupture was estimated to equal the risk of elective surgery at diameters of 50 to 60 mm [226-229, 233, 234].

Aims

The common aim of these trials was to determine whether a one-time invitation to ultrasound screening in asymptomatic adults, primarily men aged 65 years or older, would reduce AAA-specific mortality, rupture rates, and emergency surgeries compared to usual care, and to assess the overall impact on all-cause mortality and rates of surgical intervention. A key component was identifying individuals with an IAD ≥ 30 mm who were considered likely to benefit from further follow-up examinations to monitor AAA growth [57, 228, 232, 235].

Wilson & Jungner

These four major RCTs of AAA screening in men largely fulfilled the ten Wilson and Jungner screening criteria, particularly regarding disease importance, test performance, treatment efficacy, and mortality benefit. However, they were less comprehensive in addressing long-term harms, quality of life, and system-level implementation.

AAA screening according to Wilson and Jungner criteria

1. **The condition should be an important health problem:** rAAA carries a very high mortality of 70–95 %, even with emergency surgery (30–70 %).
2. **There should be an accepted treatment for patients with recognized disease:** Elective repair has a mortality of 0.5–2 %.
3. **Facilities for diagnosis and treatment should be available:** Organising ultrasound screening within standard care is feasible.
4. **There should be a recognizable latent or early symptomatic stage:** AAA is asymptomatic until rupture
5. **There should be a suitable test or examination:** US is non-invasive, rapid, and validated for detecting AAA although the definition of IAD ≥ 30 mm is discussed.
6. **The test should be acceptable to the population:** US is painless, radiation-free and widely accepted.
7. **The natural history of the condition should be adequately understood:** Well documented AAA growth rates of 2–4 mm / year, accelerating with size and rupture risks that parallels diameter.
8. **There should be an agreed policy on whom to treat as patients:** IAD ≥ 30 mm: enter surveillance; IAD ≥ 55 mm: offer elective repair.
9. **The cost of case-finding should be economically balanced:** Robust cost-effectiveness demonstrated
10. **Case-finding should be a continuing process, not "once-and-for-all":** The trials tested a one-off invitation

Mortality and Clinical Outcomes

A pooled meta-analysis of the four trials demonstrated a 35% reduction in AAA-specific mortality (Peto Odds Ratio[16] [OR] 0.65, 95 % CI: 0.57 – 0.74), as well as a 40 % reduction in emergency surgery (Peto OR 0.57, 95 % CI: 0.48 – 0.68). Screening was associated with higher rates of elective surgery and an overall increase in AAA operations, reflecting a shift from emergency to planned repair [232]. The MASS trial reported a significant reduction in AAA-related mortality and was the only study to show a statistically significant decrease in all-cause mortality (Hazards Ratio 0.97, 95 % CI: 0.95 – 0.99), in contrast to the other three trials [232].

There is no consistent evidence from observational studies or registry data to support the same magnitude of benefit from AAA screening as demonstrated in these RCTs, particularly regarding reductions in deaths from rAAA and emergency surgery in men aged 65 and over [57, 199]. This is likely explained by the declining prevalence of AAA and the impact of incidental detection in observational settings.

Diagnosing AAA in screening

A positive screening test is defined as an IAD ≥ 30 mm, which is considered to warrant further follow-up examinations to monitor AAA growth [57, 228, 232, 235].

Ultrasound is the preferred method for diagnosing AAA in population-based screening programmes [2, 57]. It offers high sensitivity (94–100 %) and specificity (98–100 %) for AAA detection, is non-invasive, free from radiation exposure, and is both cost-effective and widely accessible, making it the standard for screening and surveillance [7, 57, 236]. The inherent measurement tolerance of ultrasound (± 2–3 mm) has been validated and is considered clinically acceptable, as it does not compromise the ability to detect significant AAAs or monitor growth. Repeatability, referring to the consistency of repeated measurements of the same aortic diameter, is considered acceptable if 95 % of measurements differ by no more than 5 mm [2, 237].

Calliper positioning, the placement of points on an ultrasound image to define the diameter being measured, varies across screening programmes: outer-to-outer (OTO), leading-edge-to-leading-edge (LELE), or inner-to-inner (ITI), since there is a lack of consensus on the preferred method (Figure 2) [199, 237-240]. The different

[16] **Peto odds ratio** is a method used in meta-analyses to estimate pooled Odds Ratio, best suited for rare events and small treatment effects. It may be biased with large effects or imbalanced groups.

Yusuf, S., Peto, R., Lewis, J., Collins, R., & Sleight, P. (1985). *Prog Cardiovasc Dis*, 27(5), 335–371. https://doi.org/10.1016/0033-0620(85)90038-7

methods are broadly equivalent in terms of intra-observer variability, though interobserver variability has been shown to be lower with anteroposterior OTO calliper placement [241] However, the clinical implication of this is likely minimal [242]. More important is the significant difference in crude diameter obtained [238, 239, 243] which highlights the need for consistent use of a single method within each clinical programme and recognition of its impact on epidemiology and clinical decision-making. Inadequate attention to reporting standards, such as specifying the imaging plane and calliper positioning, is a key contributor to poor inter- and intra-observer reproducibility [237]. As an example, in Great Britain the ITI method is recommended, whereas in Sweden the LELE method is widely applied, although it is not explicitly specified in the national recommendations [199, 212, 244].

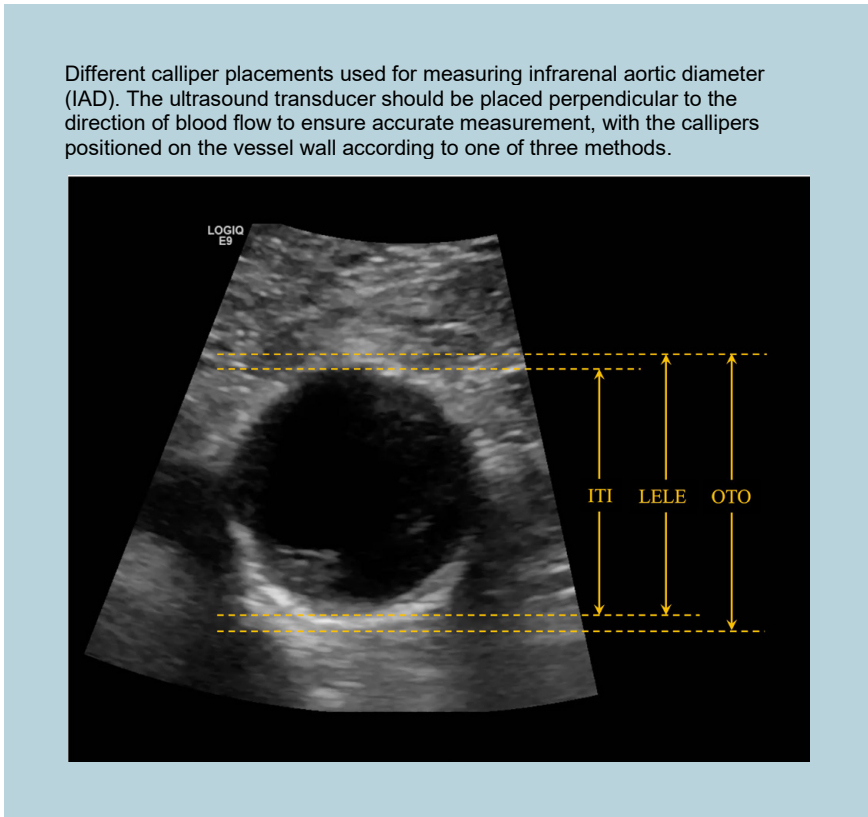

Figure 1.
Ultrasound image of infrarenal aorta in the transverse plane. Calliper placement for measurement of aortic diameter. ITI = inner to inner; LELE = leading edge to leading edge; OTO = outer to outer. Photo: Andrea Mosonyi.

Computed tomography (CT), while providing greater anatomical detail, is not recommended for routine screening due to its higher cost and radiation exposure. However, CT plays a critical role in preoperative planning and in selected cases for screening or ongoing surveillance when US results are inconclusive due to obesity, excessive bowel gas, or complex vascular anatomy [2, 57, 151].

Screening test performance

One-time screening with US is highly effective in identifying individuals with AAA progression, given its high sensitivity (87–100 %) and specificity (98–100 %) for detecting AAAs (IAD ≥ 30 mm) [232, 245]. The risk of further enlargement increases with aneurysm size [115], particularly as the diameter approaches ≥ 55–60 mm, which is the typical threshold for surgical consideration. Hence, the predictive value depends more on AAA diameter than on a positive screening test alone.

There are no published figures for the positive predictive value (PPV) or negative predictive value (NPV) of AAA screening in predicting which patients will ultimately require intervention, such as surgery [57, 91, 236]. Continued follow-up is therefore essential, and regular imaging is recommended in guidelines on the management of aortic aneurysmal disease [2, 8, 57].

Numbers needed to screen

The reported number needed to screen (NNS) pooled from the four large RCTs was 246 men (95 % CI, 207–311) to prevent one AAA rupture, with AAA prevalence in the screened populations ranging from 4.0 % to 7.6 % [57, 232]. An observational study, with an AAA prevalence of 1.5 %, estimated that screening 667 men and treating 1.5 men at IAD ≥ 55 mm would prevent one premature AAA-related death [199, 246].

However, the trials did not aim to, nor did they report, the sensitivity, specificity, positive predictive value (PPV), or negative predictive value (NPV) of screening for predicting which individuals would progress to the surgical threshold (≥ 55 mm) or require intervention. Most screen-detected AAAs were small, and only a minority progressed to the size requiring surgery during follow-up. Thus, the predictive value of a single screening for future intervention was neither a focus nor a reported outcome of these trials; instead, the emphasis was on the need for follow-up examinations triggered by an IAD ≥ 30 mm [143].

Cost-Effectiveness

MASS and Viborg both demonstrated that AAA screening is cost-effective in populations with a prevalence of 1 % or higher, with incremental cost-effectiveness ratios (ICER)[17] below accepted thresholds [247, 248]. Cost-effectiveness analyses, including meta-analyses and systematic reviews, have incorporated these pooled clinical outcomes and found that AAA screening in this population is cost-effective, with ICER below commonly accepted thresholds (approximately € 10,000 per QALY, range € 180–€ 50,000) [57, 198, 203, 249].

Model-based cost-utility analyses and economic modelling using registry and programme data confirm that screening remains highly cost-effective, even when accounting for lower contemporary AAA prevalence and increased costs [250-252].

The major RCTs that established the benefit and cost-effectiveness of screening enrolled populations with AAA prevalence in the range of 4.0 % to 7.6 %, but modelling studies have demonstrated that the cost-effectiveness threshold is maintained down to a prevalence of approximately 0.5 % to 1.0 % [57, 249, 253] and that screening is not cost-effective in populations with a prevalence substantially below 0.5 % [57].

Benefit-to-harm balance from AAA screening

Screening for AAA significantly increases elective surgery rates, with up to 60 % more procedures in screened populations, along with fewer emergency repairs, although without a corresponding reduction in all-cause mortality [199, 232, 235, 254-257]. Men invited to screening are about twice as likely to undergo repair, primarily due to detection of small, asymptomatic aneurysms unlikely to rupture (i.e., overdiagnosis). However, surgery for screen-detected AAAs did not increase mortality compared to controls [235, 258].

Registry data show that women experience higher postoperative complications and mortality, further reducing the potential benefit of screening in this group [232, 235].

Overdiagnosis in AAA screening

In the context of AAA screening, overdiagnosis has been referred to as the detection of aneurysms that would not have caused symptoms or led to death during the patients lifetime if left undetected and untreated [57, 212, 232, 235]. Although AAA diagnosis is also linked to increased cardiovascular risk and may prompt preventive

[17] **Incremental cost-effectiveness ratio (ICER):** a measure of the additional cost required to gain one additional unit of health benefit (e.g. a quality-adjusted life year, QALY) when comparing a new intervention with the standard of care.

measures, this vascular risk is distinguished from the clinical relevance of the aneurysm itself [232].

Evidence from the MASS trial using 13-year follow-up data showed that one-time AAA screening with ultrasound scan was potentially associated with an overdiagnosis of 45 % (95% CI, 42 % – 47 %) among screen-detected men [235]. However, individuals who underwent surgery for screen-detected AAA as a result of overdiagnosis did not experience an increase in mortality compared to the control group [235, 258].

Modelling studies and systematic reviews highlight that overdiagnosis results in increased detection of small, asymptomatic AAAs, many of which are unlikely to progress to rupture or require intervention. This leads to additional surveillance and elective surgeries with potential surgical harms, without a corresponding mortality benefit for these individuals [2, 57, 232].

Overtreatment in AAA screening

In the context of AAA screening, this specifically refers to performing elective AAA repair in patients for whom the risks of intervention outweigh the potential benefits, such as those with a life expectancy of less than two to three years. These patients are unlikely to live long enough to benefit from rupture prevention and are at higher risk of harm from perioperative complications, with reduced quality of life or even death as a possible consequence [140, 259].

Overtreatment also includes interventions for small, asymptomatic AAAs that do not meet established size or growth criteria for repair. Randomised trials and systematic reviews have shown no survival advantage for early elective repair of small AAAs (40–55 mm) compared to surveillance [260, 261].

Psychological harm

Some individuals under surveillance for AAA have been found to experience moderate psychological harm from being labelled with an AAA diagnosis, however, most patients describe reassurance from regular follow-up and value information and professional support to address uncertainties, rather than requiring formal psychological interventions [262, 263]. The current evidence does not support a significant or lasting negative impact on health-related quality of life from being under surveillance for AAA, but highlights the importance of adequate patient information and support to minimize unnecessary worry [263, 264].

Quality-of-life studies from MASS and Viborg found no adverse effects outweighing the benefits of screening [233], and no sustained differences in anxiety or depression have been observed [48, 203, 234–236].

Resources

Resource demands from screening may divert attention from symptomatic care and other patient groups [239]. Additionally, the increased resource utilisation required for screening and follow-up may divert healthcare resources from symptomatic care, potentially affecting the quality or availability of care for other patient groups [256].

The debate around harms from AAA screening centres on whether the small and diminishing mortality benefit justifies the increased harms and resource use, with growing calls for more targeted, risk-based screening approaches or a reconsideration of population-based programmes in low-prevalence settings [232].

Observational studies on AAA screening

Observational studies report substantially smaller benefits from AAA screening than earlier randomised trials, likely due to lower contemporary AAA prevalence, improved cardiovascular health, and increased background detection. These findings stem mainly from two Swedish cohort studies—currently the only large-scale observational evaluations of AAA screening's impact on mortality [199, 256]. Systematic reviews and guidelines (e.g., United States Preventive Services Task Force [232], ESVS [2]) cite these as the primary observational evidence, while other data derive from the RCTs or modelling [232, 258]. Further observational research is needed to assess how changing trends in prevalence, risk factors, diagnostics, and treatment influence the current balance of benefits and harms [57].

Aims

Aims

The primary aim was to explore whether the absolute infrarenal aortic diameter (IAD) or its value relative to body surface area (BSA) is the most relevant predictor for developing an abdominal aortic aneurysm (AAA) requiring treatment.

A secondary aim was to investigate the possibility of simplifying AAA screening by using more affordable, mobile equipment while maintaining diagnostic accuracy.

Overall aim

To explore whether the absolute infrarenal aortic diameter (IAD) or its value relative to body surface area (BSA) is the most relevant predictor for developing an abdominal aortic aneurysm (AAA) requiring treatment.

A secondary aim was to investigate the possibility of simplifying AAA screening by using more affordable, mobile equipment while maintaining diagnostic accuracy.

Specific aims of each study

I. To determine whether BSA is correlated with IAD in men.

II. To determine whether BSA is correlated to AAA growth in men.

III. To assess whether a BSA-related AAA criterion could identify men with an IAD of 25–29 mm at screening who are at increased risk of developing a clinically relevant AAA.

IV. To explore the feasibility of using a handheld, tablet-operated ultrasound device in AAA screening to simplify and develop the screening process for men.

Ethical approval and considerations

Ethical approval

Studies I and II

These studies were approved by the Ethics Committee of Lund University (LU 2010/239), Sweden.

Studies III and IV

These studies were approved by the Ethics Committee of Lund University (LU 2010/239) and the Swedish Ethical Review Authority (Dnr 2019-05788 and 2023-02037-02), Etikprövningsmyndigheten, Box 2110, 750 02 Uppsala, Sweden.

Written informed consent was obtained from all participants.

Ethical considerations

Within the AAA screening programme in Malmö, routine diagnostics include continued surveillance for men with an IAD ≥ 30 mm, while those below this threshold are discharged and considered healthy. For studies III and IV, men with an IAD of 25–29 mm were invited for an additional follow-up examination, which had a potential to cause increased anxiety. This concern was acknowledged and addressed in the invitation letter. However, the invitations were sent to individuals who had already consented to participate in the overarching epidemiological study [265] conducted in parallel with the screening programme and were therefore considered to have an understanding of, and hopefully a willingness to engage in, research.

Participants found to have an IAD ≥ 30 mm within the study were informed by the examiners and promptly scheduled for an appointment at the vascular clinic, where they received further information, appropriate medical treatment, and, when applicable, were evaluated for surgical intervention if an AAA ≥ 55 mm was detected. One participant had prophylactic surgery to an iliac artery aneurysm of 80 mm within a week after the examination.

Methods

The study population was drawn from the Malmö AAA screening program, initiated in 2010, together with its accompanying epidemiological project on AAA and atherosclerosis, which provided additional data on anthropometry, comorbidities, and medication. It comprises four individual studies (I–IV) using data collected through 2017, with additional follow-up ultrasonography in 2022 supplementing Studies III and IV.

Maximal infrarenal aortic diameters were measured using standardised ultrasound protocols. **Study I** developed a BSA-adjusted AAA definition using regression modelling; **Study II** analysed growth using mixed-effects models; **Study III** combined prospective follow-up with survival analysis to assess clinical progression; and **Study IV** evaluated handheld ultrasound (POCUS) performance using Bland–Altman plots and diagnostic accuracy metrics. Additional data on interventions and outcomes were obtained from medical records and the Swedish National Registry for Vascular Surgery, Swedvasc. Statistical analyses included correlation, multivariable regression, mixed-effects modelling, Kaplan–Meier and Cox models, with model assumptions thoroughly tested. All examinations followed established protocols for AAA screening with follow-up examinations performed or supervised by the author.

Sources of data

Overview

All studies in this thesis were based on data from the Malmö AAA screening programme (initiated in 2010) and an accompanying epidemiological project [265]. Study I used data through 2015; Studies II–IV through 2017, with supplementary ultrasound examinations in 2022.

To identify any AAA-related interventions or ruptures among non-attendees in Study III, data from the Swedish National Registry for Vascular Surgery (Swedvasc) [266] and local medical records were reviewed.

Setting for the studies

All four studies (I–IV) were based on data from the AAA screening programme conducted at the Department of Vascular Diseases, Skåne University Hospital in Malmö, a tertiary vascular surgical centre with a primary catchment area of approximately 650,000 individuals, covering Malmö and fifteen surrounding municipalities, encompassing both urban and rural populations.

The hospital maintains a single AAA screening facility, and since 2010, all 65-year-old men residing within this catchment area have been invited to screening, identified through the Swedish National Population Register [267].

Invitations to the screening are sent by mail with pre-booked appointments, and rescheduling is allowed. If a participant does not not attend, a follow-up invitation is issued. The cost of the screening was 13 €, and travel expenses were not reimbursed at the time for the studies.

All screened men were also invited to a an accompanying epidemiological project on AAA and atherosclerosis [265] and asked to complete a written health questionnaire capturing information on height, weight, smoking habits, medication, heredity, and comorbidities.

Those diagnosed with an AAA (IAD $\geq$ 30 mm) were offered surveillance per existing guidelines.

Study populations

Individuals who underwent screening between 2010 and 2015 and consented to participate in the aforementioned research project were eligible for study I; those screened and enrolled through 2017 were eligible for studies II to IV.

In Studies I and II, data originated solely from the screening programme and the accompanying epidemiological project. Additional clinical information was retrieved from their medical records at baseline.

In study II, data was retrieved from surveillance examinations together with baseline data from ínitital screening and the epidemiological project. Ten participants had been included in a RCT assessing the effects of ticagrelor on aneurysmal growth, but were retained in the present analysis since no treatment effect was observed [268]. Likewise, 98 participants had previously contributed to a retrospective case-control study on metformin and AAA growth [269].

Studies III and IV focused on men with an infrarenal aortic diameter (IAD) of 25–29 mm identified from the screening programme as having previously consented to the overarching epidemiological project [265]. These individuals were invited back for re-examination in 2022, to measure growth in association to height and weight, considering smoking and diabetes, known to have impact on AAA growth (study

III). Invitations with pre-booked appointments were sent by post, with the option to reschedule, and missed appointments triggered follow-up invitations. Addresses were retrieved via the electronic patient administrative system linked to the national population register[267].

For Study III, participants were categorised by smoking status, diabetes, and the presence or absence of a body surface area-related AAA (BSA-related AAA). Additional health data were collected for descriptive purposes. For comparative analysis, data were also included from men with small AAAs (30–35 mm) already under surveillance, provided relevant baseline variables were available.

For Study IV, the examinations were conducted concurrently with those for Study III. Participants were selected based on the rationale that their IADs would likely have approached or exceeded 30 mm—the diagnostic threshold for AAA—during the follow-up period, making them suitable for analysing the diagnostic performance of POCUS compared to standard ultrasound in detecting AAA (IAD $\geq$ 30 mm).

In Study I, smoking status was categorised as current smoker, ex-smoker, or never-smoker. In Studies II–IV, smoking status was dichotomised into two categories: current smoker and non-smoker (ex- and never-smokers combined).

Analysis of non-respondents

A search of the Swedish National Registry for Vascular Surgery (Swedvasc) [266], and local medical records was conducted to document all interventions, ruptures, or deaths related to AAA among non-attendees.

Ultrasound examinations

Validation

To validate the US measurements from the screening program (Study I), 1,631 randomly selected attendees from the 2015 screening cohort were cross-checked for abdominal CT or MRI within ± 1 year of their screening, yielding 237 subjects. Measurements were conducted from the anterior outer wall to posterior inner wall, in the transverse plane, to resemble the ultrasonographic measurements, LELE. The maximal infrarenal anterio-posterior aortic diameter was measured by a radiologist (Laura H Aaltonen) and a vascular surgeon (JS) in collaboration and consensus. The measurements from the screening examinations were blinded to the examinators and compared to the CT- or MRI-scans using a Bland-Altman analysis.

Examination procedures

For study III and IV, examinations were conducted using the same methodology as in the screening and surveillance programme. Participants were instructed to fast for four hours prior to the examination to improve ultrasound visibility of the aorta. Specifically, the superior mesenteric artery and iliac bifurcation were identified, and the widest IAD was measured orthogonally in the transverse plane using 2D imaging and the LELE technique. Colour flow Doppler was used solely to confirm orientation. Examinations were considered conclusive if both anatomical landmarks were visualised and the IAD could be measured with confidence. If these criteria were not met, the case would have been reported in the manuscript and the patient excluded, though still documented as such.

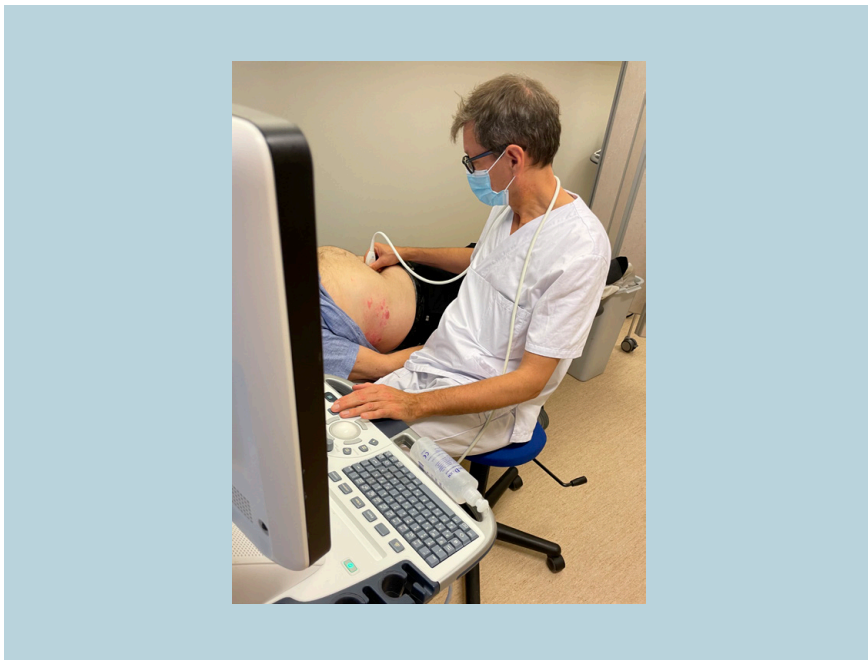

Figure 3.
Clinical ultrasound of the infrarenal aorta being performed by the author (JS) using standard, cart-based equipment. Note zoster blisters visible on the patient's right flank, and the face mask used in accordance with post–COVID-19 pandemic precautions. Photo: Jan Holst.

Three measurements of the widest IAD were first performed using the POCUS device, followed immediately by the same measurement protocol using the standard GE US equipment. Examination time for each device was limited to a maximum of three minutes.

Examinations for Study III were performed by the author and Silke Brunkwall, and for Study IV by the author alone, both in consultation with Andreas Mosonyi. An

assistant, Jan Holst, recorded the measurements while the examiners were blinded (see Figure 3).

Ultrasound equipment

For Study III, a cart-based LOGIQ™ E9 ultrasound system with a C-5 curved array probe (General Electric Healthcare Inc., UK) was used. This is the standard device employed at the centre for AAA screening and surveillance and is well-established.

The handheld POCUS device evaluated in Study IV was the Lumify™ C5-2 Android Curved Array Transducer (5–2 MHz, scan depth up to 30 cm; Koninklijke Philips N.V., Netherlands), paired with a Samsung Galaxy™ 8.7" tablet (Samsung Electronics Co., Ltd., South Korea). This device was selected due to its portability, affordability, and growing availability in point-of-care settings, making it a representative for future decentralised screening models.

For both devices, imaging protocols followed the standard abdominal vascular imaging settings recommended by their respective manufacturers.

Statistical methods

All measurements were recorded in millimetres, with one decimal place (I-IV).

Timescale for growth analysis was set to days divided by 365.25 to be presented as years (II-III).

Spearman's rank correlation coefficient[18] was used to analyse the correlation between IAD and BSA (I).

IAD values were transformed to approximate a normal distribution, while BSA was entered untransformed. These variables were then used in a quadratic, multivariable linear regression model to calculate the predicted IAD for a given BSA, including 95% prediction and confidence intervals. Predicted values were subsequently re-transformed to the original scale. To define the threshold for an aneurysmal aorta, the predicted IAD was multiplied by 1.5, in line with the original definition of a 150% enlargement (I).

[18]**Spearman's rank correlation coefficient** is a non-parametric measure of the strength and direction of the association between two ranked variables. It assesses how well the relationship between the variables can be described by a monotonic function, without assuming a linear relationship or normal distribution of the data. First introduced by Charles Spearman in 1904.

Spearman, C. (1904). *The proof and measurement of association between two things.* American Journal of Psychology, 15(1), 72–101. https://doi.org/10.2307/1412159

McNemar's test[19] was applied to measurements rounded to the nearest integer to assess differences in AAA classification outcomes between definitions (I).

A quadratic linear mixed-effects (LME) model[20] was fitted with random intercepts and slopes for each individual, using restricted maximum likelihood (REML). Fixed effects comprised observation year (linear and quadratic term), diabetes, smoking, baseline screening diameter (normalised), and BSA (normalised). Each covariate was modelled with an interaction with time, allowing estimation of their potential influence on aneurysm growth rates. Degrees of freedom and p-values for fixed effects were obtained using Satterthwaite's method[21].

Normality was assessed using Q-Q plots[22] (I–III).

Homogeneity of variances was assessed using residual plots[23] (II–III).

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[19] **McNemar's test** is a non-parametric method used on paired nominal data to determine whether there are differences in the proportions of two related groups. It is especially useful for detecting changes in classification outcomes.

McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*. 1947;12(2):153–157. doi:10.1007/BF02295996 ↩

[20] **Linear mixed-effects (LME) models** are statistical models that account for both fixed effects and random effects (e.g., individual variation), making them especially useful for repeated measures or hierarchical data structures.

Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015;67(1):1–48. doi:10.18637/jss.v067.i01

[21] **Satterthwaite's approximation** estimates denominator degrees of freedom in mixed-effects models, improving the accuracy of standard errors and p-values in the presence of random effects and finite sample sizes.

Satterthwaite, F.E. (1946). An approximate distribution of estimates of variance components. *Biometrics Bulletin*, 2(6), 110–114. https://doi.org/10.2307/3002019

Kuznetsova, A., Brockhoff, P.B., & Christensen, R.H.B. (2017). lmerTest package: Tests in linear mixed effects models. *Journal of Statistical Software*, 82(13), 1–26. https://doi.org/10.18637/jss.v082.i13

[22] A **Q-Q (quantile-quantile) plot** is a graphical tool used to assess if a dataset follows a specified theoretical distribution, typically the normal distribution. Data quantiles are plotted against the expected quantiles; if the points lie approximately along a straight line, the data are considered to follow that distribution.

Wilk MB, Gnanadesikan R. Probability plotting methods for the analysis of data. *Biometrika.* 1968;55(1):1–17. doi:10.2307/2334448

[23] **Residual plot** are a graphical method used to assess the assumption of homoscedasticity (constant variance) in regression analyses. If the residuals show a random scatter the assumption of homogeneity of variances is generally considered satisfied.

Kutner MH, Nachtsheim CJ, Neter J, Li W. *Applied Linear Statistical Models.* 5th ed. McGraw-Hill Education; 2005.

Kaplan–Meier cumulative incidence curves[24] were used to estimate time to reach an infrarenal aortic diameter (IAD) ≥ 40 mm after initial screening. Individuals not reaching this threshold were censored at the time of their last measurement (III).

Log-rank test[25] was used to analyse differences in time to reach an IAD ≥ 40 mm between BSA-related AAA and non–BSA-related AAA groups, stratified by smoking status (III).

A multivariable Cox proportional hazards model[26] was used to assess the hazard ratio (HR), adjusting for smoking and diabetes. The proportional hazards assumption was tested and not violated, as confirmed using the `cox.zph` function from the *survival* package in `R` (III).

Post hoc power calculation[27] was performed using the `pwrss.t.reg` function from the *pwrss* package in `R` (III).

A Bland-Altman plot[28] was generated to assess potential systematic differences between measurement methods (I, IV).

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[24] **Kaplan–Meier method** is a non-parametric statistic used to estimate the survival function from time-to-event data. It allows for the calculation of the probability of an event (e.g., reaching a diameter threshold) over time, even when some subjects have incomplete follow-up.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(282):457–481. doi:10.2307/2281868

[25] **Log-rank test** is a non-parametric statistical test employed in time-to-event analyses to assess whether there are significant differences between groups as timing to reach a clinical threshold.

Bland JM, Altman DG. The logrank test. *BMJ*. 2004;328(7447):1073. doi:10.1136/bmj.328.7447.1073

[26] **The Cox proportional hazards model** estimates covariate effects on event risk over time, assuming proportional hazards (i.e. constant hazard ratios over time); the hazard ratio expresses the relative event likelihood in one group versus another at any given time.

Breslow NE. Analysis of survival data under the proportional hazards model. *Int Stat Rev.* 1975;43(1):45–57; Therneau TM, Grambsch PM.; *Modeling Survival Data: Extending the Cox Model.* Springer; 2000.

[27] A **post hoc power calculation** estimates the statistical power of a study after the data have been collected and the main analyses completed. It is used to assess the likelihood that the study could detect an effect of a given size, based on the observed sample size and effect estimate.

Liu W, Tang Y. *pwrss:* Power and Sample Size Analysis for Regression Models. *R package version 1.2.1.* Available at: https://CRAN.R-project.org/package=pwrss

[28] The **Bland–Altman plot** is a graphical method for assessing agreement between two quantitative measurement techniques plotting differences between paired measurements against their mean, to visualise systematic bias or trends.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *The Lancet*. 1986;327(8476):307–310. doi:10.1016/S0140-6736(86)90837-8

Bias and limits of agreement were calculated using a linear mixed-effects model with individuals included as a random effect[29] (IV).

Sensitivity and specificity for AAA diagnostic accuracy were calculated using the largest IAD measurement per individual from each device, applying the `ConfusionMatrix` function from the *caret* package in `R` (IV).

Repeatability[30] (*R*), defined as the agreement of measurements within each device, was assessed using a linear mixed-effects model with all measurements nested within individuals as random effects. Confidence intervals for *R* were estimated using parametric bootstrapping via the `rpt` function from the *rptR* package (IV).

Agreement of measurements was also estimated using the mean within-subject standard deviation (*sw*) from all IAD measurements per individual, applying the formula $\pm 1.96 \times \sqrt{2} \times sw$. The value of *sw* was derived from the linear mixed-effects model used in the repeatability estimation above (IV).

The within-subject variance of IAD measurements was assessed for correlation with BMI using separate linear models for each device (IV).

All variables and endpoints were selected in advance based on clinical considerations (I-IV).

[29] This approach extends the traditional Bland–Altman method to account for repeated measurements within subjects by using a linear mixed-effects model, thereby separating within- and between-subject variability, see Parker RA's implementation and discussion: https://github.com/ra-parker/mixed-effects-BlandAltman.

[30] **Repeatability (*R*)** refers to the degree of agreement between repeated measurements taken under identical conditions, commonly used to assess the reliability of imaging and clinical measurements. It can be quantified using an intraclass correlation coefficient (ICC) derived from variance components, where values closer to 1 indicate higher measurement consistency.

McGraw, K. O., & Wong, S. P. (1996). Forming inferences about some intraclass correlation coefficients. *Psychological Methods*, *1*(1), 30–46. https://doi.org/10.1037/1082-989X.1.1.30

Results

Study I found that applying a BSA-adjusted threshold (IAD ≥ 150% of predicted) increased AAA detection rate from 1.5 % to 1.9 %, identifying additional cases compared to the standard ≥ 30 mm criterion. **Study II** showed that while smoking accelerated AAA growth and diabetes slowed it, BSA had no significant effect. **Study III** followed men with subaneurysmal aortas (25–29 mm); BSA-related AAA and smoking predicted higher progression rates, though median time to reach AAA of clinically relevant size remained over a decade with no large differences between groups. **Study IV** demonstrated that handheld POCUS had high diagnostic accuracy (96%) compared to standard ultrasound, with slight underestimation and slightly wider variability. Repeatability was significantly lower than standard US although clinically acceptable. Together, these studies highlight the diagnostic potential of BSA-adjusted thresholds and the feasibility of handheld devices, while growth risk remains primarily driven by smoking.

Overall design and results

The four studies in this thesis are based on, and a part of, a broad epidemiological project initiated alongside the Malmö AAA screening programme, in which participants were invited to contribute data on AAA, atherosclerosis, and medical prevention. The overall design, study populations, and main findings of the four component studies are summarised below. Figure 4 provides a schematic illustration of participant flow, while Table 1 presents a consolidated overview of populations, baseline characteristics, research questions, analytical approaches, and principal results.

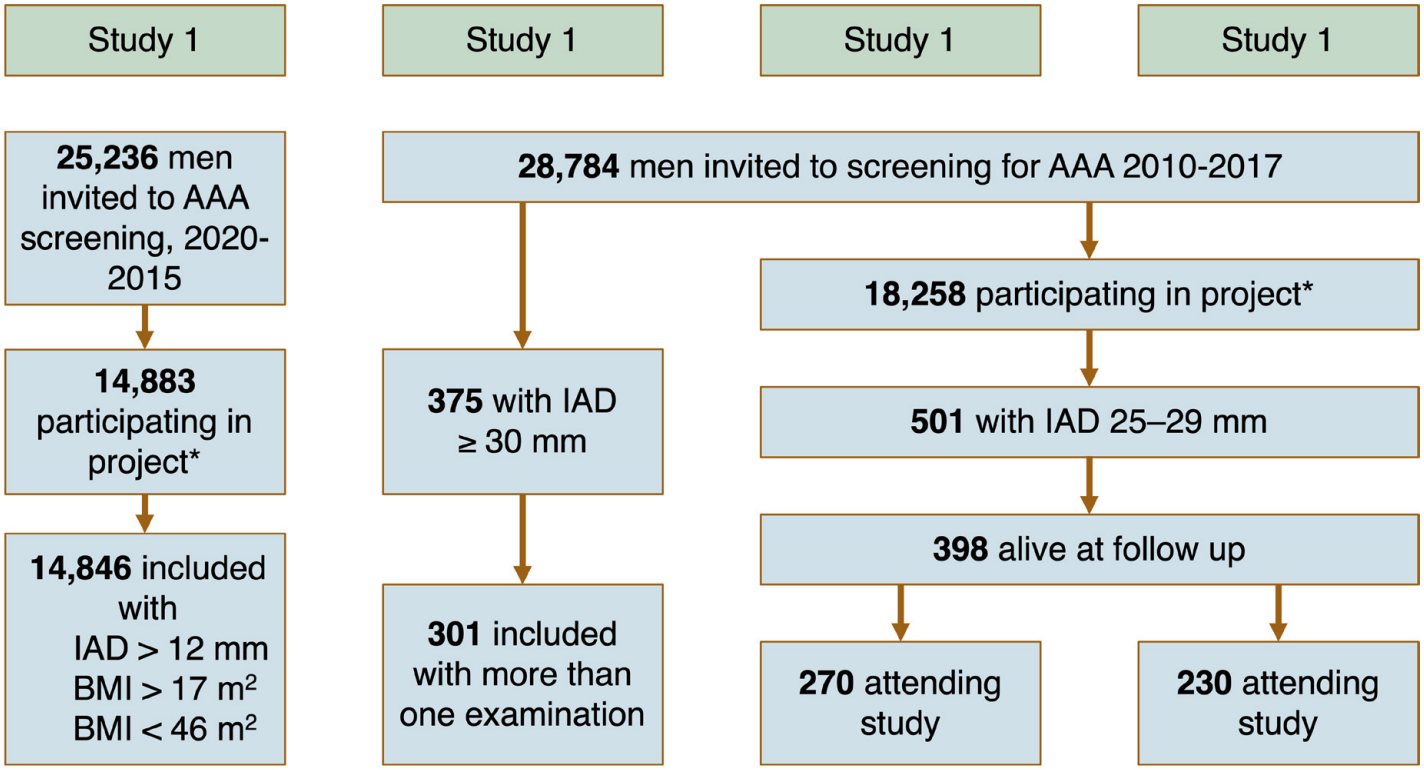

Figure 4.
Flow of participants and inclusion across the four component studies. Minor discrepancies exist compared to the published manuscripts of Studies III and IV. *) Broad epidemiological project in which screening participants were invited to contribute data on AAA, atherosclerosis, and medical prevention.

Table 1.
Summary of study populations, designs, baseline characteristics, research questions, outcomes, and main results from the four component studies of this doctoral project. All participants provided written informed consent to take part in a large epidemiological study initiated in connection with the Malmö screening program and completed a health questionnaire including information on height, weight, comorbidities, and medication. Estimates are presented with 95% confidence intervals (95% CI), p-values, and test statistics where applicable. Analytical methods include Spearman correlation ([a]), linear mixed-effects models ([b]), Cox regression ([c]), Bland–Altman analysis ([d]), and diagnostic accuracy measures with McNemar's χ^2 test ([e]). For details of analytical methods, see footnotes.

Population — Article	Design	Baseline characteristics	Main question	Outcome / Measure	Result	95% CI	p-value	Test statistic (df)
14,846 men from AAA screening 2010-2015 — Int Angiol 2019	Retro-spective screening cohort	Age 65 years (fixed); BSA mean 2.05 m² (95% CI: 2.04, 2.05); Smoking 14%	Association between BSA and IAD; diagnostic thresholds	Correlation IAD–BSA[a]	ρ = 0.26	0.25 to 0.28	< 0.001	–
				AAA (≥30 mm)	1.5 % (n = 225)	1.3 to 1.7	–	–
				BSA-related AAA	2.0 % (n = 299)	1.8 to 2.3	–	–
				Difference in detection rate	0.48%	0.41 to 0.50	< 0.001	$\chi^2(1) = 65.33$
301 men with AAA from screening 2010-2017 and ≥ 1 surveillance examinations— Int Angiol 2022	Screening and surveillance cohort	Age 65 years (fixed); BSA mean 2.10 m2 (95% CI: 2.08, 2.12); Smoking: 42%; Diabetes 24%; Heart disease 41%; Renal insufficiency 23%	Effect of BSA, smoking, diabetes on AAA growth	Baseline growth (model adjusted)[b]	1.44 mm/year	1.17 to 1.71	< 0.001	t(298) = 10.5
				Current smoking (yes vs no)[b]	0.69 mm/year	0.34 to 1.05	< 0.001	t(211) = 3.81
				Diabetes (yes vs no)[b]	-0.91 mm/year	-1.32 to -0.50	< 0.001	t(213) = -4.38
				BSA (per m²)[b]	0.75 mm/year	-0.21 to 1.21	0.126	t(217) = 1.53
270 men from AAA screening 2010-2017, IAD 25–29 — J Vasc Surg 2025	Prospective cohort	Age 65 years (fixed); FU 10.1 years (IQR 8.0 to 9.6); IAD median 26 mm (IQR 25 to 27); BSA median 2.1 m² (IQR 2.0 to 2.2); Smoking 19%; Diabetes 12%	Factors associated with aneurysm growth rate (mm/year)	Baseline growth (model-adjusted)[b]	0.05 mm/year	-0.55 to 0.65	0.870	t(269) = 0.16
				BSA-related AAA (yes vs no)[b]	0.39 mm/year	0.03 to 0.75	0.032	t(268) = 2.14
				Smoking (yes vs no)[b]	0.43 mm/year	0.18 to 0.68	0.001	t(268) = 3.37
				Diabetes (yes vs no)[b]	-0.12 mm/year	-0.44 to 0.20	0.463	t(268) = -0.73
			Factors associated with progression to AAA ≥40 mm	BSA-Related AAA (yes vs no)[c]	HR 2.77	1.34 to 5.74	0.006	z = 2.75
				Smoking (yes vs no)[c]	HR 2.10	0.99 to 4.43	0.052	z = 1.94

Population — Article	Design	Baseline characteristics	Main question	Outcome / Measure	Result	95% CI	p-value	Test statistic (df)
230 men with IAD 25–29 mm at screening 2010–2017, re-examined after 5–12 y — Ultrasound Med Biol 2025	Comparative proof of concept (POCUS vs standard US),	Age median 75 years (IQR 72.9 to 76.5); BMI median 2.1 (IQR 2.0 to 2.2); IAD median 27.1 mm (IQR 23.7 to 32.8) with 36% AAA	Diagnostic performance of handheld POCUS vs standard ultrasound	Mean bias[d]	-0.30 mm	–	–	–
				95% LoA[d]		-3.00 to 3.50	–	–
				Repeatability within devices				
				US	± 2.53 mm	–	–	–
				POCUS	± 3.34 mm	–	–	–
				Accuracy[e]	0.97	0.95 to 0.98		
				Sensitivity[e]	0.94	0.90 to 0.97		
				Specificity[e]	0.98	0.97 to 0.99		
				Positive predictive value[e]	0.97	0.94 to 0.99	0.118	$\chi^2(1) = 2.45$
				Negative predictive value[e]	0.97	0.95 to 0.99		

[a] Spearman's rank correlation coefficient (ρ); CI estimated by bootstrapping with 2000 replicates.

[b] Estimates from linear mixed-effects models; results expressed as change in infrarenal aortic diameter (mm/year). "Baseline growth (model-adjusted)" refers to the adjusted mean slope in the reference group (absence of covariates). Covariates are interaction terms with time.

[c] Hazard ratios estimated using Cox regression. Test statistic corresponds to Wald z. Outcome defined as progression to infrarenal aortic diameter ≥40 mm during follow-up.

[d] Bias and limits of agreement (LoA in mm) were derived from Bland–Altman analysis. Repeatability refers to within-device variability, expressed as the 95% repeatability limits ($\pm 1.96 \times \sqrt{(2 \times S_w)}$), where S_w denotes the within-subject variance estimated from the mixed-effects model.

[e] Diagnostic performance (sensitivity, specificity, accuracy, and predictive values for detection of AAA [IAD ≥ 30 mm]; confidence intervals by exact/binomial method; McNemar's χ^2 test used to evaluate asymmetry in discordant classifications [false positives vs false negatives]). Reference = standard ultrasound.

AAA, abdominal aortic aneurysm; BSA, body surface area (according to Du Bois and Du Bois [270]; IAD, infrarenal aortic diameter; BSA-related AAA, abdominal aortic aneurysm defined as an infrarenal aortic diameter ≥ 150% of the expected value based on individual BSA; FU, follow-up time, in years; IQR, interquartile range; POCUS, point-of-care ultrasound; US, standard ultrasound; BMI, body mass index [271]; LoA, limits of agreement, see footnote ([d]). Abbreviations are listed in order of appearance.

Study I

Of 25,236 invited men, 19,738 (78.2 %) attended screening, 14,883 (59.0 %) had information on height and weight, and 14,846 (58.8 %) were included in the study (Figure 3). The mean infrarenal aortic diameter (IAD) was 19.4 mm, and AAA (IAD ≥ 30 mm) was found in 226 men (1.5 %). Using the AAA definition of IAD ≥ 150 % of predicted IAD based on individual BSA, identified AAA in 299 men (1.9 %), a significant 30 % increase (McNemar's test, $p < 0.001$). IAD was correlated with BSA (Spearman's rank correlation = 0.26), with steeper regression slopes observed in current smokers. In the validation subset (n = 237), ultrasound underestimated IAD by 1.0 mm (95 % CI: 0.6 – 1.3 mm) compared to CT/MRI, with a variability of 5.2 mm. Smoking was common among AAA cases (93.8 % ever smokers).

Study II

Of the 28,784 men invited to AAA screening in Malmö between 2010 and 2017, 22,819 (79 %) attended, and 375 (1.6 %) were found to have an IAD ≥ 30 mm. Of these, 301 entered surveillance, contributing 1,546 observations to the growth analysis (Figure 3). The median follow-up was 5.9 years, with a median of four examinations per participant. A total of 121 men (32 %) underwent elective repair, with a median time from initial screening to surgery of 49 months and a median preoperative IAD of 55 mm. Ten men declined treatment due to comorbidities, and 47 (15 %) died during follow-up, of whom one died from a rAAA.

Unadjusted mean growth rate was 1.60 mm/year (95 % CI: 1.41 – 1.80; $p < 0.001$) with a significant quadratic factor (0.04 mm/year²). Diabetes was associated with slower, and current smoking with faster growth. Baseline diameter had a minor positive impact; BSA showed no significant influence.

In the multivariable quadratic LME model, adjusted growth was 1.44 mm/year (95 % CI: 1.17 – 1.71; $p < 0.001$) with a quadratic term of 0.03 mm/year². Diabetes remained protective, smoking promoted faster growth, and BSA remained non-significant.

Study III

Of the men invited to AAA screening (2010–2017) with a completed health questionnaire, 501 (2.7 %) had IAD measured to 25–29 mm. At follow-up, 102 had died, one from rAAA, initially measured at 27 mm. Of 399 survivors invited for re-

examination, 270 attended and 248 had full baseline data (Figure 3). Median follow-up was 10.1 years; 37 % progressed to IAD ≥ 30 mm, 12 % to ≥ 40 mm. Mean IAD growth was 0.3 mm/year. BSA-related AAA and smoking were both associated with an additional 0.4 mm/year increase in growth. No association was found with initial IAD, diabetes, or statin use. At 10 years, cumulative incidence of reaching IAD ≥ 40 mm was 6 %. The median time to reach an IAD of ≥ 40 mm was 12 years (95 % confidence level[31] [CL], 11.7 – ∞) for the entire cohort. There was a significant difference in median time to reach an IAD of ≥ 40 mm; 11.5 years (95 % CL: 11.0 – ∞) for BSA-related AAA, whereas one-half of those with non-BSA-related AAA did not reach 40 mm during the follow-up (95 % CL, 11.7 – ∞) as shown by a log-rank test stratified for smoking ($\chi^2 = 6.8$; 1 degree of freedom; $p = 0.009$). The median time to reach an IAD of ≥ 35 mm was 11.0 years for men with both BSA-related AAA and smoking, compared with 11.7 years for those without these risk factors.

BSA-related AAA and smoking predicted faster progression (HR 2.77 and 2.10), with a combined HR of 4.1. Comparing the growth rate with small AAAs (30–35 mm), BSA-related AAA showed no significant difference in growth.

Study IV

During 2010–2017, 18,543 men attended AAA screening and completed a health questionnaire. Out of these, 500 men (2.7 %) met the inclusion criteria with an IAD measured to 25–29 mm. Of the 398 eligible survivors, 230 (58 %) participated, each undergoing three paired IAD measurements using both standard ultrasound and handheld POCUS, totalling 1,380 observations. Median follow-up was 9.9 years. Median age was 75 years; BMI, 27.7; and IAD, 27.1 mm. In total, 36 % had AAA (IAD ≥ 30 mm). POCUS underestimated IAD by 0.3 mm (SD 1.6) compared to standard US. Bland-Altman analysis showed no systematic bias, with 95 % limits of agreement of –3.0 to +3.5 mm; the mixed effects model showed –3.3 to +2.7 mm. The diagnostic accuracy of POCUS for detecting an AAA (IAD ≥ 30 mm) was 0.96, using standard US as the reference method. The sensitivity and specificity of POCUS were 0.94 and 0.98, respectively. PPV and NPV were 0.96 and 0.97, respectively, compared to standard US.

There was a statistically significant difference in the agreement of measurements within each device, expressed as repeatability (R). R was estimated at 0.990 (95 % CI: 0.987 – 0.992) for standard ultrasound and 0.982 (95 % CI: 0.977 – 0.986) for

[31] **Confidence level** refers to the probability (usually expressed as a percentage, e.g., 95%) that a given confidence interval will contain the true population parameter if the study were repeated many times. In contrast, the **confidence interval** is the actual range (e.g., 1.2 – 2.5) calculated from the data that likely contains the true value with the specified confidence level.

POCUS. A total of 95 % of repeated measurements were estimated to lie within ± 2.5 mm for standard ultrasound and within ± 3.2 mm for POCUS.

No correlation was found between the largest IAD measurements and BMI using either standard ultrasound ($R^2 < 0.000$, $p = 0.81$) or handheld POCUS ($R^2 = 0.006$, $p = 0.31$).

Discussion

While the current threshold for AAA screening in men (IAD ≥ 30 mm) is well established, it may miss individuals at risk who have smaller aortic diameters. The findings presented in this thesis support the use of body size–adjusted diameter thresholds to improve case detection, especially when additional risk factors such as smoking are taken into account. However, the results are not of sufficient magnitude to warrant changes to current screening practices.

Handheld POCUS proved feasible and accurate for AAA screening, with high diagnostic accuracy, minimal bias, and no misclassifications compared to standard ultrasound. Despite slightly lower precision, performance was within guideline limits. Portability supports outreach use, though caution is needed when assessing aortas in the 20–30 mm range, where precision is most critical.

Collectively, these four studies highlight the potential benefits and limitations of individualising AAA screening and surveillance. While body size correlates with baseline aortic diameter, it does not predict aneurysm growth and should not, on its own, guide follow-up intensity. However, relative thresholds may uncover additional at-risk individuals, and handheld POCUS represents a feasible and accurate tool to extend screening reach.

Overview

Clear diagnostic criteria and effective detection strategies are crucial in all screening programmes, including that for AAA. This thesis explores when a dilated aorta should be classified as an AAA and how best to detect it. The widely used ≥ 30 mm threshold is practical but represents an approximation of the original definition of an aneurysm as a dilation 1.5 times greater than normal. Revisiting this relative definition, the feasibility and diagnostic implications of body size-adjusted thresholds were evaluated in a screening context. Study I focused on diagnostic criteria, while Study III assessed whether individuals who met the relative but not the fixed threshold exhibited aortic growth patterns more consistent with small

AAAs than with normal aging, and whether they should therefore be considered for surveillance. In parallel, Study II examined the influence of body habitus on aneurysm growth, and Study IV evaluated the feasibility of handheld ultrasound devices as scalable tools for AAA screening.

AAA is well suited for screening due to several characteristics: it is easily detectable via ultrasound, has a long latent phase meaning one-time screening is usually sufficient, is potentially fatal if untreated, and can be managed effectively with prophylactic treatment [57, 232].

Aims & rationale of AAA screening

There are two main objectives of AAA screening

First, to detect individuals with large aneurysms (≥ 55 mm) at significant risk of rupture and eligible for elective repair. The annual rupture risk in this group is estimated at 1–5%, increasing to over 10 % in aneurysms exceeding 60 mm [272]. In screening populations of elderly men, this typically identifies 0.4–0.5 %, and likely fewer today [57].

Second, to identify individuals with smaller aneurysms (30–55 mm) who are at risk of further growth and increased cardiovascular risk. These individuals are enrolled in surveillance programmes, as diameter progression is a known risk factor for rupture, and are offered best medical therapy and lifestyle interventions to reduce cardiovascular risk. Surveillance enables timely surgical referral when thresholds are reached [273], although such cases now represent less than % of screened populations [103].

A rAAA is a life-threatening event. Survival is unlikely if the patient does not reach hospital within hours [274] and even those who do, often face complex recoveries. Emergency repair is associated with high complication rates and low postoperative survival, despite gradual improvements over time [8, 275]. Moreover, rAAA imposes a significant burden on healthcare systems—requiring immediate access to emergency, radiology, and inpatient care, and often leading to prolonged rehabilitation or institutional care [276].

In contrast, elective repair of an intact AAA is generally well tolerated. Because surgery is planned, the care pathway can be optimised. Elective OAR most often involves a hospital stay of a few demanding days, followed by a recovery period of one to two months. Elective EVAR, sometimes even performed as a day procedure, allows for quicker recovery. Although EVAR requires lifelong imaging follow-up, most patients can return to normal life [91, 143]**.**

These clinical considerations highlight the importance of accurate risk stratification. While the fixed ≥ 30 mm threshold has long served as the diagnostic standard, its universal applicability has been questioned [2]. The original definition—a dilation

1.5 times the expected normal diameter—suggests that body size could influence diagnosis [3]. A relative threshold may improve detection in individuals with smaller body habitus who fall below the fixed cut-off but still harbour significant disease.

As screening increasingly focuses on identifying individuals at earlier stages of risk, not only those eligible for surgery, there is growing potential to deliver screening more proactively, reaching people rather than relying on them to respond to screening invitations. This shift places continued emphasis on avoiding overdiagnosis and maintaining public confidence in screening programmes.

Discussion of study findings

Study I: Diagnostic criteria

In this context, Study I evaluated the feasibility and diagnostic impact of implementing a body size-adjusted threshold in a screening setting. It found a statistically significant correlation IAD and BSA, consistent with earlier studies [1, 277, 278]. This correlation formed the basis for an individualised diagnostic criterion, defining AAA as an IAD ≥ 150% of the predicted diameter based on BSA. Using this approach, AAA detection rate increased from 1.5 % to 2.0 % among 65-year-old men, which is a 23 % relative increase compared to the fixed ≥ 30 mm threshold, see Figure 5.

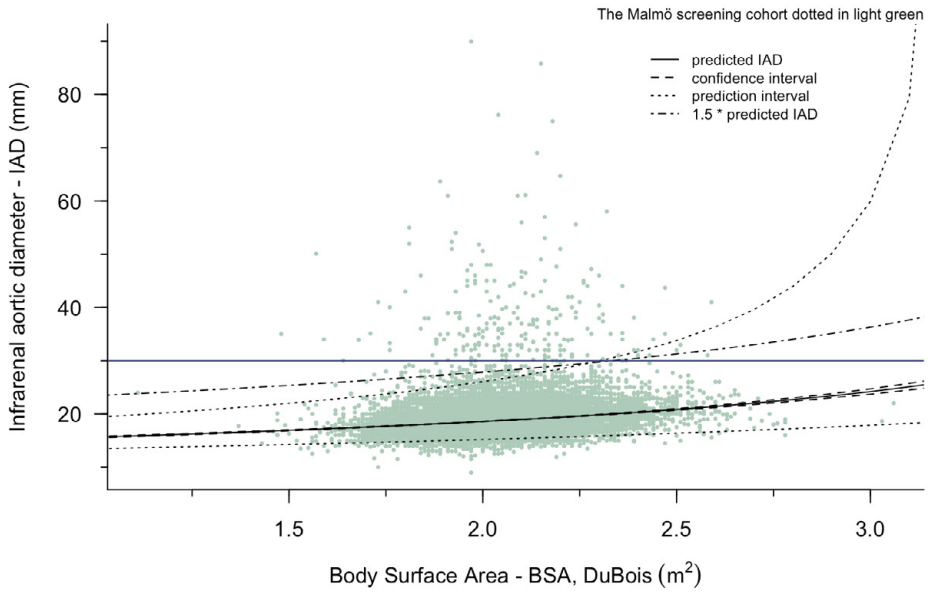

Figure 5.
Predicted infrarenal aortic diameter in 65-year-old men as a function of body surface area. The dark blue line represents the established cut-off criterion for AAA diagnosis (30 mm). AAA, abdominal aortic aneurysm. The relevant observations, representing individual measurements, are those located above the dash–dot line and below the blue line.

Notably, the distribution of IADs is positively skewed (Figure 6), indicating that the presence of aneurysmal disease inflates the mean and shifts the distribution to the right. This suggests that using two standard deviations above the mean, which is a common statistical convention for defining the upper limit of the normal reference range [279], may be problematic in this context. Because the mean is affected by the skewed tail of pathological values, applying this threshold could result in an overestimation of what constitutes "normal" variation. Study I addressed this issue by normalizing the IAD distribution prior to regression modelling, allowing for a more accurate estimation of predicted diameters based on BSA. However, despite this adjustment, it is possible that the derived 150 % threshold may still be shifted slightly to the right, potentially underdiagnosing individuals with smaller body habitus.

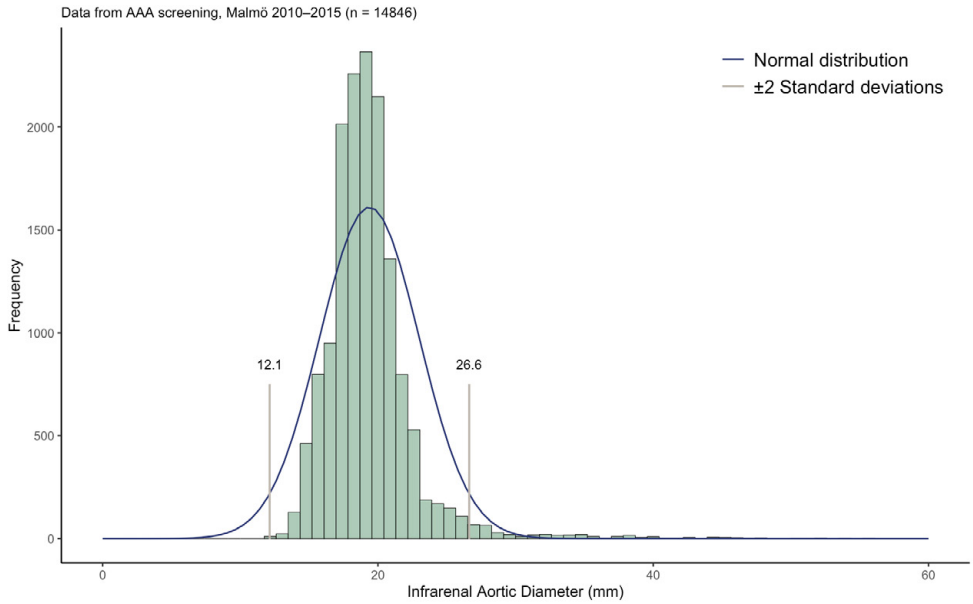

Figure 6.
Histogram (frequencies) showing positively skewed distribution of infrarenal aortic diameters including corresponding normal distribution (solid line).

Study II: AAA growth patterns

To assess whether body size is also relevant to disease progression, Study II examined the impact of BSA on AAA growth. Despite the established correlation between IAD and BSA, no statistically or clinically significant relationship was found between BSA and AAA growth rates. Neither BMI nor BSA quantiles influenced growth, and only height showed a weak but statistically significant positive correlation (0.2 mm/year; $p = 0.047$), the implications of which remain unclear.

This suggests that while body size influences baseline aortic diameter, it does not meaningfully affect aneurysm expansion in men. Consequently, adjusting surveillance intervals based on body habitus does not appear warranted. Confirming earlier research [115], current smoking and diabetes remained the only consistent predictors of aneurysm growth.

Study III: Clinical course of subaneurysmal aortas

Study III followed individuals from Study I who met the BSA-related definition of AAA (≥ 150% of predicted IAD) but had absolute diameters below 30 mm, to assess

whether they progressed to clinically relevant aneurysms. Both BSA-related AAA and current smoking were independently associated with increased IAD growth (0.4 mm/year) and a significantly elevated risk of reaching an IAD ≥ 40 mm. Growth rates in this group were comparable to those of small AAAs (30–35 mm), suggesting that individual diameter threshold for diagnosis may better reflect progression risk than absolute thresholds alone.

Although not explicitly analysed in the manuscript, Figure 7 illustrates that combining BSA-related AAA and smoking reveals a clear difference in growth rates between individuals with both risk factors and those without. However, the median time to reach 40 mm exceeded 11 years in all groups, and the difference between those with and without risk factors was less than one year. While statistically significant, this modest difference limits the clinical utility of the relative threshold for guiding surveillance intervals.

The aortic size index (ASI), defined as aortic diameter divided by body surface area (mm/m^2), has been proposed as an alternative means of individualising the diagnostic threshold, particularly in patients with borderline diameters. The findings in this study were consistent with previous ASI research [101, 280, 281], and applying a threshold of ≥ 13 mm/m^2 yielded results similar to those seen with the BSA-based definition. However, the high positive and negative predictive values for progression to 55 mm reported in earlier studies were not observed here—neither with the BSA-related criterion nor the ASI threshold—although the endpoint in this study was 40 mm. Broader application of such individualised criteria therefore requires further validation.

Taken together, Studies I–III show that individualised thresholds may improve case detection, but body size alone does not justify modified surveillance protocols, nor do these findings support changes to existing screening strategies at this stage. Smoking and diabetes remain the key drivers of aneurysm progression risk.

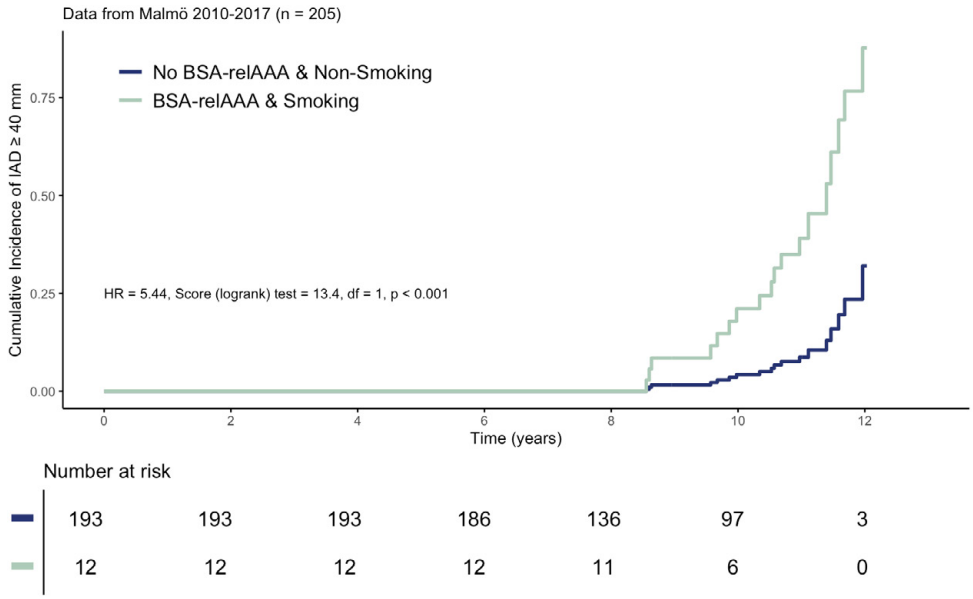

Figure 7. Cox model–predicted cumulative incidence of reaching an infrarenal aortic diameter (IAD) threshold of ≥ 40 mm, stratified by presence of BSA-related AAA and smoking.
Light green curve represents the baseline cumulative hazard for individuals with both BSA-related AAA and a history of smoking. Dark blue curve represents individuals without these risk factors.
Hazard Ratio (HR) = 5.44; Likelihood ratio test = 8.57 (1 df); p = 0.003; n = 205, numbers of events = 18.
AAA, abdominal aortic aneurysm; BSA, body surface area; BSA-related AAA, abdominal aortic aneurysm defined by IAD ≥ 1.5 × expected based on BSA.

Study IV: Handheld ultrasound performance

Building on the diagnostic questions raised in the previous studies, Study IV evaluated the feasibility of handheld POCUS for AAA screening, particularly in the context of declining prevalence and a shift toward targeting high-risk populations [2, 103, 282]. While the feasibility of POCUS and small portable US devices for AAA screening has been explored previously, it has, to our knowledge, not been assessed on this scale. A review of smaller studies supports the notion that POCUS performed by non-radiologists can achieve diagnostic accuracy comparable to that of standard radiology-performed US [283].

This study found that handheld POCUS achieved 97% diagnostic accuracy, with a mean measurement bias of just –0.3 mm compared to standard ultrasound. Although its precision, i.e. repeated measurement with the same device, was slightly lower (± 3.2 mm vs. ± 2.5 mm limits of agreement), this variation aligns with previously reported inter-observer differences using the same devices [241]. Notably, current

guidelines accept a tolerance of ± 5 mm [284]. Importantly, no participant was misclassified, and measurement performance was unaffected by BMI.

Although POCUS devices lack cine loop functionality (at least the one used in our study) and have smaller interfaces, factors that may limit peak measurement timing, they offer considerable practical advantages. Their portability and ease of use make them well suited for mobile or community-based screening, an advantage in underserved or socioeconomically disadvantaged populations where screening attendance is often low [163, 265, 285]. Such outreach could improve detection among the individuals identified in Studies I and III. In these populations however, where diagnostic thresholds are individualised based on body size, the accuracy of aortic measurements is particularly critical. This is especially true in the 20–30 mm range, where limits of agreement between devices tend to widen, see Figure 8, and small deviations can influence diagnostic classification. Therefore, higher demands are placed on measurement precision when assessing individuals near the diagnostic threshold.

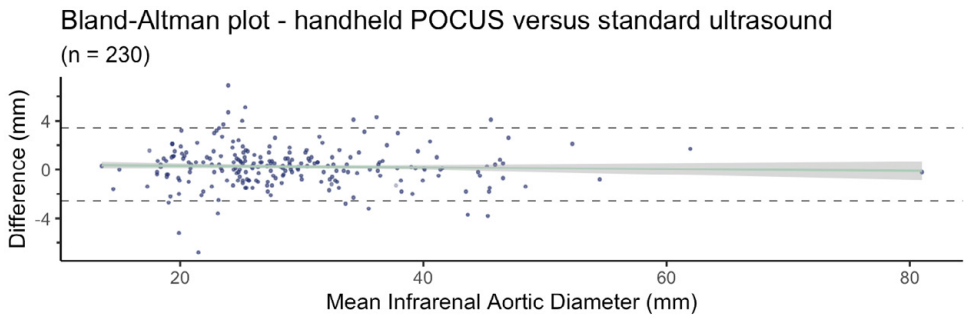

Figure 8.
Bland-Altman plot showing agreement between handheld POCUS and standard ultrasound measurements of infrarenal aortic diameter. The plot compares the largest measurement from each device per individual. Each point represents the difference between paired measurements plotted against their mean. The solid line indicates the mean difference (0.3 mm), and the dashed lines show the 95% limits of agreement (–3.0 mm to 3.6 mm).

General discussion

An effective screening programme must be both clinically sound and publicly acceptable. Participation is voluntary, so trust and clarity are essential. Screening must achieve high sensitivity, by identifying individuals at risk of rupture, and high specificity, by avoiding unnecessary diagnoses and interventions. Lowering the

diagnostic threshold and expanding the criteria for surveillance risk both overdiagnosis and overtreatment, potentially undermining the balance of benefit and harm.

Overdiagnosis

Changing the AAA definition from ≥ 30 mm to ≥ 25 mm remains controversial [257, 286, 287]. Based on the Gloucestershire study, 87% (95% CI: 84–90%) of men with aortic diameters of 26–29 mm would be classified as over-diagnosed 10–20 years after screening, raising the overall overdiagnosis rate from 38% to 58% (95% CI: 42–61%) [288].

In the Malmö screening cohort (2010–2015), 226 men (1.5%) were diagnosed with AAA using the standard threshold (IAD ≥ 30 mm). Lowering the threshold to ≥ 25 mm increased this to 630 men (4.2%). In Study III, 3 men (1%) with IAD 25–29 reached ≥ 55 mm during a median 10-year follow-up. While this suggests that some smaller AAAs progress, the study was not designed to assess this specifically and the findings should be interpreted with caution. Still to bear in mind, 0.23 % of all men with normal screening results later experienced rupture within 13 years as shown in the final follow-up of the MASS trial [257]. While rare, this highlights the risk of false reassurance, and reinforces the need for refined selection criteria and long-term follow-up.

Current guidelines recommend that all individuals under surveillance receive structured counselling, lifestyle advice, and optimisation of cardiovascular risk factors [2]. However, while the diagnostic threshold of IAD ≥ 30 mm has a high positive predictive value both for aneurysm growth and cardiovascular risk, an IAD ≥ 25 mm is not an established trigger for cardiovascular risk reduction and must be further evaluated [103].

Overtreatment

AAA screening has been criticised for its potential to lead to overtreatment, namely prophylactic surgeries in patients who might never experience a rupture [256]. Consequently, the same critique should also apply to large AAAs diagnosed incidentally outside screening. While elective surgery rates have increased since the introduction of screening [199, 256], this critique is more appropriately directed at the surgical threshold (e.g., ≥ 55 mm), which is itself under debate [141], rather than at the screening strategy as a whole. Since rupture risk correlates most strongly with diameter, and predictive models such as biomechanical stress or wall strain remain investigational and have not yet entered clinical practice, diameter continues to serve as the most practical guide for treatment decisions. What may be considered

overtreatment includes prophylactic surgery for small AAAs (< 55 mm) or in patients with limited life expectancy [103].

Implications for Screening Policies

Initially, the aim of AAA screening was to identify surgical candidates. Now, the aim is somewhat shifting towards identifying men who would benefit from surveillance and cardiovascular risk reduction [114, 232]. In this context, some individuals with aortic diameters below 30 mm exhibit early signs of aneurysmal disease and may benefit from risk factor modification and monitoring—though most will not. Using IAD ≥ 30 mm as the screening threshold yields a high positive predictive value for identifying individuals likely to experience aneurysm growth and benefit from cardiovascular risk reduction. In contrast, an IAD ≥ 25 mm threshold has lower predictive accuracy and would probably require additional risk markers to enhance its clinical utility. Moreover, if our findings are generalisable, adopting such a threshold would nearly triple the number of individuals placed under surveillance, with important implications healthcare resources.

Several studies suggest that ambulatory screening services or outreach strategies could improve early detection, particularly among men who do not respond to screening invitations. Non-attenders are more likely to have lower socioeconomic status and a higher prevalence of AAA, which means that conventional screening formats risk widening health inequalities by failing to reach those most in need [114, 265]. More accessible strategies could help mitigate this disparity, with POCUS and portable devices especially valuable in primary care and resource-limited settings. However, limitations include the need for a proper understanding of aortic anatomy and tortuosity, reduced image quality in patients with obesity or bowel gas, and the requirement for operator training to ensure measurement reproducibility within accepted tolerances [236].

Strengths & Limitations

Study population and design

A key limitation of this thesis is that all studies included only 65-year-old men from a single geographic area and were conducted at one screening centre. This homogeneity limits the generalisability of findings to women, other age groups, and more diverse populations. Participation bias is also possible, as screening attendees often have higher socioeconomic status and health literacy, which could lead to underestimation of disease prevalence and progression. These limitations mainly affect external validity; there is no obvious mechanism by which they would

systematically distort the estimated association between IAD and BSA, although range restriction among attendees could attenuate correlations.

At the same time, the use of a single-age, sex-specific, population-based screening cohort strengthens internal validity and reduces measurement variability. This controlled design enhances consistency in data collection and interpretation, providing a clean foundation for developing body size–adjusted diagnostic criteria and observing natural disease progression without selection bias from opportunistic diagnoses.

Self-reported biometric and lifestyle data

Self-reported height and weight were used to calculate BSA without internal validation. This introduces uncertainty, as self-reported biometric data are subject to recall and social desirability bias [289, 290]. Smoking status was dichotomised rather than quantified (e.g., in pack-years), and comorbidities and medications were only collected at baseline. These limitations may result in residual confounding and limit the precision of risk assessments.

However, the use of self-reported data in a homogenous screening population likely affected all participants similarly, thereby minimising systematic bias in group comparisons [289, 290]. The consistent methodology across studies supports comparability, and the available baseline data still allow for meaningful subgroup analysis and hypothesis generation for future research.

Predictive modelling and threshold derivation

In Study I and Study III, prediction models were developed and tested on the same dataset without cross-validation or external testing. This approach increases the risk of overfitting and limits the external validity of the results. The BSA-based AAA threshold was derived and applied within this same cohort, and should therefore be considered exploratory until validated in independent populations.

Nonetheless, this internal modelling provided a valuable proof of concept for individualised AAA classification based on BSA. It enabled the generation of clinically relevant thresholds within a well-defined population and demonstrated the feasibility of body size–adjusted diagnostics in practice.

Ultrasound data and follow-up structure

Study III's survival analysis was constrained by few events early in follow-up and increasing censoring later, reducing statistical precision. Most participants had only

two measurement points, which limited the ability to characterise individual growth patterns in detail.

A strength, however, is that the data were based on population-based screening and follow-up data was not contaminated by opportunistic findings. This reduces the risk of bias related to clinical indication and supports a more consistent assessment of aneurysm progression in an asymptomatic cohort. The design allows for the analysis of growth patterns under conditions reflective of routine screening practice

Evaluation of handheld ultrasound

In Study IV, both handheld POCUS and standard ultrasound were performed by a single examiner in a fixed order. Although blinding was maintained, this may introduce operator bias and limits generalisability to routine settings with less experienced staff. Moreover, without an external reference standard, the comparative accuracy of handheld and standard ultrasound was limited.

However, the use of a single, experienced examiner ensured measurement consistency and eliminated inter-observer variability, strengthening the internal validity of the comparisons. To date, few studies, if any, have directly evaluated the feasibility of handheld POCUS in AAA screening, particularly in a screening-like setting with participants who had aortic diameters close to the clinical threshold where diagnostic precision is most critical.

Conclusions

Conclusion

Individualising the aneurysm diameter threshold based on body size (height and weight) and incorporating handheld ultrasound devices could help refine AAA screening in men.

Overall conclusion

Our findings suggest that men with an IAD below 30 mm but at least 1.5 times larger than expected based on BSA exhibit a growth pattern similar to true aortic aneurysms (IAD ≥ 30 mm), whereas aortic diameters below this threshold increase more slowly. However, the differences were too small to reliably predict which individuals with an aortic diameter < 30 mm at screening are at increased risk of developing clinically relevant AAAs, highlighting the need for further research. Additionally, AAA screening in men is feasible using a handheld, tablet-operated ultrasound device.

Study-specific conclusions

I. A statistically significant correlation between BSA and IAD was found in a large, male screening population. This correlation enables the identification of individuals with an IAD below 30 mm but at least 1.5 times larger than expected based on BSA, suggesting a way to individualise the diagnostic criterion for AAA. This BSA-related AAA criterion identified over 30 % more patients while excluding fewer than 2 % compared to the standard IAD threshold of ≥ 30 mm.

II. BSA was not correlated with AAA growth in men and has therefore no clinical relevance when designing an AAA surveillance program. The

impact of smoking and diabetes on aneurysm growth was similar to previous findings.

III. A BSA-related AAA criterion, beyond IAD alone, showed a statistically significant association with diameter growth and thus aneurysm development in men with an IAD of 25–29 mm at screening. However, the differences were too small to reliably determine which individuals are at increased risk of developing clinically relevant aneurysms, warranting further studies.

IV. A handheld, tablet-operated POCUS device showed no clinically relevant systematic bias in measuring IAD in an AAA screening setting for men, although it had a slightly wider repeatability interval compared to standard ultrasound. This suggests that handheld POCUS devices could be considered for AAA screening.

Future Outlook

Future research should validate BSA-based AAA models in independent cohorts and explore machine learning to improve prediction and applicability. Studies on handheld ultrasound for mobile screening should consider feasibility, equity, and user experience. As discussions increasingly emphasise targeting high-risk groups for screening, large-scale follow-up is needed to guide risk stratification.

Within the research group

To strengthen external validity, models based on criteria established in this cohort for identifying BSA-related AAA could be tested in independent screening populations. Applying machine learning techniques could improve predictive accuracy, enhance generalisability, and support broader clinical applicability across diverse risk groups and healthcare settings.

Predictive models could also aim to assess the significance of an BSA-related AAA diagnosis, both as as a predictor of aneurysm progression to ≥ 55–60 mm, and also as a marker of cardiovascular risk, by integrating complementary data such as biometric measures, lifestyle factors, and family history.

Pilot studies could evaluate the feasibility, accuracy, and health system impact of mobile or community-based screening models using handheld ultrasound devices, with special attention to equity and access. These studies could benefit from combining clinical outcomes with qualitative data on the experiences and perspectives of patients and healthcare providers.

In general

Large-scale observational follow-up studies of contemporary screening programmes are urgently needed to assess outcomes, particularly as prevalence declines and screening becomes more targeted.

As screening shifts toward high-risk populations, this raises questions about how risk stratification should be defined and evaluated – essentially requiring "screening for screening".

Additionally, the role of targeted health consultations deserve exploration, particularly as a means of combining primary cardiovascular prevention with improved risk communication and patient engagement.

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Thesis at a glance

STUDY	AIM	METHOD	RESULT
A significant correlation between body surface area and infrarenal aortic diameter is detected in a large screening population with possibly clinical implications.	To determine whether BSA correlates with IAD in men to develop a BSA-related AAA diagnostic criterion.	Retrospective screening cohort study	A significant correlation between BSA and IAD enabled a BSA-based AAA criterion, identifying 30% more cases than the standard ≥30 mm threshold.
Body surface area does not affect growth rates of abdominal aortic aneurysms diagnosed in a male screening cohort.	To determine whether BSA correlates with AAA growth in men.	Retrospective screening and surveillance cohort study	BSA showed no correlation with AAA growth, while smoking and diabetes had effects consistent with previous findings.
Predictors of aneurysm progression in men with small infrarenal aortic diameters at screening	To assess whether a BSA-related AAA criterion (study I) identifies men with IAD 25–29 mm at screening who are at increased risk of developing a clinically relevant AAA.	Prospective cohort study	The BSA-related AAA criterion (study I) was linked to aneurysm development in men with IAD 25–29 mm, though with limited clinical relevance.
Evaluation of Point Of Care Ultrasound (POCUS) in screening for Abdominal Aortic Aneurysm in men: a comparative, cohort study	To explore the feasibility of a handheld, tablet-operated POCUS device in AAA screening for men.	Comparative proof-of-concept study (POCUS vs. standard US)	POCUS showed no clinically relevant bias in IAD measurement in men, though with a slightly wider repeatability interval than standard ultrasound.

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Paper I

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ORIGINAL ARTICLE
AORTIC DISEASE

EDITOR'S CHOICE

A significant correlation between body surface area and infrarenal aortic diameter is detected in a large screening population with possibly clinical implications

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ABSTRACT

Background: Screening for abdominal aortic aneurysm (AAA) in elderly men reduces aneurysm related mortality. AAA is commonly defined as an infrarenal aortic diameter (IAD) of ≥30 mm, which is based on the definition of an arterial aneurysm as a focal dilation of 150% or more compared to the expected diameter of about 20 mm. The IAD has been shown to correlate to body surface area (BSA). The aim of this study was to investigate the possibility to use an individualized AAA-criteria by using a BSA-based model to refine the screening for AAA.

Methods: We conducted an observational single center cohort study of 25 236 65-year old men invited to AAA screening in Malmö, Sweden 2010-2015. Out of the 19 738 (78.5%) attendees, 14 846 (58.8%) completed a health questionnaire including height, weight and smoking habits. Linear regression analysis was performed between BSA and IAD, taking smoking habits into account. This regression was used to calculate the predicted IAD for each individual according to their BSA.

Results: There was a significant correlation between BSA and aortic diameter, rho =0.26 (95% CI: 0.25, 0.28). AAA defined as an IAD≥30 mm was found in 226 men (1.5%) whereas AAA defined as ≥150% larger IAD than predicted according to the individual BSA was found in 299 men (1.9%), a relative difference in AAA detection rate of more than 30% (P<0.001).

Conclusions: We have found a statistically significant correlation between BSA and IAD in a homogenous screening population that could have clinical implications. In men with low BSA, IAD <30 mm might still be ≥150% larger than predicted according to BSA, whereas in men with high BSA, IAD≥30 mm might not be ≥150% larger than predicted. Further follow-up of these subjects is planned to investigate if the first group have an "aneurysm-in-formation," challenging the diagnostic criteria for AAA.

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Key words: Aortic aneurysm, abdominal; Body surface area; Ultrasonography; Mass screening.

The prevalence of abdominal aortic aneurysm (AAA) is 1.5-3.3% in elderly men[1-3] and several large studies have shown that screening for this condition reduces aneurysm related mortality[4-10] and is recommended in European guidelines for all elderly men[11] and in American guidelines for elderly women and men with history of tobacco use.[12]

The generally accepted definition of an arterial aneurysm is a focal and persistent vessel dilation of 150% or more compared to its expected normal diameter of the artery in question.[13] Previous studies have shown that the normal infrarenal aortic diameter (IAD) is slightly less than 20 mm in elderly men.[13-15] Accordingly, an AAA in this population has been defined as an IAD of 30 mm or more. This is usually 2 standard deviations above the mean diameter in this group and is also used in guidelines, *i.e.* the European Society for Vascular Surgery guidelines for abdominal aortic aneurysms.[11] Many studies have shown a significant correlation between IAD and body surface area (BSA) that is independent from blood pressure, sex, and age.[14-20] Such effects of BSA on IAD have so far been shown to be small, however, and the use of this "150%-paradigm" has therefore not offered any advantage over the simpler definition IAD≥30 mm in most contexts.[13, 20] Hence, AAA is therefore most often defined in the crude 30 mm fashion in screening cohorts of 65-year-old men.[4-10] Taking BSA into consideration as a factor when diagnosing a subject with AAA may be helpful for not risking false positive or false negative examinations. This may have consequences to the individual patient outcome.

The primary aim of this single center retrospective observational study was to investigate whether the correlation between the IAD and BSA seen in previous studies[14-20] can be reproduced in modern standardized screening procedures which has not been done before to our knowledge. And if so, whether this correlation affects screening outcome and thus could challenge the commonly used definition of an AAA. We also evaluated the role of smoking habits to these correlations. We have also included a computed tomography-magnetic resonance (CT/MR)-validation of our ultrasound screening method in order to lessen the risk of methodological shortcomings and thus further strengthen the presented conclusion.

Materials and methods

This study was approved by the ethics committee of Lund University (LU 2010/239), Sweden and all participants gave informed consent.

Setting

The Department of Vascular Diseases, Skåne University Hospital, Malmö (a tertiary vascular surgical center with a primary catchment population of 650 000) has a single center screening facility. In conjunction to the start of a screening program for AAA in Malmö a large project to study epidemiological aspects on this disease and atherosclerosis at large was launched. Between 2010 and 2015, all 65-year old men in the catchment area (identified through the National population-based Registry, www.skatteverket.se) were invited to an ultrasound examination of the infrarenal aorta. The invitations were written in Swedish with referral to an online source with information in other languages. The screening examination was possible to reschedule, and if the subject did not attend, a second invitation was sent. The personal cost for the screening was 13 €; no travel expenses were reimbursed. All subjects were asked to fill out a written health questionnaire, including information regarding length, weight,[21-24] and smoking habits at the time of the examination. The subjects were divided into three groups: current smokers, ex-smokers, and never smokers.

Ultrasound examination

The examinations were carried out using a standardized method by biomedical scientists and registered vascular nurses after special training and a formal exam. The measurements were conducted using LOGIQ e ultrasound machine device with 3.5 MHz probes (General Electric Healthcare Inc, Chalfont St. Giles, UK) according to the

manufacturer's instructions for use. The infrarenal aortic diameter was measured using leading-edge-to-leading-edge (LELE) technique,[25] which is the standard method in the Swedish screening program.[26] Iliac measurements were not analyzed in this study. After identifying the widest infrarenal diameter in the longitudinal plane of the aorta, the maximal infrarenal anterio-posterior aortic diameter was measured in the transverse plane perpendicular to the direction of flow, without regard to the pulse or the respiratory cycle. Upon inconclusive sonographic measurement, a computed tomography (CT) of the aorta was conducted.

To validate the ultrasound examinations a subset of the screening cohort (individuals invited in 2015, N.=3829) were selected. Among the 2937 attending, 1631 were randomly selected using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA) to be cross-checked against the radiology information system for the presence of tomographic examinations performed for any indication including the abdominal aorta ±one calendar year from the screening examination. This search yielded 237 subjects. The measurements were conducted from the anterior outer wall to posterior inner wall, in the transverse plane, to resemble the ultrasonographic measurements. The maximal infrarenal anterio-posterior aortic diameter was measured by a radiologist (LA) and a vascular surgeon (JS) in collaboration and consensus. The measurements from the screening examinations were blinded to the examinators and compared to the CT- or MRI-scans using a Bland-Altman analysis.

Statistical analysis

The infrarenal aortic diameter was measured in millimeters with one decimal. The BSA was calculated using the widely adopted DuBois and DuBois formula (BSA) = $weight^{0.425}$ *(kg) x* $height^{0.725}$ *(cm) x 0.007184*.Scatter plots of IAD *versus* BSA were made, and though the IAD is not normally distributed, analyses were calculated using a linear regression model on non-transformed data to facilitate comparison with earlier studies, that have not taken this distribution into account. Spearman's rank correlation coefficient was used to analyze the correlation of these regressions between IAD and BSA.[27]

To induce normality for the correlation and prediction analyses, the dependent variable (IAD) was transformed by inverting the squared product.[28] A multiple linear regression model (lm in R) was used to investigate the influence of smoking status on the correlation between BSA and IAD. A prediction model based on a linear regression between the transformed IAD values and BSA was used to calculate the predicted IAD according to measured BSA. The predicted values were obtained by evaluating the regression function including 95% prediction intervals and 95% confidence intervals. Men with BMI less than 17 and more than 46 as well as those with IAD less than 12 mm (N.=37) were excluded for this prediction calculation since these subjects were considered to be outliers as a result of incorrect recordings and/or measurements. This prediction function was multiplied by 1.5 to obtain the limit for an aneurysmal aorta according to the original definition of a 150% enlargement.[13] The difference in AAA-detection rate when using either the crude 30 mm definition or the relative 150% larger definition was tested for significance on the measurements rounded to nearest integer using McNemars Test,[29] used on paired nominal and dichotomous data.

The Statistical analyses were performed using R statistical programming environment (R Core Team [2015]) and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) was used as a database.

Results

Of the 25,236 invited men 19,738 (78.2%) attended the screening examination and 14,883 (59.0%) completed the health questionnaire. Thirty-seven subjects were excluded for reasons presented in methods, and data from 14,846 (58.8%) men were subsequently used in the presented study (Figure 1).

The IAD was not normally distributed (Figure 2) when checked by the eye for normality using a histogram (Figure 2) and a Q-Q-plot. The mean IAD in the whole population was 19.4 mm (95% CI: 19.3, 19.4). The median IAD was 19.0 mm (interquartile range 2.9 mm). Mean BSA in the whole population was 2.06 m^2 (95% CI: 2.04, 2.05); 4889 (33%) were never smokers, 7768 (52%) were previous smokers and 2012 men (14%) were current smokers. Among those diagnosed with an AAA, (IAD≥30 mm, N.=226), 101 (44.7%) were current smokers, 212 (93.8%) were ever smokers (ex-smokers together with current smokers), whereas 14 (7%) had no history of smoking (Table I).

There was a significant correlation between BSA and IAD in the complete cohort using Spearmans rank correlation coefficient, rho =0.26 (95% CI: 0.25, 0.28). When studying the subgroups divided by smoking status the correlation was not significantly different. Never smokers; rho =0.31 (95% CI: 0.28, 0.33), previous smokers; rho =0.26, (95% CI: 0.24, 0.28) and current smokers; rho =0.25 (95% CI: 0.21, 0.29). The slope of the linear regression though was significantly steeper for current smokers than for the

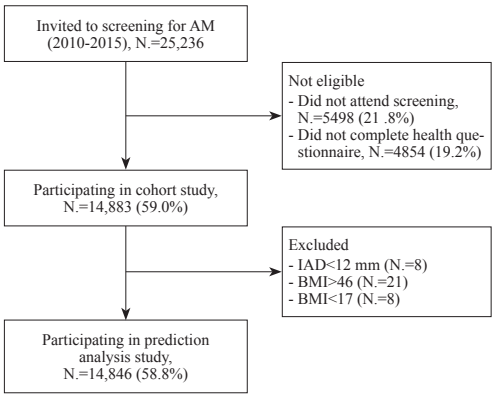

Figure 1.—Study design.

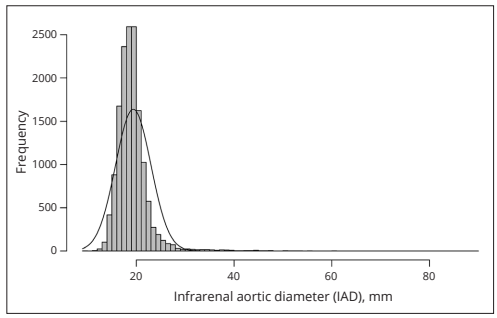

Figure 2.—Histogram showing positively skewed distribution of infrarenal aortic diameters including corresponding normal distribution (solid line).

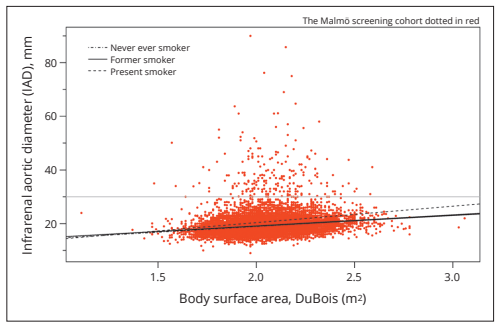

Figure 3.—Linear regressions for the correlation between body surface area and infrarenal aortic diameter. The slope for never ever smokers was 4.4 mm/m² (95% CI: 4.1, 4.8), for former smokers it was 4.5 mm/m² (95% CI: 4.0, 4.8) and for current smokers 5.9 mm/m² (95% CI: 5.3, 6.4). The grey line represents the established criteria for AAA diagnosis (30 mm).

other subgroups (Figure 3). The slope for never smokers was 4.4 mm/m² (95% CI: 4.1, 4.8), for previous smokers 4.5 mm/m² (95% CI: 4.0, 4.8) and for current smokers 5.9 mm/m² (95% CI: 5.3, 6.4). This suggests that the effect of BSA on IAD is interacting with smoking habits. A multiple regression analysis including BSA and smoking status as independent variables showed that smoking status has a significant adding impact on IAD, but the interaction effect between smoking status and BSA on IAD was not significant using ANOVA and χ^2 test.

AAA defined as an IAD≥30 mm was found in 226 men (1.5%) whereas an AAA defined as an ≥150% enlargement of the predicted IAD according to the individual BSA was found in 299 men (1.9%). In 3 men, the IAD was ≥30 mm but still not ≥150% wider than predicted according to the

TABLE I.—*65-year-old men, attending screening in Malmö, 2010-2015.*

	N.	AAA*	% *	rAAA**	% **	Mean IAD mm	Mean weight (kg)	Mean length (cm)	Mean BMI	Mean BSA
All	14,846	225	1.5 (1.3-1.7)	299	2.0 (1.8-2.3)	19.4 (19.3-19.4)	86.3 (86.1-86.5)	178.6 (178.5-178.7)	27.0 (27.0-27.1)	2.04 (2.04-2.05)
Never ever smoker	4903	14	0.3 (0.2-0.5)	22	0.4 (0.3-0.7)	19.1 (19.0-19.2)	85.4 (85.0-85.8)	178.6 (178.4-178.8)	26.8 (26.7-26.9)	2.04 (2.03-2.04)
Previous smoker	7914	111	1.4 (1.2-1.7)	146	1.9 (1.6-2.2)	19.3 (19.1-19.5)	87.7 (86.9-88.5)	178.7 (178.3-179.1)	27.4 (27.2-27.7)	2.06 (2.05-2.07)
Present smoker	2012	100	5.0 (4.1-6.0)	131	6.9 (5.8-8.1)	20.4 (20.2-20.7)	83.0 (81.9-84.0)	177.9 (177.3-178.4)	26.2 (25.9-26.5)	2.01 (2.00-2.02)
Smoking status unknown	17	0	0 (0, 2.0)	0	0 (0, 2.0)					

AAA: abdominal aortic aneurysm; IAD: infrarenal aortic diameter; BMI: Body Mass Index (kg/m²); BSA: body surface area (m²).
*AAA defined as an IAD≥30 mm; **rAAA defined as an IAD≥150% larger than predicted according to the individuals BSA (95% CI: within parentheses).

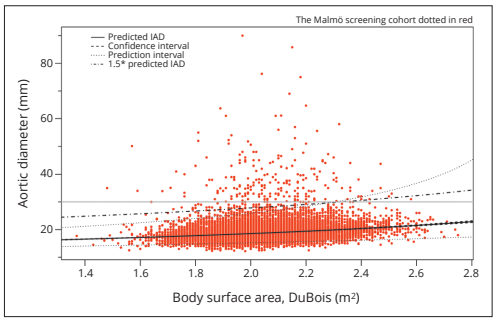

Figure 4.—Model to calculate the cut off diameter for AAA diagnosis using the relative criteria of a 150% widening of the predicted infrarenal aortic diameter according to the body surface area. The grey line represents the established criteria for AAA diagnosis (30 mm).

individual BSA (Figure 4). The difference in detection rate was more than 30% between the two definitions of a AAA and highly significant using McNemars Test (χ^2=68.321, df=1, P value <0.001) (Table II).

For the screening validation the US measurements (N.=237) was compared to their corresponding CT- or MRI-scans. There were 11 subjects (4.6%) with an infrarenal aortic diameter ≥30 mm in this group. A Bland-Altman analysis, as described under methods, was used and showed a mean of differences of 1.0 mm (95% CI: 0.6, 1.3 mm) smaller for US compared to the tomographic measurements with CT/MRI. The variability was 5.2 mm which is comparable to, or lower than earlier findings.[30, 31] No comparison was made between CT- and MRI-examinations.

Discussion

In this study, AAA prevalence at screening of 65-year old med increased from 1.5% to 1.9% (*i.e.* with 23%) when using individualized criteria for AAA based on the predicted IAD according to each individuals BSA as opposed to when using the traditional crude 30 mm criteria. Previous studies have examined the possibilities to individualize the diagnosis of a AAA.[16, 32] When it comes to the aorta, this kind of individualized definition is difficult, since the aorta normally have different diameters in different segments.[33, 34] It is also not uncommon to find a pathologic widening of more than just the abdominal segment of the aorta,[35] making it difficult to know which part of the artery to use as a reference. One way to circumvent this is to compare the IAD to another body measure, *e.g.* wrist circumference[16] and calculate an index. Another way would be to use the expected diameter of the IAD based on sex, age and body size that all have been shown to have an impact on IAD in several studies[14-20] and multiply that measure by 1.5 and thus refer to the original criteria of an AAA. This was proposed by Wanhainen *et al.*,[32] but they found a lower number of AAA using such criteria as compared to the crude diameter of 30 mm and above. The nomogram they used was based on 146 healthy volunteers[14] of both sexes and all ages and therefore all correlations were very strong but, however, not corrected for the fact that the IAD is not normally distributed. The correlation between IAD and BSA in subjects of both sexes and all ages also have different properties as compared to a correlation for subjects of the same age and sex. Another problem demonstrated in the very large study from 1997 by Lederle *et al.*[20] (a cohort of near 70.000 veterans of mixed ages and sex) was the large variability of between medical centers that performed ultrasound measurements, which cancelled out the effect of the body size to the expected IAD in a multivariate analysis.

We found a statistically significant correlation between IAD and BSA, which was comparable to earlier studies on the IAD such as those by Lederle *et al.*[20] and Pearce *et al.*[19] which both used elderly participants, as well as Rogers *et al.*,[15] from the Framingham study, with a younger population. There were no significant interaction effects between BSA and smoking status on the IAD found although it looks like it when analyzing the subgroups divided by smoking status (Figure 3).

IAD measurements are not normally distributed but positively (or right) skewed since there are quite a few large diameters and the measurements, for obvious reasons, cannot be negative to make the distribution symmetrical. The distribution has also a very high peak around the median which makes it less normal. In our study, we normalized the measurements to be able to perform a regression and build a prediction model. The prediction model gave all the par-

TABLE II.—*2 × 2 contingency table, which the McNemar Test is applied to. The test statistic is $\chi^2 = (b-c)^2 / b+c$. If the χ^2 result is significant it provides sufficient evidence to reject the null hypothesis which would mean that the marginal proportions are significantly different from each other. In this case. χ^2 =65.333, df=1, P<0.0001. N.=14,846.*

AAA≥150% widening	AAA≥30 mm widening	
	Yes	No
Yes	226 (a)	73 (b)
No	2 (c)	14545 (d)

Positive according to both definitions; positive according to relative definition but not crude definition; negative according to relative definition but positive according to crude definition; negative according to both definitions.

ticipants an individual AAA limit (1.5 times their predicted IAD according to their BSA). Their measured IAD was then compared to this limit to determine if a AAA defined as an IAD 150% wider than expected was present or not.

The ultrasonographic measurements were validated and showed a low mean of difference and a low variability despite that the examinations were not made at the same time and that this validation cohort (N.=237) consisted of 4.6% AAA which makes it more heterogenous. This shows a high accuracy for this standardized AAA detection screening program.

With standardized routines and a homogenous population in screening for AAA we found that the use of body size, *i.e.* the BSA, to individualize the criteria for diagnosis has an impact on detection rates that very well could be of clinical importance. The use of a crude ≥30 mm IAD definition of a AAA renders a diagnostic rate of 1.5% but the use of the relative definition of a IAD 150% wider than predicted according to the individual BSA renders 1.9% detected AAA. This difference was statistically highly significant. Those men that have a AAA according to the relative criteria and thus subjects of this diagnostic controversy will be followed up to see if they tend to develop AAAs more frequently than subjects with the same IAD but still not 150% wider than predicted. If this would be the case one has to figure out how to imply these individualized criteria for AAA in everyday practice. An ongoing discussion is at hand and the individualization of AAA criteria is under investigation not only by our group.[36]

Limitations of the study

The limitations of this study are that the investigated cohort is reasonably homogenous, *i.e.* of the same age and gender, and is derived from a limited geographical area, examined by one medical center. This must be born in mind and generalizations to other patients and other screening sites must be made with caution

The strength of this study is that the investigated cohort is reasonably homogenous, *i.e.* of the same age and gender, and is derived from a limited geographical area, examined by one medical center. This must though be born in mind and generalizations to other patients and other screening sites must be made with caution. An obvious limitation is that height and length measures are self-reported. There are contradictive findings regarding the accuracy for self-reported biometrics[21-24] and we have no internal validation of these biometrics in our study. Furthermore, another limitation of the present study is the potential risk of selection bias due to the fact that there was not a full adherence to invitation to the screening and the health questionnaire. Although it is hard to see how these shortcomings could strengthen the correlation between IAD and BSA. One could argue that aneurysmal aortas should be excluded but since the issue itself is the criteria for AAA it makes it difficult to decide what sizes of IAD to exclude. In Lederle's study from 1997 all IAD≥30 mm was excluded but we included also the larger diameters to ensure that subjects of a very large body size would not be disregarded. This did also not have any major impact on the degree of correlation using Spearman's rank correlation coefficient (rho) but rendered a lesser correlation using Pearson's R for obvious reasons.

Conclusions

We have found a statistically significant correlation between BSA and IAD in a large homogenous screening population that could have clinical implications. If this correlation would be used for a BSA-related criteria for AAA, it would identify significantly more patients (>30%) and discard a few (<2%) compared to the commonly used crude diameter-criteria of 30 mm. This could have an important clinical impact in the diagnosis of AAA.

Presently we are undertaking an ultrasound re-scanning program to verify these hereby presented new findings in diagnosing AAA. If BSA-related criteria for AAA would be proven clinically valuable this might suggest recording of biometrics such as length and height when screening for AAA to further refine screening standards.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors contributions.—Jan Holst and Anders Gottsäter conceived the study and were in charge of overall direction and planning; Joachim Starck analyzed the data with help and intellectual input from Fredrik Lundgren and acknowledged statisticians; Joachim Starck wrote the manuscript with input from all authors, mainly Jan Holst and H. Laura Aaltonen.

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Paper II

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ORIGINAL ARTICLE
AORTIC DISEASE

Abdominal aortic aneurysm growth rates are not correlated to body surface area in screened men

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ABSTRACT

Background: Screening for abdominal aortic aneurysm (AAA) in 65-year-old males reduces aneurysm related mortality. Infrarenal aortic diameter (IAD) has been shown to correlate to body surface area (BSA) which could influence diagnostic criteria for AAA. This study investigates whether AAA growth rates are also dependent on BSA, as that might have potential effects on surveillance of small AAAs.

Methods: We conducted a retrospective, single center cohort study of 301 men with screening detected AAA between 2010-2017 with surveillance to 2021. AAA growth rates were analyzed in relation to the subject's BSA, smoking habits, and diabetic disease using a linear mixed-effects model. All men were offered smoking cessation program, optimized medical treatment, and advice on physical activity.

Results: The screening program included 28,784 men. Of the 22,819 (79%) attending the examinations, 374 men (1.6%) were found to have an AAA out of which 301 men had undergone two or more examinations during surveillance and were included with a median follow-up of 1846 days (IQR: 1 399). Mean unadjusted AAA growth rate was 1.60 mm/year (95% CI: 1.41-1.80). Diabetes mellitus had a statistically significant negative impact, smoking had a statistically significant positive impact on AAA growth rates whereas no correlation between AAA growth rate and BSA could be found.

Conclusions: Body surface area could not be found to have a statistically significant correlation to AAA growth rates. The impact of smoking and diabetes on AAA growth rates remains similar to previously reported.

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Key words: Aortic aneurysm, abdominal; Growth; Mass screening; Male.

An abdominal aortic aneurysm (AAA) is defined as a localized widening of the infrarenal aortic diameter (IAD), ≥30 mm.[1] An AAA expands slowly over the years and poses a substantial risk for rupture if it reaches 55-60 mm which could be fatal.[2] AAA diameter is the only validated predictor of rupture although other predictors have been suggested.[3, 4] Active smoking increases AAA growth rates and the presence of diabetes mellitus decreases growth rates.[5] To date no class of drugs has proven to reduce AAA growth rate although metformin is a promising candidate.[6] AAA is common with a prevalence of 1.7-3.3% in elderly men[7] and has a latent asymptomatic phase during which it can be reliably detected with ultrasonography (US).[8] AAA screening has convincingly been shown to reduce aneurysm related mortality[9-12] and is advocated in current European guidelines for the management of AAA.[7]

Screening requires adequate diagnostic criteria.[13] In an earlier study we found a statistically significant correlation between the normal IAD and body surface area (BSA), potentially implying individualization of AAA diagnosis.[14] Screening also requires an adequate understanding of the natural history of the condition. Therefore, we aimed to find out whether the individual BSA also could be correlated to AAA growth rate, besides the known factors - current smoking and diabetes mellitus, to such an extent that it would have an impact on surveillance programs.

Materials and methods

This study was approved by the ethics committee of Lund University (LU 2010/239), Sweden.

Study population

The Department of Vascular Diseases, Skåne University Hospital, Malmö (a tertiary vascular surgical center with a primary catchment population of about 650,000 people) has a single AAA screening facility. In conjunction with the start of a screening program for AAA in Malmö in 2010, a research project was launched to study epidemiological aspects on both aneurysmal and atherosclerotic disease.[15-17] All 65-year old men in the catchment area (identified through the national population-based registry, www.skatteverket.se) were invited to this screening program and the research project and those who accepted this invitation between 2010 and 2017 were recruited to the present study, as previously described.[14] Those who accepted the invitation to the research project were asked to fill out a written health questionnaire, including height, weight, smoking habits, medication, and comorbidities. Additional information was collected from the medical records at the time for entry into the surveillance program. Smoking habits were divided into current smokers and non-smokers with previous smokers and never smokers included in the latter group as in earlier studies.[5] Pack years or date of smoking cessation were not recorded.

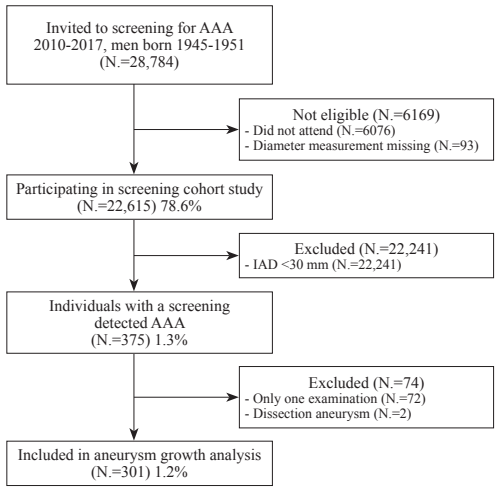

Figure 1.—Study design.

Ten subjects in this study were part of a randomized control trial concerning the possible effects of ticagrelor on aneurysmal growth[18] and since no effect was found, the patients were not excluded in the present study. 98 subjects in this study were part of a retrospective case-control study that showed an association between metformin prescription and reduced AAA growth.[19]

Study design is presented in Figure 1.

Screening and surveillance examinations

The measuring method used was leading-edge-to-leading-edge technique,[20] which is the standard method in Swedish screening programs.[21] After identifying the maximal IAD in the longitudinal plane, the maximal anterio-posterior IAD was measured in the transverse plane perpendicular to the direction of flow. Validation of the US exams is described previously.[14] Upon inconclusive US measurement a computed tomography (CT) of the aorta was conducted and was used for all following surveillance examinations

in those individuals. Previous studies have shown CT imaging to estimate IAD significantly larger than US though no effect on growth rates[5] why modality was not included in the analysis. All imaging results, both from US and CT, were electronically saved in the radiology information system (Sectra RIS, Linköping, Sweden. www.sectra.com).

Surveillance program

Subjects found to have a maximal IAD≥30 mm were offered a consultation with a vascular physician and invited to surveillance.[17] The patient's medical treatment was optimized according to European guidelines for cardiovascular risk reduction,[7] and, if smoking, was offered a smoking cessation program conducted regionally.[22] The patient was also encouraged to physical activity. Surveillance examinations were free of charge and until 2018 conducted at the vascular department and after 2018 the department of Clinical Physiology at the same hospital with the same standards and routines. Surveillance intervals were determined by aneurysm size: 30-34 mm: 3 years, 35-40 mm: 2 years, 41-45 mm: 1 year, 46-50 mm: 6 months, >51 mm: 3-6 months. The surveillance examinations were evaluated by a vascular surgeon and when AAA size was found to be approaching 55 mm a visit was offered with the purposes of information and evaluation of the possibilities for prophylactic surgery to prevent rupture.

Statistical analysis

The timescale for the growth analysis was set to days from screening divided by 365.25 to be presented as years. Since the subjects were followed with examinations at different time points the data was unbalanced. A quadratic, linear mixed-effects (LME) model was fitted by maximum likelihood with measurements nested within subjects using IAD, *i.e.* AAA diameter, as the dependent variable and time (observational years) as the independent variable to allow for non-linear growth. BSA, diabetes, smoking habits at time for screening, and screening diameter of the AAA were used as independent, fixed covariables as interaction terms with the linear component of time to investigate their potential influence on growth rate. First in an unadjusted analysis, one factor at a time and secondly in an adjusted, multivariable analysis. Medication initiated at time for screening was not included in the growth analysis since no class of drugs have been proven to influence AAA growth rates.[7] The IAD as well as BSA were considered normally distributed using QQ-plots and the variance of IAD was considered homogenous using a residual plot (Supplementary Digital Material 1: Supplementary Text File 1). Missing values were deleted listwise. With over 200 individuals and four covariables we expected to detect a small effect size with a power of more than 90%. The statistical analyses were performed using R statistical programming environment (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/) and the LME model was fitted using the lme4 package.[23] Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) was used as a database.

Results

Screening cohort

Out of the 28 784 men born 1945-1951 invited at 65 years of age to the screening program from 2010 to 2017, 22 819 (79%) accepted the invitation and attended the screening examination. Of these, 374 (1.6%) men were found to have an IAD of ≥30 mm, 124 (0.5%) had an AAA≥40 mm, 42 (0.2%) had an AAA≥50 mm, and 28 (0.1%) had an AAA≥55 mm. 44 (13%) of these AAAs were previously known and 3 had had AAA-repair prior to the screening examination. The mean screening diameter was 36.5 (SD 5.7) mm.

Surveillance cohort

From the screening cohort 303 men were followed in surveillance (including one subject with normal IAD at screening that were accidentally found to have an AAA on a CT scan 18 months after screening) and underwent two or more examinations between October 2010 and April 2021. Two patients had aneurysms due to dissection and were excluded from the growth analysis and the others had an AAA diameter that was indicative for surgical repair or had had AAA-repair prior to screening. Data on BSA were available for 219 (73%) and data on smoking habits for 287 (95%). Medication, comorbidities, and smoking status at time for screening are presented in Table I. Surveillance was conducted with US except for nine individuals that for technical reasons, as described in methods, were followed by CT.

In total, 301 subjects underwent 1546 observations used for analysis of mean AAA growth and 242 subjects with complete data on smoking habits, diabetes mellitus, and BSA underwent 1236 observations used for multivariable analysis on factors influencing AAA growth (Figure 1).

Follow-up time ranged from 189 to 3662 day (median 2158, IQR 1083) days. Median number of examinations per individual were 4 (IQR 4, range: 2-14). Median sur-

TABLE I.—*Description of the surveillance cohort, N.=301.*

Characteristics	Values	Missing data (%)
Age at screening, years [mean (SD)]	65.4 (0.5)	0 (0)
Height, cm [mean (SD)]	179.3 (6.3)	70 (23)
Weight, kg [mean (SD)]	91.1 (15.6)	82 (27)
BSA, m^2 [mean (SD)]	2.10 (0.18)	82 (27)
BMI, kg/m^2 [mean (SD)]	28.3 (4.4)	82 (27)
AAA screening diameter, mm [mean (SD)]	36.5 (5.7)	0 (0)
Screening detected AAA, yes (%)	267 (88.7)	0 (0)
Number that underwent surgery (%)	83 (27.6)	
IAD at time for AAA repair, mm (median [IQR])	55.00 [52.7, 56.5]	-
Medication		
Antihypertensive treatment. N. (%)	229 (77)	2 (0.7)
Lipid lowering treatment, N. (%)	255 (85)	2 (0.7)
Platelet aggregation inhibitor, N. (%)	209 (70)	3 (1)
Anticoagulant treatment, N. (%)	33 (11)	3 (1)
Metformin treatment, N. (%)	39 (13)	2 (0.7)
Low density lipoprotein (LDL) levels, mmol/L[a] (median [IQR])	1.90 [1.60, 2.50]	98 (33)
Comorbidities		
Diabetes mellitus, N. (%)	62 (24)	40 (13)
Heart disease, N. (%)[b]	122 (41)	35 (12)
Renal insufficiency, N. (%)[c]	69 (23)	21 (7)
Pulmonary disease, N. (%)[d]	42 (14)	32 (11)
Cerebrovascular event, N. (%)	36 (12)	45 (15)
Cancer, N. (%)[e]	55 (18)	43 (14)
Smoking status [f]		14 (5)
Never ever smoker, N. (%)	17 (6)	
Previous smoker, N. (%)	150 (52)	
Current smoker, N. (%)	120 (42)	

Mean is reported for normally distributed variables and median for non-normally distributed variables.
[a]Last noted LDL-level (mmol/L) at medical record review; [b]previous cardiovascular event, atrial fibrillation, or heart failure (New York Heart Association class I-IV); [c]Estimated Glomerular Filtration Rate (Creatinine) <60 mL/min/1.73 m^2 [40, 41] at screening; [d]chronic obstructive pulmonary disease (COPD) and/or asthma; [e]cancer diagnosis noted in patient records; [d]at screening.

veillance interval was 347 days (IQR 540, range 35-2513). Non-smokers had a small but statistically significant higher mean BSA of 2.12 (95% CI: 2.11-2.13) m^2 compared to current smokers, whose mean BSA were 2.06 (95% CI:, 2.05-2.08) m^2 using Welch two sample *t*-test (t=6.04, 1043.1 df, P<0.001). Due to severe comorbidity, ten men were exempted from surveillance or were followed with image surveillance at the patients request without intention to treat. All these were deceased at five years; two died from ruptured abdominal aortic aneurysm (rAAA) and another two from unknown causes. Six men actively chose not to pursue surveillance, two of these were deceased from non-aneurysm-related causes at time for this investigation. One screening detected AAA was found to be <30 mm (28 mm) during surveillance, and was therefore discontinued with informed consent from the subject. Seven men moved out of the catchment area and three of these were referred to another vascular center. Of the 47 deaths (15%) during surveillance, one was due to rAAA and two due to unknown causes, the remaining were not aneurysm-related. One man survived acute aortic repair due to rAAA eight months after screening detection of a 46 mm AAA, and two men underwent subacute repair due to symptomatic aneurysms during surveillance. Nine men (3%) were lost to follow-up despite repeated summonses, all alive at the time for this analysis according to the Swedish population registry. Of all screening detected AAA (N.=374) 121 men (32%) underwent elective aneurysm repair during surveillance with a median time from screening to surgery of 48.7 (IQR 35.7) months and a median IAD at the last surveillance examination before surgery of 55 mm (IQR 4.25).

Growth analysis

Mean, unadjusted aneurysmal growth rate was found to be 1.60 mm/year (95% CI: 1.41-1.80, P<0.001) with a statistically significant quadratic factor of 0.04 mm/year (95% CI: 0.03-0.06, P=0.001) (Supplementary Text File 1). Un-

TABLE II.—*Impact on growth rate in screening detected AAAs, unadjusted and adjusted.*

	Unadjusted				Adjusted			
	N. of subjects	Estimate (mm/year)	95% CI	P value	N. of subjects	Estimate (mm/year)	95% CI	P value
Screening diameter (mm)	301	0.11	0.07-0.14	<0.001	242	0.11	0.08-0.15	<0.001
Smoking (current *vs.* ex/never smoker	287	0.61	0.26-0.96	0.001	242	0.69	0.34-1.05	<0.001
Diabetes mellitus (yes *vs.* no)	261	-0.58	-1.00 to -0.16	0.006	242	-0.91	-1.32 to -0.50	<0.001
BSA (per m^2)	285	-0.33	-1.31 to 0.65	0.514	242	0.75	-0.21 to 1.71	0.126

adjusted analysis of each cofactor showed that diabetes mellitus was associated with a statistically significant lower growth rate and current smoking was associated with a statistically significant higher growth rate compared to non-smokers (*i.e.*, previous and never smokers) (Table II). Baseline AAA diameter at time for screening had a smaller, statistically significant positive impact on growth rate. BSA, however, did not have any statistically significant influence on growth rate.

In a multivariable, quadratic LME-model with diabetes mellitus, smoking, screening diameter, and BSA as cofactors interacting with time, growth rate was estimated to 1.44 mm/year (95% CI: 1.17-1.71, P<0.001) with a quadratic component of 0.03 mm/year (95% CI: 0.01-0.05, P=0.003). Diabetes present at screening had a statistically significant negative influence whereas current smoking had a statistically significant positive influence on aneurysmal growth rate. BSA did not show any significant impact on growth rate in the adjusted analysis (Table II). The overall regression analysis with prediction intervals is plotted in Figure 2. Individual growth measurements for the nine individuals with the longest surveillance are plotted in Figure 3 with the prediction from the LME-model superimposed.

Discussion

Analyzing and understanding the natural history of AAA is central for a robust screening and surveillance program[13] as well as in the quest for finding ways of controlling the disease. The expansion rate of AAA is complex and difficult to model since measurements of IAD in a surveillance

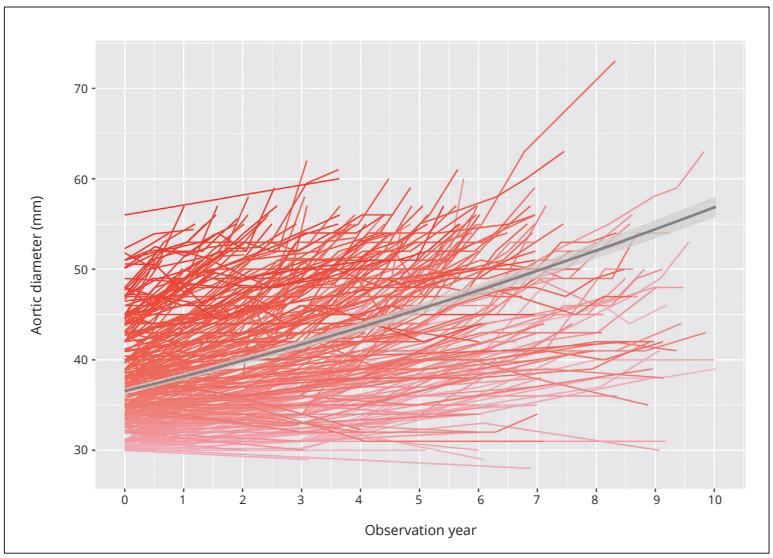

Figure 2.—AAA diameters of all subjects plotted individually with the linear mixed-effects model including 95% confidence intervals superimposed in grey.

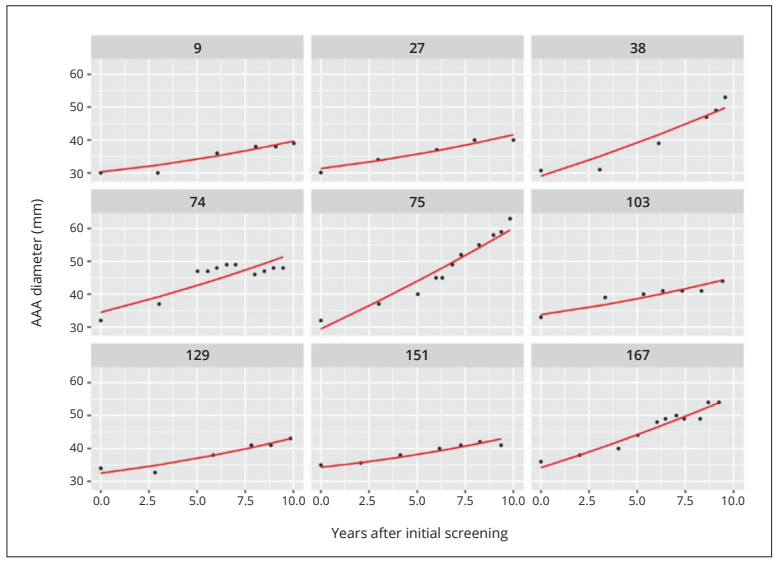

Figure 3.—The nine subjects with the longest surveillance identified by the figures on top of each plot. Black dots represent measured IAD and the red curves represent the predicted growth curves for each subject derived from the linear mixed-effects model with random intercepts and random slopes.

program are done in different phases of growth and at different intervals for each individual. There are also both inter-individual and inter-observer variance to take into account. Many growth models for AAA have been proposed; Limet *et al.*[24] reported in 1991 that median expansion rate of small AAAs (35-55 mm) was exponential which is close to the 10% yearly increase in AAA diameter reported by Cronenwett *et al.* in 1990.[25] Aneurysms also display different growth patterns[26, 27] and 3D profiling detecting sub-maximum growth has been suggested to be taken into consideration in surveillance of small aneurysms[28] since surveillance is conducted using a two-dimensional method (US) measuring a three-dimensional structure (AAA). Also comparing growth rates between studies is difficult as growth rate can vary substantially depending on the method used for its estimation.[5] In recent years, longitudinal, linear mixed-effects models with the measurements nested within the individuals as a random effect have been used to describe aneurysmal growth[29-31] which can accommodate both unbalanced data and inter-observational variances. In this study we used a random-effects quadratic growth model allowing for individual baseline diameters (intercepts) and slopes with factors known to affect AAA growth rates together with the unknown BSA as fixed effects. Baseline AAA diameter was introduced as a fixed covariable to account for the presumed correlation between AAA development and body habitus[32, 33] since this study analyses AAA growth and not AAA development. We chose BSA over BMI since this variable reflects the stature and built of a person rather than the person's body fat mass. The correlation between AAA growth and body habitus has sparsely been investigated in earlier studies; higher BMI was shown to reduce growth rate marginally in an unadjusted analysis from 2012[5] and height correlated weakly to lower growth rate in another study from 2017.[34] Since AAA growth is correlated to the aneurysmal diameter[7] and IAD seems to be correlated to BSA[14, 35] one could argue that a 35-mm AAA in a small person would be more prone to expand than an AAA of the same size in a large person.

However, this study showed no statistically significant correlation between AAA growth rate and BSA and we believe it was sufficiently sized to rule out a clinically significant correlation that could have an impact on the surveillance of AAAs. Furthermore, neither BMI nor subdividing BSA or BMI into quantiles had any statistically significant impact on AAA growth rates. When height of the subjects in this study were divided into quartiles, a significant positive impact on aneurysmal growth rate by 0.2 mm/year (95% CI: 0.00-0.41, P=0.047) for each quartile was found. As this seems contradictory to the aforementioned find-

ings, further studies in this area would be of interest. The only factors that so far have been found to have a correlation to AAA growth rate are diabetes and current smoking as no class of drugs, nor any lifestyle interventions have proven to have an effect on AAA growth rates.[7] This study confirmed those findings.

Limitations of the study

The investigated cohort was homogenous, *i.e.*, of same age and gender, derived from a limited geographical area, and examined at one medical center which constitutes both limitations and strengths of the study. In a screening cohort it is well known that the attendants might be of higher socio-economic status,[36] and therefore both lower prevalence and severity of disease may be expected. Generalizations to other patient groups and other screening sites should therefore be made with caution, also as this is a retrospective cohort study. Another limitation is that weight and height measures were self-reported without internal validation as there are contradictive findings regarding the accuracy of self-reported biometrics.[37-39] Data on comorbidities, medication and smoking habits were registered at the time of screening. As this was not a prospective study adherence to medication or lifestyle interventions were not recorded. Smoking habits were divided into two categories, not taking quantitative exposure to tobacco such as pack-years into account and could be a confounding factor as non-smokers had a statistically significant higher BSA than current smokers.

Conclusions

As BSA had no statistically significant impact on AAA growth, it is of no clinical importance when designing a AAA surveillance program.

The impact of smoking and diabetes on AAA growth rates were similar to previously reported. Reporting standards on AAA growth rates are warranted in the quest for understanding the natural history of AAA and factors that could slow aneurysm progression.

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Paper III

Predictors of abdominal aortic aneurysm progression in men with small infrarenal aortic diameters at screening

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ABSTRACT

Objective: Screening for abdominal aortic aneurysm (AAA) defined as an infrarenal aortic diameter (IAD) of ≥30 mm reduces mortality, but managing patients with diameters of 25 to 29 mm is debated. Incorporating body surface area into the diagnostic criteria may improve the identification of those at risk of developing treatment-requiring aneurysms in this group. In a previous study, we defined a relative AAA as an IAD ≥150% larger than expected, with the normal diameter calculated using body surface area as a scaling factor. This study aimed to determine if this criterion could identify those at risk of aneurysmal development among patients with aortic diameter of 25 to 29 mm at screening.

Methods: A cohort study was conducted on men with abdominal aortic diameters of 25 to 29 mm at AAA screening in Malmö, Sweden, with a median follow-up of 9.9 years. Growth rates were compared between the relative aneurysm group and the nonrelative aneurysm group using a linear mixed-effects model to account for both fixed and random effects. Time and hazard ratio to reach 40 mm, a marker of significant aneurysmal progression, were assessed using a log-rank test and a Cox proportional hazards model, both adjusted for smoking status and diabetes.

Results: In a cohort of 270 men, three developed AAAs ≥55 mm. The baseline growth rate was 0.1 mm/year (95% confidence interval [CI], 0.0-0.3). Growth rates were increased by 0.4 mm/year (95% CI, 0.0-0.7) in the relative aneurysm group, and by 0.4 mm/year (95% CI, 0.2-0.7) in smokers. The median time to reach an IAD of ≥40 mm was 11.5 years for relative aneurysms and was not reached for those without, with a significant difference shown by a log-rank test stratified for smoking ($P = .009$). Hazards ratio to reach an IAD of ≥40 mm for relative aneurysms was 2.77 (95% CI, 1.34-5.74; $P = .006$) compared with those without.

Conclusions: In men with diameters of 25 to 29 mm at screening for AAAs, the use of an individualized diagnostic criterion, based on height and weight, could identify those with increased aneurysm growth and a significantly shorter time to reach 40 mm compared with baseline. The relative aortic diameter, beyond the absolute diameter, seemed to be important for aneurysmal development. However, the differences were likely too small to warrant changes in clinical practice, highlighting the need for further research to establish clinical relevance. (J Vasc Surg 2025;81:1309-18.)

Keywords: Male; Aortic aneurysm; Abdominal; Mass screening; Growth rate

Screening for abdominal aortic aneurysm (AAA) in men >65 years of age reduces AAA-related mortality, as demonstrated in three out of four large, controlled randomized trials,[1-4] in a meta-analysis,[5] in a national evaluation of the introduction of an AAA screening program,[6] and is recommended in major guidelines.[7,8] The diagnostic criterion for AAA used in these studies was a fixed infrarenal aortic diameter (IAD) of ≥30 mm, which prompts surveillance owing to the significant risk of developing treatment-requiring AAA. This criterion is based on the definition of an arterial aneurysm as a localized dilation of 150% larger diameter than expected as the mean IAD in men of this age has been shown to be about 20 mm.[9] This criterion is also used in the AAA screening program offered by National Health Service in the UK.[10] The screening program was only offered to men in accordance to the guidelines from the European Society for Vascular and Endovascular Surgery, as well as

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the National Board of Health in Sweden at the time, owing to the much lower AAA prevalence in women.[7]

Studies have shown that more than one-half of men with an IAD of 25 to 29 mm at screening exceed the 30-mm threshold within 5 years, and 10% to 30% reach 55 mm (the recommended diameter for prophylactic intervention) within 10 years.[11,12] This evidence has led European guidelines to sharpen the recommendation of surveillance of subaneurysmal aortas starting at 25 mm, upgrading from Class IIb to Class IIa, Level B.[13] However, aneurysm ruptures are relatively rare in this group[14] and evidence regarding the cost-effectiveness of surveillance is limited.[15,16]

Refining AAA diagnostic criteria to identify individuals with an IAD of 25 to 29 mm at risk of developing significant aneurysms (IAD ≥55 mm) would be beneficial, allowing a clearer distinction between those at risk and those considered healthy. In a previous study, we identified a significant correlation between body surface area (BSA) and IAD in men screened for AAA between 2010 and 2017. An increase of 1 m^2 in BSA was associated with an approximate 4.6 mm increase in IAD, predicting the expected IAD relative to BSA.[17] An AAA related to BSA was thus diagnosed when the IAD exceeded 150% of the predicted IAD according to BSA. This approach adjusts the diagnosis for different body sizes, ensuring that the aorta is compared with an individualized standard rather than a fixed threshold for everyone (Fig 1). In the current paper, we define the term *body surface area-related abdominal aortic aneurysm* (BSA-related AAA) to refer specifically to these individually diagnosed abdominal aneurysms.

There is evidence that smoking is linked to increased AAA growth, whereas diabetes is associated with reduced growth.[17] However, the role of arterial diameter in relation to body habitus is not elucidated fully. The aim of this study was to investigate whether the BSA-related AAA criterion could identify individuals with an IAD of 25 to 29 mm at AAA screening who are at increased risk of developing a clinically significant AAA, considering known risk factors for aneurysmal growth, including initial screening diameter.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, observational, cohort study
- **Key Findings:** We followed 270 men who were screened for abdominal aortic aneurysms with infrarenal aortic diameter of 25 to 29 mm for 10 years. Men with aortic diameter ≥150% of expected based on height and weight, showed a growth rate similar to small aneurysms (30-35 mm). They also reached 40 mm significantly faster than the rest ($P = .009$).
- **Take Home Message:** Aortic diameter relative to body surface area, beyond the absolute aortic diameter alone, was important for aneurysmal development. However, the differences were too small to determine reliably which individuals with an aortic diameter of <30 mm at screening are at significant risk of developing clinically relevant aneurysms.

METHODS

This study was approved by the ethics committee of Lund University (LU 2010/239) and the Swedish ethical review authority (Dnr 2019-05,788 and 2023-02,037-02). Written consent was obtained from all participants.

Setting. The Department of Vascular Diseases at Skåne University Hospital in Malmö operates a single AAA screening facility for a catchment population of 650,000. All men aged 65, identified through the national registry (skatteverket.se), were invited to screening. Those diagnosed with an AAA (IAD ≥30 mm) were offered surveillance in accordance with guidelines[7] at the time. Surveillance was initiated with a doctor's visit to provide information, optimize medical treatment, and offer life style advice. This was followed by ultrasound scans every 3 years for AAA ≤40 mm, every year for AAA 40 to 50 mm, and every 6 months for AAA measuring ≥50 mm. When an AAA approached 55 mm, the participant was offered surgery if applicable. Those with an IAD of <30 mm were considered at low risk of developing an AAA and were not offered surveillance. All screening participants were encouraged to join a research project on AAA disease and atherosclerosis epidemiology[18] and complete a health questionnaire covering height, weight, smoking, medication, heredity, and medical history. All data were self-reported. Loss to follow-up from the regular surveillance program was very low (3%), with one death owing to a ruptured AAA in a patient being evaluated for lung cancer.[19]

Study population. This study included men from the AAA screening program described above, conducted between 2010 and 2017, who had an IAD of 25 to 29 mm, had completed a health questionnaire, and would not normally have been enrolled in surveillance. Invitations with prebooked appointments were mailed, allowing for rescheduling, and missed appointments prompted follow-up invitations. Subjects were categorized as smoker/nonsmoker, diabetes/nondiabetes, and BSA-related AAA/non-BSA-related AAA with the latter classification based on the individual IAD and BSA. Heredity was defined as a self-reported family history of first- or second-degree relative with aneurysmal disease. All epidemiological data were collected from the health questionnaires at time for initial screening (Table I).

From the screening program described under Setting, measurements from men under surveillance with small AAAs (30-35 mm) were included for comparison with BSA-related AAA, provided that data on height and

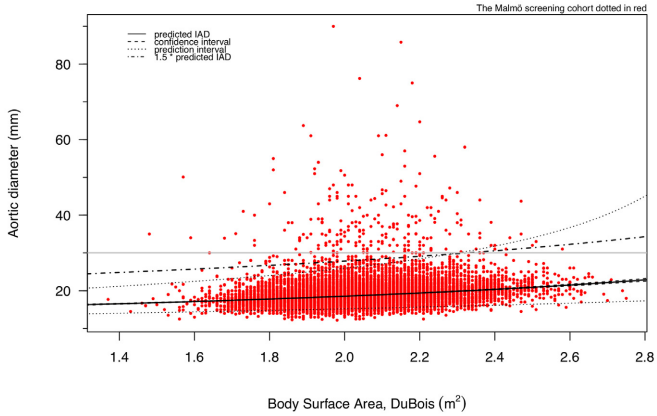

Fig 1. Model to calculate the cut off diameter for abdominal aortic aneurysm (AAA) diagnosis using the relative criteria of a 150% widening of the predicted infrarenal aortic diameter (*IAD*) according to the body surface area (BSA-related AAA). Data from 18,302 AAA screening participants from 2010 to 2017 with information on height and weight, were used to predict the individual threshold diameter for BSA-related AAA. The grey line represents the established criteria for AAA diagnosis (30 mm).

Table I. Baseline characteristics at initial AAA-screening of men attending re-examination study (infrarenal aortic diameter [IAD] ≥25-30 mm)

Characteristics	All	Non-BSA-related AAA	BSA-related AAA	Test statistic, BSA-related vs non-BSA-related AAA, *P* value
No.	270	232	38	
Age at screening, years	65.2 (65.0 65.5)	65.1 (65.0 65.5)	65.3 (65.2 65.5)	<.01[a]
AAA ≥55 mm during follow-up	3/270 (1%)	1/232 (0)	2/38 (5)	.05[c]
Infrarenal aortic diameter at initial screening, mm	26 (25 27)	26 (25 27)	28 (27 29)	<.01[a]
BSA, m^2	2.1 (2.0 2.2)	2.1 (2.0 2.2)	1.9 (1.9 2.0)	<.01[a]
Smoking	51/270 (19)	39/232 (17)	12/38 (32)	.05[b]
Diabetes	30/248 (12)	28/214 (13)	2/34 (6)	.36[b]
Lower extremity arterial disease	8/243 (3)	6/209 (3)	2/34 (6)	.31[c]
Cardiovascular disease	53/251 (21)	44/214 (21)	9/37 (24)	.76[b]
Cerebrovascular disease	18/250 (7)	16/216 (7)	2/34 (6)	.99[b]
Hypertension	121/254 (48)	108/218 (50)	13/36 (36)	.19[b]
Renal insufficiency	2/249 (1)	2/215 (1)	0/34 (0)	.97[c]
COPD/asthma	21/248 (8)	19/214 (9)	2/34 (6)	.64[c]
Malignancy diagnosis	24/252 (10)	21/216 (10)	3/36 (8)	.96[c]
Lipid lowering medication	68/225 (30)	58/192 (30)	10/33 (30)	.99[b]
Heredity for aneurysmal disease	36/256 (14)	30/220 (14)	11/75 (15)	.82[b]

AAA, Abdominal aortic aneurysm; *BSA*, body surface area; *BSA-related AAA*, body surface area related abdominal aortic aneurysm; *COPD*, chronic obstructive pulmonary disease.
Continuous variables are presented in median (first and third quartile). Categorical variables are presented as numbers/complete observations and percentage, n/N (%).
Heredity is defined as self-reported first- or second-degree relative with history of aneurysmal disease, not further specified.
Lipid-lowering therapy consists exclusively of statins.
[a]Wilcoxon rank-sum test with continuity correction.
[b]Pearson's χ^2 test with Yates' continuity correction.
[c]Fisher's exact test for count data.

weight were available. Men who did not meet the criteria for BSA-related AAA in this group were excluded from this analysis.

Ultrasound examinations. Participants were asked to fast for 4 hours before examination to improve ultrasound visibility of the aorta. The superior mesenteric and iliac arteries were identified, and the widest IAD was measured three times using leading-edge-to-leading-edge technique[20] in the transverse plane. All examinations were conclusive using a LOGIQ e machine with a 3.5-MHz probe (General Electric Healthcare Inc, Chalfont St. Giles, UK). The examination methodology was the same as during initial screenings and has been previously validated.[17] Examinations were conducted by a single examiner (J.S.), with initial screening diameter and potential BSA-related AAA diagnosis undisclosed.

Analysis of nonrespondents. A search within the Swedish National Registry for Vascular Surgery, Swedvasc (www.ucr.uu.se/swedvasc), and local medical records was conducted to document all interventions for, or ruptures of, AAA among nonattending men.

Growth analysis. BSA was computed using the DuBois and DuBois formula[21]: $BSA = weight^{0.425}(kg) \times height^{0.725}(m) \times 0.007184$. IAD measurements were expressed in millimeters with one decimal point accuracy. Time was recorded as days divided by 365.25 to be presented as years. BSA-related AAA was defined as an IAD exceeding 150% of the expected diameter based on the person's BSA as detailed in Starck et al[17] (Fig 1). Missing data were imputed with a decision tree model trained by bootstrap aggregating, using "bagImpute" model in the Caret package in R.

Growth analysis used a linear mixed effects model owing to unbalanced data, with IAD as outcome and observation year as explanatory variable. Measurements were nested within individuals as a random effect term. Fixed covariates included BSA-related AAA, smoking, diabetes, lipid-lowering medication (exclusively statins), heredity (first- and second-degree relative), and initial screening diameter centered by subtracting the mean. Covariates were introduced as interaction terms with time analyzing growth changes. QQ plots confirmed a normal distribution of IAD measurements, and residual plots showed an even distribution.

Unadjusted overall IAD growth was calculated in a univariate regression. Baseline IAD growth was calculated in a multivariable regression with covariables absent, centered on the initial screening diameter, and designated as such. Partial residual plots were used to visualize the impact of BSA-related AAA on IAD growth for smokers and nonsmokers, which helps to isolate the influence of the covariable of interest after accounting for other explanatory variables.

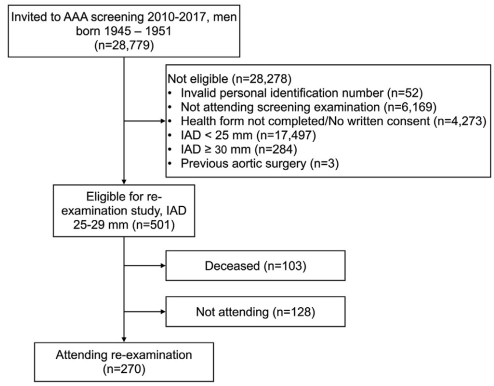

Fig 2. Consort diagram of study protocol. Exclusion criteria stated in order. Deceased: rAAA 1; malignancy 39; cardiac disease 19; infection 11; pulmonary disease 5; stroke 4; general morbidity 3; type A dissection 2; ruptured thoracic aortic aneurysm 1; ruptured AAA 1; no specific cause 17. *AAA*, abdominal aortic aneurysm; *rAAA*, ruptured AAA; *IAD*, infrarenal aortic diameter; *FU*, follow-up.

Nonparametric cumulative curves were calculated for time to reach an IAD of ≥40 mm after initial screening. An IAD of ≥40 mm was chosen as a marker of significant AAA progression and as a threshold for more intense surveillance intervals.[22] Censoring was applied at last measurement for those not reaching this threshold. A log-rank test analysed differences in time to reach an IAD of ≥40 mm between the BSA-related AAA and non-BSA-related AAA groups, stratified by smoking. A multivariable Cox proportional hazards model was used to assess the hazard ratio, adjusting for covariables with a significant impact on growth rates—specifically, smoking in this study. Two Kaplan-Meier graphs plotted predicted proportions of men progressing to an IAD of ≥40 mm, one for smokers and one for nonsmokers. The proportional hazards assumption was not violated.

To achieve >80% statistical power for detecting clinically relevant effect sizes specifically, a >30% difference in growth rate between the study groups during the follow-up period, a sample size of approximately 50 individuals plus controls was required, which was not entirely met. Variables and end points were selected beforehand based on clinical considerations.

Statistical analysis was conducted using R software, version 2022, provided by the R Core Team (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). The LME model was fitted using lme4-package, and a regression plot was made using the visreg-package.[23] The proportional hazards model was fitted using the survival-package.

Table II. Linear mixed effects model fit by restricted maximum likelihood; Multivariable analysis of growth rates IAD ≥25-29 mm (n = 270)

	Estimated growth, mm/year (95% CI)	SE	*P* value
Baseline IAD growth	0.05 (−0.55 to 0.65)	0.068	.870
Initial screening diameter (per mm increase)	0.02 (−0.09 to 0.12)	0.054	.767
BSA-related AAA	0.39 (0.03 to 0.75)	0.183	**.032**
Smoking	0.43 (0.18 to 0.68)	0.127	**.001**
Diabetes	−0.12 (−0.44 to 0.20)	0.164	.463
Lipid-lowering medication	0.03 (−0.19 to 0.26)	0.116	.767
Heredity	−0.02 (−0.30 to 0.27)	0.145	.900

AAA, Abdominal aortic aneurysm; *BSA*, body surface area; *BSA-related AAA*, body surface area-related abdominal aortic aneurysm; *CI*, confidence interval; *IAD*, infrarenal aortic diameter; *SE*, standard error.
Boldface entries indicate statistical significance.
Heredity is defined as self-reported first- or second-degree relative with history of aneurysmal disease, not further specified.
Lipid-lowering therapy consists exclusively of statins.
Baseline IAD growth represents IAD growth in the absence of the risk factors such as BSA-related AAA, smoking, and diabetes, with the screening diameter centered by its mean. The estimated growth rates for each risk factor indicate their respective additional effects on baseline growth.

RESULTS

Cohort description. There were 28,779 men aged 65 years invited to the AAA screening program between 2010 and 2017, of whom 22,567 (78.4%; 95% confidence interval [CI], 77.9-78.9) attended; 18,303 men (63.6%; 95% CI, 63.0-64.2) also completed a health questionnaire and thus were eligible for this study. In this group, 284 (1.5%; 95% CI, 1.4-1.7) were found to have an AAA (defined as an IAD of ≥30 mm), and 501 (2.7%; 95% CI, 2.5-3.0) had an IAD of 25 to 29 mm.

At follow-up, 102 men (20.4%; 95% CI, 17.0-24.2) had died, with 1 death attributed to a ruptured AAA. The latter was measured at 27 mm at the initial screening and did not meet the criteria for BSA-related AAA. A computed tomography examination performed 5 years later measured the AAA at 40 mm. The patient was subsequently lost to follow-up and was found deceased 2.5 years later, unobserved. An autopsy revealed a ruptured AAA measuring >12 cm. The remaining deaths were determined to be unrelated to AAA disease.

Including nonrespondents and deceased (n = 501), there were significant differences observed between BSA-related AAA and non-BSA-related AAA in terms of age, IAD, BSA, and smoking at initial screening. However, no discernible variations in comorbidities between the groups were seen. One man in the BSA-related AAA group (1%) and two men in the non-BSA-related AAA group (<1%) underwent AAA surgery during the follow-up period (odds ratio [OR], 2.8; $P = .39$, Fischer's exact test). Three men in the BSA-related AAA group (6%) and four men in the non-BSA-related AAA group (1%) had their IAD measured to ≥55 mm, excluding the one AAA rupture (OR, 4.4; $P = .07$, Fisher's exact test).

Surviving men from this cohort (n = 399) were invited to a re-examination; 270 men (68%) accepted and 248 (62%) had complete information on height, weight, smoking and diabetes at the time of initial screening and 38 men had a BSA-related AAA (Table I). The median follow-up time was 10.1 years (interquartile range, 8.0-9.6). During follow-up, there were 99 men (36.7%) who had progressed to an IAD of ≥30 mm and 31 men (11.5%) who had progressed to an IAD of ≥40 mm (Fig 2).

From regular surveillance, 110 men with completed health questionnaires, an IAD of 30 to 35 mm at initial screening, and more than one measurement, were included, except for five individuals who did not meet the criteria for BSA-related AAA owing to a small IAD in proportion to a large BSA.

Growth analysis. The estimated mean IAD for the whole cohort was 26.2 mm (95% CI, 26.1-26.4 mm) and the unadjusted, overall IAD growth rate was 0.3 mm/year (95% CI, 0.2-0.4 mm/year).

In the multivariable linear mixed-effects regression, no baseline growth was detected in the absence of covariables, 0.05 mm/year (95% CI, −0.55 to 0.65 mm/year). Both BSA-related AAA and smoking were independently associated with an additional increase in IAD growth rate of 0.4 mm/year (95% CI, 0.0-0.7 mm/year; $P = .032$) and 0.4 mm/year (95% CI, 0.2-0.7 mm/year; $P = .001$), respectively. No correlation was found between the initial screening diameter and the growth rate of IAD in the regression analysis. Similarly, no association was observed between diabetes, statin use, and heredity for aneurysmal disease and IAD growth rate (Table II). Partial residual plots for BSA-related AAA and non-BSA-related AAA are shown in Fig 3, *A* and *B*, stratified by smoking status.

Comparing the growth rate with small AAAs (30-35 mm), BSA-related AAA showed no significant difference in growth. Diabetes was associated with a slower growth rate, while smoking was associated with a higher growth rate, consistent with previous findings[17] (Table III).

In the survival analysis, the cumulative, estimated incidence of reaching AAA of ≥35 mm, ≥40 mm,

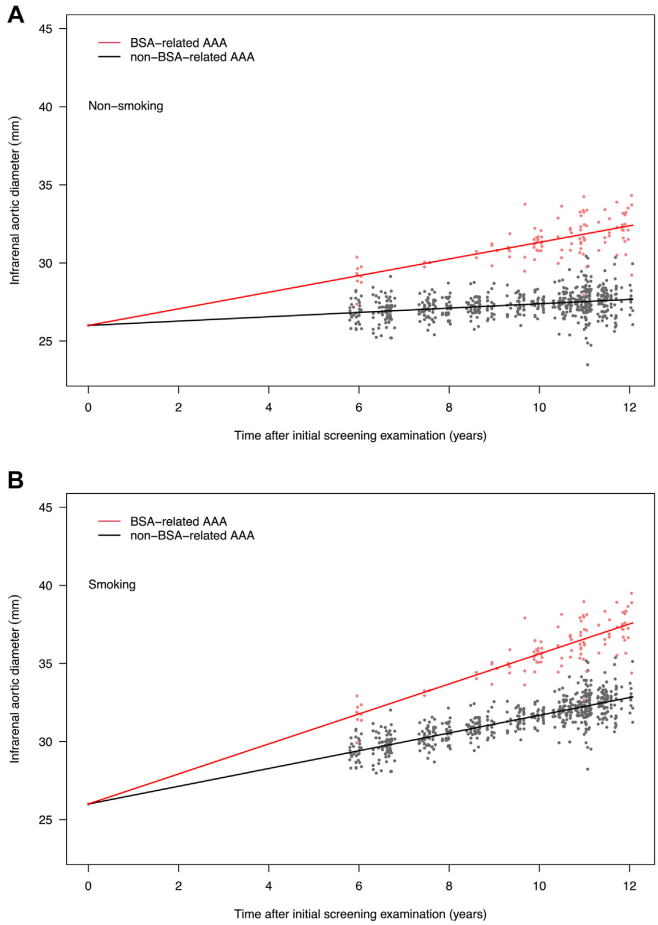

Fig 3. Partial regression plots illustrating the specific association between having a BSA-related AAA and IAD growth after subtracting off the contribution from the other explanatory variables, initial screening diameter, diabetes, lipid lowering medication, and heredity. **(A)** Adjusted for nonsmoking. **(B)** Adjusted for smoking. The corresponding regression coefficients can be found in Table II. *AAA*, abdominal aortic aneurysm; *BSA*, body surface area; *IAD*, infrarenal aortic diameter.

≥50 mm, and ≥55 mm at 10 years for the entire cohort were 0.12 (95% CI, 0.06-0.16), 0.06 (95% CI, 0.02-0.09), 0.01 (95% CI, 0-0.02), and 0.01 (95% CI, 0-0.02), respectively.

The median time to reach an IAD of ≥40 mm was 12 years (95% confidence level [CL], 11.7-∞) for the entire cohort. There was a significant difference in median time to reach an IAD of ≥40 mm; 11.5 years (95% CL: 11.0-∞) for BSA-related AAA, whereas one-half of those with non-BSA-related AAA did not reach 40 mm during the follow-up (95% CL, 11.7-∞) as shown by a log-rank test stratified for smoking ($\chi^2 = 6.8$; 1 degree of freedom; $P = .009$). The median time to reach an IAD of ≥35 mm was 11.0 years for men with both BSA-related AAA and smoking, compared with 11.7 years for those without these risk factors. In a multivariable Cox proportional hazards regression model, BSA-related AAA was associated with a hazard ratio of 2.77 (95% CI, 1.34-5.74; $P = .003$), and smoking was associated with a hazard ratio of 2.10 (95% CI, 1.00-4.43; $P = .005$) for progression to an IAD of

Table III. Linear mixed effects model fit by restricted maximum likelihood for individuals with relAAA, along with surveillance data for individuals with AAA ≥30-34 mm at initial screening

Multivariable analysis BSA-related AAA and small AAA, IAD 30-34 mm (n = 158)			
	Estimated growth, mm/year (95% CI)	SE	*P* value
Baseline IAD growth	1.28 (0.96 to 1.59)	0.160	**<.001**
Initial screening diameter (per mm increase)	0.13 (−0.02 to 0.28)	0.078	.096
BSA-related AAA	−0.03 (−0.74 to 0.68)	0.363	.933
Smoking	0.65 (0.24 to 1.06)	0.209	**.002**
Diabetes	−0.65 (−1.64 to 0.09)	0.378	.085
Lipid lowering medication	−0.21 (−0.65 to 0.24)	0.227	.361
Heredity	−0.17 (−0.72 to 0.38)	0.282	.549

AAA, Abdominal aortic aneurysm; *BSA*, body surface area; *BSA-related AAA*, body surface area-related abdominal aortic aneurysm; *CI*, confidence interval; *IAD*, infrarenal aortic diameter; *SE*, standard error.
Boldface entries indicate statistical significance.
Heredity is defined as self-reported first- or second-degree relative with history of aneurysmal disease, not further specified.
Baseline IAD growth represents IAD growth in the absence of the risk factors: such as BSA-related AAA, smoking, and diabetes, with the screening diameter centered by its mean. The estimated growth rates for each risk factor indicate their respective additional effects on baseline growth.
Lipid-lowering therapy consists exclusively of statins.
Individuals with IAD defined as non-BSA-related AAA within the 30-34 mm group are excluded (n = 5).

≥40 mm. For BSA-related AAA and smoking combined, the hazard ratio was 4.1 (95% CI 1.6-10.1; $P = .009$). Fig 4, *A* and *B* show the cumulative incidence of reaching an IAD of ≥40 mm for nonsmoking and smoking, respectively.

DISCUSSION

This cohort study evaluated factors associated with aortic expansion in men with an IAD of 25 to 29 mm at AAA screening, with a particular focus on IAD in relation to BSA. In a previous study, an individualized criterion for AAA diagnosis based on a person's BSA, termed BSA-related AAA, was established, aligning with the original definition of an arterial aneurysm as a permanent focal dilation of ≥150% larger than the expected diameter.[9] Using this criterion enabled the identification of >30% more AAAs compared with the conventional diagnostic threshold of ≥30 mm.[17]

In the present study, BSA-related AAA was associated independently with an increased IAD growth rate of 0.4 mm per year, as was current smoking at the time of initial screening, consistent with previous findings.[24] No IAD growth could be found in the absence of risk factors in this cohort with an IAD of 25 to 29 mm and no significant difference in growth rate was observed between BSA-related AAA and small AAA (30-35 mm) when correcting for initial screening diameter. Also, in a survival analysis, BSA-related AAA and smoking were associated independently with a significantly elevated hazard ratio for progression to an AAA width of ≥40 mm. These findings suggest that the aortic diameter in relation to BSA, independent of smoking status, is of importance in the development of AAAs, and not just the absolute aortic diameter. With contemporary, standardized screening methods, additional biometrics, such as height and weight, could be of importance as tools for an individualized diagnostic criterion to identify men with initial aortic diameters in the 25- to 29-mm range who need follow-up. However, the median time (>11 years) for men with BSA-related AAA and smoking, to reach an IAD of ≥35 mm was <1 year shorter than for those without these risk factors. Although these differences were statistically significant, the short time span between the groups suggests that such findings still may not be clinically relevant.

Previous studies have shown the possibility to adjust the criteria for AAA based on BSA using the aortic size index (ASI): IAD divided by BSA expressed as mm/m^2. This has been suggested as a better measurement than a fixed diameter, especially in women, although without impact on prevalence[25,26] and, as such, has been used to compare AAA prevalence between different populations.[27] The ASI has also been shown to have a positive predictive value in identifying men with an IAD of ≥25 to 29 mm at risk of progressing to clinically relevant AAA where an ASI, dichotomized by the cut-off value of ≥13 mm/m^2, was associated with a more than nine-fold risk of developing an AAA of ≥55 mm in 10 years.[28] A much stronger association than what this study showed using the BSA-related AAA criteria, possibly implying different characteristics between study cohorts. When we applied an ASI of ≥13 mm/m^2, we found similar results as with the BSA-related AAA criterion. The findings in this study could also benefit from validation by analysis of differences in percentage diameter increase between groups before translation into clinical practice.

In the recently updated European Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms, the recommendation regarding subaneurysmal aortas (IAD 25-29) to be included in surveillance, has been upgraded from Class IIb to Class IIa, Level B.[13] The findings in this study could only find limited support for differentiated inclusion in surveillance or varying surveillance intervals based on the BSA-related AAA criterion

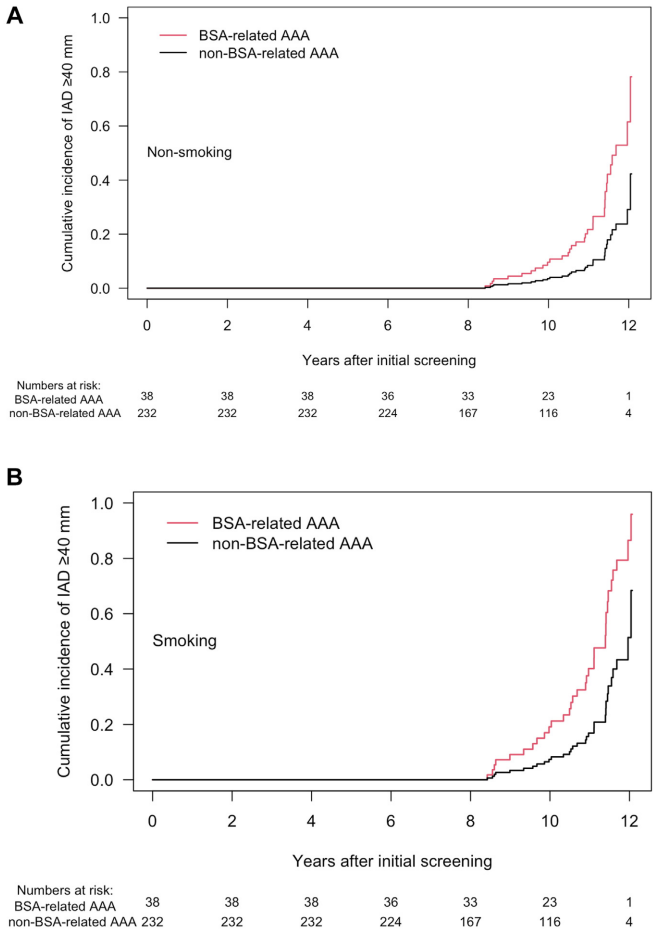

Fig 4. Cumulative incidence of reaching an IAD threshold of ≥40 mm for those with and without BSA-related AAA. **(A)** Black curve represents the baseline cumulative hazard without risk factors. **(B)** Black curve represents the baseline cumulative hazard for smokers. Likelihood ratio test for the whole model is 18.28 on 2 degrees of freedom, $P < .001$. *AAA*, abdominal aortic aneurysm; *BSA*, body surface area; *IAD*, infrarenal aortic diameter.

or smoking status. Although those with an IAD of 25 to 29 mm are a small group of all screened men (<5%), this group would double the numbers under surveillance, should the data in this study apply generally.

A method to identify men in this group who are at risk of developing aneurysms requiring treatment during the initial screening could enable more targeted follow-up. The outcomes of these moderately enlarged abdominal aortas are of interest to both individuals and health care systems. For a screening program to be reliable, it must demonstrate high specificity and sensitivity in detecting the disease and identifying those in need of treatment while being feasible on a nationwide scale.[29]

Limitations. The growth analysis focused on IAD in relation to BSA in men only, as the screening program at hand only concerned men, with consideration given to known risk factors for AAA growth, whereas the survival analysis did not include risk factors other than smoking

owing to limited evidence on the impact of drugs on AAA growth rates, especially in small aortic diameters,[13,30] as well as for the study results to be easily transferred to daily screening operations. However, the analysis was not intended to study the direct impact of smoking on growth rate per se. The BSA-related AAA criterion used in this study was based on a correlation between IAD and BSA in the specific cohort in which it was applied that may limit the generalizability of the method together with the fact that height and weight were self-reported. The low occurrence of events during the initial 7 to 8 years of follow-up and a high number of censoring instances in the later part of the follow-up contribute to uncertainty in the survival analysis but are unlikely to introduce bias into the results. Nearly all participants had only two examination points, the initial screening and the invited measurement, resulting in long intervals between observations. It should also be noted that, in 10 years, the cumulative incidence of reaching an IAD of ≥40 mm was only about 0.09, much lower compared with earlier studies, suggesting perhaps an overall healthy study cohort.[11,13,28]

CONCLUSIONS

This study found that the use of an individualized AAA criterion based on BSA, termed BSA-related AAA, could identify men with an infrarenal aortic diameter of 25 to 29 mm at screening who exhibited significantly higher growth rates compared with those without BSA-related AAA. Additionally, the estimated median time until AAA diameter of >40 mm was significantly shorter for those with BSA-related AAA than those without. Thus, aortic diameter relative to BSA, beyond absolute diameter alone, sems to be important for AAA development. However, the observed differences did not seem to be large enough to warrant earlier recalls of those with BSA-related AAA compared with those without, indicating that further research is needed to confirm the clinical relevance of these findings.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT in order to check spelling and improve readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHOR CONTRIBUTIONS

Conception and design: JS, SB, FL, JH
Analysis and interpretation: JS, SB, FL, HP, AG, JH
Data collection: JS, SB, JH
Writing the article: JS, JH
Critical revision of the article: JS, SB, FL, HP, AG, JH
Final approval of the article: JS, SB, FL, HP, AG, JH
Statistical analysis: JS, FL
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Overall responsibility: JH

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Paper IV

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Original Contribution

Evaluation Of Handheld Point-of-Care-Ultrasound (POCUS) in Screening for Abdominal Aortic Aneurysm in Men: A Comparative, Cohort Study

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ABSTRACT

Objective: Screening for abdominal aortic aneurysm (AAA) using ultrasound in men reduces aneurysm-related mortality. Ambulatory screening and surveillance procedures facilitated by point-of-care ultrasound (POCUS) may improve adherence to screening programs. This proof-of-concept study evaluated whether infrarenal aortic diameter (IAD) can be accurately and interchangeably measured using handheld POCUS—an ultrasound probe connected to a tablet—compared to standard cart-based ultrasound equipment.
Methods: This comparative cohort study included men with an IAD of 25–29 mm during AAA screening and re-examined them after 5–12 years, anticipating most would approach the 30 mm AAA threshold. Three IAD measurements were taken using both POCUS (Lumify™, Philips) and standard US (LOGIQ™ 9E, GE). Bias, limits of agreement between devices and repeatability within devices were evaluated. Sensitivity and specificity of POCUS for AAA detection (IAD ≥30 mm) compared to standard ultrasound were also assessed.
Results: In total, 230 men participated. The median age was 75.0 years (IQR: 72.9–76.5), BMI 27.7 (26.0–30.5), and IAD 27.1 mm (23.7–32.8) respectively. POCUS underestimated IAD by 0.3 mm compared to standard US, with 95% limits of agreement ±3.0 mm. Repeatability was ±2.5 mm for standard ultrasound and ±3.2 mm for POCUS. The sensitivity and specificity of POCUS for AAA diagnosis, compared to standard ultrasound, are 94% and 98%, respectively.
Conclusion: POCUS showed no systematic bias of clinical importance in measuring IAD although with a slightly wider repeatability interval compared to standard US implying the possibility to consider POCUS devices for AAA-screening purposes.

Introduction

Large-scale, population-based screening for abdominal aortic aneurysms (AAA) in men has been shown to be effective in reducing aneurysm-related mortality [1–4], and reducing all-cause postoperative mortality for patients undergoing surgical aneurysm repair [5].

Ultrasound (US) imaging is the recommended modality for AAA screening and for surveillance of small AAAs to measure the infrarenal aortic diameter (IAD), according to European guidelines (Class I, Level B) [6]. Advances in technology have resulted in ultrasound devices becoming more compact, mobile, affordable, and easy to use, enabling healthcare professionals, who may not have formal ultrasound training, to perform examinations conveniently in various settings, focusing on specific organs and clinical questions. This development has given rise to the term point-of-care ultrasound (POCUS) [7]. Ambulatory use of handheld ultrasound devices—substantially more affordable than high-end systems—could help improve adherence and compliance with AAA screening. This is particularly relevant as guidelines recommend more targeted screening strategies aimed at high-risk populations, who are also known to have lower adherence to screening programs [6,8].

Limited data exist on the comparison of handheld POCUS devices with standard, cart-based US machines for detecting abdominal aortic aneurysms. To our knowledge, the applicability of POCUS in an AAA screening setting compared to standard US has not yet been evaluated. To investigate this, we conducted this proof-of-concept study to assess accuracy, defined as the closeness of measurements from the two devices for the same subject, and precision, referring to the consistency or repeatability of measurements by each device. We also evaluated the diagnostic sensitivity and specificity of POCUS for detecting AAA ≥ 30 mm compared to standard US.

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The aim of this study was to investigate whether IAD could be measured using POCUS while maintaining diagnostic accuracy compared to standard, high-end ultrasound, in order to assess its potential for use in ambulatory AAA screening and surveillance.

Methods

This cross-sectional, comparative cohort study was approved by the ethics committee of Lund University (LU 2010/239) and the Swedish ethical review authority (Dnr 2019-05788 and 2023-02037-02), Etikprövningsmyndigheten, Box 2110, 750 02 Uppsala, Sweden. Written consent was obtained from all participants.

Setting

In Sweden, nationwide aortic screening for all 65-year-old men has been in place since 2016 [9]. This is in accordance with the European recommendations (Class I, Level A) [10] and national guidelines [11] at the time, excluding women due to the much lower AAA prevalence in that group.

The Department of Vascular Diseases at Skåne University Hospital in Malmö serves a heterogeneous catchment area comprising Malmö and 15 surrounding municipalities, encompassing both rural and urban populations. The total population from which all 65-year-old men are invited for AAA screening is approximately 650,000.

These individuals are identified through the national population register (skatteverket.se) and examined by sonographers within the AAA screening programme using a standardized method with cart-based standard ultrasound.

Men diagnosed with an AAA (IAD ≥30 mm) are offered surveillance, while those with an IAD of less than 30 mm are considered at low risk of developing an AAA and are not offered surveillance. Surveillance begins with a doctor's visit to provide information, optimize medical treatment, and offer lifestyle advice. Follow-up includes US scans every three years for AAAs measuring up to 40 mm, annually for AAAs measuring 40 −50 mm, and every six months for AAAs measuring 50 mm or more. Surgery is offered when an AAA reaches 55 mm, provided it is deemed appropriate for the patient.

As part of the screening program, a research project on AAA and atherosclerosis epidemiology has been conducted [8]. Screening participants are encouraged—but not obliged—to complete a health questionnaire covering medication, lifestyle, comorbidities, height, and weight. The present study constitutes a small part of this project and, as a purely methodological study, includes only variables with a clear impact on aortic diameter in the analysis [8].

Study population

This study included men who, at age 65, had an IAD of 25−29 mm measured during routine AAA screening conducted between 2010 and 2017. At the time of screening, these individuals were not enrolled in AAA surveillance, as their IADs did not meet the threshold for follow-up.

For the current study, they were specifically selected and invited for re-examination 5−12 years later. The rationale for inclusion was that their IADs may have progressed to or beyond 30 mm—the diagnostic threshold for AAA—during the interval, making them relevant to the present analysis.

Inclusion criteria required that participants had provided written informed consent for the research project associated with the screening programme [8] and had an IAD of 25−29 mm at the time of screening.

Exclusion criteria included cases in which standard ultrasound could not be used to measure the IAD—such as instances of excessive bowel gas—since these participants could not be included in a direct comparison with point-of-care ultrasound (POCUS). Because the aim was to compare POCUS with standard ultrasound, alternative imaging methods such as computed tomography were not considered. No additional exclusion criteria, including prior AAA surgery, were applied.Invitation letters with prescheduled appointments were sent by mail, and participants were given the option to reschedule if necessary. Those who missed their initial appointment received a follow-up invitation.

Participants were instructed in the same manner as in the general screening programme, including fasting for four hours prior to the examination to optimize visualization of the infrarenal aorta.

Ultrasound measurements

The handheld POCUS device used was the Lumify™ C5-2 Android Curved Array Transducer (5−2 MHz, up to 30 cm scan depth; Koninklijke Philips N.V., Netherlands) paired with a Samsung Galaxy™ 8.7-inch tablet (Samsung Electronics Co., Ltd., South Korea), hereafter referred to as the "handheld POCUS device." This was compared to a cart-based LOGIQ™ E9 ultrasound system with a C-5 curved array probe (General Electric Healthcare Inc., UK), routinely used at our centre for AAA screening and surveillance, hereafter referred to as "standard ultrasound" (standard US). Imaging protocols on both devices followed standard abdominal vascular settings as recommended by each manufacturer.

Examinations were conducted following the same methodology as in the screening and surveillance program [8,12]. Specifically, the superior mesenteric artery and iliac bifurcation were identified, and the widest IAD was measured orthogonally in the transverse plane using the leading-edge-to-leading-edge (LELE) technique [13]. and 2D imaging, with colour flow Doppler only to verify orientation. See Figure 1. Measurements were aimed at capturing the aorta during systole; however, this was not consistently achievable, particularly with the handheld POCUS device (see Limitations section).

Three measurements of the widest IAD were first performed using the handheld POCUS, followed immediately by the same measurement protocol using the standard US. Examination time for each device was limited to a maximum of three minutes. All examinations were conducted by the same examiner (JS), and considered conclusive, if the superior mesenteric artery and the iliac bifurcation were visualized, and the IAD could be measured. If these steps had not been fulfilled, this would have been reported in the manuscript, and the patient would have been excluded but still documented as such.

An assistant (JH) recorded the measurements, with the examiner blinded. The examiner (JS) was an attending vascular surgeon with more than ten years of experience in performing and valuing ultrasound examinations for IAD.

Statistical analysis

IAD measurements were recorded in millimetres with precision to one decimal point.

Bland−Altman plots, depicting the difference against the mean and 95% limits of agreement—the range within 95% of the differences between the two measurement methods are expected to lie—were generated from the largest IAD measurements for each individual from each device to identify possible systematic errors.

Bias and limits of agreement between the two devices were also calculated in a linear mixed effects model using all IAD measurements nested within individuals as random effects to account for within-subject correlations [14,15].

A sensitivity and specificity analysis comparing handheld POCUS and standard US for the diagnostic accuracy of AAA (defined as IAD ≥30 mm) was performed, based on the largest IAD measurement from each device per individual, to evaluate the performance of handheld POCUS in routine screening practice.

Agreement of measurements within each device, repeatability (R), was assessed using a linear mixed effects model. An R value of 1 indicates perfect consistency, while 0 signifies no consistency. All IAD measurements were used and nested within individuals as random effects,

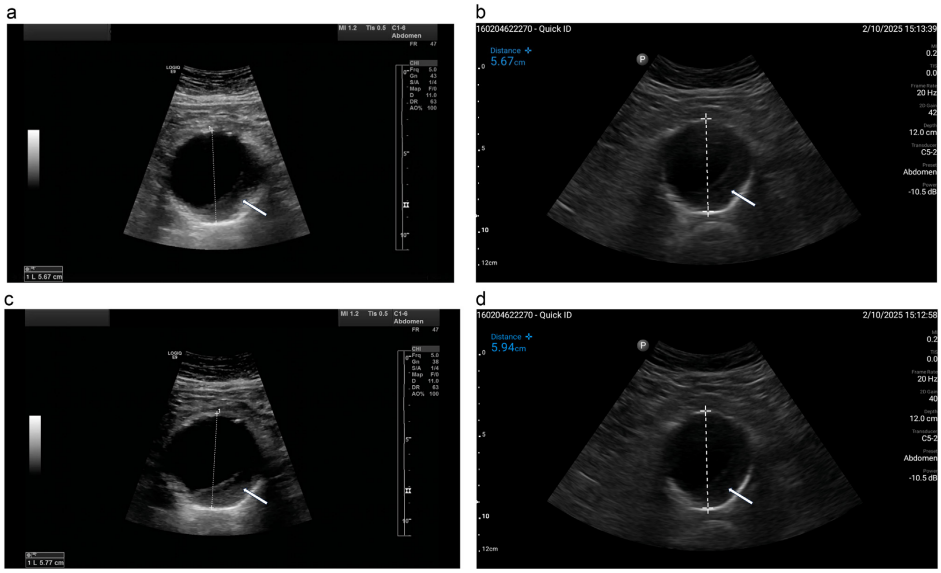

Figure 1. All measurements were obtained using the leading-edge-to-leading-edge technique in the transverse plane. Thrombus is indicated by a white arrow. Panels (a) and (b) show identical measurements of an abdominal aortic aneurysm (AAA) using standard ultrasound and handheld POCUS, respectively. Panels (c) and (d) show measurements that differ between the two modalities. Photo: A Mosonyi.

with confidence intervals for R estimated using parametric bootstrapping [16].

Agreement of measurements was also expressed as the interval within which 95% of two measurements taken by the same device will fall. This was calculated from the mean variance of all IAD measurements from each individual such as $\pm 1.96 \times \sqrt{2 \times s_w}$, where s_w denotes the mean variance. s_w was calculated using the mixed effects model from the repeatability estimation above.

The within-subject IAD measurement variances were checked for correlation to body mass index in separate linear models for each device.

Statistical analysis was conducted using the R programming language [17]. within the RStudio environment [18]. The analysis employed R language packages, including the 'caret' package for sensitivity and specificity analysis. Bias and limits of agreement were calculated using the 'lme4' function from the 'nlme' package and the 'rmbr' function from the 'rmbr' package. Agreement of measurements, including repeatability, was analysed using the 'rptr' package.

Results

During 2010 to 2017, 18,543 men attended AAA screening and accepted participation in the aforementioned epidemiological research project [8]. Out of these, 500 men (2.7%) met the inclusion criteria with an IAD measured to 25−29 mm. At the time of the study, 398 men were alive and invited, of whom 230 (58%) responded to the invitation and were examined three times with both devices. The median time from initial screening examination to re-examination was 9.9 years (interquartile range [IQR]: 8.0−11.0). One person had undergone endovascular AAA repair before the re-examination but was still included in the study. All 270 participants had their IAD measured three times by each device. In total, 1380 observations were recorded, and as all examinations were conclusive, no exclusions were made. See Figure 2. The median age was 75.0 years (IQR: 72.9−76.5) and median BMI was 27.7 (IQR: 26.0 −30.5), for further details and comparison to the screening cohort as a whole, see table 1.

Median IAD in the cohort was 27.1 mm (IQR: 23.7−32.8), with 97 men (36%) classified as having an AAA (IAD ≥ 30 mm) based on measurements from the standard US.

There were 10 (0.7 %) measurements, not individuals, that differed more than five millimetres between the devices. No systematic errors were observed when measurements from the two devices were plotted against a line of equality (Fig. 3). Similarly, the Bland−Altman plot showed no systematic errors between the devices (Fig. 4). The 95%

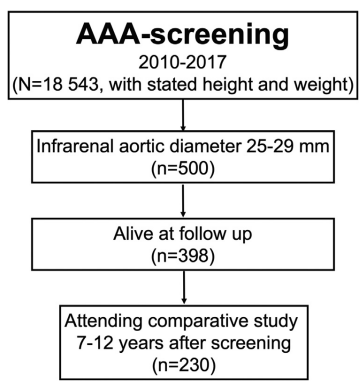

Figure 2. Consort diagram, comparative study with re-examination 7−12 years after screening (n = 230). AAA, abdominal aortic aneurysm.

Table 1
Demographic characteristics of the study cohort and the total screening population it was drawn from

	Study cohort, N = 230	Total screening cohort, N = 18,543
Age at re-examination, years	75.0 (72.9 76.5)	Age at screening, years 65.1 (65.0 65.4)
Diabetes mellitus	27/212 (13)	2325/14 886 (16)
Smoking status	47/230 (20)	2448/15 855 (15)
Height, cm	177.5 (174.0 181.3)	179.0 (174.0 183.0)
Weight, kg	87.4 (80.9 97.4)	85.0 (77.4 94.0)
Body surface area, m^2	2.1 (2.0 2.2)	2.0 (1.9 2.1)
Body mass index, kg/m^2	27.7 (26.0 30.5)	26.6 (24.5 29.1)

Continuous variables are presented in the median (1st and 3rd quartile). Categorical variables are presented as numbers/complete observations and percentage, n/N (%).

limits of agreement ranged from −3.0 mm to 3.5 mm, with a mean difference of 0.3 mm (standard deviation 1.6) for handheld POCUS compared to standard US.

In the mixed effects model, which included all measurements, handheld POCUS underestimated IAD by a mean of 0.3 mm compared to standard US, consistent with the Bland–Altman analysis, but with slightly narrower limits of agreement (−3.3 mm to +2.7 mm).

The diagnostic accuracy of POCUS for detecting an AAA (IAD ≥30 mm) was 0.96 (95% CI: 0.93–0.98), using standard US as the reference method. The sensitivity and specificity of POCUS for diagnosing AAA were 0.94 and 0.98, respectively, with positive and negative predictive values at 0.96 and 0.97 respectively compared to standard US.

There was a significant difference in agreement of measurements within each device, expressed as repeatability (R) between the two devices: R was estimated to 0.990 (95% CI 0.987–0.992) for the standard US and 0.982 (95% CI 0.977–986) for POCUS. 95% of repeated measurements were estimated to lie within ± 2.5 mm for standard US and within ± 3.2 mm for POCUS.

No correlation between the largest IAD measurements and body mass index (BMI) was found with standard US ($R^2 < .000$, $p = 0.81$), nor with handheld POCUS ($R^2 = .006$, $p = .31$).

Discussion

This study aimed to investigate whether handheld POCUS could be used interchangeably with standard ultrasound (US) equipment in screening for AAA.

POCUS was originally evaluated in emergency settings for heart and lung examinations [19]. and trauma care through the Focused Assessment with Sonography in Trauma (FAST) protocol [20]. It refers to a method of ultrasound examination performed at the point of care, rather than to a specific type of ultrasound machine [21]. It has also been shown to accurately detect AAA in emergency departments [22].

Gupta et al. showed in a study of 80 patients under surveillance for known infrarenal AAA that POCUS, used by a nonphysician after a brief training session, could provide accurate aortic measurements for AAA surveillance. However, a high-end US device was used in a POCUS setting [23]. In a study by Bonnafy et al. involving 56 patients, it was demonstrated that abdominal aortic diameter could be safely measured by nonspecialist physicians after brief training with handheld US systems [24]. However, to our knowledge, the explicit diagnosis of AAA with POCUS has only been reported in comparison to physical examination [25] and we have not found any evaluations of the technique in a screening setting, specifically not using a handheld device.

In the light of lower prevalence of AAA, decreasing from over 4% −1% over the last 20–30 years [26], www.gov.uk, and in some Swedish regions even lower [27], the recommendation to conduct population-

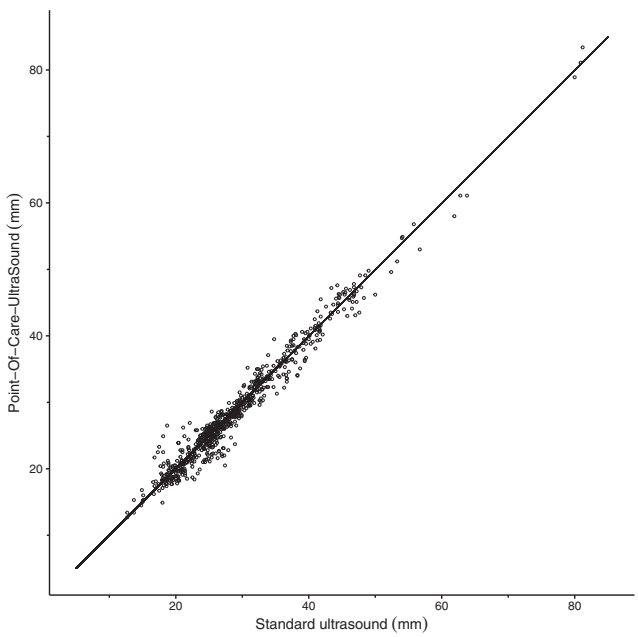

Figure 3. Measurements of infrarenal aortic diameter obtained using standard ultrasound equipment plotted against corresponding measurements obtained with handheld point-of-care ultrasound (POCUS), with all measurements included, and a line of equality.

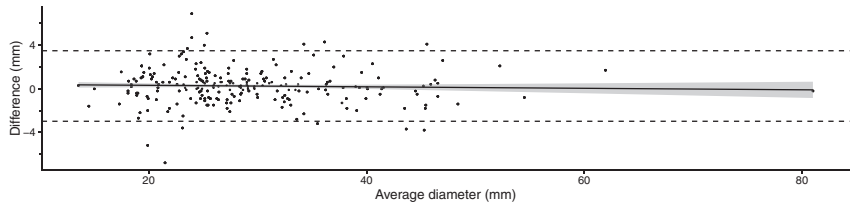

Figure 4. Bland–Altman plot showing agreement between handheld POCUS and standard ultrasound measurements of infrarenal aortic diameter. The plot compares the largest measurement from each device per individual. Each point represents the difference between paired measurements plotted against their mean. The solid line represents a linear regression of the measurement differences over the average diameter, and the shaded grey area shows the 95% confidence interval for this regression. The dashed lines indicate the 95% limits of agreement (−3.0 mm to 3.6 mm).

based screening has been updated to target high-risk groups in the European guidelines for the treatment of aortic and iliac disease [6]. The definition of high-risk patients is left to the discretion of the screening clinic and may include factors such as smoking, hypertension, other cardiovascular diseases, or known familial predisposition, for example.

Previous research indicates that individuals who do not attend screening, often have lower socio-economic status and a higher burden of risk factors for the disease [8]. Higher rates of emergency and rupture repairs have also been reported in more socio-economically deprived areas compared to less deprived areas [28]. This places greater demands on screening efforts to ensure acceptance [29], as individuals within the populations with high-risk for aneurysmal disease may be less inclined to adhere to invitations for screening.

One approach could involve mobile screening examinations. With smaller equipment, such as handheld POCUS, it would be easier to conduct rapid examinations with limited resources in various settings. A mobile screening and surveillance program presupposes that the equipment in use is accurate and able to match the performance of standard US equipment. It also has to be possible to connect the equipment to reliable patient administrative systems to ensure that no patient is lost to follow-up. This latter issue is not addressed in this proof-of-concept study, which focused on the performance of IAD measurements with handheld POCUS compared to standard US.

In this study, accuracy for the handheld POCUS was high as it underestimated IAD by only 0.3 mm compared to standard US. In this cohort, where 36% had AAA, POCUS also demonstrated a high level of agreement with the standard US, achieving a diagnostic accuracy of 97% for AAA detection. Precision, though, was slightly lower with POCUS compared to standard US where 95% of repeated measurements (limits of agreement) were estimated to lie within ±2.5 mm for standard US and ±3.2 mm for POCUS. This discrepancy could pose challenges for individuals with aortic diameters around 25–30 mm, affecting decisions regarding inclusion in follow-up protocols, and around 55 mm, influencing decisions on surgical aneurysm repair. The difference between the two devices was, however, comparable to previously reported inter-observer differences using the same devices [30].

In this cohort however, no participant was impacted by differences in IAD measurements due to device selection that could influence clinical decisions. This is also reflected by the high rate of accuracy in the sensitivity and specificity analysis. Furthermore, no correlation was found between within-subject variance and body mass index, suggesting that both devices performed similarly regardless of body stature.

A potential explanation for the slight difference in precision observed between devices could be the method of obtaining measurements from the POCUS device. Measurements were taken using finger-positioned markers on an 8.7-inch tablet. Due to the small size of the tablet, this method might be less precise than using a trackball, as is common with most cart-based US machines. The standard US equipment also allowed retrospective cine loop review upon image freeze, enabling frame-by-frame selection to optimise measurement timing, for peak systole. The handheld POCUS device software at the time of the study did not support this function; therefore, measurements were based on single static images, which were more difficult to time with peak systole [31]. To improve accuracy and repeatability, further studies could compare larger and smaller tablets and explore the use of a digital pen, for example.

For a screening program to be reliable, it needs a high level of attendance as well as high specificity and sensitivity for both detection of the disease and for the identification of those eventually in need of treatment [29]. Ambulatory screening procedures could improve attendance rates, both for initial screening and for surveillance programs, should an AAA be detected. This study serves as a proof of concept, demonstrating that handheld POCUS could enhance the feasibility of such an ambulatory screening for AAA.

Limitations

This study comprised only men, as the Swedish AAA screening program targets a male population due to the significantly lower prevalence in women. No data on waist circumference or the distance from probe to infrarenal aorta were available. All examinations were carried out by a single examiner for both devices, first with POCUS and then with standard ultrasound. Although the examiner was blinded to the measurements, total blinding could not always be achieved, as the measurements were displayed on the tablet before being recorded by the assistant which may have led to the examiner inadvertently viewing some values. Also, the use of only one examiner and the fixed order of measurements—without counterbalancing to reduce potential order effects—represent methodological limitations. Furthermore, the setting in which the study was conducted does not fully reflect an ambulatory screening environment with perhaps less trained examiners. The sensitivity and specificity analysis warrants cautious interpretation, as it is influenced by the distribution of measurements around the AAA threshold (≥30 mm) and by the use of high-end ultrasound rather than an external gold standard such as computed tomography.

Conclusion

In this study, POCUS demonstrated a bias in measuring IAD of such small magnitude that it did not affect diagnostic accuracy, although with a slightly wider repeatability interval compared to standard US. This suggests that POCUS devices could be considered suitable for AAA screening.

Conflict of interest

The authors certify that there are no conflicts of interest. AG receives consultancy fees from Bayer, Pfizer, and Sanofi, none of which have any bearing on this study. The Lumify™ device was provided free of charge

by Philips Healthcare, Sweden, with no other contributions or involvement from the provider in the study's conception, design, interpretation, or results.

Data availability

The ethical approval for this study did not include permission to publicly share the original data.

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ChatGPT™ was used to check spelling and improve readability. After using this tool, the authors reviewed and edited the content as needed. Any remaining shortcomings are the sole responsibility of the authors.

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