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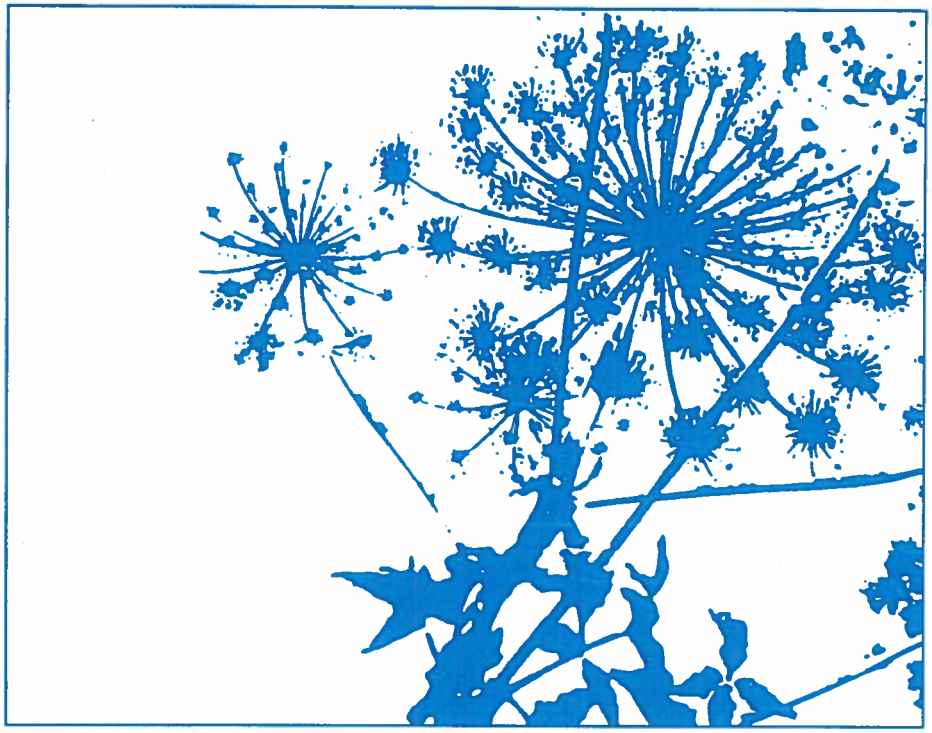

ECHOCARDIOGRAPHIC SCREENING IN A GENERAL POPULATION

Normal distribution of echocardiographic measurements and their relation to cardiovascular risk factors and disease.
The Tromsø Study.

by Henrik Schirmer

Tromsø 2000

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The Norwegian Health Association
The Norwegian Council on Cardiovascular Diseases

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In memory of my mother, Kirsten Schirmer.

Acknowledgements

Growing up in an environment with a strong faith in alternative medicine, I heard a lot about the wrongdoing of modern medicine, and of scientific innovations opening up for a scientific validation of alternative therapies and theories. In order to bridge the paradoxes and conflicts, I sensed that medicine was the only way to go. To be accepted for medical school, I worked one year as an untrained nurse at the National Cancer Hospital. The fate of the patients who spent the last months of their lives in my ward, was overwhelming. So overwhelming that I decided not to have any treatment if I were struck by cancer myself. My years of work with patients have later learned me that patients often fare better than we expect, but that we rarely hear about the successful outcomes.
The only way to come around this is to approach the total population and hear the full variety of histories.

Science is seldom generated by one person alone. This thesis has been the result of five fruitful years at the University of Tromsø. The possibility of discussing scientific problems with other research fellows and more experienced colleagues at the Institute of Community Medicine and the Institute of Clinical Medicine has been invaluable.

I am indebted to many and would especially like to thank;

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Contents

List of papers

This thesis is based on the following papers;

I. Schirmer H, Lunde P, Rasmussen K. Prevalence of left ventricular hypertrophy in a general population. The Tromsø Study. *European Heart Journal 1999;20:428-37*

II. Schirmer H, Omland T. Circulating N-terminal pro-atrial natriuretic peptide is an independent predictor of left ventricular hypertrophy in the general population. The Tromsø Study. *European Heart Journal 1999;20:755-63*

III. Schirmer H, Lunde P, Rasmussen K. What determines echogenisity in a general population? *Journal of the American Society of Echocardiography 1999;12:314-8*

IV. Schirmer H, Lunde P, Rasmussen K. Mitral flow derived Doppler indices of left ventricular diastolic function. The Tromsø Study. *Accepted for publication in European Heart Journal December 17th 1999*

Introduction

The change in cardiovascular disease incidence, mortality and risk factors.

In the last century, Norway has experienced a steady increase in life expectancy (figure 1), mainly caused by a dramatic decline in infant mortality.[1] The decline started long before important medical breakthroughs such as anaesthesia, penicillin and streptomycin, and was to a large extent due to improvements in nutrition and hygiene.[2; 3]

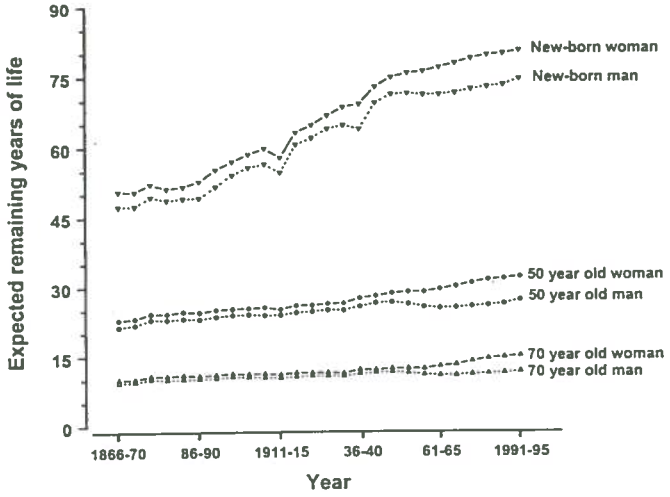


Figure 1
Expected remaining years of life for different age groups the last 130 years in Norway.

After 1950 the increase in life expectancy for men levelled off mainly due to a marked increase in cardiovascular mortality.[4] This cardiovascular epidemic triggered numerous epidemiological projects showing the detrimental effects of cigarette smoking, diets high in cholesterol and saturated fat, hypertension, obesity and a sedentary life style.[5-10] The public has to some extent grasped this, and in Norway there has been a positive change in all major cardiovascular risk factor levels apart from body mass index and physical activity.[11] As a result, there has been a 50% decline in the cardiovascular mortality in those 70 years or younger the last 10 years.[12] Even though the favourable change in risk factor levels could account for most of the decline on its own by decreasing the incidence of cardiovascular disease,[4; 13] it is likely that part of the decline is due to declining case fatality rates, as has been documented in Sweden and Finland.[14,15] Decline in case fatality rates have been shown to be related both to cardiovascular risk factor levels as well as introduction of new therapies such as thrombolysis and acetylsalicylic acid.[16-18] From an agrarian society with a shortage of energy rich food and mainly hard physical labour, we now have a post industrial affluent society with an overflow of energy rich food and a

workforce with mainly intellectual demands.[4, 19-21] Probably as a consequence of the changing labour demands as well as of an increased access to energy rich food and consumer goods such as automobiles and television, there has been a particularly steep decrease in physical activity the last decade and a subsequent increase in the prevalence of obesity.[11; 22] As indicated by the dramatic drop in cardiovascular mortality, these risk factors are probably of less importance than smoking and total cholesterol. This view is supported by a study by Wannamethee et al. (1989), showing higher mortality for smokers than for non-smokers at all levels of body mass index.[9]

Cardiovascular disease is still highly prevalent and accounts for approximately half the acute admissions to medical wards. Despite the knowledge of preventable risk factors for cardiovascular disease, most cases occur among subjects with risk factor levels within the normal range in the general population. This is due partly to the higher number of subjects in the middle range of a given risk factor and partly due to the high level of most risk factors in the population. The first has led to a search for genetic markers for identification of those with high cardiovascular risk despite low risk factor levels. It is questionable whether this search will have a large impact on primary prevention. The genetic pool in the western societies has changed little the last hundred years, implying that environmental changes account for the change in cardiovascular disease mortality. The importance of environment for the development of cardiovascular disease has been shown in ecological studies, as well as migration studies.[23-26] In large cohort studies, the importance of inheritance is clear, but it's predictive power vary and is mostly mediated through the known risk factors, implying that genetic factors predict the ranking of individuals according to risk factor levels in changing environments, as has been shown for body mass index.[27; 28] In a follow-up of 22 000 Norwegian men and women aged 35-39 years, Tverdal showed only a reduction from 1.8 to 1.6 of the risk of coronary heart disease associated with a positive family history when adjusting for risk factor score.[29] This may reflect the high average risk factor level in the seventies, weakening the contribution of a positive family history.

From a population perspective it is clear that cardiovascular disease is highly preventable, but in order to prevent cardiovascular disease in an individual, knowledge of the risk factor levels and the family history is not enough. Apart from the classical risk factors, there are numerous others of importance for a given individual. Some are constitutional, such as a depressive personality, childhood environment and coagulation defects.[30, 31] Others are modifiable, such as

work stress, infections, body mass index and physical activity.[8; 32-34] Since cardiovascular disease mostly consists of myocardial infarction and stroke, it is especially important to identify an individuals modifiable risk factors before disease is manifest, due to the high fatality rate during the first hours after onset of these diseases.

Given the multifactorial causality of cardiovascular disease and the lack of identifiable sufficient causes as defined by Rothman,[35] there is a need not only to establish risk factors, but also to identify protective factors. This could identify individuals with low risk despite elevated levels of one of the classical risk factors. Lack of hypertrophic response to moderate hypertension combined with a negative family history of cardiovascular disease could be such an indicator of low absolute risk of subsequent events.

For a subject with more than one risk factor an additive, and for some risk factors also a synergistic increase in risk has been shown. This implies that the risk associated with one characteristic is added to the risk of an other, or for synergistic associations, results in a risk larger than the sum of the two. For a forty year old man with a cholesterol of 11 mmol/l the ten year risk of a myocardial infarction is 24%.[4] If he in addition smokes, the risk increases to 52%. Still, 48% of smokers with such a cholesterol level, does not experience a myocardial infarction during this long time span. Further stratification of risk for groups with values as extreme as 11 mmol/l in total cholesterol is usually not possible due to the limited sample size in most epidemiological studies. This is tried solved by pooling of data from different cohort studies, but this will only provide sufficient causes of relevance to the majority of future cardiovascular cases, who will have moderate risk factor levels, if new risk factors are detected.

There is obviously a need for studies that investigate the causal pathways of old risk factors and the possibility of new ones. Rose (1990) stresses the importance of addressing current uncertainties and of doing this by combining epidemiology with clinical and laboratory disciplines.[36] Due to the limitations set by time, funding and ethical considerations of procedures applicable in healthy samples, large scale population based studies are restricted to collection of blood and urine samples, interview or questionnaire data and non-invasive measurements. With the advance in technological medicine this has opened up fields such as genetic testing, dietary questionnaires verified by blood tests and ultrasound measurements of cardiovascular function and structure. This has, among other, led to the discovery of the role of

angiotensin converting enzyme genes in hypertension and hypertrophy, and to homocystein as a possible modifiable cardiovascular risk factor.[37; 38]

Among unsolved questions are the causal pathways for the increased risk of cardiovascular disease associated with male gender, low birth weight, socio-economic status and depressive illness, as well as the importance for cardiovascular risk of polyunsaturated fatty acids and infectious disease.

In this study ultrasound technique is introduced in a large prospective population study, opening up the possibility of addressing gender differences in the myocardial response to cardiovascular risk factors, as well differences in the normal distribution of left ventricular (LV) dimensions and function.

Left ventricular hypertrophy

In addition to the established risk factors, LV hypertrophy was early identified as a strong independent predictor of subsequent cardiovascular disease. In the early publications from The Framingham Study, hypertrophy was determined from ECG registrations.[39] Ultrasound evolved as an important tool both in diagnosis of clinical and subclinical disease and in determining the individual response to risk factors, especially hypertension. M-mode echocardiography made non-invasive measurements of cardiac function and dimensions possible. Ultrasound determined hypertrophy showed a better correlation with anatomical hypertrophy and identified those in a hypertensive cohort with the highest risk of subsequent cardiovascular events.[40; 41]

In the Framingham study M-mode determined hypertrophy was a strong independent predictor of cardiovascular events and mortality, even after correction for ECG diagnosed hypertrophy, body mass index, total to high density lipoprotein cholesterol, hypertension, cigarette smoking and diabetes.[42]

Interestingly, hypertrophy had a stronger predictive value for cardiovascular and total mortality than non-fatal cardiovascular events both in the general population and in a sample of hypertensive patients (RR $\approx$ 4 vs. RR $\approx$ 2), implying that hypertrophy might identify a group with higher risk of sudden death. This has later been documented as an association to ventricular arrhythmia in studies by Haider et al.[43]

Hypertrophy has been thought to be a physiological response to increased myocardial workload. The associated increase in risk was thought to be caused by the risk factors that cause increased LV mass, i.e. mainly body mass index and systolic blood pressure. This view was not supported by the prospective studies of risk associated with increased LV mass and in the recent study by

Verdecchia et al.,[44] a reduction of LV mass was associated with an improvement in risk of subsequent cardiovascular events independent of decrease in systolic blood pressure, total cholesterol and initial LV hypertrophy by ECG. Similar results were found in the study by Muiesan et al.[45]

In the study by Verdecchia et al., regression of LV hypertrophy was induced by randomised allocation to antihypertensive medication. A small intervention study in obese hypertensive men with LV hypertrophy, showed a greater reduction in LV mass by weight reduction than by antihypertensive medication, even after adjustment for the reduction in blood pressure induced by weight reduction.[46] Similarly, the THOMS study showed no additional reduction of LV mass of any of six different antihypertensive drugs after advice in lifestyle changes had been given to mildly hypertensive patients.[47]

In a sample of hypertensive men, Gottdiener et al. found that there was a synergistic association between the two main predictors of LV mass, systolic blood pressure and body mass index. This was not confirmed in a large normotensive sample from the general population in the Framingham study.[48; 49]

Whether obesity as such carries a risk of excess morbidity and mortality has been debated, but recent research have shown that the increased mortality associated with low body mass index was due to increased cancer mortality in lean smokers.[7] In non-smokers, increased body mass index is associated with excess mortality from both cancer and cardiovascular diseases.[8] The risk of cardiovascular diseases associated with body mass index is mainly mediated through the increased risk of hypertension, diabetes and LV hypertrophy, but even after adjusting for these risk factors, body mass index carries an independent risk of cardiovascular death.[50] Increase in body mass index is the main factor related both to increase in blood pressure and to failure of reaching treatment goals for antihypertensive medication.[51-53] In populations with a high prevalence of hypertension also among lean subjects, as in the Afro-Americans, psycho-social factors are of greater importance for development of hypertension than weight increase.[54]

Weight reduction is probably as effective as antihypertensive medication in reducing LV hypertrophy. When choosing the main focus of hypertension treatment in a given population, the question would be whether the distribution of LV hypertrophy and hypertension is determined by body mass index levels or not. A greater diversity in treatment strategies would meet the variety in patients preferences and also acknowledge the heterogeneity of effect in randomised trials as shown for body mass index levels in the Hypertension Detection and Follow up Program and in a Hypertension Optimal Treatment trial substudy.[53; 55]

Heart failure

For those who have acquired coronary heart disease, heart failure measured as low ejection fraction, is a strong predictor of subsequent mortality.[56] Heart failure is a difficult diagnosis as shown by Remes et al.[57] No single objective gold standard for heart failure has emerged and consequently the disease is defined by different sets of clinical symptoms alone, as in the New York Heart Associations Classification, or in combination with objective signs of heart failure, as in The Boston Criteria.[58; 59] In clinical practice echocardiography, radionucleide ventriculography or angiography are most often used to verify the diagnosis of heart failure. This has proved problematic due to the presence of patients with indisputable clinical signs of heart failure, i.e. acute pulmonary oedema, with normal ejection fraction. These patients have been shown to have a better prognosis than patients with low ejection fraction. Invasive studies of heart failure patients have shown heart failure to be a disease consisting of both a systolic, i.e. pump, dysfunction and a diastolic, i.e. filling, dysfunction.[60] Several attempts have been made to identify patients with isolated diastolic heart failure non-invasively by using M-mode echocardiography, radionucleide ventriculography or Doppler techniques. In small selected samples, differences between heart failure patients and healthy controls have been documented for various indices of diastolic heart failure.[61; 62] But the diagnostic accuracy have yet not been documented in unselected samples from the general population. A diagnostic accuracy has been assumed by the use of criteria based on reference limits generated from small reference samples with little opportunity to estimate age or gender specific differences.[63; 64]

After the documentation of an improved survival of patients with low ejection fraction receiving angiotensin converting enzyme inhibitors, several attempts have been made to develop simple diagnostic tools for identification of these patients.[65] Among others, the cardiac natriuretic peptides have shown promising abilities to distinguish selected patients with symptomatic and asymptomatic heart failure from healthy controls, and has been shown to predict survival after myocardial infarction.[66; 67] The first had not been tested in a general population until McDonagh et al. in 1998 published their report of the diagnostic accuracy of Brain Natriuretic Peptide in identifying LV systolic dysfunction in a general population sample from Glasgow.[68] Due to the low prevalence of heart failure in a general population, high specificity is needed for a diagnostic test to be useful in an unselected population. Most studies have failed to show that any of the cardiac peptides fulfil this criterion. Even in selected

samples of patients with a high prevalence of heart failure the cardiac peptides have not proved particularly useful.[69; 70]

Studies of cardiac peptides show a correlation both to low ejection fraction and LV mass.[71] Because hypertrophy is a much more prevalent phenomenon than heart failure, the a priori likelihood of identifying hypertrophy by elevated cardiac peptide levels, is higher than of diagnosing heart failure.

Aims of the thesis

1. To establish new sex and age specific percentile derived criteria for LV hypertrophy based on M-mode echocardiography and to elucidate the prevalence and predictors of LV hypertrophy.

2. To assess whether circulating N-ANP is predictive of LV hypertrophy, as estimated by M-mode echocardiography, in a general population. Further, to determine whether this relationship is independent of LV dysfunction and other risk factors for LV hypertrophy.

3. To estimate the efficacy of echocardiography in a screening setting, to estimate the determinants of non-measurability and how cardiovascular disease influences measurability.

4. To establish age specific percentiles of mitral flow derived Doppler indices of LV diastolic function in the total sample and in a «healthy» subgroup within this sample, and to estimate the relation of these Doppler indices to age, gender, LV mass, blood pressure, a history of cardiovascular disease and LV ejection fraction.

Study population and methods

In the fourth health screening in The Tromsø Study, a total of 27159 subjects older than 24 years, 77% of the eligible population in the municipality of Tromsø, attended the first visit. A protocol similar to the previous surveys and to the Norwegian Counties Study was followed.[72-76] The standardised measurements and the two self administered questionnaires are presented in appendix 1 and 2. A total of 6891 subjects attended the second visit (see fig. 2), 98% of those who participated in the first visit. These subjects had by computer been alternately allocated to one of two lines of examination when attending the first. Due to lack of capacity only 3287 subjects on one line were examined by echocardiography. These 3287 did not differ from the total sample attending the second screening in baseline characteristics (table 1). Nor were there any difference in baseline characteristics for subjects examined by each of the three observers.

Table 1. Characteristics of the echo subgroup versus the rest of phase II eligible for echocardiography

Variables	Allocated to echo N = 3287 Mean ± SD or %	Not allocated to echo N = 3604 Mean ± SD or %	P value
Age (years)	58.1 ± 10.3	58.5 ± 9.9	0.07
Female gender (%)	49.3	52.1	0.02
Body mass index (kg/m^2)	26.1 ± 4.0	26.0 ± 3.9	0.42
Systolic blood pressure (mmHg)	144.9 ± 22.5	145.5 ± 22.6	0.31
Diastolic blood pressure (mmHg)	83.5 ± 12.8	83.3 ± 13.2	0.61
Total cholesterol (mmol/l)	6.71 ± 1.28	6.77 ± 1.30	0.11
HDL cholesterol (mmol/l)	1.53 ± 0.44	1.54 ± 0.43	0.44
A history of myocardial infarction (%)	6.4	6.1	0.63
A history of angina (%)	9.4	9.3	0.88
A history of stroke (%)	2.4	3.0	0.16
Antihypertensive medication (%)	13.6	13.6	0.95
A history of diabetes (%)	3.0	3.3	0.48
Smoking (%)	32.8	32.9	0.91
Education (years)	9.5	9.3	0.001

HDL = high density lipoprotein

Echocardiography

All subjects were examined by medical doctors, (2717 subjects by one doctor, the remaining 570 by two expert cardiologists), using a VingMed CFM 750 (VingMed Sound A/S, Horten, Norway). The screening set-up allowed a maximum of 20 minutes per examination. Standard 2 dimensional guided M-mode registrations were measured according to the leading edge to leading edge convention,[77] using the EchoPAC software (VingMed Sound A/S, Horten, Norway).

LV mass was calculated using the correction of the cube formula proposed by Devereux et al for leading edge to leading edge measurements:[78]

LV mass = 0.8*([1.04*([Interventricular septal thickness + posterior wall thickness + end diastolic diameter]^3 - [end diastolic diameter]^3)] + 0.6)

LV mass was indexed by height to allow for the increase of LV mass with increasing height, without masking the increase in LV mass with increasing body mass index.[79]

The formula used for calculating LV ejection fraction was the cube formula;

LV ejection fraction = ((LV Diameter$_{diastole}$)^3 - (LV Diameter$_{systole}$)^3) / (LV Diameter$_{diastole}$)^3

The presence of valvular heart disease was evaluated by 2 dimensional colour Doppler for mitral insufficiency (colour area >4.0 cm^2), colour M-mode for aortic insufficiency (jet >30% of LV outflow tract, or if not measurable; jet reaching the bottom of the ventricle), and pulsed wave Doppler for mitral (peak gradient > 30 mmHg) and aortic stenosis.[80-82] The presence of other cardiac abnormalities was noted.

For measurements of mitral valve flow pattern, the sample volume of the pulsed Doppler recordings was placed caudal to the mitral annulus at the tip of the mitral liflets, where maximal flow velocity in the early diastole was recorded,[62] measurements were done on-line in one heart cycle only, using the EchoPac software (VingMed Sound A/S, Horten, Norway). The following variables were measured; peak flow velocity in early diastole, i.e. early inflow (E wave) and during atrial contraction, i.e. atrial inflow (A wave), the ratio of peak passive to peak atrial inflow (E/A ratio), the duration of the atrial inflow (AT), and the deceleration time of the E wave.

In an apical Doppler recording of both aortic and mitral flow, the isovolumetric relaxation time (IRT) was measured as the time from where the aortic outflow reach the zero baseline to where the mitral valve opening was clearly delineated. In a subset of 1703 subjects the duration of lung vein reflux during atrial contraction was recorded. The lung veins were

identified using colour Doppler in an apical two chamber view. The lung vein in which an optimal alignment of the ultrasound beam and the lung vein flow was obtained, was chosen for measurement.

All recordings used for measurement were stored on optical discs together with cine-loop registrations of one heart cycle of an apical two chamber and an apical four chamber view.

Only four subjects did not have any measurements or recordings done. This was due to poor echogenisity or inability to be positioned in a supine posture. Of the rest, 2794 (85%) had M-mode registrations of good quality making calculations of LV dimensions and function possible. The aortic root and left atrium was measurable in 95% of subjects. At least one of the Doppler measurements, E wave, A wave, E/A ratio, DT or IRT, were successful in 99% of subjects. Measurement of the duration of lung vein reflux was successful in 79% of subjects. As the method was introduced in the protocol after the first of January 1995, this constitutes 1703 subjects.

Reproducibility

In a subsample of 58 subjects a reproducibility study was performed by the two main observers. Both observers examined all subjects twice with one week interval. At each examination both observers examined each subject without change of position. All measurements were done on line by the observer doing the examination. All subjects had measurement pairs of Doppler registrations, but only 49 subjects had measurement pairs of M-mode registrations.

For the two observers the mean $\pm$ SD intra-observer difference in LV mass (one week interval) was 3.0 $\pm$ 39.0 g and 7.0 $\pm$ 25.5 g, respectively. The inter-observer difference in LV mass (no time interval) was 14.8 $\pm$ 32.5 g. The variability measures for the other variables presented in paper I-IV are listed in table 2. Indexation of LV mass did not affect the coefficients of variation.

Table 2. Inter and intraobserver variability of the variables presented in paper I -IV;

Variable	Interobserver mean diff. ± SD	CV*	Intraobserver mean diff. ± SD		CV*
			HS	PL	HS/PL
LV mass (g)	14.8 ± 32.5	15.9%	3.0±39.0	7.0±25.5	15.8/11.9
LV ejection fraction	0.016 ± 0.097†	9.1%	0.014±0.094	0.068±0.085	8.8/9.5
E wave m/sec	0.034±0.078	9.3%	-0.001±0.117	0.025±0.096	12.5/10.7
A wave m/sec	-0.008±0.091	8.8%	0.031±0.156	-0.003±0.084	9.6/14.3
E/A ratio	0.015±0.29†	14.1%	0.007±0.28	0.056±0.19	19.4/21.3
DT (sec)	-0.001±0.034	13.1%	-0.001±0.030	-0.009±0.036	12.4/9.5

* Coefficient of variation = $\left(\sqrt{\sum SD_{pair}^2 / \text{number of pairs}}\right)$ /mean $Mean_{pair}$ * 100.[83]

† For the marked interobserver estimates the SD significantly changes with the value of the measured variable. For LV ejection fraction there is an increase in SD with decreasing LV ejection fraction values, indicating an increase in CV with decreasing values. For E/A ratio there is an opposite trend, with increase in CV with increasing E/A ratio values. (I.e. greater CV for values in the pathological range.) The intention of using a centre estimate of the SD's from each pair in stead of the SD of the mean pair difference, is to minimise the effect on the coefficient of variation of an increasing pair difference with increasing values, i.e. the intersubject variability. This approach also minimises the effect of the SD distribution being skewed to the right. Accordingly the overall CV * 1.96 using this method approaches the 97.5th percentile of the pair CV distribution.

Figure 2 Flowchart of the Tromsø Echo Study

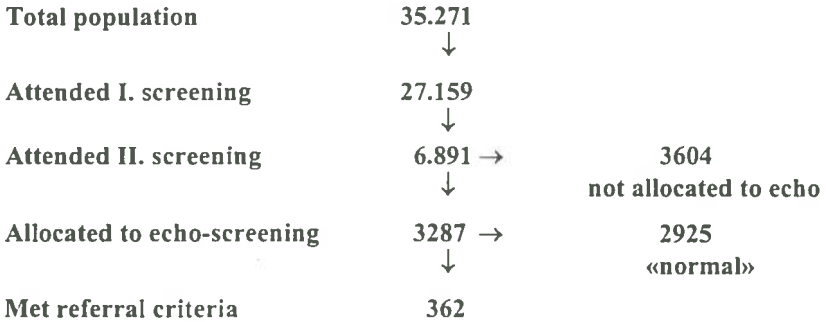


Table 3. Predefined criteria for referral of identified pathology

Diagnosis	Criteria
Doppler	
Mitral insufficiency	Regurgitant jet area > 4 cm^2
Mitral stenosis	All identified subjects
Aortic insufficiency	Jet > 30% of LV outflow tract diam., or if not measurable; jet reaching the bottom of the ventricle
Aortic stenosis	Peak gradient > 30 mm Hg
2 D guided M-mode	
Wall thickness	> 1.4 cm
LV diastolic diameter	> 6.5 cm
Aortic root diameter	> 4.5 cm
Heart failure	LV ejection fraction < 0.50
2 D echo or ECG	
Hereditary abnormalities	All suspected cases
Anatomical abnormalities	Where clinical relevance is suspected
Atrial fibrillation	Subjects not on anticoagulant therapy

Self-reported risk factors or symptoms

A history of cardiovascular disease was set to yes if one or more of the following items were reported; myocardial infarction, angina or stroke. Units of alcohol consumption per fortnight is a sumscore of self reported intake of glasses of wine, beer or liquor in average over a period of 14 days. Strenuous physical activity in leisure time was graded in four according to hours of sweating or breathlessness during an average week. Dyspnea was registered as the presence of breathlessness at rest or during exertion.

Reference sample

For estimation of reference limits in paper I, a reference sample of 954 subjects was defined as subjects with normal weight,[84] no signs or history of hypertension, cardio-pulmonary disease or diabetes and no evidence of valve disease by echocardiography (see figure 3). Interestingly, for those younger than 55 years, significantly fewer women than men were excluded, mainly due to women having body mass index values within reference limits (39% vs. 17%, for men and women respectively, $p < 0.001$). In paper IV, subjects with a heart rate above 100/minute were excluded as well, leaving a reference sample of 1005 subjects. (Larger sample due to higher success rate for Doppler than for M-mode registrations.)

Table 4. Frequency of possible exclusion criteria for the reference samples in the total population (N=3287).

Variable	Frequency (%)	Cumulative frequency (%)
Used in paper I and IV:		
Blood pressure >= 140/90	1536 (46.7)	-
Antihypertensive medication	444 (13.5)	1648 (50.1)
Weight ± 20% of normal	1072 (32.6)	1979 (61.7)
Cardiovascular disease	461 (14.0)	2076 (63.2)
Asthma	280 (8.5)	2162 (65.6)
Valvular heart disease	184 (5.4)	2197 (66.8)
Diabetes	99 (3.0)	2202 (67.0)
Only used in paper IV:		
Heart rate ≥ 100	117 (3.6)	2218 (67.5)
Not used:		
Cholesterol < 8 mmol/l	464 (14.1)	2311 (70.3)
Smoking	1084 (33.0)	2678 (81.5)

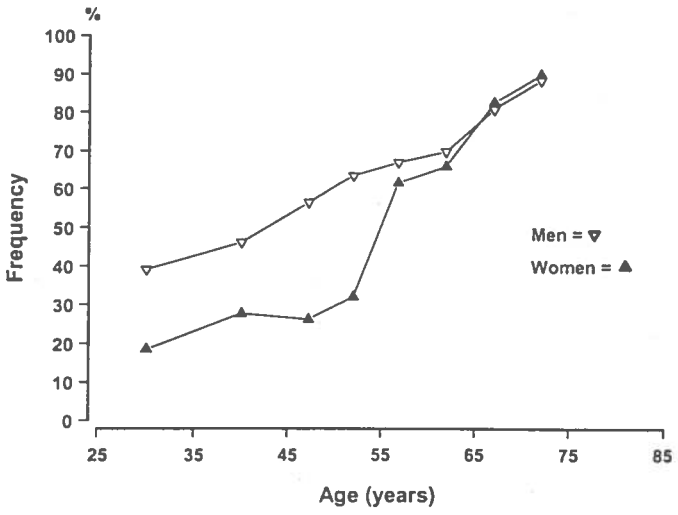


Figure 3. Age and sex specific prevalence of the exclusion criteria used in paper IV.

Use of cardiac peptides in The Echo Study

To test the diagnostic accuracy of different cardiac natriuretic peptides in identifying LV systolic dysfunction, N-terminal pro-atrial natriuretic peptide (NANP) and brain natriuretic peptide (BNP) were measured in serum. These cardiac peptides were the most promising for identification of LV dysfunction at the time the protocol was written. For N-ANP this was due to longer half-life than C-terminal atrial natriuretic peptide (ANP), and for BNP, an increased in vitro stability compared to ANP, the first natriuretic peptide isolated.[85; 86] Both N-ANP and BNP had shown to be correlated to both LV systolic dysfunction, LV mass and survival after myocardial infarction.[67; 71; 87; 88]
Cardiac peptides are usually measured in plasma, but plasma was not available for this part of the Tromsø Study. Serum analysis of N-ANP had been documented to be equivalent to plasma measurements, but this had not been documented for BNP.[89] Since plasma was not available for comparison within the Tromsø Study, a validation of the equality of plasma and serum measurements of BNP levels is being performed outside the main study.
To guide the choice of cardiac peptide used for analysis in our sample, a receiver operating characteristic analysis (ROC) of the diagnostic accuracy of identifying LV systolic dysfunction was performed in a nested case control study.[90] Cases were identified as subjects with LV ejection fraction ≤ 0.45 in the total sample (i.e. the 1% distribution of LV ejection fraction) and 2 - 4 age and sex matched controls were drawn for each case from the sample with serum within the Echo Study. Serum from cases became available as serum was thawed for an other study not part of the Echo Study. Due to little available serum from these cases, only 12 of 28 cases had serum for both N-ANP and BNP measurement. This left 12 cases and 42 controls with measurements of both N-ANP and BNP.

Biochemical measurements;

Ten to twenty minutes after echocardiography, with the subjects in a sitting position venous blood was drawn from a cubital vein after 3 minutes of rest. It was left to coagulate for one hour and serum was then stored at -70^{0}C until analysis. Both serum BNP and N-ANP were determined without prior extraction. BNP levels were determined using immunoradiometric assays and N-ANP with radioimmuno assay.[67; 85; 86; 89] The inter and intra-assay variation in our laboratory was < 12 %, with decreasing variation with increasing values of N-ANP. For BNP, the intra and inter-assay variation coefficients were 17.8% and 20.1%, respectively. 7 of 55 (i.e. 13%) samples had undetectable levels of BNP. The undetectable samples were given the value of the lower limit of detection, 0.8 pmol/L, to allow statistical analysis. The corresponding N-ANP values in these samples were in the lower

half of the distribution in the control group. Among the cases LV ejection fraction ranged from 0.22-0.45 and among controls from 0.59 to 0.85. The correlation between levels of BNP and N-ANP was 0.74. The correlation coefficient with LV ejection fraction was highest for N-ANP with an r = -0.51 vs. -0.33 for BNP.

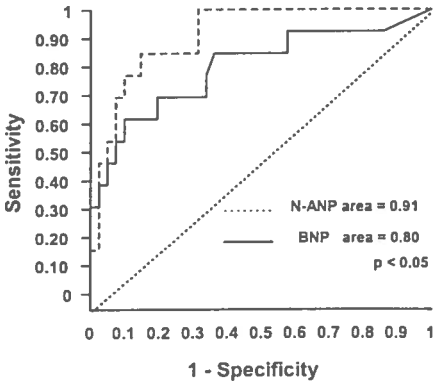
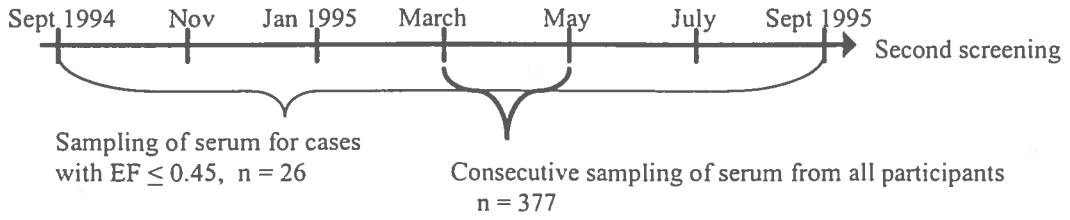


Figure 4.
The diagnostic accuracy of all measured levels of N-ANP and BNP for identification of subjects with LV ejection fraction ≤ 0.45 expressed as ROC curves.

As shown in figure 4, N-ANP had a ROC area of 0.91 and BNP a ROC area of 0.80. This difference was significant with a p value < 0.05 according to the method of Hanley and McNeil.[90] This implies that N-ANP is 9 % better than BNP in identifying a randomly chosen case correctly. Given the better diagnostic accuracy of N-ANP in identifying LV dysfunction and the lack of documentation of the validity of serum measurements of BNP, N-ANP was chosen as cardiac peptide in the analysis of the relationship between cardiac peptide, LV mass and LV systolic dysfunction in paper II. Due to the described sampling procedure, there was serum available from 26 cases with LV ejection fraction ≤ 0.45, of whom 12 had N-ANP measurements. Two of these were from within the serum sampling period of the Echo Study. In addition 375 subjects with LV ejection fraction > 0.45 in the consecutive sampling period, had serum available for N-ANP measurement.

Figure 5. Flowchart for sampling of serum for the echo study (paper II)



Main results

Paper I; *Prevalence of left ventricular hypertrophy in a general population. The Tromsø Study.*

As an alternative to the American criteria presently in use, a new European framework for defining left ventricular hypertrophy is provided. Sex specific 97.5 percentiles for left ventricular mass by height, based on the reference sample, were 145.5 and 125.4 g/m, for men and women, respectively. The prevalence of left ventricular hypertrophy in the total population were 14.9% for men and 9.1% for women. The main independent predictors of left ventricular hypertrophy were male gender, body mass index, systolic blood pressure, valvular heart disease, cardiovascular disease and antihypertensive medication. Body mass index and systolic blood pressure had a strong synergistic association with left ventricular hypertrophy in men, but not in women. With body mass index being the culprit factor for risk of left ventricular hypertrophy, our study indicates that weight reduction is a relevant measure for treatment and possibly prevention of left ventricular hypertrophy in a substantial part of the general population.

Paper II; *Circulating N-terminal pro-atrial natriuretic peptide is an independent predictor of left ventricular hypertrophy in the general population. The Tromsø Study.*

In the population-based sample of 3287 subjects, circulating N-ANP was measured in a subgroup of 389 subjects. The 51 subjects with left ventricular hypertrophy had significantly higher N-ANP levels than controls. A gradually increasing prevalence of left ventricular hypertrophy over increasing 500 pmol/l intervals of N-ANP was observed (1.8 to 64.3%; χ^2 p for trend < 0.001). N-ANP was an independent predictor of left ventricular hypertrophy after adjustment for ejection fraction, body mass index, hypertension, valvular disease, a history of myocardial infarction, gender, and age. The adjusted odds ratio for left ventricular hypertrophy was 1.79 (95% CI 1.04 - 3.07) for an 500 pmol/l increase in N-ANP. A substantial proportion of subjects with elevated N-ANP levels had combined left ventricular hypertrophy and left ventricular dysfunction. These results suggests that N-ANP is an independent predictor of left ventricular hypertrophy in the general population. N-ANP determination is however, poorly suited to distinguish between subjects with isolated left ventricular hypertrophy and those with left ventricular dysfunction with or without left ventricular hypertrophy.

Paper III; *What determines echogenisity in a general population?*

Of the 3287 subjects in the study, only 0,4% could not be measured by any technique. 2794 had M-mode registrations of good quality enabling calculation of LV mass and LV ejection fraction. Being unmeasurable was independently predicted by higher age, body mass index, diastolic blood pressure, waist / hip ratio, and smoking and male gender. In subjects reporting a history of cardiovascular disease there was a significantly higher prevalence of unmeasurable subjects (23.4% vs. 13.6%). This difference persisted when adjusting for age, but was no longer significant after adjusting for all independent predictors of measurability.
Subjects with high cardiovascular risk factor levels or a history of cardiovascular disease are less likely to be measurable with echocardiography, indicating a need for other non invasive diagnostic methods in as much as 23% of these individuals.

Paper IV: *Mitral flow derived Doppler indices of left ventricular diastolic function. The Tromsø Study.*

In those studied by echocardiography without atrial fibrillation or mitral valve stenosis, 3184 subjects had measurements of both the deceleration time of the passive mitral valve inflow (DT) and the ratio of the peak passive to peak active mitral inflow velocities (E/A). Age specific percentiles showed significant decline by age for the peak passive mitral inflow velocity and the E/A ratio, whereas DT and peak atrial inflow velocity showed a significant increase by age. According to currently used Doppler criteria for diastolic dysfunction, the prevalence in the general population decreased by age, contrary to what would be expected, also in the subgroup with cardiovascular disease. Only 6% of the variance of DT was explained by cardiovascular disease or risk factors. For E/A, however, 36 and 41% of the variance were explained for men and women, respectively. In a «healthy» subgroup of 1005 subjects the age related decline in E/A ratio was linked to an increase in DT, indicating that this change elsewhere described as «abnormal diastolic filing pattern» is a normal phenomenon of ageing. Our results indicate a need for validation of age specific abnormal Doppler indices of diastolic function against invasively diagnosed diastolic dysfunction.

General discussion

Methodological considerations

Selection bias

Is our sample representative of the population we investigated?

Total sample.

There was no predefined selection apart from age of those invited. The most apparent selection bias in this study is consequently non-respondence. Of the invited population, 88% attended the second visit, thus minimising the effect of non-respondence on the estimated associations. The attendance rate increased by age. In many population studies non-responders are found to have a higher frequency of disease and cardiovascular risk factors and higher mortality than responders. This was found in the Finnmark Study, in earlier Tromsø Studies, in the Oslo Study and in the Norwegian Counties Study.[29; 91; 92] In the fourth Tromsø Study, non-respondence was highest in the younger age groups. For the older age groups only mobile volunteers would respond, possibly limiting the proportion of responders with present cardiovascular disease, especially stroke. This would weaken any associations found between the echocardiographic measurements and cardiovascular disease, but would not affect the estimated reference limits of the measurements, since the subjects with high risk factor levels or present cardiovascular disease were excluded from the reference samples. The Echo Study was performed in a subgroup of those attending the second visit. This subgroup had a lower proportion of women than those not examined by echocardiography, and due to lower educational status among women, the echo subgroup had significantly more education. Otherwise the echo subgroup was comparable to the rest (table 1).

Reference sample.

Normality is not easily defined and any chosen normality criteria consequently reflects the focus of the study.[93]

For LV hypertrophy (paper I), which both can be a risk factor for and a consequence of cardiovascular disease, to exclude subjects with a history of cardiovascular disease is mandatory. But due to the slow development of atherosclerosis and other organ manifestations leading to cardiovascular disease, a substantial proportion of the population without irreversible end-organ damage, is likely to have subclinical disease. Since the risk factors for cardiovascular disease is increasingly prevalent as the population gets older, exclusion of subjects with high

risk factor levels will exclude most elderly subjects. This may be an exclusion of those who have survived to an old age despite a high risk factor level. The effect of risk factors such as hypertension and obesity is weakened by increasing age, but due to the increasing prevalence of cardiovascular disease by age the absolute risk is increased.[5, 8] Two major risk factors for cardiovascular disease are also the main prognostic determinants for development of LV hypertrophy. It seems therefore reasonable to exclude hypertensive and obese subjects. For other cardiovascular risk factors such as smoking and cholesterol, there are no association to LVM and exclusion on basis of these risk factors would consequently only weaken the precision of the estimated reference limits due to smaller reference sample. Exclusion of subjects with levels above the «ideal» cholesterol level of 5.5 mmol/l would exclude 84% of the population, which would make stratification on age and gender difficult. The estimated reference limits were a function of the exclusion criteria employed, with lower reference limits as more strict exclusion criteria was introduced. Interestingly, the associations of LV hypertrophy to the risk factors, especially hypertension and body mass index, was not altered by the change in reference limits. The prevalence of LV hypertrophy increased as the reference limits decreased. To facilitate comparison with earlier studies, our exclusion criteria are a replica of the Framingham study, which is widely used for comparison.

For E/A ratio and DT, the choice of reference sample is even less obvious (paper IV). Here, exclusion of cardiovascular disease was found to be mandatory, not only self-reported cardiovascular disease, but also echocardiographic sign of disease such as low ejection fraction and valvular heart disease, and ECG signs of atrial fibrillation. Mitral flow is highly influenced by heart rate, so subjects with tachycardia should be excluded as well. Since various studies have found signs of diastolic dysfunction in groups with hypertension and obesity, these cardiovascular risk factors should also be used as exclusion criteria. As these exclusion criteria are stricter than those employed for LV mass, LV hypertrophy will be excluded as well. Even with these strict exclusion criteria the distribution of the DT percentiles were remarkably similar in the total and the reference sample.

Peptide sample (paper II)

The sampling of subjects with low ejection fraction from the total sample and controls without low ejection fraction only from the serum sample, precludes assessment of the relative prevalence of isolated LV hypertrophy vs. low ejection fraction in subjects with elevated N-

ANP levels in a general population. The prevalence of isolated LV hypertrophy is as expected from the total sample, whereas the prevalence of low ejection fraction is three times higher than expected. This indicates that in a general population the chance of identifying isolated LV hypertrophy versus low ejection fraction should be nearer 3 to 2 than 2 to 3, as estimated.

Confounding

It is important, for estimates of associations between variables to consider possible confounding explaining the observed association. A confounder must be associated both with the dependent and the independent variable under study. In addition, if a variable is included in an intermediate step in the causal pathway between the dependent and the independent variable, the variable is not a confounder.[35]

In paper I, body mass index might be a surrogate estimate of physical activity and diet in the form of total energy intake or percent fat intake. None of the latter remained as independent predictors when body mass index was in the model. This could be due to the more precise estimation of body mass index than of total energy and fat intake estimates from the questionnaires. But the association of body mass index to two factors causing increased vascular volume, i.e. sodium retention and hyperglucosemia, and the importance of increased body mass index for increase in blood pressure and development of hypertension, is a more likely explanation for the strong association of body mass index to LV hypertrophy.[52; 94-96]

In paper II, possible confounding of the association between LV hypertrophy and N-ANP could have been caused by elevated N-ANP levels due to diastolic dysfunction. However, neither adjustment for E-wave deceleration time nor E/A ratio changed the estimates in the model. Thirty subjects fulfilled ESC (see appendix 3), but non the internal criteria for abnormal diastolic function (stage 2) based on E-wave deceleration time and E/A ratio. No subjects fulfilled criteria for diastolic dysfunction stage 3 or 4. Adjustment for ESC criteria of diastolic dysfunction stage 2, were neither significant nor changed the other estimates.

For the estimates of the diagnostic accuracy of N-ANP, diastolic dysfunction measured by DT and E/A ratio, is only of relevance as a possible alternative diagnostic method, and were, as indicated, not relevant for diagnosing LV hypertrophy in our study.

We used serum creatinine to adjust for a possible confounding effect of renal failure on the association between N-ANP and LV hypertrophy. Serum creatinine is a rough estimate of renal function as there must be at least 50% reduction in renal function before abnormally elevated creatinine levels can be detected in serum. As noted above, a possible confounding effect of

minor renal failure can not affect the estimates of the diagnostic accuracy of N-ANP, only the estimated independent association to LV hypertrophy.

Generalisability

Are our results valid for use in other populations?

Our sample is a representative sample of the population of Tromsø due to the 88% attendance rate. In the Troms County, there is a mixed population of Norse, Finnish and Lappish origin. In the Tromsø screenings in 1974 and 1979/80, the participants were asked whether two or more grandparents were of either Lappish or Finnish descent. Of the 3287 subjects in the Echo Study, 1980 participated also in one or both of the two first Tromsø screenings. 86% were of Norse descent, 6% of Finnish, 2% of Lappish, 1% of mixed Lappish and Finnish descent, and 6% did not know the ethnic status of their grandparents. In the reference sample the proportion of subjects with Norse descent increased to 88% with a concomitant minor decrease in the frequency of the other groups. Ethnicity was a significant predictor of LV mass even after indexation for height, with Lappish descent predicting a significantly higher LV mass by height than all other groups but those of mixed decent. The latter had an intermediate level. Exclusion of those with known Lappish descent, lowered the reference limits for LV hypertrophy by 0.1 g/m each, i.e. not significantly. The Doppler indices of Lappish or Finnish descendants were not significantly different from those of Norse descent. In the prediction of LV hypertrophy in paper I, ethnicity was not a confounder of the estimated associations, but was an independent predictor. This opens up the possibility of identifying new predictors of hypertrophy among genetic or environmental differences between these ethnic groups.

In Tromsø there is a low proportion of elderly due to a large net immigration the last decades.[20] Due to the large sample and the high attendance rate among the elderly, the proportion of «healthy» elderly is sufficient to enable estimation of age specific reference limits for the age span 25 to 85. Otherwise the inhabitants of Tromsø are comparable to the rest of Norway regarding lifestyle, education, social status and cardiovascular risk factors and disease incidence.[11; 12]

Estimation error

How may the design have influenced the results?

The difference in prevalence of hypertrophy for women between a method using percentiles and a method using mean + 1.96 SD relies on the two estimated cut-off values being significantly different. The confidence interval of a 95% upper reference limit is dependent of the number of

the group and is estimated according to the formula; width (in multiples of SD) = SD * $\sqrt{3}/N$, as shown by Altman (1991).[93] This will give an estimated width of the 95% confidence interval of LV mass indexed by height of 114.0-115.4 g/m, well below the 97.5th percentile estimated as 124.5-126.3 g/m according to the method described by Linnet (1987).[97] Alternatively to the non-parametric approach used in our study, Linnet suggests a log-transformation of the data to achieve a normal distribution. The estimated 95%CI interval is then re-transformed to the original values and expanded by 25%. This approach will allow for narrow confidence intervals for the 95%CI limits in small samples. In large reference sample as ours the confidence intervals will be narrow also for the non-parametric approach and the information imbedded in the actual distribution of increasing percentiles is conveyed in addition to the arbitrarily chosen statistical normality.

When estimating associations between the estimated age specific percentiles and age, the varying number in each age group would cause a possibility of finding associations present due to chance only. By weighting the regression models with the number in each age group, the imprecision of the percentile estimates in groups with small numbers are accounted for. This method is conservative because an enlargement of the total sample will not account for the relatively steeper improvement in precision in the smaller groups compared to the larger. This only constitutes a problem when finding an association of clinical interest with borderline significance, like in paper I for the increasing values for the upper 10% male distribution with increasing age. In this example the contrast between the upper 10% with an increase by age and the lower distribution without, may be caused by undetected subclinical pathology like large individual increases in body mass index within the exclusion criteria or undiagnosed diabetes. This assumption would render the significance testing of the age trend irrelevant. If on the other hand, the age trend is a relevant finding, i.e. significant with a hypothetical regression model taking account for the exponential improvement in precision of percentile estimates by increasing numbers,[93] this would imply a less steep increase in the prevalence of hypertrophy by age. Interestingly, the synergistic association between body mass index, systolic blood pressure and LV hypertrophy, is not affected by such a change of reference limits (data not shown).

An other important methodological problem is concerned with the dichotomising of continuous variables as done for LVEF, LVM and the Doppler indices in paper I, II and IV. When there is a linear relationship between a variable and the phenomenon of interest, valuable information is

lost. The validity of dichotomising is assured only when a threshold for subsequent risk of adverse events can be found or, for diagnostic purposes, when dichotomising assures a high diagnostic accuracy. Definitions based on statistical normality are useful for comparisons of prevalences of abnormal measurements and for calculation of the predictive value when using the variable diagnostically, but are dependent on external validation against a gold standard to assure true diagnostic relevance.

Hense et al. raises the hypothesis that the relation of LV mass to body mass index is confounded by the relation of body mass index to lean body mass, i.e. that the association only is a result of larger hearts in larger subjects, and questions the indexation of LV mass by height or body surface as a correction for this.[98] The relative contribution of body mass index vs. lean body mass to LV mass, could not be tested in our study. But as increasing height is associated with a decreased risk of cardiovascular disease, their proposal of an adjustment of LV mass with lean body mass probably will reduce the predictive power of identifying hypertrophy. This is a probable consequence because the known association between LV mass and body mass index no longer will be present and the gender difference in level of LV mass is lost. Body mass index is a risk factor for cardiovascular disease and the age specific incidence of cardiovascular disease is higher in men than in women.[12]

Measurement error

Measurement error of a continuous variable can be of two categories; Lack of validity or lack of precision. With lack of validity, the method does not measure the phenomenon of interest. Lack of precision can be either differential or non-differential. If a measurement error is a characteristic of the method employed, the error is non-differential, such as a high unsystematic inter or intraobserver variability, whereas if the error is associated with characteristics of the measured subjects like asymmetric LV wall motility, or with the observer in the form of a systematic inter or intra observer variability, the error is differential.
Non-differential measurement error weakens the possibility of finding associations between phenomenon of interest, whereas differential measurement error opens up the possibility of weakening or strengthening true associations or of finding false associations.[35]

M-mode

Ejection fraction

The validity of LV ejection fraction calculations based on M-mode measurements has been questioned due to the differential error introduced by asymmetrical wall motility in patients with myocardial infarction.[99] 24 subjects with asymmetric wall motility were identified and all of these had either a history of cardiovascular disease or were on antihypertensive medication. This could have relevance for the prediction of LV hypertrophy or indices of diastolic dysfunction by LV ejection fraction in the total sample, but the introduction of asymmetric motility in the models in paper I, II or IV, did not change the estimates apart from a moderate lowering of the impact of cardiovascular disease or myocardial infarction and a similar strengthening of the impact of low ejection fraction. This was as expected, due to the relatively low prevalence of myocardial infarction in the proximal septum and posterior wall, resulting in an overestimation of LV ejection fraction in most subjects with asymmetric wall motility.

Left ventricular mass

Asymmetric wall motility could also introduce a differential error in the estimated LV mass. It could result both in an over and an underestimation of LV mass depending on whether the measurements in an asymmetric ventricle were done in a hypokinetic area with an unrepresentative long LV end-diastolic diameter, or in an area without hypokinesia but with an asymmetric hypertrophic response. Since all of these had either a history of cardiovascular disease or hypertension, this is of no importance to the estimated reference limits, and as mention above, did not confound the estimated predictors of LV hypertrophy. The variability is comparable to that reported in other studies, but the high non differential variability limits the use of these measurements to identify change in an individual patient.

New methods of measuring LV mass has been introduced, i.e. 2 dimensional echocardiographic estimation or magnetic resonance imaging.[100] In large scale population based studies where myocardial infarctions are relatively rare, M-mode echocardiographic measurements is still the method of choice due to the quick, non-invasive technique without radiation exposure, as long as asymmetry is accounted for.

Doppler

Diastolic function

The validity of DT and E/A ratio measurements as an index of left atrial pressure has been questioned in many small scale studies.[101-103] Measurements of mitral inflow have been shown to be highly dependent of LV loading conditions, heart rate and age. The last can be adjusted for by age specific criteria, but the two first will influence the association between these Doppler indices and left atrial pressure in a less predictable way. LV loading conditions are mainly determined by early relaxation and late diastolic elastic properties. The elastic properties are characterised by the pressure - volume curve of the LV chamber, and the inverse of the slope (dV/dP) is the compliance. A decreasing compliance results in an increase of the LV diastolic pressure and consequently also of the left atrial pressure. Relaxation on the other hand, is an energy dependent process of Ca^{++} resequestering and dissociation of the actin myosin pairs, occurring in late systole and early diastole. If the relaxation rate is considerably reduced due to myocardial energy depletion, it may influence the compliance of the LV chamber in late diastole and cause an increase in LV diastolic pressure.[104]

Delayed relaxation and decreased compliance are both components of stage III-IV diastolic dysfunction and causes opposite changes in the DT and E/A ratio measurements. This results in a phase of «pseudonormalisation» in the progression of diastolic dysfunction. Consequently diagnostic use of these Doppler indices in patients without LV systolic dysfunction is problematic. In stage II where delayed relaxation is dominating, the longer time needed to fill the left ventricle results in a decrease in E wave velocity and consequently an increase in deceleration time. This is, as shown in paper IV, a phenomenon occurring in healthy ageing. The specificity of this combination of changes in DT and E/A ratio for diagnosing decreased compliance of the left ventricle, is poor. Nishimura et al. describes an elevated LV diastolic pressure under stress for some patients with stage II diastolic function.[64] This could be a method for validating an abnormal combination of low E/A ratio and high DT as an indicator of pathological relaxation in symptomatic subjects in a general population.

Whether other Doppler indices of diastolic function will show better diagnostic performance in a general population remains unanswered, but the finding of Caruana et al. of no overlap between groups of symptomatic patients identified with different Doppler indices indicates at least a low sensitivity for the criteria in present use.[105]

As for M-mode, there was no systematic variation of the Doppler measurements, but the large confidence limits for intra- and inter-observer variation, hampers the use of these indices to detect change in the individual patient.

Valvular heart disease

Estimation of mitral valve insufficiency by colour area is highly gain dependent. To account for this we set gain of the colour Doppler at maximal gain without distortion. The gradation of mitral insufficiency in < 4 cm^2, 4 - 8 cm^2, and > 8 cm^2, was indirectly validated by only the to upper grades being significantly associated with LV hypertrophy or abnormal Doppler indices of diastolic function. Better ways of quantifying mitral insufficiency exists, but these were inapplicable due to time restraints of the study. The number of subjects with valvular heart disease in the variability study was to small to allow estimation of inter or intra observer agreement.

Cardiac peptides

The validity of the cardiac peptide N-ANP as a diagnostic indicator of LV dysfunction is questioned in paper II. Cardiac peptides are usually measured in plasma, but no difference in measurements in plasma and serum has been documented.[86] Accordingly our estimates of diagnostic accuracy are externally valid.

Questionnaire

Physical activity

The four categories of leisure time physical activity were changed between the third and the fourth Tromsø Health Survey. Whereas the first set of categories was validated against exercise testing in the third Tromsø Study, this has not been done yet for the new set.[91] The lower range of mean heart rate for comparable age groups, may imply that the new set differentiates levels of physical activity to a lesser extent, or that the categories opens up for a larger misclassification. This will weaken the possibility of finding an association between LV hypertrophy and physical activity in paper I. Still, a significant association was found between physical activity and LV mass in the age groups below 60 years of age (data not presented).

Cardiovascular disease

The self reported history of cardiovascular disease or lack of such is being verified against hospital records in the Tromsø University Hospital, the only hospital serving the participants in the study. The results of this verification is not yet completed. From the Finnmark Studies,

Tretli et al. 1982, reported good reliability of the questionnaire data regarding myocardial infarction, whereas there were some underreporting of stroke when compared with medical records.[106] In the third Tromsø Study, Løchen et al. reported 11.8% underreporting of myocardial infarction.[91] Such an underreporting of cardiovascular disease could explain the divergent age trend for LV mass percentiles for the upper 10 % of the reference sample (paper I). As the age trend is similar for all percentiles of the Doppler indices in the reference sample, the possible underreporting does not seem to have any impact (paper IV). If this underreporting should affect the estimated synergistic effect of body mass index and systolic blood pressure on LV hypertrophy in men not reporting cardiovascular disease, underreporting would have to be associated to both variables (paper I). Our identification of one subject with asymmetric LV wall motility without a history of cardiovascular disease, indicates either a misclassification of cardiovascular disease status or of the wall motility status of the subject.

Implications and further research

Clinical implications:

A substantial part of the population has a high likelihood of having LV hypertrophy based on simple measurements of body mass index and systolic blood pressure. Weight reduction in treatment of hypertension is highly relevant for these patients.

Cardiac peptides useful for identification of subjects with a high likelihood of benefit of an echocardiographic examination, but not for diagnosis of specific disease.

The mitral inflow derived Doppler indices are when using current guidelines, not useful in diagnosis of diastolic dysfunction in a symptomatic or asymptomatic general population.

Further research:

Within study:

The acquired data represent an unique possibility of generating age and specific reference limits for additional Doppler indices of diastolic function and LV dimensions.

The assessment of valve status in a sample of 3287 subjects opens the possibility of estimating predictors of early signs of valvular heart disease, before the pathological development has affected blood pressure and other possible risk factors.

New studies:

A follow up screening would allow determination of individual change in LVmass, especially in relation to change in body mass index and systolic blood pressure. This would clarify whether the shown associations are causal and modifiable. In addition, the effect of change in body mass index on the effect of antihypertensive medication on blood pressure and LV hypertrophy in a general population could be elucidated.

Prediction of cardiovascular disease by LV hypertrophy will be possible as soon as the collection of cardiovascular end-points and total mortality is completed. This will allow the validation of reference criteria by relative risk for subsequent cardiovascular disease, and give answers to questions like whether identification of hypertrophy identifies those with hypertension responsible for the elevated risk associated with elevated blood pressure. Another question of interest is whether hypertrophy mainly caused by high body mass index or caused by high systolic blood pressure carries different risk of subsequent events?

Collection of incident cases of cardiovascular disease and total mortality, will also allow estimation of risk associated with abnormal Doppler indices. In addition, a validation of indices of diastolic dysfunction in symptomatic and asymptomatic subjects from the general population should be of high priority to ensure the general applicability of the diagnostic criteria.

General conclusions

1. In a Norwegian population, there is a higher prevalence of left ventricular hypertrophy in men than in women. Body mass index and systolic blood pressure are the main predictors of left ventricular hypertrophy. There is a synergistic association between these predictors and prevalence of left ventricular hypertrophy in men only. For women, body mass index has by far the strongest association to LV hypertrophy. This indicates a relevance for weight reduction in the treatment of hypertension and hypertrophy in a substantial part of the population.

2. N-terminal atrial natriuretic peptide (N-ANP) is independently associated with increased left ventricular mass as well as left ventricular systolic dysfunction in the general population. Because of the higher prevalence of the former, the chance of identifying left ventricular hypertrophy with elevated N-ANP levels, is as great or greater than the chance of identifying left ventricular systolic dysfunction.

3. The property of being measurable by echocardiography is associated with low age, body mass index, waist / hip ratio, low diastolic blood pressure, being a non-smoker and of female gender. Because of high risk factor levels, 23% of subjects with cardiovascular disease are not measurable by M-mode echocardiography, precluding these measurements to be part of clinical decision making. In addition, it will result in a selection bias in studies based on echocardiography.

4. The mitral flow derived Doppler indices of diastolic function, E/A ratio and DT, show a strong relation to age both in the total sample and a «healthy» reference sample. The combination of a reduced E/A ratio and an increased DT is a normal ageing phenomenon. Current guidelines for diagnosis of diastolic dysfunction show a bimodal age distribution, an artefact caused by basing reference values on too small samples. These guidelines need revision.

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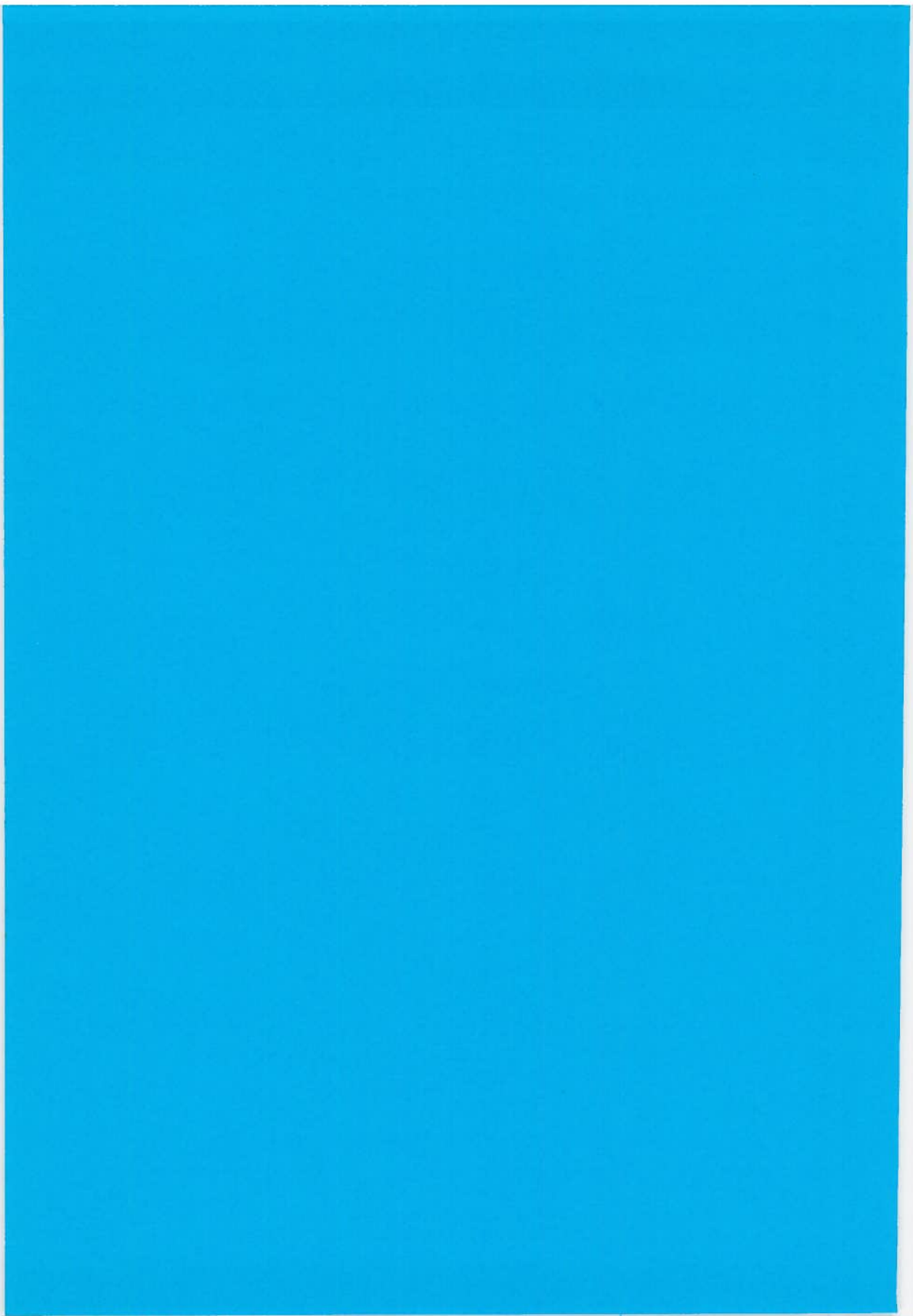
Paper I



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Prevalence of left ventricular hypertrophy in a general population

The Tromsø Study

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Aims Left ventricular hypertrophy has been shown to be an independent predictor of cardiovascular morbidity. Acknowledging the skewed distribution of left ventricular mass, we wanted to develop criteria for left ventricular hypertrophy based on percentiles of left ventricular mass, and observe the effect on estimates of left ventricular hypertrophy prevalences in different subgroups and on the relationship to cardiovascular risk factors in a general population.

Methods and Results In a population-based sample of 3287 subjects aged 25–85 years, left ventricular mass was estimated using M-mode echocardiography. A 'healthy' subgroup was used as a reference sample to define sex-specific left ventricular hypertrophy criteria. Sex-specific 97·5 percentiles for left ventricular mass by height, based on the reference sample, were 145·5 and 125·4 $g \cdot m^{-1}$, for men and women, respectively. The prevalences of left ventricular hypertrophy in the total population were 14·9% for men and 9·1% for women. The main independent predictors of left ventricular hypertrophy were male gender, body mass index, systolic blood pressure, valvular heart disease, cardiovascular disease and antihypertensive medication. Body mass index and systolic blood pressure had a strong synergistic association with left ventricular hypertrophy in men, but not in women.

Conclusion An alternative framework for defining left ventricular hypertrophy is provided. Body mass index is the culprit factor for risk of left ventricular hypertrophy. Our study indicates that weight reduction is a relevant measure for treatment and possibly prevention of left ventricular hypertrophy in a substantial part of the general population. **(Eur Heart J 1999; 20: 429–438)**

Key Words: Hypertrophy, population, echocardiography, obesity, hypertension, sex.

See page 400 for the Editorial comment on this article

Introduction

Left ventricular hypertrophy has been associated both with hypertension and increased cardiovascular morbidity and mortality[1]. Hypertrophy is commonly considered a physiological response to the increased workload imposed by risk factors of cardiovascular disease[2]. This view of left ventricular hypertrophy, as a marker of exposure to other cardiovascular risk factors, has recently been contradicted by studies showing a decreased risk of cardiovascular events following reduction in left ventricular hypertrophy, independent of reductions in other cardiovascular risk factors[3,4].

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Calculations of left ventricular mass with M-mode echocardiography was early established as a valid non-invasive measure of hypertrophy verified by autopsy[5,6]. Despite the development of new diagnostic methods, M-mode echocardiography is still the method of choice in epidemiological surveys[7].

The criteria for left ventricular hypertrophy have been established from samples, from which individuals exceeding the upper normal limits of the main predictors of left ventricular mass have been excluded. These predictors have been body mass index, systolic blood pressure, cardiovascular disease, antihypertensive medication and valvular heart disease. Previous analysis of left ventricular hypertrophy suffers from two methodological limitations. First, most studies have ignored the fact that the distribution of left ventricular mass is skewed even in 'healthy' reference samples, and have accordingly used the mean left ventricular mass +2 SD as the upper limit. If the skewed distribution is not caused by pathology, this would cause lower reference

limits, and consequently an overestimation of left ventricular hypertrophy prevalence. Secondly, since the prevalence of hypertension increases by age, a large number of elderly have been excluded from the reference samples. This has reduced the generalizability of the currently used left ventricular hypertrophy criteria.

Most population-based echocardiographic data on left ventricular hypertrophy are based on the Framingham study. Since both the incidence of cardiovascular disease and the cardiovascular risk factor levels varies over time and space, there is a need for a validation of these results in a new population, using the ultrasound technology and analytical methods available today.

In a large sample of 2794 men and women with a high mean age, we wanted to establish new sex- and age-specific percentile-derived criteria for left ventricular hypertrophy-based M-mode echocardiography. Our sample was randomly selected from a screening of the general population where possible cardiovascular risk factors were recorded by questionnaire and general examination. Thereby we could elucidate the prevalence and predictors of left ventricular hypertrophy. The relative importance of the main modifiable predictors of left ventricular hypertrophy, body mass index and systolic blood pressure in each gender, was assessed.

Material and methods

Study population

The Tromsø Study was started in 1974 and is a prospective follow-up study of the municipality of Tromsø, Norway. The main focus has been on the epidemiology of cardiovascular disease. The study design includes repeated population health surveys to which selected birth cohorts and random samples of other cohorts were invited. The previous surveys were conducted in 1974, 1979 and 1986[8–12]. The fourth survey started in September 1994 and was completed in September 1995. A total of 27 159 subjects older than 24 years, 77% of the eligible population, attended the first visit. A protocol similar to that of the previous surveys and to the Norwegian Counties Study was followed[8–12]. The examination included standardized measurements of blood pressure, weight, height, and non-fasting serum lipids. Two self-administered questionnaires, checked by trained nurses, covered previous and present diseases and symptoms, use of drugs, smoking, alcohol intake and physical activity. All subjects aged 55–74 and random 5–10% samples of the other age groups were invited to a second visit for more extensive screening. A total of 6891 subjects attended the second visit, 98% of those who participated in the first visit. Because of high attendancy rates at the first visit in these age groups, the second visit comprised 88% of those initially invited. These subjects had been alternately allocated by computer to one of two lines of examination when attending the first visit. Due to lack of capacity, only 3287 subjects on one line were examined by echocardiography. These 3287 did not differ from the total sample attending the second screening in baseline characteristics. 2794 (85%) had M-mode registrations of good quality, making left ventricular mass calculations possible.

Echocardiography

All subjects were examined by medical doctors, (2362 subjects by one doctor, the remaining 432 by two expert cardiologists), using a VingMed CFM 750 (VingMed Sound A/S, Horten, Norway). The subjects were examined in a supine, left lateral position with a combined 3·25 MHz mechanical and 2·5 MHz Doppler probe. The echocardiographic examinations were performed using the standard apical and parasternal long and short-axis views. Left ventricular diastolic dimensions were measured from standard two-dimensional guided M-mode registrations according to the leading edge to leading edge convention[13], using EchoPAC software. Only one heart cycle was measured per subject.

Left ventricular mass was calculated using the correction of the cube formula proposed by Devereux *et al.* for leading edge to leading edge measurements[14]:

$$\text{Left ventricular mass} = 0{\cdot}8 \times [1{\cdot}04 \times ([\text{Interventricular septal thickness} + \text{posterior wall thickness} + \text{end diastolic diameter}]^3 - [\text{end diastolic diameter}]^3)] + 0{\cdot}6$$

The presence of valvular heart disease was evaluated by two dimensional colour Doppler for mitral insufficiency, colour M-mode for aortic insufficiency and pulsed wave Doppler for mitral and aortic stenosis. The presence of other cardiac abnormalities was noted.

Reproducibility

In a subsample of 49 subjects, a reproducibility study was performed by the two main observers. Both observers examined all subjects twice with the measurements done on line. For the two observers the mean ± SD intra-observer difference in left ventricular mass (one week interval) was 3·0 ± 39·0 g and 7·0 ± 25·5 g, respectively. The inter-observer difference in left ventricular mass (no time interval) was 14·8 ± 32·5 g. There was no difference in baseline characteristics for subjects examined by each observer. Left ventricular mass was indexed by height to allow for the increase of left ventricular mass with increasing height, without masking the increase in left ventricular mass with increasing body mass index[15].

Self-reported risk factors

A history of cardiovascular disease was confirmed if one or more of the following items were reported: myocardial infarction, angina or stroke. Units of alcohol

consumption per fortnight is a sum of self-reported intake of glasses of wine, beer or liquor over 14 days. Strenuous leisure time physical activity was graded according to hours of exercise resulting in sweating or breathlessness during an average week.

Reference sample

A reference sample of 954 subjects had the following characteristics: a systolic blood pressure of less than 140 mmHg and a diastolic blood pressure of less than 90 mmHg at the echocardiographic screening; no antihypertensive medication; no cardiopulmonary disease or history of diabetes; weight no more than 20% above or below the Norwegian middle weight by height tables[16]; and no evidence of valve disease by echocardiography (mitral regurgitant area less than 4 cm^2, diameter of aortic regurgitant jet less than 30% of outflow tract diameter and aortic outflow gradient less than 30 mmHg). These criteria excluded 29% of those younger than 40, gradually rising to 87% in those 70 years or older. The weight and hypertension criteria caused 89·7% of exclusions and cardiopulmonary diseases 8·3%. The remaining were excluded due to valvular heart disease.

Statistics

To contrast differences between groups, analysis of covariance were used in the general linear model procedure in the SAS statistical package[17]. Means and prevalences were adjusted for age. The aim was to define left ventricular hypertrophy criteria by estimating sex-specific 97·5 percentile values for left ventricular mass by height for each age group 25–39, 40–44, 45–54, 55–59, 60–64, 65–69 and >69 years. This was done both in the total and reference samples. Any effect of age on left ventricular mass by height percentiles was tested in a weighted linear regression model, the weight being the number of subjects in each age group. Left ventricular hypertrophy criteria were chosen as the sex-specific 97·5 percentiles from the reference sample.

A general association between left ventricular hypertrophy prevalence and single variables was tested with age- and sex-adjusted logistic regression analysis for each variable. The multivariate association was tested with age and all other variables significant in at least one gender. Any gender difference in odds ratios were tested with gender and all gender interaction terms in the full model. The main predictors of left ventricular mass, body mass index and systolic blood pressure were divided in quintiles to assess whether an association was caused by outliers or showed a linear relationship with left ventricular hypertrophy over the whole distribution. For body mass index, the quintile limits were as follows: <22·3, 22·3–24·2, 24·3–26·1, 26·2–28·8 and >28·8 kg . m^{-2} for men and <23·5, 23·5–25·1, 25·2–26·5, 26·6–28·6 and >28·6 kg . m^{-2} for women. Cut-off levels for systolic blood pressure quintiles were <124, 124–132, 132·5–141, 141·5–155, >155 and <120, 120–129, 129·5–141, 141·5–156·5, >156·5 mmHg, for men and women, respectively. To simplify an evaluation of body mass index independent of systolic blood pressure, age-adjusted prevalences of left ventricular hypertrophy for quintiles of body mass index were estimated in three strata of systolic blood pressure according to the WHO criteria for hypertension[18]. Two strata of systolic blood pressure were entered in the logistic regression model as indicator variables. The middle stratum was regarded as the reference. A two sided value of $P<0·05$ assessed statistical significance.

Results

The characteristics of the total population and the reference sample are summarized in Table 1. Of the total population, 28·9% were more than 20% over, and 1·3% more than 20% below Norwegian midweight tables (no significant gender difference). A history of cardiovascular disease was reported in 15·6% of men and 9·9% of women. The prevalence of hypertension according to WHO criteria (systolic >140 or diastolic >90 or being on antihypertensive medication) was 48·1% and 47·7%, for men and women, respectively (data not shown). The reference sample was leaner, younger, had a higher high density lipoprotein cholesterol level (women only) and a higher prevalence of smoking than the total population. The prevalence of valvular heart disease was 4·7% in men and 6·7% in women.

In Fig. 1 the percentiles of left ventricular mass by height are plotted for each age group. As shown, there was little overall increase in left ventricular mass associated with age in the reference sample. Age affected the upper 10% of the population only, although not significantly ($P \geq 0·07$). In the total sample, there was an increasing effect of age from the 50th percentile and upwards. There were two striking gender differences: first, that each percentile was significantly lower in women; second, there was a difference in the relationship between the 97·5 percentile of the total sample and the reference sample. In men, the 97·5 percentile of the total sample was higher than that of the reference sample in all age groups. However, for women the curves were almost identical up to the age of 65, indicating that the allowance for hypertension, a history of cardiovascular disease and obesity in the total sample had a stronger impact on the upper percentiles in men. The increase in left ventricular mass by height for women in the total sample started around the mean age for menopause in our material (48·5 ± 4·9 years).

Since there was no significant prediction by age in the reference sample of the 97·5 percentile, for either sex, the percentile for left ventricular mass by height was estimated for the whole reference sample and was

Table 1 Characteristics of the study subjects. Age-adjusted means ± SD (or percent of total)

Variable	Total		Reference sample	
	Men n=1374	Women n=1420	Men n=444	Women n=510
Age (years)	58·6 ± 10·6	54·6 ± 11·2	56·0 ± 11·6	54·0 ± 11·8
Body mass index (kg . m^{-2})	26·0 ± 3·2	25·6 ± 4·3	24·4 ± 1·9	23·7 ± 2·2
Waist/hip ratio	0·91 ± 0·06	0·82 ± 0·06	0·89 ± 0·05	0·80 ± 0·05
Systolic BP (mmHg)	141·3 ± 18·7	139·9 ± 22·0	130·0 ± 9·1	127·2 ± 11·0
Diastolic BP (mmHg)	80·8 ± 11·2	78·1 ± 12·1	74·5 ± 7·3	71·9 ± 7·7
Total cholesterol (mmol . l^{-1})	6·51 ± 1·19	6·76 ± 1·27	6·43 ± 1·17	6·63 ± 1·26
HDL cholesterol (mmol . l^{-1})	1·38 ± 0·37	1·67 ± 0·42	1·42 ± 0·35	1·73 ± 0·42
Echocardiography				
LV mass (g)	201·2 ± 61·1	145·0 ± 41·7	177·4 ± 40·0	127·6 ± 30·4
LV mass by height (g . m^{-1})	114·9 ± 34·9	89·7 ± 26·0	100·7 ± 22·3	78·2 ± 18·6
97·5 percentile LVM . h^{-1} (g . m^{-1})	209·9	150·4	145·5	125·4
Valvular heart disease (%)	4·7	6·7	—	—
Questionnaire				
Myocardial infarction (%)	8·3	3·0	—	—
Angina (%)	9·4	7·4	—	—
Stroke (%)	2·6	1·8	—	—
Diabetes (%)	3·1	2·2	—	—
Antihypertensive med. (%)	12·3	12·5	—	—
Units of alcohol intake	5·0 ± 7·5	1·9 ± 3·4	4·4 ± 5·6	2·2 ± 3·7
Physical activity (graded 1–4)	1·9 ± 1·1	1·5 ± 0·8	2·1 ± 1·1	1·6 ± 0·9
Present smoking (%)	34·7	31·1	40·5	36·9

BP=blood pressure; HDL=high density lipoprotein; LV=left ventricular; LVM . h^{-1}=left ventricular mass indexed by height.

145·5 g . m^{-1} for men and 125·4 g . m^{-1} for women. When these reference values were applied on the total population, the prevalences of left ventricular hypertrophy were 14·9% for men and 9·1% for women (Table 2). The age-adjusted prevalences of left ventricular hypertrophy were significantly higher in subjects who reported myocardial infarction, angina, antihypertensive medication or who had valvular heart disease diagnosed, than in those without cardiovascular disease. There was a substantial increase in left ventricular hypertrophy prevalence over groups with stroke, angina alone or myocardial infarction with or without angina in men, but not in women (chi-squared for trend $P<0·001$ for men and 0·40 for women, not shown in table). An independent association between valvular heart disease, antihypertensive medication, cardiovascular disease and left ventricular hypertrophy is suggested. Among those with a history of cardiovascular disease, the increasing prevalence of left ventricular increased as more of these criteria were fulfilled (P for trend <0·02 for both sexes, not shown in table). Similarly, users of antihypertensive medication with valvular heart disease had a significantly higher prevalence of left ventricular hypertrophy than those without. The use of antihypertensive medication gave a prevalence of left ventricular hypertrophy similar to that of valvular heart disease alone and of cardiovascular disease alone.

The independent predictors of left ventricular hypertrophy by multivariate logistic regression were age, male gender, body mass index, valvular heart disease, systolic blood pressure, a history of cardiovascular disease and the use of antihypertensive medication (Table 3). The presence of valvular heart disease gave the highest risk, with an odds ratios for left ventricular hypertrophy of 4·19 (95% CI 2·79–6·30). Body mass index was, as shown by a Wald chi-square score of 107·9, the most important variable for categorizing subjects as having left ventricular hypertrophy. The odds ratio for left ventricular hypertrophy was 1·96 (1·72–2·22) for an increase in body mass index of 3·8 kg . m^{-2} (1 SD). The odds ratio for systolic blood pressure was 1·46 (1·29–1·69) for an 20·8 (1 SD) mmHg increase. Units of alcohol consumption, serum cholesterol, daily smoking, physical activity, waist/hip ratio and a history of diabetes were left out of the final model since they did not cause a significant change in the maximal likelihood estimate. There was no significant gender difference in odds ratio for any of the variables entered in the model.

In order to assess the relative contribution of the potentially modifiable risk factors, we stratified body mass index and systolic blood pressure. Since subjects with a history of cardiovascular disease could have increased their left ventricular mass as a consequence of cardiovascular disease as well as of their risk factor level, these subjects were excluded from the analysis. As shown in Fig. 2, there was a parallel, gradual and significant increase in left ventricular hypertrophy prevalences for increasing quintiles of body mass index, with women lower at all levels, ($P<0·0001$, not shown in Fig. 2). The increasing gender difference in left ventricular hypertrophy prevalence over increasing systolic blood pressure quintiles was non significant, ($P=0·16$, not shown in Fig. 2). In order to investigate any

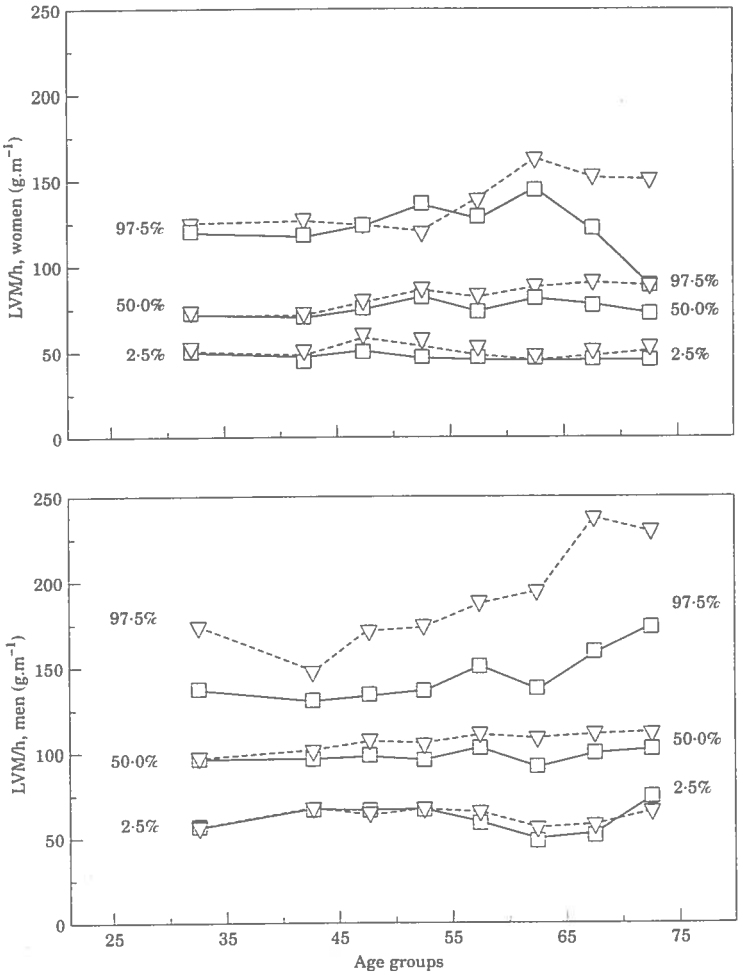

Figure 1 **Age specific percentiles of left ventricular mass by height (LVM . h^{-1}) for the 1420 women in the total sample (▽) or for the reference sample of 510 women (□), and the 1374 men in the total sample (▽) or for the reference sample of 444 men (□).**

intercorrelation between body mass index and systolic blood pressure (r=0·16 for men and 0·33 for women). the two variables were stratified in the same analysis (Fig. 3). In both men and women there was a significant association between left ventricular hypertrophy and systolic blood pressure. For women this was evident in the presence of high pressure only; the threshold above 159 mmHg was significant with an odds ratio for left ventricular hypertrophy of 2·13 (1·32–3·44) compared with the lower systolic blood pressure (no statistical results shown in figure). Body mass index was, however, a significant predictor in all three blood pressure strata in women. For men, all three blood pressure strata were significantly different and the prevalence of left ventricular hypertrophy had a consistently steeper increase over body mass index quintiles with increasing blood pressure levels. The odds ratios for left ventricular hypertrophy of increasing systolic blood pressure strata were 1·86 (1·17–2·98) and 4·92 (3·03–7·98) compared with the lowest stratum. In these subjects without a history of cardiovascular disease, the multivariate odds ratios for left ventricular hypertrophy for 1 SD change in systolic blood pressure were 1·87 (1·54–2·28) in men, vs 1·26 (0·99–1·61) in women. This gender difference in the independent odds ratios was the only significant gender difference in this subgroup (P=0·003, all interaction terms with gender entered in the same model).

***Table 2** Age-adjusted prevalences of sex-specific left ventricular hypertrophy (LVH) for groups of cardiovascular disease*

Variable	Men			Women		
	n	% LVH	*P* value against no CVD	n	% LVH	*P* value against no CVD
CVD	214	30·5	<0·0001	139	21·2	<0·0001
CVD+valve/AHM	9	76·0	<0·0001	9	54·0	<0·0001
CVD+valve	8	35·4	0·03	9	43·6	<0·0001
CVD+AHM	66	29·0	<0·0001	42	27·6	<0·0001
CVD alone	131	27·9	<0·0001	79	11·7	0·07
Alternative subgroups						
MI and angina	53	45·8	<0·0001	26	21·9	0·004
MI alone	61	34·9	<0·0001	16	30·5	0·0005
Angina alone	75	19·8	0·01	79	21·6	<0·0001
Stroke alone	25	19·0	0·17	18	10·5	0·48
AHM+valve	6	47·8	0·006	10	28·9	0·009
AHM only	88	29·7	<0·0001	117	19·8	<0·0001
Valvular disease only	42	30·1	<0·0001	67	16·0	0·004
No CVD	1024	9·6		1087	5·8	
Total	1374	14·9		1420	9·1	

CVD=a history of myocardial infarction, angina and/or stroke; valve=with valvular heart disease; MI=myocardial infarction; AHM=antihypertensive medication; LVH defined as LVM . h^{-1} ≥145·5 g . m^{-1} for men and 125·4 g . m^{-1} for women. The subgroups of different cardiovascular diseases are mutually exclusive, as are all main groups.

Discussion

In this general population, 15% of men and 9% of women were found to have left ventricular hypertrophy as defined by M-mode derived percentile criteria. The main predictors of left ventricular hypertrophy in our study of 2794 subjects were age, male gender, body mass index, valvular heart disease, systolic blood pressure, a history of cardiovascular disease and present use of antihypertensive medication. The most important variable for categorizing subjects as having left ventricular hypertrophy was body mass index. Weight reduction to treat left ventricular hypertrophy has previously been documented either as more, or as potent as antihypertensive treatment in selected groups of patients[19,20]. The finding of a gradually increasing prevalence of left ventricular hypertrophy over the whole distribution of body mass index may thus have clinical implications for a substantial part of the population.

***Table 3** Independent risk factors of sex-specific left ventricular hypertrophy*

Variable	Odds ratio (95% CI) for LVH	Wald score
	n=2794 (cases=334)	
Age (10 years)	1·19 (1·02–1·39)	4·94
Gender (male=1, female=0)	2·20 (1·68–2·88)	33·4
Body mass index (3·8 kg . m^{-2})	1·96 (1·72–2·22)	107·9
Valvular heart disease	4·19 (2·79–6·30)	47·7
Systolic blood pressure (20·8 mmHg)	1·46 (1·29–1·67)	33·1
Cardiovascular disease	2·22 (1·63–3·03)	25·3
Antihypertensive medication	1·60 (1·16–2·19)	8·32
ROC area	0·80	

LVH=left ventricular hypertrophy. Apart from age and gender, variables are listed according to decreasing contribution of explained variance (Wald chi-square).

The hypothesis of a possible synergistic association between body mass index and systolic blood pressure with left ventricular hypertrophy have seldom been a focus of population-based studies, and have only been described in one large group of hypertensive men[21–25]. Our population-based study supports this hypothesis, and is the first to indicate that this synergism is gender specific.

The population-based approach and the high participation rate reduce selection bias and strengthen the external validity of our results. The validity of M-mode echocardiography in estimating left ventricular mass has been well documented. Accordingly, the correlations between M-mode estimated and autopsy determined left ventricular mass range from 0·81 to 0·96[5,6]. The possible error introduced by the few subjects with asymmetrical ventricles after myocardial infarction who attend a population screening, will not affect our reference limits, or the prediction of left ventricular hypertrophy in subjects without a history of cardiovascular disease. No systematic intra-observer bias was evident. Moreover, the inter-observer bias was of minor importance for the internal validity of our results, since 85% of the measurements were done by one observer. Our inter- and intra-observer variability was slightly higher than

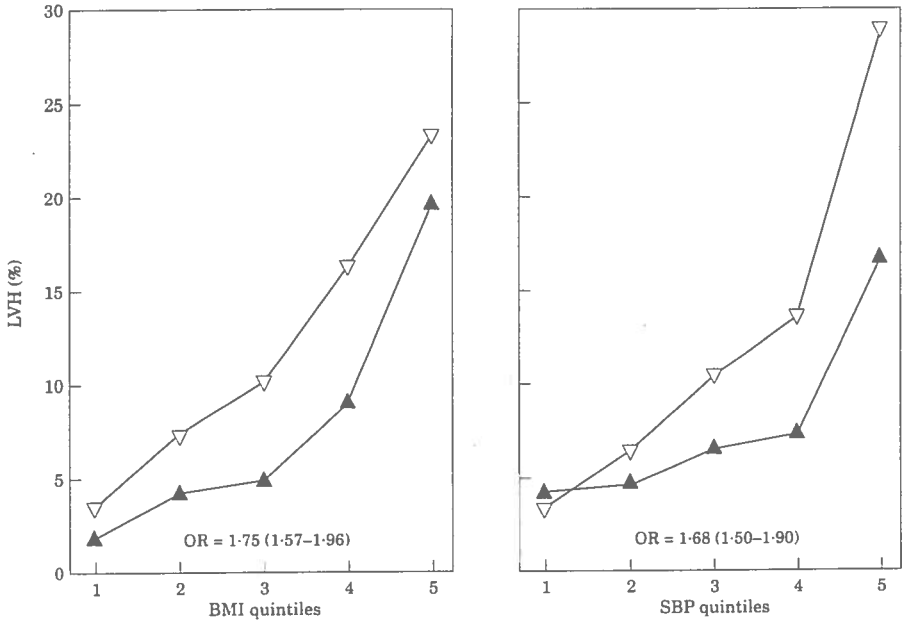

Figure 2 **Age-adjusted sex-specific prevalences of left ventricular hypertrophy plotted against quintiles of body mass index (BMI) and systolic blood pressure (SBP) in subjects without a history of cardiovascular disease. Age and sex adjusted odds ratios for one quintile increase. ▽ = men; ▲ = women.**

the reader variability and the observer variability reported in other studies[26–28]. This indicates that basing our estimates on only one heart cycle only has had little effect on the variability of the M-mode measurements. Due to the potential bias introduced by inter-observer variability, the use of percentile derived criteria from our population assures a more accurate categorization than if external criteria had been used.

In order to ensure a clinically relevant risk for subsequent disease or death for the patient diagnosed with left ventricular hypertrophy, criteria should preferably be based on hard end-points from prospective follow-up studies. In the absence of such end-points in this population, the choice of criteria from a reference sample, in which subjects with cardiovascular disease or left ventricular hypertrophy risk factor levels exceeding upper normal limits have been excluded, seems preferable. Most of the exclusions from the reference sample were due to hypertension and obesity. These predictors of left ventricular hypertrophy are also important risk factors for cardiovascular disease[29–31], and modification of both risk factors cause a reduction in left ventricular hypertrophy[19,26].

In earlier Framingham studies, mean left ventricular mass by height + 2 SD was used as left ventricular hypertrophy criteria. With these criteria they found a left ventricular hypertrophy prevalence of 16% for men and 19% for women[15]. Exchanging our percentile derived left ventricular hypertrophy criteria with criteria based on means + 2 SD, our sex-specific prevalences would have increased from 14·9 to 15·1% for men and from 9·1 to 15·4% for women. We consider the use of percentiles in a general population as more meaningful, and the ensuing result is also more in accordance with known incidences of heart disease in men and women[32]. Similarly to us, Vasan *et al.* recently reanalysed the Framingham data using sex-specific percentiles from a healthy reference sample[33]. They acknowledge that when a continuous risk factor is dichotomized, possible information about a gradually increasing risk is lost. They showed that the relative risk of meeting hard end-points gradually increased as left ventricular mass increased above the upper normal limits for left ventricular mass by height. Women had a lower absolute risk at all levels. They confirm their previous report that left ventricular hypertrophy is more prevalent among women than men (28 vs 23%).

The fact that we, when defining our reference sample, used criteria similar to those of the Framingham Study, suggests a true population difference with regard to left ventricular hypertrophy development. Our population differed from the Framingham study in having a higher prevalence of hypertension (48% compared to 37%) and in being older (59·2 ± 10·6 vs 50·8 years). These differences should yield higher prevalences of left ventricular hypertrophy, contrary to what was found. The mostly Italian heritage in Framingham might imply a different genetic disposition for left ventricular

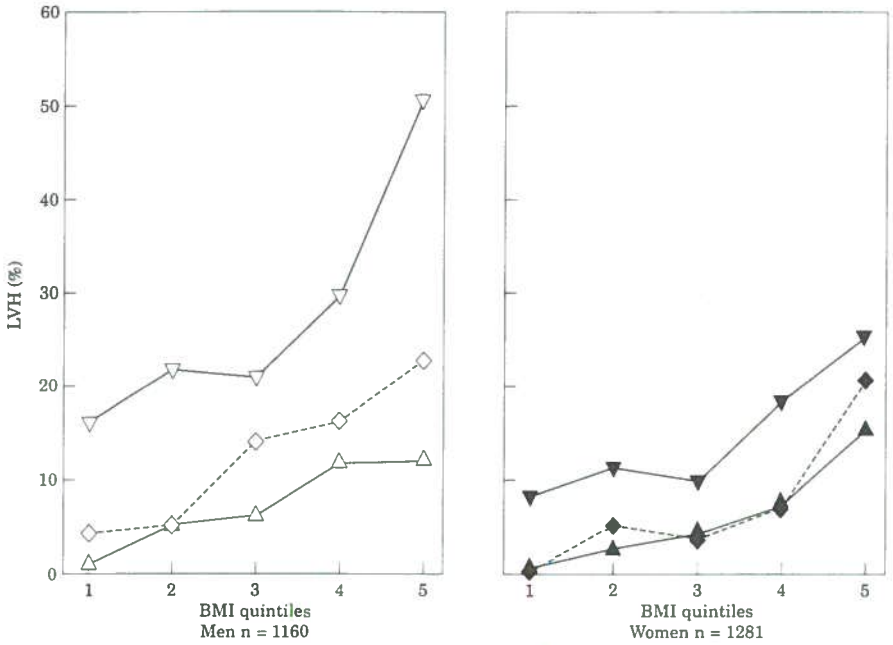

Figure 3 **Age-adjusted prevalences of sex-specific left ventricular hypertrophy (LVH) over body mass index (BMI) quintiles, stratified by systolic blood pressure (SBP) for subjects without a history of cardiovascular disease. Systolic blood pressure >159 mmHg=▽, ▼; 140–159 mmHg=◇, ◆; <140 mmHg=△, ▲.**

hypertrophy compared to the population in a Nordic country. Another difference with potential importance for left ventricular hypertrophy development is the substantially higher level of alcohol consumption in Framingham, especially among women[34].

As in the Framingham study[35], we observed no association between age and left ventricular mass in a reference sample. However, in the multivariate analysis of main predictors for left ventricular hypertrophy, age was a weak independent predictor of left ventricular hypertrophy. If subjects with a history of cardiovascular disease were excluded from the multivariate analysis, age is no longer significant, indicating that the importance of age in left ventricular hypertrophy development is due either to changes imposed by cardiovascular disease or by increasing levels of risk factors common both for left ventricular hypertrophy and cardiovascular disease.

There was a significant gender difference in the importance of systolic blood pressure in predicting left ventricular hypertrophy. For women, the additive effect of systolic blood pressure to that of body mass index was only apparent above 159 mmHg, and less so than in men. For men, there was a gradually increasing prevalence of left ventricular hypertrophy with increasing systolic blood pressure levels at all levels of body mass index, indicating a strong synergistic association. Thus, for women there was little additional information obtained from taking systolic blood pressure into account. Because of the low intercorrelation of these predictors, this could imply a partial 'protection' of the effect of systolic blood pressure on left ventricular hypertrophy induction in women.

Of the few studies addressing the relative importance of body mass index and systolic blood pressure in the development of left ventricular hypertrophy, only Gottdiener *et al.*, who found a synergistic association in hypertensive men, assess hypertrophy over increasing levels of body mass index[25]. The other studies dichotomize body mass index and have few or no hypertensive subjects[22–24]. The hypertensive reveals a gender difference in left ventricular hypertrophy prevalence.

No explanation of the observed gender difference in left ventricular hypertrophy prevalences is derived from our cross sectional study. Changes in body mass index have been shown to be the most important determinants of hypertension[36–38]. A gender difference in the response to weight change, as indicated in the study by Kuller *et al.*[37] could be a possible explanation for the sex-specific synergism of body mass index, systolic blood pressure and prevalence of left ventricular hypertrophy in our study.

Conclusions

This study provides new data and analysis of echocardiographically measured left ventricular hypertrophy in a large general population. The observations support the existence of a gender difference in the relationship between body mass index, systolic blood pressure and left ventricular hypertrophy prevalence. Criteria for left ventricular hypertrophy, which may be used both in clinical practice and in research, are proposed. The strong influence of body mass index on the prevalence of left ventricular hypertrophy may contain a lesson in prevention. Based on these results, further prospective population-based studies addressing the interaction between obesity, weight reduction, left ventricular hypertrophy, hypertension and its medical treatment seem warranted.

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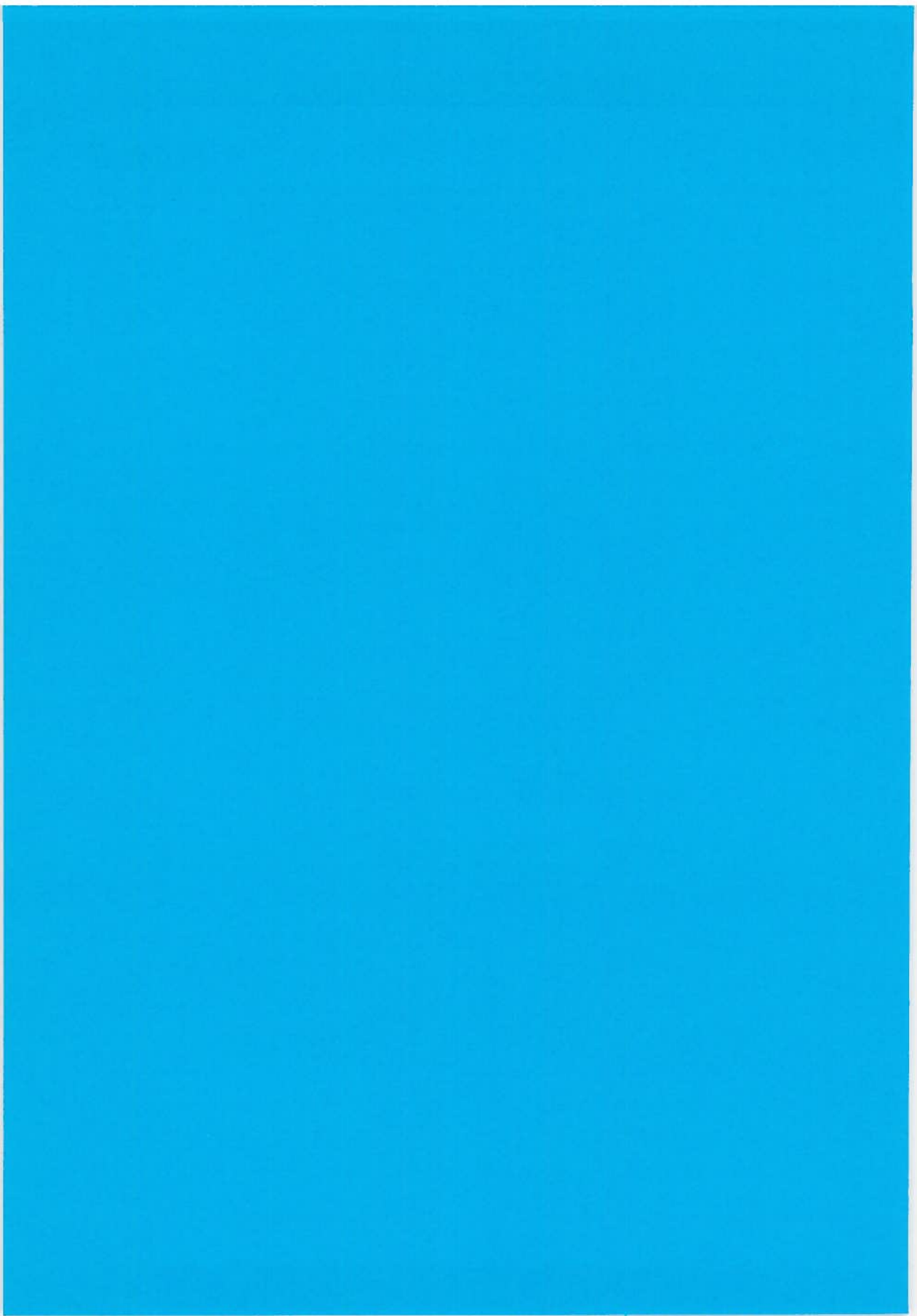
Paper II



Correction of errata in table 3:

Number of subjects with left ventricular hypertrophy and left ventricular ejection fraction ≤ 45% for increasing levels of N-ANP*

N-ANP* level (pmol/l)	0-713	714-1291	>1291	Total	CMH† test for general association
LVEF‡ > 45% and no LVH§	184(95.3)	138(83.1)	14(46.7)	336(86.4)	
LVEF‡ > 45% and LVH§	9(4.7)	26(15.7)	6(20.0)	41(10.5)	
LVEF‡ ≤ 45% and no LVH§	0	1(0.6)	1(3.3)	2(0.5)	
LVEF‡ ≤ 45% and LVH§	0	1(0.6)	9(30.0)	10(2.6)	
Total	193(100)	166(100)	30(100)	389(100)	p < 0.001
% of total	49.6	42.7	7.7		

* N-terminal pro-atrial natriuretic peptide. † Cochran-Mantel-Haenszel. ‡ Left ventricular ejection fraction. § Left ventricular hypertrophy. Column percentages in brackets.

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Circulating N-terminal pro-atrial natriuretic peptide is an independent predictor of left ventricular hypertrophy in the general population

The Tromsø Study

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Purpose The purpose of this study was to determine whether circulating N-terminal pro-atrial natriuretic peptide (N-ANP) levels predict left ventricular hypertrophy in the general population after adjustment for relevant risk factors.

Method and Results In a population-based sample of 3287 subjects aged 25–85 years, circulating N-ANP was measured in a subgroup of 389 subjects. Left ventricular mass and ejection fraction were determined by two-dimensional guided M-mode echocardiography. Left ventricular hypertrophy was defined as height adjusted mass above 145·5 g . m^{-1} and 125·4 g . m^{-1}, in men and women, respectively. Fifty-one subjects with left ventricular hypertrophy had significantly higher N-ANP levels than controls (1075 vs 763 pmol . l^{-1}; $P<0·0001$). A gradually increasing prevalence of left ventricular hypertrophy over increasing 500 pmol . l^{-1} intervals of N-ANP was observed (1·8 to 64·3%; (Chi-squared P for trend <0·001). N-ANP was an independent predictor of left ventricular hypertrophy after adjustment for ejection fraction, body mass index, hypertension, valvular disease, a history of myocardial infarction, gender, and age. The adjusted odds ratio for left ventricular hypertrophy was 1·79 (95% CI 1·04–3·07) for a 500 pmol . l^{-1} increase in N-ANP. A substantial proportion of subjects with elevated N-ANP levels had combined left ventricular hypertrophy and left ventricular dysfunction.

Conclusion These results suggests that N-ANP is an independent predictor of left ventricular hypertrophy in the general population. N-ANP determination is, however, poorly suited to distinguish between subjects with isolated left ventricular hypertrophy and left ventricular dysfunction with or without left ventricular hypertrophy.
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Key Words: Natriuretic peptides, echocardiography, hypertrophy, heart failure, population.

See page 712 for the Editorial comment on this article

Introduction

Left ventricular hypertrophy, as determined by M-mode echocardiography, has been shown to be superior to hypertension, smoking and total cholesterol in predicting cardiovascular morbidity and mortality in the general population[1]. Hypertrophy is commonly considered a physiological response to risk factors of cardiovascular disease[2]. Even so, in patients with essential hypertension, left ventricular hypertrophy is considered a major risk factor, and its presence is an indication for more aggressive antihypertensive treatment. Recently it has been shown that a reduction in left ventricular mass results in a decreased risk of subsequent cardiovascular adverse events, independent of changes in blood pressure[3]. Since left ventricular hypertrophy responds to both pharmacological and lifestyle interventions[4–7], there is a need for a simple screening test for left ventricular hypertrophy. Electrocardiography has a low sensitivity for detecting increased left ventricular mass[8]. Although echocardiography is currently considered the

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screening method of choice, referral of all patients at risk of having left ventricular hypertrophy, will probably exceed the current capacity for this investigation in many countries.

The myocardium synthesizes and secretes a family of peptides with natriuretic, vasodilatory and antimitogenic properties, as a response to increased atrial and ventricular wall stretch and tension[9]. In the presence of increased ventricular wall stress, the expression of the ANP gene and the production of the predominantly atrial-derived A-type natriuretic peptide (ANP) and the N-terminal fragment of the ANP prohormone (N-ANP), are augmented[10]. Circulating levels of these peptides, including ANP, the predominantly ventricular-derived B-type natriuretic peptide (BNP) as well as N-ANP, are increased both in patients with left ventricular hypertrophy and in patients with left ventricular dysfunction[11–16]. However, previous studies have encompassed selected groups of patients, probably resulting in an over-estimation of the diagnostic value of the cardiac natriuretic peptides. Some features of N-ANP make this peptide far more suitable for widespread population screening than ANP or BNP. First, the in vivo half-life is markedly longer, resulting in a 10- to 50-fold increase in plasma concentrations compared to C-terminal ANP[17]. Second, enhanced in vitro stability, even at room temperature, simplifies blood sampling, processing and storage procedures. Finally, higher plasma concentrations have permitted the development of prototypes of semiquantitative rapid assays for N-ANP determination.

The aims of the present study were, therefore, to assess whether circulating N-ANP is predictive of left ventricular hypertrophy, as estimated by M-mode echocardiography in a general population health survey. Further, it has set out to determine whether this relationship is independent of left ventricular dysfunction and other risk factors for left ventricular hypertrophy.

Methods

Study population

The Tromsø Study was started in 1974 and is a prospective follow-up study of the inhabitants of the municipality of Tromsø, Norway. The fourth survey started in September 1994 and was completed in September 1995. A total of 27 159 subjects older than 24 years, 77% of the eligible population, attended the first visit. A protocol similar to that of the previous surveys and to the Norwegian Counties Study was followed[18–21]. The examination included standardized measurements of blood pressure, weight, height, and non-fasting blood tests. Two self administered questionnaires, checked by trained nurses, covered previous and present diseases and symptoms, use of drugs, smoking, alcohol intake, physical activity, and length of education. All subjects aged 55–74 years and random 5–10% samples of the other age groups were invited to a second visit for more extensive screening. A total of 6891 subjects attended the second visit, 98% of those who participated in the first visit. Because of high attendency rates at the first visit in these age groups, the second visit encompassed 88% of those initially invited. By use of a computer, these subjects had been alternately allocated to one of two lines of examination when attending the first visit. Due to lack of capacity, only 3287 subjects on one line were examined by echocardiography. These 3287 did not differ from the total sample attending the second visit with regard to baseline characteristics. 2794 (85%) had M-mode registrations of good quality making left ventricular mass calculations possible.

Venous blood for this substudy was sampled in a 2-month period of the screening only, leaving a subgroup of 379 consecutive subjects with both serum and left ventricular mass calculations. This group differed in baseline characteristics from the total population sample with regard to age (58·4 vs 60·2 years; $P=0·001$), diastolic blood pressure (80·7 vs 82·0 mmHg; $P=0·03$) and prevalence of daily smoking (27·3 vs 33·7% $P=0·01$). After adjustment for educational level, the differences in diastolic blood pressure and in smoking prevalence were no longer significant. The higher educational level was probably linked to the geographical sequence of the screening process within the community. In the subgroup, only two subjects had a left ventricular ejection fraction $\leq 45\%$. To enable comparison of N-ANP levels in subjects with left ventricular dysfunction and subjects with left ventricular hypertrophy alone, 10 additional subjects with both serum available for N-ANP determination and left ventricular ejection fraction $\leq 45\%$, from the total sample, were included in the analysis. These 10 subjects are the cases from an ongoing case control study comparing the diagnostic accuracy of BNP and N-ANP. Left ventricular ejection fraction $\leq 45\%$ comprised the lower 1% of the left ventricular ejection fraction distribution in the total echo sample. Altogether 389 subjects were available for this study.

Echocardiography

Subjects were examined by three experienced investigators, using a VingMed CFM 750 (VingMed Sound A/S, Horten, Norway). The subjects were examined in the supine, left lateral position with a combined 3·25 MHz mechanical and 2·5 MHz Doppler probe. The echocardiographic examination was performed using standard apical and parasternal long and short-axis views. Left ventricular dimensions from one heart cycle were measured online from standard two-dimensional guided M-mode registrations according to the recommendations of the American Society of Echocardiography[22], using the EchoPac software (VingMed Sound). Registrations were regarded as adequate for measurement if both margins of the septum and the posterior wall were visible throughout one heart cycle. Left ventricular ejection fraction was calculated by the cube

formula, and left ventricular mass was calculated using the correction formula by Devereux and Reichek and indexed by height[23,24]. Left ventricular hypertrophy was defined by sex-specific 97·5 percentiles of left ventricular mass/height in a healthy reference group from the total echo sample, defined as in the Framingham heart study[25,26]. Cut-off values were 145·5 g . m^{-1} for men and 125·4 g . m^{-1} for women. Valvular disease was evaluated by two-dimensional colour Doppler for mitral insufficiency (colour area >4·0 cm^2), colour M-mode for aortic insufficiency (jet >30% of left ventricular outflow tract diameter, or if not measurable; jet reaching the bottom of the ventricle), and pulsed Doppler for aortic stenosis (peak gradient >30 mmHg) and mitral stenosis.

Biochemical analyses

Ten minutes after echocardiography, with the subject in the sitting position, venous blood was drawn from a cubital vein after 3 min of rest. Blood samples were left to coagulate in room temperature for 1 h. Serum samples were frozen and stored at −70 °C until analysis. Determination of serum N-ANP was performed by radioimmunoassay without prior chromatographic extraction, as described previously[17,27]. The inter-assay coefficient of variation in our laboratory was <12% and the intra-assay coefficient of variation <12%, with decreasing variation with increasing values of N-ANP.

Statistics

Adjusting for sex and age in the general linear model procedure in the SAS package[28], analysis of covariance was used to contrast differences between subjects with and without left ventricular hypertrophy. The hypothesis that N-ANP is an independent predictor of hypertrophy, was tested using multiple logistic regression adjusted for other known predictors of hypertrophy. A linear trend in the association between left ventricular hypertrophy and increasing N-ANP levels (500 pmol . l^{-1} intervals, arbitrarily chosen) was tested with indicator variables for each of the upper three levels. Trends were also tested with Cochran-Armitage trend tests on unadjusted data. Gender differences were tested with a multiplicative interaction term between the N-ANP value and gender. To test for an arbitrary effect of dichotomizing left ventricular mass indexed by height, the association between left ventricular mass indexed by height and N-ANP was tested in a linear regression model adjusted for gender only. The independent effect of N-ANP was assessed in a multivariate linear regression model with the addition of other risk factors for left ventricular hypertrophy. Using the MedCalc statistical software, receiver operating characteristics analysis was used to determine the optimal cut-off levels for identification of left ventricular hypertrophy or left ventricular ejection fraction ≤45%[29]. Hypertension was defined as blood pressure equal to or above 140/90 mmHg, or as a history of present antihypertensive medication. A *P*-value (two sided) of <0·05 was selected to signify statistical significance.

Results

The characteristics of the study subjects are summarized in Table 1. Subjects with left ventricular hypertrophy were significantly older, were more likely to be men, to have valvular heart disease, a lower frequency of smoking, a history of myocardial infarction, and to report being on antihypertensive medication than subjects without hypertrophy. They also had higher levels of systolic blood pressure, high density lipoprotein cholesterol, and body mass index.

Subjects with left ventricular hypertrophy had significantly higher N-ANP values than subjects with normal left ventricular mass (Fig. 1). Age- and sex-adjusted values for subjects with hypertrophy were 1075 pmol . l^{-1} vs 765 pmol . l^{-1} for controls (P<0·0001). In an univariate logistic regression model, the odds ratio for having left ventricular hypertrophy was 3·20 (95% CI 2·11–4·84) for a 500 pmol . l^{-1} increase in N-ANP levels. The corresponding receiver operating characteristics area was 0·73 (0·69–0·78). There was no significant interaction between N-ANP and gender in this model.

In a multiple logistic regression model with age, gender, body mass index, presence of hypertension, valvular disease, and a history of myocardial infarction included in the model, the odds ratio for having left ventricular hypertrophy decreased to 1·79 (1·04–3·07) for a 500 pmol . l^{-1} increase in N-ANP (Table 2). Adjustment for body mass index increased the estimated odds ratio of N-ANP, whereas adjustment for all the other variables decreased the odds ratio. Hypertension and a history of myocardial infarction were not independently significant predictors of left ventricular hypertrophy, but caused a 12% reduction in the odds ratio of N-ANP and were, considered together, significant (P<0·05).

A linear increase in odds ratios for left ventricular hypertrophy over N-ANP values categorised in intervals of 500 pmol . l^{-1} after adjusting for age, gender, body mass index, hypertension, valvular disease and a history of myocardial infarction was observed (P=0·02, Fig. 2). The number of subjects with left ventricular hypertrophy and the total number in each interval were 1/55, 28/260, 13/60 and 9/14 (Cochran-Armitage trend test P<0·001). The corresponding numbers for subjects with left ventricular ejection fraction (Cochran-Armitage trend test P<0·001). In a linear regression model adjusted for gender, an increase of 500 pmol . l^{-1} in N-ANP was associated with an 25·1 g . m^{-1} increase in left ventricular mass/h (P<0·0001). As shown in Fig. 3, there was a significant linear trend for increasing levels of N-ANP. In a multivariate model with age, gender, left ventricular

Table 1 Characteristics of subjects with and without left ventricular hypertrophy

Variable	Normal LV mass n=338	LV hypertrophy n=51	*P* value
Demographics			
Women (%)	55·2	32·1	0·002
Age (years)	57·9 ± 12·0	63·6 ± 7·0	0·001
Biochemical and physical characteristics			
N-ANP (pmol . l^{-1})	763 ± 279	1075 ± 561	<0·0001
Cholesterol (mmol . l^{-1})	6·61 ± 1·32	6·50 ± 1·06	0·55
HDL cholesterol (mmol . l^{-1})	1·49 ± 0·42	1·42 ± 0·39	0·25
Serum creatinine (μmol . l^{-1})	81·6 ± 18·1	85·3 ± 28·7	0·17
Systolic blood pressure (mmHg)	137·1 ± 20·3	145·9 ± 26·5	0·005
Diastolic blood pressure (mmHg)	78·5 ± 12·2	81·5 ± 12·3	0·11
Body mass index (kg . m^{-2})	25·7 ± 3·6	28·1 ± 4·3	<0·0001
Echocardiographic indices			
LV mass (g)	162·2 ± 41·4	278·0 ± 68·0	group def.
LV mass by height (g/m)	95·4 ± 21·8	163·5 ± 35·4	group def.
LV ejection fraction (%)	75·3 ± 7·5	66·6 ± 17·0	<0·0001
Valvular heart disease (%)	5·0	17·3	0·001
Self-reported data			
Previous myocardial infarction (%)	2·4	24·1	<0·0001
Antihypertensive medication (%)	8·4	28·1	<0·0001
Smoking (%)	30·4	15·3	0·03

Age- and sex-adjusted means ± SD (or percent of total). N-ANP=N-terminal pro-atrial natriuretic peptide; HDL=high density lipoprotein; LV mass=left ventricular mass (0·8*ASE).

ejection fraction, body mass index, systolic blood pressure, valvular heart disease, a history of myocardial infarction and treatment with antihypertensives as covariates, an increase of 500 pmol . l^{-1} in N-ANP was associated with an 8·5 g . m^{-1} increase in left ventricular mass per hour (P=0·0003). Serum creatinine levels did not contribute significantly to either the univariate or the multivariate models in linear or logistic regression analysis.

By receiver operating characteristics analysis, the receiver operating characteristics area of N-ANP for identifying subjects with left ventricular ejection fraction ≤45% was 0·94 (95% CI 0·91–0·96) with an optimal cut-off value of 1291 pmol . l^{-1}. This cut-off value resulted in a sensitivity of 94·7% and a specificity of 83·3% for identifying subjects with systolic left ventricular dysfunction. For left ventricular hypertrophy, the optimal cut-off value from the receiver operating characteristics analysis was 713 pmol . l^{-1}. This cut-off value resulted in a sensitivity of 82·4% and a specificity of 54·4%. Using the cut-off values for left ventricular hypertrophy and left ventricular systolic dysfunction suggested by the receiver operating characteristics analysis, to subdivide N-ANP concentrations in three categories (Table 3), a 20% probability of isolated left ventricular hypertrophy was observed for subjects with N-ANP levels above 1291 pmol . l^{-1} (the optimal cut-off for identifying left ventricular systolic dysfunction), compared to a 33·3% probability of left ventricular dysfunction with or without left ventricular hypertrophy. For the 41 subjects with left ventricular hypertrophy alone, there was a significant increase in left ventricular mass/height from the two lower to the upper N-ANP categories (153 g . m^{-1} to 184 g . m^{-1}; P=0·0002, age- and sex-adjusted).

Discussion

The new information obtained from the current study is that circulating levels of N-ANP are independently related to left ventricular hypertrophy in the general population. Plasma levels of natriuretic peptides, including N-ANP, have previously been shown to be elevated in selected patient groups with left ventricular hypertrophy[16,30]. However, to our knowledge such a relationship has not previously been demonstrated in a population-based study. Moreover, previous investigations have not addressed the question whether this relationship remains significant after adjustment for relevant confounders. Our findings may have important implications for clinical practice. Due to the superior in vitro stability of N-ANP as compared to other peptide hormones and the relative simplicity of the analysis, N-ANP measurements may represent a useful screening tool for the identification of subjects in the general population, who may benefit from referral to echocardiographic examination.

Pathophysiological mechanisms

Several pathophysiological mechanisms may play a role in the increased production of natriuretic peptides observed in patients with left ventricular hypertrophy. First, left ventricular hypertrophy is associated with

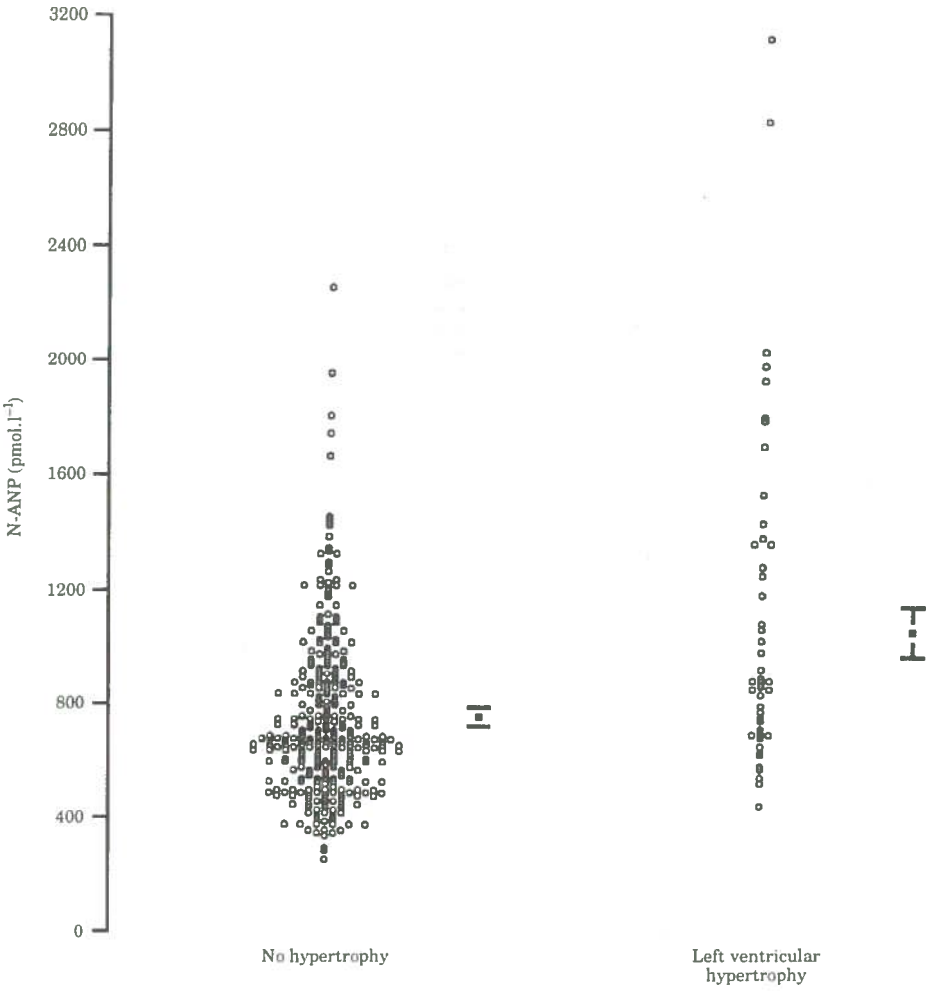

Figure 1 **Distribution of N-ANP in hypertrophic and non-hypertrophic patients. The distributions are marked with means and 1·96 × SE.**

increased ventricular wall tension, a potent stimulus for increased expression of the ANP gene in ventricular cardiomyocytes[10]. Second, increased left ventricular mass per se may be associated with increased net production of natriuretic peptides. Third, left ventricular hypertrophy is associated with left ventricular relaxation abnormalities with a subsequent increase in end-diastolic pressure, which will tend to increase not only ventricular, but especially atrial release of ANP and N-ANP[9,31–33]. ANP production may also be stimulated by other neurohormonal systems which may be activated in hypertension and left ventricular hypertrophy. Finally, since renal filtration is an important determinant of circulating N-ANP concentrations[15,34], consideration of a confounding effect of decreased renal function on any observed association between N-ANP concentrations and manifestations of cardiac disease is pertinent. In our study, however, the observed association between N-ANP and left ventricular hypertrophy was not altered by renal function, as assessed by serum creatinine concentrations.

Our study shows an independent relationship between N-ANP and left ventricular hypertrophy, but we do not advocate the use of N-ANP as a diagnostic tool for identification of left ventricular hypertrophy due to the low specificity (54%) of our optimal cut-off values. Increasing the cut-off value of N-ANP raises the question of a distinction between isolated left ventricular

Table 2 Multivariate prediction of left ventricular hypertrophy by N-ANP levels and other risk factors

Variables	Odds ratio for LVH (95% CI) 51 cases, n=389
N-ANP (500 pmol . l^{-1})	1·79 (1·04–3·07)
LVEF (10%)	0·66 (0·45–0·97)
Age (10 years)	1·26 (0·83–1·93)
Gender (male=1, female=2)	0·46 (0·22–0·97)
Body mass index (4 kg . m^{-2})	2·09 (1·43–3·05)
Valvular disease (yes=1, no=0)	3·39 (1·13–10·1)
A history of myocardial infarction (yes=1, no=0)	2·97 (0·76–11·6)
Hypertension* (yes=1, no=0)	2·14 (0·97–4·72)

N-ANP=N-terminal pro-atrial natriuretic peptide. LVH=Left ventricular hypertrophy LVEF=Left ventricular ejection fraction. *A blood pressure ≥140/90 or a history of antihypertensive medication. Hosmer and Lemeshow Goodness of Fit test; P=0·77.

hypertrophy and left ventricular systolic dysfunction. Although it is well documented that natriuretic peptide levels are increased both in patients with left ventricular hypertrophy and in patients with left ventricular systolic dysfunction[11–16,30–35], previous studies have not addressed the question of the relative contribution of these commonly co-existing conditions to increased circulating concentrations of the natriuretic peptides. Using the cut-off value suggested by the receiver operating characteristics nalysis to provide optimal discriminatory power for the detection of left ventricular dysfunction (i.e. 1291 pmol . l^{-1}), we found that an increased N-ANP concentration was associated with a 20% probability of isolated left ventricular hypertrophy and with a 33% probability of left ventricular systolic dysfunction with or without increased left ventricular mass. As shown in our study, most subjects with left ventricular systolic dysfunction will also have left ventricular hypertrophy.

In our total population examined by echocardiography, the prevalence of left ventricular ejection fraction ≤45% was 1%. To enable analysis of the ability of N-ANP to discriminate isolated left ventricular hypertrophy from left ventricular hypertrophy with left ventricular systolic dysfunction in this study, an additional 10 cases with left ventricular ejection fraction ≤45% was identified in the total sample. This over-sampling of left ventricular systolic dysfunction in the subgroup under

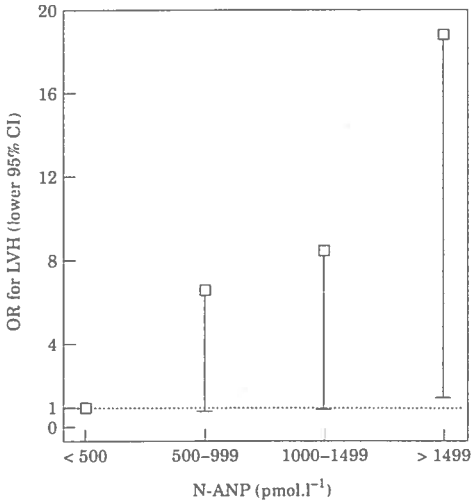

Figure 2 **Odds ratios (OR) (with lower 95% confidence interval) for having left ventricular hypertrophy (LVH) for each 500 pmol . l^{-1} increase in N-ANP after adjusting for left ventricular ejection fraction, age, gender, body mass index, hypertension, valvular disease and a history of myocardial infarction.**

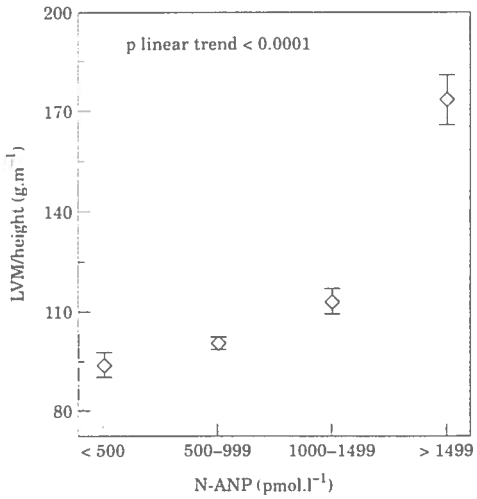

Figure 3 **Sex adjusted means of left ventricular mass (LVM) by height (± 1·96 × SE) for each 500 pmol . l^{-1} interval of N-terminal pro-atrial natriuretic peptide (N-ANP).**

***Table 3** Number of subjects with left ventricular hypertrophy and left ventricular ejection fraction ≤45% for increasing levels of N-ANP*

N-ANP level (pmol . l^{-1})	0–713	714–1291	>1291	Total	CMH test for general association
LVEF >45% and no LVH	184 (95·3)	138 (83·1)	14 (46·7)	336 (86·4)	
LVEF ≤45% and LVH	9 (4·7)	26 (15·7)	6 (20·0)	41 (10·5)	
LVEF ≤45% and no LVH	0	1 (0·6)	1 (3·3)	2 (0·5)	
LVEF >45%	0	1 (0·6)	9 (30·0)	10 (2·6)	
Total	193 (100)	166 (100)	30 (100)	389 (100)	$P<0·001$
% of total	49·6	42·7	7·7		

*N-ANP=N-terminal pro-atrial natriuretic peptide; CMH=Cochran-Mantel-Haenszel; LVEF=Left ventricular ejection fraction. LVH=Left ventricular hypertrophy. Column percentages in brackets.

study will under-estimate the relative proportion of left ventricular hypertrophy alone compared to left ventricular systolic dysfunction. Although subjects with isolated left ventricular hypertrophy tended to have lower levels of N-ANP than subjects with left ventricular dysfunction, the proportion of cases with isolated left ventricular hypertrophy above the optimal cut-off for left ventricular systolic dysfunction was considerable, suggesting that natriuretic peptide screening will not be helpful in distinguishing between the two. Consequently, natriuretic peptide screening should not be considered a diagnostic tool, but rather a non-specific indicator of cardiac structural or functional abnormality.

On the other hand, this lack of diagnostic specificity may imply that cardiac production of natriuretic peptides is a good measure of overall stress on the myocardium. It has already been documented that natriuretic peptides are powerful prognostic indicators in patients with chronic heart failure and myocardial infarction[36–38]. A recent population-based study in octogenarians also suggested that natriuretic peptides may provide prognostic information in an unselected population of elderly subjects[39]. The ability of natriuretic peptides to integrate information concerning ventricular mass and systolic function, both strong markers of cardiovascular risk, indicates that natriuretic peptide measurements may be strongly associated with cardiovascular mortality in the general population as well.

Methodological issues

No systematic intra-observer bias was evident. Moreover, inter-observer bias did not influence our results substantially as 92% of the measurements were performed by one of the investigators. The validity of M-mode echocardiography in estimating left ventricular mass is well documented. Accordingly, correlations between M-mode estimated and autopsy determined left ventricular mass range from 0·81 to 0·96[40,41]. Due to the potential bias introduced by inter-observer variability, the use of percentile defined criteria for left ventricular hypertrophy in our population assures a more accurate categorization of study subjects than if external criteria had been used. In the current study, we used serum for N-ANP measurements. Previous studies have shown that N-ANP levels measured in serum and plasma do not differ significantly[27]. All inhabitants of Tromso over the age of 24 were invited to the initial screening. The use of a random sample from a general population and an attendency rate as high as 88% assures the external validity of our results. The higher educational level in the subgroup included in the present analysis was linked with a marginally lower mean diastolic blood pressure and a lower prevalence of smoking, but the main predictors of left ventricular hypertrophy did not differ from those identified in the total sample, assuring the validity of the current study sample.

Conclusion

The current study documents that circulating N-ANP levels are independently associated with left ventricular hypertrophy in the general population. Moreover, N-ANP measurements are poorly suited to distinguish between subjects with isolated severe left ventricular hypertrophy and subjects with left ventricular dysfunction. However, our results suggest that N-ANP may be utilized as a screening test for identification of subjects, who due to left ventricular hypertrophy or left ventricular dysfunction, are likely to benefit, diagnostically and therapeutically, from echocardiographic evaluation of cardiac structure and function.

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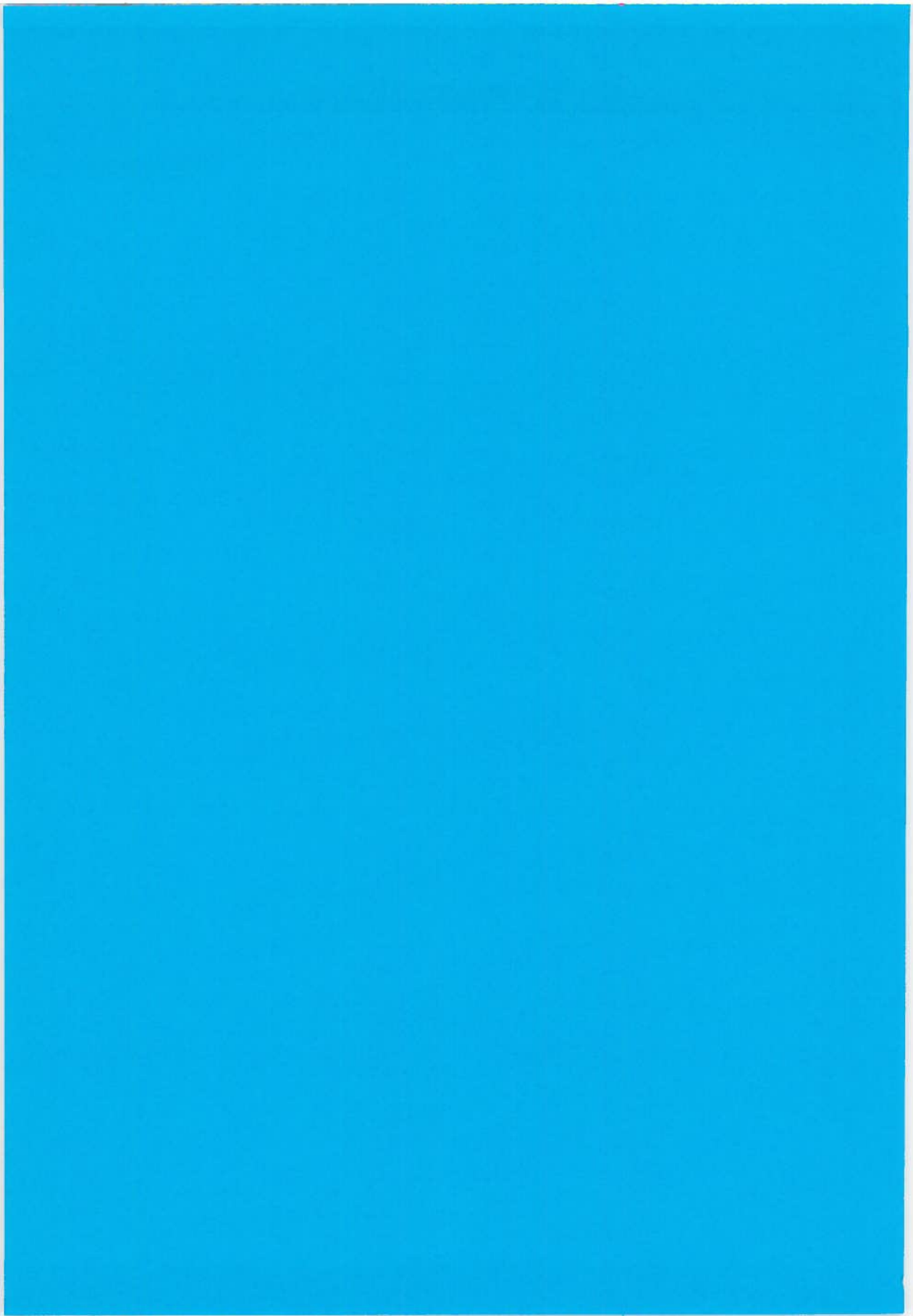
Paper III



What Determines Echogenicity in a General Population? The Tromsø Study

Henrik Schirmer, MD, Per Lunde, MD, and Knut Rasmussen, MD, PhD, *Tromsø, Norway*

Background: **It is widely recognized that in some people it is difficult or impossible to acquire adequate measurements of cardiac performance and anatomy by any echocardiographic technique. We used our population-based screening to determine the characteristics of such unmeasurable subjects.**

Method: **In a sample of 3287 subjects aged 25 to 85 years, we used standard 2-dimensional guided M-mode echocardiography and pulsed and color Doppler to assess left ventricular (LV) structure and function.**

Results: **Of 3287 subjects only 0.4% could not be measured by any technique. In 2794 subjects M-mode registrations of good quality were obtained, which allowed calculation of LV mass and LV ejection fraction. Those in whom measurements could not be obtained had a significantly higher age, body mass index, blood pressure, waist/hip ratio, and were more likely to smoke, be a man, be taking antihypertensive medication, have a history of ischemic heart disease, and have a low level of physical activity.**

Conclusion: **Because subjects with high cardiovascular risk factor levels are less likely to be measurable with echocardiography, a need exists for other noninvasive diagnostic methods in these persons.** (J Am Soc Echocardiogr 1999;12:314-8.)

The introduction of echocardiography as a noninvasive tool for measurements of cardiac performance and anatomy has vastly expanded the possibilities for cardiovascular diagnostics, both in clinical decision making and research. M-mode measurements of cardiac dimensions first allowed noninvasive calculations of left ventricular mass (LVM) and ejection fraction (LVEF) with good validity.[1-3] With the introduction of 2-dimensional (2D) echocardiography, the task of performing the M-mode registrations was simplified, leading to a more extensive use of the method in clinical practice. Two-dimensional echocardiography also introduced new methods for determining LVM and LVEF. In particular, this new approach solved many of the difficulties with assessment of LVEF in patients with asymmetric motility.[4] Furthermore, the Doppler technique allowed noninvasive evaluation of valvular heart disease, decreasing the need for cardiac catheterization.[5-7]

The problem of unmeasurable subjects has been identified in large epidemiologic studies with M-mode,[8,9] but it has not been analyzed further. For 2D measurements of LVM and LVEF, the main difficulty has been that of border detection, but this has been minimized gradually as the ultrasonographic machines have improved. It remains to be seen whether the number of unmeasurable subjects will decrease as the 2D resolution increases.

Compared with 2D measurements, 2D-guided M-mode measurements have the advantage of being a quick method easily performed on-line with the present ultrasonographic technology. Although still used mostly on a research basis, 3-dimensional echocardiography and tissue imaging Doppler techniques open new possibilities for noninvasive diagnosis. These methods are even more sensitive to difficulties with image acquisition because images from several angles and more complete visualization of the total myocardium are required.

It is widely recognized that in some people it is difficult or impossible to acquire adequate measurements of cardiac dimensions by any echocardiographic technique. These subjects will constitute a source of error in any systematic use of echocardio-

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Table 1 Age and sex adjusted means (±SD) or percentage of total for measurable and unmeasurable study subjects

Variable	LV mass measurable (n = 2794)	LV mass unmeasurable (n = 493)	*P* value
Women (%)	50.8	40.2	<.0001
Age (y)	59.2 ± 10.6	64.9 ± 7.0	<.0001
Measured:			
Cholesterol (mmol/L)	6.71 ± 1.24	6.71 ± 1.24	.90
HDL cholesterol (mmol/L)	1.53 ± 0.42	1.50 ± 0.41	.06
Systolic blood pressure (mm Hg)	139.8 ± 20.7	143.7 ± 21.9	<.0001
Diastolic blood pressure (mm Hg)	79.9 ± 11.7	82.7 ± 13.1	<.0001
Body mass index (kg/m2)	25.9 ± 3.8	27.2 ± 4.9	<.0001
Waist/hip ratio	0.87 ± 0.08	0.89 ± 0.09	<.0001
Self-reported:			
Myocardial infarction (%)	5.9	8.5	.04
Angina (%)	8.8	12.4	.01
Stroke (%)	2.3	3.1	.32
Diabetes (%)	2.8	4.3	.08
Antihypertensive medication	12.9	16.7	.03
Units of alcohol intake	3.3 ± 6.0	3.2 ± 5.1	.76
Physical activity (1–4)*	1.68 ± 0.99	1.54 ± 0.88	.004
Smoking (%)	32.0 (11.4 cig)	38.4 (11.5 cig)	.007

LV, Left ventricular; *HDL*, high density lipoprotein; *DT*, deceleration time of the mitral e-wave; *cig*, average number of cigarettes per day for regular smokers only.
*Physical activity = amount of strenuous leisure-time exercise resulting in sweating or breathlessness during an average week; 1 = none, 2 = less than 1 hour, 3 = 1 to 2 hours, and 4 = 3 hours or more per week.

graphy. The goals of this study were to estimate the efficacy of echocardiography in a screening setting, to estimate the determinants of nonmeasurability, and to determine the ways in which cardiovascular disease (CVD) influences measurability.

METHODS

Study Patients

The Tromsø Study began in 1974 and is a prospective follow-up study of the inhabitants of the municipality of Tromsø, Norway. The fourth survey started in September 1994 and was completed in September 1995. A total of 27,159 subjects older than 24 years (77% of the eligible population) attended the first visit. A protocol similar to that of the previous surveys and to the Norwegian Counties Study[10-13] was followed, and approved by the regional ethical committee on human research. The examination included standardized measurements of blood pressure, weight, height, and nonfasting serum lipids. Two self-administered questionnaires covered previous and present diseases and symptoms, use of drugs, smoking, alcohol intake, physical activity, and length of education. All subjects who were aged 55 to 74 years were invited to a second visit for more extensive screening along with a randomly selected 5% to 10% of persons from the other age-groups. A total of 6891 subjects attended the second visit, 98% of whom met at the first screening. Because of high attendance rates at the first screening in these age groups, the second screening comprised 88% of those initially invited. Of these, 3287 subjects were randomly selected to undergo an echocardiographic examination. These 3287 did not differ in baseline characteristics from the total sample attending the second screening.

Echocardiography

All subjects were examined by 1 medical doctor (n = 2362) or 2 expert cardiologists (n = 432) with a VingMed CFM 750 ultrasonographic system (VingMed Sound A/S, Horten, Norway). The subjects were examined in a supine, left lateral position with a combined 3.25-MHz mechanical and 2.5-MHz Doppler probe. The 20-minute echocardiographic examination was performed with the standard apical and parasternal long- and short-axis views; if unsuccessful, a subcostal view was attempted. Left ventricular dimensions were measured on-line from standard 2D-guided M-mode registrations according to the recommendations from the American Society of Echocardiography,[14] with EchoPac software (VingMed Sound A/S). Registrations were regarded as adequate for measurement if both margins of septum and the posterior wall were visible throughout 1 heart cycle. Good quality M-mode registrations were obtained in 2794 (85%) of subjects, making LVM and LVEF calculations possible. In addition, valvular disease was evaluated by pulsed, continuous, and 2D color Doppler.[5-7] Left ventricular diastolic function was evaluated by Doppler of mitral flow, with the sample volume of the pulsed Doppler recordings placed just below the mitral annulus between the tips of the mitral leaflets where max-

Table 2 Prediction of measurability with M-mode echocardiography

Variable	Odds ratio (95% CI) for nonmeasurability (N = 2794, cases = 493)
Age (10 y)	2.09 (1.81-2.43)
Body mass index (4.0 kg/m^2)	1.31 (1.17-1.46)
Smoking (yes = 1, no = 0)	1.64 (1.32-2.04)
Waist/hip ratio (0.08)	1.26 (1.10-1.44)
Systolic blood pressure (21.1 mm Hg)	1.23 (1.02-1.25)
Gender (male = 1, female = 2)	0.76 (0.58-0.99)
ROC area	0.72

Hosmer Lemeshow Goodness-of-fit test: $P = .62$. Odds ratios adjusted for all other variables in the table. For continuous variables, odds ratios are presented for 1 SD increase. Variables are listed according to decreasing χ^2 score in the model. A history of myocardial infarction, angina, diabetes, and antihypertensive medication were left out of the model because they did not contribute significantly. *CI*, Confidence interval; *ROC*, receiver operating characteristics.

imal flow velocity in early diastole was recorded.[15] Recordings were regarded as optimal when a clear delineation of the maximal flow velocity curve was achieved in 3 or more succeeding heart beats.

Statistics

Adjusting for sex and age in the general linear model procedure in the SAS statistical package,[16] analysis of covariance was used to contrast differences between measurable and unmeasurable subjects. All measured variables were entered into a stepwise forward logistic regression analysis of measurability. All variables with a significant difference between groups were entered into a multiple logistic regression analysis. Only significant predictors were kept in the final model. Differences between sexes were tested with an multiplicative interaction term between each variable and sex. A 2-sided value of $P < .05$ assessed statistical significance.

RESULTS

Of the 3287 subjects who were examined with echocardiography, only 12 (0.4%) subjects had no measurements registered after the echocardiographic screening. Examinations of a quality allowing estimation of LVM and LVEF occurred with 2794 (85%) subjects (Table 1), whereas they did not occur with 493 subjects. The measurable subjects were younger, more likely to be women, and had lower systolic and diastolic blood pressures, body mass index, and waist/hip ratio. The unmeasurable subjects more frequently had a history of myocardial infarction or angina, or were taking antihypertensive medication. They also had a lower level of physical activity and a higher frequency of daily smoking.

In a multivariate logistic regression analysis, only age, sex, body mass index, daily smoking, waist/hip ratio, and systolic blood pressure were independent predictors of measurability (Table 2). In an overall receiver operating characteristics analysis the area was 0.72 (95% confidence interval [CI] 0.69 to 0.75), implying that a randomly chosen unmeasurable patient would have higher overall values of the explanatory variables compared with a randomly chosen measurable control patient in 72 of 100 cases. In addition, no gender interaction was found with any of the explanatory variables in the model.

The subjects with CVD (a history of myocardial infarction, angina, or stroke) had a higher prevalence of nonmeasurability than those without CVD (23.4% versus 13.6%; $P_{\chi^2} < .001$). When adjusted for differences in the independent predictors of measurability, the subjects with CVD were no longer significantly different regarding measurability, from those without CVD (17.7% versus 14.4%; $P_{\chi^2} = .06$).

This was contrasted by Doppler measurements of mitral flow in which 98.5% of the subjects had a measurable deceleration time of the E-wave. Age and body mass index were the only significant independent predictors of the 48 subjects without measurable deceleration time of the E-wave. For a 10-year increase in age, the odds ratio for being unmeasurable was 1.60 (CI 1.08 to 1.38). Likewise the odds ratio for an 4 kg/m^2-increase in body mass index was 1.33 (1.04 - 1.70). The aortic valve was visualized by either M-mode or Doppler in 94.8% of subjects. Nonmeasurability was predicted independently only by age and body mass index as previously explained.

DISCUSSION

To our knowledge, this is the first study to analyze the independent relationship of predictors of subjects not measurable by echocardiography. Only 0.4% had no measurements registered after an echocardiographic examination, showing the versatility of the technique as a global screening instrument. For specific measurements, our study shows that in a screening situation with limited time for examination, M-mode measurements of LVM and LVEF were possible in 85% of the subjects. Age, body mass index, smoking, and waist/hip ratio, in descending order, were the most important predictors of nonmeasurability. These variables also explained the lower frequency of measurability for most of the subjects reporting a history of CVD.

This success rate is similar, but significantly lower (85.0% versus 89.5%; $P_{\chi^2} < .0001$), to that reported

from 2D measurements of LVEF by McDonagh et al,[17] who had registrations good enough for tracing of LV internal wall margins in 1479 of 1653 subjects. However, their population was 10 years younger; this age difference probably explains most of the difference in efficiency.

M-mode is a fast on-line procedure compared with tracing of wall margins. The M-mode method can now be performed with inexpensive ultrasonographic machines, which also are accessible for developing countries and centers with small budgets. In the Framingham study in which a 2.25-MHz transducer was used for M-mode recordings, 20.3% had unmeasurable echocardiograms,[8] implying a lower efficiency, most likely caused by the less sophisticated ultrasonographic equipment that was available in 1979 to 1983. Reports of echocardiography in large populations show inadequate recordings in a range from 7% to 20% for 2.5-MHz transducers with increasing failure rate in older and larger studies.[8,18-20] In studies of hypertensive subjects, transducers with a 3- to 3.5-MHz frequency have most often been used, and adequate recordings could not be obtained in 12% of such subjects.[9,21] In our study a 2.5-MHz transducer was available, but it was not used because the 3.5-MHz transducer provided better resolution, thereby leaving unanswered the question of the effect of changing frequency when inadequate recordings are obtained.

Of the Doppler measurements, deceleration time of the mitral E-wave gave the highest yield with a 98.5% success rate. Subjects with CVD were more likely not to be measurable because age, body mass index, and systolic blood pressure were higher among subjects with CVD. Even so, the lower echogenicity of subjects with CVD implies that less information is available for clinical decision making and for registration of epidemiologically interesting variables such as LVEF or LVM. Such lack of information will cause underestimation of the association between body mass index, age, hypertension, and echocardiographically identified diseases such as LV hypertrophy (LVH) and LV systolic dysfunction. For weaker determinants of LVH such as smoking, the increasing prevalence of unmeasurable subjects among those exposed might explain the divergence in the reported studies regarding the independent prediction of LVH.

Valve function was more easily examined by echocardiography, with unmeasurable valves in only 5.2% of the subjects for the aortic valve and in 1.5% for the mitral valve. In the population-based study by Stewart et al,[22] adequate recordings of the aortic valve were obtained in more than 99% of their more than 5000 elderly subjects. In our study the lower efficiency in visualization of the aortic valve could be attributed to the short time available for examination of each patient or to the fact that we focused mainly on left ventricular dimensions.

The design of this cross-sectional study limits our ability to draw conclusions about causal relationships of the documented associations, but some possible pathophysiologic explanations exist. Smoking is known to be the main cause of clinical or subclinical emphysema with enlarged lung volume. The air content of lung tissue causes it to be impenetrable to ultrasonic waves,[23] therefore daily smokers are more likely than nonsmokers to be unmeasurable. The increase of adipose tissue in obesity is an obstacle to ultrasonographic measurements all over the body because of the high attenuation of the ultrasound beam in adipose tissue and because of the increased distance to the organ of interest.[24,25] Age is a marker of both these changes and, in addition, accounts for emphysema in ex-smokers and detrimental effects of long-standing obesity. Waist/hip ratio is an indirect marker of the visceral obesity and may be linked to less echogenicity because of an unfavorable dislocation of the heart and because the internal fat deposits are not compressible to the same extent as the subcutaneous ones.

The independent association between smoking, body mass index, and waist/hip ratio is of little interest when examining an acutely ill patient with CVD but represents amendable causes of poor prognosis and a weaker basis for decision making. Of greater importance is the fact that echocardiographic studies will represent selected samples of subjects with lower cardiovascular risk factor levels than unmeasurable subjects and consequently will weaken the association between risk factors and pathology.

Conclusion

In a general population, measurability by echocardiography is predicted by cardiovascular risk factor levels. For M-mode echocardiography in our study, the prevalence of unmeasurable subjects was 15% of the total population. As many as 23% of subjects with CVD were not measurable with M-mode, probably because of high risk factor levels, which limited the usefulness of this method for those in highest demand. Such limits also will cause an underestimation of the prevalence estimates of pathology detectable by echocardiography. For patients with CVD in whom adequate measurements cannot be obtained, use of other modalities for diagnosing heart failure or LV hypertrophy will be needed.

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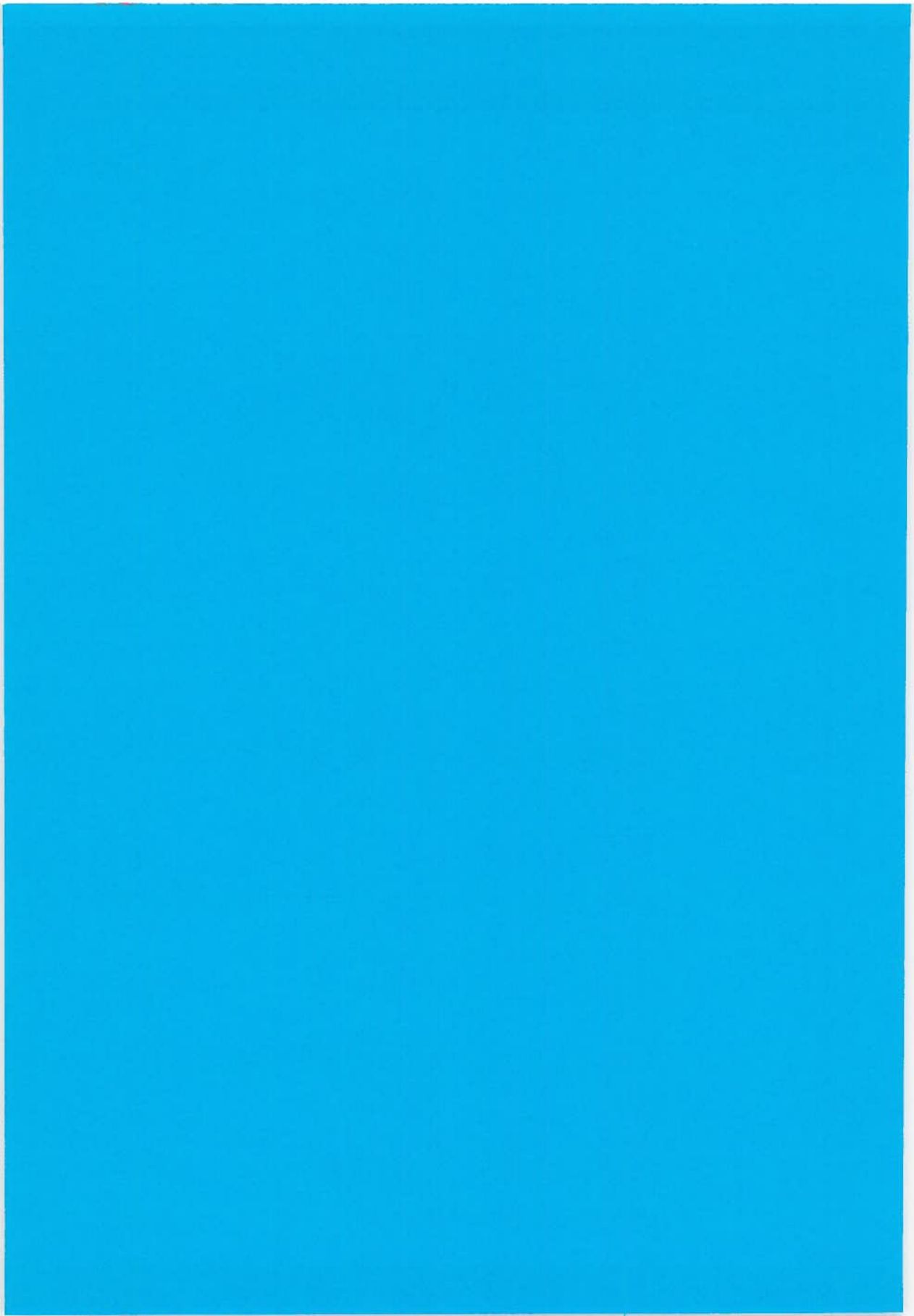
Paper IV



Mitral flow derived Doppler indices of left ventricular diastolic function in a general population.

The Tromsø study

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Abstract

Aims Left ventricular diastolic dysfunction has been proposed as the basis of heart failure with normal left ventricular systolic function. Doppler indices of mitral inflow have been widely used to diagnose this condition and have been shown to correlate well with increased left atrial pressure in patients with cardiovascular disease. We wanted to establish age specific criteria for normality of these indices in a large population and determine the association of abnormal values to age and cardiovascular disease.

Methods and Results In our sample of subjects aged 25-85 years, 3022 had pulsed Doppler measurements of mitral inflow velocities and early inflow deceleration time. The association of these indices to age and gender were established in a «healthy» reference subsample of 949 subjects.

Age specific percentiles showed significant decline by age for peak early mitral inflow velocity and the ratio of peak early and atrial inflow velocities (E/A ratio), whereas early inflow deceleration time and peak atrial inflow velocity showed a significant increase by age. According to current criteria for diastolic dysfunction, the prevalence of dysfunction decreased by age in the general population, as well as in the subgroup with cardiovascular disease. Only 7% of the variance of deceleration time was explained by cardiovascular disease or risk factors. For E/A ratio, however, 41 and 48% of the variance were explained for men and women, respectively.

Conclusion Age and gender specific criteria for normality are provided. Our data confirm the existence of a significant effect of age and gender on mitral Doppler indices of diastolic dysfunction. However, Doppler criteria for diastolic dysfunction based on these measurements probably need revision.

Condensed abstract

Diastolic heart failure has been proposed as the cause of acute heart failure in one third of acute admissions. This study presents the distribution of mitral derived Doppler indices of diastolic function in a large sample from the general population and in a large «healthy» reference subsample. Percentile derived criteria of abnormal Doppler indices and their relation to cardiovascular disease and age are provided. The prevalence of subjects identified by currently used Doppler criteria for diastolic dysfunction decreased by age in a subsample with signs or history of cardiovascular disease. Since it is known that the prevalence of heart failure increase by age, these criteria probably need revision.

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Introduction

With an increased life expectancy, heart failure has become an increasing health problem in industrialised countries[1]. Heart failure was earlier understood as pump failure or left ventricular systolic dysfunction, but several studies have shown that as much as one third of patients admitted for acute heart failure had normal left ventricular systolic function[2-4]. This group of patients consisted of elderly patients, mostly with delayed left ventricular relaxation, and some also with decreased left ventricular compliance and consequently reduced left ventricular filling dynamics. Left ventricular diastolic dysfunction has been described in terms of invasively measured abnormal pressure-volume relationships, showing an elevated left ventricular diastolic pressure curve as the common critical factor[5]. This in turn causes an elevation of left atrial pressure. Doppler indices of mitral flow have been shown to correlate well with left atrial pressure in patients with heart failure caused by coronary artery disease, but have shown little discriminative power in younger subjects, subjects with hypertrophic cardiomyopathy and in heart failure due to obesity[6,7]. Among the many Doppler indices used to describe diastolic dysfunction, the ratio of the peak early to the peak atrial mitral inflow velocities (E/A ratio) and the deceleration time of the peak early inflow (in the following termed deceleration time) have been most widely used and are recommended in the latest guidelines for diagnosing diastolic dysfunction[8,9].

For the E/A ratio values, an U-shaped relation to left atrial pressure has been described, with an overlap between normal function and diastolic dysfunction for values between 1 and 2. For E/A ratios above 2, a sensitivity of 43% and a specificity of 99% for identifying subjects with increased left atrial pressure were found[10]. Several studies have shown good sensitivity and specificity for deceleration time in identifying heart failure patients with elevated left atrial pressure[6,10], but in heart failure patients with normal systolic function the association was questionable[11]. Deceleration time has in patients with left ventricular systolic dysfunction been shown to predict a poor outcome both in symptomatic and asymptomatic heart failure patients[12], and changes in deceleration time after optimal oral therapy have been shown to identify patients with improved prognosis[13]. In patients admitted for acute myocardial infarction, deceleration time was the best independent predictor of subsequent death or development of clinical heart failure[14,15]. In less selected samples the specificity of deceleration time for identification of increased left atrial pressure is thought to be lower. Consequently, diagnostic use of Doppler indices for diagnosis of diastolic dysfunction has been advocated only for symptomatic patients with other signs of cardiovascular disease[9]. Doppler indices of left ventricular diastolic

dysfunction has also been shown to vary with age, body mass index and heart rate in selected small samples[16-20].

It is important to established to what extent these variables influence the mitral derived Doppler indices in an unselected population. This is especially important since breathlessness, an unspecific and passing experience of many subjects, is used as one of the diagnostic criteria for diastolic dysfunction[9].

Having screened a sample of 3287 subjects from the general population we had the opportunity to establish age specific percentiles of E/A ratio and deceleration time in the total sample and in a «healthy» subgroup within this sample. We also estimated the relation of these Doppler indices to age, gender, left ventricular mass, blood pressure, a history of cardiovascular disease and left ventricular ejection fraction.

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Study population and methods

The Tromsø Study was started in 1974 and is a prospective follow-up study of the inhabitants of the municipality of Tromsø, Norway. In 1994-95, a total of 27159 subjects older than 24 years, 77% of the eligible population, attended the first visit. The examination included, among others, standardised measurements of blood pressure, weight, height, non-fasting serum lipids and two self administered questionnaires, checked by trained nurses [21-26]. All subjects aged 55-74 and random 5-10% samples of the other age-groups were invited to a second visit for more extensive screening. In addition, in the age group 44-54 years, all the men who had participated in The Family Intervention trial in 1979 were invited[27]. Because of high attendency 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. A total of 6891 subjects attended the second visit, 94% of the pre-selected who met at the first visit.. At the second visit, a sample of 3287 subjects, described elsewhere, was examined by echocardiography[26]. To secure a representative sample, the additional 166 men who were invited only due to The Family Intervention trial, were excluded. In addition, subjects with atrial fibrillation or mitral stenosis were excluded (n = 44), leaving 3022 subjects with Doppler tracings adequate for measurement of both deceleration time and E/A ratio (98.2% of the eligible). Of these, 2579 had M-mode registrations of good quality making calculations of left ventricular mass and left ventricular ejection fraction possible[26].

Echocardiography

All subjects were examined by a medical doctor (HS; n = 2509) or two expert cardiologist (PL, AS; n = 513), using a VingMed CFM 750 (VingMed Sound A/S, Horten, Norway). The M-mode registrations have been described elsewhere[26]. Registrations were regarded as adequate for measurement if both margins of septum and the posterior wall were visible throughout one heart cycle. Left ventricular ejection fraction was dichotomised at ≤ 0.57, the 2.5th percentile in the total sample. In addition, valvular disease was evaluated by 2 dimensional colour Doppler for mitral insufficiency, colour M-mode for aortic insufficiency, and for mitral stenosis and pulsed or continuous Doppler for aortic stenosis[28-31].

For measurement of mitral valve flow pattern the pulsed Doppler sample volume was placed caudal to the mitral annulus between the tips of the mitral leaflets, where maximal flow velocity in early diastole was recorded[10]. The Doppler beam was aligned to produce the narrowest possible angle between the beam and the blood flow vector. When an optimal tracing of mitral flow velocity was achieved, measurements were done on-line in one heart cycle only. Among

others the following variables were measured; peak flow velocity in early diastole (E wave) and during atrial contraction (A wave), peak E/A ratio and the deceleration time of the E wave. To minimise the influence of heart rate, deceleration time was measured as the time between peak E wave and the upper deceleration slope extrapolated to the zero baseline[10].

Reproducibility

Reproducibility was evaluated in 58 consecutively recruited patients as the variability between one cardiologist (PL) and a medical doctor trained in echocardiography (HS), of the whole process from recording to on line measurement of the Doppler indices. For the E wave the mean differences ± SD were -0.001 ± 0.117, 0.025 ± 0.096 and 0.034 ± 0.078 m/sec, for intraobserver(HS), intraobserver(PL) and interobserver pairs, respectively. For the A wave, the corresponding values were -0.008 ± 0.091, 0.031 ± 0.156 and -0.003 ± 0.084 m/sec. For the E/A ratio, the values were 0.015 ± 0.29, 0.007 ± 0.28 and 0.056 ± 0.19 and for the deceleration time, -0.001 ± 0.034, -0.001 ± 0.030 and -0.009 ± 0.036 sec.

Self-reported risk factors

A history of cardiovascular disease was set to yes if one or more of the following items were reported; myocardial infarction, angina or stroke. Hypertension was defined as self-reported use of antihypertensive medication or blood pressure higher or equal to 140/90 mm Hg.

Dyspnea

At the echocardiographic examination subjects were asked whether they had health complaints or not. If yes, they were asked whether they at present had symptoms of dyspnea, either at rest or at exertion.

Reference sample

A reference sample of 949 subjects was defined as subjects without hypertension at the echocardiographic screening, no cardio-pulmonary disease or diabetes by history, weight no more than 20% above or below the Norwegian middle weight by height tables[32], heart rate below a hundred, and no evidence of valve disease by echocardiography (mitral regurgitant area less than 4 cm^2, diameter of aortic regurgitant jet less than 30% of outflow tract diameter and aortic outflow gradient less than 30 mmHg). These criteria excluded 30% of those younger than 35, gradually rising to 88% in those 70 years and older (table I). The hypertension criterion caused 73% of the exclusions, weight an additional 17% and a history of cardiovascular or

pulmonary disease 8%. The remaining were excluded due to observed valvular heart disease. Of the 875 subjects in this reference sample with measurable M-mode recordings, none had a left ventricular ejection fraction below 0.45 or left ventricular hypertrophy according to internal criteria[26].

Statistics

Adjusting for sex and age in the general linear model procedure in the SAS statistical package[33], analysis of covariance were used to contrast differences between genders. The hypothesis of an age and gender effect on each percentile of the Doppler indices of diastolic dysfunction was tested using linear regression analysis, weighted with the number of subjects in each age group. To assure meaningful percentile values, five year age groups with less than 30 subjects were merged. Only where gender had a significant independent prediction of the percentiles were the percentiles estimated for each gender. All further analysis were age adjusted. Given an U-shaped relation between diastolic dysfunction and both deceleration time and E/A ratio in earlier studies, abnormal deceleration time or E/A ratio values in the total sample were established as subjects with values below the 2.5th percentiles or above the 97.5th percentiles in the reference sample. Independent predictors of abnormal diastolic indices were estimated using logistic regression analysis. Odds ratios were estimated for one standard deviation change in continuous variables and one unit change in categorical variables. To test an alternative to an U shaped relation between indices of diastolic dysfunction and cardiovascular disease, deceleration time and E/A ratio were analysed as continuous variables in multivariate general linear models. A two sided value of $p<.05$ assessed statistical significance.

Results

General description of the study population

Characteristics of the study population is presented in table 2. In the representative sample of 3121 subjects, 3022 had measurements of both E/A ratio and deceleration time. Determinants of measurability by Doppler technique were age and body mass index, as has been described earlier[31]. 18% of the men and 10% of the women reported a history of cardiovascular disease. 30.0% were 20% or more above the Norwegian height by weight tables, and 1.5% were 20% or more below. A history of asthma was reported by 10% of women and 7% of men.

Deceleration time of early mitral inflow

Age and sex specific percentiles of deceleration time are presented both for the total sample and for the «healthy» reference sample (figure 1). In the reference sample there was a significant increase in deceleration time by age from the 2.5th percentile and upwards in men, and from above the 10th percentile in women. The percentile values were lower in women than men from the 25th to the 97.5th percentile ($p<0.05$). Otherwise, values for the total and the reference sample differed only with respect to the lower and upper 2.5% of the population.

In the total sample 61 subjects had deceleration time values below the age and sex specific 2.5th percentiles in the reference sample. These subjects were independently predicted by a history of myocardial infarction, systolic blood pressure and low left ventricular ejection fraction (table 3).

For the 91 subjects in the total sample with deceleration time values above the 97.5th percentile, age, high diastolic blood pressure and daily smoking were independent predictors.

In a multivariate linear regression model, only 5.4 and 7.6 % of the variance of deceleration time values were explained for men and women respectively. For men; only age, low left ventricular ejection fraction and heart rate were independent predictors of deceleration time. For women; age, left ventricular mass by height and body mass index were independent predictors (table 4).

Ratio of peak early to peak atrial mitral inflow velocities

For the E/A ratio there was no significant gender difference in any percentile. Consequently, age specific percentiles were established for both gender together (figure 2). Age specific percentiles for the total and the reference sample showed a significant decline by age for all percentiles except the 100th percentile in the total sample. The age decline was caused by a significant decline in E wave velocity and similarly a significant and stronger increase in A wave velocity by age (data not shown).

In the total sample 225 subjects had E/A ratio values below the age specific 2.5th percentile in the reference sample. The likelihood of belonging to this group was predicted independently by increasing heart rate, diastolic blood pressure and left ventricular mass by height (table 3). There were 84 subjects in the total sample with E/A ratio values above the age specific 97.5th percentile in the reference sample. These values were predicted by decreasing body mass index, heart rate, serum triglycerides and total cholesterol, presence of mitral insufficiency, low left ventricular ejection fraction and a history of myocardial infarction.

In a linear regression model 41 and 48% of the E/A ratio variance was explained, for men and women, respectively (table 5). Age, mitral and aortic insufficiency and low left ventricular ejection fraction predicted the largest independent variation in E/A ratio values, but because of low prevalence of valvular heart disease and low ejection fraction, heart rate and body mass index explained a greater proportion of the total variance. The gender difference in predicted change was only significant for low ejection fraction, mitral insufficiency and total cholesterol.

Deceleration time and E/A ratio relations

To test whether the observed increase in deceleration time and decrease in E/A ratio values by age was linked in «healthy» subjects, the mean E/A ratio was estimated for each decentile of deceleration time in the reference sample (figure 3). As shown, low E/A ratio values were linked to high deceleration time values, independently of age ($p < 0.0001$), and vice versa, even in this «healthy» reference sample.

Interestingly, heart rate was associated with both high and low abnormal E/A ratio values, but not with abnormal deceleration time values, indicating that the technique used minimises the effect of heart rate on deceleration time measurements, as described by Gianuzzi et al.[10].

As indicated by the modest odds ratios for most independent predictors of abnormal diastolic indices, few of the groups identified by the independent predictors had mean values of deceleration time or E/A ratio significantly different from the «healthy» reference sample, and even when significant, the means for the groups were placed well within the 95% distribution of the «healthy» reference sample.

Relation to age for currently used deceleration time and E/A ratio criteria for diastolic dysfunction

Subjects were identified with E/A ratio and deceleration time criteria according to the proposed guidelines from The European Study Group[9] for diagnosing diastolic dysfunction with an abnormal filling pattern (figure 4). There was a bimodal change in prevalence by age using the

Doppler criteria alone. The bimodal change in prevalence was even more pronounced in the sample with a history or signs of cardiovascular disease, i.e. hypertension, valvular heart disease, left ventricular ejection fraction ≤ 0.57 or left ventricular hypertrophy.

Only one 70 year old subject with abnormal filling pattern was identified with symptoms of dyspnea in addition to signs or a self-reported history of cardiovascular disease. Using different fixed cut-off values for E/A ratio and deceleration time according to proposed guidelines for Doppler diagnosis of diastolic dysfunction with restrictive filling pattern [5,10,15], the prevalence was highest in the younger age groups and then decreased. Using the criteria for diastolic dysfunction suggested by Nishimura et al. in patients with left ventricular systolic dysfunction[15], i.e. deceleration time < 0.15 sec. or E/A ratio ≥ 2.5, the frequency of low deceleration time values fell from 13 to 6% and for high E/A ratio, from 4 to 0.2%, over a thirty years age span. These findings were not altered by restricting the sample to symptomatic subjects with cardiovascular disease (data not shown).

Relation to age for percentile derived deceleration time and E/A ratio criteria for diastolic abnormality

The prevalence in the total sample of deceleration time values above the sex and age specific 97.5th percentiles in the reference sample showed a significant increase by age ($p = 0.003$), see figure 5. Prevalence of deceleration time values below the age and sex specific 2.5th percentiles showed no increase by age ($p = 0.88$). For E/A ratio values there was a significant increase by age ($p < 0.0001$), but with only a moderate odds ratio for having E/A ratio values below the 2.5th percentile of 1.48 (1.26-1.74) for every 10 years increase in age due to the bimodal age distribution. This association was not significant after adjustment for other independent predictors (table 3). When restricting the analysis to the age group above 50, age was an independent predictor with an odds ratio of 1.77 (1.32-2.37) for each 10 year increase in age. Prevalence of E/A ratio values above the 97.5th percentiles did not increase by age ($p = 0.97$).

The prevalence of the combination of abnormally low E/A ratio and high deceleration time by internal criteria is shown in figure 4. The odds ratio of having both abnormally low E/A ratio and high deceleration time was 1.88 (1.17-3.01) for every 10 years increase in age in the total sample. In a multivariate model adjusted for age, only low ejection fraction and high diastolic blood pressure were independent predictors. The age adjusted odds ratios were 4.56 (1.02-20.4) and 2.09 (1.43-3.06), respectively. In the sample with a history or signs of cardiovascular disease, there was no association to age.

Discussion

Diastolic dysfunction has been established as a component of heart failure that can predict adverse outcomes[12,13]. As much as 20 to 40 % of patients admitted with acute heart failure have been shown to have normal systolic function[4], and the prevalence of heart failure with normal systolic function in the general population is thought to be higher and to increase by age[34]. Since it is questionable to assume that all patients with symptoms of heart failure and normal systolic function have diastolic heart failure[35], there is a need for a diagnostic test. Doppler measurements of mitral inflow have opened up the possibility for distinguishing non-invasively which patients that have diastolic dysfunction[5]. So far reference values have been based on small reference samples limiting the possibility for age stratification of Doppler indices that vary with age[9,36].

Based on a large representative sample from the general population, age and gender specific percentiles of Doppler indices of left ventricular diastolic function are provided.
A definite and strong impact of age is confirmed for these indices, both in the general and in the reference population.
The observed shift from a high peak E velocity with short deceleration time and a low peak A velocity, to a low E with long deceleration time and a relatively higher A by age, in both samples, implies a shift from a normal mitral filling pattern to an «abnormal» relaxation pattern as a normal phenomenon of ageing. This transition occurs independently of the presence of cardiovascular disease, hypertension, obesity and left ventricular hypertrophy, as shown in the reference sample (figure 3). Given such a shift in a «healthy» reference population, it is questionable whether these Doppler indices alone signifies pathology in an individual subject.
The validity of our results is good due to the use of a representative sample from a general population with a large age span and a high attendency rate. The reliability of measurements from independently recorded heartbeats is good, and the reliability is further strengthened by 83% of the examinations being done by one observer. There was no systematic measurement variability invalidating the data, but the large unsystematic variability weakens the chance of finding associations between these Doppler indices and possible explanatory variables. The large unsystematic variability also hampers the use of these Doppler indices to detect change in the individual patient.
In the general population, a high prevalence of subjects fulfilling the currently used E/A ratio and deceleration time criteria for diastolic dysfunction, was found (figure 4). As expected, the prevalence was higher in subjects with signs or history of cardiovascular disease.

Contrary to what should be expected, the prevalence of subjects fulfilling the currently used criteria for stage III and IV diastolic dysfunction decreased with age, both in the total sample and in samples with an a priori higher likelihood of diastolic dysfunction. This may imply that the currently used deceleration time and E/A ratio criteria for left ventricular diastolic dysfunction has a low specificity for pathology, especially in the population below the age of 50.

The high prevalence of abnormal diastolic filling pattern below the age of 50, is not present when using our internal percentile derived criteria for combined abnormally low E/A ratio and high deceleration time in the total sample (figure 4). The cause of this discrepancy is mainly the different span of age groups. The use of large age spans as in the currently used criteria, will cause misclassification of these Doppler values as abnormal due to the strong impact of age on the values even within each age span.

As shown in table 4 and 5, age is by far the strongest independent predictor of both Doppler parameters and is independent of disease or risk factor status as shown in figure 1 and 2. On the other hand, cardiovascular risk factors and disease are most strongly associated with different ends of the distribution as shown in table 3, supporting the recognised U-shaped relation of these Doppler indices to cardiovascular pathology.

Our percentile derived criteria may somewhat improve the specificity of identifying subjects with diastolic dysfunction, but the low odds ratios for subgroups such as in patients with low ejection fraction, may indicate a low prevalence of diastolic dysfunction in the subgroups or a low specificity for diastolic dysfunction. The criteria should therefore be validated in unselected samples of symptomatic patients against an invasive gold standard before they are put into general diagnostic use.

In the current guidelines for diagnosis of diastolic dysfunction, other Doppler indices such as the ratio of the duration of atrial reverse of lung vein flow to mitral atrial inflow time are put as alternatives, and the use of a combination of several indices is advocated[9]. Recently, colour M-mode and tissue Doppler has been introduced as new diagnostic techniques for diagnosing diastolic dysfunction[37,38]. This gives a wide choice of methods of diagnosing diastolic dysfunction. As pointed out by Caruana et al, however, there is poor overlap between groups identified by these measures and the likelihood of diagnosing diastolic dysfunction varies considerably between methods[39]. Before these techniques can be applied generally, their diagnostic accuracy, individually or in combination, should be established in population based samples of symptomatic subjects without systolic dysfunction.

Conclusion

Our results indicate that fixed cut-off values for deceleration time and E/A ratio, as used in current guidelines, are not suitable for diagnosis of diastolic dysfunction in a general population. This does not preclude the usefulness of these measurements in carefully selected patients or that other Doppler indices may have better diagnostic performance. We have developed new age specific Doppler indices, which are statistically more meaningful, but even these showed only moderate associations to disease. Before being used for diagnosis of isolated diastolic dysfunction the internal criteria should be validated against an invasive gold standard and against prospective data both in the general population and in symptomatic subgroups.

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Table 1. Age and gender distribution of the total and reference sample.

Gender \ Age group	25-34	35-44	45-49	50-54	55-59	60-64	65-69	70 -	Total
Men total sample	59	62	33	37	384	338	278	255	1446
Men ref. sample	35	35	31		129	106	55	32	423
Women total sample	54	98	46	45	402	313	343	275	1576
Women ref. sample	44	67	33	30	153	106	63	30	526

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Table 2.

Age adjusted means ± SD or percent of total for men and women in the total sample.

Variable	Men n = 1446	Women n = 1576	p value
Age (years)	60.5 ± 10.2	60.3 ± 10.4	0.74
Measured:			
Cholesterol (mmol/l)	6.45 ± 1.16	6.87 ± 1.29	< 0.0001
HDL cholesterol (mmol/l)	1.42 ± 0.38	1.67 ± 0.41	< 0.0001
Triglycerides (mmol/l)	1.57 ± 0.93	1.43 ± 0.78	< 0.0001
Systolic blood pressure (mm Hg)	141.3 ± 19.9	139.6 ± 22.1	0.02
Diastolic blood pressure (mm Hg)	81.5 ± 11.5	78.7 ± 12.2	< 0.0001
Body mass index (kg/m^2)	26.0 ± 3.4	26.0 ± 4.5	0.95
Heart rate pr minute	71.4 ± 12.7	76.1 ± 12.1	< 0.0001
Doppler of mitral flow:			
Early inflow deceleration time (sec)	0.206± 0.044	0.196± 0.042	< 0.0001
Peak early inflow velocity (m/s)	0.66 ± 0.15	0.70 ± 0.16	< 0.0001
Peak atrial inflow velocity (m/s)	0.67 ± 0.16	0.72 ± 0.18	< 0.0001
E/A ratio	1.04 ± 0.38	1.03 ± 0.34	0.19
Valvular heart disease:			
Aortic stenosis (%)	0.3	0.4	0.43
Aortic insufficiency (%)	2.3	2.9	0.37
Mitral insufficiency (%)	1.9	3.4	0.01
M mode measurements:			
Left ventricular ejection fraction	0.73 ± 0.09	0.76 ± 0.08	< 0.0001
Left ventricular mass by height (g/m)	114.5 ± 35.4	89.3 ± 25.5	< 0.0001
Self-reported:			
Myocardial infarction (%)	9.2	3.3	< 0.0001
Angina (%)	10.8	7.8	0.004
Stroke (%)	2.8	2.0	0.15
Diabetes (%)	3.4	2.5	0.14
Dyspnea (%)	5.2	5.2	0.94
Antihypertensive medication	13.4	13.3	0.90
Smoking (%)	34.3	30.5	0.02

E/A = the ratio of peak early and atrial inflow velocities. HDL = High density lipoprotein.

Table 3. Independent predictors of abnormal early mitral inflow deceleration time and abnormal ratio of peak early to peak atrial mitral inflow velocities values in a general population.

Variable	Odds ratios and 95% CI for DT below 2.5th %	Odds ratios and 95% CI for DT above 97.5th %	Odds ratios and 95% CI for E/A below 2.5th %	Odds ratios and 95% CI for E/A above 97.5th %
Age (10 years)	0.79 (0.59-1.05)	1.43 (1.09-1.86)	1.19 (0.99-1.44)	0.97 (0.77-1.23)
Daily smoking		1.85 (1.20-2.84)		
Myocardial infarction	3.39 (1.49-7.72)			3.22 (1.51-6.91)
LV ejection fraction ≤ 0.57	9.43 (4.01-22.2)			3.46 (1.23-9.72)
Diastolic BP (SD)		1.47 (1.21-1.79)	1.51 (1.28-1.78)	
Systolic BP (SD)	1.40 (1.05-1.86)			
Heart rate (SD)			1.86 (1.59-2.17)	0.39 (0.29-0.53)
LV mass by height (SD)			1.30 (1.12-1.51)	
Mitral insufficiency				4.73 (2.08-10.8)
Body mass index (SD)				0.70 (0.51-0.95)
Triglycerides (SD)				0.60 (0.39-0.90)
Total cholesterol (SD)				0.73 (0.54-0.99)
ROC area	0.73	0.67	0.77	0.83

DT = early mitral inflow deceleration time, E/A = the ratio of the peak early to peak atrial mitral inflow velocities, LV = left ventricular, ROC = Receiver Operating Characteristics[40].
Multivariate odds ratios with 95% confidence interval for having values below the 2.5th or above the 97.5th percentile in the reference sample, for one SD change in continuous variables or one unit in dichotomous variables. Gender did not contribute significantly in any of these models, nor change the odds ratio of the variables in the models significantly.

Table 4. Independent predictors of early mitral inflow deceleration time in a general population.

Variable	Men		Women		p value
	predicted change (sec)	p value	predicted change (sec)	p value	gender difference
Age (10 years)	0.009	< 0.0001	0.009	< 0.0001	0.83
LV ejection fraction ≤ 0.57	- 0.021	0.002	0.005	0.56	0.02
LV mass by height	0.001	0.32	0.005	< 0.0001	0.002
Body mass index	- 0.0002	0.88	- 0.003	0.007	0.11
Heart rate	0.003	0.02	0.001	0.20	0.31
r^2 total model (%)	5.4		7.6		

LV = left ventricular. Change per SD for continuous variables.

Table 5. Independent predictors of ratio of peak early to peak atrial mitral inflow velocities in a general population.

Variable	Men		Women		p value gender difference
	predicted change	p value	predicted change	p value	
Age (10 years)	- 0.18	< 0.0001	- 0.17	< 0.0001	0.42
Heart rate (SD)	- 0.10	< 0.0001	- 0.09	< 0.0001	0.73
Mitral insufficiency	0.65	< 0.0001	0.14	< 0.0001	< 0.0001
Diastolic blood pressure (SD)	- 0.04	< 0.0001	- 0.03	< 0.0001	0.33
Body mass index (SD)	- 0.04	< 0.0001	- 0.04	< 0.0001	0.28
LV ejection fraction $\leq$ 0.57	0.15	0.002	- 0.16	0.01	< 0.0001
Triglycerides (SD)	- 0.02	0.01	- 0.01	0.05	0.65
Aortic insufficiency	0.18	0.002	0.10	0.02	0.23
Smoking	- 0.04	0.02	- 0.03	0.06	0.52
Total cholesterol (SD)	0.01	0.44	- 0.03	0.0005	0.005
r^2 total model (%)	41		48		

LV = left ventricular. Variables are listed according to decreasing F value for men in the general linear model analysis.

Accepted for publication in European Heart Journal December 17th 1999

Figure 1. Age and sex specific percentiles of the E wave deceleration time for the total sample (above) and the «healthy» reference sample (below).

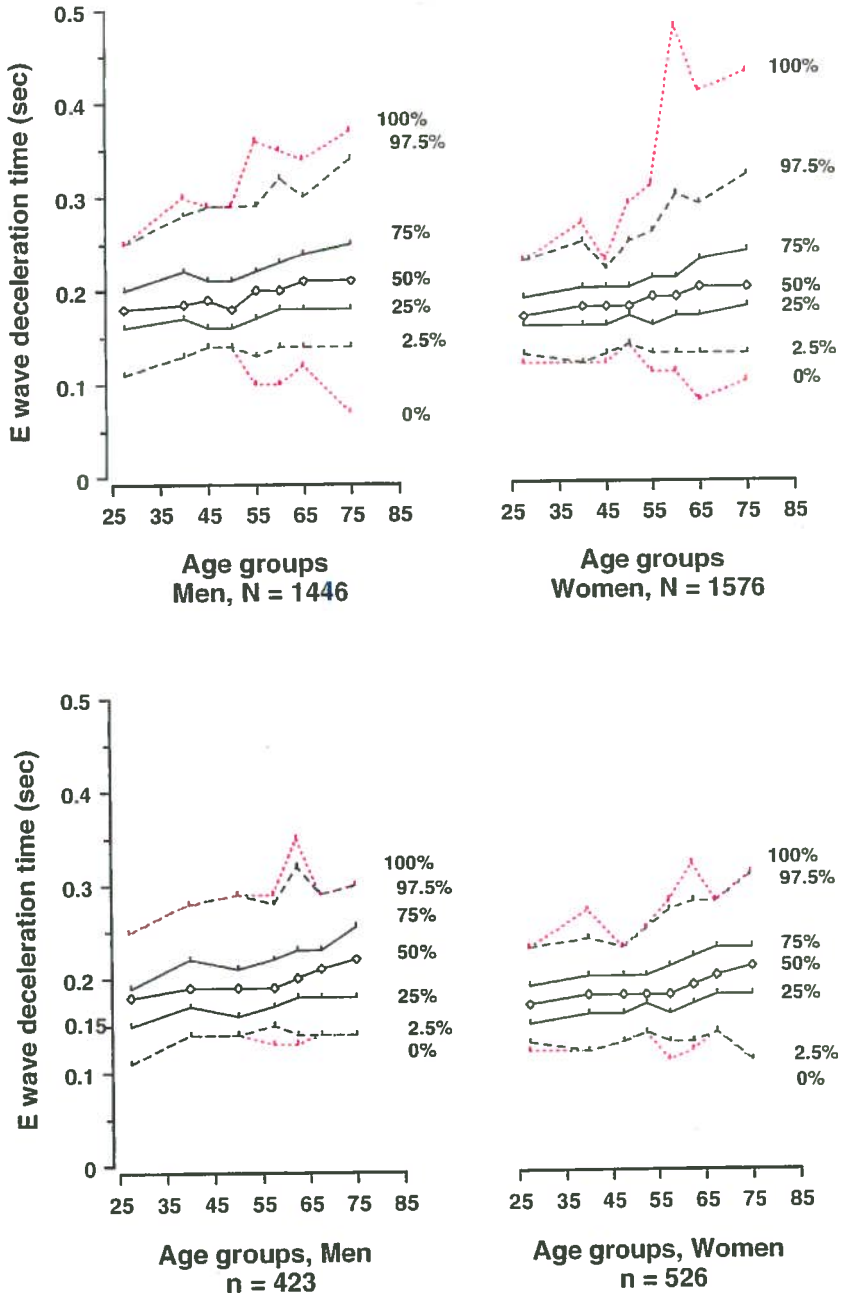


Figure 2. Age specific percentiles for E/A ratio in total and reference sample.

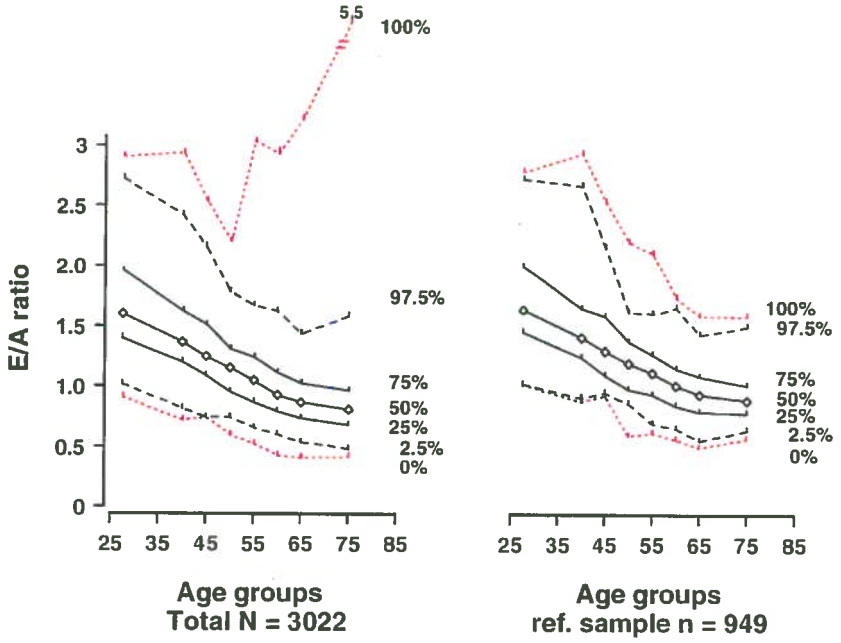
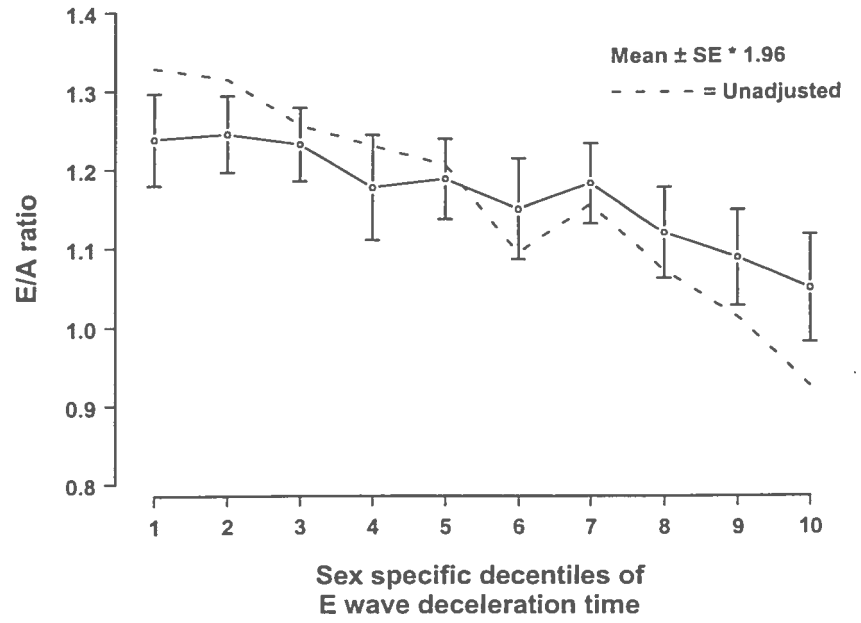


Figure 3. Age adjusted mean E/A ratio for increasing decentiles of E wave deceleration time in the reference sample with 1.96 * SE. Unadjusted values as stapled lines.



Accepted for publication in European Heart Journal December 17th 1999

Figure 4. A comparison of the age specific prevalence of Doppler diagnosed diastolic dysfunction with abnormal filling pattern according to Doppler criteria from the European Society of Cardiology 1998 and according to internal percentile derived criteria for abnormal low E/A ratio and high deceleration time in the total sample (black) and in a sample with signs or history of cardiovascular disease (red)[9].

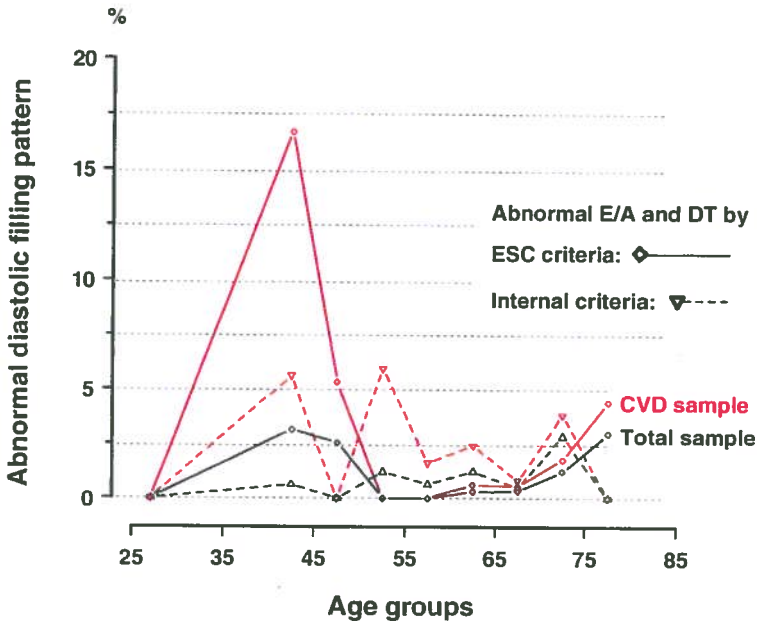
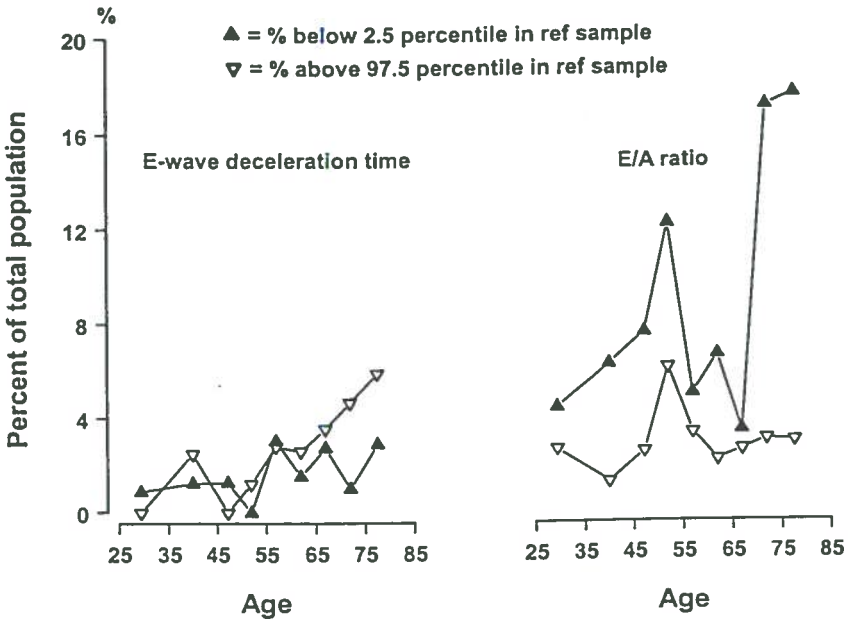


Figure 5. Prevalence in the total sample of subjects with e-wave deceleration time values (left) or E/A ratio values (right) below or above the 2.5th or 97.5th percentile in the reference sample.

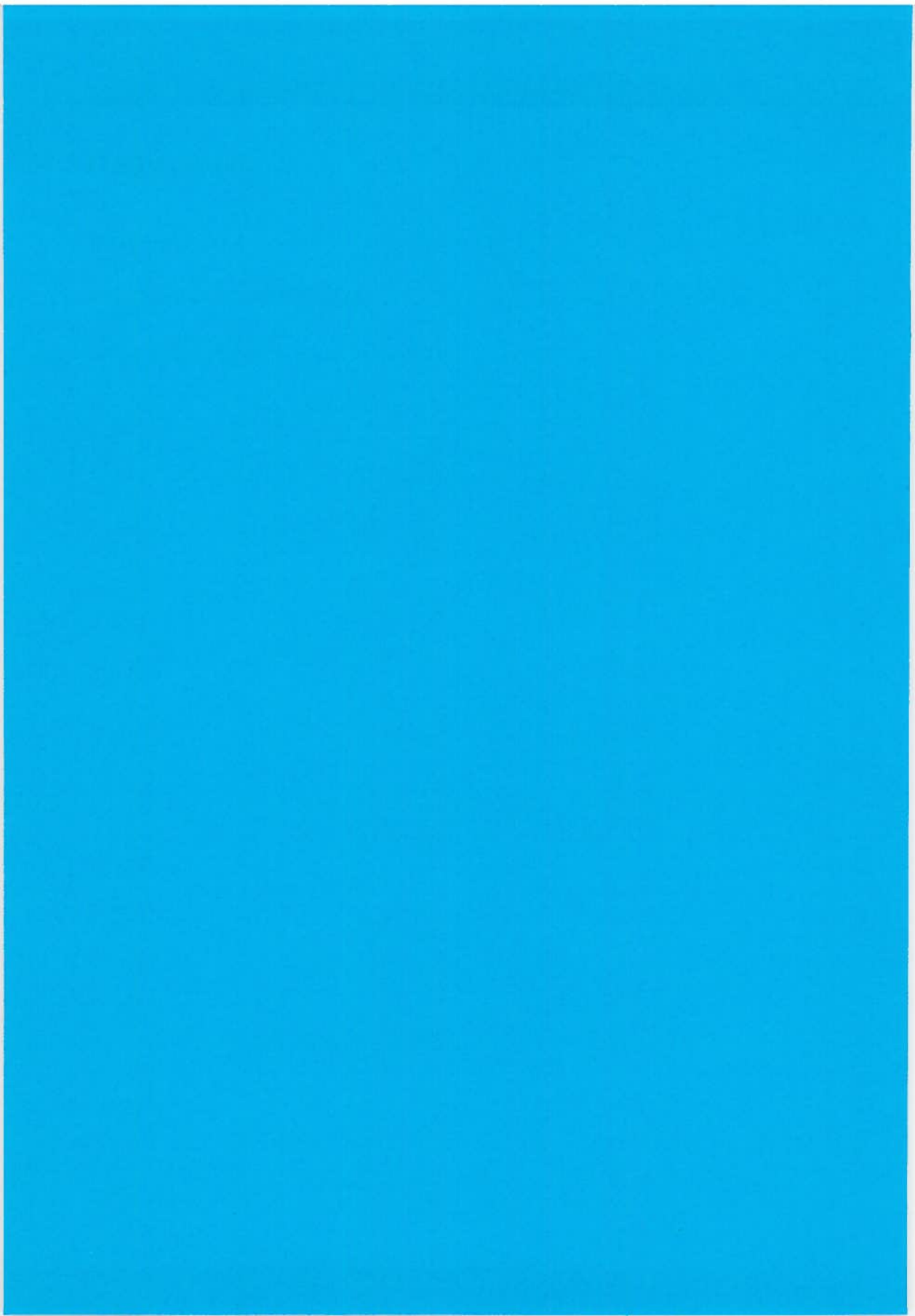


Appendix 1

Questionnaires:

Original Norwegian Versions

English translations



Innbydelse til

HELSEUNDERSØKELSEN

Fødselsdato Personnr. Kommune Kretsnr.

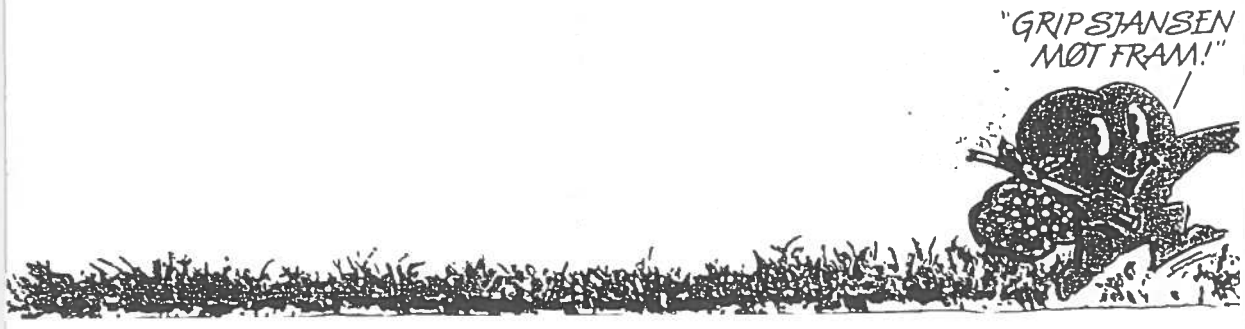
Velkommen til helseundersøkelsen i Tromsø!

Helseundersøkelsen kommer nå til Tromso. Tid og sted for frammote 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 frammotet blir så fullstendig som mulig. Vi håper derfor at du har mulighet til å komme. Mot 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 Tromso
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 daglrøykere 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

English translation of invitation with the first questionnaire used in the health survey in Tromsø 1994/95

Translation based on translations by Kevin McCafferty and Anne Clancy

HEALTH SURVEY INVITATION

"This is your chance"

Date of birth Social security No.

Municipality Electoral ward No.

Welcome to the Tromsø Health Survey!

The Health Survey is coming to Tromsø. This leaflet will tell you when and where. You will also find information about the survey in the enclosed brochure.

We would like you to fill in the form overleaf and take it with you to the examination.

The more people take part in the survey, the more valuable its results will be. We hope, therefore, that you will be able to come. Come along even if you feel healthy, if you are currently receiving medical treatment, or if you have had your cholesterol and blood pressure levels taken recently.

Yours sincerely,
Municipal Health Authorities
Faculty of Medicine - University of Tromsø
National Health Screening Service

"This is a real opportunity — Take it!"

Your own health

What is your current state of health?
Tick one box only.

Poor	☐
Not so good	☐
Good	☐
Very good	☐

Do you have, or have you ever had:

	YES	NO	Age first time
Myocardial infarction	☐	☐	_____ years
Angina pectoris	☐	☐	_____ years
Stroke/ brain haemorrhage	☐	☐	_____ years
Asthma	☐	☐	_____ years
Diabetes	☐	☐	_____ years

Do you take medicine for high blood pressure?

At the moment	☐
Used to, but not any longer	☐
Never have	☐

Have you during the last year suffered from pains and/or stiffness in muscles and joints that have lasted continuously for at least 3 months?

YES ☐ NO ☐

Have you in the last two weeks felt:

	No	A little	A lot	Very much
Nervous or worried?	☐	☐	☐	☐
Anxious?	☐	☐	☐	☐
Secure and calm?	☐	☐	☐	☐
Irritable?	☐	☐	☐	☐
Happy and optimistic?	☐	☐	☐	☐
Down/depressed?	☐	☐	☐	☐
Lonely?	☐	☐	☐	☐

Smoking

Did any of the adults at home smoke while you were growing up? YES ☐ NO ☐

Do you now, or have you previously, lived with daily smokers after your 20th birthday?

YES ☐ NO ☐

If "YES", for how many years in all? ____Years

How many hours a day do you normally spend in smoke-filled rooms? _____Hours
Put 0 if you do not spend time in smoke-filled rooms.

Do you yourself smoke:	YES	NO
Cigarettes daily?	☐	☐
Cigars/cigarillos daily?	☐	☐
Pipe daily ?	☐	☐

If you previously smoked daily, how long is it since you stopped? _____ Years

If you smoke daily at the moment, or have smoked before:

How many cigarettes do you smoke/did you smoke per day? _____ Cigarettes

How old were you when you began smoking daily? Age _____ Years

How many years in all have you smoked daily? _____ Years

Exercise

How has your physical activity in leisure time been during this last year? *Think of your weekly average for the year. Time spent going to work counts as leisure time.*

	Hours pr. week None	Less than 1	1-2	3 or more
Light activity (*not sweating or out of breath*)	☐	☐	☐	☐
Hard activity (*sweating/ out of breath*)	☐	☐	☐	☐

Coffee

How many cups of coffee do you drink daily? *Put 0 if you do not drink coffee daily.* Cups ☐☐☐

Boiled coffee (i.e., grind boiled and allowed to draw) ☐☐☐

Other coffee ☐☐☐

Alcohol

Are you a teetotaler? YES ☐ NO ☐

How many times a month do you normally drink alcohol? *Do not count low-alcohol beer. Put 0 if less than once a month.* ____ Times

How many glasses of beer, wine or spirits do you normally drink in a fortnight? *Do not count low-alcohol beer. Put 0 if less than once a month.*

Beer Glasses	Wine Glasses	Spirits Glasses
☐☐	☐☐	☐☐

Fat

What kind of margarine or butter do you normally use on bread? *Tick one box only.*

- Don't use butter/margarine ☐
- Creamery butter ☐
- Hard margarine ☐
- Soft margarine ☐
- Butter/margarine blend ☐
- Light margarine ☐

Education/work

What is the highest level of education you have completed?

- 7-10 years primary/secondary school, modern secondary school, folk high school ☐
- Technical school, middle school, vocational.. school, 1-2 years' senior high school ☐
- A-levels/High school diploma, (3-4 years) ☐
- College/university, less than 4 years ☐
- College/university, 4 or more years ☐

What is your current work situation?

- Paid work ☐
- Full-time housework ☐
- Education, military service ☐
- Unemployed, redundant ☐

How many hours of paid work do you have pr. week? ____ Hours

Do you receive any of the following benefits?

- Sickness benefit (sick leave) ☐
- Rehabilitation benefit ☐
- Disability pension ☐
- Old-age pension ☐
- Social welfare benefits ☐
- Unemployment benefit ☐

Illness in the family

Have one or more of your parents or siblings had a heart attack or had angina (heart cramp)?

YES	NO	DON'T KNOW
☐	☐	☐

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.

Hvis du er i tvil om hva du skal svare, sett kryss i den ruten som du synes passer best.

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

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? ..... 33 _____ 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 _____ m²

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	☐	☐ 1 310
1-2 ganger i måneden	☐	☐	☐ 2
Omtrent 1 gang i uken	☐	☐	☐ 3
2-3 ganger i uken	☐	☐	☐ 4
Omtrent hver dag	☐	☐	☐ 5

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 forsok.

- 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	For	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

English translation of the second questionnaire used in the health survey in Tromsø 1994/95 for subjects younger than 70 years.

Based on translations by K. McCafferty and A. Clancy

TROMSØ HEALTH SURVEY

The main aim of the Tromsø survey is to improve our knowledge of heart and circulatory conditions in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and nervous conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses.

This form is part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are unsure about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire. ☐

Date for filling in this form: Day/Month/Year

CHILDHOOD/YOUTH

What Norwegian municipality did you live in at the age of 1 year? _____

If you did not live in Norway, give country of residence instead of municipality.

How was your family's economic situation while you were growing up?

- Very good ☐
- .Good ☐
- Difficult ☐
- Very difficult ☐

For how much of the first three years of your life

- did you live in a town/city? ____ Years
- did your family have a cat or dog in the home? ____ Years

For how much of the first 15 years of your life

- did you live in a town/city? ____ Years
- did your family have a cat or dog in the home? ____ Years

HOME

Who do you live with?

Tick once for each item and give the number of persons.

	YES	NO	Number
Spouse/partner	☐	☐	_____
Other persons over 18 years	☐	☐	_____
Persons under 18 years	☐	☐	_____

How many of the children go to day care/kindergarten/ nursery school? ____

What type of home do you live in?

- Villa/ detached house ☐
- Farm ☐
- Flat /Apartment ☐
- Terraced /semi-detached house ☐
- Other ☐

How big is your home? _____ m^2

Approximately what year was your home built? _____

	YES	NO
Has your home been insulated after 1970?	☐	☐
Do you live on the bottom floor/cellar level?	☐	☐
If "YES", is the floor laid on concrete?	☐	☐

What is the main source of heat in your home?

- Electric heating ☐
- Wood-burning stove ☐
- Central heating system using:
  - Paraffin ☐
  - Electricity ☐

	YES	NO
Do you have fitted carpets in the living-room?	☐	☐
Is there a cat in your home?	☐	☐
Is there a dog in your home?	☐	☐

WORK

If you are in paid or unpaid work, which statement describes your work best?

- I am mainly seated while working (*e.g., at a desk/assembly work*) ☐
- My work requires a lot of walking (*e.g., shop assistant, light industrial work, teaching*) ☐
- My work entails a lot of walking and lifting (*e.g., postman/woman, nurse, building work*) ☐
- I do heavy physical work (*e.g., forestry, heavy agricultural/construction work*) ☐

Do you have any influence on how your work is organised?

- No, not at all ☐
- To a small extent ☐
- Yes, to a large extent ☐
- Yes, I decide myself ☐

	YES	NO
Are you on call; do you work shifts or nights?	☐	☐

Do you do any of the following jobs (full- or part-time)?

Tick one box only for each item.	YES	NO
Driver	☐	☐
Farmer	☐	☐
Fisherman	☐	☐

YOUR OWN ILLNESSES

Have you ever had:

Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you last time?

	YES	NO	AGE
Hip fracture	☐	☐	____
Wrist/forearm fracture	☐	☐	____
Whiplash	☐	☐	____
Injury requiring hospital admission	☐	☐	____
Stomach ulcer	☐	☐	____
Duodenal ulcer	☐	☐	____
An operation for stomach/ duodenal ulcer	☐	☐	____
Throat/ neck operation	☐	☐	____

Have you you ever had, or do you still have:

Tick one box only for each item.	YES	NO
Cancer	☐	☐
Epilepsy	☐	☐
Migraine	☐	☐
Chronic bronchitis	☐	☐
Psoriasis	☐	☐
Osteoporosis	☐	☐
Fibromyalgia/fibrositis/ chronic pain syndrome	☐	☐
Psychological problems for which you have sought help	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Kidney stone	☐	☐
Appendectomy	☐	☐
Allergy and hypersensitivity:		
Atopic eczema (e.g., childhood eczema)	☐	☐
Hand eczema	☐	☐
Hay fever	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy)	☐	☐

How many times have you had a cold, influenza (flue), vomiting/diarrhoea, or similar in the last six months?

_____ times

Have you had any of these in the last two weeks?

YES	NO
☐	☐

ILLNESS IN THE FAMILY

Tick the appropriate box for relatives that have, or have ever had the following illnesses: *Tick "None" if none of your relatives have had the condition.*

	Mother	Father	Brother	Sister	Child	None
Stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Myocardial infarction before age 60	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Stomach/ duodenal ulcer	☐	☐	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐	☐	☐
Psychological problems	☐	☐	☐	☐	☐	☐
Allergy	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
-age when they got diabetes	___	___	___	___	___	___

SYMPTOMS

	YES	NO
Do you cough approximately every day of the year?	☐	☐
If "Yes": Is your cough productive ?	☐	☐
Have you had this kind of cough for as long as 3 months in each of the last two years?	☐	☐
Have you had periods of wheezing in your chest?	☐	☐
If "Yes", has this occurred: *Tick one box only for each item.*		
At night	☐	☐
In connection with respiratory infections	☐	☐
In connection with physical exertion	☐	☐
In connection with very cold weather	☐	☐
Have you noticed sudden changes in your pulse or heart rhythm in the last year?	☐	☐

How often do you suffer from sleeplessness?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

If you suffer from periods of sleeplessness, what times of the year does it affect you most?

- No particular time of year ☐
- Especially during the dark winter months ☐
- Especially during the midnight sun period ☐
- Especially in spring and autumn ☐

Have you in the last twelve months suffered from sleeplessness to the extent that it has affected your ability to work? YES ☐ NO ☐

How often do you suffer from headaches?

- Seldom/Never ☐
- Once a month or more ☐
- Once a week or more ☐
- Every day ☐

Does the thought of getting a serious illness ever worry you?

- Not at all ☐
- Only a little ☐
- Some ☐
- Very much ☐

USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness? *Tick 0 if you have not had such contact*

	Number of times the past year
To a general practitioner (GP)/ Emergency GP	____
Psychologist or psychiatrist	____
Other medical specialist (not at a hospital)	____
Hospital out-patient clinic	____
Hospital admission	____
Medical officer at work	____
Physiotherapist	____
Chiropractor	____
Acupuncturist	____
Dentist	____
Alternative medical practitioner (homoeopath, foot zone therapist, etc.)	____
Healer, Faith healer, clairvoyant	____

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines every day or almost daily? Indicate how many months you used them for. *Write 0 for items you have not used.*

Medication:	
Painkillers	____ mths
Sleeping pills	____ mths
Tranquilizers	____ mths
Antidepressants	____ mths
Allergy drugs	____ mths
Asthma drugs	____ mths
Dietary supplements	
Iron tablets	____ mths
Calcium tablets or bonemeal	____ mths
Vitamin D supplement	____ mths
Other vitamin supplements	____ mths
Cod liver oil or fish oil capsules	____ mths

Have you in the last 14 days used the following medicines or dietary supplements? *Tick one box only for each item.*

Medicines	YES	NO
Painkillers	☐	☐
Antipyretic drugs (to reduce fever)	☐	☐
Migraine drugs	☐	☐
Eczema cream/ointment	☐	☐
Heart medicine (not blood pressure)	☐	☐
Lipid lowering drugs	☐	☐
Sleeping pills	☐	☐
Tranquilizers	☐	☐
Antidepressants	☐	☐
Other drugs for nervous conditions	☐	☐
Antacids	☐	☐
Gastric ulcer drugs	☐	☐
Insulin	☐	☐
Diabetes tablets	☐	☐
Thyroxin tablets (for metabolic disorder)	☐	☐
Cortisone tablets	☐	☐
Other medicine(s)	☐	☐
Dietary supplements	**YES**	**NO**
Iron tablets	☐	☐
Calcium tablets or bonemeal	☐	☐
Vitamin D supplement	☐	☐
Other vitamin supplements	☐	☐
Cod liver oil or fish oil capsules	☐	☐

FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? _____ good friends

Do not count people you live with, but do include other relatives!

How many of these good friends do you have contact with at least once a month? _____

Do you feel you have enough good friends? YES ☐ NO ☐

How often do you normally take part in organised gatherings, e.g., sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

DIET

If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the portion packs served on planes, in cafés, etc. (i.e., 10-12g)

A catering portion is enough for about ____ slices.

What kind of fat is normally used in cooking (not on the bread) in your home?

- Creamery butter ☐
- Hard margarine ☐
- Soft margarine ☐
- Butter/margarine blend ☐
- Oils ☐

What kind of bread (bought or home-made) do you usually eat? *Tick one or two boxes!*

The bread I eat is most similar to

- White bread ☐
- Light textured brown bread ☐
- Ordinary brown bread ☐
- Coarse brown bread ☐
- Crisp bread ☐

How much (in number of glasses, cups, potatoes or slices) do you usually eat or drink daily of the following foodstuffs? *Tick one box for each foodstuff.*

	0	Less than 1	1-2	3-4	5-6	More than 6
Full cream milk (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Semi-skimmed milk (low-fat) (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Skimmed milk (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Tea (cups)	☐	☐	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐	☐	☐
Slices of bread with fish (e.g., mackerel in tomato sauce	☐	☐	☐	☐	☐	☐
- lean meat (e.g., ham)	☐	☐	☐	☐	☐	☐
- fat meat (e.g., salami)	☐	☐	☐	☐	☐	☐
- cheese (e.g. Gouda/ Norvegia)	☐	☐	☐	☐	☐	☐
- brown cheese	☐	☐	☐	☐	☐	☐
- smoked cod caviar	☐	☐	☐	☐	☐	☐
- jam and other sweet spreads	☐	☐	☐	☐	☐	☐

How many times per week do you normally eat the following foodstuffs? *Tick a box for all foodstuffs listed.*

	Never	Less than 1	1	2-3	4-5	Roughly every day
Yoghurt	☐	☐	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐	☐	☐
Breakfast cereal/ oat meal, etc.	☐	☐	☐	☐	☐	☐
For dinner						
- meat	☐	☐	☐	☐	☐	☐
- sausage/meatloaf/ meatballs	☐	☐	☐	☐	☐	☐
- fat fish (e.g., salmon/ redfish)	☐	☐	☐	☐	☐	☐
- lean fish (e.g., cod)						
- fishballs/fishpudding/ fishcakes	☐	☐	☐	☐	☐	☐
- vegetables	☐	☐	☐	☐	☐	☐
Mayonnaise, remoulade	☐	☐	☐	☐	☐	☐
Carrots	☐	☐	☐	☐	☐	☐
Cauliflower/cabbage/ broccoli	☐	☐	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐	☐	☐
Oranges, mandarines	☐	☐	☐	☐	☐	☐
Sweetened soft drinks	☐	☐	☐	☐	☐	☐
Sugarfree ("Light") soft drinks	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐
Waffles, cakes, etc.	☐	☐	☐	☐	☐	☐

ALCOHOL

How often do you usually drink	beer?	wine?	spirits?
Never, or just a few times a year	☐	☐	☐
1-2 times a month	☐	☐	☐
Roughly once a week	☐	☐	☐
2-3 times a week	☐	☐	☐
Roughly every day	☐	☐	☐

Approximately how often in the last year have you drunk alcohol that equals at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?

- Not in the last year ☐
- Just a few times ☐
- 1-2 times a month ☐
- 1-2 times a week ☐
- 3 or more times a week ☐

For approximately how many years has your alcohol comsumption been as you described above? _____ years

WEIGHT REDUCTION

About how many times have you deliberately tried to lose weight? *Write 0 if you never have.*

- before age 20 _____ times
- after age 20 _____ times

If you have lost weight, about how many kilos have you ever lost at the most?

- before age 20 _____ times _____ kg
- after age 20 _____ times _____ kg

What weight would you be satisfied with (your "ideal weight")? _____ kg

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

Never	☐
Not more than once a month	☐
Two or more times a month	☐
Once a week or more	☐

Your comments:

Thank you for helping us! Remember to post the form today!
Tromsø Health Survey

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you had your first menstruation? _____ years

If you no longer menstruate, how old were you when you stopped having menstruation? _____ years

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more? YES ☐ NO ☐

If "Yes", how many times? _____ times

If you still menstruate or are pregnant:
What date did your last menstruation begin?
day/month/year ___ / ___ / ___

Do you normally use painkillers to relieve period pains? YES ☐ NO ☐

PREGNANCY

How many children have you given birth to? _____ children

Are you pregnant at the moment? YES ☐ NO ☐ Don't know ☐

During pregnancy, have you had high blood pressure and/or proteinuria? YES ☐ NO ☐

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

If you have given birth, fill out for each child the year of birth and approximately how many months you breastfed the child.

Child:	Year of birth:	Number of months breastfed:
1	_____	_____ months
2	_____	_____ months
3	_____	_____ months
4	_____	_____ months
5	_____	_____ months
6	_____	_____ months

CONTRACEPTION AND OESTROGEN

Do you, or have you ever, used:	Now	Used to	Never:
Contraceptive pills (incl.minipill)	☐	☐	☐
A hormonal intrauterine device	☐	☐	☐
Oestrogen (tablets or patches)	☐	☐	☐
Oestrogen (cream or suppositories)	☐	☐	☐

If you use contraceptive pills, hormonal intrauterine device, or oestrogen, what brand do you currently use?

_____

If you use, or have ever used, contraceptive pills:

Age when you began taking the pill? _____ years

How many years in total have you taken the pill? _____ years

If you have given birth, how many years did you take the pill before your first child? _____years

If you have stopped taking the pill:

Age when you stopped? _____ years

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.

Hvis du er i tvil om hva du skal svare, sett kryss i den ruten som du synes passer best.

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

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 ☐ 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 sl'k 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 ..... 256 ☐ 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!

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

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 nedersl 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:

English translation of the second questionnaire used in the health survey in Tromsø 1994/95 for subjects 70 years or older.

Based on translations by Kevin McCafferty and Anne Clancy.

TROMSØ HEALTH SURVEY for the over 70s

The main aim of the Tromsø survey is to improve our knowledge of heart and circulatory conditions in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and nervous conditions. The ultimate aim is to gain an overview of the general health of the elderly population. We would therefore like you to answer the questions below.

This form is part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are unsure about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire. ☐

Date for filling in this form: Day/Month/Year

CHILDHOOD/YOUTH

What Norwegian municipality did you live in at the age of 1 year?

If you did not live in Norway, give country instead of municipality.

How was your family's financial situation while you were growing up?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

How old were your parents when they died?

- Mother _____ years
- Father _____ years

HOME

Who do you live with?
Tick one box for each item and give the number of persons.

	YES	NO	Number
Spouse/partner	☐	☐	_____
Other persons over 18 years	☐	☐	_____
Persons under 18 years	☐	☐	_____

What type of home do you live in?

- Villa/detached house ☐
- Farm ☐
- Apartment/flat in block/terrace ☐
- Terraced/semi-detached house ☐
- Other ☐

How long have you lived in your present home? ____years

Is your home adapted to your needs? YES ☐ NO ☐
If "No", do you have problems with:

- Space ☐
- Variable temperature/too cold/too warm ☐
- Stairs ☐
- Toilet ☐
- Bath/shower ☐
- Maintenance ☐
- Other (please specify) ☐

Would you like to move into a retirement home?
YES ☐ NO ☐

PREVIOUS WORK AND FINANCIAL SITUATION

Which statement best describes the type of work you did for the last 5-10 years before you retired?

- I was mainly seated while working (*e.g., desk/assembly work*) ☐
- My work required a lot of walking (*e.g., shop assistant, housewife, teaching*) ☐
- My work required a lot of walking and lifting (*e.g., postman, nurse, construction work*) ☐
- I did heavy physical work (*e.g., forestry, heavy agricultural work, heavy construction work*) ☐

Did you do any of the following jobs (full- or part-time)?
Tick one box only for each item.

	YES	NO
Driver	☐	☐
Farmer	☐	☐
Fisherman	☐	☐

How old were you when you retired? _____ years

What kind of pension do you have?

- Basic state pension ☐
- Additional pension ☐

How is your current financial situation?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

HEALTH AND ILLNESS

Has your state of health changed in the last year?

- Yes, it has got worse ☐
- No, unchanged ☐
- Yes, it has got better ☐

How do you feel your health is now compared to others of your age?

- Much worse ☐
- A little worse ☐
- About the same ☐
- A little better ☐
- Much better ☐

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you last time?

	YES	NO	AGE
Hip fracture	☐	☐	_____
Wrist /forearm fracture	☐	☐	_____
Whiplash	☐	☐	_____
Injury requiring hospital admission	☐	☐	_____
Stomach ulcer	☐	☐	_____
Duodenal ulcer	☐	☐	_____
Stomach/duodenal ulcer operation	☐	☐	_____
Throat/neck surgery	☐	☐	_____

Have you ever had, or do you still have:
Tick one box only for each item.

	YES	NO
Cancer	☐	☐
Epilepsy	☐	☐
Migraine	☐	☐
Chronic bronchitis	☐	☐
Psoriasis	☐	☐
Osteoporosis	☐	☐
Fibromyalgia/fibrositis/ chronic pain syndrome	☐	☐
Psychological problems for which you have sought help	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Recurrent urinary incontinence	☐	☐
Glaucoma	☐	☐
Cataract	☐	☐
Arthrosis (osteoarthritis)	☐	☐
Rheumatoid arthritis	☐	☐
Kidney stone	☐	☐
Appendectomy	☐	☐
Allergy and hypersensitivity		
Atopic eczema (e.g., childhood eczema)	☐	☐
Hand eczema	☐	☐
Hay fever	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy)	☐	☐

How many times have you had a cold, influenza (flue), diarrhea/vomiting, or similar in the last six months?
_____ times

Have you had any of these in the last two weeks?
YES ☐ NO ☐

ILLNESS IN THE FAMILY

Tick off relatives who have, or have ever had, any of the following conditions:
Tick "None" for conditions which none of your relatives have had.

	Mother	Father	Brother	Sister	Child	None
Stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Myocardial infarction before age 60	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Hypertension	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐	☐	☐
Arthrosis (osteoarthritis)	☐	☐	☐	☐	☐	☐
Psychological problems	☐	☐	☐	☐	☐	☐
Dementia	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
-age when they got diabetes	___	___	___	___	___	___

SYMPTOMS

	YES	NO
Do you cough daily for periods of the year?	☐	☐
If "Yes":		
Is your cough productive?	☐	☐
Have you had this kind of cough for as long as 3 months in each of the last two years?	☐	☐
Have you had periods of wheezing in your chest?	☐	☐
If "Yes", has this occurred: *Tick one box only for each item.*		
At night	☐	☐
In connection with respiratory infections	☐	☐
In connection with physical exertion	☐	☐
In connection with very cold weather	☐	☐
Have you noticed sudden changes in your pulse or heart rhythm in the last year?	☐	☐
Have you lost weight in the last year?	☐	☐
If "Yes": How many kilograms?	_____ kg	

How often do you suffer from sleeplessness?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

If you suffer from periods of sleeplessness, what times of the year does it affect you most?

- No particular time of year ☐
- Especially during the 'dark winter months' ☐
- Especially during the midnight sun period ☐
- Especially in spring and autumn ☐

Do you usually take a nap during the day? YES ☐ NO ☐

Do you feel that you normally get enough sleep? YES ☐ NO ☐

	No	A little	A lot
Do you suffer from:	☐	☐	☐
Dizziness	☐	☐	☐
Poor memory	☐	☐	☐
Lack of energy	☐	☐	☐
Constipation	☐	☐	☐

Does the thought of getting a serious illness ever worry you?

Not at all	☐
Only a little	☐
Some	☐
Very much	☐

BODILY FUNCTIONS

Can you manage the following everyday activities on your own without help from others?

	Yes	With some help	No
Walking indoors on one level	☐	☐	☐
Walking up/down stairs	☐	☐	☐
Walking outdoors	☐	☐	☐
Walking approx. 500 metres	☐	☐	☐
Going to the toilet	☐	☐	☐
Washing yourself	☐	☐	☐
Taking a bath/shower	☐	☐	☐
Dressing and undressing	☐	☐	☐
Getting in and out of bed	☐	☐	☐
Eating meals	☐	☐	☐
Cooking	☐	☐	☐
Doing light housework (e.g., washing up)	☐	☐	☐
Doing heavier housework (e.g., cleaning floors)	☐	☐	☐
Going shopping	☐	☐	☐
Taking the bus	☐	☐	☐

	Yes	With difficulty	No
Can you hear normal speech (if necessary with a hearing aid)?	☐	☐	☐
Can you read (if necessary with glasses)?	☐	☐	☐

Are you dependent on any of the following aids?

	Yes	No
Walking stick	☐	☐
Crutches	☐	☐
Walking frame/Zimmer frame	☐	☐
Wheelchair	☐	☐
Hearing aid	☐	☐
Safety alarm device	☐	☐

USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness:
Tick 0 if you have not had such contact

	Number of times the past year
To a general practitioner (GP)/ emergency GP	____
Psychologist or psychiatrist	____
Other medical specialist (not at a hospital)	____
Hospital out-patient clinic	____
Hospital admission	____
Physiotherapist	____
Chiropractor	____
Acupuncturist	____
Dentist	____
Chiropodist	____
Alternative medical practitioner (homoeopath, foot zone therapist, etc.)	____
Healer, Faith healer, clairvoyant	____

Do you have domestic help?	Yes	No
Private	☐	☐
Municipal	☐	☐

Do you receive services from the district nurse? ☐ Yes ☐ No

Are you pleased with the health care and home assistance services your municipality supplies?

	Yes	No	Don't know
Assigned family GP	☐	☐	☐
District nurse	☐	☐	☐
Home assistance	☐	☐	☐

Do you feel confident that you can receive the health care and home assistance you require if you need it?

Confident	☐
Not confident	☐
Very unsure	☐
Don't know	☐

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines every day or almost daily?
Indicate how many months you used them for.
Write 0 for items you have not used.

Medication:

Painkillers	____ mths
Sleeping pills	____ mths
Tranquillizers	____ mths
Antidepressants	____ mths
Allergy drugs	____ mths
Asthma drugs	____ mths
Heart medicine (not blood pressure)	____ mths
Insulin	____ mths
Diabetes tablets	____ mths
Thyroxin tablets (for metabolic disorder)	____ mths
Cortisone tablets	____ mths
Remedies for constipation	____ mths

Dietary supplements:

Iron tablets	____ mths
Vitamin D supplement	____ mths
Other vitamin supplements	____ mths
Calcium tablets or bonemeal	____ mths
Cod liver oil or fish oil capsules	____ mths

FAMILY AND FRIENDS

Do you have close relatives who can give you help and support when you need it? Yes ☐ No ☐

If "Yes", who can give you help?

Spouse/partner	☐
Children	☐
Others	☐

How many good friends do you have whom you can talk confidentially with and who give you help when you need it?
_____good friends
Do not count people you live with, but do include other relatives!

Do you feel you have enough good friends?
Yes ☐ No ☐

Do you feel that you belong to a community or group of people who can depend on each other and who feel committed to each other (e.g., a political party, religious group, relatives, neighbours, work place, or organisation)?

- Strong sense of belonging ☐
- Some sense of belonging ☐
- Not sure ☐
- Little or no sense of belonging ☐

How often do you normally take part in organised gatherings, e.g., sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

DIET

How many meals a day do you normally eat (dinner and smaller meals)? _____ Number

How many times a week do you eat a hot dinner? _____ Number

What kind of bread (bought or home-made) do you usually eat? *Tick one or two boxes!*

The bread I eat is most similar to

- White bread ☐
- Light textured brown bread ☐
- Ordinary brown bread ☐
- Coarse brown bread ☐
- Crisp bread ☐

What kind of fat is normally used in cooking (not on the bread) in your home?

- Creamery butter ☐
- Hard margarine ☐
- Soft margarine ☐
- Butter/margarine blend ☐
- Oils ☐

How much (in number of glasses, cups, potatoes or slices) do you usually eat or drink daily of the following foodstuffs? *Tick one box for each foodstuff.*

	0	Less than 1	1-2	3-4	5-6	6-
Milk of all types (glasses)	☐	☐	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐	☐	☐
Slices of bread with fish (e.g., mackerel in tomato sauce)	☐	☐	☐	☐	☐	☐
- cheese (e.g., Norwegia)	☐	☐	☐	☐	☐	☐
- smoked cod caviar	☐	☐	☐	☐	☐	☐

How many times per week do you normally eat the following foodstuffs? *Tick a box for all foodstuffs listed.*

	Never	Less than 1	1	2-3	4-5	Roughly every day
Yoghurt	☐	☐	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐	☐	☐
Breakfast cereal/ oat meal, etc.	☐	☐	☐	☐	☐	☐
For dinner - meat	☐	☐	☐	☐	☐	☐
- fat fish (e.g., salmon/ redfish)	☐	☐	☐	☐	☐	☐
- lean fish (e.g., cod)						
- vegetables (raw or cooked)	☐	☐	☐	☐	☐	☐
Carrots (raw or cooked)	☐	☐	☐	☐	☐	☐
Cauliflower/cabbage/broccoli	☐	☐	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐	☐	☐
Oranges, mandarines, etc.	☐	☐	☐	☐	☐	☐

WELL BEING

How content do you generally feel with growing old?

- Good ☐
- Quite good ☐
- Up and down ☐
- Bad ☐

What is your view of the future?

- Bright ☐
- Not too bad ☐
- Quite worried ☐
- Dark ☐

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you had your first menstruation? _____ years

How old were you when you stopped having menstruations? _____ years

PREGNANCY

How many children have you given birth to? _____ children

If you have given birth, fill out for each child the year of birth and approximately how many months you breastfed the child. If you have given birth to more than 6 children, note their birthyear and number of months you breastfed at the space provided below for comments.

Child:	Year of birth:	Number of months breastfed:
1	_____	_____ months
2	_____	_____ months
3	_____	_____ months
4	_____	_____ months
5	_____	_____ months
6	_____	_____ months

During pregnancy, have you had high blood pressure and/or proteinuria? Yes ☐ No ☐

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

OESTROGEN

Do you, or have you ever used oestrogen:

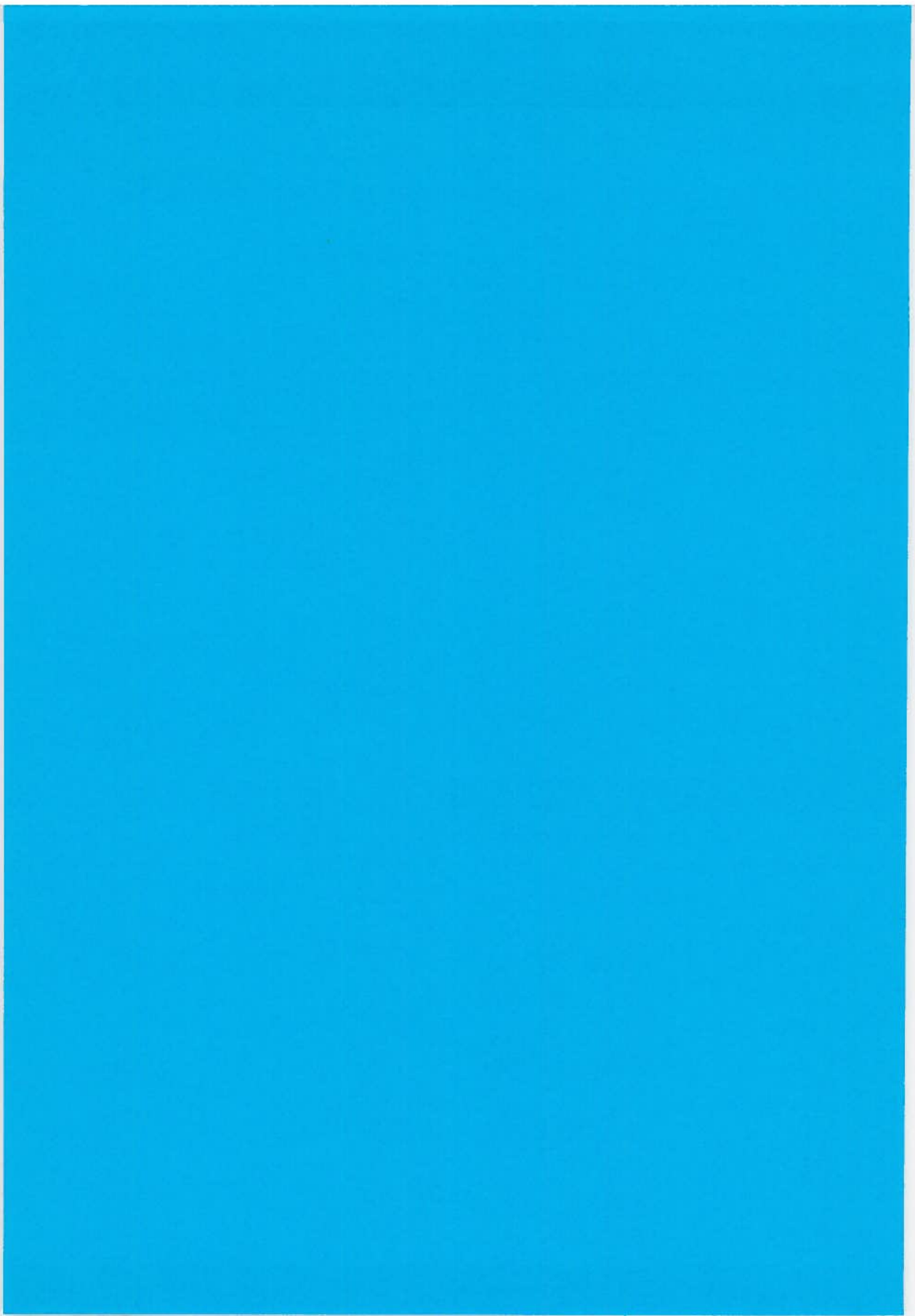
	Now	Used to	Never
Tablets or patches	☐	☐	☐
Cream or suppositories	☐	☐	☐

If you use oestrogen, what brand do you currently use?

Your comments:

Thank you for helping us! Remember to post the form today! **Tromsø Health Survey**

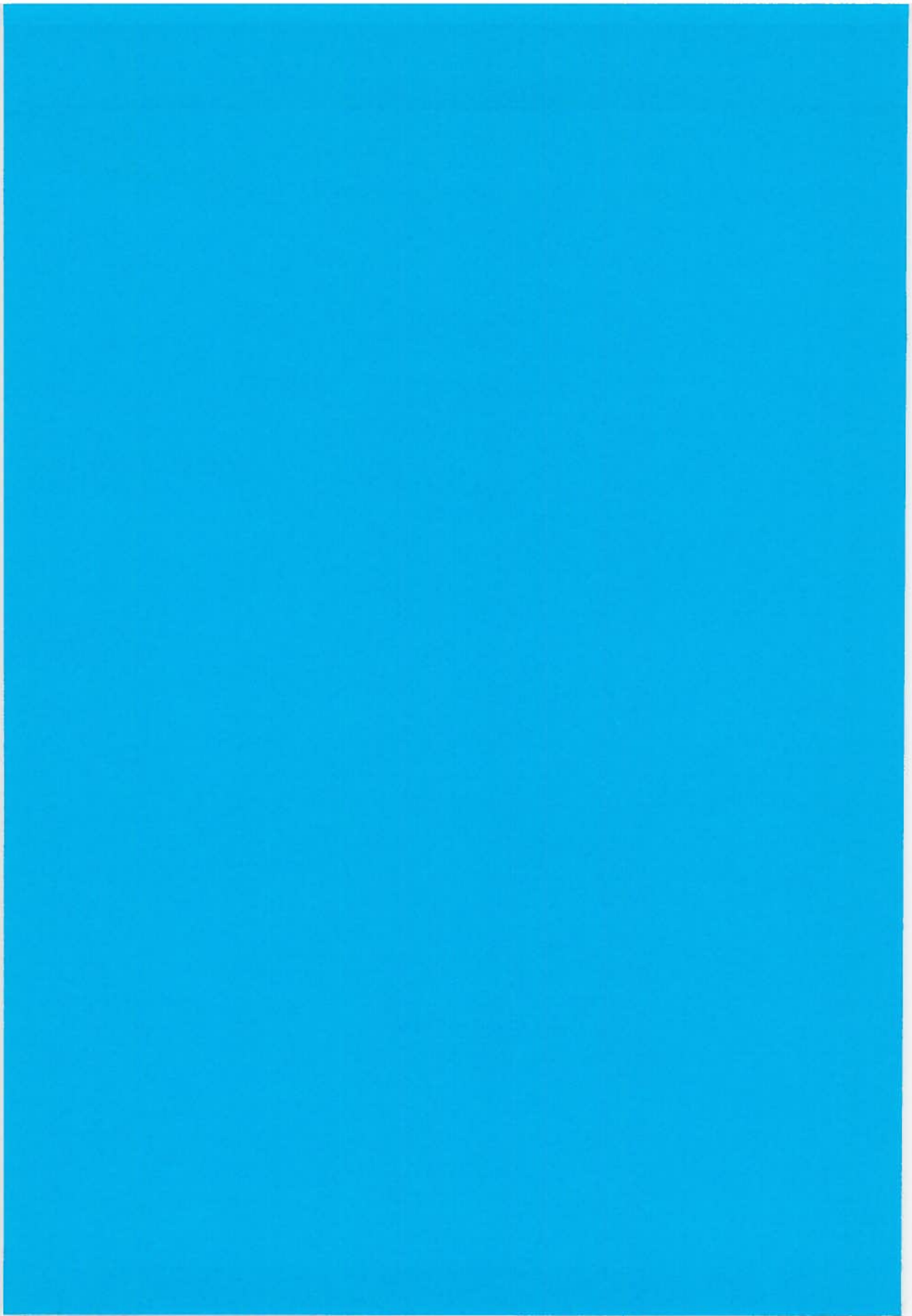
Appendix 2



Measurements included in the fourth Tromsø Study 1994/95

	First Screening	Sec. Screening
Number examined	27159	6891
Age range (years)	25-99	25-85
Blood pressure	x	x
Heart rate	x	x
Height and body weight	x	
Waist/hip ratio		x
Blood measurements:		
Total cholesterol	x	x
Triglycerids	x	x
HDL cholesterol	x	x
Non fasting serum glucose		x
γ-glutamyl transferase	x	x
Calcium	x	x
Ionised calcium and PTH	x	x
Creatinin		x
Non fasting insulin		x
Proinsulin		x
Glycosylated haemoglobin		x
Haemoglobin		x
Plot (blood cell count)	x	
Fibrinogen		x
Storage of serum	x	x
Storage of plasma	x	
Storage of blood cells	x	
Urinary albumin /creatinine /stix /culture / NAG (3days)		x
Ultrasound carotis		x
Ultrasound aorta		x
Echocardiography		x
Bone density		x
Body fat composition		x
10-20 sec one-lead ECG	x	
10 sec 12 lead ECG		x
90 sec 8 lead ECG (R-R variability)		
Questionnaires	x	

Appendix 3



European Society of Cardiology's Diagnostic Doppler criteria for diastolic heart failure:[63]

Signs or symptoms of congestive heart failure

Exertional dyspnoea, orthopnea, gallop sounds, lung crepitations, pulmonary oedemea

and

Normal or mildly reduced left ventricular systolic function:

LVEF $\geq$ 0.45

and

Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness:

Slow isovolumic left ventricular relaxation:

$IVRT_{<30\,y} > 92$ msec, $IVRT_{30\text{-}50\,y} > 100$ msec, $IVRT_{>50\,y} < 105$ msec

and / or slow early left ventricular filling:

$E/A_{<50\,y} < 1.0$ and $DT_{<50\,y} > 220$ msec, $E/A_{>50\,y} < 0.5$ and $DT_{>50\,y} > 280$ msec

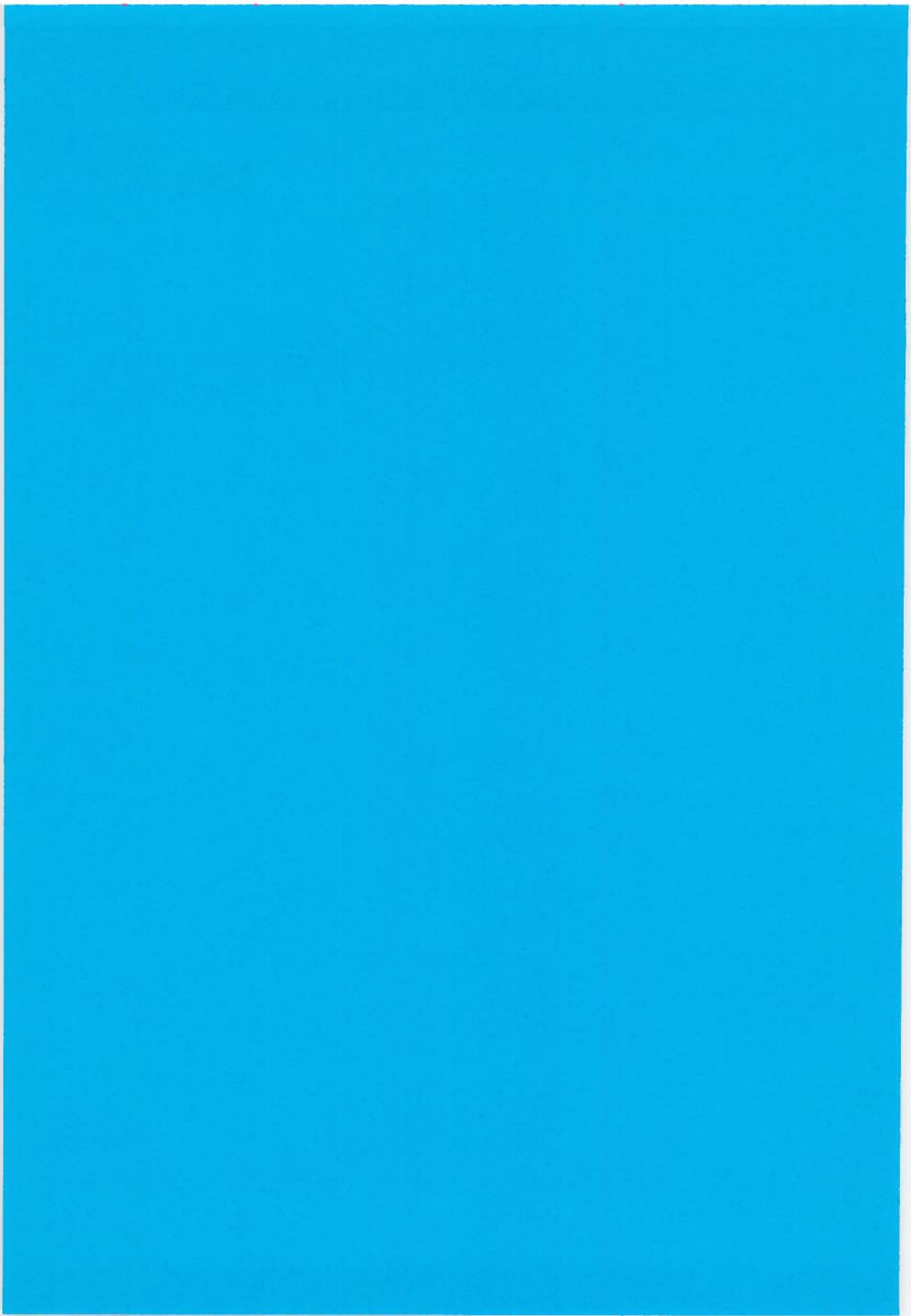
and / or reduced left ventricular diastolic distensibility:

PV A velocity > 35 cm / sec

and / or PV A duration > MV A duration + 30 msec

IVRT = isovolumetric relaxation time, E/A = ratio of early to late mitral inflow velocities, DT = deceleration time of early mitral inflow velocity, PV A = pulmonary venous atrial flow

Appendix 4



Errata;

In the process of securing the quality of the Tromsø Study Database, errors have been detected. These were mainly connected with the selection to the second visit in the health survey in 1994/95. In addition to the representative sample, all men in the age group 44-54 years who had participated in the Family Intervention Trial following the second Tromsø Study, were invited. These subjects were part of the 1373 men who had been selected in 1979 on the basis of high total cholesterol and/or low HDL cholesterol and randomly allocated to a lifestyle intervention or to control follow-up (Knutsen and Knutsen Scan J Soc Med 1989). This represented 166 men in the echo sample.

Exclusion of these individuals gave the following results:

1. Regarding paper I

«Prevalence of Left Ventricular Hypertrophy in a General Population. The Tromsø Study.»

The reference sample was changed to 384 men and 512 women.
There was no effect of age on the age and sex specific 97.5 percentiles in the reference sample ($p > 0.11$). Gender specific 97.5 percentiles for total reference sample was 145.4 g/m for men and 125.4 g/m for women. The crude prevalence was 12.3% for men and 8.0% for women. (Of the excluded men 20 subjects had LVH.) Standardised prevalence was 7.8% for men and 4.6% for women (WHO European Standard population, World Health Statistic Annual 1996).
The changes in tables and figures shown below, did not, apart from the crude and standardised prevalences, change the main results, the discussion or the conclusion of the article.

2. Regarding paper II

«Circulating N-terminal pro-atrial natriuretic peptide is an independent predictor of left ventricular hypertrophy in the general population. The Tromsø Study.»

In a reanalysis of the data with exclusion of the additional men from the family intervention trial, the associations between N-terminal pro-atrial natriuretic peptide and left ventricular hypertrophy was still significant and neither the discussion nor the conclusions in the article were changed.

3. Regarding paper III

«What determines echogenisity in a general population. The Tromsø Study.»

Exclusion of the men from the family intervention trial did not change the predictors of non-measurability.

4. Regarding paper IV

«Mitral flow derived Doppler indices of diastolic function in a general population. The Tromsø Study.»

The present version in the thesis has been rewritten with new tables and figures after exclusion of the additional 166 men from The Family Intervention Trial.
Only minor changes occurred as result of the exclusion.

Table 1 Characteristics of the study subjects.

Variable	Total		Reference sample	
	Men N = 1222	Women N = 1420	Men N = 384	Women N = 512
Age (years)	59.8 ± 10.6	59.7 ± 10.5	55.4 ± 11.8	54.0 ± 11.8
Body mass index (kg/m^2)	25.9 ± 3.3	25.7 ± 4.3	24.3 ± 1.9	23.4 ± 2.2
Waist/hip ratio	0.92 ± 0.06	0.82 ± 0.06	0.89 ± 0.05	0.79 ± 0.0
Systolic BP* (mmHg)	140.3 ± 19.7	138.8 ± 22.1	125.6 ± 8.5	121.8 ± 9.6
Diastolic BP* (mmHg)	80.8 ± 11.3	78.5 ± 12.1	73.6 ± 7.3	70.9 ± 7.8
Total cholesterol (mmol/l)	6.43 ± 1.17	6.85 ± 1.27	6.23 ± 1.13	6.43 ± 1.2
HDL† cholesterol (mmol/l)	1.41 ± 0.38	1.68 ± 0.42	1.44 ± 0.35	1.73 ± 0.4
Echocardiography:				
LV‡ mass (g)	201.5 ± 62.2	144.9 ± 41.7	176.4 ± 40.1	127.7 ± 30.4
LV‡ mass by height (g/m)	115.1 ± 35.6	89.6 ± 26.0	100.3 ± 22.6	78.3 ± 18.6
97.5 percentile LVM/h§ (g/m)	210.9	150.3	145.4	125.4
Valvular heart disease (%)	4.1	6.3	-	-
Questionnaire:				
Myocardial infarction (%)	8.5	3.0	-	-
Angina (%)	10.1	7.4	-	-
Stroke (%)	2.8	1.8	-	-
Diabetes (%)	3.4	2.2	-	-
Antihypertensive med. (%)	12.3	12.5	-	-
Units of alcohol intake	4.7 ± 7.0	1.8 ± 3.4	4.8 ± 5.8	2.4 ± 3.7
Physical activity (1-4)	1.9 ± 1.1	1.5 ± 0.9	2.1 ± 1.1	1.6 ± 0.9
Present smoking (%)	32.7	30.6	38.4	38.6

Age adjusted means ± SD (or percent of total) within total sample and within reference sample. *BP = blood pressure, † HDL = high density lipoprotein, ‡LV = left ventricular, §LVM/h = Left ventricular mass indexed by height.

Table 2.

Age adjusted prevalences of sex specific left ventricular hypertrophy (LVH) for groups of cardiovascular disease.

	Men			Women		
Variable	N	% LVH	p value against no CVD*	N	% LVH	p value against no CVD*
CVD*	201	30.4	< 0.0001	139	21.2	< 0.0001
CVD + valve†/AHM§	10	78.1	< 0.0001	9	54.1	< 0.0001
CVD + valve	11	52.8	0.03	9	43.6	< 0.0001
CVD + AHM§	63	28.9	< 0.0001	42	27.6	< 0.0001
CVD alone	117	25.2	< 0.0001	79	11.7	0.07
Alternative subgroups:						
MI‡ and angina	50	46.5	< 0.0001	26	21.9	0.004
MI alone	54	33.7	< 0.0001	16	30.5	0.0005
Angina alone	73	20.4	0.01	79	21.6	< 0.0001
Stroke alone	24	19.9	0.15	18	10.5	0.47
AHM§ + valve	6	47.8	0.007	10	28.9	0.009
AH medication only	81	27.4	< 0.0001	117	19.8	< 0.0001
Valvular disease only	35	33.0	< 0.0001	62	17.3	0.002
No CVD	899	9.7		1092	5.7	
Total	1222	12.3		1420	8.0	

*CVD = a history of myocardial infarction, angina and/or stroke. † valve = with valvular heart disease. ‡ MI = myocardial infarction. §AHM = antihypertensive medication. LVH defined as LVM/h $\geq$ 145.4 g/m for men and 125.4 g/m for women. The subgroups of different cardiovascular diseases are mutually exclusive, as are all main groups.

Table 3.

Independent risk factors of sex specific left ventricular hypertrophy.

Variable	Odds Ratio (95% CI) for LVH*	Wald score
	N = 2642 (cases = 314)	
Age (10 years)	1.21 (1.03-1.43)	5.1
Gender (male = 1, female = 0)	2.17 (1.64-2.82)	30.6
Body mass index (3.8 kg/m^2)	1.95 (1.71-2.22)	99.9
Valvular heart disease†	4.75 (3.15-7.15)	55.6
Systolic blood pressure (20.8 mmHg)	1.46 (1.28-1.67)	31.0
Cardiovascular disease†	2.13 (1.54-2.93)	21.3
Antihypertensive medication†	1.54 (1.11-2.13)	6.7
ROC area	0.80	

*Left ventricular hypertrophy; LVM/h $\geq$ 125.4 g/m for women, LVM/h $\geq$ 145.4 g/m for men. † Yes =1, no = 0. Apart from age and gender, variables are listed according to decreasing contribution of explained variance (Wald χ^2).

Figure 1

Age specific percentiles of left ventricular mass by height (LVM / h) for the 1420 women in the total sample or for the reference sample of 512 women, and the 1222 men in the total sample or for the reference sample of 384 men.

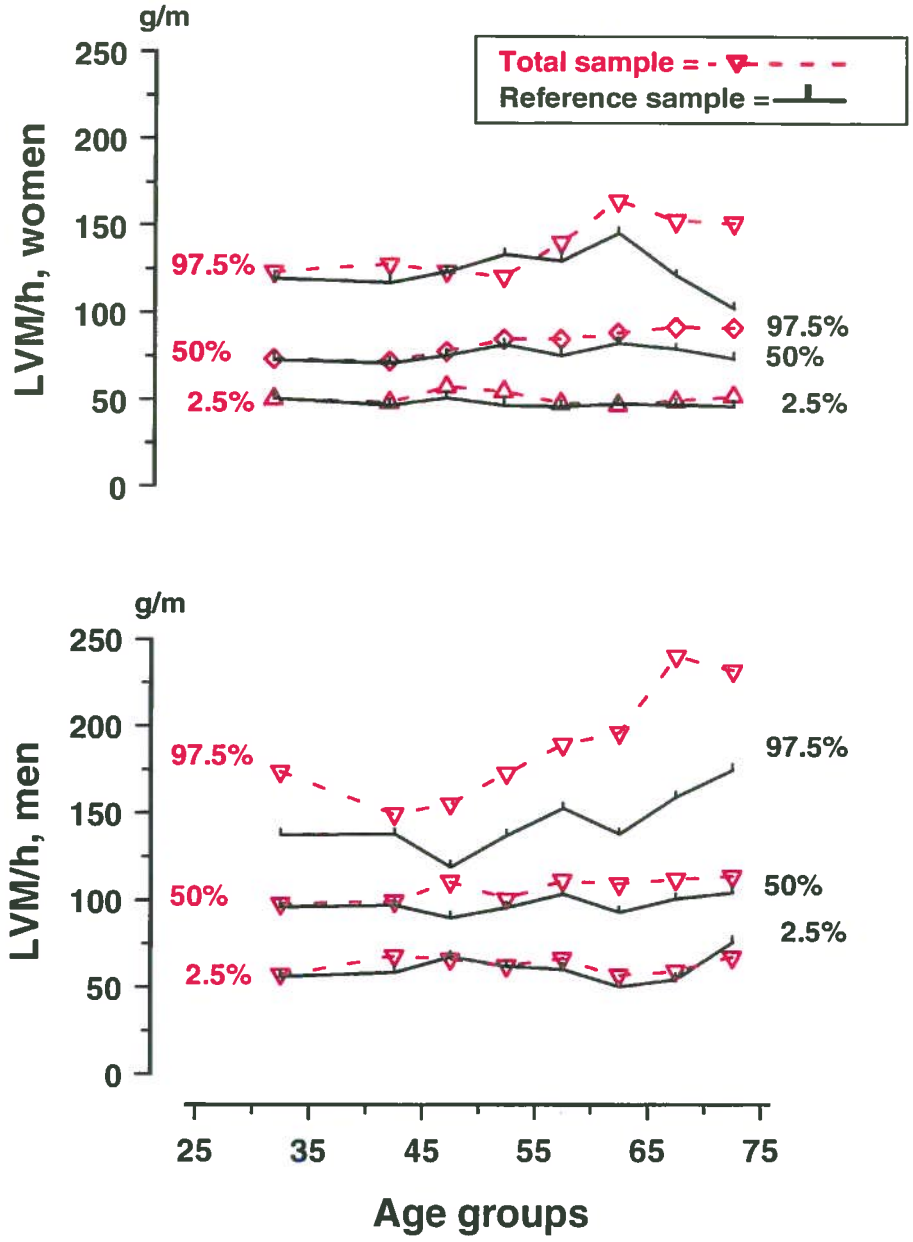


Figure 2

Age-adjusted sex-specific prevalences of left ventricular hypertrophy plotted against quintiles of body mass index (BMI) and systolic blood pressure (SBP) in subjects without a history of cardiovascular disease. Age and sex adjusted odds ratios for one quintile increase. ∇ = men; Δ = women;

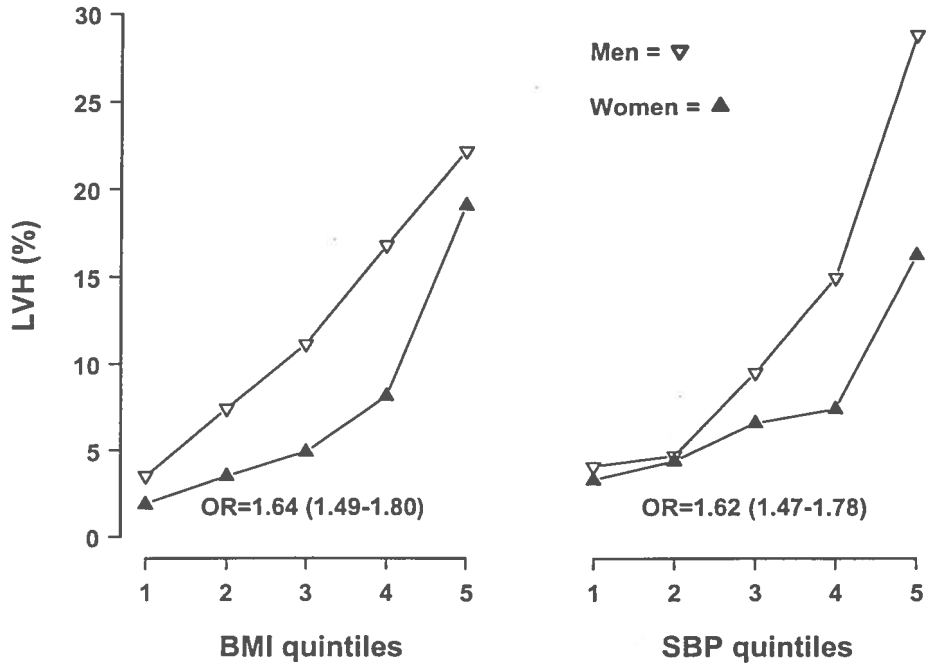
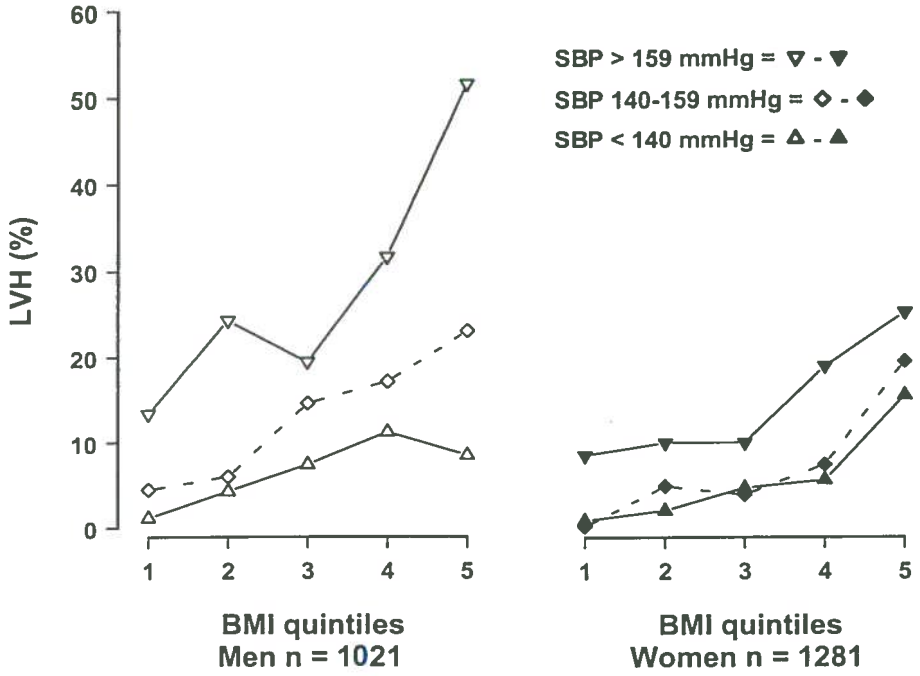


Figure 3

Age-adjusted prevalences of sex-specific left ventricular hypertrophy (LVH) over body mass index (BMI) quintiles, stratified by systolic blood pressure (SBP) for subjects without a history of cardiovascular disease.



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