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The Epidemiology of Valvular Aortic Stenosis

Prevalence, incidence, mortality, risk factors and progression of aortic stenosis in a general population.

The Tromsø Study 1994-2008

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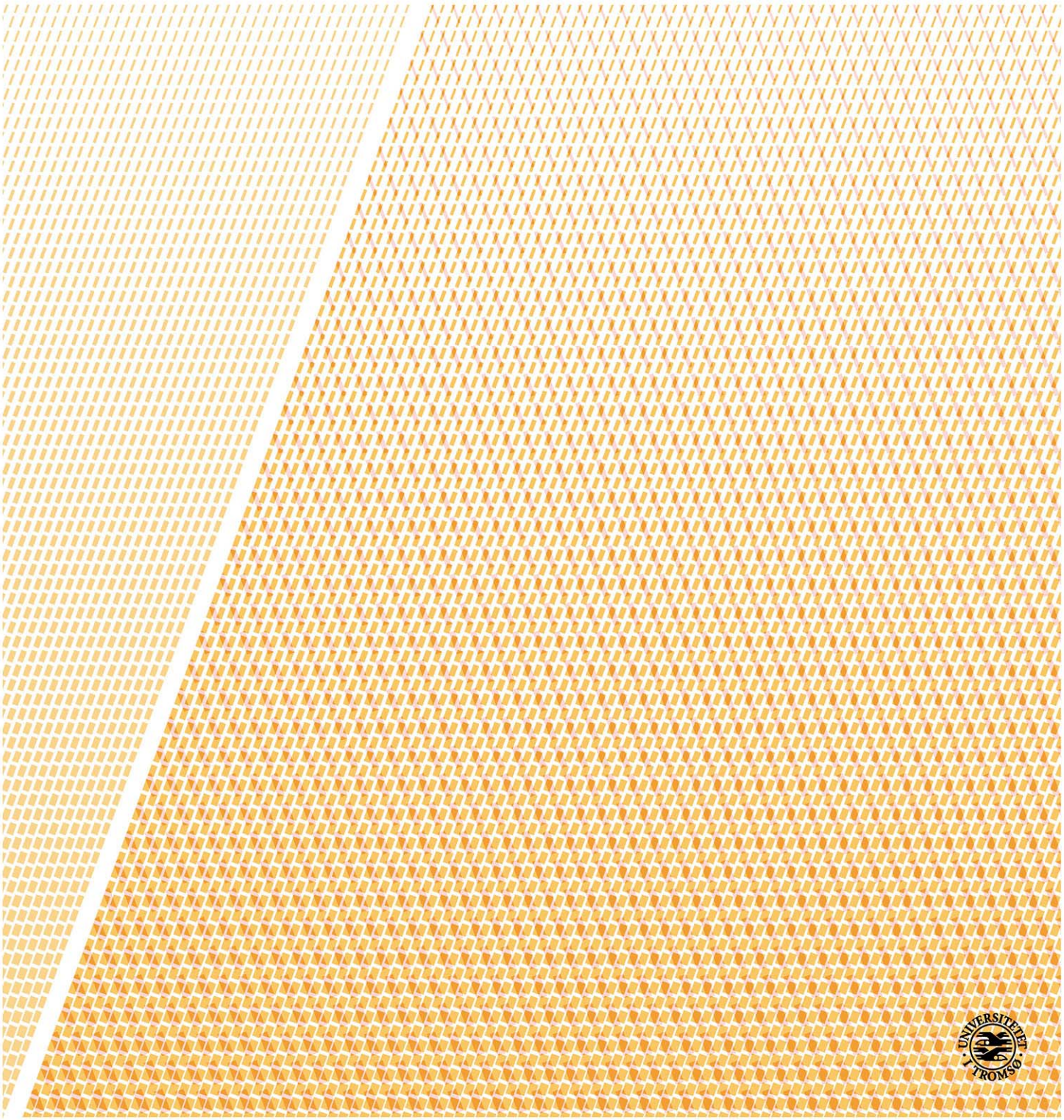
A dissertation for the degree of Philosophiae Doctor – 2015



Contents

Acknowledgements

My first encounter with the Tromsø Study was in 2001 where I, while in training to be a cardiologist, conducted about 1000 of the echocardiographic examinations performed. This under guidance of the Department of Cardiology`s former mentor in echocardiography: Per Lunde. My present PhD tutor, Henrik Schirmer, was the enthusiastic supervisor of the complete Tromsø 5 study. At this point of time I was not involved in the research, clinical work was my main focus, and thus I participated as an echo-technician. Through my clinical work I have become more and more interested in aortic stenosis, being the valve disease we encounter most in daily practice, and where marked changes has occurred both regarding how to diagnose the disease and its treatment in the last decade. So, when the opportunity arose to become a PhD student on this project, I saw it as a possibility to learn more about aortic stenosis in specific as well as epidemiology and research, the latter being an important basis for modern medicine.

Sincere thanks are directed to my tutors Knut Rasmussen, professor emeritus in Cardiology and Henrik Schirmer, professor at the Department of Clinical Medicine, for their continuous support and encouragement. Their profound experience in clinical cardiology and cardiac epidemiology made a fundamental basis for the present work.

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List of papers

This thesis is based on the following papers, referred to in the text with their Roman numerals;

I. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K.
The evolving epidemiology of valvular aortic stenosis. The Tromso Study. Heart 2012.

II. Eveborn GW, Schirmer H, Lunde P, Heggelund G, Hansen JB, Rasmussen K.
Risk Factors for developing Calcific Aortic Valvular Disease. The Tromsø Study. European Journal of Epidemiology 2014.

III. Eveborn GW, Schirmer H, Heggelund G, Rasmussen K.
Risk of developing Aortic Stenosis in subjects with subclinical Mean Aortic Valve Gradients. The Tromsø Study. Submitted to Heart, May 2015.

Abbreviations

ACE	Angiotensin Converting Enzyme
AS	Aortic Stenosis.
ASc	Aortic Sclerosis.
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
AVAI	Aortic Valve Area Index
BMI	Body Mass Index
BP	Blood Pressure
CAVD	Calcific Aortic Valve Disease
CI	Confidence Interval
CT	Computed Tomography
HDL	High Density Lipoprotein
Hgb	Haemoglobin
HR	Hazard Ratio
LDL	Low Density Protein
Lp(a)	Lipoprotein(a)
LTPA	Leisure-Time Physical Activity
OPG	Osteoprotegerin
OR	Odds Ratio
RANKL	Receptor Activator of Nuclear factor Kappa B (RANK)/RANK Ligand
RHD	Rheumatic Heart Disease.
SD	Standard Deviation
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis trial
TAVI	Transcatheter Aortic Valve Implantation

Introduction

Over the last couple of decades there has been a marked change in the understanding of the pathogenesis, clinical evaluation and treatment of degenerative aortic valve stenosis. The present work was initiated to describe the epidemiology of both degenerative aortic stenosis (AS) and its precursor aortic sclerosis (ASc). This included an evaluation of the prevalence, incidence and progression rate of the condition into severe stages where surgical treatment is needed. We also wanted to understand which risk factors contribute to the development of AS and its further progression. Finally, we wanted to know more about the early stages of the disease and thus at what subclinical level follow-up of patients is reasonable.

Background

Over the past 60 years the predominant etiology of valvular disease has shifted from a rheumatic to a degenerative one in industrialized countries.[1] In contrast, valvular disease in developing countries is still mainly caused by rheumatic heart disease.[2] In The Euro Heart Survey degenerative disease represented 63% of all cases of native heart valve disease, followed by rheumatic heart disease in 22 %.[3] Inflammatory diseases and congenital heart disease accounted for less than 10% of all cases of valvular disease.[4]

Rheumatic heart disease is a late consequence of acute rheumatic fever. It is initiated by pharyngeal or cutaneous infection caused by group A ß-haemolytic Streptococci. An immune response leads to multiorgan involvement, including valvular inflammation, which becomes chronic and initiates delayed valvular disease in 60 % of the patients.[5] Asian prevalence estimates are 1.2 ‰ among children and adolescents,[6] African estimates 2.7- 14.3 ‰.[7] It is argued that antibiotic prophylaxis partly explains the reduced incidence of rheumatic fever in

industrialized countries, but improved socioeconomic conditions are likely to have had the greatest impact.[1]

Calcific aortic valve disease (CAVD) constitutes a disease continuum ranging from aortic sclerosis (ASc), defined by mild valve thickening/calcification without significant obstruction of blood flow to more severe calcification with impaired leaflet motion, termed aortic stenosis (AS).

Epidemiology of aortic valve sclerosis and stenosis

Aortic sclerosis is a highly prevalent condition, being present in 21 - 26 % of elderly above 65 years of age.[8,9] In addition, there is an increasing prevalence with age; 20% in the age group from 65-74, 35% in the age group from 75 - 84 and 48% in the age group >85.[8,10] Three population based studies have presented data on the prevalence of manifest AS, two large from the USA and one from Finland.[8,9,11] The prevalence of moderate AS in these studies were approximately 2% among individuals aged 70-80 years, increasing to 3-9% after the age of 80 years.[12] AS was strongly associated with age, with an odds ratio of 2.5 (95% CI 2.0-3.1) per decade of increasing age.

Bicuspid/Tricuspid valve

In industrialized countries AS is the most common valvular disease among patients referred for treatment.[4] It is most commonly a consequence of degenerative remodelling on a normal tricuspid valve or due to a congenital bicuspid aortic valve. We know that a genetic component is likely to exist for bicuspid aortic valves.[13] The prevalence of bicupid valves is estimated to be 0.6-0.8% in males and 0.2% in females.[14,15] Young adults with an initially normally functioning bicuspid aortic valve have a 24% risk of aortic valve replacement

(AVR) over the next 20 years, most often due to AS.[16] One study also revealed that 49% of the 932 aortic valves explanted because of AS in a surgical pathological series were bicuspid, which contrasts with a prevalence of < 1% of bicuspid aortic valves in a general population.[17] Further, bicuspid valves were more frequent than tricuspid valves up to the seventh decade of life in this surgical series.[17] A bicuspid valve most often results from fusion of the right and left coronary cusps (80%), less often as a fusion of the right and non-coronary cusps (20%).[18] [19]

Staging of aortic valve stenosis

The 2006 AHA/ACC Practice Guidelines has graded the condition of AS. Mild AS is defined to be present with an aortic valve area (AVA) > 1,5cm², peak aortic valve flow velocity <3m/s and/or a mean gradient <25mmHg. Moderate AS is defined by a valve area of 1-1.5cm², peak aortic valve flow velocity of 3- 4m/s and/or a mean gradient of 25-40mmHg. Severe AS is present when the aortic valve area is <1cm², the aortic valve flow velocity is >4m/s and/or the mean gradient >40mmHg.[20] A clear-cut distinction between ASc and AS has not been made.

Pathophysiology of calcific aortic valve disease

<u>Anatomy of the normal aortic valve:</u>

The aortic valve is located between the left ventricle and the aorta. It consists of three semi-lunar leaflets that are attached to and supported by a ring of tough fibrous tissue called the annulus. This arrangement results in an even distribution of mechanical stress to the valvular ring and aorta.[21] The valve opens during cardiac systole (contraction of the heart) and closes during diastole (relaxation of the heart). During systole, pressure in the left ventricle rises above that in the aorta, the valve opens, allowing blood flow into the aorta. At the beginning

of diastole the transvalvular pressure drops rapidly, which makes the aortic valve close, thus achieving unidirectional blood flow. Each cusp is <1 mm thick and appears smooth, thin and opalescent and are composed of 4 layers. The endothelium covers both the aortic and ventricular side of the leaflet. The fibrosa on the aortic side of the leaflet comprises fibroblasts and collagen fibres arranged circumferentially. The spongiosa is a layer of loose connective tissue predominantly found at the base of the leaflet, between the fibrosa and ventricularis. It is composed of fibroblasts, mesenchymal cells and a mucopolysaccharide-rich matrix, whose function is to resist compressive forces within the cusps. The ventricularis on the ventricular side of the leaflet is composed of elastin-rich fibrers, aligned in a radial direction, perpendicularly to the collagen in the fibrosa. The leaflets provide tensile strength and pliability for decades of repetitive motion. Collagen fibres can withstand high tensile forces but have low torsional and flexural stiffness.[22] Much of the observed change in collagen structure is due to straitening of the collagen fibres, but this is a finely tuned process. Straitening must occur at the right strain level to facilitate coaptation of the leaflets, yet not allow excessive tissue deformation that may lead to regurgitation.[22]

Pathology:

In CAVD the valve cusps become progressively thickened, fibrosed and calcified, resulting in increased valve stiffness, reduced cusp excursion and progressive valve orifice narrowing. This contrasts with the disease process in rheumatic disease where cusp fusion is seen.

Mechanical stress and endothelial damage:

The initiating event is believed to be endothelial damage induced by increased mechanical stress, including pressure, cyclic stretch and shear stress.[23] Mechanical tissue stress is highest around the flexion areas of the cusps near their attachment to the aortic root, and half of the lesions can be observed in this region.[24] Further, calcification occurs primarily in the fibrosa

on the aortic side of the valve leaflets, where flow is most turbulent, suggesting that shear stress and its interaction with valvular endothelium plays a role in the process[25] The bicuspid valve perhaps illustrates best the role of mechanical stress. The two-cusp structure results in a less efficient distribution and concentration of mechanical forces within the valve so that AS develops on average 2 decades earlier than in patients having tricuspid valves.[26] Although tricuspid aortic valves are often depicted as symmetrical, they rarely are.[27] It is in fact unusual for all three leaflets to have the same area, thus stress on the leaflets vary.[28]

Inflammation:

The endothelial injury may allow lipids to penetrate the valvular endothelium and accumulate in areas of inflammation.[29,30] Lipoproteins are present in early valve lesions[29] and undergo oxidative modification,[30] becoming highly cytotoxic and capable of stimulating intense inflammatory activity and subsequent mineralization[31] The expression of adhesion molecules allows infiltration of the endothelial of monocytes that differentiate into macrophages[32] and T-cells that release pro-inflammatory factors, including transforming growth factor-beta-1, tumor necrosis factor–alpha and interleukin-1-beta.[33] These in turn help stimulate the subsequent fibrotic and calcific processes that increase the valve stiffness.

Histological studies have suggested that the inflammatory processes are sustained by angiogenesis in the valve. Thin neovessels are observed in areas of intense inflammation. Furthermore, both intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression is increased in these vessels, implying they may act as an important portal of entry for inflammatory cells.[34] Haemorrhage is present in these neovessels in 78% of patients with severe AS and is thus associated with an accelerated disease progression.

Fibrosis:

Extensive thickening due to accumulation of fibrous tissue and remodelling of the extracellular matrix characterize the stenotic aortic valve. In all 3 layers of the valve there are abundant fibroblast-like cells. A subpopulation of these cells are activated by the inflammation and differentiate into myofibroblasts, which in turn are believed to be responsible for the accelerated fibrosis observed in this condition.[35] Both these myofibroblasts and inflammatory cells interact in the restructuring of the valve leaflet matrix.[33,36]

Calcification:

Valve calcification plays a key role in the development of AS, and the degree of calcification correlates with disease severity, progression and the development of symptoms and adverse events.[37-39] In addition, disorders of mineral metabolism, including Paget disease, osteoporosis, vitamin D polymorphisms and haemodialysis, are all associated with increased prevalence of AS.[40-43]

Also in the early stages of aortic sclerosis microscopic areas of calcification can be observed, The progression into aortic valve stenosis is thought to be driven by the differentiation of myofibroblasts into osteoblasts under the influence of the Wnt3-Lrp5-ß catenin signalling pathway, the osteoprotegerin (OPG)/ receptor activator of nuclear factor kappa B (RANK)/RANK ligand (RANKL) pathway and Runx-2/NOTCH-1signaling.[13,44,45]

Osteoblasts subsequently coordinate calcification as part of a highly regulated process, akin to new bone formation. There is local production of many factors, more commonly associated with skeletal bone metabolism, including osteopontin, osteocalcin, bone sialoprotein and bone morphogenic protein 2.[46-48]

In the early stages of AS the calcification is composed of nodules. These contain hydroxyapatite deposited on a bonelike matrix of collagen, osteopontin and other bone matrix proteins.[47-49] During progression of AS remodelling of the calcification occurs and in the later

stages of the disease lamellar bone, microfractures and haemopoetic tissue are present within the valve.[48] The calcification seems to be the key process in the pathogenesis of aortic valve narrowing.

Genetics:

The above–mentioned players in aortic valve pathobiology are subject to genetic variations, displaying only the top of the iceberg to date. Regarding bone metabolism, vitamin D receptor polymorphisms in Notch 1 have been described. The receptor B allele, leading to reduced calcium absorption, bone loss, and higher parathormone levels, is more frequent among patients with AS, thus one might deduct that calcium mobilization from bone enhance aortic valve calcification.[42] There has been conflicting data regarding the association between allelic variants of apolipoproteins and CAVD.[50-52]

Left ventricular hypertrophy:

AS causes an increase in after load and ventricular wall stress that stimulates hypertrophy of the left ventricular myocardium. This initially restores wall stress and preserves the left ventricular function,[53,54] whereas increasing levels of hypertrophy seems to be maladaptive. The Framingham studies first linked increasing hypertrophy with the progression to heart failure.[55] However, AS patients have a marked variation in the magnitude of their hypertrophic response. This has been demonstrated to be of prognostic importance.[21] Further, it might explain the heterogeneity between symptom onset and the severity of valve narrowing that is observed. The degree of left ventricular hypertrophy is only weakly related to the severity of valve obstruction,[56-58] established both by echocardiography and cardiac magnetic resonance. The latter showed no correlation between peak aortic valve velocity and indexed left ventricular mass.[59] The hypertrophic response appears more associated with age, male sex and obesity,[56,60,61] as well as genetic factors. The SEAS (Simvastatin and Ezetimibe

in Aortic Stenosis) trial demonstrated that coexistent hypertension was associated with increased left ventricular mass.[62] Increased arterial stiffness is also frequently observed due to advanced age, atherosclerosis, diabetes and high blood pressure. This results in a further increase in afterload and contributes to left ventricular dysfunction. On this basis a global measure of afterload, Z_{VA}, has been proposed as a predictor of adverse prognosis among patients with moderate and severe AS.[63] The degree of hypertrophic response seems to have important clinical implications. Patients with inappropriately high left ventricular mass have increased mortality compared with patients having a comparable valve narrowing but more moderate hypertrophy.[64]

Heart Failure:

The transition from hypertrophy to heart failure marks the tipping point where the left ventricle fails to meet a further increase in afterload and thus is no longer able to maintain forward flow through the valve. This heralds the onset of symptoms, adverse events and a poor prognosis. This key progression is associated with increased myocyte apoptosis and fibrosis and it is postulated that these two processes are responsible for the transition.[65]
The rate of apoptosis in a hypertrophied myocardium is 5-10% of myocytes per year.[66] Apoptosis is being balanced by myocyte regeneration, but in hypertrophy there seems to be a net loss of cells. This is related to several factors. Increased apoptotic rates may be related to direct mechanical forces associated with increased afterload.[67,68] As angiotensin receptor blockers reduce apoptosis in patients with hypertension, even at doses that does not reduce blood pressure, increased angiotensin II levels are probably a cause of apoptosis.[69,70]
Myocardial ischemia may also be of importance. In AS there is an increased oxygen demand due to increased myocardial mass and afterload, but the density of coronary capillary network does not expand sufficiently to meet the demand, thus coronary flow reserve is impaired.[71,72]

Fibrosis is an integrated part of the hypertrophic process.[73,74] Fibrosis is observed to co-localize with areas of myocyte-apoptosis and may thereby be seen as a form of scarring. A midwall pattern of fibrosis has been observed in the myocardium of up to 38% of patients with moderate or severe AS and has been associated with a more advanced hypertrophic response.[75] There is also an 8-fold increase in mortality associated with midwall fibrosis.[75] Further, patients with AS remain predisposed to sudden death even after AVR, related to advanced left ventricular hypertrophy.[76,77]

Neighbouring structures:

The functional assembly of the valve leaflets, corresponding sinuses and sinotubular junction is important. Intact sinuses and sinotubular junction create an optimal distribution of pressure load and proper valve opening and closure, while loss of aortic wall compliance leads to significant stress overload of the leaflets. Loss of vascular compliance occurs in every aging subject due to gradual loss of elastin fibres in the media and is more pronounced in patients with hypertension, diabetes and renal failure, the latter due to superposition of media calcification. Thus, the role of mechanical stress is not restricted to the initiating step, but is continuous and progressive. Once sclerosis is initiated in the leaflets, their stiffness also promotes an unfavourable stress distribution, leading to a self-perpetuating process.[78,79]

Risk factors for development of aortic stenosis

The pathophysiology underlying AS remains incompletely defined, and there are currently no effective medical treatments capable of altering its course.

There have been many previous studies trying to define predictors of AS. They have contradictory results, many of them are retrospective, have varying definition of AS and referral bias.[80] There are 4 previous population based studies; In the Cardiovascular Health

Study age, male gender, current smoking, hypertension, elevated lipoprotein(a) and low density protein (LDL) cholesterol levels were correlated with the presence of echocardiographically detected aortic sclerosis.[8] More recent data from the MESA study revealed diabetes, the metabolic syndrome and renal dysfunction as risk factors.[81,82] In the KORA/MONICA study age, smoking status and increased total cholesterol predicted AS at echocardiographic assessment 10 years later.[83] Three of these studies are cross-sectional and have therefore analysed risk factors sampled at the same time as the condition of the aortic valve was studied. All four studies were image based and have observed aortic sclerosis, defined as small morphological changes of the aortic valve either by computed tomography (CT) or two-dimensional echocardiography. The functional importance of these changes has not been assessed and very few patients with properly defined AS seems to have been included. The KORA/MONICA study is prospective, but had an echocardiographic evaluation of the valve only at follow-up and there were only three cases with AS. The results of these studies along with histological feature of the valve lesions have led to the assumption that the continuum of ASc/AS is closely related to atherosclerosis.

In view of the previous diverging study results on predictors of AS our prospective population based survey, with a time-span of 14 years, gave an opportunity to evaluate this with more appropriate methods.

Risk factors for progression of aortic stenosis

Similarly the factors affecting AS progression are not yet clearly defined.[39,84-89] The condition is often not discovered until it is well established since it has a rather long asymptomatic phase, commonly revealed by cardiac auscultation. Identifying the risk factors of progression is thus of interest as they may allow secondary prevention.

Several early retrospective studies associated statin therapy with slowed progression of AS, but the negative results of 3 large prospective randomized trials: SEAS, SALTIRE and ASTRONOMER did not corroborate any causal relation to AS progression.[90-92]

A number of explanations to the lacking effect of statins have been given. First, the selected study patients did not have advanced dyslipidemia.[93] Second, it has been argued that the trials failed because statins were administered too late in the disease progression, supported by Antonini-Canterin et al showing that statins only reduced progression in aortic sclerosis and mild AS, but not at more advanced stages.[94] Third, statins do not act on all pathways of AS pathophysiology, which further does not fully resemble atherosclerosis. Fourth, plaque stabilisation accounts for most of the beneficial effects of statins in atherosclerosis but is not an issue in AS.

The hypothesis that angiotensin converting enzyme-I (ACE) therapy might be beneficial is based on studies of human valve tissue and experimental animal models. ACE activity and angiotensin I receptors are present in the early lesions of aortic stenosis.[95,96] Inhibition of the angiotensin pathway with angiotensin receptor-1 blockade in cholesterol-fed rabbits was associated with decreased macrophages and reductions in osteopontin and ACE in aortic valves.[97]

Progression rate of aortic sclerosis and aortic stenosis

Three previous studies regarding progression of ASc to AS have been reported.[98-100] The definition of ASc was similar in all 3 studies, based on echocardiographic examination showing focal areas of increased echogenisity and thickening of the aortic valve leaflets without restriction of leaflet motion and a peak aortic jet velocity <2.0-2.5m/s.

Two of the previous studies are retrospective and based on an echo database population.[98,99] Faggiano et al found that 33% of patients with ASc developed AS, with a mean follow-up

time of 44 months. Cosmi found a progression rate of ASc to AS of 15.9% over 7.4 years, also here predominantly into mild stenosis. There is one prospective population based study by Novaro et al demonstrating a lower rate of progression to AS; 9 % over a mean follow-up of 5 years.[100] Thus, the progression estimates vary widely, maybe due to subjective evaluation of morphology in these studies.

Recently, a Norwegian study showed that healthy men aged 40-59 years with a low-grade or moderate-grade systolic murmur after 35 years of follow-up had a 4.7-fold and 89-fold increased risk of having aortic valve replacement, respectively, compared to the population without a murmur.[101] One may speculate that many of the subjects with an initial murmur actually had bicuspid aortic valves.

Previous prospective natural history studies of AS patients have disclosed an overall annual progression rate in jet velocity of 0.3 m/s and in mean gradient of 7mmHg.[39,102] More recent data from medical trials of statin therapy for mild/moderate AS showed somewhat slower rates of progression with an increase in mean gradient of 3-4 mmHg/yr.[90,91]

Treatment/ Mortality

AS is an insidious disease with substantial morbidity and mortality after the onset of symptoms, resulting in a 2-year mortality risk in the range of 20-50% among untreated patients.[11,39,102-104] In symptomatic patients AVR has been the treatment of choice for >40 years, and in the absence of serious coexisting conditions, AVR is associated with low operative mortality.[105-108]. Due to advanced age, left ventricular dysfunction and/or the presence of other comorbidities, as many as 30-60% of patients with severe symptomatic AS were not treated with AVR, and for them TAVI has emerged as an alternative therapeutic approach, being introduced by Cribier in 2002.[4,109-113]

Aortic valve stenosis is the number one indication for surgical valve replacement in the US and Europe. On average, 50,000 AVR´s are performed every year both in Europe and in the US.[4,114]

Over the past decade, the number of aortic valve replacements performed in the United States has doubled, and with an increasingly elderly population, the prevalence of AS is likely to double again in the next 20 years.[11] Being a treatable condition by open surgery or TAVI, it is of importance for public health that it is detected and followed appropriately.

Aims of the thesis

The main aim of the thesis was to describe the epidemiology of AS and explore different risk factors for development of the valve disease in a general population.

Our main focus has been:

- To determine the incidence and prevalence of AS in a Norwegian population.

- To assess the mortality in the population having aortic stenosis compared to a general population.

- To study the progression rate of the condition in an observational population study.

- To evaluate which variables that are predictors of incident aortic stenosis and which predict the progression rate of the condition.

- To investigate whether differentiating subclinical aortic valve mean gradients in a general population can predict whom that will progress from aortic sclerosis to aortic stenosis.

Material and methods

Study design

The Tromsø Study is a single centre prospective follow-up study of the population of Tromsø. The studies have been carried out by the Department of Community Medicine at the University of Tromsø, in collaboration with the Norwegian Institute of Public Health, the University Hospital of Northern Norway and Tromsø City Council. The main focus of the Tromsø Study has been on cardiovascular disease. The first survey was carried out in 1974 (Tromsø 1), followed by new surveys at 6-7 year intervals. The population-survey in Tromsø comprises the cohorts presented in table 1. A total of 40,051 different people have participated in at least one of the studies, while 15,157 have taken part on three or more occasions.

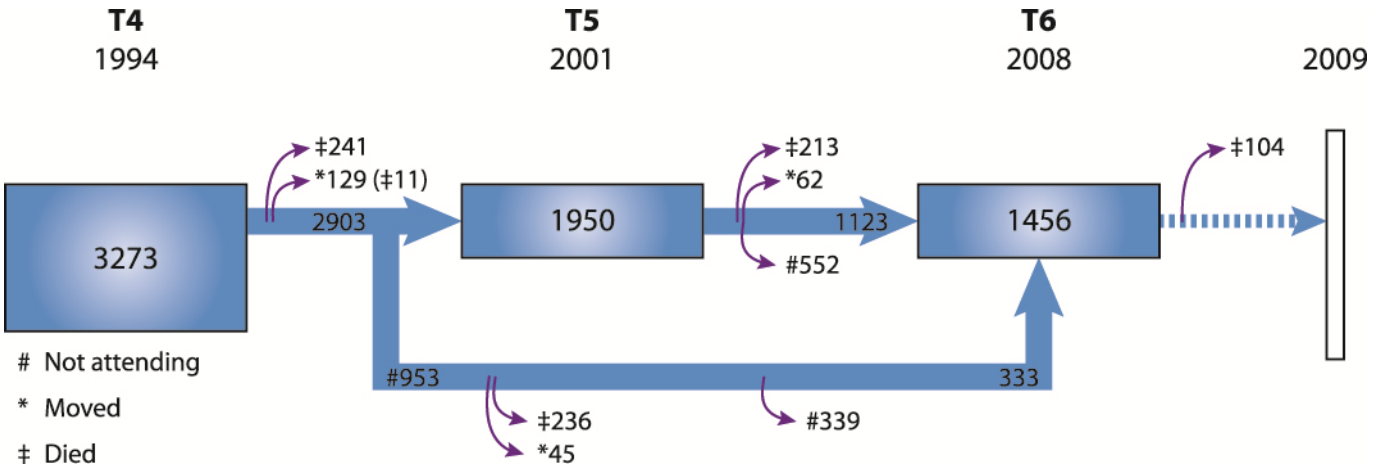
Table 1: The Tromsø Study, 1974-2008

Study Year	Study`s name	Number of participants	Age group	Attendance rates
1974	Tromsø 1	6595 men	20-49	74%
1979-80	Tromsø 2	16621 men and women	20-54	78%
1986-87	Tromsø 3	21826 men and women	12-67	76%
1994-95	Tromsø 4	27158 men and women	25-97	73%
2001-02	Tromsø 5	8130 men and women	30-89	79%
2007-08	Tromsø 6	12984 men and women	30-89	66%

Study population

The fourth survey consisted of two screening visits 4-12 weeks apart. All registered inhabitants of Tromsø 25 years or older were invited to the first screening visit. The invitation letter also contained a questionnaire about cardiovascular risk factors and disease as well as a declaration of consent (Appendix I). Of 35,443 invited, 27,168 (76.6%) attended the first visit. At the second visit (phase 2) all subjects aged 55-74 years as well as smaller (5-8%) random samples of other age groups (25-84years) were invited, with an attendance rate of 76%. Participants invited to the second visit were allocated to 1 of 2 lines of examination based on simple randomization using computer-generated random numbers. They were randomized to avoid selection bias because only one of the lines of examination included echocardiography due to lack of capacity. Because of high attendance rates at the first visit in the age group above 54 years, the second visit comprised 88% of those initially invited and who were pre-selected for the second visit in T4

Paper 1**:** Participants for this study comprise the 3,273 persons who attended the echocardiographic examination in phase 2 of the fourth survey in 1994/95. They represent a cohort within the cohort and have been the basis for invitations to second visits in T5/T6. Of these, 1,950 were re-examined in T5. There were 1,456 participants in T6, 1,123 of them had been examined with echocardiography in T5 and 333 in T4. During follow-up 236 had moved/emigrated and 805 had died. There were 953 subjects not attending echocardiographic screening in T5 and 891 in T6.



Paper 2: The study population was the same as in paper 1 with the exception of 30 subjects defined to have AS at baseline who were excluded. The echocardiography subgroup thus consisted of 3,243 subjects.

Paper 3: Of the 1,950 participants who had an echocardiographic examination performed in T5, 66 subjects had prevalent AS and were excluded. The remaining 1,884 participants constitute the baseline population of this study.

Data from the questionnaire and physical examinations

Questionnaires printed on the reverse side of letters of invitation were distributed to the eligible population in each Tromsø survey. In T4 (1994/95) two sets of questionnaires were handed out. The first one as described (Appendix I), while the second one, with different versions for those above and below 70 years of age, was handed out at the health examinations to be returned by mail (Appendix II).

The first questionnaire was checked for inconsistency by a trained nurse at the health examination. It included questions on disease and symptoms, habits with respect to leisure-time physical activity (LTPA), diet, smoking, coffee consumption and work related issues.

The second questionnaire included questions on health condition, earlier disease in the family, use of medication and health service, marital status, education level and more thorough questions on diet and LPTA. This second questionnaire differed for those younger or older than 70 years, having more focus on activity of daily living and cognitive function in the elderly.

Trained nurses measured blood pressure (BP) using an automatic device (Dinamap, Critikon Inc). The cuff size was chosen after measuring the upper arm circumference. After two minutes of seated resting, 3 recordings were obtained at 1-minute intervals. The mean value of the second and third measurements was used in the analysis. The participants were considered to have hypertension if he or she had systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg or reported being on antihypertensive medication. Height and weight was measured at screening with light clothing without shoes, body mass index (BMI) was computed as kg/m². The waist and hip circumference were measured in cm. The resting pulse was measured three times sitting, the third measurement was used in the analysis. Coronary disease was defined through the questionnaire as a composite of previous myocardial infarction and/or a history of angina pectoris. Diabetes was present if the participants confirmed the diagnosis in the questionnaire, or if their non-fasting blood-glucose level was measured above 11.1mmol/L (n=7). Osteoporosis was defined to be present if the participant confirmed the condition in the questionnaire. The registration of vitamin D supplementation was based on a yes/no answer to the following question: Have you in the last 14 days used vitamin D supplements? The registration of Cod Liver Oil supplementation was based on the yes/no answer to the following question: Have you in the last 14 days used cod liver oil or fish oil capsules? Smoking status was ascertained as current, previous or never smoker. Physical inactivity was defined as less than 3 hours/week of light activity in leisure time without sweating or dyspnoea. Moderate LTPA was defined as ≥3 hours of light activity and/or 1-2 hours of hard

LTPA/week which caused sweating or dyspnoea. Hard LTPA was defined as hard activity with sweating or becoming out of breath, for ≥3 hours/week.

Non-fasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after one hour respite at room temperature, and analysed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analysed by enzymatic colorimetric methods and commercially available kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides: Boeringer Mannheim). Serum high density lipoprotein-cholesterol (HDL) was measured after precipitation of lower density lipo-proteins with heparin and manganese chloride. Other measurements used in the analyses were: Haemoglobin (Hgb) (g/dL), pl-Glucose (mmol/L), pl-Creatinine (µmol/L), se-Calcium (mmol/L), OPG (pg/m).

To compensate for the incomplete attendance we retrospectively integrated data collected from the only hospital serving the study population. We retrieved data from patient records, both from those re-examined in T5 or T6 and those dying, emigrating or not attending further re-examinations after T4. The time span of the study made us search for both ICD 9 (424.1, n=115) and ICD 10 (I 35.0 n=159, I 35.2 n=42) coding of the disease as well as AS-related surgery codes in The NOMESCO Classification of surgical procedures. ICD-9 had a coding system that included both AS and aortic regurgitation under the same code number, ICD 10 had separate numbers for isolated AS and the combination of AS and regurgitation. Reading through all retrieved patient journals we avoided registration of patients with isolated aortic regurgitation or only aortic sclerosis. Due to the scattered arctic population the distance to the closest hospital outside our region treating AS exceeds 1000 km, making it probable that the database was almost complete. Data registered were hospital diagnosis of AS, the first and last measured aortic mean gradient and examination dates. Decisions regarding treatment of symptomatic patients were also recorded, classified as either surgical or conservative

treatment. The conservatively treated group consisted both of patients with comorbidity preventing them from choosing surgery (n=7) as well as patients refusing it (n=6).
We had vital data on all subjects from the National Death Registry until 2009.

Echocardiography

All echocardiographic examinations were performed according to the American Society of Echocardiography´s Guidelines.[115] In T4 we used a VingMed CFM 750 (VingMed Sound A/S Horten, Norway) with a 3.25 MHz mechanical and 2.5 MHz Doppler probe and in T5/T6 an Acuson Sequoia C256/C512 with a combined 3.5 MHz second harmonic ultrasound and 2.5 MHz Doppler probe (Acuson, Mountain View, CA, USA) having a frame rate of 70 frames/sec.
The screening included complete evaluation of cardiac anatomy and function with measurement of the parameters of mitral flow, pulmonary venous flow, antero-posterior diameter of the left atrium, left ventricle end-diastolic and -systolic diameters, ejection fraction according to Teichholz, left ventricle end-diastolic diameter of septum and posterior wall in short axis view. Pulsed wave tissue Doppler recordings of the left ventricle were made in septal and lateral positions (T6 only). Two-dimensional assessment of the aortic valve was performed from the parasternal long axis, short axis and apical five-chamber view. Aortic valve morphology, diameter and cusp separation in short axis and aortic velocity time integral, giving jet velocity, mean- and maximal gradients, were recorded. Aortic valve area was not calculated in any of the surveys. We defined AS to be present if the transvalvular mean gradient was ≥15 mmHg and graded AS as follows: mild AS ≥15-29 mmHg, moderate AS ≥30-49 mmHg, severe AS ≥50 mmHg. Those with mean gradients ≥15 mmHg due to aortic regurgitation alone or subaortic stenosis were not classified as AS (n=4 in T5, n=3 in T6).

Those with any pathology were referred to the out-patient clinic for further follow-up, criteria being: moderate/severe mitral regurgitation (colour Doppler area >4cm², AS max.gradient > 30mmHg, bicuspid aortic valve, aortic regurgitation jet >30% of LVOT, ejection fraction <50%, left ventricle wall end-diastolic diameter >1.4 cm, left ventricle end-diastolic diameter >6.5 cm, aortic root dilatation >4.5 cm, atrial fibrillation not previously known, pericardial effusion or other findings predefined in the protocol as indications for clinical follow up at the hospital. In T4 290 participants (8.9%) underwent follow-up examinations due to abnormal findings on the echocardiogram.[116]

Statistical analysis

The statistical tests were two-sided, and a p-value of <0.05 was defined as significant.

Paper 1

Prevalence: It is defined as the frequency of existing cases of a disease in a given population at a certain time or period. We performed prevalence calculations, first as point prevalence related to the surveys in T4, T5, T6 and as a weighted mean of all three studies combined (T4/5/6). The study population was divided into 4 age-cohorts. Those with prior AVR were included. Secondly we calculated prevalence numbers by adding information of prevalent AS from hospital data at the same time points as the surveys. Doing this, we followed the original study population (n=3273) at 3 time points, retracting the number of dead at each step from the denominator in the prevalence calculations.

Incidence: We used the following equation: Incidence rate/year = X / (N – ½ C – ½ X), when X= number of incident cases with AS, N= number in the study population and C= censored participants. The approach of subtracting one half of the total number of censored observations from the denominator is based on the assumption that censoring occurred

uniformly throughout that period, and thus on average, these individuals were at risk for only half of the follow-up period.[117]

Mortality: Survival analysis was conducted using an extended Cox Proportional Hazards model with a time-dependent variable for groups (AS/No AS), adjusting for age. Censoring occurred when participants moved, at the time of AVR, decision of conservative treatment or at the end of the study, not as a result of non-attendance. The same analysis was used comparing the AS subgroup treated with AVR versus those without AS. Here the time-dependent group variable changed at the time of surgery.

An extended Cox model with a time-dependent variable does not satisfy the Cox proportional hazard assumption. A time-dependent variable is defined as any variable whose value for a given subject may differ over time. Since the exposure variable is time-dependent, an alternative interpretation of the hazard ratio estimate is that, at a given time point, the hazard for a person who has not yet been diagnosed to have AS is approximately x times the hazard for a person who has been diagnosed by that time.[118]

Paper 2

Predictors of incident AS: Univariate analyses and age adjusted analyses were performed using Cox proportional hazards regression. Censoring occurred when participants moved, at death or end of follow up. Being a slowly progressive disease, and with long echocardiographic examination intervals of 7 years, we assumed that those found to be incident cases in 2001 and 2008 had the disease a few years prior to the examination. Thus, the diagnostic time-point for incident cases was estimated to be at ¾ of the time interval from baseline to 2001/2008. Independent risk factors for AS were determined by a backward multivariate analysis using Cox proportional hazards regression. The proportional hazards assumption was assessed by visual inspection of plots, statistical analysis of Schoenfeld

residuals and by time-dependant variables for each predictor. A p-value from the univariate analyses of <0.25 was used for entry into the multivariate analysis.

Predictors of progression rate of AS: A subgroup of 118 of the 132 participants with incident AS had two or more measurements of the mean aortic gradient either in the survey and/or at the hospital, and were thus eligible for evaluation of risk factors for increased progression rate of AS. We performed both crude and multivariate regression analyses of predictors. A p-value of < 0.25 from the crude analyses was used for entry into the multivariate model.

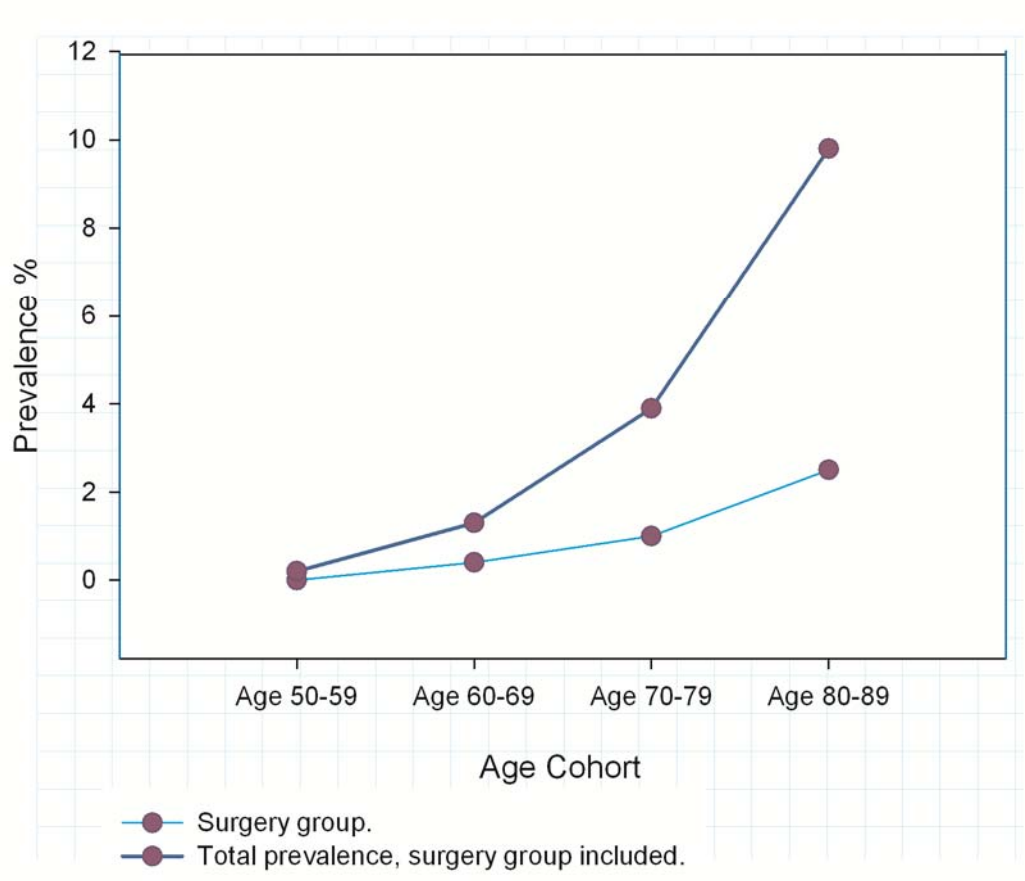
Paper 3

We evaluated the participants` risk of progression to AS according to their mean aortic valve gradient at baseline. The participants had gradients below 15 mmHg and were stratified into three groups: <5 mmHg, 5-9.9 mmHg and 10-14.9 mmHg. A morphological evaluation of the aortic valve was not part of the echocardiographic protocol. At follow-up after 7 years we observed the prevalence of AS in the three stratified groups and defined these subjects' AS stage. Data comparisons were performed according to the presence or absence of AS using the Student unpaired t test or χ^2-test as appropriate. We used crude and multivariate logistic regression to analyse predictors of progression to AS (age, sex, aortic jet velocity, mean aortic valve gradient stratified in three groups, aortic cusp separation and aortic diameter). In the multivariate analysis aortic jet velocity was excluded due to colinearity with the mean aortic gradient. Survival analysis was performed using Cox proportional hazards regression.

Main results

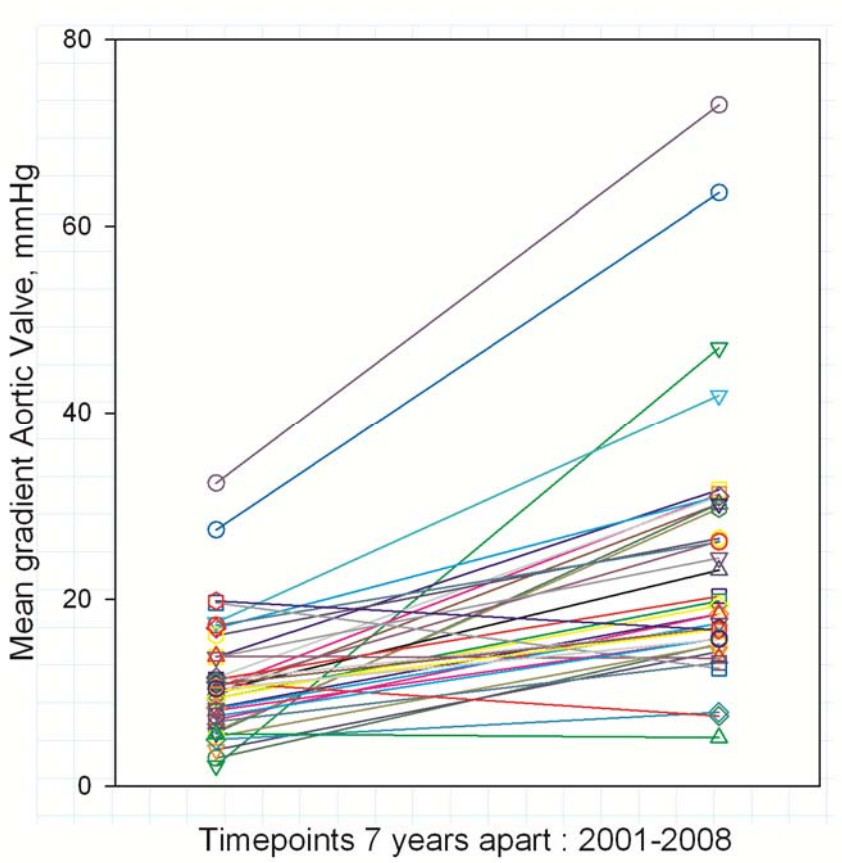
Paper I: Estimation of prevalence, incidence and the progression rate of AS in the study population. Evaluation of mortality in the AS-subgroup compared to the general population.

Over a 14 year span we performed 3 repeated echocardiographic examinations (1994, 2001 and 2008) of a random sample of initially 3,273 participants. Data from the only hospital serving this population were included. There were 164 subjects with AS. At all three time points we consistently found an increase in prevalence with age, weighted mean values in the combined survey "T4/5/6 and hospital data" being 0.2% (95% confidence interval(CI) 0-0.4) in the 50-59 year cohort , 1.3% (95%CI 0.9 – 1.7) in the 60-69 year cohort, 3.9% (95%CI 3.2 – 4.6) in the 70-79 year cohort and 9.8 % (95%CI 7.8 – 11.8) in the 80-89 year cohort (fig.2). Thus, the prevalence increases exponentially with age. There were no sex differences in point prevalence with increasing age.



Throughout the study period T4-T6 the summarized number of incident cases was 134. The dataset for the whole period, including those detected at the hospital only, thus gave an incidence rate of 4.9‰/year (95%CI +/- 0.81‰).

A subgroup of 118 participants with AS had two or more measurements of the mean gradient. They had a mean follow-up time of 6.4 years (range 1-14 years). The mean gradient progression/year was 3.2 mmHg, with a wide standard deviation of 2.36 and a range from -1.0 - 13.0. Subdividing them we found that the asymptomatic AS group (n= 88) had a progression of 2.6 mmHg/year, those who later underwent surgery 4.9 mmHg/year and the conservative treatment group 4.5 mmHg/year.



The progression rate in participants with an initial gradient ≥30 mmHg was 4.5 mmHg/year, exceeding the rate of 3.0 mmHg/year in those with a gradient <30 mmHg ($p<0.05$).

Summarized, these results demonstrate a more rapid progression with advancing valve calcification.

When comparing the AS-group with the no-AS group at a given time point there was no significant difference in age adjusted survival, hazard ratio(HR)= 1.28 (95%CI 0.94 – 1.76).

Analysis of the AS surgery group versus those without AS also gave no significant difference in age adjusted survival; HR=0.93 (95% CI 0.42 – 2.08).

When evaluating causes of death an age adjusted logistic regression analysis disclosed an increased risk of cardiovascular death in the AS group (57.4%) compared to the normal population (37.1%) with a HR of 2.14 (95%CI 1.21, 3.76).

Our data delineate AS as a progressive disease accelerating both with age and degree, where prevalence increases exponentially with age.

Paper II: Evaluation of risk factors for development of incident aortic stenosis and risk factors for progression of the condition.

Of the 3,243 participants, 132 developed incident AS during follow up. At the end of the study, AS stage status was: mild AS 64, moderate AS 29, severe AS 19 and aortic valve replacement 20.

We found that age, systolic and diastolic BP, antihypertensive treatment, OPG, waist circumference, BMI, hip circumference, weight and coronary disease were unadjusted significant predictors. After adjusting for age, only systolic BP, diastolic BP, waist circumference, weight, and hip circumference had a p-value <0.05. BMI and active smoking had borderline values <0.055.

The backward multivariate analysis showed that age, systolic BP, active smoking and waist circumference were significant independent predictors, with a Wald score of 51.3, 6.03, 5.49 and 5.28, respectively. Active smokers had a HR for AS of 1.7 compared to non-smokers. For each decade increase in age there was a 171% increase in risk of developing AS, whereas each standard deviation(SD) increase in waist circumference (11.4 cm) gave a 23% increased risk of AS. Further, each SD increase in systolic BP (22.3mmHg) gave a 25% increased risk of incident AS.

Factors affecting the progression rate was initially evaluated in a crude regression analysis, finding the mean aortic gradient at first measurement (p= 0.01), hip circumference (p= 0.034) and Hgb (p= 0.039) to be predictors. Entry of variables into multivariate regression analysis disclosed a higher mean aortic gradient at baseline (p= 0.015), weight (p= 0.015), a low Hgb (p= 0.030), and a high HDL (p= 0.032) as significant independent predictors of the progression rate of AS.

Paper III: Evaluation of progression from aortic sclerosis to aortic stenosis by use of the mean aortic valve gradient, including progression rate from aortic sclerosis to AS.

Over a 7 year span we performed 2 repeated echocardiographic examinations (2001 and 2008) of a random sample of 1,884 participants free of manifest AS. Data from the only hospital serving this population were included in the follow up. The three groups were stratified by their mean aortic valve gradient from 0-5mmHg, 5-9.9 mmHg and 10-14.9 mmHg. Those developing AS (n= 40) during follow-up had 5.5 years higher mean age than the remaining study group ($p = 0.001$). They also had a significantly smaller cusp separation at baseline compared to those without developing AS ($p <0.001$).

In the group with an initial mean aortic valve gradient of 0-4.9 mmHg only 0.3% (3/1113) of those surviving progressed to manifest AS. In those with a baseline gradient of 5-9.9 mmHg 3.7% (18/487) developed AS. In contrast, we found that as many as 33.3% (19/57) progressed to AS in the group with a baseline mean aortic valve gradient of 10-14.9 mmHg. Thus, there was an exponential 10-fold increase in the risk of developing AS going from one mean gradient group to the next.

Crude logistic regression analyses identified mean aortic valve gradient, aortic cusp separation, aortic jet velocity and age as significant predictors of developing AS. In multivariate analyses the mean aortic gradient and aortic cusp separation were significant predictors. Comparing the 10-15 mmHg and 5-10 mmHg groups gave an odds ratio (OR) for developing AS of 8.52, 95%CI 4.0 – 18.0. The aortic cusp separation was significant both as a continuous variable (OR 0.08, 95%CI 0.02 – 0.33) and as a dichotomous variable separated at 1.6 cm (OR 0.37, 95%CI 0.16 – 0.84).

Of those who developed AS, 70 % were mild, 25 % moderate and 5 % severe.

The progression rate during the 7 year follow up among those developing AS shows a wide range from 0.7 mmHg/year to 12.6 mmHg/year. The maximum value was extreme in this dataset, and when excluded the mean progression rate was 2.5 mmHg/year.

General discussion

Methodological considerations

Echocardiography

The echocardiography session was only one of several examinations of the extended second visit that a subcohort in the Tromsø Study was invited to. Each examination was allocated 20 minutes per subject and the echocardiography was structured to be feasible within this time. It is recommended to use AS jet velocity, mean transaortic gradient and the valve area for clinical evaluation of AS severity.[119] We used the mean gradient as the primary measure. It is easy to obtain, though mal-alignment of the jet and ultrasound beam, neglect of an elevated proximal velocity and the phenomenon of pressure recovery are known sources of error. The presence of aortic regurgitation may increase the mean gradient, though rarely significantly unless it is severe. Systolic left ventricular dysfunction can give low gradients despite a severe AS. These factors were considered when we graded participants with AS, but none changed classification due to this. We can, however, not rule out the possibility of minor stage misclassification related to a reduced ventricular function. The jet velocity was evaluated from an apical 4-chamber view alone and the left ventricular outflow tract diameter was not measured, thus AVA was not used in our study. It is more prone to errors of measurement and inaccuracy, thus use of the mean gradient, a more reproducible measurement, will give less misclassification.[104,119,120]

Our study used the transvalvular mean aortic gradient both for separating ASc from AS and in staging of AS into mild, moderate and severe disease. Observational studies have shown that a mean aortic valve gradient of 20 mmHg refers to a peak aortic jet velocity of 3 m/s.[119] In addition, the hemodynamic cut off value for AS that we made at 2.5m/s is comparable with previous studies using peak aortic jet velocity. The staging at 15-29mmHg, 30-49mmHg and

≥50mmHg for mild, moderate and severe AS, respectively, given a normal systolic function of the left ventricle, differs from the staging of AS in current guidelines.[121] We chose to use the staging upon which clinical decisions were made in the time period of our study, where a mean gradient >50mmHg marked a severe AS, and could lead to surgery if symptoms were present as well.

The screening of aortic stenosis had some limitations in T4. Aortic jet velocity was not routinely measured in all subjects, only in those with any indication of pathology (turbulent flow or aortic valve separation less than 1 cm in parasternal short axis, M-mode). Hence, some mild cases of AS may have been overlooked in T4. This is consistent with the finding of lower prevalence numbers for T4 compared to T5 and T6.

Intra- and inter-observer studies were performed both in T5 (n=40) and T6. The Bland Altman test of 42 participants in T6 showed mean inter-observer differences (95% limits of agreement) in the mean aortic gradient of -0.06mmHg (-3.06 - 3.18). Intra-observer analysis gave a mean difference of -0.04mmHg (-1.86 - 1.78) and 0.30mmHg (-3.96 - 4.56).

Study design, bias and misclassification

This thesis is based on a prospective population cohort study where echocardiography was conducted both at baseline and after a follow-up of 7 and 14 years, respectively. In addition risk factors for incident AS could be analyzed through baseline questionnaires, blood samples and other tests. This design enabled both descriptive and analytical epidemiology. In cohort studies it is possible to evaluate the difference in outcome between exposed and non-exposed subjects. To accumulate sufficient person-time and endpoints the follow-up time needed is determined by the incidence of the endpoints and the number screened. If the number screened and the incidence are both low, patience is needed. On the other hand, to screen a large enough sample for a short follow-up to be sufficient, is resource demanding.

Selection bias

Cohort studies are vulnerable to selection bias, as the relationship between exposure and disease might differ in subjects participating compared to the rest of the eligible population. In the Tromsø study participants were selected by age. Selection bias has probably occurred to some extent in our study with attendance rates in Tromsø 4-6 of 73%, 78% and 66%, respectively. Being a population study the overall participation rate is high, with exception of Tromsø 6, due to lower attendance rate among the relatively young and those who had never participated in the previous surveys. Accordingly the attendance rates in the older second visit invitees were higher (88% in T4).[115] In the follow-up phase of the study some of the non-attendees could be thought to represent a subgroup of older persons with more comorbidity. Legal restrictions given by the Norwegian Data Inspectorate preclude detailed analyses of mortality and morbidity according to attendance. However, the total age and sex adjusted mortality demonstrated a lower mortality in the subjects who were consistent attendees in the Tromsø Study. Generally the non-attendees tended to be younger and had a higher proportion of men and single.[122] To compensate for the incomplete attendance we retrospectively integrated data on the T4 cohort collected from the only hospital serving the study population, thus minimising follow-up bias otherwise made by non-attendees in T5 and/or T6.

Information bias

Information bias can occur when obtained information regarding exposures and/or disease is incorrect. When sampling of data is inaccurate, subjects may be misclassified. A misclassification bias can be either differential or non-differential. A differential misclassification bias occurs when the rate of misclassification differs in the different study groups. This can lead to an apparent association that is false or an apparent lack of association that is false. In non-differential classification there is on the other hand an inaccuracy in the gathering of information in both exposed and non-exposed subjects. The effect is usually that

the relative risk/odds ratio tends to be diluted, i.e. shifted toward 1.0, thus an association is less likely to be detected. Our study could be vulnerable to these kind of biases through the questionnaires, for instance presence of cardiovascular disease, diabetes or osteoporosis relied on self-reporting of the participants alone, giving the opportunity for recall bias. This was also the case for vitamin D and cod liver oil supplementation. Smokers were classified as present, previous or never smokers. An obvious bias occurs when a previous smoker just recently stopped smoking. Also, neither the duration of the smoking habit nor grade of consumption was taken into consideration.

Validity

The term validity (or accuracy) refers to absence of bias. In an epidemiological study the internal validity refers to whether the results are representative for the population under study.[123] Generally, the internal validity may be threatened by selection bias, information bias and confounding.

External validity is to what degree the results of a study are generalizable to other populations. This can be evaluated by comparing findings between similar studies in different populations or applying the same models on other datasets. The age and sex distribution of the Tromsø Study reflects the general Norwegian population. The Tromsø study is based in the seventh largest Norwegian city with relatively few immigrants. It is therefore limited with regard to ethnic diversity. The population of Tromsø seems representative of the Norwegian/Scandinavian population, being a largely middle-class Caucasian population.[122] The educational level in T6 was somewhat higher as compared to the general Norwegian population and to the Tromsø population, though decreasing strongly with increasing age for both sexes.[124]

Reliability

The term reliability refers to the precision and reproducibility of the data collected. Variability due to imprecision of the observer or the method can be classified into two types. Intra-observer variability refers to the variability of for instance the measurement of a parameter by echocardiography conducted twice by the same echocardiographer at different points in time. Inter-observer variability refers to the variability of a measurement on the same participant by two different echocardiographers. Intra- and inter-observer studies were performed both in Tromsø 5 (n=40) and Tromsø 6.

Confounding and effect modification (interaction)

A confounding factor predicts the outcome (here a disease), differs between the groups studied and is associated with the exposure under study. The factor`s association with disease arises from a causal pathway other than the one under study. A confounding factor is not affected by the exposure or the disease.[123] It may lead to an underestimation or overestimation of the effect of an explanatory variable. Confounding may be controlled for by using matching when designing the study, by stratification or by use of multivariable statistical methods in the analyses of the data. We were not able to detect confounding variables in the multivariate logistic regression analyses when publishing paper II.

When running a large number of statistical tests in a dataset there is always a chance of false positive associations (type I error). To avoid this one could be more stringent with significance levels, moving to $p<0.01$ rather than $p<0.05$. On the other hand this reduces the power unless the sample size is increased accordingly. Type II error occurs when the test hypothesis is false but not rejected. The risk of a type II error increases with the number of variables included in the regression models, as degrees of freedom and thus power decrease.

We therefore only entered variables into multivariate regression analysis if crude regression analysis gave a $p<0.25$.

Interaction is present when the effect of a risk factor on an outcome is changed by the value of a third variable. It can be synergistic (positive interaction) or antagonistic (negative interaction), and can be controlled for by stratified analyses. Because the value of the third variable changes the effect of the risk on an outcome, interaction is often called effect modification.[125] Evaluating the predictors in the multivariate logistic regression analyses for interaction in paper II revealed a multiplicative interaction between age and systolic BP. Analyses also revealed a multiplicative interaction between coronary disease and waist as well as coronary disease and systolic BP. The presence of coronary disease as a predictor in the final analyses did however not alter the results for the significant variables. Thus, this finding seems related to random variability.

Missing values

Subjects with missing values for a covariate in the regression models used (logistic regression and proportional hazard model) were not included in our studies. It is a valid approach when the missing data are missing completely at random. A drawback is that recorded data will be discarded. Imputation methods predict and fill in the missing values based on the observed data and the missing-data pattern. We performed imputation for some variables, generally with very few missing values, where later measurement data in T5 or T6 were available. A simple method of imputation is to replace missing values with the average value for that variable. This method was used for 8 missing values of BP. One could also do this more refined, for instance using the mean value gained by stratifying on predictors of BP such as age and BMI. Imputation is likely to reduce the standard deviation and standard error. In a large sample like ours, few missing values will not be a serious problem. In the end-stage

multivariate Cox regression analyses of paper II with only the significant predictors left, there were only 9 cases with missing values. However, if there are many missing values it is potentially dangerous because it will more likely lead to significant results for the imputed variable that are a product of the data replacement rather than a genuine effect.

Causality

To assess causality the strength of the statistical association (relative risk or odds ratio) has been considered important. The stronger the association, the more likely it is that a causal relationship exists. Strong associations are neither necessary nor sufficient for causality, and weakness is neither necessary nor sufficient for absence of causality.

Consistency refers to repeated observations of an association in different populations under different circumstances. Lack of consistency does on the other hand not rule out causality because some effects are produced by their causes only under certain circumstances. Furthermore, a conclusion about inconsistency may be falsely drawn due to different power in studies compared.

Temporality means that a cause must precede the effect in time. As the dose of exposure increases, the risk of disease also increase (biological gradient).

Plausibility refers to the scientific plausibility of an association and coherence with the biological knowledge. A set of sufficient criteria to ensure causality in observational studies cannot definitely examine whether biomarkers are causally related to a disease.

Discussion of the main results:

AS is a condition that has undergone both epidemiologic and demographic changes over several decades in the industrialized world. An updated mapping of the condition seemed warranted and thus we performed a population based study entering a new millennium.

Prevalence and incidence:

Much of the current knowledge concerning AS is based on hospital series. Since the disease progresses over years with a long asymptomatic phase, such data can never give a full picture of the prevalence and development of AS. Therefore, population based data are necessary. The wide time span made us able to follow this slowly progressing disease over 14 years, adding knowledge to standard clinical descriptions of the condition. We believe paper I is the first epidemiological study to provide incidence- and progression data based on a representative population sample.

No uniform definition of AS exists, or to be more specific, a defined transition point from ASc to AS is lacking. Using different anatomical and hemodynamic criteria to define ASc in addition to different AS stage definitions based on the aortic valve jet velocity, the mean gradient or area, does have implications when registering the prevalence of the condition. Nkomo et al. have published the largest epidemiological study on prevalence of AS among 11,911 individuals.[11] AS was defined as limited leaflet motion, increased transvalvular Doppler flow velocity, or both, corresponding to the criteria for moderate/severe stenosis according to guidelines when the study was conducted (area <1.5 cm^2).[20,126] They found an overall prevalence of 2.5%. In the age cohort 55-64 years of age the prevalence was 0.2%, in the 65-74 year cohort 1.3% and in the age cohort ≥75 years it was 2.8%, thus finding a striking increase with advancing age. Adjusted for sex the OR for the association of valve

disease with increasing age was 2.51(2.02- 3.12). Further, men had higher prevalence of AS than women, OR 1.52 (1.02-2.26) after age adjustment.[11]

Lindroos et al defined AS as valve area <1.2 cm², including moderate to severe AS by modern definitions, finding a prevalence in their study population aged ≥75 years of 4.8%.[9]

Stewart et al have conducted a study most comparable to ours, since they used peak aortic flow velocity of 2.5m/s as definition of AS. They found an overall population prevalence among participants ≥65 years of age of 2%. The prevalence increased with age, being 1.3% in the age range of 65-74 years, 2.4% in the age range of 75-84 years and 4% in the population aged 85 or more.[8]

In our survey we were able to estimate the point prevalence at three different time points and as a weighted mean of all three studies combined (T4/5/6). New calculations were made after the inclusion of hospital data as well. The results were quite consistent at all three time points, delineating AS strongly related to age, thus confirming the previous cross-sectional population studies. [8,9,11]

Incidence rates are not proportions, but estimates of number of events divided by the amount of time at risk. Assumptions necessary for this type of analyses are that censored observations have an outcome probability that is similar to that of individuals remaining in the study, that losses are uniform over the interval and that there is a lack of secular trends over the time period with regard to the characteristics that affect the outcome of the individuals. Incidence numbers increased during our study due to aging of the population. The study period T5-T6 differs from the others with an incidence rate of only 2.2‰/year. The fraction of non-attendees in this period was 26%, 13% died and 4% moved. We believe this information bias contributed to an under-estimation of incident cases, as demonstrated by the joined study/hospital data, giving a doubled incidence rate for that period. A recent Swedish study of temporal trends in AS observed that, despite an aging population, the unadjusted incidence

rate of AS remained stable, whereas the age-adjusted incidence rate declined in Sweden over the past 20 years (from 15.0 to 11.4 per 100,000 in 3 years for men, and 9.8 to 7.1 per 100,000 in 3 years for women).[127] Their incidence estimates are much lower than ours, due to identification of cases through the Swedish hospital discharge register, thus mainly comprising moderate to severe AS.

Progression rate:

The results on progression of AS in the SEAS study are compatible with our results, showing a mean gradient increase of 3.2mmHg/yr. In addition, our progression analysis reveals a non-linear development of the disease, being more rapid with increasing mean gradient. One could explain this by assuming a constant calcification process over time. A given narrowing of an already small valve area has a greater influence on the jet velocity/gradient than the same degree of narrowing by calcification in a valve with only slight/moderate area reduction. Regardless of the initial gradient participants did however show a large inter-individual variability in disease progression. Our data implies that previous progression rate should be considered as a primary factor when future visit intervals for each patient are decided.
Paper III displayed a mean rate of progression of 2.5 mmHg/year among those who progressed from ASc to AS. This is in accordance with our analysis in paper I, finding progression to be more rapid with increasing mean gradient. Previous studies have displayed a high prevalence of ASc, but seem to overestimate the progression into manifest AS (9-33% in 4-7 years) as we know that the incidence number of AS in our population was 5‰/year. Further, it would be both a too large and unnecessary task to follow up all patients with ASc. Our stratification of subclinical mean aortic valve gradients identifies a small high-risk proportion of the population comprising only 4%.

Mortality

In 1968 Ross and Braunwald published an important paper showing a dramatic increase in the mortality of patients with AS after symptom onset.[128] This contributed to a world-wide policy of selecting AS patients to surgery based on symptoms. At that time rheumatic disease was still prevalent, the mean age at death was 63 years and echocardiography was not implemented. The study therefore does not represent the epidemiology of AS today, now being dominated by octogenarians with degenerative AS.

One previous population based study evaluating mortality reported a markedly increased risk of death in those with severe AS (RR= 3.93).[129] No participants underwent valve surgery, which makes the study less representative in view of today's active treatment strategy.

Pellikka et al performed a follow up study of 622 asymptomatic AS patients recruited from an echocardiography database.[103] Comparing them with a matched general population a trend towards increased all-cause mortality after 2 years of follow-up was observed. This is consistent with our analysis (HR= 1.28).

Our population based mortality data show no significantly increased mortality in the asymptomatic AS group or in those treated with AVR compared with the general population, indicating that the AS-patient group has received qualified follow-up and appropriate timing of the surgical interventions. The screening with secondary follow-up may of course have contributed to this low mortality rate. Our subanalysis showed no significant difference in mortality between mild, moderate or severe asymptomatic AS. This finding could be limited by misclassification related to low-flow participants.[130,131] As expected, the conservatively treated subgroup with severe AS had the worst survival outcome, although some survived for several years after onset of symptoms (mean 2.3 years, range 0.1 – 5.6 years). This group included both patients who refused AVR and those who did not undergo surgery due to comorbidity. The Swedish incidence study, referred to above, also found that, despite a

median age increase of 4 years in the study from 1989-2009, mortality after diagnosed AS declined markedly.[127] Age-adjusted mortality rate at 3 years declined from 9.3 to 4.8 in men and 8.3 to 4.8 in women. The proportion of patients undergoing AVR remained relatively stable during the study period, and increased in patients >75 years of age at diagnosis. They also noted a significant reduction in 30-day mortality after AVR. The study suggests that increased use of AVR in the elderly and a reduction in perioperative mortality, potentially in combination with improved risk factor control, have translated into favorable effects for patients with AS.[127]

Risk factors of incident AS

Our results confirm that aging is an important risk factor, with a close to tripled increase in risk for each 10 year. Smoking, systolic BP and waist circumference were also significant factors in the multivariate analyses. Active smoking has been significantly related to AS both in the KORA/MONICA study (OR 1.7) and in the Cardiovascular Health Study (OR 1.35).[8,83] Our data (HR 1.7) confirm these results.

The association with obesity was confirmed by the significant results regarding hip circumference, weight and BMI in the univariate analysis. Systolic BP, diastolic BP and antihypertensive treatment were all significant risk factors in the crude analyses, and both systolic and diastolic BP maintained significance when entered separately into the multivariate model.

In contrast to the image based studies, we found no association between AS and lipids. The links to factors influencing calcification were also very weak. OPG, a protein that inhibits osteoclast activity, was a significant factor only in the crude analysis and in stratified multivariate analysis in subjects under the age of 65, but not in the main multivariate model.

The traditional view has been that AS primarily is an age-associated degenerative condition, aggravated by mechanical stress. The association with age is confirmed both by our paper I and II. Recently two alternative models have been discussed, seeing AS either as an atherosclerotic process or as linked to factors influencing calcification.

Several clinically based retrospective studies and three of the population based papers quoted above have linked AS to lipids.[8,80,82,83] Combined with the associations with other core cardiovascular risk factors this led to the hypothesis that AS was essentially an atherosclerotic disease. In marked contrast to previous studies we did not find any association between lipids and AS, neither with regard to initiation, nor progression of the disease. This is compatible with the negative results of the three intervention studies on lipid lowering in AS, as well as a SEAS substudy that did not find an effect of lipid lowering treatment even in the group with the mildest AS (aortic jet velocity <2.8 m/s)[90-92,132] Although several other "atherosclerotic factors" may have a role in the pathogenesis of the disease, conventionally measured lipids do not. A small study indicating that statins still may have a role in mild AS needs support from larger trials.[94] Further, a recent Swedish study based on European and American population cohorts, found that genetic predisposition to elevated LDL cholesterol was associated with presence of aortic valve calcium and incidence of AS.[133] They argue that the negative randomized trials enrolled older patients with established valve disease, where LDL cholesterol may no longer be an important mediator, but mainly promote calcification in early lesions. These studies are not supported by our findings of zero effect of lipids in the transition from no disease to early disease. A recent genetic study indicates a causative role of lipoprotein(a) (Lp(a)), and another study demonstrated a stepwise increase in risk of AS with increasing levels of Lp(a) in a general population[134,135]. Lp-PLA2 uses oxidized LDL as substrate and produces free fatty acids and lysophosphatidylcholine, a powerful proinflammatory and procalcifying factor.[136] Individuals carrying this single nucleotide

polymorphism have a risk of clinical AS that is approximately two thirds greater than the normal risk. Why do there seem to be divergent conclusions in the genetic studies and in the outcome of the therapeutic intervention trials? In an editorial they report that the frequency of the specific LPA gene variant is reported to be 0.03, thus only representing a small subgroup of persons that are genetically susceptible to benefit from specific Lp(a)-lowering therapy due to their predisposition.[137]

Thus, the atherosclerotic model for AS seems weakened. Although several factors involved in the development of AS are also atherosclerotic factors, the dissociation regarding lipids indicate a different type of process. This is supported by other differences making AS appear as a distinctive pathophysiological entity. Early lesions of AS are characterized by subendothelial accumulation of oxidised LDL and inflammation with T-lymphocytes and macrophages.[24] Smooth muscle cells are prominently involved in atherosclerosis but are not seen in aortic valve lesions, where the fibroblasts and myofibroblasts dominate.[138] In addition, the calcific changes are present at an earlier stage and more prominently in AS than in an atherosclerotic plaque.[93] Only one-half of the patients with AS have coronary artery disease, and a minority of patients with coronary artery disease have concomitant AS.[102]

The calcification process in AS seems to be an active process initiated by locally produced factors, transforming fibroblasts into osteoblasts.[139] It is also well known that diseases with altered calcium metabolism, like end-stage renal disease, Paget's disease and hyperparathyroidism are associated with AS.[140] A polymorphism of the vitamin D receptor is associated with both AS and osteoporosis.[42] In contrast, we did not find any strong associations with calcium metabolism. A recent study used positron emission tomography and CT imaging in patients with calcific aortic valve disease to compare calcification of the aortic valves with that of thoracic atheromas and skeletal bone.[141] They found that active calcification was most pronounced in aortic valves, whereas inflammation dominated in

atheromas. Valve calcifications were poorly related to calcific activity in the aorta, coronary arteries and bone but strongly related to the severity of aortic valve disease. In accordance with our findings, they imply that once valvular calcification has begun, it proceeds largely independently of external factors.

Although an active inflammatory process is involved in the development of AS, none of the inflammatory markers in our study (c-reactive protein, white blood cells and fibrinogen) were significant, neither in the crude nor multivariate analyses.

A key initiating factor appears to be mechanical stress. Several recent studies indicate that various types of abnormal hemodynamic stress cause tissue inflammation and secondary calcification and stenosis.[23] Another aspect of importance is the anatomical relations between valve leaflets, corresponding sinuses and the sinotubular junction. Normal anatomy in these structures seems to create an optimal distribution of pressure load. Due to aging the aortic root is stiffened by the loss of elasticity, and the aortic leaflet dynamics change. The role of aging is thus not restricted to mechanical stress on the valve alone, but also to the changing dynamics of neighbouring structures, making the process continuous and progressive.[93] When sclerosis is established, the leaflets themselves also promote unfavourable stress distribution, causing a self-perpetuating process.

If age is important it is easy to imagine that all factors increasing the mechanical stress on the valve may enhance the process. This is in accordance with our findings regarding BP and obesity. Thus, an age-dependant process aggravated by “wear and tear” and the toxic effect of smoking may still be the best model of the causes of AS in the general population. The wear and tear theory may also gain support from the experience with bicuspid valves, where AS develop 10-20 years earlier than in the tricuspid AS population.[17]

The clinical implications of this study are simple. Sticking to a healthy life-style, similar to that advocated to prevent coronary heart disease, may probably reduce your risk of having AS

to some extent, as shown in the recent Swedish population registry study.[127] However, when the disease has started to develop it constitutes mostly a self-perpetuating process, uninfluenced by external factors.

Risk factors for progression of AS

The first measured mean aortic gradient was the major predictor of the AS progression rate in article II. This correlates to our results in paper I delineating a more rapid progression with advancing valve calcification, also demonstrated in some prior retrospective studies.[39,84-87] When this was accounted for, age did not appear as an important factor for progression. Weaker findings were associations between progression rate and a lowered Hgb level and, paradoxically, with an elevated HDL level. The finding of a low Hgb as a risk factor is supported by one previous study.[142] It may be speculated that a fall in Hgb could add to the hemodynamic burden on the valve through the demand for an increased stroke volume. However, the relationship could also be reverse, through hemolysis induced by an advanced AS.[143,144]

AS is also sometimes associated with loss of high molecular von Willebrand multimers, and thus a greater tendency to bleed.[145,146] These issues are only of clinical relevance in cases of severe anaemia requiring transfusion, but mild anaemia might exist in milder forms of AS due to these mechanisms. If so, low Hgb may not have a causal association with progression of AS but may rather be caused by advancing valve calcification.

Capoulade et al found that increased Lp-PLA2 activity was associated with faster stenosis progression rate in the subset of patients with mild AS, thus supporting the hypothesis that lipid-mediated mineralizing processes may be predominantly involved in earlier stages of the disease.[147] Further, lower levels of HDL cholesterol were independently associated with higher activity of circulating Lp-PLA2. As such, this very recent study could imply that HDL

may have been confounded by Lp-PLA2 in our progression analyses of paper II. As previously mentioned genetic association to LPA has also been demonstrated, suggesting that further studies are needed to evaluate whether lowering Lp(a) levels during the early-stages of aortic valve disease with either niacin or novel specific Lp(a) lowering drugs will delay the progression of this condition.[135]

In an ASTRONOMER substudy metabolic syndrome was found to be an independent predictor of faster AS progression, only significant in those 57 years of age or younger.[148] In addition rosuvastatin worsened the insulin resistance state and LDL particle phenotype. This is in line with the now established fact that statin treatment both in randomized trials and carriage of common single nucleotide polymorphisms in the 3-hydroxy-3-methylglutaryl-coenzyme gene in population studies were associated with body weight gain and higher risk of type 2 diabetes.[149] Hence, the insulin resistant state and atherogenic dyslipidemia linked to visceral obesity may have a role in development of aortic valve inflammation and calcification in the younger population.

Implications for public health practice

Our study gives updated information on prevalence, incidence and progression rate of AS, both in its early and later phase. With an increasingly elderly population and new technologies that has made it possible to treat also the elderly with AS and those with comorbidity, one must expect a rise in number of both AVR and TAVI. Our estimates of prevalence and incidence makes it possible to better predict future need for surgical treatment.

Further, our population based mortality data show no significantly increased mortality in the asymptomatic AS group or in those treated with AVR compared with the general population, indicating that the AS-patient group received qualified follow-up and appropriate timing of the surgical interventions justifying guidelines for follow-up and intervention.

The clinical implications of paper II are that the general population through a healthy life-style, similar to that advocated for prevention of coronary heart disease, may reduce the incidence rate of AS to some extent. Our results seem to challenge current thinking on the causes of AS and also gives some credibility to the traditional model of "wear and tear". Neither lipids nor calcification modifying factors seems to be heavily involved. From our study AS appears to constitute a distinctive age related degenerative and inflammatory disease, which may be aggravated by smoking and a number of factors increasing the mechanical stress on the valve.

Based on the data in paper III, we would recommend that subjects with aortic gradients in the upper normal stratum, 10-15 mmHg, should be followed routinely by echocardiography at about 5 years intervals. Those who regress to lower gradients may be dropped from follow-up. Subjects with mean gradients of less than 10 mmHg should probably be followed primarily on clinical indications. Thus, a number of unnecessary controls of subclinical aortic valve disease may be avoided. The large inter-individual variability in progression rate should always be remembered.

Conclusions

Paper I: Over a 14 year span we performed 3 repeated echocardiographic examinations (1994, 2001 and 2008) of a random sample of initially 3,273 participants. There were 164 subjects with AS. We found that prevalence consistently increased with age, average values being 0.2% in the 50-59 year cohort, 1.3% in the 60-69 year cohort, 3.9% in the 70-79 year cohort and 9.8% in the 80-89 year cohort. The incidence rate in the study was 4.9‰/year. The mean annual increase in mean transvalvular pressure gradient was 3.2 mmHg. The increase was lower in mild AS than in more severe disease, disclosing a non-linear development of the gradient, but with large individual variations.

Mortality was not significantly increased in the asymptomatic AS-group (HR=1.28), nor in those who received aortic valve replacement (n=34, HR= 0.93), compared with the general population.

Paper II: Over a 14 year span 132 participants were diagnosed with incident AS, defined as mean aortic valve gradient ≥15 mmHg.

Cox proportional hazards regression disclosed age (HR 1.11, 95%CI 1.08 to 1.14), systolic blood pressure (HR 1.01, 95%CI 1.00 to 1.02), active smoking (HR 1.71, 95%CI 1.09 to 2.67), and waist circumference (HR 1.02, 95%CI 1.00 to 1.03) as independent predictors of incident AS.

Analysis of risk factors for progression of AS disclosed a higher mean aortic gradient at first measurement (p=0.015), weight (p=0.015), a low Hgb (p=0.030) and HDL (p=0.032) as significant independent predictors.

From our study AS appears to constitute a distinctive age related degenerative and inflammatory disease, which may be aggravated by smoking and a number of factors increasing the mechanical stress on the aortic valve.

Paper III: Over a 7 year span (2001-2008) we performed 2 repeated echocardiographic examinations of 1,884 participants. AS was defined as a mean aortic valve gradient ≥15 mmHg. Those with a gradient <15 mmHg were stratified into 3 groups: <5 mmHg, 5-9.9 mmHg and 10-14.9 mmHg. At baseline 73 participants had gradients from 10-14.9 mmHg, of whom 33.3 % developed AS during follow up. In contrast, AS developed in only 3.7 % of those with a baseline gradient of 5-9.9 mmHg (n = 556) and in 0.3% of those with a gradient < 5 mmHg (n = 1,255).

Of the 40 subjects who developed incident AS, 70 % acquired mild, 25 % moderate and 5 % severe AS. Their gradient progression had a mean rate of 2.5mmHg/year (range: 0.7-12.6 mmHg/year). It is in accordance with our previous progression rate analysis in paper I which revealed a non-linear development of the disease, being more rapid with increasing mean gradient.

Further research

ASc/AS is an asymptomatic condition for a long period of time, thus often well established before it is diagnosed. To obtain secondary prevention it would be of clinical interest to better disclose which factors are involved in the progression of AS. Both further prospective population studies and clinical case-control trials may add knowledge on this matter. We have yet to reveal why patients with severe renal failure seem to progress fast when they have AS. New knowledge of Lp(a) give reason to believe there is a causal relationship between Lp(a) and calcific aortic valve disease and strongly implicate genetic variation at the Lp(a) locus in the pathogenesis of the disease. The size and design of the Tromsø Study is optimal for validation of these findings due to the Norwegian Research Council funded project HARVEST with genome wide analysis of more than 12000 participants which will be ready for use in 2016. Six thousand of these will have echocardiographic data. HARVEST also gives an opportunity to detect new genetic risk markers and to validate a causal relationship for the found risk factors through Mendelian Randomization Studies. With the newly started health screening T7, a randomized life style intervention trial is planned targeting BMI and hypertension through diet and physical activity programs. If successful, it will strengthen the hypothesis of a causal relation between these two risk factors and AS development.
Our results seem to challenge current thinking on the causes of AS and also gives some credibility to the traditional model of “wear and tear” by factors increasing the mechanical

stress on the aortic valve. As such, basic research is needed; focusing on to what extent the anatomy of the valve leaflets itself predisposes the development of disease, also in tricuspid valves.

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Du er innbudt til den store helseundersøkelsen i Tromsø kommune 1994 - 95

Vi når fram til alle

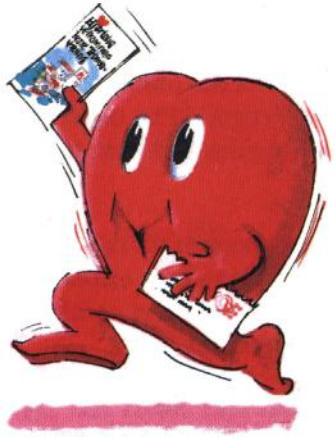
Vi begynner i de ytre distriktene i kommunen. Her vil undersøkelsen pågå i skolehus og andre lokaler - se opplysningene i innbydelsen som følger dette brevet.
Fra slutten av oktober 1994 til sommeren 1995 vil undersøkelsen foregå i Mellomveien 50 (Elisabeth-senteret; den gamle kvinneklinikken). Vi ser helst at du møter på stedet som er oppført i innbydelsesbrevet.

Hvorfor har du fått tilbudet ?

Fordi vi tilbyr undersøkelsen til alle som er født i 1969 eller tidligere.

Hva er formålet ?

Undersøkelsen er i første rekke rettet mot hjerte-karsykdom, men er også viktig for å få ny viten om andre alvorlige kroniske sykdommer (bl.a. kreft).
Denne gangen vil en i tillegg se spesielt på smertetilstander i muskler og skjelett, blant annet fibromyalgi. Derfor vil noen høsten 1995 bli invitert til en spesialundersøkelse.
Store hjerte-karundersøkelser ble gjort i Tromsø i 1974, 1979-80 og 1986-87. Det var stort frammøte, og det ble funnet en rekke tilfeller av hjerte-karsykdom - som nå får behandling.
Undersøkelsene har også gitt oss viktig kunnskap for å bekjempe disse sykdommene. Den kunnskap vi har fått gjennom de tidligere undersøkelsene, har gjort Universitetet i Tromsø til et av de fremste forskningsmiljøer i verden på hjerte-karsykdommer. Også denne gangen tar vi sikte på å finne personer som har hjerte-karsykdom uten å vite det. Vi vil også gjerne nå dem som har særlig høy risiko, slik at de kan få tilbud om forebygging og andre tiltak som kan hindre at sykdom utvikler seg. Hjerte-karsykdom er fortsatt et av våre største helseproblemer.



Ikke bare for din egen skyld.....

Undersøkelsen har ikke bare betydning for deg personlig. Det er også viktig at resultatene blir brukt i medisinsk forskning, bl.a. ved at vi sammenholder dem med framtidig forekomst av sykdom. Dermed lærer vi mer om hvordan hjerte-karsykdom, kreft og andre folkesykdommer oppstår og hvordan de kan forebygges. Ved å møte fram er du med i kampen mot disse sykdommene.

Undersøkelsen omfatter

- **Måling av høyde og vekt**
- **Måling av blodtrykk**
- **Blodprøve.** I denne måler vi innholdet av fettstoffer (bl.a. kolesterol), kalk og et leverenzym. Resultatet av disse målingene sendes din lege om du ønsker det. Resultatet av andre prøver blir bare brukt til medisinsk forskning. Prøven blir frosset ned, slik at det senere kan måles andre stoffer om det blir nødvendig for utforskning av sykdom. Før slike målinger blir gjort, blir studien forelagt den forskningsetiske komité for Nord-Norge.
- **EKG** er en undersøkelse som registrerer hjertets aktivitet. Den gjøres på en forenklet måte, og registreringene blir bare brukt til forskning.

- **Spørreskjema**
- **Spesialundersøkelse.** Alle født mellom 1920-1939, og et utvalg av de øvrige, blir tilbudt en mer omfattende undersøkelse gratis. Hva undersøkelsen omfatter varierer noe, men gir en bedre beskrivelse av hjertet, hovedpulsårens funksjon, åreforkalkning, og tendens til beinskjørhet. Du får time til undersøkelsen ved frammøte.

Spørreskjema

Dette finner du på baksiden av det brevet du har fått. Vennligst fyll ut skjemaet på forhånd og ta det med til undersøkelsen. Dersom enkelte spørsmål er vanskelige å fylle ut, kan du få hjelp når du møter fram.

Om samtykke

Opplysningene om deg blir behandlet strengt fortrolig. De oppbevares og brukes etter regler gitt av Datatilsynet og den forskningsetiske komité for Nord-Norge. For at opplysningene skal brukes i medisinsk forskning, må du samtykke til det. Samtykke er også nødvendig for at din lege skal få resultat av de målinger som gjøres (og som du selv får tilsendt resultat av) og svar du gir på spørreskjemaet som ligger ved dette brevet. Vi ber derfor at du ved frammøte samtykker i:

- at melding om dine resultat sendes til din faste lege, og inngår i din journal hos legen.
- at blodprøven kan brukes til analyser som ledd i medisinsk forskning. Hensikten med slike analyser er å forstå årsak til sykdom.
- at dine resultater kan brukes til medisinsk forskning, ved å sammenholde opplysningene med andre helse- og sykdomsregister (f.eks. kreftregister og dødsårsaksregister) og opplysninger fra de tidligere helseundersøkelsene i Tromsø. Før opplysningene analyseres, blir navn og person-nummer fjernet. Selv om du gir samtykke, kan du senere reservere deg mot bruk av dine resultat.

Etterundersøkelse

Noen av dem som blir undersøkt, blir senere innkalt til egen lege for nærmere kontroll. Trenger du behandling, får du tilbud om det.

Hva koster undersøkelsen ?

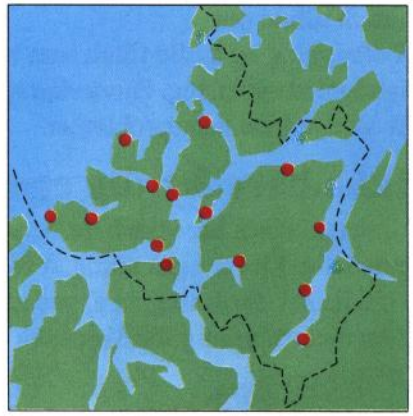
Det er nødvendig med en egenandel ved undersøkelsen. Den er beskjeden i forhold til de totale kostnadene. Beløpets størrelse vil du finne i brevet du nå har mottatt. Spesialundersøkelsen er gratis. Trenger du ny undersøkelse hos egen lege eller ved Regionsykehuset, betaler du vanlig egenandel.

Antrekk

Av hensyn til blodtrykkmålingen ber vi om at du tar på plagg uten ermer eller med korte ermer som ikke strammer. Det er ikke nødvendig å ta av seg på overkroppen.

Steder som får besøk av helseundersøkelsen

- Kaldfjord
- Tromvik
- Lakselvbukt
- Sjursnes
- Breivikeidet
- Fagernes
- Skittenelv
- Ersfjordbotn
- Straumsbukta
- Brensholmen
- Vikran
- Trondjord
- Sjøtun
- Tromsø sentrum



Vel møtt!

Hjertelig hilsen

- Kommunehelsetjenesten
- Fagområdet medisin, Universitetet i Tromsø

Statens helseundersøkelser

Repro & Skive A/S 380 96 955

Hjertelig velkommen, kjære Tromsøværing

Innbydelse til

HELSEUNDERSØKELSEN

Fødselsdato	Personnr.	Kommune	Kretsnr.

Velkommen til helseundersøkelsen i Tromsø!

Helseundersøkelsen kommer nå til Tromsø. Tid og sted for frammøte finner du nedenfor. Du finner også en orientering om undersøkelsen i den vedlagte brosjyren.

Vi ber deg fylle ut spørreskjemaet på baksiden og ta det med til undersøkelsen.

Undersøkelsen blir mest verdifull om frammøtet blir så fullstendig som mulig. Vi håper derfor at du har mulighet til å komme. Møt selv om du kjenner deg frisk, om du er under legebehandling, eller om du har fått målt kolesterol og blodtrykk i den senere tid.

Vennlig hilsen
Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser

EGEN HELSE

Hvordan er helsen din nå? *Sett bare ett kryss.*

Dårlig	12	1
Ikke helt god		2
God		3
Svært god		4

Har du, eller har du hatt:

	JA	NEI	Alder første gang
Hjerteinfarkt 13			år
Angina pectoris (hjertekrampe) 16			år
Hjerneslag/hjerneblødning 19			år
Astma 22			år
Diabetes (sukkersyke) 25			år

Bruker du medisin mot høyt blodtrykk?

Nå	28	1
Før, men ikke nå		2
Aldri brukt		3

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende? 29 — JA / NEI

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Nervøs og urolig? 30				
Plaget av angst? 31				
Trygg og rolig? 32				
Irritabel? 33				
Glad og optimistisk? 34				
Nedfor/deprimert? 35				
Ensom? 36				
	1	2	3	4

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? 37 — JA / NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? 38 — JA / NEI

Hvis "JA", hvor mange år tilsammen? 39 — Antall år

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? 41 — Antall timer

Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:

	JA	NEI
Sigaretter daglig? 43		
Sigarer/sigarillos daglig? 44		
Pipe daglig? 45		

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 46 — Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 48 — Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? 52 — Alder år

Hvor mange år tilsammen har du røykt daglig? 54 — Antall år

MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*
Arbeidsvei regnes som fritid.

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)* 56				
Hard fysisk aktivitet *(svett/andpusten)* 57				
	1	2	3	4

KAFFE

Hvor mange kopper kaffe drikker du daglig?
Sett 0 hvis du ikke drikker kaffe daglig.

Kokekaffe	58	Antall kopper
Annen kaffe	60	Antall kopper

ALKOHOL

Er du total avholdsmann/-kvinne? 62 — JA / NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. 63 — Antall ganger

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker? 65
Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol.

Øl	Vin	Brennevin
glass	glass	glass

FETT

Hva slags margarin eller smør bruker du vanligvis på brødet? *Sett ett kryss.*

Bruker ikke smør/margarin	71	1
Meierismør		2
Hard margarin		3
Bløt (soft) margarin		4
Smør/margarin blanding		5
Lettmargarin		6

UTDANNING/ARBEID

Hvilken utdanning er den høyeste du har fullført?

Grunnskole, 7-10 år, framhaldsskole, folkehøgskole	72	1
Realskole, middelskole, yrkesskole, 1-2-årig videregående skole		2
Artium, øk.gymnas, allmennfaglig retning i videregående skole		3
Høgskole/universitet, mindre enn 4 år		4
Høgskole/universitet, 4 år eller mer		5

Hva slags arbeidssituasjon har du nå?

Lønnet arbeid	73	
Heltids husarbeid	74	
Utdanning, militærtjeneste	75	
Arbeidsledig, permittert	76	

Hvor mange timer lønnet arbeid har du i uka? 77 — Antall timer

Mottar du nå noen av følgende ytelser?

Syketrygd (sykmeldt)	79	
Attføring	80	
Uførepensjon	81	
Alderspensjon	82	
Sosialstøtte	83	
Arbeidsløshetstrygd	84	

SYKDOM I FAMILIEN

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 85 — JA / NEI / VET IKKE

Helseundersøkelsen i Tromsø

for dem som er 70 år og eldre.

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. De skal også øke kunnskapen om kreftsykdommer og alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Endelig skal de gi kunnskap om hvorledes den eldste delen av befolkningen har det. Vi ber deg derfor svare på spørsmålene nedenfor.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

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Med vennlig hilsen

Fagområdet medisin
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Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten under og returner skjemaet. Da slipper du purring.

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ❑

Dato for utfylling av skjema: ..... 18 Dag ...../ Mnd ...../ År .....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 -28

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ❑ 1
- Gode ..... ❑ 2
- Vanskelige ..... ❑ 3
- Meget vanskelige ..... ❑ 4

Hvor gamle ble dine foreldre?

- Mor ble ..... 30 _____ år
- Far ble ..... 32 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.	Ja	Nei	Antall
Ektefelle/samboer 34	❑	❑	
Andre personer over 18 år 35	❑	❑	_____
Personer under 18 år 38	❑	❑	_____

Hvilken type bolig bor du i?

- Enebolig/villa ..... 41 ❑ 1
- Gårdsbruk ..... ❑ 2
- Blokk/terrasseleilighet ..... ❑ 3
- Rekkehus/2-4 mannsbolig ..... ❑ 4
- Annen bolig ..... ❑ 5

Hvor lenge har du bodd i boligen du bor i nå? ..... 42 _____ år

	Ja	Nei
Er boligen tilpasset til dine behov? 44	❑	❑
Hvis "Nei", er det problemer med:		
Plassen i boligen 45	❑	❑
Ujevn, for høy eller for lav temperatur 46	❑	❑
Trapper 47	❑	❑
Toalett 48	❑	❑
Bad/dusj 49	❑	❑
Vedlikehold 50	❑	❑
Annet (spesifiser) 51	❑	❑
Ønsker du å flytte til en eldrebolig? 52	❑	❑

TIDLIGERE ARBEID OG ØKONOMI

Hvordan vil du beskrive det arbeidet du hadde de siste 5-10 årene før du ble pensjonist?

- For det meste stillesittende arbeid? ..... 53 ❑ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ❑ 2
  (f.eks. ekspeditørarbeid, husmor, undervisning)
- Arbeid hvor du går og løfter mye? ..... ❑ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ❑ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Har du hatt noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.	Ja	Nei
Sjåfør 54	❑	❑
Bonde/gårdbruker 55	❑	❑
Fisker 56	❑	❑

Hvor gammel var du da du ble pensjonert? ..... 57 _____ år

Hva slags pensjon har du?

- Minstepensjon ..... 59 ❑
- Tilleggspensjon ..... 60 ❑

Hvordan er din økonomi nå?

- Meget god ..... 61 ❑ 1
- God ..... ❑ 2
- Vanskelig ..... ❑ 3
- Meget vanskelig ..... ❑ 4

HELSE OG SYKDOM

Er helsen din blitt forandret det siste året?

- Ja, dårligere ..... 62 ❑ 1
- Nei, uforandret ..... ❑ 2
- Ja, bedre ..... ❑ 3

Hvordan synes du at helsen din er nå i forhold til andre på samme alder?

- Mye dårligere ..... 63 ❑ 1
- Litt dårligere ..... ❑ 2
- Omtrent lik ..... ❑ 3
- Litt bedre ..... ❑ 4
- Mye bedre ..... ❑ 5

EGNE SYKDOMMER

Har du noen gang hatt:

Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen. Hvis det har skjedd flere ganger, hvor gammel var du siste gang?

	Ja	Nei	Alder
Lårhalsbrudd 64	❑	❑	_____
Brudd ved håndledd/underarm 67	❑	❑	_____
Nakkesleng (whiplash) 70	❑	❑	_____
Skade som førte til sykehusinnleggelse 73	❑	❑	_____
Sår på magesekken 76	❑	❑	_____
Sår på tolvfingertarmen 79	❑	❑	_____
Magesår-operasjon 82	❑	❑	_____
Operasjon på halsen 85	❑	❑	_____

Har du eller har du hatt:

Sett ett kryss for hvert spørsmål.	Ja	Nei
Kreftsykdom 88	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Parkinsons sykdom	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis 93	❑	❑
Benskjørhet (osteoporose)	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren 98	❑	❑
Gjentatt, ufrivillig urinlekkasje	❑	❑
Grønn stær	❑	❑
Grå stær	❑	❑
Slitasjegikt (artrose)	❑	❑
Leddgikt 103	❑	❑
Nyrestein	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue 108	❑	❑
Matvareallergi	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? 111 ____ ganger

	Ja	Nei
Har du hatt dette de siste 14 dager? 113	❑	❑

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:

Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 114	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 120	❑	❑	❑	❑	❑	❑
Kreftsykdom 126	❑	❑	❑	❑	❑	❑
Høyt blodtrykk 132	❑	❑	❑	❑	❑	❑
Astma 138	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 144	❑	❑	❑	❑	❑	❑
Slitasjegikt (artrose) 150	❑	❑	❑	❑	❑	❑
Psykiske plager 156	❑	❑	❑	❑	❑	❑
Alderdomssløvhet 162	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 168	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 174	__	__	__	__	__	

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 184	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 185	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 186	❑	❑
Har du hatt episoder med piping i brystet? 187	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 188	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde 191	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 192	❑	❑
Har du gått ned i vekt siste året? 193	❑	❑
Hvis "Ja":		
Hvor mange kilo? 194	_____ kg	

Hvor ofte er du plaget av søvnløshet?

- Aldri, eller noen få ganger i året ..... 196 ❑ 1
- 1-2 ganger i måneden ..... ❑ 2
- Omtrent en gang i uken ..... ❑ 3
- Mer enn en gang i uken ..... ❑ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?

- Ingen spesiell tid ..... 197 ❑ 1
- Særlig i mørketiden ..... ❑ 2
- Særlig i midnattsoltiden ..... ❑ 3
- Særlig vår og høst ..... ❑ 4

	Ja	Nei
Pleier du å ta en lur på dagen? 198	❑	❑
Føler du at du vanligvis får nok søvn?	❑	❑

Er du plaget av:	Nei	Litt	I stor grad
Svimmelhet 200	❑	❑	❑
Dårlig hukommelse	❑	❑	❑
Kraftløshet	❑	❑	❑
Forstoppelse 203	❑	❑	❑

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

- Ikke i det hele tatt ..... 204 ❑
- Bare i liten grad ..... ❑
- En del ..... ❑
- Ganske mye ..... ❑

LEGEMLIGE FUNKSJONER

Klarer du selv disse gjøremålene i det daglige uten hjelp fra andre?	Ja	Med noe hjelp	Nei
Gå innendørs i samme etasje 205	❑	❑	❑
Gå i trapper	❑	❑	❑
Gå utendørs	❑	❑	❑
Gå ca. 500 meter	❑	❑	❑
Gå på toalettet	❑	❑	❑
Vaske deg på kroppen 210	❑	❑	❑
Bade eller dusje	❑	❑	❑
Kle på og av deg	❑	❑	❑
Legge deg og stå opp	❑	❑	❑
Spise selv	❑	❑	❑
Lage varm mat 215	❑	❑	❑
Gjøre lett husarbeid (f.eks. oppvask)	❑	❑	❑
Gjøre tyngre husarbeid (f.eks. gulvvask)	❑	❑	❑
Gjøre innkjøp	❑	❑	❑
Ta bussen	❑	❑	❑

	Ja	Vanskelig	Nei
Kan du høre vanlig tale (evt. med høreapparat)? 220	❑	❑	❑
Kan du lese (evt. med briller)? 221	❑	❑	❑

Er du avhengig av noen av disse hjelpemidlene?

	Ja	Nei
Stokk 222	❑	❑
Krykke	❑	❑
Gåstol (rullator)	❑	❑
Rullestol	❑	❑
Høreapparat	❑	❑
Trygghetsalarm 227	❑	❑

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært: *Sett 0 hvis du ikke har hatt slik kontakt.*	Antall ganger siste år
Hos vanlig lege/legevakt 228	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 234	_____
Innlagt i sykehus	_____
Hos fysioterapeut	_____
Hos kiropraktor 240	_____
Hos akupunktør	_____
Hos tannlege	_____
Hos fotterapeut 246	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

Har du hjemmehjelp?	Ja	Nei
Privat 252	❑	❑
Kommunal	❑	❑

Har du hjemmesykepleie? ..... ❑ ❑

Er du fornøyd med helse- og hjemmetjenesten i kommunen?	Ja	Nei	Vet ikke
Prinsippet med fast lege 255	❑	❑	❑
Hjemmesykepleien	❑	❑	❑
Hjemmehjelpen	❑	❑	❑

Er du trygg på at du kan få hjelp av helse- og hjemmetjenesten hvis du trenger det?

- Trygg ..... 258 ❑ 1
- Ikke trygg ..... ❑ 2
- Svært utrygg ..... ❑ 3
- Vet ikke ..... ❑ 4

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig? Angi hvor mange måneder du brukte dem.
Sett 0 hvis du ikke har brukt midlene.

Legemidler

- Smertestillende ..... 259 _____ mnd.
- Sovemedisin ..... _____ mnd.
- Beroligende midler ..... _____ mnd.
- Medisin mot depresjon ..... 265 _____ mnd.
- Allergimedisin ..... _____ mnd.
- Astmamedisin ..... _____ mnd.
- Hjertemedisin (ikke blodtrykksmedisin) ..... 271 _____ mnd.
- Insulin ..... _____ mnd.
- Tabletter mot diabetes (sukkersyke) ..... _____ mnd.
- Tabletter mot lavt stoffskifte (thyroxin) ..... 277 _____ mnd.
- Kortisontabletter ..... _____ mnd.
- Midler mot forstoppelse ..... _____ mnd.

Kosttilskudd

- Jerntabletter ..... 283 _____ mnd.
- Vitamin D-tilskudd ..... _____ mnd.
- Andre vitamintilskudd ..... _____ mnd.
- Kalktabletter eller benmel ..... 289 _____ mnd.
- Tran eller fiskeoljekapsler ..... _____ mnd.

FAMILIE OG VENNER

Har du nær familie som kan gi deg hjelp og støtte når du trenger det? 293	Ja	Nei
	❑	❑

Hvis "Ja": Hvem kan gi deg hjelp?

- Ektefelle/samboer ..... 294 ❑
- Barn ..... ❑
- Andre ..... ❑

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ..297 ____ **gode venner**
Tell ikke med dem du bor sammen med, men ta med andre slektninger!

	Ja	Nei
Føler du at du har nok gode venner? 299	❑	❑

Føler du at du hører med i et fellesskap (gruppe av mennesker) som stoler på hverandre og føler forpliktelse overfor hverandre (f.eks. i politisk parti, religiøs gruppe, slekt, naboskap, arbeidsplass eller organisasjon)?

- Sterk tilhørighet ..... 300 ❑ 1
- Noe tilhørighet ..... ❑ 2
- Usikkert ..... ❑ 3
- Liten eller ingen tilhørighet ..... ❑ 4

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?

- Aldri, eller noen få ganger i året ..... 301 ❑ 1
- 1-2 ganger i måneden ..... ❑ 2
- Omtrent en gang i uken ..... ❑ 3
- Mer enn en gang i uken ..... ❑ 4

KOSTVANER

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? ..... 302 _____ Antall

Hvor mange ganger i uken spiser du varm middag? ..... 304 _____

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss.

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 306	❑	❑	❑	❑ 310

Hva slags fett blir til vanligvis brukt til *matlaging* (ikke på brødet) i din husholdning?

- Meierismør ..... 311 ❑
- Hard margarin ..... ❑
- Bløt (Soft) margarin ..... ❑
- Smør/margarin blanding ..... ❑
- Oljer ..... 315 ❑

Hvor mye (i antall glass, poteter eller brødskiver) spiser/drikker du vanligvis daglig av følgende matvarer?
Kryss av for alle matvarene.

	Ingen	Mindre enn 1	1-2	3 og mer
Melk alle sorter (glass) 316	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑
Poteter	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød) ...	❑	❑	❑	❑
Brødskiver med				
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑
– gulost	❑	❑	❑	❑
– kaviar 322	❑ 1	❑ 2	❑ 3	❑ 4

Hvor mange ganger i uka spiser du vanligvis følgende matvarer?
Kryss av for alle matvarene.

	Aldri	Sjeldnere enn 1	1	2 og mer
Yoghurt 323	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑
Middag med				
– rent kjøtt	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer)	❑	❑	❑	❑
– mager fisk (f.eks. torsk) 328	❑	❑	❑	❑
– grønnsaker (rå eller kokte)	❑	❑	❑	❑
Gulrøtter (rå eller kokte)	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑
Appelsiner, mandariner o.l. 333	❑ 1	❑ 2	❑ 3	❑ 4

TRIVSEL

Hvordan trives du med å bli gammel - alt i alt?

- Godt ..... 334 ❑ 1
- Ganske bra ..... ❑ 2
- Opp og ned ..... ❑ 3
- Dårlig ..... ❑ 4

Hvordan ser du på livet fremover?

- Lyst ..... 335 ❑ 1
- Ikke så verst ..... ❑ 2
- Nokså bekymret ..... ❑ 3
- Mørkt ..... ❑ 4

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 336 _____ år

Hvor gammel var du da menstruasjonen sluttet? ..... 338 _____ år

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.
Hvis du har født mer enn 6 barn, noter fødselsår og antall måneder med amming for dem nederst på siden.

Barn:	Fødselsår:	Antall måneder med amming:
1	342 _____	_____
2	346 _____	_____
3	_____	_____
4	_____	_____
5	358 _____	_____
6	_____	_____

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? ..... 366 Ja ❑ Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 367	❑	❑
Eggehvite i urinen 369	❑	❑

ØSTROGEN-MEDISIN

Bruker du, eller har du brukt, østrogen-medisin?

	Nå	Før	Aldri
Tabletter eller plaster 371	❑	❑	❑
Krem eller stikkpiller 372	❑	❑	❑

Hvis du bruker østrogen, hvilket merke bruker du nå?

..... 373

Dine kommentarer:

Takk for hjelpen! Husk å postlegge skjemaet idag!
Helseundersøkelsen i Tromsø

Helseundersøkelsen i Tromsø

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. I tillegg skal undersøkelsen øke kunnskapen om kreftsykdommer og andre alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Vi ber deg derfor svare på noen spørsmål om forhold som kan ha betydning for risikoen for disse og andre sykdommer.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

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På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø **Statens helseundersøkelser**

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten under og returner skjemaet. Da slipper du purring.

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ❑

Dag Mnd År

Dato for utfylling av skjema: ..... 18 ...../...../.....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 - 28

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ❑
- Gode ..... ❑
- Vanskelige ..... ❑
- Meget vanskelige ..... ❑

Hvor mange av de første 3 årene av ditt liv
- bodde du i by? ..... 30 _____ år
- hadde dere katt eller hund i hjemmet? ..... 31 _____ år

Hvor mange av de første 15 årene av ditt liv
- bodde du i by? ..... 32 _____ år
- hadde dere katt eller hund i hjemmet? ..... 34 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.		Ja	Nei	Antall
Ektefelle/samboer	36	❑	❑	
Andre personer over 18 år	37	❑	❑	_____
Personer under 18 år	40	❑	❑	_____

Hvor mange av barna har plass i barnehage? ..... 43 _____

Hvilken type bolig bor du i?
- Enebolig/villa ..... 45 ❑ 1
- Gårdsbruk ..... ❑ 2
- Blokk/terrasseleilighet ..... ❑ 3
- Rekkehus/2-4 mannsbolig ..... ❑ 4
- Annen bolig ..... ❑ 5

Hvor stor er din boenhet? ..... 46 _____ m^2

I omtrent hvilket år ble boligen bygget? ..... 49 _____

		Ja	Nei
Er boligen isolert etter 1970?	53	❑	❑
Bor du i underetasje/kjeller?	54	❑	❑
Hvis "Ja", er gulvbelegget lagt på betong?	55	❑	❑

Hvordan er boligen hovedsakelig oppvarmet?
- Elektrisk oppvarming ..... 56 ❑
- Vedfyring ..... ❑
- Sentralvarmeanlegg oppvarmet med:
  - Parafin ..... ❑
  - Elektrisitet ..... ❑

		Ja	Nei
Er det heldekkende tepper i stua?	60	❑	❑
Er det katt i boligen?	61	❑	❑
Er det hund i boligen?	62	❑	❑

ARBEID

Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive ditt arbeid?
- For det meste stillesittende arbeid? ..... 63 ❑ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ❑ 2
  (f.eks. ekspeditørarb., lett industriarb., undervisning)
- Arbeid hvor du går og løfter mye? ..... ❑ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ❑ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Kan du selv bestemme hvordan arbeidet ditt skal legges opp?
- Nei, ikke i det hele tatt ..... 64 ❑ 1
- I liten grad ..... ❑ 2
- Ja, i stor grad ..... ❑ 3
- Ja, det bestemmer jeg selv ..... ❑ 4

		Ja	Nei
Har du skiftarbeid, nattarbeid eller går vakter?	65	❑	❑

Har du noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.		Ja	Nei
Sjåfør	66	❑	❑
Bonde/gårdbruker		❑	❑
Fisker		❑	❑

EGNE SYKDOMMER

Har du noen gang hatt:
Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen.
*Hvis det har skjedd flere ganger, hvor gammel var du **siste** gang?*

	Ja	Nei	Alder
Lårhalsbrudd 69	❑	❑	_____
Brudd ved håndledd/underarm 72	❑	❑	_____
Nakkesleng (whiplash) 75	❑	❑	_____
Skade som førte til sykehusinnleggelse 78	❑	❑	_____
Sår på magesekken 81	❑	❑	_____
Sår på tolvfingertarmen 84	❑	❑	_____
Magesår-operasjon 87	❑	❑	_____
Operasjon på halsen 90	❑	❑	_____

Har du eller har du hatt:
Sett ett kryss for hvert spørsmål.

	Ja	Nei
Kreftsykdom 93	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis	❑	❑
Benskjørhet (osteoporose) 98	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren	❑	❑
Nyrestein 103	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue	❑	❑
Matvareallergi 108	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? ..110 ____ ganger

	Ja	Nei
Har du hatt dette siste 14 dager? 112	❑	❑

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:
Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 113	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 119	❑	❑	❑	❑	❑	❑
Kreftsykdom 125	❑	❑	❑	❑	❑	❑
Astma 131	❑	❑	❑	❑	❑	❑
Mage/tolvfingertarm-sår 137	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 143	❑	❑	❑	❑	❑	❑
Psykiske plager 149	❑	❑	❑	❑	❑	❑
Allergi 155	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 161	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 167	____	____	____	____	____	____

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 177	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 178	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 179	❑	❑
Har du hatt episoder med piping i brystet? 180	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 181	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 185	❑	❑

Hvor ofte er du plaget av søvnløshet?

Aldri, eller noen få ganger i året 186	❑ 1
1-2 ganger i måneden	❑ 2
Omtrent en gang i uken	❑ 3
Mer enn en gang i uken	❑ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?

Ingen spesiell tid 187	❑ 1
Særlig i mørketiden	❑ 2
Særlig i midnattsoltiden	❑ 3
Særlig vår og høst	❑ 4

	Ja	Nei
Har du det siste året vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 188	❑	❑

Hvor ofte er du plaget av hodepine?

Sjelden eller aldri 189	❑ 1
En eller flere ganger i måneden	❑ 2
En eller flere ganger i uken	❑ 3
Daglig	❑ 4

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

Ikke i det hele tatt 190	❑ 1
Bare i liten grad	❑ 2
En del	❑ 3
Ganske mye	❑ 4

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært:
*Sett **0** hvis du **ikke** har hatt slik kontakt.*

	Antall ganger siste år
Hos vanlig lege/legevakt 191	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 197	_____
Innlagt i sykehus	_____
Hos bedriftslege	_____
Hos fysioterapeut 203	_____
Hos kiropraktor	_____
Hos akupunktør	_____
Hos tannlege 209	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig? Angi hvor mange måneder du brukte dem.
*Sett **0** hvis du **ikke** har brukt midlene.*

Legemidler
- Smertestillende ....215 _____ mnd.
- Sovemedisin .... _____ mnd.
- Beroligende midler .... _____ mnd.
- Medisin mot depresjon ....221 _____ mnd.
- Allergimedisin .... _____ mnd.
- Astmamedisin .... _____ mnd.

Kosttilskudd
- Jerntabletter ....227 _____ mnd.
- Kalktabletter eller benmel .... _____ mnd.
- Vitamin D-tilskudd .... _____ mnd.
- Andre vitamintilskudd ....233 _____ mnd.
- Tran eller fiskeoljekapsler .... _____ mnd.

Har du de siste 14 dager brukt følgende legemidler eller kosttilskudd?
*Sett **ett** kryss for **hvert** spørsmål.*

	Ja	Nei
Legemidler		
Smertestillende medisin 237	❑	❑
Febersenkende medisin	❑	❑
Migrenemedisin	❑	❑
Eksemsalve	❑	❑
Hjertemedisin (ikke blodtrykksmedisin)	❑	❑
Kolesterolsenkende medisin 242	❑	❑
Sovemedisin	❑	❑
Beroligende medisin	❑	❑
Medisin mot depresjon	❑	❑
Annen nervemedisin	❑	❑
Syrenøytraliserende midler 247	❑	❑
Magesårsmedisin	❑	❑
Insulin	❑	❑
Tabletter mot diabetes (sukkersyke)	❑	❑
Tabletter mot lavt stoffskifte (thyroxin)	❑	❑
Kortisontabletter 252	❑	❑
Annen medisin	❑	❑
Kosttilskudd		
Jerntabletter	❑	❑
Kalktabletter eller benmel	❑	❑
Vitamin D-tilskudd	❑	❑
Andre vitamintilskudd 257	❑	❑
Tran eller fiskeoljekapsler	❑	❑

VENNER

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ....259 ____ gode venner
Tell ikke med de du bor sammen med, men ta med andre slektninger!

Hvor mange av disse gode vennene har du kontakt med minst en gang i måneden? ....261 ____

	Ja	Nei
Føler du at du har nok gode venner? 263	❑	❑

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?
- Aldri, eller noen få ganger i året ....264 ❑ 1
- 1-2 ganger i måneden .... ❑ 2
- Omtrent en gang i uken .... ❑ 3
- Mer enn en gang i uken .... ❑ 4

KOSTVANER

Hvis du bruker smør eller margarin på brødet, hvor mange skiver rekker en liten porsjonspakning vanligvis til? Vi tenker på slik porsjonspakning som du får på fly, på kafé o.l. (10-12 gram).

Den rekker til omtrent ....265 _____ skiver

Hva slags fett blir vanligvis brukt til **matlaging** (ikke på brødet) i din husholdning?
- Meierismør ....266 ❑
- Hard margarin .... ❑
- Bløt (Soft) margarin .... ❑
- Smør/margarin blanding .... ❑
- Oljer ....270 ❑

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss!

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 271	❑	❑	❑	❑ 275

Hvor mye (i **antall** glass, kopper, poteter eller brødskiver) spiser eller drikker du vanligvis **daglig** av følgende matvarer?
*Kryss av for **alle** matvarene.*

	0	Færre enn 1	1-2	3-4	5-6	Mer enn 6
Helmelk (søt eller sur) (glass) 276	❑	❑	❑	❑	❑	❑
Lettmelk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Skummet melk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Te (kopper)	❑	❑	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑	❑	❑
Poteter 281	❑	❑	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød)	❑	❑	❑	❑	❑	❑
Brødskiver med						
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑	❑	❑
– magert kjøttpålegg (f.eks. skinke)	❑	❑	❑	❑	❑	❑
– fetere kjøttpålegg (f.eks. salami)	❑	❑	❑	❑	❑	❑
– gulost 286	❑	❑	❑	❑	❑	❑
– brunost	❑	❑	❑	❑	❑	❑
– kaviar	❑	❑	❑	❑	❑	❑
– syltetøy og annet søtt pålegg	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Hvor mange **ganger i uka** spiser du vanligvis følgende matvarer?
*Kryss av for **alle** matvarene.*

	Aldri	Færre enn 1	1	2-3	4-5	Omtrent daglig
Yoghurt 290	❑	❑	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑	❑	❑
Middag med						
– rent kjøtt	❑	❑	❑	❑	❑	❑
– pølser/kjøttpudding/-kaker	❑	❑	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer) 295	❑	❑	❑	❑	❑	❑
– mager fisk (f.eks. torsk)	❑	❑	❑	❑	❑	❑
– fiskeboller/-pudding/-kaker	❑	❑	❑	❑	❑	❑
– grønnsaker	❑	❑	❑	❑	❑	❑
Majones, remulade o.l.	❑	❑	❑	❑	❑	❑
Gulrøtter 300	❑	❑	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑	❑	❑
Appelsiner, mandariner o.l.	❑	❑	❑	❑	❑	❑
Sukkerholdige leskedrikker	❑	❑	❑	❑	❑	❑
Sukkerfrie («Light») leskedrikker	❑	❑	❑	❑	❑	❑
Sjokolade	❑	❑	❑	❑	❑	❑
Vafler, kaker o.l. 307	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

ALKOHOL

Hvor ofte pleier du å drikke	øl?	vin?	brennevin?
Aldri, eller noen få ganger i året	❑ 308	❑	❑ 1
1-2 ganger i måneden	❑	❑	❑ 2
Omtrent 1 gang i uken	❑	❑	❑ 3
2-3 ganger i uken	❑	❑	❑ 4
Omtrent hver dag	❑	❑	❑ 5 310

Omtrent hvor ofte har du i løpet av siste år drukket alkohol tilsvarende minst 5 halvflasker øl, en helflaske vin eller 1/4 flaske brennevin?

- Ikke siste år ..... 311 ❑ 1
- Noen få ganger ..... ❑ 2
- 1 - 2 ganger per måned ..... ❑ 3
- 1 - 2 ganger i uken ..... ❑ 4
- 3 eller flere ganger i uken ..... ❑ 5

I omtrent hvor mange år har ditt alkoholforbruk vært slik du har svart i spørsmålene over? ..... 312 _____ år

SLANKING

Omtrent hvor mange ganger har du bevisst prøvd å slanke deg? Sett **0** hvis ingen forsøk.

- – før 20 år ..... 314 _____ ganger
- – senere ..... 316 _____ ganger

Hvis du har slanket deg, omtrent hvor mange kilo har du på det meste gått ned i vekt?

- – før 20 år ..... 318 _____ kg
- – senere ..... 320 _____ kg

Hvilken vekt ville du være tilfreds med (din "trivselsvekt")? ..... 322 _____ kg

UFRIVILLIG URINLEKKASJE

Hvor ofte har du ufrivillig urinlekkasje?

- Aldri ..... 325 ❑ 1
- Ikke mer enn en gang i måneden ..... ❑ 2
- To eller flere ganger i måneden ..... ❑ 3
- Ukentlig eller oftere ..... ❑ 4

Dine kommentarer:

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 326 _____ år

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? ..... 328 _____ år

Når du ser bort fra svangerskap og barselsperiode, har du noen gang vært blødningsfri i minst 6 måneder? 330	Ja ❑	Nei ❑

Hvis "Ja", hvor mange ganger? ..... 331 _____ ganger

Hvis du fremdeles har menstruasjon eller er gravid:

Hvilken dato startet din siste menstruasjon? ..... 333 dag/ mnd/ år ___/___/___

Bruker du vanligvis smertestillende legemidler for å dempe menstruasjonsplager? 339	Ja ❑	Nei ❑

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Er du gravid nå? 342	Ja ❑	Nei ❑	Usikker ❑

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? 343	Ja ❑	Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 344	❑	❑
Eggehvite i urinen 346	❑	❑

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.

Barn:	Fødselsår:	Antall måneder med amming:
1	348 _____	_____
2	_____	_____
3	356 _____	_____
4	_____	_____
5	364 _____	_____
6	_____	_____

PREVENSJON OG ØSTROGEN

Bruker du, eller har du brukt:	Nå	Før	Aldri
P-pille (også minipille) 372	❑	❑	❑
Hormonspiral	❑	❑	❑
Østrogen (tabletter eller plaster) 374	❑	❑	❑
Østrogen (krem eller stikkpiller)	❑ 1	❑ 2	❑ 3

Hvis du bruker p-pille, hormonspiral eller østrogen; hvilket merke bruker du nå?

376 .....

Hvis du bruker eller har brukt p-pille:

Alder da du begynte med P-piller? ..... 380 _____ år

Hvor mange år har du tilsammen brukt P-piller? ..... 382 _____ år

Dersom du har født, hvor mange år brukte du P-piller før første fødsel? ..... 384 _____ år

Hvis du har sluttet å bruke P-piller:

Alder da du sluttet? ..... 386 _____ år

Takk for hjelpen! Husk å postlegge skjemaet idag!

Helseundersøkelsen i Tromsø