

# Screening for abdominal aortic aneurysm in patients with clinically manifest vascular disease

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## Aims

Declining prevalence of abdominal aortic aneurysm (AAA) might force a more targeted screening approach (high-risk populations only) in order to maintain (cost-)effectiveness. We aimed to determine temporal changes in the prevalence of screening-detected AAA, to assess AAA-related surgery, and evaluate all-cause mortality in patients with manifest vascular disease.

## Methods and results

We included patients with manifest vascular disease but without a history of AAA enrolled in the ongoing single-centre prospective UCC-SMART cohort study. Patients were screened at baseline for AAA by abdominal ultrasonography. We calculated sex- and age-specific prevalence of AAA, probability of survival in relation to the presence of AAA, and the proportion of patients undergoing AAA-related surgery. Prevalence of screening-detected AAA in 5440 screened men was 2.5% [95% confidence interval (CI) 2.1–2.9%] and in 1983 screened women 0.7% (95% CI 0.4–1.1%). Prevalence declined from 1997 until 2017 in men aged 70–79 years from 8.1% to 3.2% and in men aged 60–69 years from 5.7% to 1.0%. 36% of patients with screening-detected AAA received elective AAA-related surgery during follow-up (median time until surgery = 5.3 years, interquartile range 2.5–9.1). Patients with screening-detected AAA had a lower probability of survival (sex and age adjusted) compared to patients without screening-detected AAA (51%, 95% CI 41–64% vs. 69%, 95% CI 68–71%) after 15 years of follow-up.

## Conclusion

The prevalence of screening-detected AAA has declined over the period 1997–2017 in men with vascular disease but exceeds prevalence in already established screening programs targeting 65-year-old men. Screening for AAA in patients with vascular disease may be cost-effective, but this remains to be determined.

## Keywords

Abdominal aortic aneurysm • Screening • Vascular disease • High-risk population • Follow-up

## Introduction

Abdominal aortic aneurysm (AAA) is a serious and life-threatening condition, with upon rupture a mortality rate of 67–94%, often without any symptoms prior to rupture.<sup>1</sup> From 2006 through 2013, Sweden and the UK have implemented screening programs for AAA in men  $\geq 65$  years old while screening is recommended in the USA, Canada, and Germany.<sup>2–5</sup> These screening

programs were initiated on the basis of four randomized controlled trials conducted between 1991 and 2004 showing a reduction in AAA-related mortality rates and AAA rupture after implementation of screening.<sup>6–9</sup> However, over the last 20 years, the prevalence of AAA in Western-Europe and the USA has declined from 5.0–16.9% to 1.3–1.7%,<sup>10–12</sup> probably due to a reduction of smoking, better blood pressure control, and increased statin use.<sup>10,13</sup>

During the European Society of Cardiology congress in August 2019, we presented a scientific abstract with preliminary results of this research.

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Effectiveness and cost-effectiveness of screening are greatly influenced by the prevalence of the disease. Continuation of the decline in the prevalence of AAA may result in lower effectiveness and cost-effectiveness of these nationwide screening programs. More targeted screening of high-risk populations with an expected higher prevalence of AAA should be considered and investigated with regard to feasibility and (cost-)effectiveness. Patients who already have a clinical manifestation of vascular disease have a higher probability of developing an AAA and share many of the known risk factors for AAA such as smoking, elevated blood pressure, and dyslipidaemia.<sup>14–16</sup> As such, patients with the vascular disease could be a suitable population for a more targeted screening approach.

The purpose of this study is to determine the temporal changes in the prevalence of screening-detected AAA, to assess AAA-related surgery, and evaluate all-cause mortality in a prospective cohort of patients with clinically manifest vascular disease.

## Methods

### Study population

For this study, we obtained data from patients enrolled in the Utrecht Cardiovascular Cohort – Second Manifestations of ARterial disease (UCC-SMART) study, an ongoing single-centre, prospective cohort at the University Medical Center Utrecht (UMCU) in the Netherlands. Inclusion started in 1996, after which participating patients, aged 18–80 years, referred to the UMCU with clinically manifest atherosclerotic vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, or AAA), or cardiovascular risk factors (hyperlipidaemia, diabetes, or hypertension) underwent vascular screening. Exclusion criteria were short lifetime expectancy, pregnancy, or not sufficiently fluent in Dutch. A detailed description of the study rationale and design has previously been published.<sup>17</sup> The study was approved by the Medical Ethics Committee of the UMCU and written consent was obtained from all participants. For the current study, we included data of patients aged 40–80 years, included between September 1996 and March 2018 with a history of manifest atherosclerotic vascular disease, but without a history of AAA. Patients without an abdominal ultrasonography at baseline were excluded.

### Baseline measurements and abdominal aortic aneurysm screening

At baseline, information on medical history, history of vascular disease, family history of AAA, medication use, and cardiovascular risk factors (e.g. smoking, hypertension, hyperlipidaemia) was obtained with the use of questionnaires. Additionally, patients underwent physical examination and laboratory examination in the fasting state including measurement of traditional cardiovascular risk factors (blood pressure, waist circumference, plasma lipids, C-reactive protein, eGFR). Included within the vascular screening, an ultrasound of the abdominal aorta was performed. Well-trained vascular technologists in a certified vascular laboratory took supra- and infrarenal measurements by ultrasonography of the abdominal aorta. We defined the presence of AAA as local dilatation of the antero-posterior diameter of the abdominal aorta of 30 mm or larger in accordance with international standards.<sup>18</sup> If an AAA was detected during screening, this finding was reported to the treating specialist and general practitioner with a follow-up and treatment suggestion. Subsequently, the treating specialist and patient made the final decision about the final treatment. The following treatment policy was recommended if an AAA was

detected: if the diameter of the AAA was between 30 and 55 mm follow-up ultrasound examinations were advised to determine the growth rate; if the diameter of the AAA was 40 mm or larger it was also recommended to consider referral to a vascular surgeon for further policy.

### Follow-up

We followed patients from inclusion in the cohort until death, loss to follow-up, or the predefined end date of 1 March 2018. Data collection during follow-up included AAA-related surgeries [either endovascular aortic repair (EVAR) or open surgical repair (OSR)], 30-day operative mortality, AAA rupture, and cause of death including death due to AAA rupture. During follow-up, we annually asked patients to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. When a patient reported a possible event, we collected all relevant hospital documents, and laboratory and radiologic findings. The cause of death was verified with general practitioners, medical specialists, or relatives. Three members of the UCC-SMART-study endpoint committee, comprised of physicians from different departments, independently audited all events.

### Data analyses

We presented characteristics of the study population for those with and without the presence of AAA during screening (screening-detected AAA). Continuous variables are presented as the median and interquartile range (IQR) and categorical variables as counts and percentages. Subsequently, we calculated sex- and age-specific prevalence including 95% confidence interval (95% CI) of screening-detected AAA as well as the number needed to screen (NNS) to detect one AAA. To detect possible temporal changes in the prevalence of screening-detected AAA during the study, we calculated prevalence and accompanying 95% CI of screening-detected AAA for the following time periods: 1 January 1997 until 31 December 2001, 1 January 2002 until 31 December 2006, 1 January 2007 until 31 December 2011, and 1 January 2012 until 31 December 2017. We calculated both all-cause mortality and death due to AAA rupture rates per 1000 patient-years of follow-up for men and women. To describe the association between screening-detected AAA and all-cause mortality, we fitted Cox proportional hazard models to estimate hazard ratios (HR) and accompanying 95% CIs for both men and women and the entire study population. First, we fitted a model without adjustments. Second, we fitted a model adjusted for age. Subsequently, we plotted accompanying survival curves and calculated the survival probability and accompanying 95% CI after 15 years of follow-up. We visually checked the assumption of proportionality by plotting the Schoenfeld residuals. All statistical analyses were performed in R Statistical Software version 4.3, Foundation for Statistical Computing, Vienna, Austria.

## Results

### Baseline characteristics

A total of 7423 patients between 40 and 80 years of age with clinically manifest vascular disease but without an already established AAA diagnosis enrolled in the UCC-SMART cohort were included in this study. Patients with a history of AAA (590 men and 109 women) were excluded, as were patients without an abdominal ultrasonography at baseline ( $n = 53$ ). Table 1 shows the baseline characteristics of the study population. In the group with screening-detected AAA ( $n = 149$ ), the majority were men (91%) and compared to the group without screening-detected AAA they were older, more

**Table 1** Baseline characteristics of patients with vascular disease with and without screening-detected AAA

	Screening-detected AAA	
	Yes (n = 149)	No (n = 7274)
Male sex, n (%)	136 (91)	5304 (73)
Age in years, median (IQR)	66 (61–71)	61 (53–67)
Smoking status, n (%)		
Yes	63 (42)	2138 (29)
Former	67 (45)	3457 (48)
Family history of AAA, n (%)	10 (7)	330 (5)
Medical history and medication use		
Cerebrovascular disease, n (%)	48 (32)	2225 (31)
Coronary artery disease, n (%)	94 (63)	4642 (64)
Peripheral artery disease, n (%)	35 (24)	1275 (18)
Diabetes mellitus, n (%)	24 (16)	1295 (18)
Lipid-lowering agents, n (%)	100 (67)	5170 (71)
Blood pressure-lowering agents, n (%)	117 (79)	5543 (76)
Antithrombotics, n (%)	129 (87)	6197 (85)
Measurements		
Body mass index, kg/m <sup>2</sup> , median (IQR)	27.5 (25.1–29.7)	26.5 (24.3–29.1)
Waist circumference, cm, median (IQR)	100 (94–107)	96 (88–103)
Systolic blood pressure, mmHg, median (IQR)	139 (128–157)	137 (125–151)
Diastolic blood pressure, mmHg, median (IQR)	81 (75–89)	80 (73–87)
Total cholesterol mmol/L, median (IQR)	4.8 (4.1–5.6)	4.6 (3.9–5.5)
LDL-cholesterol, mmol/L, median (IQR)	3.0 (2.3–3.5)	2.6 (2.1–3.4)
HDL-cholesterol, mmol/L, median (IQR)	1.1 (0.9–1.3)	1.2 (1.0–1.4)
Triglycerides, mmol/L, median (IQR)	1.5 (1.1–2.1)	1.4 (1.0–2.0)
C-reactive protein, mg/L, median (IQR)	3.2 (1.4–7.1)	1.9 (0.9–4.1)
eGFR, mL/min/1.73 m <sup>2</sup> , median (IQR)	71 (60–84)	78 (67–89)

AA, abdominal aortic aneurysm; IQR, interquartile ranges.

often smoker and had a higher waist circumference and C-reactive protein.

**Prevalence of abdominal aortic aneurysm and trend in prevalence over time**

Screening of 5440 men yielded 136 AAA, translating into a prevalence of 2.5% (95% CI 2.1–2.9%). In 1983 women 13 AAA were detected during screening resulting in a prevalence of 0.7% (95% CI 0.4–1.1%). In both men and women, the prevalence of AAA increased with age (Table 2; Supplementary material online, Figure S1).

From 1997 until 2017, the prevalence of screening-detected AAA declined in the entire study population of men aged 40–80 years from 3.9% (95% CI 3.0–5.2%) in 1997 until 2001 to 1.5% (95% CI 1.0–2.4%) in 2012 until 2017 (Figure 1). The prevalence in men aged 70–79 years declined from 8.1% (95% CI 5.2–12.4%) in 1997 until 2001 to 3.2% (95% CI 1.5–6.4%) in 2012 until 2017, and in men aged 60–69 years from 5.7% (95% CI 3.7–8.6%) in 1997 until 2001 to 1.0% (95% CI 0.4–2.3%) in 2012 until 2017 (Figure 1). Prevalence of screening-detected AAA in men aged 40–60 years remained essentially the same in the period 1997 until 2001 compared to 2012 until 2017.

In men, 109 out of 136 screening-detected AAA were 30–39 mm (80%), 16 were between 40–49 mm (12%), 5 were between 50–55 mm (4%) and 6 were ≥55 mm (4%). In women, 10 out of 13 screening-detected AAA were 30–39 mm (77%), 2 were between 40–49 mm (15%), 1 was ≥50 mm (8%) (Supplementary material online, Figure S2). Number needed to screen to detect one AAA (NNS) in men was 40 and in women 153. NNS in men was lower at higher age. In older women (≥55 years), the NNS was higher compared to men (Table 2; Supplementary material online, Figure S3).

**Abdominal aortic aneurysm-related surgery and 30-day operative mortality**

Total years of follow-up of 7423 patients were 67 032 person-years and median follow-up time was 8.7 years (IQR 4.8–12.9 years). Of the 7423 patients in this study, 445 patients (6.0%) were lost to follow-up due to migration or withdrawal. During follow-up, 53 out of 149 (36%) patients with a screening-detected AAA received elective surgery [49 out of 136 (36%) men and 4 out of 13 (31%) women]. The median time until surgery was 5.3 years (IQR 2.5–9.1 years). In patients without screening-detected AAA at baseline, 69 out of 7274 patients (0.9%) received elective AAA surgery [62 out of 5304 (1.2%) men and 7 out of 1970 (0.4%) women] because they developed an

AAA during follow-up. The median time until surgery in these patients was 8.9 years (IQR 6.5–12.6 years). Patients without screening-detected AAA, but who did receive AAA surgery during follow-up, were mainly men (88%), mean aorta diameter at baseline

**Table 2** Prevalence and NNS of screening-detected AAA in men and women with vascular disease

	Men (n = 5440)	Women (n = 1983)
Prevalence, % (95% confidence interval)		
40–44 years	0.0 (0.0–1.8)	0.0 (0.0–2.8)
45–49 years	0.6 (0.2–1.8)	0.0 (0.0–1.8)
50–54 years	0.7 (0.3–1.6)	0.8 (0.2–2.8)
55–59 years	2.0 (1.3–3.1)	0.3 (0.0–1.9)
60–64 years	2.7 (1.8–3.9)	1.2 (0.5–3.0)
65–69 years	4.0 (2.9–5.4)	0.6 (0.2–2.2)
70–74 years	4.7 (3.3–6.6)	1.1 (0.4–3.3)
75–79 years	3.8 (2.2–6.3)	0.7 (0.0–3.6)
<b>40–80 years</b>	<b>2.5 (2.1–2.9)</b>	<b>0.7 (0.4–1.1)</b>
NNS		
40–44 years	NA	NA
45–49 years	163	NA
50–54 years	137	129
55–59 years	51	297
60–64 years	38	85
65–69 years	25	165
70–74 years	21	87
75–79 years	27	153
<b>40–80 years</b>	<b>40</b>	<b>153</b>

AAA, abdominal aortic aneurysm; NA, not applicable; NNS, number needed to screen to detect one aneurysm.

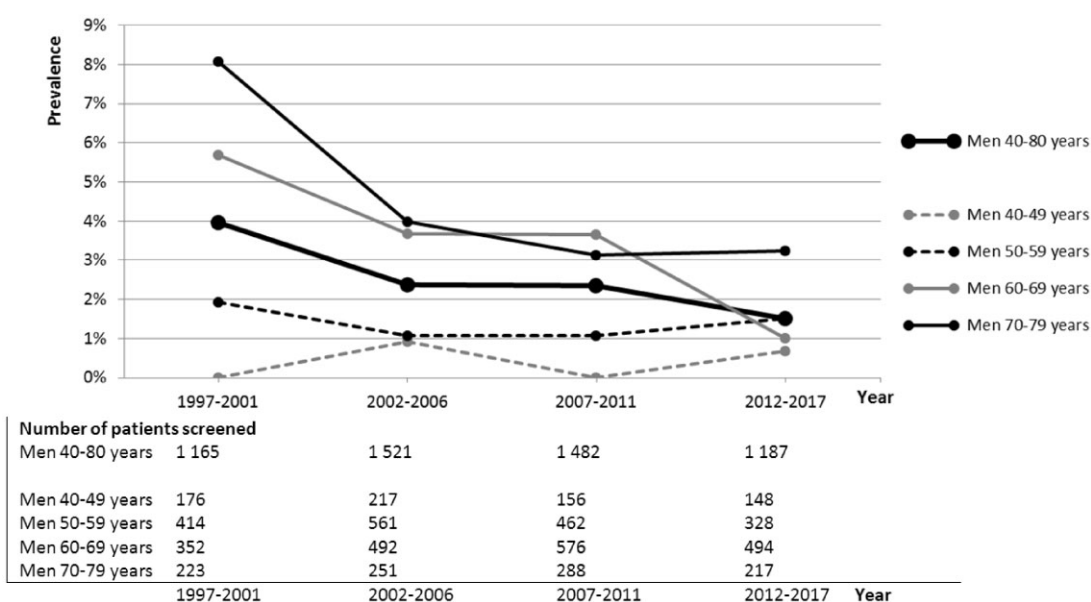
was 22 mm (standard deviation 3.4 mm) and the median age at baseline was 60 years (IQR 53–65 years). Both patients with and without screening-detected AAA were most often treated with EVAR. One man with screening-detected AAA died within 30 days after elective OSR (Table 3).

## Abdominal aortic aneurysm-related death and all-cause mortality

During follow-up, 9 patients died due to AAA rupture; 3 men with screening-detected AAA and 5 men and 1 woman without screening-detected AAA (Table 3). Both men and women with screening-detected AAA had a higher risk of all-cause mortality compared to patients without screening-detected AAA (men: HR 2.38; 95% CI 1.85–3.07 and women: HR 3.45; 95% CI 1.63–7.28). After age adjustment, this difference attenuated (men: HR 1.65; 95% CI 1.28–2.13 and women: HR 2.82; 95% CI 1.33–5.97) (Table 3; [Supplementary material online, Figures S4 and S5](#)). Sex and age-adjusted survival probability after 15 years of follow-up for all patients (both men and women) with screening-detected AAA was 51% (95% CI 41–64%) vs. 69% (95% CI 68–71%) for patients without screening-detected AAA ([Supplementary material online, Figure S6](#)).

## Discussion

In patients with clinically manifest vascular disease, the prevalence of screening-detected AAA was higher in men compared to women and higher at a higher age. Over the period 1997–2017, there was a steady decline in prevalence, in particular in men aged 60–79 years. One-third of patients with screening-detected AAA received elective surgery at some point within 15 years after AAA diagnosis. After sex and age adjustment, patients with screening-detected AAA had a higher risk of all-cause mortality compared to patients without screening-detected AAA.



**Figure 1** Trends in prevalence of screening-detected abdominal aortic aneurysm between 1997 and 2017 in men with vascular disease. AAA, abdominal aortic aneurysm.

**Table 3** Surgery, operative mortality, AAA rupture, and all-cause mortality after screening for AAA

	Screening-detected AAA		No screening-detected AAA		Total study population	
	Men (n = 136)	Women (n = 13)	Men (n = 5304)	Women (n = 1970)	Men (n = 5440)	Women (n = 1983)
Person-years of observation	1133	101	47 827	17 970	48 960	18 072
Surgery + operative mortality						
Elective EVAR, n (%)	33 (24)	3 (23)	41 (0.8)	5 (0.3)	74 (1.4)	8 (0.4)
Elective OSR, n (%)	16 (12)	1 (8)	21 (0.4)	2 (0.1)	37 (0.7)	3 (0.2)
30-day operative mortality, n	1	0	0	0	1	0
Non-fatal emergency surgery, n	0	0	1	0	1	0
Mortality						
Fatal AAA rupture, n (%)	3 (2.2)	0 (0)	5 (0.09)	1 (0.05)	8 (0.15)	1 (0.05)
AAA rupture mortality rate per 1000 person-years (95% CI)	2.65 (0.55–7.74)	0 (0–36.35)	0.10 (0.03–0.24)	0.06 (0.00–0.31)	0.16 (0.07–0.32)	0.06 (0.00–0.31)
All deaths, n (%)	63 (46)	7 (54)	1168 (22)	382 (19)	1231 (23)	389 (20)
All-cause mortality rate per 1000 person-years (95% CI)	55.6 (42.7–71.2)	69.0 (27.7–142.1)	24.4 (23.0–25.9)	21.3 (19.2–23.5)	25.1 (23.8–26.6)	21.5 (19.4–23.8)
Hazard ratio (95% CI)						
Crude	2.38 (1.85–3.07)	3.45 (1.63–7.28)	1.0 (reference)	1.0 (reference)	NA	NA
Age adjusted	1.65 (1.28–2.13)	2.82 (1.33–5.97)	1.0 (reference)	1.0 (reference)	NA	NA

95% CI, 95% confidence interval; AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; OSR, open surgical repair.

Few recent studies describe the prevalence of newly detected AAA in patients with already established vascular disease. Most other studies only report prevalence including already established AAA instead of newly detected AAA by means of screening. Studies that do report the prevalence of screening-detected AAA are in line with our findings. A study retrospectively examining screening-detected AAA by viewing medical records of 5924 patients referred for peripheral vascular examination between 1993 and 2005, reported AAA prevalence in men of 4.2% (95% CI 3.5–4.9%) and in women of 1.5% (95% CI 1.0–2.0%). In men, AAA prevalence increased with age: men aged >60 years 5.5% (95% CI 4.6–6.5%) to 6.7% (95% CI 5.4–7.9%) in men aged >70 years.<sup>19</sup> In men undergoing coronary angiography prevalence of newly detected AAA ranging between 1.9% and 3.9% have been reported in studies conducted between 2009–10 and 2012–13.<sup>20,21</sup> Unfortunately, no age-specific prevalence of screening-detected AAA was reported limiting direct comparison with our findings. Jones *et al.*<sup>21</sup> (conducted between 2012 and 2013) reported the prevalence of newly diagnosed AAA in men >50 years old suspected of peripheral arterial disease of 5.1%, and in men with a 5-year cardiovascular event risk assessment score greater than 10% assessed by their general practitioner of 3.4%. Again, no age-specific data usable for comparison. As age and sex are such important drivers of AAA prevalence, age- and sex-specific reporting is mandatory in order to expand knowledge on this issue.

Over the period 1997 to 2017, the prevalence of screening-detected AAA declined considerably in men with the vascular disease aged ≥60 years, while for younger men and women the prevalence remained low and did not change over time. A similar observation and decline in prevalence can be seen in the general population and is probably due to a reduction of smoking, better blood pressure control, and increased statin use.<sup>10,12,13,22,23</sup> In our cohort of patients

with vascular disease, a declining trend between 1996 and 2014 in these same risk factors has been described which may potentially explain the decrease in prevalence: percentage of current smokers (43–25%), systolic blood pressure ( $147 \pm 20$  mmHg to  $134 \pm 18$  mmHg), LDL-c ( $3.7 \pm 1.0$  mmol/L to  $2.5 \pm 0.9$  mmol/L).<sup>23</sup> In the same period of time, the percentage of patients using blood pressure-lowering drugs and lipid-lowering drugs increased from respectively 59% to 75% and 30% to 79%.<sup>24</sup> Despite the decline of AAA prevalence seen in older men, the most recent prevalence estimates of AAA in our patient population of men with the vascular disease was still higher compared to the prevalence of screening-detected AAA reported in the European screening programs such as Sweden (1.5% between 2006 and 2014), England (1.3% 2009–15), Scotland (1.4% between 2012 and 2019), and Wales (1.2% between 2016 and 2017) targeting men aged ≥65 years.<sup>25–28</sup> This concerns a comparison between our study population of patients with clinically manifest vascular disease and the screening program population that targets all men ≥65 years of age (thus containing both men with and without vascular disease). Showing that on the basis of prevalence patients with vascular disease would be a suitable population to target for AAA screening. The declining prevalence as seen in our study population was also seen in previously mentioned screening programs. The latest reported prevalence in the English screening program was 0.97% in the period between April 2018 and March 2019.<sup>29</sup> In the Netherlands, the National Health Council recently advised against a nationwide screening program for men/women older than 65 years old.<sup>30</sup> The main arguments were the declining AAA mortality rates and the relatively high number of incidental findings of AAA in usual care.<sup>30</sup> Among the important factors influencing the effectiveness of a screening program is the prevalence of the disease. Our findings indicate that in men with the vascular disease, especially those over the



age of 50, the prevalence of AAA is higher than currently seen in screening programs, and thus with lower NNS to detect one AAA. Considering that screening was cost-effective in the screening programs,<sup>31,32</sup> one could argue that screening in men with vascular disease could also be cost-effective.

The decision to implement screening for AAA in patients with vascular disease should not be based solely on prevalence. Among other things, information about diameter distribution, elective surgery, and the accompanying risk of complications, AAA death, and life expectancy is needed to assess harm and benefit as well as carry out cost-effectiveness analysis. For patients with vascular disease, this study provides some of these estimates that can be used for such analyses. For example, to experience benefit from a screening program, patients should have a good enough prognosis to outlive a possible prevented rupture. Patients with vascular disease have an overall worse prognosis than the general population. Yet, we expand the evidence by showing that even within this patient group, those with a screening-detected AAA have a higher mortality risk than the screen negative patients. Furthermore, we provide evidence showing that more than one-third of screening-detected AAA becomes clinically relevant and requires surgery at some point in their life. Note, that these events occurred in a population at high cardiovascular risk and who were in principle optimally managed with respect to cardiovascular risk (lifestyle advice, pharmacological treatment).

Strengths of this study include the prospective study design, a large patient population with clinically manifest vascular disease, yearly inclusion of patients since 1996, and extensive follow-up. Some limitations of this study should be addressed. First, despite the large patient population, the numbers of postoperative 30-day mortality and non-fatal AAA ruptures necessary to perform cost-effectiveness analyses were too low to calculate reliable rates. Second, the possibility of false-positive or false-negative results on abdominal ultrasonography could have led to respectively over- or underestimation of the prevalence of AAA. However, given the high specificity (95–100%) and high sensitivity (97–100%) of abdominal ultrasonography to detect AAA a large over- or underestimation is not very likely.<sup>33</sup> Third, the absence of mandatory autopsy to determine the cause of death could have resulted in an underestimation of AAA-related mortality, especially in patients without a screening-detected AAA.

In conclusion, the prevalence of screening-detected AAA in men with clinically manifest vascular has declined over the period 1997–2017, but exceeds prevalence in already established screening programs targeting 65-year-old men. Screening for AAA in patients with established vascular disease may be cost-effective but this remains to be determined.

## Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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