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Correcting for Body Surface Area Identifies the True Prevalence of Abdominal Aortic Aneurysm in Screened Women

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WHAT THIS PAPER ADDS

AAA is widely reported as having a significantly higher prevalence in males. This study adds to a body of evidence suggesting that sex differences in AAA prevalence are largely an artefact of the application of a single (male derived) absolute size threshold. Any discussion on the retention or future development of AAA screening programmes must use appropriate sex specific prevalence rates in order to provide a balanced and equitable consideration.

Objective: Recently, the prevalence of abdominal aortic aneurysm (AAA) using screening strategies based on elevated cardiovascular disease (CVD) risk was reported. AAA was defined as a diameter $\geq$30 mm, with prevalence of 6.1% and 1.8% in men and women respectively, consistent with the widely reported AAA predominant prevalence in males. Given the obvious differences in body size between sexes this study aimed to re-evaluate the expanded CVD risk based AAA screening dataset to determine the effect of body size on sex specific AAA prevalence.
Methods: Absolute (26 and 30 mm) and relative (aortic size index [ASI] equals the maximum infrarenal aorta diameter (cm) divided by body surface area (m^2), ASI $\geq$ 1.5) thresholds were used to assess targeted AAA screening groups (n = 4115) and compared with a self reported healthy elderly control group (n = 800).
Results: Male AAA prevalence was the same using either the 30 mm or ASI $\geq$1.5 aneurysm definitions (5.7%). In females, AAA prevalence was significantly different between the 30 mm (2.4%) and ASI $\geq$ 1.5 (4.5%) or the 26 mm (4.4%) thresholds.
Conclusion: The results suggest the purported male predominance in AAA prevalence is primarily an artefact of body size differences. When aortic size is adjusted for body surface area there is only a modest sex difference in AAA prevalence. This observation has potential implications in the context of the ongoing discussion regarding AAA screening in women.

Keywords: Abdominal aortic aneurysm, Population screening, Ultrasound, Women
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INTRODUCTION

The recent meta-analysis of screen detected abdominal aortic aneurysm (AAA) in women conducted by the "Screening Women for Aortic aNeurysm (SWAN) Collaborative Group"[1] suggested potentially cost effective[2] prevalence rates may be present within selected groups of older women. The potential relevance of AAA screening in women has also been highlighted in a contemporary report which suggests that almost one third of screen detected (>30 mm) aneurysms go on to be electively repaired within five years.[3] Despite this, it is worth noting that the SWAN meta-analysis reported prevalence rates in women that were still only a quarter to a third of that observed in similar male groups. Such observations appear to substantiate the widely held belief that AAA is predominantly a male condition and hence the screening focus towards older men.

The International Society for Cardiovascular Surgery defined arterial aneurysms as a segmental dilation of 50% greater than normal vessel diameter.[4] The use of absolute threshold values (30 mm in men and 26—27 mm in women) has been suggested, largely for practical reasons relating to

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ease of clinical implementation.[5] In practice, however, a single value of 30 mm has been widely applied to both men and women,[1] resulting in a significant potential sex bias in AAA screening prevalence rates when such a single diameter threshold is applied. This difference was substantially reduced when AAA was redefined as a 50% diameter increase referenced against a sex specific population nomogram.[6]

Given the obvious difference in body size between men and women, and the previous studies that show the importance of relative aortic size in terms of clinical evaluation, it seems rather surprising that the discussion regarding the prevalence of AAA in women still largely persists in the context of a male derived absolute size threshold. This study therefore asked the question, "What is the sex specific AAA prevalence in a series of screening populations when aortic size is assessed relative to body surface area using the infrarenal Aortic Size Index (ASI)?" It was previously reported that AAA ($\geq$30 mm) increased (male and female) prevalence rates in a series of cohorts with elevated cardiovascular disease (CVD) risk.[7] In this study, these (expanded) datasets, examining over 4900 screened individuals, following reanalysis with AAA defined using either absolute (26 and 30 mm) or relative (ASI $\geq$ 1.5) size thresholds are reported.

METHODS

The cohort study datasets used in this current investigation are substantively based upon a previously published study examining the utility of cardiovascular disease risk factor profile based strategies to improve the efficiency of AAA screening.[7] In brief, study participants were over 50 years of age and were recruited from the Otago—Southland region of New Zealand. Subjects were invited to attend the screening facility in the local hospital.

Cohort 1 consisted of a consecutive series of 1366 patients undergoing coronary angiography with the cardiology department at Dunedin Public Hospital (recruited between January 2008 and May 2013).

Cohort 2 consisted of a consecutive series of 1441 patients undergoing assessment for suspected carotid or peripheral arterial disease within the Vascular Laboratory Surgery Department at Dunedin public hospital (recruited between January 2008 and April 2014).

Cohort 3 consisted of 1046 patients in the community who had previously been identified by their general practitioner as having a five year cardiovascular disease event risk (CVDRA) greater than 10%. The five year CVDRA score was calculated using the New Zealand adapted Framingham Cardiovascular risk scoring system (Best Practice Advocacy Centre Incorporated).[8]

Cohort 4 consisted of 262 patients with a (CT or MRI) confirmed history of cerebral infarction (stroke).[9] This group was not included in the previous CVD based AAA screening strategies paper.[7]

A fifth group consisting of 800 self reported healthy individuals over 60 years of age was recruited by community newspaper advertisement from the same geographical region as the four groups above. These "control" group individuals had no prior history of ischaemic heart disease (including angina pectoris), peripheral vascular disease (confirmed by ankle brachial index and carotid ultrasound), and stroke (including transient ischaemic attack) at time of recruitment.

Each participant completed a detailed demographic, risk factor, and clinical history questionnaire and underwent an abdominal aortic ultrasound scan in the Vascular Laboratory, Department of Surgical Sciences, University of Otago. All scans were performed by trained vascular sonographers.

Smoking exposure was assessed by determining lifetime consumption in pack years. One pack year was defined as 20 cigarettes (or equivalent) per day for one year.

AAA definitions

The maximum (outer wall to outer wall) diameter of the infrarenal abdominal aorta was measured between the renal arteries and aortic bifurcation in three planes (transverse, antero-posterior longitudinal and coronal/frontal). AAA was initially defined as the maximum infrarenal aorta diameter greater than or equal to 30 mm, or alternatively as (1) $\geq$ 26 mm or (2) ASI greater than 1.5. ASI was calculated as (maximum) infrarenal aorta diameter (cm)/body surface area (BSA). BSA was calculated using the DuBois formula ($0.20247 \times (\text{weight (kg)}^{0.425}) \times (\text{height (m)}^{0.725})$).[10] Defining an AAA as ASI$>$ 1.5 was not arbitrary since in an average size male in this cohort (BSA 1.99 m^2) an ASI equal to 1.5 corresponded to an infrarenal diameter of 29.9 mm. In average sized women (BSA 1.75 m^2) this corresponded to an infrarenal diameter of 26.3 mm.

Statistical analysis

Statistical analysis was performed with StatView version 5.01 (SAS Institute, Cary, NC) and MedCalc version 18.6 (MedCalc Software, Ostend, Belgium). Chi-squared tests were used to determine differences between nominal variables. Fisher's protected least significance difference t-tests were used to compare normally distributed continuous variables. Those with non-Gaussian distributions (Kolmogorov—Smirnov test $p < .001$) were assessed using Mann—Whitney U tests. Correlations between continuous variables were calculated using Spearman's rank tests. Forward stepwise multiple logistic regression was used to test the interactive effects of other variables on the observed associations across screening subgroups. Univariable terms were fitted to the model based on their order of significance. The sample size of the combined CVD risk cohorts (2502 males and 1613 females) was calculated to be sufficient to detect a 1.9% difference in AAA prevalence between sexes (80% power, $\alpha = 0.05$).

Results were expressed as means $\pm$ 1 standard deviation or medians and interquartile range. Odds ratios were expressed with 95% confidence intervals. A p value $< .05$ was considered statistically significant.

RESULTS

In all, 4115 individuals were recruited into the four AAA screening groups (60.8% male). The AAA prevalence for this

Table 1. Combined AAA prevalence in cardiovascular disease risk based screening groups

	Males ($n = 2502$)	Females ($n = 1613$)	p
Infrarenal aortic diameter, mm[a]	19.9 (18.1–21.9)	16.8 (15.3–18.7)	<.001
Aortic size index	1.00 (0.90–1.11)	0.97 (0.86–1.08)	<.001
Absolute size ≥ 30 mm	143 (5.7%)	38 (2.4%)	<.001
Absolute size ≥ 26 mm	254 (10.2%)	71 (4.4%)	<.001
Aortic size index ≥ 1.5	143 (5.7%)	72 (4.5%)	.078
Mean age ± SD, years	68.5 ± 9.2	70.5 ± 9.2	<.001
Body mass index, kg/m^2	27.5 (23.8–31.8)	27.7 (24.9–30.8)	.116
Mean body surface area ± SD, m^2	1.98 ± 0.19	1.75 ± 0.19	<.001
AAA (absolute size ≥ 30 mm)	*n = 143*	*n = 38*	
Mean AAA patient age ± SD, years	72.9 ± 8.8	74.6 ± 9.4	.295
Absolute AAA size, mm	35.7 (32.1–44.1)	34.5 (32.0–40.5)	.337
Relative AAA size (ASI)	1.82 (1.63–2.20)	2.04 (1.79–2.47)	.011
AAA (relative size, ASI ≥ 1.5)	*n = 143*	*n = 72*	
Mean AAA patient age ± SD, years	74.1 ± 9.0	75.2 ± 9.0	.330
Absolute AAA size (mm)	35.9 (31.6–44.2)	29.9 (26.8–34.6)	<.001
Relative AAA size (ASI)	1.82 (1.65–2.20)	1.78 (1.63–2.06)	.307

Abdominal aortic aneurysm (AAA) prevalence was significantly different between males and females using absolute aortic size thresholds but not aortic size index (ASI). Note that this appeared to be due to sex related differences in body surface area rather than body mass index. Data are expressed as absolute numbers (%) or medians (interquartile range), if not stated otherwise. SD = standard deviation.
[a] To enable comparison with other reports means (±1 SD) were 21.1 ± 6.0 mm and 17.6 ± 4.5 mm respectively.

combined group is shown in Table 1. A more complete set of demographic data for each screening group is shown in Table S1.

There was a significant 3.5 mm sex related difference in average infrarenal aortic size, which appeared to be consistent across the vast majority of the population size range (Fig. 1A).

AAA prevalence: 30 mm threshold

Using a 30 mm threshold, a total of 181 AAA were detected in the four CVD risk based screening groups, with a total population prevalence of 4.4%. In males, the prevalence was 5.7% (143 AAA) and significantly lower in females at 2.4% (38 AAA, chi-squared $p < .001$).

AAA prevalence: ASI 1.5 threshold

When ASI (≥1.5) was used to define AAA in the same combined group of individuals, males had the same prevalence as that observed using a 30 mm threshold (143 AAA, 5.7%). Of note, however, 20 of these individuals had absolute aortic sizes below 30 mm, while a further 20 individuals, who had absolute aortic sizes greater than 30 mm, had an ASI less than 1.5; hence, while prevalence rates were identical, these two AAA definitions were not perfect surrogates for one another (86% concordance).

In females, prevalence was 4.5% (72 AAA) and included all 38 individuals detected using the 30 mm threshold plus an additional 34 (47%) who had absolute sizes < 30 mm (Fig. 2). The increased female prevalence associated with the ASI ≥1.5 AAA definition was significantly different from that associated with the 30 mm threshold (4.5% vs. 2.4%, chi-square $p < .001$).

There was a strong linear relationship between absolute aortic size and ASI (Fig. 2), with the following regression formula, male absolute infrarenal aortic size (mm) = 1.66 + 18.26 × ASI, $r^2 = 89$, and female absolute infrarenal aortic size (mm) = 2.22 + 15.19 × ASI, $r^2 = .84$ respectively.

AAA prevalence: 26 mm threshold

Using a smaller absolute threshold resulted in increased AAA prevalence in men, rising from 5.7% to 10.2% (30 mm–26 mm respectively, Fig. 3A). In women, prevalence rose from 2.4% (≥30 mm) to approximately 4.4% regardless of whether a 26 or ASI ≥ 1.5 threshold was applied (Fig. 3B).

When 30 mm and 26 mm thresholds were used in men and women respectively, AAA prevalence was not significantly different between sexes (5.7 and 4.5%, chi-square $p = .07$).

Both 30 mm and ASI ≥1.5 AAA prevalence was significantly lower in self reported healthy controls than the increased CVD risk screening cohorts (Table S1, ASI ≥ 1.5 odds ratio 0.20, 95% CI 0.01–0.38, $p < .001$, adjusted for sex and age).

Demographic confounders of AAA prevalence

Stepwise multiple logistic regression was used to determine confounding demographic effects on AAA prevalence (Table 2). Age, smoking (lifelong pack year consumption), diabetes (protective), and history of cardiovascular disease were associated with both AAA definitions regardless of how AAA was defined. However, while male sex was associated with AAA risk when using the 30 mm threshold, there was no difference between sexes when AAA was defined using the ASI criteria.

Sex differences in absolute size and aortic size index in those with a screening detected AAA

When AAA was defined as ≥ 30 mm, there was no difference in the (absolute) size of screening detected aneurysms between sexes, although women had AAAs with greater ASI ($P = .01$).

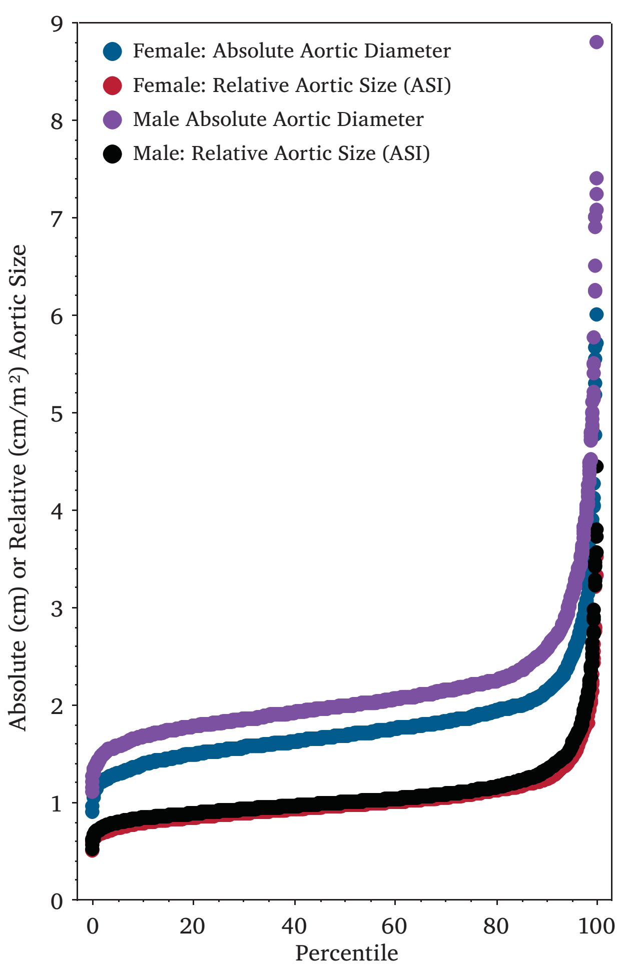

Figure 1. Percentile plots showing sex specific absolute (cm) and relative (cm/m^2) aortic size distributions in the combined abdominal aortic aneurysm (AAA) screening populations. In the AAA screening groups ($n = 4115$), note the approximately 3.5 mm sex related difference between absolute aortic size measures (two curves at the top). This difference is less apparent when aortic size was adjusted for body size using the aortic size index (ASI, two curves at the bottom).

When AAA was defined as ASI $\geq$1.5, men had significantly larger (absolute) sized aneurysms than women (Table 1).

Age distribution of AAA prevalence

AAA prevalence in different age strata are shown in Fig. 3A and B. Age was significantly correlated with both absolute aortic size ($r = .11$, $Z = 7.3$, $p < .001$) and ASI ($r = .23$, Z-value 14.9, $p < .001$).

In females, the 30 mm AAA threshold prevalence appeared to plateau in those below 75 years of age, before rising significantly in older women (1.7 vs. 3.8%, chi-square $p < .01$), while in men the rise in prevalence was more linear across age strata, before levelling off in those over 70 years of age.

DISCUSSION

In this study a series of elderly population cohorts was examined to determine the prevalence of AAA using different disease thresholds: (1) a single absolute size (30 mm, which is widely used internationally), (2) sex specific absolute thresholds (males 30 mm and females 26 mm), and (3) a relative aortic size (ASI) which adjusted each individual for their body surface area. The widely used 30 mm threshold resulted in prevalence rates largely consistent with other reports,[11,12] and appeared to recapitulate the perception of a strong male predominance of AAA disease. In contrast, sex specific and relative aortic size thresholds, while having little effect on male prevalence, suggested that female prevalence was almost twice as high than that reported using the (male derived) 30 mm threshold.

It is important to note that AAA is formally defined as a segmental dilation of 50% greater than normal vessel diameter,[4] but both the European Society of Vascular Surgery[13] and U.S. Preventive Services Task Force[14] guidelines state that an absolute size threshold of 30 mm can be applied, this being the prevalent practice internationally.[15] The practical reasons for selecting a single absolute diameter, without the need for correction using a reference diameter, are obvious. Nevertheless, if male and female prevalence rates are to be compared common sense dictates that a lower threshold value (26 mm) should be used for women. Even then, absolute size thresholds do not account for body size differences as would be the case in the formal "normal vessel size" adjusted definition. In this study each individual's infrarenal aortic diameter was divided by their body surface area to calculate an ASI. AAA was defined as an infrarenal ASI greater than or equal to 1.5; however, it should be noted that this was not an arbitrary determination (despite this numbers obvious apparent association with a 50% change in diameter and potentially convenient utility in screening practice). In this cohort an ASI of 1.5 corresponded to infrarenal aortic diameters of 29.9 and 26.3 mm in an average sized man or women respectively. It is argued that ASI $\geq$1.5 is a reasonable proxy by which to define AAA and it may have significant advantages over that of absolute thresholds, particularly in smaller individuals whose aortic diameters could be below an absolute threshold but still constitute a greater than 50% enlargement of their predicted normal size. Nevertheless, regardless of whether ASI or sex specific absolute thresholds are used, this study suggests that the "true AAA prevalence" in these screening cohorts, is not vastly different between men and women.

Comparison with other studies

While this is at odds with the historically reported high male associated prevalence (typically 3:1), it is not a new observation. Indeed, Anders Wanhainen[16] commented in his review in 2008 that, not only does a single "fixed diameter threshold not serve as a proper definition of an aneurysm", it may also introduce false positives (mostly in men) and false negatives in women. These issues were substantially reduced when AAA was redefined as a 50% diameter increase referenced against a sex specific population nomogram.[6] Observations in this current study

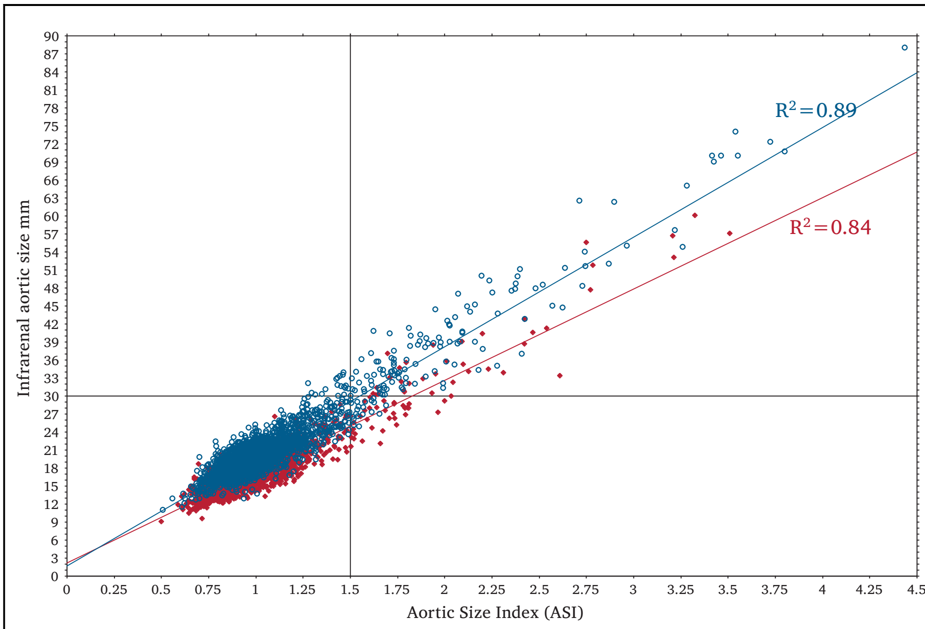

Figure 2. Scatter plot showing the relationship between absolute (*y* axis) and relative (*x* axis) aortic size. *Note.* There is a clear offset between males (blue open circles) and females (red diamonds) resulting in 34 women (in the lower right quadrant) with aortic size index ≥ 1.5 but absolute aortic sizes less than 30 mm. There were 20 men in each of the upper left and lower right quadrants that were defined as having an abdominal aortic aneurysm in only one of the two definitions. Regression lines and correlation values are shown for both men (blue) and women (red).

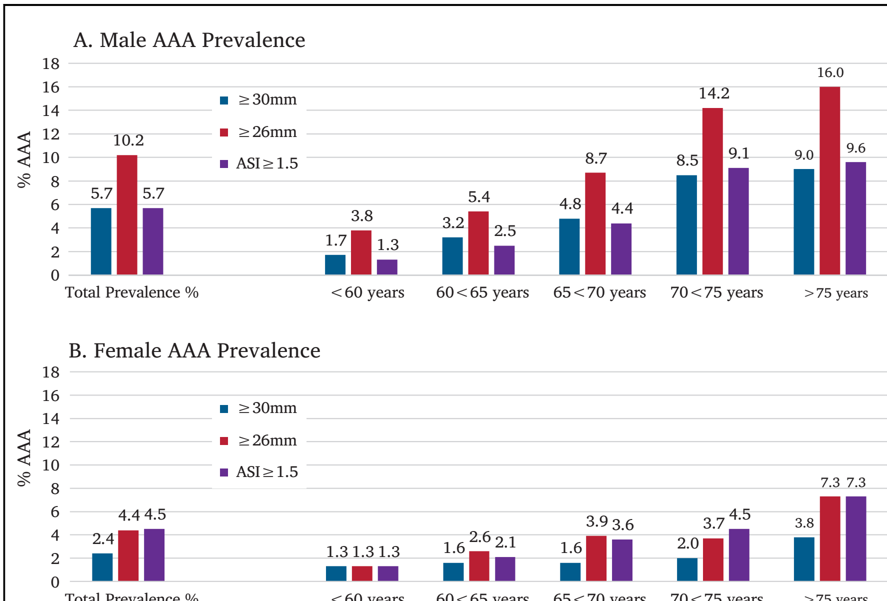

Figure 3. Age distribution of abdominal aortic aneurysms (AAAs) detected using different definitions in (A) males and (B) females. (A) In males, AAA prevalence using absolute size ≥ 30 mm and aortic size index (ASI) ≥ 1.5 had similar combined and inter-age group prevalence. (B) In females, AAA prevalence using absolute size ≥ 26 mm and aortic size index (ASI) ≥ 1.5 had similar combined and inter-age group prevalence.

Table 2. Multiple logistic regression for AAA risk factors compared using absolute size or ASI ≥1.5 definitions

	Infrarenal diameter ≥30 mm	Infrarenal diameter ≥30 mm (males), or ≥26 mm (females)	ASI ≥ 1.5
Age	1.06 (1.05–1.08), <.001	1.07 (1.05–1.09), <.001	1.08 (1.07–1.10), <.001
Smoking history			
Moderate, 1–25 pack years	2.04 (1.31–3.17), <.002	2.45 (1.64–3.68), <.002	2.54 (1.71–3.77), <.001
Heavy, > 25 pack years	4.10 (2.70–6.22), <.001	4.70 (3.17–6.96), <.001	4.70 (3.19–6.94), <.001
Diabetes	0.61 (0.41–0.91), .014	0.61 (0.42–0.89), .010	0.46 (0.31–0.69), <.001
History of ischaemic heart disease	4.61 (2.24–9.49), <.001	1.87 (1.40–2.49), <.001	1.66 (1.25–2.21), <.001
Male sex	2.25 (1.55–3.29), < 0.001	0.86 (0.72–1.32), 0.857	0.98 (0.72–1.33), 0.880

This analysis was conducted using all study participants (CVD risk based screening groups and healthy controls, consisting of 3129 males and 1786 females). Each AAA definition (≥30 mm; ≥30 mm [males] or ≥26 mm [females]; and ASI ≥1.5) was analysed in a stepwise multiple logistic regression model that indicated that age, smoking, diabetes (protective), and history of cardiovascular disease were independently associated with AAA (shown as multivariable OR with 95% CI, *p* values). Importantly, male sex was only independently associated with AAA risk when using the 30 mm (for both sexes) threshold. Sex was not a significant independent confounder when AAA was defined using the aortic size index or sex specific criteria. AAA = abdominal aortic aneurysm; ASI = Aortic Size Index; CVD = cardiovascular disease; CI = confidence interval.

strongly support these conclusions, in that 20 men (14%) with a 30 mm defined AAA were observed and were reclassified as non-aneurysmal (false positives) when assessed using the ASI. More significantly, however, 34 women were observed who were reclassified as having AAA using the ASI, resulting in a 1.9 fold increase in female prevalence. On this basis, it is suggested that the concept of AAA being a disease of elderly males is primarily a definition artefact and its continued consideration as a strong AAA risk feature should be discouraged, or at the very least modified to include appropriate caveats. This concept has potentially generated inequality between sexes with regard to accessing appropriate screening.

In New Zealand, there are significant health inequalities between the indigenous Māori population and non-Māori. Māori women have rates of AAA related deaths that are similar to both Māori and non-Māori men.[17] Maori women also appear to have (30 mm defined) AAA prevalence rates equivalent to men[18] and Maori in general present with AAA at a younger age[19] and have poorer outcomes.[20] This may be due, in part, to the high rates of smoking among all Māori, but especially Māori women,[21] but it is nevertheless clear that any proposed national AAA programme must include such high risk individuals or risk creating further inequality.

Some investigators have reported worse outcomes for women following AAA repair[21,22] with a potential inference being that screening may be less advantageous in women, because they are less likely than men to benefit from subsequent interventions. However, when mortality and major complication outcomes are considered in the context of relative aortic size (ASI) there is no significant difference between sexes,[23] suggesting that differences in outcome are more likely to be related to the advanced nature of the pathology in those women who are currently undergoing surgical repair compared to their male counterparts.

A limitation of this study is that primarily participants with elevated cardiovascular disease risk were examined in a population that was predominantly of European descent. In addition, there is potential for selection bias among the healthy elderly control group because of its self selected nature. Although the observation that women have a greater AAA prevalence, approaching that of men, appears to be consistent with prior reports,[6] the generalisability of this observation within less targeted AAA screening groups also remains to be determined.

There has been a suggestion that it may be appropriate to lower the AAA detection threshold in men to include those in the 25–29 mm range,[24] with some evidence indicating that such "pre-aneurysmal" dimensions are associated with increased cardiovascular disease mortality.[24–26] Conversely, there is concern that changing AAA detection thresholds risks increasing "over diagnosis".[27] Indeed, the data suggests that lowering the threshold from 30 to 26 mm would effectively double AAA prevalence in men. The cost benefit evaluation of such an alteration would need very careful consideration, but from a health delivery perspective would probably be problematic, not the least of which, for the significant additional burden that this would place on existing ultrasound surveillance services.

At present the European Society of Vascular Surgery guidelines[13] do not strongly support screening women for AAA, in part due to the low (30 mm threshold) prevalence compared with men and a single study suggesting little difference between rupture incidence in screened and control individuals.[28] Recently a modelling analysis for AAA screening in UK women was conducted by Sweeting et al.[29] They concluded that an AAA screening programme for women, similar to that used to screen UK men, is unlikely to be cost effective. However, it is important to note that their analysis did not consider the likely higher cardiovascular risk in women with AAA. It is worth noting that potentially the greatest benefits of a AAA diagnosis may be the resulting more intensive global cardiovascular risk management, leading to reduced all cause and (non-AAA) CVD related mortality.[30]

Conclusions and policy implications

AAA overdiagnosis is a potential issue and both quality of life consequences and clinical outcomes for those with a small AAA need to be carefully considered.[31] Nevertheless the widely used current status quo (30 mm definition of AAA) precludes the true detection of AAA disease in women and any discussion on the retention or future development of AAA screening programmes must use appropriate sex specific prevalence rates in order to have balanced and fair consideration.

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CONFLICTS OF INTEREST

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. The study underwent scientific peer review and locality assessment by the University of Otago and was pre-registered with the Institutional Research Office. All participants gave written informed consent and the study was approved by the New Zealand Health And Disability Ethics Committee.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.08.048.

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Eur J Vasc Endovasc Surg (2019) 57, 228

COUP D'OEIL

Do Multiple Streams Do As Well As the Big River?

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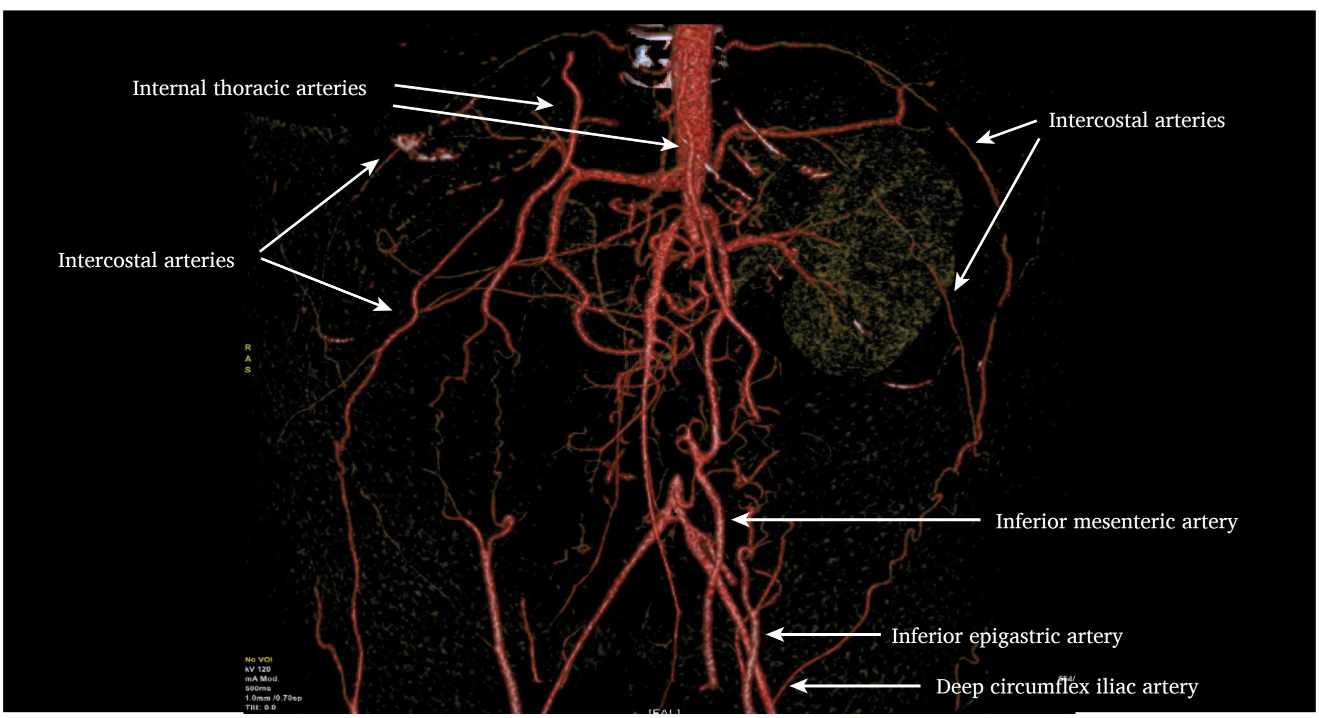

A 16 year old girl presented with hypertension (150/90 mmHg). Magnetic resonance angiography revealed a stenosis of the visceral aorta and occlusion of the infrarenal aorta, with intercostal and internal thoracic arteries providing collateral pathways (arrowed). Middle aortic syndrome of congenital aetiology was diagnosed. The patient did not complain of any intermittent claudication; pedal pulses were present and left and right ankle brachial indices were 0.8. Hypertension was easily controlled with angiotensin converting enzyme inhibitor therapy. No surgical treatment was proposed, however, surgery might be required in the future for vascular decompensation or during pregnancy as indicated.

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