Hovedoppgave

NTNU
Norges teknisk-naturvitenskapelige universitet
Fakultet for medisin og helsevitenskap

Lise Haugan Ulset

Elevated diastolic blood pressure and the risk of Abdominal Aortic Aneurysm. A HUNT study.

Hovedoppgave i Profesjonsstudiet medisin
Veileder: MD, PhD Linn Åldstedt Nyrønning, Department of Vascular Surgery – St. Olavs hospital Department of Circulation and Medical Imaging – NTNU

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Kunnskap for en bedre verden

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Abstract

Background: Hypertension is often considered an established risk factor for abdominal aortic aneurysm (AAA). However, previous studies have shown inconsistent results. Moreover, some studies have proposed that elevated diastolic blood pressure (DBP) poses a greater risk for AAA than elevated systolic blood pressure (SBP) or hypertension in general. Further studies are needed to look more closely at the role of isolated diastolic hypertension as a risk factor for AAA. The aim of this student thesis was to determine whether there is an increased risk of later being diagnosed with AAA in individuals with elevated DBP in the HUNT population.

Methods: This population-based prospective study included 68 335 participants from the HUNT study in Trøndelag, Norway. Of these, 899 individuals in this study were diagnosed with AAA during the follow-up period. The median follow-up time was 14.3 years (range 1 day – 26 years). All individuals were diagnosed with AAA after the first participation in HUNT. Differences in groups was analysed by AAA status. The Kaplan-Meier method was used to estimate the proportions free from an AAA diagnosis during follow up, whereas Cox proportional hazard regression analyses, were performed to estimate hazard ratios (HR) with 95 % confidence intervals (CI). In the regression analyses, DBP was included as a dichotomous variable (≥ 90 mmHg vs < 90 mmHg) and as quartiles. Adjustments were made for known risk factors of AAA.

Results: At baseline, 50% of the study participants had hypertension. The proportion of individuals with hypertension was higher in those who were later diagnosed with AAA, than those who were not (69.2% vs 55.7%, p<0.001). Moreover, the mean SBP (146 mmHg vs. 137 mmHg, p<0.001) and the mean DBP (86 mmHg vs. 80 mmHg, p<0.001) was higher in those with AAA than without AAA. A greater proportion of those with than without AAA were smokers or prior smokers and had known coronary heart disease. Individuals with elevated DBP had a significant increased risk for later being diagnosed with AAA both in unadjusted and adjusted analyses (unadjusted HR 1.59, 95% CI 1.39-1.83 vs. adjusted HR 1.60, 95% CI 1.37-1.87). Individuals with DBP in the highest quartile (88-125 mmHg) had twice the risk of having an AAA (HR 2.18, 95% CI 1.64-2.88) compared to those in the lowest quartile.

Conclusion: Individuals with elevated DBP (≥90 mmHg) have an increased risk of later being diagnosed with AAA.

Introduction

Aneurysms

An aneurysm is a localized and pathological dilatation of a blood vessel that occurs due to weakening of the vessel wall. True aneurysms include all three layers of the vessel wall, the tunica intima, media, and adventitia. In contrast, a pseudoaneurysm usually occurs because of trauma to the vessel wall and does not include all three layers.[1, 2] Arterial aneurysms are most common in the aorta, and the most frequent of all aortic aneurysms are abdominal aortic aneurysms (AAA). [3]

Abdominal aortic Aneurysms (AAA)

An AAA is defined as a permanent, full- thickness dilatation that is at least 50 % larger than the average diameter of the normal aorta. [4] An infrarenal aortic diameter ≥ 3.0 cm is the most widely used definition of an AAA in daily clinical practice. [5, 6, 7] The average aortic diameter at the abdominal level has been estimated to approximately 2.0 cm (with a range from 1.4 -3.0 cm),[8, 9] and women generally have a smaller aortic diameter than men. Therefore, the definition of AAA as a 50% increase compared to an aortic diameter might be more accurate. The overall prevalence of AAA ranges from 1.5-6 %, and AAAs are more common in men than women. [10, 11, 12] The prevalence before the age of 50-60 years is insignificant, but after that age the prevalence increases steadily every year. [13]

Most cases of AAA remain asymptomatic throughout life. [14] Hence, many AAAs are incidental findings on imaging examinations such as ultrasonography or CT scans, that are performed for unrelated medical conditions. In some patients it might be possible to reveal a palpable and pulsatile mass during examination, but the sensitivity is below 50%.[15] In contrast, a ruptured AAA is immediately life-threatening, with a mortality rate of more than 80 %.[2, 15] The patients often present with sudden and serve abdominal and back pain, and hemodynamic collapse. A rupture occurs when the mechanical stress on the aortic vessel wall exceeds the tensile strength of the wall tissue.[16] This leads to bleeding either retroperitoneal or intraperitoneal, causing a massive blood loss that needs immediate surgical treatment.

When an aortic diameter above 3.0 cm is identified, follow-up for expansion is initiated. The frequency of check-ups depends on the diameter of the aneurysm. According to current guidelines for men, small AAAs (3.0-3.9 cm) should to be monitored every third year. [14] If

the aneurysm is larger, the intervals are shorter, annually for diameters 4.0-4.9 cm and every sixth months for ≥ 5.0cm. In women, the follow-up should be adjusted to a lower diameter threshold. For AAAs with a diameter ≥ 5.5 cm for men and ≥ 5.0 cm for women, prophylactic repair is recommended. In addition, if the aneurysm expands > 0.5 cm in diameter during a period of six months, it should be considered for surgery despite the initial size.[8] Moreover, an AAA causing symptoms ought to be repaired immediately, regardless of size. Surgery of AAA is performed with either open technique using a synthetic graft or endovascular repair (EVAR) which is performed percutaneously with a covered stent (stent graft). [15].

Screening of the aorta with ultrasonography is a method with high accuracy for detecting AAAs, with a sensitivity of 95% and specificity of 100%.[2, 17] Only a few countries have a screening program for detecting aneurysms. UK, Sweden, Germany and United States of America have nationwide organized screening programs for men aged 65 or older[18] In Norway, there is no screening of AAAs in neither men nor women, but there is an ongoing study in Oslo in 65 year old men[19], and recently a recommendation for screening was published.[20]

Pathogenesis and risk factors

AAAs are characterized by progressive and irreversible expansion. The growth rate can vary, where some remain stable for several years whereas others grow more rapidly. [15] In general, the growth increases with larger diameters and the growth can be exponential. The underlying pathogenesis is not fully understood but AAAs seem to develop through a complex interaction between different factors. Animal research indicates four important events in the pathogenesis, starting with macrophages and lymphocytes infiltrating the vessel wall. This leads to the destruction of collagen and elastin in the vessel wall. As a result of the destruction, smooth-muscle cells will be lost in the media layer. A neovascularization then occurs, which leads to weakness in the aortic vessel wall. [21]

Several predisposing factors for AAA development are established. Some risk factors are non-modifiable, such as male sex, high age, and heritage. Moreover, strong associations have been found for several modifiable risk factors such as smoking, coronary heart disease and hypertension.[18, 22] Smoking is the dominant risk factor for developing AAA. A study from 2018 among veterans in the USA estimated that the highest prevalence of AAA was 5.1% in male, white smokers aged 50 to 79.[14] It has been found that current smokers have almost

eight times higher risk of developing an AAA than non-smokers.[23] In addition, ex-smokers have three times higher risk compared to non-smokers.[23] It is assumed that the prevalence of AAA has decreased in recent decades due to the decrease in the number of smokers.[14]

Hypertension has been considered a factor associated with an increased risk of developing AAA, although it is a somewhat controversial theory. Several studies have reported that hypertension may be a less solid risk factor than previously considered.[18, 24, 25, 26, 27]. On the other hand, many studies have found consistency between hypertension and increased risk of AAA[28, 29, 30, 31, 32, 33, 34, 35, 36, 37]. The majority of previous studies have focused on the role of hypertension in general or increased systolic blood pressure.[22, 34, 36, 37, 38, 39, 40, 41, 42, 43] A meta-analysis from 2019 suggests that hypertension increases the risk of developing AAA by 66%. The study used The World Health Organization (WHO) definition of hypertension as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. The study concludes that the relative risk of getting AAA was increased for every 20 mmHg SBP and every 10 mmHg for DBP by respectively 14% and 28%.[6]. Few studies have evaluated the role of DBP in the risk of AAA, but some have suggested that the importance of elevated DBP values might be an even more decisive risk factor. [6, 44, 45, 46, 47, 48] Of these studies, only a few were prospective and population-based, and more research is needed.

Aim and hypothesis

The aim of this student thesis was to investigate if there is an increased risk of being diagnosed with AAA in individuals with elevated DBP in the HUNT study population. The hypothesis was that elevated DBP increases the risk for later being diagnosed with AAA.

Material and methods

The present study is a prospective cohort study using data from the HUNT study (HUNT).

The HUNT-study

HUNT is a multiphase, population-based health study based on the population of Nord-Trøndelag County. HUNT is one of the leading population studies in the world and has been a source of important information about the general population´s health condition. HUNT1 in 1984 was the first survey, and since then 240,000 individuals have participated in four surveys in total, HUNT1-4. Information about relevant risk factors for AAA are not available from HUNT1, and HUNT4 was completed as late as 2019. This study will therefore use data from HUNT2 (1995-1997) and HUNT3 (2006-2008) [49].

HUNT variables

Age and gender were available from HUNT questionnaires. In HUNT, blood pressure was measured three times, and an average of the two last measurements was used. Both SBP and DBP was recorded. Measurement of blood pressure was done using a Dinamap 845XT (Critikon) based on oscillometry [49] Body mass index (BMI) was calculated using weight and height measurements and categorized into four groups (< 25 kg/m2, 25-30 kg/m2, 30-35 kg/m2 and ≥35 kg/m^2 (WHO).

Information about smoking status, use of antihypertensive medication, previous coronary heart disease and diabetes mellitus was based on self-reported questionnaires. Smoking status was divided into “current, “past”, and “never”. History of previous or current coronary heart disease or diabetes was categorized into “yes” or “no”. Coronary heart disease (CHD) was defined by any previous event of myocardial infarction or angina pectoris.

Information about AAA

There is no information about AAA in HUNT, and ultrasound of the aorta is not part of the HUNT database. [50, 51] Information about an AAA diagnosis in the HUNT participants has in

previous projects therefore been collected from the registries at the three local hospitals in the region (St. Olav Hospital, Levanger Hospital and Namsos Hospital) that are responsible for outpatient clinics, follow-up, and treatment for AAA in Nord- Trøndelag.[50, 51, 52] Individuals with AAA in Nord-Trøndelag were identified according to the International Classification of Diseases, Ninth and Tenth revisions (ICD-9, ICD-10 codes, 441.3-4 and 171.3-4) in the period from 1995 to 2020. Patient charts were used to verify all diagnoses manually. The personal identification number was used to link data on AAA diagnoses and death with exposure data in HUNT. This process was done by HUNT. All individuals with AAAs were diagnosed after enrolment in HUNT.

Definition of blood pressure variables

In this study, elevated *DBP* was defined as average DBP ≥90 mmHg, whereas increased *SBP* was defined as an average SBP ≥140 mmHg. Hypertension was defined by a SBP ≥140 mmHg or a DBP ≥90 mmHg or reported use of any antihypertensive medication. The different quartiles for DBP were calculated as 1: 51-71 mmHg, 2: 72-78 mmHg, 3: 79-86 mmHg and 4: 88-125 mmHg.

Study population

The total study population included 68 335 individuals, of whom 899 were diagnosed with AAA during the follow-up. Overall, 25 471 of the individuals participated in HUNT 2, 7 321 in HUNT 3, whereas 35 546 participated in both HUNT2 and HUNT3. In this study population, only three individuals were diagnosed with AAA before the age of 50. Because of this, only participants ≥50 years were included. The follow-up time ended when an individual was diagnosed with AAA, died, or when the study ended. The Norwegian Cause of Death Registry was used to gather information about time of death.

Table 1. Criteria used to define the study population

Inclusion criteria	Exclusion criteria
Age ≥50 years*	Age < 50 years*
Diagnosed AAA during 1995-2020	Diagnosed AAA before 1995 or after 2020
Not diagnosed AAA at start of follow-up	Diagnosed AAA prior to HUNT participation
Participation in HUNT2 and/or HUNT3	Participation in HUNT1 only
Available measurement of blood pressure	No available measurement of blood pressure
Available data for included covariates **	Missing data on ≥1 covariate(s)**

AAA = Abdominal Aortic Aneurysm, HUNT = Trøndelag Health Study.

Follow-up period

The primary endpoint was a diagnosed AAA (defined as ≥3.0 cm). The median follow-up time was 14.3 years (range 1 day to 26 years). The mean age at start of follow-up was 57.7 years (range from 50-101.4 years). Among those with diagnosed with AAA, the mean time from participation in HUNT to the date of AAA diagnosis was 10.3 years (range 0.24-24.7 years). Mean age at diagnosis was 72 years (range 50-106.9 years).

Statistical analysis

Descriptive data are presented as mean (standard deviation, SD), median (min-max) or frequencies (percentage). The chi-square test for categorical variables was used to analyze the differences in groups, defined by AAA status. For continuous variables the Mann-Whitney U-test or independent sample T-test were used. The Kaplan-Meier method was used to estimate the proportions free from an AAA diagnosis at any age during follow up. Kaplan Meier curves were created for groups defined by elevated DBP (≥ 90 mmHg vs. < 90 mmHg) and quartiles of DBP. The analyses were evaluated with the log-rank test. Hazard ratios (HR), with 95% confidence intervals (CI) for AAA, were calculated in univariable and multivariable Cox proportional hazard (PH) regression models. In the regression analyses, DBP was included as a dichotomous variable and as quartiles. Adjustments were done for the following covariates: age, smoking status, sex, BMI, diabetes mellitus, coronary heart disease (CHD) and total cholesterol. BMI was included in the model as a categorical variable to allow for a nonlinear association. Total cholesterol was included as a continuous variable. To avoid

confounding by age, attained age was used as the time scale (entry at age ≥50). Using log-log plots, the proportional hazard assumption was assessed for all variables graphically.

Only individuals with complete information on all covariates were included in the multivariable cox regression models. The proportion of missing values was in general low (range 0.07% -2.3%), highest for smoking (2.3%) and cholesterol (1.9%). Only 48 (0.07%) of all the participants in this study lacked information on hypertension. All statistical analyses were performed using Stata (Version 17.0). A p-value < 0.05 was considered statistically significant.

Ethics

Every participant in the HUNT-study have provide written informed consent in accordance with the Declaration of Helsinki. The Hunt Study board of directors and the Regional Ethics Committee (REK 23124) approved this study.

Results

Characteristics of the study population

In total, 68 335 persons participated in this study, and 899 were diagnosed with AAA. There was a predominance of men compared to women with AAA (73.7 % vs 26.3 %, p<0.001). The characteristics of the study population at the start of follow-up are summarized in Table 2.

Overall, 50 % of the participants had hypertension. The proportion with hypertension was higher among those with AAA compared to those without an AAA diagnosis (69.2% vs 55.7%, p<0.001). Moreover, the mean SBP for those with AAA was 146 mmHg versus 137 mmHg for those without AAA (p<0.001), whereas the mean DBP was 86 mmHg those with AAA versus 80 mmHg in the individuals without AAA (p<0.001). In total, 15.5% of the study participants reported that they were treated with antihypertensive drugs. The proportion was higher among those with AAA (29.9%) than without AAA (15.3%) (p-value <0.001).

The number of current smokers was significantly higher in the group diagnosed with AAA compared with those without AAA (58.7% vs 28.9%, p<0.001). There was a higher proportion with CHD among individuals with AAA than in persons without AAA (24.9% vs. 6.6%, p<0.001). The mean value for total cholesterol was higher among those with than without AAA (6.5 mmol/L versus 5.9 mmol/L, p<0.001). The distributions of BMI values and known diabetes were similar between those with and without AAA. About 50% of the study population (in both groups) had a BMI 25-29.9 kg/m^2, meaning that they were slightly overweight.

Table 2: Characteristics of Study Population at Start of follow-up

Characteristics	**Total population, n (%)**	**AAA**		
		Yes n, (%)	**No** n, (%)	**P value**
	68 335 (100.0)	899 (100.0)	67 436 (100.0)	
Gender				
Men	32 405 (47.4)	663 (73.7)	31 742 (47.1)	<0.001
Women	35 930 (52.6)	236 (26.3)	35 694 (52.9)	
Age at first measured BP (years)				
<50	33 068 (48.4)	90 (10.0)	32 978 (48.9)	<0.001
50-60	13 441 (19.7)	207 (23.0)	13 234 (19.6)	
60-70	10 112 (14.8)	321 (35.7)	9 791 (14.5)	
70-80	8 584 (12.6)	245 (27.3)	8 339 (12.4)	
≥80	3 130 (4.6)	36 (4.0)	3 094 (4.6)	
Hypertension				
Yes	37 168 (55.4)	621 (69.2)	36 891 (55.7)	
No	30 498 (45.3)	277 (30.8)	30 498 (45.3)	<0.001
Systolic BP (mmHg) *Mean (range)*	67 864	146.2 (86-229)	137.3 (70-253)	<0.001
Diastolic BP (mmHg) *Mean (range)*	67 864	86.6 (51-125)	80.0 (38-168)	<0.001
Antihypertensives				
Yes	10 546 (15.5)	269 (29.9)	10 277 (15.3)	<0.001
No	57 634 (84.5)	630 (70.1)	57 004 (84.7	
Smoking status				
Never	27 318 (40.9)	97 (11.0)	27 221 (41.3)	<0.001
Past	19 889 (29.8)	266 (30.1)	19 623 (29.8)	
Current	19 526 (29.2)	520 (58.9)	19 006 (28.9)	
BMI category				
<25 kg/m^2	23 697 (35.1)	271 (30.5)	23 426 (35.2)	
25-29.9 kg/m^2	30 670 (45.4)	449 (50.5)	30 221 (45.3)	
30-34.9 kg/m^2	10 350 (15,3)	141 (15.8)	10 209 (15.3)	<0.005
≥35 kg/m^2	2 849 (4.2)	29 (3.2)	2 820 (4.2)	
Diabetes				
Yes	2 412 (3.5)	27 (3.0)	2 385 (3.5)	<0.402
No	65 762 (96.5)	866 (97.0)	64 896 (96.5)	
CHD				
Yes	4 769 (6.99)	223 (24.9)	4 546 (6.7)	<0.001
No	63 502 (93.01)	676 (75.1)	62 826 (93.3)	
Cholesterol (mmol/L) *Mean (range)*	67 009	6.56 (2.2-11.0)	5.94 (1.3-19.9)	<0.001

*Abbreviations: ***AAA = abdominal aortic aneurysm, BP = blood pressure, BMI = body mass index, CHD = coronary heart disease*

**Missing data (n=): Smoking n=1602 (2.3%), BMI n= 769 (1.1%), hypertension n= 48 (0.07%), diabetes n=161 (0.2%), CHD n=64 (0.09%), cholesterol n = 1326 (1.9%), systolic/diastolic blood pressure = 471 (0.69%), antihypertensives n = 919 (1.3%)*

Table 3 shows the distribution of DBP at the start of follow-up in persons with and without AAA divided into a dichotomous variable and quartiles. There was a higher number with elevated DBP (≥90 mmHg) among those with AAA than in the group without AAA (38.9% vs 20.5%, p-value <0.001).

A significant part of the study population overall had DBP values in quartile four (88-125 mmHg), but the proportion was higher for individuals with AAA (45.5%) than for those without AAA (29.2 %). There were fewer with a low diastolic blood pressure in the group with AAA compared to the group without AAA, quartiles 1 (8.9 % vs 19.3 %) and 2 (16.5 % vs 23.1%). The distribution in the group without AAA was more even compared to the group with AAA.

Table 3: Diastolic Blood Pressure

	Total	**AAA yes**	**AAA no**	**p value**
Diastolic bp, mmHg, n (%)				
<90	53 757 (79.2)	546 (61.1)	53 212 (79.5)	<0.001
≥90	14 107 (20.8)	347 (38.9)	13 760 (20.5)	
Quartiles diastolic bp, mmHg, n (%)				
1 (51-71 mmHg)	13 030 (19.2)	80 (8.9)	12 950 (19.3)	<0.001
2 (72-78 mmHg)	15 624 (23.0)	147 (16.5)	15 477 (23.1)	
3 (79-86 mmHg)	19 243 (28.4)	259 (29.1)	18 984 (28.4)	
4 (88-125 mmHg)	19 967 (29.4)	406 (45.5)	19 561 (29.2)	

**Abbreviations: bp = blood pressure, AAA = abdominal aortic aneurysm*

Diastolic blood pressure and risk of AAA

Figure 1 and Figure 2 show the results from the univariate Kaplan-Meier analysis of the association between DBP and AAA at all ages, according to elevated DBP (≥ 90 mmHg vs < 90 mmHg) and divided into quartiles.

Figure 1 illustrates that the proportion free of AAA is significantly higher for people with normal DBP compared to elevated DBP (log-rank test, p <0.001).

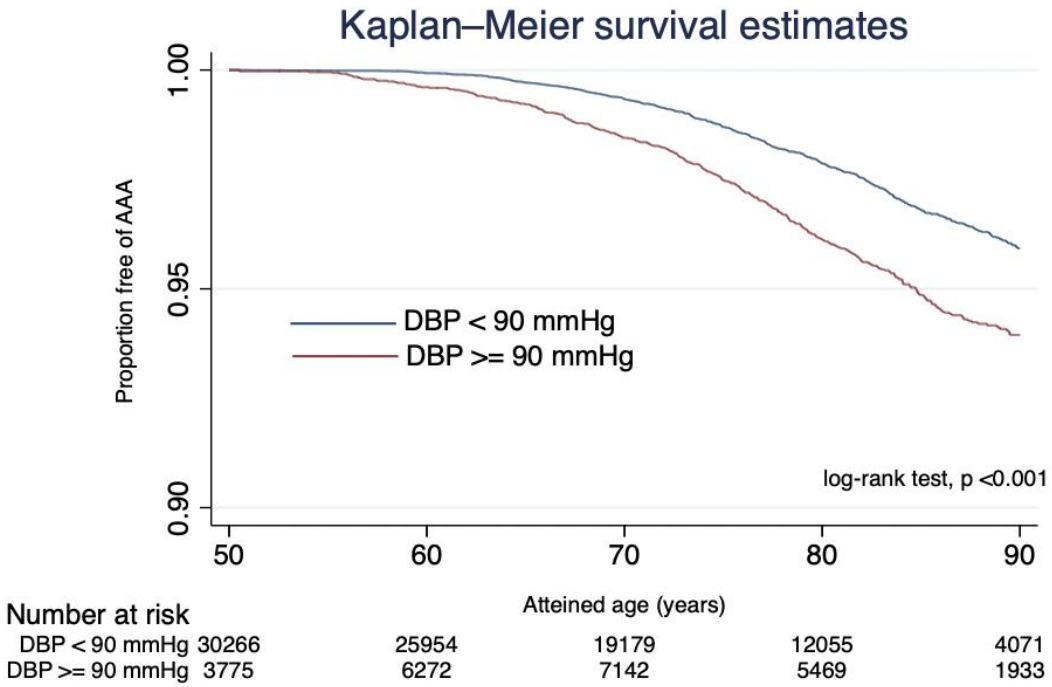

Figure 1: The Kaplan-Meier curve of incident AAAs and numbers at risk during follow-up according to DBP ≥ or < 90 mmHg.

In Figure 2, the Kaplan-Meier curves demonstrate the outcome for the different quartiles of DBP. At all ages, a lower proportion free of AAA was seen in the highest quartile of DBP compared to lowest DBP (log-rank test, p <0.001).

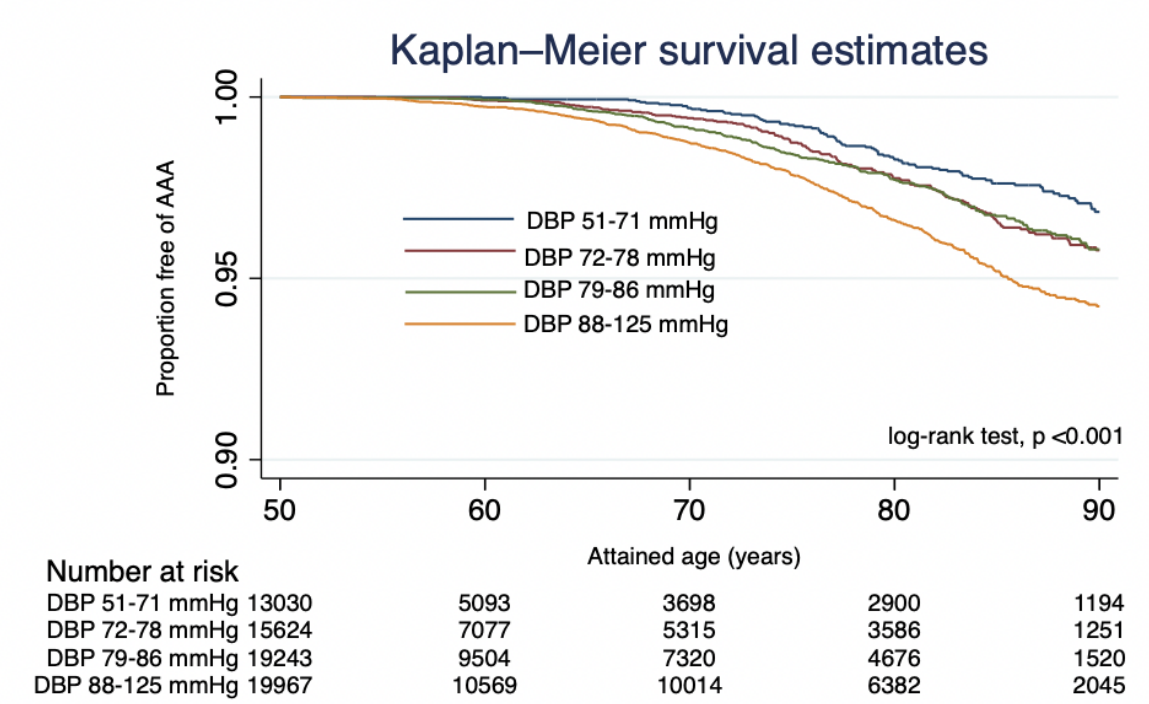

Figure 2: The Kaplan-Meier curve of incident AAAs and numbers at risk during follow-up according to the four different quartiles.

Regression analyses (time to event analyses)

We performed Cox proportional hazard regression analyses with DBP included as a dichotomous variable (< vs ≥ 90) and as quartiles (Table 4).

Unadjusted analyses

Individuals with a DBP ≥ 90 mmHg had more than 1.5 times higher risk of being diagnosed with AAA compared to those with DBP <90 mmHg (HR 1.59, 95% CI 1.39-1.83).

Individuals with DBP in the highest quartiles (2-4), all had significantly higher risk of AAA compared to individuals with DBP in quartile 1. In the second and third quartile, there was approximately 40 % increased risk compared to quartile 1, whereas individuals in the highest quartile had two times higher risk of being diagnosed with AAA (HR 2.01, 95% CI 1.57-2.56), compared to participants in quartile 1.

Adjusted analyses

The results after adjustments showed an even higher risk for individuals with elevated DBP (HR 1.60, 95% CI 1.37-1.87) compared to those with normal DBP.

Similarly, we observed a gradual increase in HR from the lowest quartile to the highest. The HR value for the top DBP quartile (88-125 mmHg) became even higher after adjustment with more than a doubling of the risk of AAA (HR 2.18, 95% CI 1.64-2.88) compared to those in the lowest quartile (51-71 mmHg).

Table 4. HR with 95% CI for the association between diastolic hypertension and risk of AAA

	Univariable HR (95% CI)	**Multivariable HR (95% CI)**
Diastolic bp, mmHg		
< 90	Ref.	Ref.
≥ 90	1.59 (1.39-1.83)	1.60 (1.37-1.87)
Diastolic bp, mmHg		
51-71	Ref.	Ref
72-78	1.24 (0.94-1.64)	1.36 (1.04-1.78)
79-86	1.51 (1.17-1.95)	1.43 (1.10-1.86)
88-125	2.01 (1.57-2.56)	2.18 (1.64-2.88)

**Abbreviations: HR = hazard ratio, CI = confidence interval, AAA = aortic abdominal aneurysm, bp = blood pressure.*

*** Multivariable adjustments were performed for sex, systolic blood pressure, antihypertensives, CHD, diabetes, smoking, BMI and total cholesterol. Attained age was the timeline.*

Sensitivity analyses

A comparison of the impact of DBP versus SBP on AAA risk was beyond the scope of this thesis. However, brief analyses were performed to investigate how inclusion of SBP in the model would affect the association between DBP and risk of AAA. In a model where both DBP and SBP were included, the association with DBP was strengthened (HR 2.18, 95% CI 1.65-2.88, p-value <0.001). No increased risk was found for SBP (HR 0.99, 95% CI 0.99-1.00, p-value 0.04). In another model were SBP was included but not DBP, no increased risk

of AAA with was found for SBP (HR 1.00, 95% CI 0.99-1.00). In a model where hypertension was included instead of SBP and DBP, a positive association was confirmed (HR 1.33, 95% CI 1.14-1.55, p-value <0.001).

Discussion

The main finding of this large prospective cohort study based on more than 60 000 individuals and a median follow-up time of 14.3 years, was that individuals with elevated DBP have an increased risk of AAA. The results remained significant after adjustment for the most important risk factors, such as smoking, sex, diabetes, BMI, CHD, and total cholesterol.

Hypertension is considered an important risk factor for AAA[34, 35, 37, 38] , which has been confirmed in our HUNT material both in the present study and previously [50]. In line with this, a Danish population-based study, found that apart from smoking and male gender, hypertension was the most significant risk factor associated with the development of AAA [32]. Vardulaki et al. [36] and Takagi et al. [26] found that hypertension was a risk factor but suggested that it does not significantly increase the growth rate of existing aneurysm. On the other hand, Jódar et al. [24] did not find any association between AAA and hypertension at all, and several studies [12, 24, 33, 39] indicate that the association is unclear and therefore open for discussion.

One possible reason for the varying results is that different definitions of hypertension are used. For instance, some take into account the use of antihypertensive medication[31, 45], whereas others do not.[39, 47] Furthermore, the various studies use different statistical methods in their analyses. In our study, we were able to consider information on whether the patients were treated with antihypertensive medication or not. The proportion was significantly higher in the AAA group. This is relevant information as this could affect the proportion of people in the group with elevated blood pressure. In our study, introducing treatment with antihypertensive drugs in our multivariable model, did not change the HR for the association between AAA and elevated DBP notably and the association remained significant.

Given the conflicting results in previous studies regarding hypertension as a risk factor for AAA, more research is needed. One approach is to look at the individual values of DBP and SBP separately. Most previous studies have examined the association between SBP and AAA. [34, 37, 41, 42] A population-based cohort by Forsdal et al. based on data from the Tromsø study, suggested that those with hypertension had an increased risk of developing AAA. Moreover, the results showed an association between increasing SBP and AAA in women, but not in men [37]. Similarly, Manapurathe et al.[41] found an increased risk of developing AAA if

elevated SBP was present. Other studies, however, report no significant association for high SBP. [31, 37, 43] Our study found that SBP alone as a variable has no significant association with AAA. When SBP and DBP were included in the same model, the risk remained increased for DBP. The association with SBP was also significant, but the HR value was below 1, suggesting no increased risk. This result was not investigated further in the present study. However, the conflicting results emphasize the importance of looking at SBP and DBP as separate variables.

The main finding of our prospective study was a consistent association between DBP and increased risk of AAA, both as a dichotomous variable and as quartiles. It is notable that for the dichotomous variable, an increase in risk for AAA of 60% was seen at DBP ≥90 mmHg. Moreover, for the quartiles, a gradually increasing risk was seen from the lowest quartile upwards to more than a doubling of the risk of AAA at the top quartile. In comparison, the HR value for hypertension showed an approximately 30% increased risk of AAA. The number of previous studies on the role of DBP in the risk of AAA are rather few in numbers. [6, 44, 45, 46, 47, 48], but show interesting results that our study supports. Rodin et al. [45] assessed SBP and DBP as two variables included in separate models. The study showed that a smaller increase in mmHg is needed for DBP for an even stronger HR association for risk of AAA than for SBP. In line with this, Rapsomaniki et al.[46] found that increased diastolic blood pressure had a more significant impact on AAA than increased systolic blood pressure alone. However, some studies have different results for DBP. Fattahi et al. [31] performed a prospective study to investigate risk of AAA using data sets on 50-year old men from an AAA screening program with ultrasound commenced in Sweden. The study found no significant results for neither DBP (p-value ≥0.20) or SBP (p-value 0.18).

Elevated DBP is common in the elderly population.[53] With regards to AAA, this is important, because the prevalence of AAA increases with age. In light of our results, one can speculate that GPs detecting isolated diastolic hypertension in a patient should consider performing an examination of the abdominal aorta. There is no routine screening for AAA in Norway as of today. If further analysis of DBP as a risk factor show that DBP is a more important risk factor than SBP or hypertension in general, perhaps DBP can be considered as part of a potential targeted screening program for AAA. Other risk factors to consider in targeted screening are gender, smoking and heredity. Such an approach may contribute to make a possible diagnosis earlier in both men and women.

Our study did not aim to compare the impact of SBP vs. DBP on the risk of AAA. This comparison is, however, of interest. To our knowledge, this has only been evaluated in a few previous studies.[31, 46] However, the methods used to compare the impact of DBP vs. SBP can be discussed. Including SBP and DBP in the same Cox models can lead to a collinearity problem. Moreover, it is not appropriate to compare HR values from different Cox models. One approach could be to compare different Cox models instead of the HR values. To do so, one can use the AIC (Akaike's information criterion) and BIC (Bayesian information criterion). The AIC and BIC measures are estimators of the relative quality of a statistical model for a given data set.[54] The models with lowest values will give the best prediction of these two models. However, further analyses of this issue were beyond the scope of this thesis.

Strengths and limitations

Important strengths of this study are the large study population, a prospective study design, and a long follow-up period. A prospective study design is less prone to bias as it provides more reliable evidence. A homogenous study population with almost only Caucasian and with a stabile migration is suitable for a large population-based study. Several known risk factors for AAA were adjusted for to reduce the impact of confounding factors. There were few missing values in this study (only 0.07% missing on hypertension).

Significant limitations of the study are worth addressing. Ultrasound of the aorta is not part of the HUNT study, and in our study, we therefore used diagnosed AAAs. Because AAA is often an asymptomatic disease, this may have led to a possible underestimation of cases with AAA which may have influenced the result. On the other hand, as the study population is large, it is assumed that the influence of random errors will be small in this study. Information bias will likely occur since the participants submitted health information on covariates via a self-reported questionnaire. This may have given rise to misunderstandings about questions and further inaccuracy about relevant information. Selection bias may have occurred since the participation in HUNT was voluntary.

Conclusion

This thesis has shown that individuals with elevated DBP have increased risk of developing AAA during a mean follow-up time of 14.3 years. The risk increased with every quartile, and individuals in the highest DBP quartile had more than a doubled risk of AAA compared to individuals in the lowest DBP quartile.

Future perspectives

Further research can aim at clarifying the impact of DBP vs. SBP as risk factors of AAA. Moreover, most studies on AAA have been done on men, and few studies have investigated the risk of AAA in women using prospective design and large cohorts. This is often related to low statistical power due to lower prevalence in women. Women with AAA have higher risk of rupture, and future studies should aim at clarifying risk of AAA in women, including the impact of DBP.

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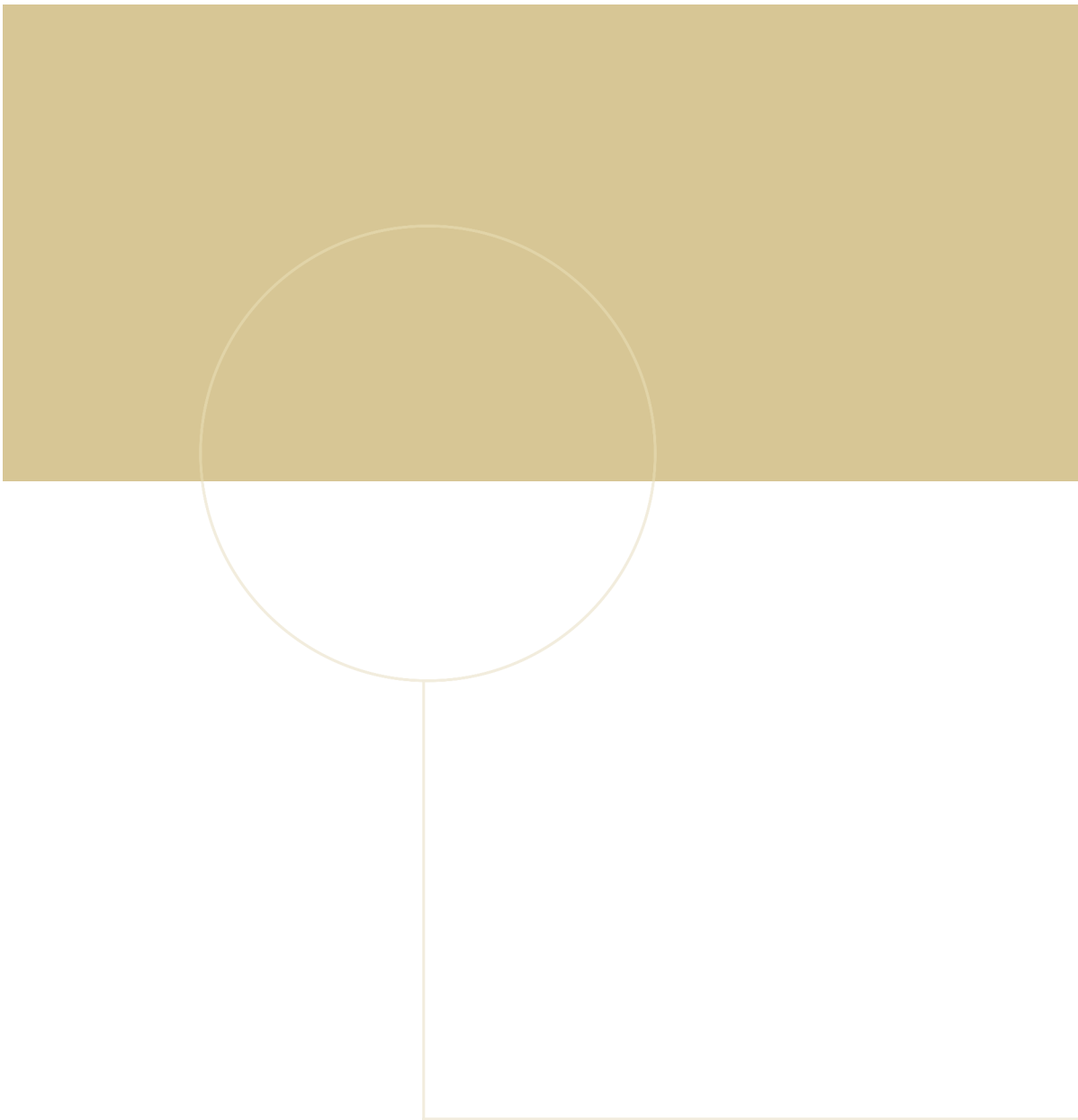

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