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Thesis for the degree of
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Norsk tittel: Ekkokardiografiske mål på hjertefunksjon: Normalverdier og assosiasjon med risikofaktorer hos personer uten hjertesykdom, høyt blodtrykk og diabetes. Data fra HUNT 3.

Sammendrag:
Ultralydundersøkelse av hjertet (ekkokardiografi) er den undersøkelsen som samlet sett gir mest informasjon om hjertets struktur og funksjon. Undersøkelsen er en hjørnestein i utredning og diagnostikk av hjertesykdom. Vevsdoppler- (hastighetsdata fra hjertemuskelen) og deformasjonsanalyser (grad av forkortning av hjertemuskelen og hastigheten det skjer med) er nye ekkokardiografiske metoder som har vist seg følsomme for påvisning av redusert hjertefunksjon.

Forutsetningen for at legene mest nøyaktig skal kunne påvise svekket hjertefunksjon relatert til sykdom er at man har god kjennskap til hva som er normalt. Hovedmålet for studiene var derfor å etablere normalverdier for spesifikke metoder for kvantitering (måling) av hjertefunksjonen og å belyse hvordan hjertefunksjonen hos friske personer er assosiert med ulike risikofaktorer for hjertesykdom.

I forbindelse med Helseundersøkelsen i Nord-Trøndelag (HUNT 3) ble i alt 1.296 personer undersøkt med ultralyd av hjertet (ekkokardiografi) på Steinkjer og i Namsos. Deltakerne i studiene ble tilfeldig trukket ut blant deltakere i HUNT 3 som var hjertefriske og ikke hadde forhøyet blodtrykk eller sukkersyke.

Arbeidet består av fire delstudier. I studie 1 ble repeterbarheten av de ulike hjertefunksjonsmålene studert. Alle metodene hadde akseptabel repeterbarhet og de fleste hadde utmerket repeterbarhet. Gjennom studie 2 og 3 ble normalverdier for ulike nye hjertefunksjonsmål både for venstre og høyre hjertekammer publisert. Målt med de nye metodene fant man at hjertefunksjonen avtok med alder og var forskjellige mellom kvinner og menn. Normalverdiene ble derfor utarbeidet i forhold til alder og kjønn. I studie 4 ble de ulike hjertefunksjonsmålene til deltakerne studert mot nivået av ulike risikofaktorer for hjertesykdom. Studien viste at overvekt, høyt blodtrykk, høyt nivå av det ugunstige kolesterolet og røyking var assosiert med dårligere hjertefunksjon (målt med de beskrevne metodene) selv hos friske personer. Høyere nivå av det gunstige kolesterolet var assosiert med bedre hjertefunksjon. Studien konkluderte med at risikofaktorene svekker hjertefunksjonen allerede før man kan påvise sykdom.

Navn kandidat: Håvard Dalen
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Veileder(e): 1. Amanuensis Asbjørn Støylen, Institutt for sirkulasjon og bildediagnostikk, DMF, NTNU og professor Lars Vatten, Institutt for samfunnsmedisin, DMF, NTNU.
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Content

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And finally, a good wife is the best support a man can have. I acknowledge the tolerance and love of my wife, Kristin. Without her extremely patience this thesis would not have been finished. My lovely son Leo deserves the last thank for still showing me enthusiastic attention when I return after spending too much time away from home.

List of papers

1) Thorstensen A, Dalen H, Amundsen BH, Aase SA, Støylen A. Reproducibility in echocardiographic assessment of the left ventricular global and regional function, the HUNT Study. Eur J Echocardiogr 2010; 11:149-56.

2) Dalen H, Thorstensen A, Vatten L, Aase SA, Støylen A. Reference values and distribution of conventional echocardiographic Doppler measures and tissue Doppler velocities in a population free from cardiovascular disease. The HUNT Study in Norway. Circ Cardiovasc Imag 2010; 3:614-22.

3) Dalen H, Thorstensen A, Aase SA, Ingul CB, Torp H, Vatten L, Støylen A. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the HUNT Study in Norway. Eur J Echocardiogr 2010; 11:176-83.

4) Dalen H, Thorstensen A, Romundstad PR, Aase SA, Støylen A, Vatten L. Cardiovascular risk factors and systolic and diastolic cardiac function: a tissue Doppler and speckle tracking echocardiographic study. Submitted 2010

Selected abbreviations

A	late (atrial) mitral inflow	LV	left ventricle
a’	peak late diastolic (atrial) annular velocity	PRF	pulse repetition frequency
BMI	body mass index	pw	pulsed wave Doppler
BSA	body surface area	pwTD	pulsed wave/spectral tissue Doppler
cTD	colour tissue Doppler	RV	right ventricle
cw	continuous wave Doppler	S	peak systolic flow
D	peak diastolic flow	S’	peak systolic annular velocity
DT	deceleration time	S_{es}	end-systolic strain
E	early mitral inflow	SR_A	peak late (atrial) diastolic strain rate
e’	peak early diastolic annular velocity	SR_E	peak early diastolic strain rate
EF	ejection fraction	SR_s	peak systolic strain rate
HDL	high density lipoprotein	ST	speckle tracking
IVRT	isovolumic relaxiation time	TD	tissue Doppler

1 Introduction

1.1 Echocardiography

Echocardiography is the most widely used method for assessing cardiac function and anatomy (1). It is an important method used in diagnosing and monitoring of cardiac patients, especially with regard to left and right ventricular function, valvular disease and cardiac abnormalities.

1.1.1 Selected history

The development of echocardiography to become the widely used diagnostic tool of today started in the 1950s with the first description of ultrasound reflectoscope recordings of myocardial walls by the Swedish cardiologist Edler (2). However, the method was only used by a few researchers to visualize the mitral apparatus and the wall motion of the left ventricle (LV). Later, the development of continuous wave (cw) Doppler methods used to measure blood flow (mainly in aorta), and scanners used to assess real-time grey scale (B-mode or Brightness-mode) visualisation of cardiac structures, were invented by Hertz and Asberg in 1967. Thereafter, Baker invented pulsed waved Doppler (pw) around 1970. Until then, the methods were regarded with scepticism, and invasive catheterization remained the main method to assess cardiac function. In Trondheim, Liv Hatle and Bjørn Angelsen made important contributions in further developing and validating the Doppler methods as tools for diagnosing and monitoring of cardiac diseases. Angelsen and colleagues developed PEDOF (pulsed Echo DOppler Flow velocity meter) which was the basis for the first publication of non-invasive assessment of pressure gradient in mitral stenosis by Holen in 1976 (3), and after some modifications the PEDOF was able to operate also in cw Doppler mode. Subsequently, several pioneering studies were conducted by the Trondheim group on the

clinical use of Doppler showing that non-invasive Doppler examination could replace cardiac catheterization in diagnosing different non-coronary cardiac diseases (4-7). However, the breakthrough for clinical use of Doppler took place in 1982 when Vingmed included the Doppler modality into the two-dimensional echo/Doppler scanner and by the development of colour Doppler from 1984 (Omoto) and 1986 (Vingmed). These developments were followed by new important studies for the diagnosis of cardiac disease by the Trondheim group (8-13). Current scanners are further equipped with tools that enable the quantification of cardiac function by tissue Doppler and speckle tracking methods in addition to other advanced features.

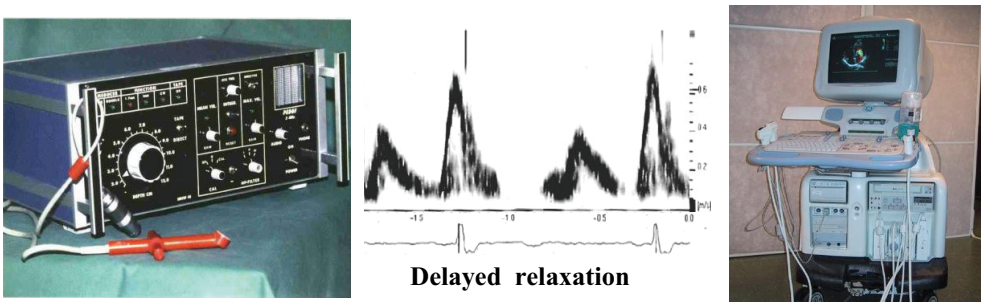

Figure 1. Left: PEDOF (Pulsed and continuous wave Doppler (1976), Middle: Mitral inflow by PEDOF showing delayed relaxation and Right: GE Vivid 7 scanner from 2000 (the scanner used for the echocardiographic examinations to which this thesis is based). Pictures applied from Hans Torp.

1.1.2 Grey scale (B-mode)

B-mode (brightness mode) made two-dimensional live visualisation of structures possible by ultrasound. This is still the most important ultrasound mode for visual evaluation of cardiac function, and is further used as underlying guiding tool when cardiac anatomy or function is

quantified. With the latter, the grey scale image is either superimposed on the other modality (Figure 2) or an additional guiding view is added to the measurement view (Figure 5).

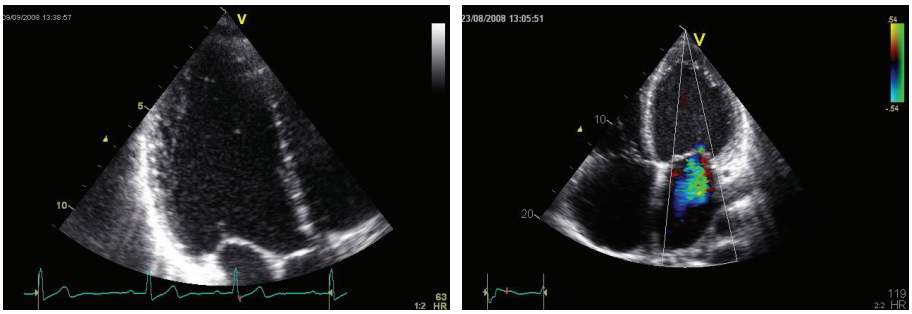

Figure 2. Left figure: Apical long axis view of left ventricle in healthy individual. Right figure: Colour Doppler revealing moderate mitral regurgitation in an individual with dilated cardiomyopathy.

1.1.3 Doppler measurements

The Doppler methods are based on detection of the Doppler shift from moving scatters (14). This principle states that the frequency of reflected ultrasound is altered by moving targets (red blood cells or myocardium). The magnitude of the Doppler shift relates to the velocity of the moving target and the polarity of the Doppler shift reflects the direction the moving target towards (positive) or away (negative) from the ultrasound transducer. The Doppler shift for reflected ultrasound ($f_d = f - f_0$) is given by the equation (Eq. 1):

Eq. 1: $$\boxed{f_d \approx 2 * f_o * v * \cos(\theta) / c}$$

where f_d = Doppler shift, f_o = transmitted frequency, v = target (blood or myocardium) velocity, θ = insonation angle and c = speed of sound (1540 m/s). The Doppler shift is directly proportional to the velocity of the moving target. The Doppler equation for reflected

ultrasound can be solved for the velocity (v) of the moving target (blood cells or myocardium) as follows (Eq. 2):

Eq. 2: $v \approx f_d * c / 2 * f_o * \cos(\theta)$

Thus, misalignment of the beam with the moving target of more than ±15 degrees will cause ≥3% error in the measurement of velocity (because cos(15) = 0,966), and correspondingly misalignment of more than ±30 degrees will cause ≥13% error in the measurement. As the measured velocity depend on the alignment of the ultrasound beam this is a crucial point in all Doppler analyses.

Blood flow velocity can be measured within a specific site (sample volume) by pulsed wave (pw) Doppler or all velocities along the ultrasound beam can be assessed by continuous wave (cw) Doppler. By cw Doppler the beam is transmitted continuously, and the received echoes are sampled continuously. Thus, there is no information about the depth of the different signal components. In order to measure velocity at a certain depth by pw Doppler, the next pulse cannot be transmitted before the last signal has returned. This prevents pw Doppler from measuring velocities beyond a given threshold, called the Nykvist limit (15). The Nykvist limit is dependent on the distance between the transducer and the sample volume. At larger distance from the probe, the ultrasound pulse requires longer time to pass to the desired depth and back to the probe. When the pulse repetition frequency (PRF) is decreased, the Nykvist limit also decreases. Frequency aliasing occurs at a Doppler shift that is equal to half of the PRF and the Nykvist velocity limit (v_N) is given by the following equation (Eq. 3):

Eq. 3: $v_N = c^2 / 8Df_o$

where c is the velocity of sound, D is the depth (distance between the transducer and the sample volume) and f_0 is the probe frequency. In clinical practice this means that for pw Doppler, the ability to measure high velocities decreases when the distance to the sampled

volume increases. Tissue velocities, being about $1/10^{th}$ of blood flow velocities, are in practice not affected by the Nykvist limit. The cw Doppler has no Nykvist limit, and is therefore suitable for measuring high velocities. Thus, both methods have limitations: pw Doppler has velocity ambiguity at high velocities, and cw Doppler has depth or range ambiguity.

Spectral Doppler: Pulsed and continuous waved Doppler are both spectral analyses. The content of frequencies is analysed according to the amplitude and time. The spread of frequencies reflects the spread of measured velocities according to the Doppler equation. The amplitude reflects the intensity of the reflected signal. Since velocity of blood and cardiac structures are time dependent, Doppler recordings are presented by time (cardiac cycles) in cardiac ultrasound. Thus, pw Doppler measures velocity at a specific site and therefore, the velocities are more homogenous compared to cw Doppler where the measured velocities are spread between zero and maximal velocity. Gain settings are important for optimal measurements in the Doppler spectrum both for pw and cw Doppler, even though the band-shaped spectrum of the pw Doppler is more affected.

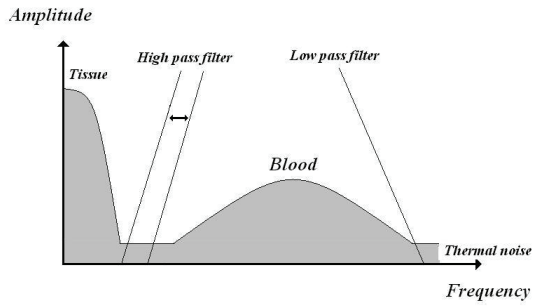

Figure 3. Spectral analysis; the Doppler frequencies are distributed according to this frequency-amplitude diagram. The Tissue echoes have high amplitude of the reflected signal, but low velocities (resulting in low Doppler frequencies). Blood has high velocity with a wider distribution, but lower amplitude. For blood flow Doppler, a high pass filter (low

velocity reject) is applied to suppress the tissue echoes. A low pass filter (high velocity reject) can be applied to suppress noise above the velocity range. In tissue Doppler, the high pass filter can be removed, or at least partially, to allow the low velocities from the tissue (usually on the order of 1/10 of flow). It can partially be maintained to suppress absolutely stationary echoes, among other from reverberations. The blood signal can be removed both by reducing the gain, and by applying a low pass filter. This is further explained below (Figure 4). Figure applied from A Støylen.

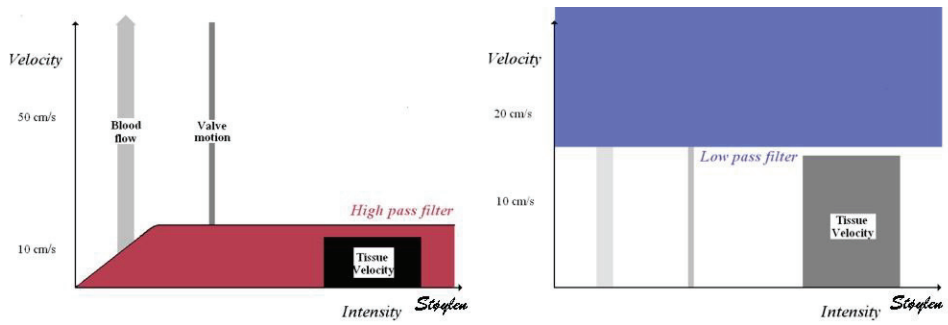

Figure 4. Left: High pass filter (red) removes tissue velocities and other low velocities and is used when assessing blood flow velocities. Right: Low pass filter (blue) removes high velocities and is used for assessment of tissue velocities. Notification: The velocity scales differ between left and right illustration. Explanations as in Figure 3. Courtesy both illustrations: A Støylen.

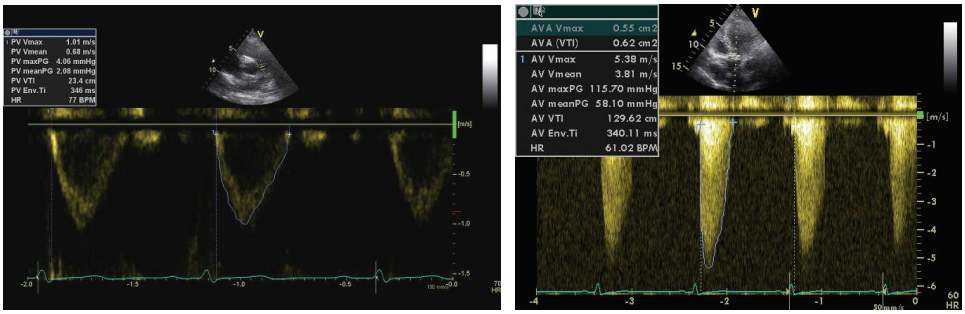

Figure 5. The velocities are variable with time. Amplitude is shown as brightness; velocity is shown on the y-axis and time on the x-axis. This results in the typical Doppler flow velocity curves. Left figure: Normal pulmonary artery blood flow assessed by pw Doppler and right figure: maximal velocity through a stenotic aortic valve assessed by cw Doppler.

1.1.4 Colour Doppler imaging

Colour coded Doppler imaging is used to visualize blood flow, most often used with respect to detect valvular insufficiency or shunts. The method has limited information content in the signal, but is widely used for visual evaluation of valvular function especially (Figure 2).

1.1.5 Pulsed wave tissue Doppler velocities

Pulsed wave tissue Doppler (pwTD) uses the Doppler shift to assess localized myocardial velocity analogue to pulsed wave Doppler assessment of blood flow, but the low pass filter is used to exclude the high velocity blood flow. The method is most often used to assess myocardial velocities in the base of the left or right ventricle. Measurements of systolic and diastolic velocities are performed in the Doppler spectrum curve. Thus, the beam alignment, gain settings and localization of the measurement in the Doppler spectrum are the most crucial points regarding pwTD analysis.

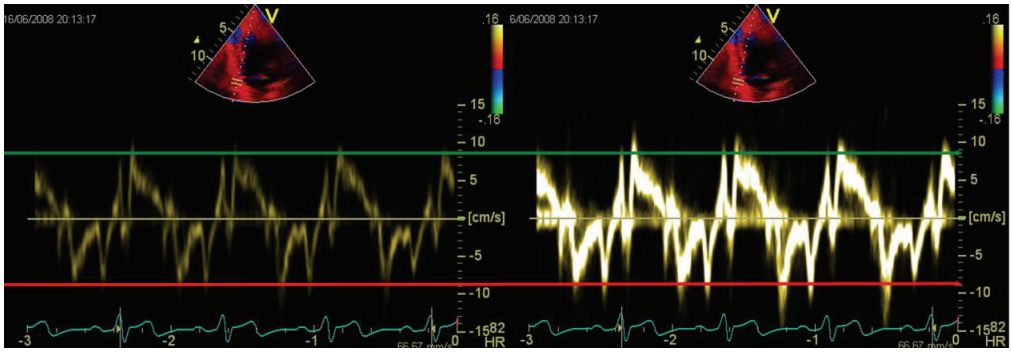

Figure 6. Pulsed wave TD assessed velocities from the base of the inferior LV wall with low gain settings in the left recording and the high gain settings in the same recording at right. Green line refers to peak systolic velocity measured at the outer edge of the Doppler spectrum at low gain, and with high gain it is obvious that similar method measure higher velocity. Red line refers to peak early diastolic velocity at low gain, and similarly it looks like the velocities are higher when gain is increased. The alignment of the beam with the myocardial wall is not optimal, but within the advised 15-20 degrees.

For both pulsed wave and colour tissue Doppler velocities S' reflects peak systolic velocity, and e' and a' reflect peak early and late diastolic velocities (Figure 7).

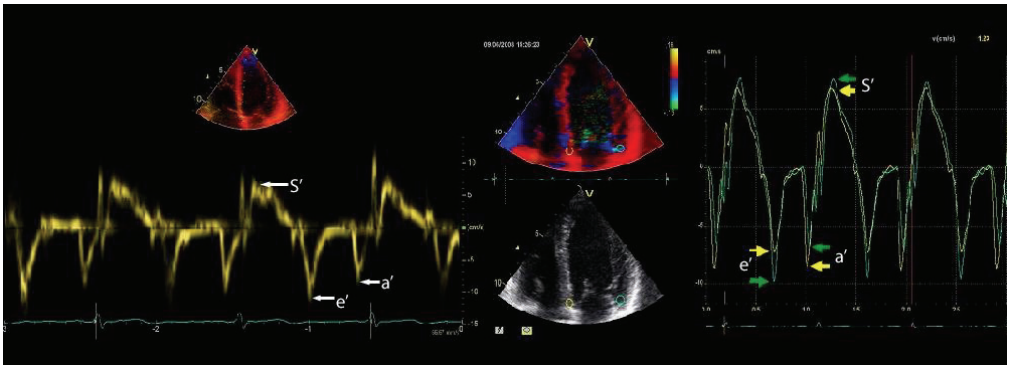

Figure 7. Peak systolic velocity (S'), and peak early (e') and late (a') diastolic velocities assessed by pulsed wave (left) and colour tissue Doppler (right). Left figure: Doppler curve with sample volume in the base of the inferoseptum and right figure: Yellow curve with region of interest (ROI) in the base of the inferoseptum and green curve with ROI in the base of the lateral wall.

1.1.6 Colour tissue Doppler velocities

Colour tissue Doppler (cTD) velocities are assessed from high frame rate tissue Doppler mode with underlying low frame rate grey scale images for localization of regions of interest (ROIs). The pwTD velocities are calculated from the Doppler spectrum, and the outer edge of the band-shaped spectrum refers to the maximal velocities. By cTD the mean velocities of the ROIs are assessed (autocorrelation method) (16). This will give lower values by the cTD method compared to pwTD (17), since also low velocity components are included in the analyses (Figure 8).

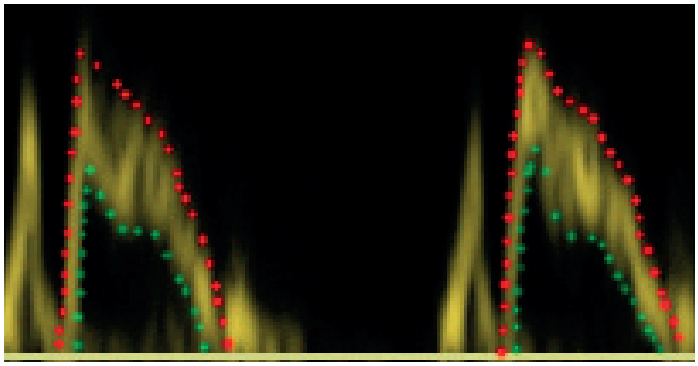

Figure 8. Extract from a pwTD curve. Two systolic velocity curves are marked by red dots (outer edge of the clear Doppler spectrum) and green dots (inner edge of the clear Doppler spectrum). The cTD method does not only average the velocities between the dotted lines, but the autocorrelation method includes the low velocities below the green dots as well, resulting in lower values of the measured myocardial velocity compared to pwTD. (The pwTD spectrum in the illustration is only used as an illustration of the difference in the measured velocity between pwTD and cTD, and does not reflect the method used to assess cTD measurements.)

By the cTD method, velocities are calculated from phase shifts by an autocorrelation method. This acquisition is pulsed, not continuous and there has been a controversy about

whether tissue Doppler imaging deserves to have 'Doppler' in its name or not since the velocity is not estimated by the spectral content of one received ultrasound pulse, but by using an autocorrelation method on several pulses (18). Irrespective of this debate, the methods used to assess myocardial velocities by pulsed wave overlaid tissue velocity imaging described and used in this thesis, will be referred to as tissue Doppler imaging.

1.1.7 Quantification of longitudinal ventricular function

The concept of the heart functioning as a double pump, with the atrioventricular plane as a piston, is indeed a concept dating back to Leonardo da Vinci (19). The latter two paragraphs describe two commonly used methods to quantify longitudinal left and right ventricular function. The basis for all measurements of longitudinal function is the understanding of that the apex relatively fixed with respect to the chest wall, and changes in the longitudinal direction was actually measured by changes in the position of the atrioventricular plane (20). The position of the atrioventricular plane was first measured directly by M-mode (21) and secondly the velocity was measured directly by Doppler as described in the latter paragraphs (22). Myocardial velocities can also be determined by differentiating the M-mode traces, and displacement can be calculated from the time integral of the tissue Doppler velocities. However, due to methodological differences the values obtained by the different methods are not interchangeable (17, 23). Longitudinal left ventricular measurements have been proposed to be the best indices of left myocardial function (24).

As the myocardium is incompressible (25), the volume of the myocardium must remain relatively constant during a cardiac cycle. The outer contour of the heart also remains relatively constant during systole and thus, systolic longitudinal shortening is accompanied by thickening of the myocardium inwards (26). Due to the principle of incompressibility of the myocardium the systolic wall thickening has to follow systolic shortening (25, 27). However,

all kind of myocardial hypertrophy will in fact reduce the luminal diameter of the LV, and thus, the percentage fractional or radial shortening and ejection fraction will increase (27), even when the longitudinal shortening decreases. There is a usual misconception that reduced systolic longitudinal function is compensated by increased radial function (27). This is due to the fact that longitudinal function is measured in the myocardium, while radial function is measured in the cavity.

1.1.8 Global vs. regional and segmental left ventricular evaluation

Grey scale mode made quantification of global left ventricular function possible and the most commonly used method is the calculation of ejection fraction (EF). From two-dimensional images the endocardial borders are traced end-diastolic and end-systolic in apical 4-chamber and 2-chamber (alternative long axis) views to calculate an estimate for volumes and stroke volume. Ejection fraction is defined as the percentage volume of blood ejected during systole, and is to some degree adjusted for size. Nevertheless, the EF method has significant limitations (12). Wall motion score is the most widely used method for segmental evaluation of LV function, where each segment of the myocardium is given a contractility score based on visual assessment (28). This method is only semi-quantitative, and it was first with development of deformation imaging by tissue Doppler and speckle tracking that segmental left ventricular function was measurable (13).

1.1.9 Deformation imaging by tissue Doppler and speckle tracking

Deformation imaging is a collective term of methods used to assess myocardial deformation, most often used as a measurement of systolic function. Cardiac deformation is three-dimensional, but as longitudinal left ventricular indices may be the best measurements of global left ventricular function (24, 29), the segmental longitudinal shortening may be the

most useful indices of regional function. Different methods are used to assess myocardial deformation. Firstly, the described tissue Doppler velocity method where strain rate can be assessed by the velocity gradient along the ultrasound beam, and by temporal integration strain is calculated (Figure 9). Secondly, the technique of speckle tracking (ST), where kernels (chosen regions of the myocardium) are tracked during a full cardiac cycle. This method is based on the interference of the reflected ultrasound giving rise to an irregular random speckled pattern of the myocardium, which is tracked forwards and backwards during the cardiac cycle (Figure 9). By the speckle tracking method it is possible to measure the percentage shortening of a myocardial segment during systole (strain) and by temporal derivation strain rate can be calculated (Figure 10). Longitudinal end-systolic strain (S_{es}) is the systolic shortening of a myocardial segment relative to the end diastolic length ($S_{es} = \frac{L - L_0}{L_0}$), expressed in percent, and strain rate (SR) is the rate by which this shortening occurs, expressed in s^{-1}. Different commercial tools used for assessing cardiac deformation are available, but the methods differ, and since information about technical aspects often are hidden for the user this limits the use of these methods. However, ST echocardiography has been shown superior in prediction of long term mortality compared to ejection fraction and wall motion score (29).

Deformation analyses were developed to assess segmental myocardial function, but the average of these segmental data is commonly used to assess global ventricular function. Thus, global strain corresponds to displacement per ventricular length and global strain rate corresponds to the spatial derivative of the velocity (Figure 10). In addition, cardiac deformation can be assessed in other axis than the longitudinal (circumferential and radial), but these methods are not included in this thesis.

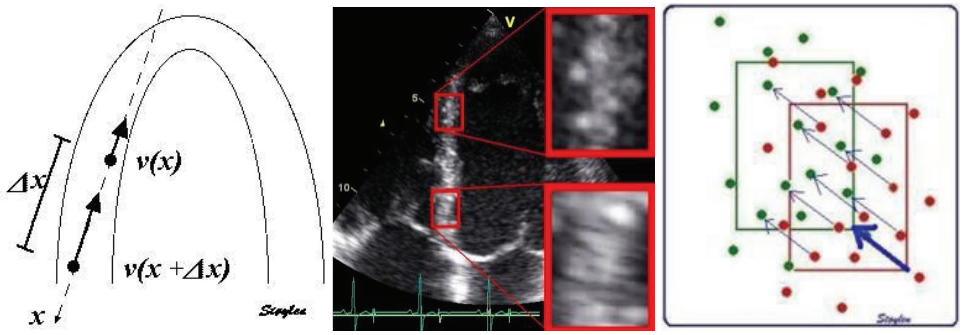

Figure 9. Left: Illustration of the velocity gradient based calculation of longitudinal strain rate $\left(SR = \frac{v(x) - v(x + \Delta x)}{\Delta x} = \frac{\Delta v}{\Delta x}\right)$. Middle: Typical speckle pattern from the myocardium (inferoseptum). Right: Defining a kernel (red frame) will define a speckle pattern within (red dots) and within a defined search area (blue frame) the new position of the kernel (green frame) can be found by the best match of the speckle pattern (green dots). The movement of the speckles (arrows) can then be measured. Courtesy all figures: Asbjørn Støylen (http://folk.ntnu.no/stoylen).

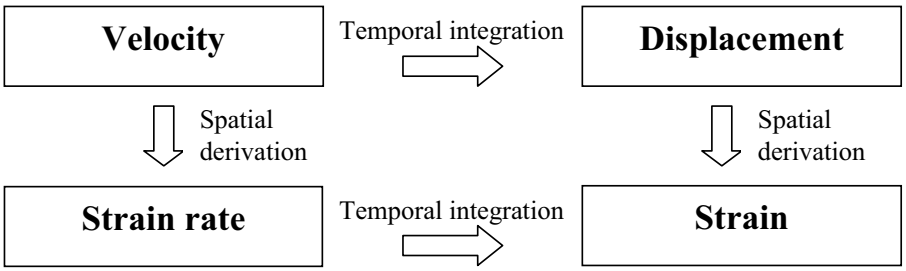

Figure 10. Strain rate is equal to the velocity gradient (spatial derivative of velocity), and strain is the displacement gradient (spatial derivative of displacement). Velocity and displacement are global measurements (measures the whole ventricle apical to the localization of the measurement), while strain and strain rate measures regional deformation. Courtesy: Asbjørn Støylen (http://folk.ntnu.no/stoylen).

1.1.10 GcMat

GcMat is customised semiautomatic software (GcMat; GE Vingmed Ultrasound, Horten, Norway) which runs on a MATLAB platform (MathWorks, Inc., Natick, MA, USA). Myocardial deformation is assessed by tracking of kernels defining segment borders with tissue Doppler along the ultrasound beam and grey-scale speckles perpendicular to the ultrasound beam. The kernels are tracked both forwards and backwards during a full heart cycle, and averaged to eliminate the effect of drift. Strain is calculated from the variation of segment length, and SR is calculated as the temporal derivative of strain, with correction to Eulerian SR. Alternative, deformation imaging can be assessed by tissue Doppler alone with fixed or dynamic ROIs. These methods have been described previously (30-33).

Figure 12 shows that both segments adjacent to a segment border with non-optimal tracking have to be discarded by this method. Thus, by the GcMat method the proportion of accepted segments will be lower compared to other software when the purpose is to obtain normal segmental deformation indices. However, by most commercial software information about segmental borders, tracking and how the indices are calculated are often hidden for the user, and this is a limitation of these methods.

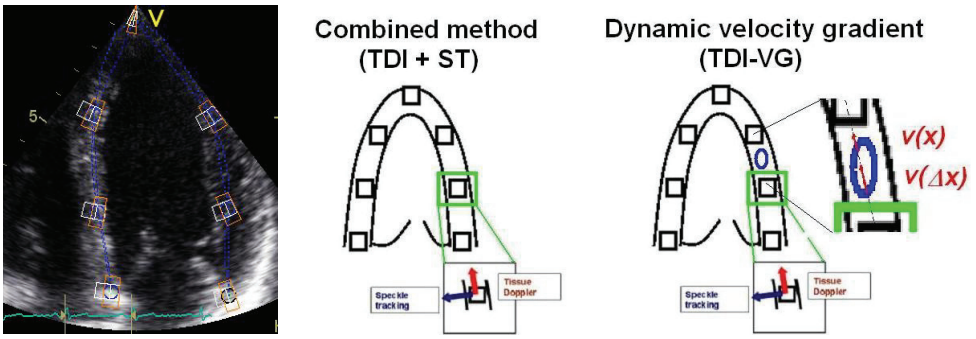

Figure 11. Left image illustrates the tracking view in GcMat. 7 landmarks are positioned in the LV myocardium. White boxes refer to search area for speckle tracking and orange boxes

refer to search area for tissue Doppler. Right illustrations show this schematically. With both methods tracking along the ultrasound beam is performed by tissue Doppler and tracking perpendicular to the ultrasound beam is performed by speckle tracking. The combined method calculates strain from the variation of segment length and the dynamic velocity gradient method calculates strain rate from the velocity gradient by tissue Doppler. In Study 3 we also used the latter method without tracking of the ROIs (TD with fixed ROIs). Courtesy middle and right figure: Brage H Amundsen.

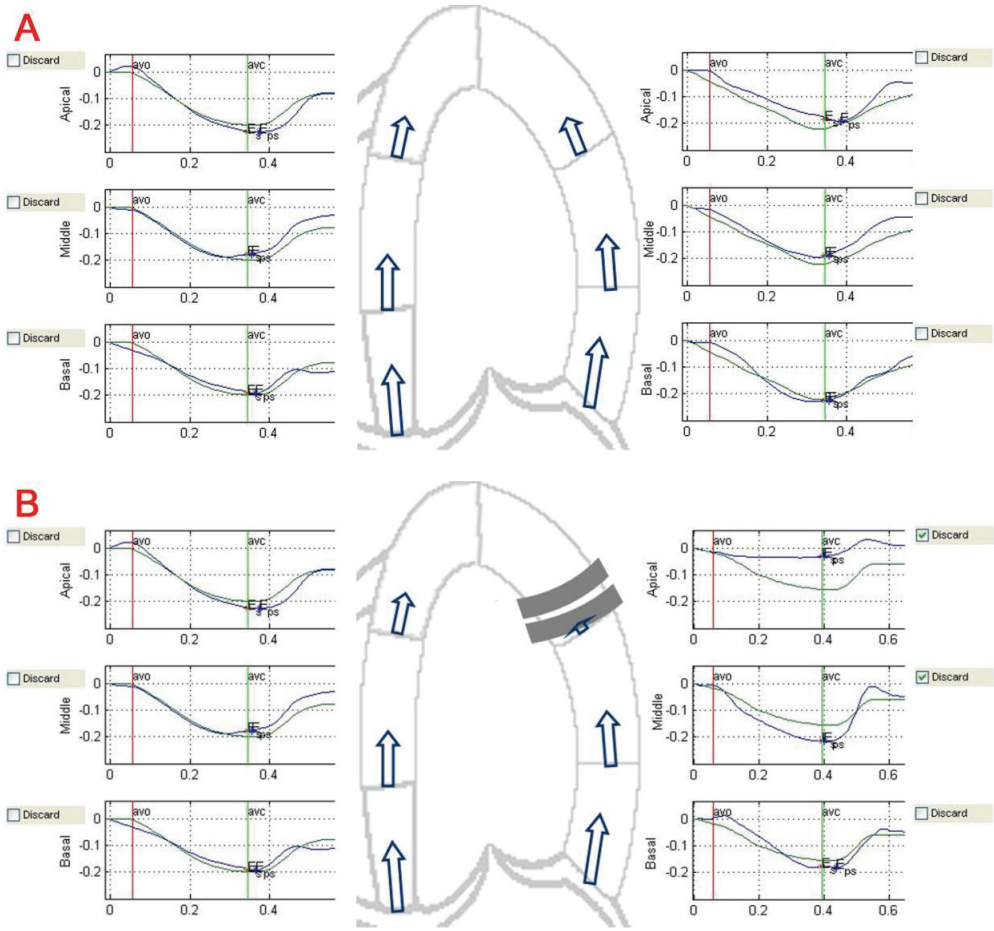

Figure 12. Figures A and B illustrate the displacement of the segmental borders by blue arrows in the middle figures and the corresponding segmental strain curves at left and right.

Blue strain curves reflect the measured longitudinal strain, and green strain curves reflect the measured average of the respective wall. Figure A shows normal tracking of all segmental borders, with a corresponding normal gradient in displacement from base to apex. Thus, all corresponding strain curves should be accepted. Figure B illustrates the influence of a typical reverberation (grey shadows) that influences the border between the apical and mid-ventricular anterolateral segment. Due to the reverberations the region of interest (segmental border) is almost stationary (short blue arrow). If the more basal regions of interest are still tracked well this results in underestimation of strain in the apical segment and overestimation of strain in the mid-ventricular segment shown by the corresponding strain curves. Thus, both the apical and mid-ventricular anterolateral segments should be discarded.

1.1.11 Two-dimensional strain

Two-dimensional strain (2DS) is an algorithm that calculates strain from tracking of ultrasound speckles in the grey scale images. For data in this thesis this method is performed by the automated function imaging packet (Figure 13) (AFI; EchoPAC PC version BT 09, GE Vingmed, Horten, Norway) with tracing of the endocardial border. The regions of interest were manually adjusted to include the entire LV myocardium and simultaneously avoid the pericardium. The software automatically tracked speckles frame by frame throughout the cardiac cycles, and segments with poor tracking were excluded manually. Since end-systolic changes of the LV are less time dependent compared to peak velocities the high frame rate of tissue Doppler is not necessary, but an adequate temporal resolution is needed for optimal tracking of the speckles. A commonly used limit is ≥40 frames per second. Nevertheless, as this algorithm uses relatively low frame rate this remains a limitation when strain rate curves are assessed by this method.

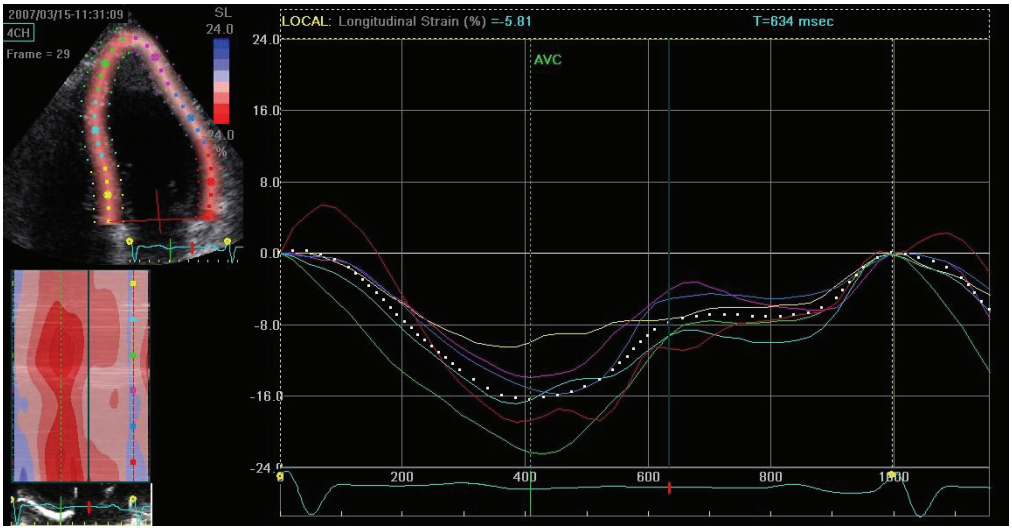

Figure 13. The different segments are colour coded in the upper left image and the corresponding strain curve is shown in the large image. At left the curved M-mode showing reduced strain in the base of the inferoseptum corresponding to the yellow curve in the large image is shown. End-systolic strain is the value defined by the Y-axis at end-systole defined by the vertical dotted line at approximately 400 ms in the large image.

1.2 Cut-off values vs. normal values

Many publications have described optimal cut-off values for deformation analyses between healthy controls and patients with disease (34, 35). For this small studies are sufficient. As cut-off values depend on the populations studied, the main limitation of cut-off values is the limited possibility to generalize these values to other populations. Figure 14 illustrates to some degree the difference between cut-off values and normal limits.

A common definition of normal values is the range of 2 standard deviations of the mean. This approximation applies to populations following a normal distribution, and corresponds to approximately 95% of the population. In a non-normally distributed population the use of 2.5 and 97.5 percentiles could define the normal ranges.

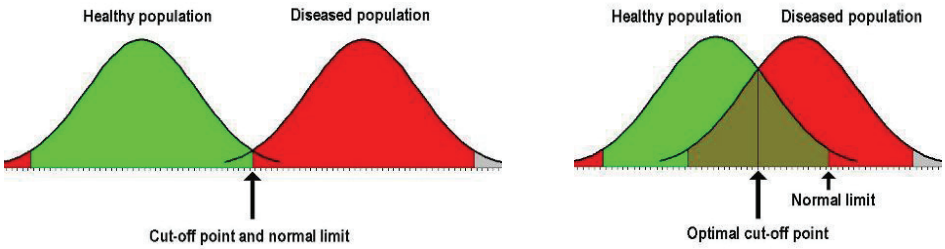

Figure 14. Left figure; the distributions of the healthy and diseased population are widely separated, and the cut-off point corresponds to the upper normal limit. Right figure; the distributions of the two populations have a high degree of overlap. The optimal cut-off point is the value that best defines the separation, i.e. the values that gives the highest area under curve (AUC). However, as illustrated this cut-off value is much lower than the upper normal limit of the healthy population. Illustrations applied from Støylen A (http://folk.ntnu.no/stoylen/).

1.3 Risk factors

The influence of common cardiovascular risk factors on the risk of morbidity and mortality is well known (36-40). In general, the higher level of cardiovascular risk factors, the higher risk for cardiovascular disease and mortality. Patophysiological aspects of these associations include atherosclerosis, blood clotting disturbances, micro vascular abnormalities, inflammation and myocardial cellular and interstitial abnormalities (41-45). In this thesis we present associations of age, smoking, blood pressure, measurements of obesity, serum lipids, measurements of renal function and glucose with cardiac function. Previously, some echocardiographic studies have suggested that patients with hypertension, metabolic syndrome, diabetes, renal failure or obesity may have subclinical cardiac dysfunction, and that cardiac function decreases with increasing age also in subjects without cardiovascular

disease (43, 46-56). Few studies have addressed whether cardiac function in healthy people, assessed by modern echocardiographic methods, is associated with blood pressure, serum lipids, renal function, or BMI.

Age is not a modifiable risk factor, but other common risk factors may be modified by interventions (blood pressure, cholesterol, smoking, diabetes or impaired glucose tolerance and impaired renal function) (36, 37, 39, 57-59). As age is a confounding variable, associated with both cardiac function (dependent variable) and the risk factors (exposure variables), it is usually controlled for in analyses of the different risk factors association with cardiac function, morbidity and mortality (36, 37, 40). In general, a 10 year risk for cardiovascular mortality higher than 5% or a 10 year risk higher than 10% for cardiovascular mortality and morbidity is regarded as high risk (36). In high-income countries cardiovascular disease and diabetes count for approximately 30 % of the total mortality (60), and the corresponding proportion in low-income countries is gradually approaching this level. Cardiovascular disease alone counts for more than 25% of the total burden of disease in the western world (60). As attributable factors, hypertension, smoking and high cholesterol are the 3 most important risk factors (60).

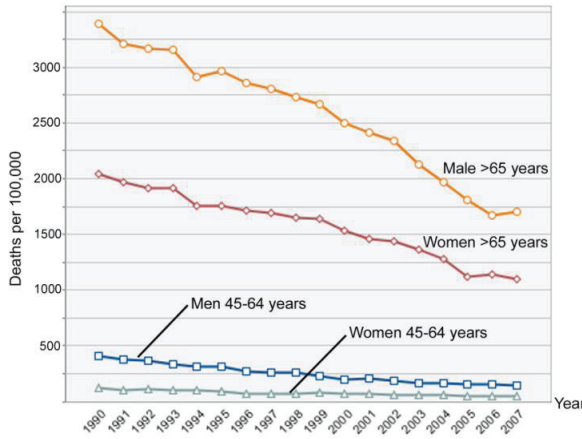

Figure 15. Cardiovascular mortality in Norway 1990 to 2007. Out of a total number of 41,963 deaths in 2007, 14,610 (~34%) subjects died related to cardiovascular disease (ischemic heart

disease, stroke and other) in 2007. As shown by the figure, the number of cardiovascular deaths has decreased over years. Figure applied from Statistics Norway.

2 Aims

2.1 General aims

To obtain general normal reference values for tissue Doppler velocities and deformation imaging and study cardiac function related to sex, age and common cardiovascular risk factors in a healthy population.

2.2 Specific aims

1) To study and compare the reproducibility of new and conventional measurements of the LV global and regional function based on both separate recordings and analyses.
2) To study conventional Doppler indices, and tricuspid and mitral annular systolic and diastolic velocities related to sex and age in a healthy population and provide population-based reference values for tricuspid and mitral annular velocities, including the corresponding E/e' ratios. In addition, to compare myocardial velocities assessed by pulsed wave and colour tissue Doppler.
3) To study longitudinal left ventricular segmental, regional and global deformation related to sex and age in a healthy population with regard to provide reference ranges according to sex and age, and in addition, to compare 4 different methods used to assess longitudinal deformation.
4) To study the associations of cardiac function with common cardiovascular risk factors in a healthy population.

3 Material

3.1 The HUNT Study

The HUNT Study (Nord-Trøndelag Health Study) is collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology), Nord-Trøndelag County Council and The Norwegian Institute of Public Health. The HUNT Study of adults from Nord Trøndelag County in Norway was initiated in the 1980s (61). The first wave of the HUNT Study was conducted from 1984 to 1986, the second wave from 1995 to 1997 and the third wave of the study was conducted from 2006 to 2008. All waves of the Study are independent cross-sectional studies where all citizens (except for children) in the County receive personalized invitation to participate. However, participants who attend to more waves can be followed across the different waves of the HUNT Study.

3.1.1 Nord-Trøndelag County; Steinkjer and Namsos

Nord-Trøndelag County is situated in the middle of Norway (Figure 16). The county had 130.708 citizens per January 1st 2009. Ethnicity is homogenous with mainly Caucasians and immigration and emigration are modest with 2.8% and 2.3% respectively. Mean age in Nord-Trøndelag county was 40 years per January 1st 2009. The population of Nord-Trøndelag County is fairly representative for the Norwegian population. However, there is no large city in the county, average income is somewhat higher and educational level is somewhat lower than in the rest of the country. Data from: Statistics Norway (http://www.ssb.no/en/).

The community of Steinkjer with its 20.868 inhabitants (per January 1st 2009) is one of Norway's largest agricultural communities. Namsos is somewhat smaller with 12.723 inhabitants. Both communities are structurally similar, with a densely populated town centre

with surrounding larger agricultural areas. In Steinkjer, about 70% of the inhabitants live in the town. Only 3% of the citizens in Steinkjer and Namsos were of non-Caucasian origin.

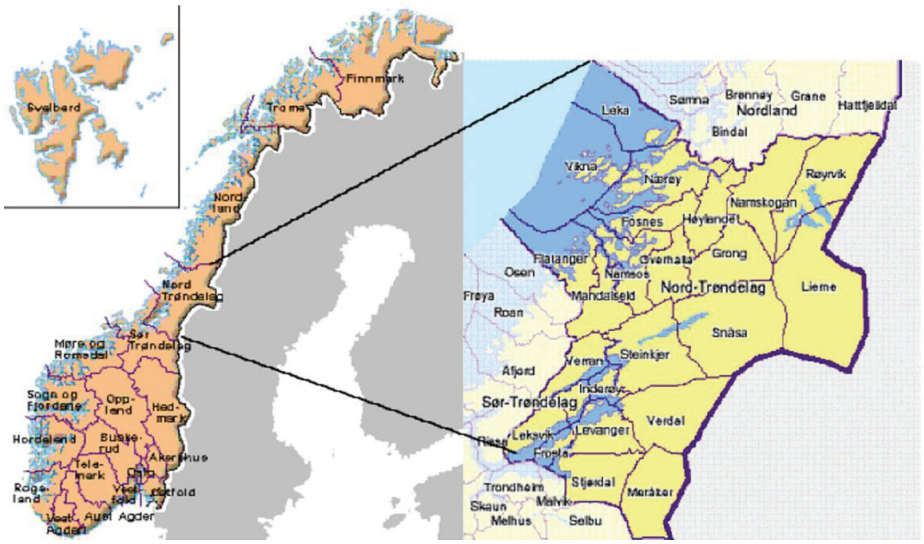

Figure 16. Norwegian counties at left and Nord-Trøndelag County with the different communities at right. Courtesy: HUNT (61).

3.1.2 The HUNT3 Study

In the third wave of the HUNT Study a total of 93,210 people were invited, and 50,839 (54%) participated. The participation rate for Steinkjer and Namsos was 58% and 45%, respectively. The HUNT3 Study was performed from autumn 2006 to June 2008. As all waves of the HUNT Study are independent cross-sectional studies, the three waves make prospective cohort studies possible.

3.1.3 Echocardiography in HUNT3

Within the third wave of the HUNT Study, we conducted an echocardiography study among a randomized sample of participants in predetermined communities (Steinkjer and Namsos) in

the county. To be eligible, people had to be free from known cardiovascular disease, diabetes or hypertension.

3.2 The reproducibility study

In this echocardiographic study 10 healthy volunteers (7 men, age 30 ± 6 years) were prospectively recruited. None were excluded due to inadequate echocardiographic images.

4 Methods

4.1 Study design

Study 1: Two experienced physician echocardiographers (AT and HD), blinded to each other's recordings, performed separate complete echocardiographic examinations on all the participants (20 examinations in total). The recordings on the same subject were separated by a time interval of approximately 30 minutes. Both echocardiographers analysed all measurements.

Study 2-4: Cross-sectional design with echocardiographic examination at participants' attendance to the third wave of the HUNT Study. This prepared the necessarily logistics to perform such an amount of echocardiographic examinations on a randomized sample in a limited time, and allowed coupling of the echocardiographic measurements and the additional data acquired by the HUNT organization. In total 1296 individuals were included in the echocardiographic study. 30 were excluded after echocardiographic examination due to findings that could influence cardiac function. Thus, the normal reference ranges are based on the echocardiographic studies of 1266 individuals. In Study 2 mitral annular velocities assessed by pwTD (GE Vingmed) and cTD (GcMat) were compared in the whole population

and in a random sample of 100 subjects. Comparison of cTD systolic mitral annular velocities assessed by customised software (GcMat) and commercial software (GE Vingmed) was done in the random sample of 100 participants. In Study 3 longitudinal strain and strain rate assessed by speckle tracking (AFI; GE Vingmed Ultrasound AS), tissue Doppler (GcMat) and combination of speckle tracking and tissue Doppler (GcMat) were compared in a random sample of 57 subjects.

4.2 Inclusion and randomization

Study 1: Participants were prospectively recruited among the staff at the Department of Circulation and Medical Imaging at the Norwegian University of Science and Technology. No randomization was done. The study was approved by the Regional Committee for Medical Research Ethics, and conducted according to the Helsinki Declaration. Written informed consent was obtained.

Study 2-4: The selection of healthy participants was based on the self-administered main questionnaire of the HUNT Study (Q1), where participants were not eligible if they answered 'Yes' to any of the questions about 'having' or 'ever had' cardiovascular disease, hypertension or diabetes (Q1; question 10, 11 and 12). Participants were then selected by randomization. Among the 1296 that were selected and consented to participate, 30 were excluded due to significant pathology that could influence the deformation analysis. Echocardiographic findings among the excluded individuals were aortic aneurysms and/or valvular pathology in 13 individuals, left ventricular dysfunction (cardiomyopathies, hypertensive heart disease, etc) in 9, atrial fibrillation in 3, and other reasons (infectious disease, malignancy, breast implants) in 5 individuals, respectively. Thus, these studies are based on echocardiographic examinations of 1266 men and women. The study was approved by the Regional Committee for Medical Research Ethics, and conducted according to the Helsinki Declaration. Written informed consent was obtained.

4.3 Data acquired by the HUNT3 organization

Questionnaires: All participants completed self-filled questionnaires (Main questionnaire (Q1) is attached in the Appendix section). Other questionnaires were used for additional data, but these were not included in this thesis. Smoking information was categorized as never, former, occasional or current smoking from the questionnaires. The latter three categories were grouped into a category of 'ever smoking' in the analyses in Study 3 and the latter two were grouped into a category of 'daily and occasional smokers' in Study 2.

Clinical examinations: The trained staff at the Study Centres performed anthropometric measurements and collected blood samples (61). Height and weight was measured wearing light clothes and without shoes; height to the nearest 1 cm, and weight to the nearest 0.5 kg. Waist circumference was measured horizontally at umbilical level with a steel band to the nearest 1 cm, with participants at standing position and arms relaxed. Blood pressure was measured three times using a Dinamap 845XT (Critikon; GE HealthCare). Measurements were made after two minutes rest with the arm on a table, and the average of the second and third measurement was used in the analyses.

Blood tests: Non-fasting blood samples were collected at study attendance, centrifuged and placed in a refrigerator before transportation to the IEC 17025 accredited laboratory at Levanger Hospital on the same day. Serum analyses were performed in fresh blood samples, on an Architect ci8200 (Abbott Laboratories, IL, USA). All analyses were performed by photometric methods. The coefficients of variation at the laboratory were 1.4-1.7% for glucose, 1.1-1.3% for cholesterol, 1.0-1.7% for HDL cholesterol and 1.9-2.4% for creatinine (62). In the analyses in Study 4 we calculated serum non-HDL cholesterol from total cholesterol minus HDL cholesterol, and renal function was assessed by the Modification of Diet in Renal Disease (MDRD) equation to calculate the estimated glomerular filtration rate

(eGFR) (63), where reduced renal function is usually indicated by values lower than 60 ml/min per 1.73m^2.

4.4 Echocardiographic data

Echocardiographic acquisition: In Study 1 two experienced physician echocardiographers (AT and HD) performed separate complete studies on all the participants in a random order, blinded to each other's recordings. All examinations in Study 2-4 were conducted by the author (HD). All participants were examined in the left-lateral decubitus position with a Vivid 7 scanner (version BT06, GE Vingmed Ultrasound, Horten, Norway) using a phased-array transducer (M3S and M4S). The echocardiographic examination included parasternal long and short axis views and three standard apical views. For each view, three consecutive cardiac cycles were recorded during quiet respiration or breath-hold. From the three apical planes separate grey-scale second harmonic mode and colour tissue Doppler mode were recorded. The Doppler pulse repetition frequency was 1 kHz. Colour tissue Doppler mode was recorded at a mean frame rate of 100 s^{-1} with underlying grey-scale images at a mean frame rate of 25 s^{-1}. Grey-scale recordings were optimized for evaluation of the left ventricle at mean frame rate of 44 s^{-1}. Echocardiographic data were stored digitally and analysed subsequently.

Echocardiographic data analyses: Interventricular septal and posterior wall thickness, fractional shortening, and LV internal dimension were analysed on parasternal M-mode echocardiograms with the ultrasound beam at the tip of the mitral leaflet. LV volumes were measured by M-mode (Teichholz formula) in study 2-4 and biplane Simpson's rule from the apical four- and two-chamber views in Study 1 (1).

From the pwTD recordings peak systolic mitral annular velocities (S'), peak early diastolic annular velocities (e') and late diastolic velocities (a') were measured at the

maximum of the Doppler spectrum with low gain setting. Peak systolic annular velocities were in addition measured at the peak of the curve obtained from colour tissue Doppler imaging (cTD). The cTD mitral annular velocities were assessed by EchoPAC PC(version BT09; GE Vingmed Ultrasound) in Study 1, and by GcMat in Study 4. In Study 2 both methods are used to assess cTD mitral annular velocities. The technical basis for these methods is described in paragraph 1.1.6. In addition, systolic mitral annular excursion was measured in reconstructed longitudinal M-mode from the apical position and from tissue Doppler by integration of the systolic cTD velocity curves in Study 1. The annular plane motion and velocity measurements of the septal, lateral, inferior and anterior walls were averaged to get measurements of global LV performance.

The mitral early diastolic filling velocity (E), late diastolic (atrial) filling velocity (A), E-wave deceleration time (DT), and E/A-ratio were measured. Isovolumic relaxation time (IVRT) was measured from the start of the aortic valve closure signal to the start of mitral flow. E/e' (pwTD) ratio was calculated by dividing E by the e' (pwTD). The e' used for these calculations were either the average of the septal, lateral, inferior and anterior walls, or by specified walls. In Study 2, E/e' was also calculated by E divided by e'(cTD). From the pulmonary venous flow waveforms, peak systolic (S) velocity, peak antegrade diastolic velocity (D) and S/D ratio were measured. All measurements reflected the average of 3 cardiac cycles during quiet respiration or breath-hold (64).

Longitudinal end-systolic strain (S_{es}) was measured at aortic valve closure, peak systolic strain rate (SR_s) as the maximal negative value during ejection time, early diastolic peak strain rate (SR_E) as the maximal positive strain rate during the first part of diastole, and late diastolic peak strain rate (SR_A) as the maximal positive strain rate during the last part of diastole. Diastolic deformation indices are shown in Study 1, only. Segmental S_{es}, SR_s, SR_E, and SR_A were measured in the three standard apical views. Speckle tracking in B-mode

recordings were done by two-dimensional speckle tracking echocardiography by the AFI packet (Automated Function Imaging; EchoPAC PC version BT 09, GE Vingmed, Horten, Norway). The region of interest was manually adjusted to include the entire left ventricular myocardium and simultaneously avoid the pericardium. The software automatically tracked speckles frame by frame throughout the cardiac cycle, and segments with poor tracking were excluded manually. Measurements performed by the AFI packet are shown in Study 1 and 3.

Combined tissue Doppler and B-mode recordings were analysed by customised software (GcMat). Seven kernels (chosen regions of the myocardium) sized 5x5 mm defining segment borders were tracked by tissue Doppler along the ultrasound beams and by grey-scale speckles perpendicular to the ultrasound beam. Lagrangian strain was calculated from the variation of segment length, and strain rate was calculated as the temporal derivative of strain, with automatic correction to Eulerian SR. This method has been described previously (30-33, 65). Aortic valve closure was automatically detected by tissue velocities (66). Only segments with good tracking of the kernels assessed by visual evaluation were accepted. Measurements of deformation acquired by GcMat are shown in Study 1, 3 and 4.

Segmental longitudinal strain and SR were analysed in an 18 segment model of the left ventricle, i.e. three segments per wall. As this model gives too much weight to the apex compared to the actual amount of myocardium, global averages were calculated following recommendations from the American and the European Society of Echocardiography in a 16 segment model, with only four segments at the apical level (1).

4.5 Statistics

Mean differences between sexes were tested using independent samples student's *t*-test, and differences in different measurements performed in the same individual by paired samples student's *t*-test and linear mixed effect models with post-hoc LSD method. Differences

between age-groups, myocardial walls and segments were tested by one-way ANOVA with post-hoc analysis with Bonferroni and least significant difference (LSD) correction. In general differences in myocardial function between regions were analysed with Bonferroni correction and differences between different methods were compared and tested by one-way ANOVA with post-hoc LSD method to enable detection of even smaller differences between the methods. A p-value <0.05 was considered significant. Coefficients of repeatability (COR) were calculated according to Bland and Altman's method (67) as twice the standard deviation of the differences in repeated measurements. Mean error was calculated as the absolute difference between the two sets of observations, divided by the mean of the observations (68-70), and coefficients of variation were calculated as the within-subject standard deviation divided by the mean of the observations. As we tested the reproducibility of two observations per subject, the coefficient of variation is related to the mean error by the following equations (Eq. 4 and 5):

Eq. 4: $$\mathrm{COV} = \frac{\mathrm{SD}}{\bar{x}} = \frac{\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2}}{\bar{x}}$$

Eq. 5: $$\mathrm{ME} = \frac{(x_1 - x_2)}{\bar{x}} = \sqrt{2} \times \mathrm{COV}$$

In Study 2 and 3 the association between measurements of cardiac function (dependent variables) and age was tested in multivariate analyses, with adjustment for body surface area, end-diastolic left ventricle internal diameter, heart rate and systolic or diastolic blood pressure. In Study 4 Pearson's method was used to test correlations between different echocardiographic measurements of cardiac function, and associations between cardiovascular risk factors and cardiac function were estimated by multivariate linear regression analyses with the different cardiac function measurements as dependent variables. The cardiac function measurements were log transformed, and the regression coefficients are presented as the percentage difference in cardiac function per standard deviation higher risk factor level with the corresponding 95% confidence intervals. In the analyses, age was

included as a covariate, and in the analyses of lipids and glucose we also included time since last meal as a covariate, since the blood samples were non-fasting. We used fractional polynomial regression analyses to model associations of the risk factors with cardiac function.

In Study 1, 2 and 4 the deformation and velocity data were presented as absolute values and in Study 3 deformation data were presented as negative values, where higher level of deformation is reflected in higher absolute values.

All statistical analyses were performed using SPSS for Windows (version 15.0 and 16.0, SPSS Inc., Chicago, IL, USA) and Stata for Windows (version 10, 1985–2007; StataCorp LP, College Station, TX, USA).

5 Summary of results

Study1: This study showed that for systolic function, a conventional method like systolic annular excursion by M-mode was equal or better in terms of reproducibility, compared to averaging segmental values from newer speckle tracking and tissue Doppler based methods. Furthermore, reproducibility data based on repeated measurements of single datasets severely underestimate the more clinically relevant inter-observer reproducibility based on separate recordings. The inter- and intra-analyser average mean error of the global systolic measurements based on repeated measurements of the same recording was 34 % and 43 % (both $p \leq 0.02$) lower than the average inter-observer mean error calculated by separate recordings and analyses. The corresponding reduction for the global diastolic measurements was 44 % and 64% (both $p<0.001$).

Mean error of segmental S_{es} and SR_s was significantly higher than all the respective global averages (all $p<0.001$). The inter-observer segmental S_{es} and SR_s mean error was 14% and 17% and the COR 7.1% and 0.52 s^{-1} by the ST method (AFI; GE VingMed Ultrasound).

When the segmental S_{es} and SR_s were averaged into global S_{es} and SR_s, the strain inter-observer mean error was reduced by 60% and the SR_s mean error was reduced by 44%. There were no significant differences in the reproducibility of global S_{es} and SR_s by the ST method compared to the combined method (ST and TD), but the inter-observer mean error of segmental S_{es} was significantly lower for the ST method ($p=0.03$).

Estimation of biplane EF, mitral annulus velocity and -motion measurements and all flow measurements were feasible in all recordings. 133/180 (74 %) segments post-processed by the ST method and 114/180 (63 %) post processed by the combined method were accepted for inter-observer validation by both echocardiographers. The rest of the segments were excluded by at least one of the observers because of reverberations, valvular interference, tracking difficulties, or poor image quality.

Study 2: A total of 1266 echocardiograms were analysed for blood flow Doppler and tissue Doppler measurements and all these measurements were accessible in at least 96% of the participants.

Normal reference ranges, corresponding to approximately 95% of the population (two standard deviations of the mean), based on our results for mitral and tricuspid S' and e' by pwTD, and E/e' ratios are shown in Table 1. Systolic velocities were higher in men compared to women, and early diastolic velocities were higher in women (all $p<0.001$). Mitral and tricuspid annular velocities decreased with age in both sexes (all $p<0.001$), and the E/e' ratio increased with age. The differences by age were significant for each wall (all $p<0.001$).

Table 1: Normal reference ranges for mitral and tricuspid S'and e' and E/e' ratio by age group and sex

	LEFT VENTRICLE			RIGHT VENTRICLE	
	S' (cm/s)	**e' (cm/s)**	**E/e'**	**S' (cm/s)**	**e' (cm/s)**
Women, <40 years	6.7-11.1	10.0-19.2	3.0-8.2	9.4-16.6	8.9-20.5
Women, 40-59 years	5.7-10.5	6.5-16.1	3.2-10.4	8.6-16.2	7.3-18.9
Women, ≥60 years	4.8-9.6	1.8-14.6	3.1-14.3	7.8-15.8	6.4-15.6
Women, overall	5.6-10.6	5.4–18.2	2.5-10.9	8.7-16.3	7.3-19.3
Men, <40 years	6.6-12.2	8.7-19.5	2.5-8.5	9.2-17.2	8.7-20.3
Men, 40-59 years	6.0-11.2	6.1-15.3	3.0-9.4	8.4-17.2	6.1-18.9
Men, ≥60 years	5.4-10.6	4.4-12.0	3.1-12.3	7.9-17.1	5.0-17.0
Men, overall	5.8-11.4	4.8– 16.8	2.4-10.4	8.4-17.2	5.9-19.1

Table 1: Normal reference ranges for mitral and tricuspid S'and e' and E/e' ratios according to sex and age. All tissue Doppler data are assessed by pwTD.

The measured mitral and tricuspid annular velocities differed by the different methods used. The cTD methods (EchoPAC PC and GcMat) measured lower mitral annular velocities compared to the pwTD for all myocardial walls (all $p<0.001$), but there were only a slight difference (overall 0.2 cm/s) between the two cTD methods ($p\leq0.08$). Measuring mean mitral annular velocities by averaging the inferoseptal and anterolateral wall and by averaging velocities for the four myocardial walls yielded similar results. The correlation between pwTD and cTD was high in our data ($r=0.85$, $p<0.001$).

The blood flow Doppler velocities decreased with increasing age. Differences were highly significant between the youngest and oldest age group for all displayed parameters and in both sexes, except for LV outflow tract measurements in both sexes (all $p\leq0.002$). The

pulmonary venous S/D ratio did not differ by sex, but other indices showed consistently higher velocities in women (all $p<0.05$).

Study 3: Out of a total of 22,788 analysed segments, 13,765 were accepted as yielding optimal tracking, and these segments were the basis for estimating reference values for systolic strain and SR, yielding an overall feasibility of 60%. Longitudinal end-systolic strain (S_{es}) and peak systolic strain rate (SR_s) were normally distributed. The study participants were stratified according to age (<40, 40-59, and ≥60 years) and sex and reference ranges were provided for segmental and global deformation indices according to age and sex.

Table 2: Normal reference ranges for longitudinal global left ventricular strain and strain rate by age group and sex

	Women		**Men**	
	Strain (end-systolic, %)	**Strain rate (peak systolic s^{-1})**	**Strain (end-systolic, %)**	**Strain rate (peak systolic s^{-1})**
<40 years	-22.1 to -13.7	-1.33 to -0.85	-20.8 to -12.8	-1.32 to -0.80
40-59 years	-21.8 to -13.4	-1.32 to -0.80	-20.2 to -11.4	-1.25 to 0.77
≥60 years	-20.7 to -11.1	-1.25 to -0.69	-20.2 to -10.6	-1.25 to -0.69
Overall	-22.0 to -12.8	-1.31 to -0.79	-20.5 to -11.3	-1.27 to -0.75

Table 2: Normal reference ranges for global left ventricular end-systolic strain and peak systolic strain rate according to sex and age. Data assessed by the combined method (tissue Doppler and speckle tracking).

Over all, mean global S_{es} for women and men was -17.4% and -15.9%, and mean global SR_s was -1.05 s^{-1} in women and -1.01 s^{-1} in men. With increasing age, there was a general

decrease in both indices at all ventricular levels and walls. S_{es} and SR_s differed significant between different levels and walls of the left ventricle, but the differences were too small to be of major clinical importance. S_{es} and SR_s were significantly and consistently lower in men than women (all $p<0.001$), except in the oldest age group (≥60 years).

The combined method using speckle tracking (ST) and tissue Doppler (TD) to assess LV deformation gave significantly lower values ($p=0.02$) for global strain compared to the ST method (AFI; GE Vingmed Ultrasound AS). However, the mean difference was only 1 percentage point strain, and the difference was not significant when the ventricle was subdivided into basal, mid-ventricular and apical regions. For strain analyses the overall difference between the combined method and the two TD methods was small. Strain rate did not significantly differ between the combined method and ST method. Strain rate values obtained by TD were significantly higher in all parts of LV compared to the combined method and ST method.

Study 4: In this population study of 1266 men and women without known cardiovascular disease, hypertension or diabetes, traditional cardiovascular risk factors were clearly associated with reduced left and right ventricular function assessed by tissue Doppler and speckle tracking echocardiography. Cardiac function was gradually reduced with increasing blood pressure, BMI and non-HDL cholesterol, and with decreasing HDL cholesterol and eGFR. Cardiac function was poorer in ever smokers compared to never smokers. Except for smoking, the strength of the associations was consistently stronger for left than right ventricular function.

For BMI and diastolic blood pressure, there was some evidence for J-shaped associations with cardiac function. LV strain was slightly reduced for men with BMI under 23 kg/m^2 and for women with BMI under 20 kg/m^2. Among men, there was a similar J-shaped

association for diastolic blood pressure with reduced LV strain under diastolic pressure of 50-60 mmHg. For some of the other factors, there was suggestive but not consistent evidence for J-shaped associations with cardiac function.

The overall results showed that LV strain was reduced by approximately 5% per 5 kg/m^2 increase in BMI, and reduced by approximately 4% and 2% per 10 mmHg increase in diastolic and systolic blood pressure, respectively. The corresponding reductions in early diastolic LV function (e`) were approximately 7% for both BMI and diastolic blood pressure, and 4% for systolic blood pressure. LV strain was reduced by approximately 2% per mmol/L increase in non-HDL cholesterol, and increased by approximately 4% per 0.5 mmol/L increase in HDL cholesterol, respectively. Ever smokers had approximately 4-5% reduced systolic and early diastolic RV function (e`) compared to never smokers.

Ever smoking was associated with reduced LV function in women, but not in men, whereas lower eGFR was associated with reduced LV function in men, but not in women. In both sexes, higher HDL cholesterol was associated with better LV function. Higher diastolic blood pressure was also associated with reduced RV function, except for systolic function in women. Reduced RV function was observed in men, but not in women with high BMI.

Mitral inflow E/A ratio was lower with higher age, body mass index (BMI), systolic and diastolic blood pressure and non-HDL cholesterol. In addition, mitral E/A ratio was lower with lower HDL cholesterol and among smokers ($p=0.18$ for HDL cholesterol in women, $p=0.13$ for male smokers and all other $p\leq0.07$). Age influenced all measurements, but for LV outflow tract velocity time integral and mitral peak E velocity the associations with other risk factors were weak and not consistent. There were no clear associations of any risk factor with cardiac function, as measured by fractional shortening or one-dimensional EF. The majority (>98%) of the study participants had normal diastolic function or mild diastolic dysfunction.

Table 3 shows that higher level of different measurements of obesity was associated with lower LV function. Inversely, height was associated with higher indices of LV function, most pronounced for the mitral annular velocities which are not adjusted for size.

Table 3. Percentage difference in LV function indices per SD change in anthropometric measurements

	Women			
	BMI *(SD 4.2kg/m^2)*	**BSA** *(SD 0.16m^2)*	**Waist circumference** *(SD 11.7cm)*	**Height** *(SD 6.1cm)*
Mitral S'	-1.3 %, p=0.03	0.2 %, p=0.79	-0.5 %, p=0.35	1.8 %, p=0.001
Mitral e'	-4.3 %, p<0.001	-2.7 %, p<0.001	-4.2 %, p<0.001	1.1 %, p=0.18
Long S_{es}	-3.1 %, p<0.001	-1.7 %, p<0.01	-3.2 %, p<0.001	1.2 %, p=0.04
Long SR_s	-1.9 %, p<0.001	-0.8 %, p=0.14	-1.6 %, p<0.01	1.1 %, p=0.04
EF	-0.9 %, p=0.20	-0.5 %, p=0.53	-0.8 %, p=0.27	0.4 %, p=0.61
	Men			
	BMI *(SD 3.5kg/m^2)*	**BSA** *(SD 0.16m^2)*	**Waist circumference** *(SD 9.8cm)*	**Height** *(SD 6.5cm)*
Mitral S'	-2.7 %, p<0.001	-0.8 %, p=0.22	-2.3 %, p<0.001	1.6 %, p=0.02
Mitral e'	-6.4 %, p<0.001	-3.2 %, p<0.001	-5.9 %, p<0.001	1.8 %, p=0.06
Long S_{es}	-3.9 %, p<0.001	-2.4 %, p<0.001	-4.3 %, p<0.001	0.3 %, p=0.60
Long SR_s	-2.6 %, p<0.001	-1.9 %, p<0.001	-2.9 %, p<0.001	-0.2 %, p=0.69
EF	-1.9 %, p<0.01	-1.6 %, p=0.03	-1.8 %, p<0.01	-0.5 %, p=0.51

Table 3: All data are adjusted for age and presented as mean differences with corresponding p-value. Abbreviations: SD = standard deviation, Long=longitudinal

6 Discussion

6.1 Population

In Study 2-4 the distribution of age among the participants followed a normal distribution. Participant fulfilling the inclusion criteria were selected by randomization and included at study attendance. Nevertheless, all population studies are sensitive to a selection bias. In this study this is probably most pronounced among the youngest and the oldest participants. For all participants simultaneous symptoms or unfavourable levels of cardiac risk factors may increase the attendance rate in a cardiac ultrasound study (71). However, the Echocardiography in HUNT3 was only one of many sub-studies in HUNT 3. Both the randomization of participants to the different sub-studies, and the exclusion of participants with known cardiovascular disease, diabetes and hypertension may, at least partly, reduce this bias. Nevertheless, the attendance rate bias may especially influence the finding among the youngest participants, as the attendance rate was lower and it may be suggested that a free health examination may be more attractive to subjects with any symptoms or higher level of risk (71). Particularly among the oldest participants, the selection of only participants capable of attending in the HUNT Study, and in addition, without history of hypertension, diabetes and cardiovascular disease may select only those with the very best standard of health (71). Such capability is even at old age a function of general health. Subjects with reduced functional capability may be considered to be in low health, and thus not eligible for the normal study. As shown in Study 2-4 mean body mass index was approximately 25 kg/m^2 among the participants, which indicate that approximately half the population is classified as overweighed or obese (36, 72). However, with the today's epidemic of obesity in mind this may reflect normality, as it reflects the worldwide change in body mass index (44).

The randomization process was administered by the HUNT organization. Among those eligible for inclusion (no history of hypertension, cardiovascular disease and diabetes) most of the participants were randomized either to the Echocardiography in HUNT3 Study, or to other sub-studies (with similar or different inclusion criteria) and in addition a smaller proportion was randomized to several sub-studies. The time aspect of one participants' total time spent the attendance to the HUNT3 study was the reason for that only a small proportion of participants were randomized to several sub-studies, since the goal was that each participant should complete her attendance in one hour.

6.1.1 Age and sex

In Study 2-4 we show a reduction in cardiac function by age, as measured by myocardial velocities and deformation imaging. The finding was consistent both in women and men. Few previous echocardiographic studies have assessed deformation parameters by age, and these studies were too small to reliably assess whether the degree of deformation were dependent on age or gender (46, 73-75). However, previous studies have shown age dependency of both diastolic and systolic function assessed by LV filling, mitral annular displacement and TD velocities of the mitral annulus (47, 49, 76-80).

We present consistent findings with higher myocardial deformation in women compared to men, except in the oldest age group (≥60 years) (Study 3), and also higher blood flow velocities and early diastolic mitral annular velocity in women (Study 2). Similar results have been reported for LV (47), but data for RV are scarce (81). The difference by sex was less clear in tricuspid annular velocities compared to mitral annular velocities. Most anthropometric and physiological factors differed significantly between sexes and this may influence the results. The described sex difference by the different methods was not substantially altered after adjustment for size (height, body surface area or BMI, in addition to

LV size), heart rate and blood pressure in multivariate analyses. The deformation indices are also adjusted for LV size due to the method used, as strain and strain rate, being measurements of deformation per length, are already normalised for LV size, and normalising for body size as well, may be inappropriate.

In Study 2-4 we present reduced difference between sexes of annular velocities and deformation indices at higher age, which may indicate that the sex difference may be influenced by sex hormones. On the other hand, this may be explained by age as a more important factor for cardiac function at higher levels, as seen in population studies regarding morbidity and mortality (82). However, the observed sex and age difference of the different measurements of cardiac function verifies the need of sex and age specific reference ranges.

6.1.2 Race

Since a very small amount of the study population is of non-Caucasian origin, race-specific data is not provided. To which degree the results can be generalized to other ethnic populations is unclear. Nevertheless, results from the large Multi-Ethnic Study of Atherosclerosis suggest that race may not be associated with LV function as measured by cardiac tagged magnetic resonance imaging (83). However, this study did not detect any difference in cardiac function by age, which may reflect a limitation of the magnetic resonance imaging method, since the present evidence of reduced cardiac function by increasing age is sufficient (46, 47, 49, 56, 75, 84, 85).

6.2 Echocardiographic acquisitions and analyses

Aspects that may influence both echocardiographic acquisitions and analyses are discussed in short terms in the following sections. Overall, a total of 20 echocardiograms were analysed in

Study 1 and a total of 1266 echocardiograms were analysed in Study 2-4. All measurements of cardiac function indices followed a normal distribution. This is in line with recent publications of deformation indices assessed by ST (75) and cTD velocity data (47).

6.2.1 Dimensions and blood flow measurements

The age dependency of diastolic flow indices are in line with former studies (49, 56, 76, 81, 86). In the Tromsø Heart Study, probably the largest population-based echocardiographic studies, mitral inflow velocities and IVRT were similar to our findings, but DT was slightly different from our results (56, 86). LV size was measured by M-mode to describe the basic characteristics of the population, and the results were in line with previous studies (46, 81).

6.2.2 Annular tissue Doppler velocities

Myocardial velocities were assessed by pulsed wave and colour tissue Doppler methods, which are two fundamentally different methods. The cTD method calculates the mean velocities of the sample volume, while pwTD method gives the maximal velocities of the sample volume. With regard to the cTD method different filter settings and how the methods deal with low velocity clutter will significantly affect the results. These factors are usually considered as company secrets and differ between systems. Gain settings and localization of the measurement in the Doppler spectrum are crucial points in pwTD analysis. As described in the introduction, pulsed wave Doppler is a spectral analysis. The signal intensity of the myocardium is high and the velocity is low compared to blood. Thus, the relative width of the Doppler spectrum is much larger for pwTD velocities compared to blood flow velocities. Higher gain will further increase the width of the spectrum, and this may lead to

overestimation of the velocity (Figure 6). Secondly, misalignment of the ultrasound beam will cause underestimation of the tissue velocity.

The cTD values were in line with former publications (47, 81, 87, 88), but the pwTD assessed mitral annular velocities were somewhat lower than reported from other smaller studies (64, 89, 90). In a recent population study the overall normal ranges by pwTD were somewhat higher with regard to systolic velocities and somewhat lower regarding early diastolic velocities (80). This study did not provide sex specific data and as the proportions of participating men and women (56 % men) differed from our population, direct comparison is difficult. Thus, the described difference may at least in partial be explained by the sex difference. Diastolic pwTD indices were in line with those previously reported, based on data from 80 healthy individuals (76). In former studies gain settings and localization in the Doppler spectrum used for measurement are rarely completely specified (64, 80, 89). As the tissue signal is strong, we measured the peak velocities at the outer edge of the Doppler spectrum at low gain settings in order to avoid week signal noise. This approach corresponds well to the maximal velocities, and in abstract presentation from our group, we found that this approach fairly well reflects the 'true' velocity of the myocardium (91). The most important reason why the pwTD velocities differ between studies is probably the use of different gain settings between the different studies (80, 89, 90, 92).

6.2.3 Deformation imaging

Especially with regard to deformation imaging signal noise and acoustic artefacts pose a challenge in the analyses, and for tissue Doppler measurements, angle dependency also limits the method. Drop outs and reverberations lead to low or zero values in the area of artefacts, giving both under- and overestimation of strain and strain rate values, as they are based on

subtraction of values. Inclusion of errors as described may add skewness to the distribution of measurements in the population.

Since the aim was to obtain reference values for segmental deformation indices in healthy individuals, we tried to minimize these measurements error by including only segments with optimal tracking of segment borders by visual evaluation. Using the customised method, both segments adjacent to the kernel were rejected in case of poor tracking (Figure 12). By commercial and customised software, it is usually left to the discretion of the analyst to decide whether the segments should be discarded, which means that they may be included even though they should be discarded for the same reasons (32). This may be explained by the settings of spatial smoothing and temporal averaging in commercial software. By commercial software, the user does not have full information about segment borders and spatial resolution. This is less of a problem for global measurements, but as our aim was to achieve segmental normal values, the use of customised software was in fact the only way to achieve full information about segmental borders, and the process used to calculate myocardial deformation. By the use of customised software it is left to the analyser to place the region of interest, compared to commercial software were this is based on expectation of curve shape. Thus, commercial software may lead to biased post processing, while the customised software only allows the user to accept or reject curves from a segment. In addition, the use of customised software was the best practical solution for using a TD-based method to assess deformation indices in such a large population since the commercial tools are more time consuming (31). Nevertheless, compared to other methods this will increase the percentage share of discarded segments and due to the large study population we could afford to discard segments with non-optimal tracking, even though tracking of kernels could be reasonable good. Our goal was to reduce the effect of noise, reverberations and artefacts as much as possible. Thus, the software may be useful in a higher proportion of

segments in a clinical population, but in this case the aim of the analyses was different. The need of discarding both segments adjacent to a kernel without sufficient tracking reduces the feasibility and remains a limitation of the method used, thus, it still is a strength, rather than a weakness of the study since the extent of biased data are reduced.

The presented deformation data are in line with a recent publication by speckle tracking (75). As shown in Study 3, the presented normal ranges are useful in a wide clinical setting. However, reference ranges obtained by a specified method can not be directly transferred to another method, illustrated by the large difference in strain rate by the velocity gradient methods and the segment length methods in Study 3.

6.2.4 Global vs. segmental analyses

As shown in Study 1 and 3, segmental analyses are challenging. In Study 1 the test-retest variability, assessed by mean error (absolute difference divided by the mean of two observations) of global analyses by two different methods (AFI and GcMat) was 4-10%, compared to 14-18% in segmental analyses. In Study 3, segmental and global reference ranges are shown. The normal ranges are much wider at the segmental level compared to the global level. These findings indicate the main limitations of segmental analyses. Before classification of an isolated segment as dysfunctional the measured value must be approximately 40-50% below the mean, while the corresponding relationship at the global level is 20-30%. Nevertheless, deformation imaging is the best method to quantify segmental cardiac function (93), but the method has major limitation as illustrated above. Thus, the need for special awareness of methodological and technical limitations of the method used is warranted when segmental evaluation is used in decision making in clinical practice.

6.2.5 Methodological differences - strengths and weaknesses

The different methods used in these studies illustrate to some degree the armamentarium of methods used in echocardiographic laboratories. The different methods differ with respect to the technological basis, how user-friendly the interface is and also with respect to what they possibly can obtain.

The different methods used to evaluate LV (and RV) function differ in the same way. Low ejection fraction correlates well to mortality, but the method is inferior to the more modern methods with respect to quantify LV function (12, 29).

The tissue Doppler velocity methods used to quantify cardiac function are easy to use and have shown ability to differentiate between sick and healthy myocardium, as well as to predict mortality (47, 77, 94). The pwTD method is performed online, while the cTD method is performed offline on colour coded tissue Doppler recordings. The pwTD method is recommended by the European and the American Associations of Echocardiography for diastolic quantification due to more validation studies than the cTD method (64). However, in the Copenhagen Heart Study cTD systolic mitral annular velocity predicted mortality (77). As shown in this thesis the two tissue Doppler methods of assessing myocardial velocities differ with respect to methodology and the absolute values obtained, with lower values by the cTD method. However, they seem equal with respect to reproducibility and differentiation of cardiac function by age, sex and risk factors (Study 1, 2 and 4).

The methods used for deformation imaging are promising and was shown superior to ejection fraction and wall motion score to predict mortality in a recent publication (29). As discussed above, two main methods are basis for deformation imaging. The tissue Doppler methods are one-dimensional, angle dependent, time consuming and the user have no way to monitor the measurement as it is based on the Doppler velocity gradient. Compared to speckle tracking methods, the advantage is the high frame rate with respect to assess strain rate. The

speckle tracking methods are two-dimensional, less time consuming and more user-friendly, but still they are very user dependent with regard to avoid the pitfalls discussed above.

6.2.6 Reproducibility

The reproducibility of the different echocardiographic measurements is influenced by aspects related to both the methodology and the user. The most reproducible measurements are easy to perform and are based on methodology where the influence of random noise is low. This is exemplified by the M-mode of longitudinal atrioventricular displacement. On the other hand, measurements that are more difficult for the user and in addition more influenced of random noise will have poorer reproducibility.

In Study 1-3 measurements that represent the average of several measurements, showed better reproducibility compared to single measurements. In addition, the clinical interesting test-retest variability of measurements performed in separate echocardiograms is not well illustrated by reproducibility testing on single datasets.

Overall, the echocardiographic indices used in this thesis show fair to excellent test-retest reproducibility. Diastolic indices showed higher variability compared to systolic measurements, which may rely on higher short term biological variation in addition to other reasons discussed above.

6.3 Cardiovascular risk factors

The results presented in Study 4 suggest that conventional risk factors are reliable and consistent markers for cardiac function assessed by echocardiography. Thus, our findings correspond to the evidence from large follow-up studies of unselected populations that have

shown strong associations with the risk and mortality of cardiovascular disease related to the same risk factors (36, 37, 40, 58).

Many studies have displayed U- or J-shaped associations of blood pressure and BMI with cardiac morbidity and mortality (58, 95, 96). In Study 4 we found evidence for inverted J-shaped associations of diastolic blood pressure and BMI with LV function. Thus, LV function was not only reduced at high levels of diastolic pressure, but also among people with pressure lower than approximately 60 mmHg. A recent meta-analysis and clinical guidelines suggest that people with diastolic blood pressure under 70 mmHg may be at increased risk for coronary heart disease (36, 95, 97), and it has been suggested that low diastolic pressure may reflect underlying pre-clinical disease, or increased pulse pressure due to vascular disease or aggressive antihypertensive treatment (95). However, none of the participants of the present study were taking hypertensive medication.

Associations between overweight or obesity and reduced left ventricular function have also been shown by others (43, 50, 53). However, the inverted J-shaped form of the association, suggesting reduced LV function in very lean or thin people, has not been noted previously. The J-shape was most pronounced when LV function was assessed by longitudinal strain (Figure 17). This may add credibility to the finding, because strain measurements are adjusted for LV size, and LV size is correlated with lean body mass. Our finding may indicate pre-clinical reduced cardiac function or occult underlying disease also at very low levels of risk factors as BMI and diastolic blood pressure.

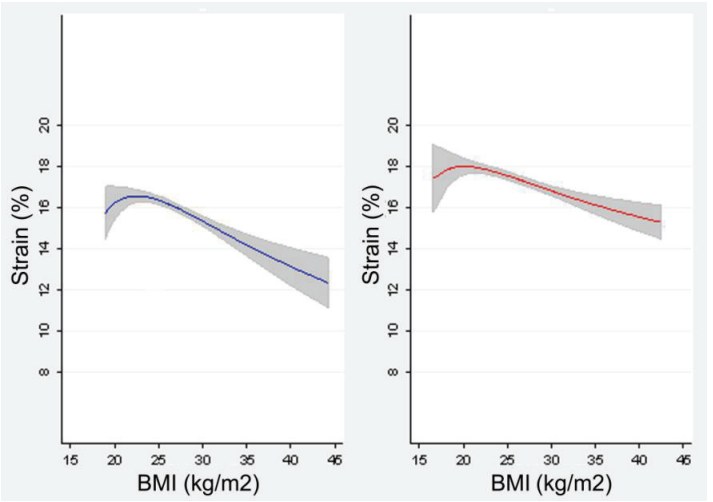

Figure 17. The inverted J-shaped curves are illustrated by fractional polynomial regression plots of longitudinal LV end-systolic strain by BMI in men (left) and women (right). The highest strain value is observed when BMI is 23 kg/m^2 in men and 20 kg/m^2 in women, with lower observed strain values with lower and higher BMI. However, as shown by the grey shadow reflecting the 95% confidence interval the variability and therefore the accuracy are lowest at both ends of the scale (x-axis).

There is a well established association of smoking with increased cardiovascular risk (38, 98), and we found that ever smoking was associated with reduced systolic and diastolic RV function in both men and women, and associated with reduced systolic and diastolic LV function in women. Based on our results, smoking appears to be more strongly related to RV than LV function, and if correct, it seems plausible that increased pulmonary arterial resistance related to smoking may increase RV load and reduce RV function. However, only 65 of the men who participated reported daily smoking, and the low prevalence of daily smoking limited our possibility to detect any association of smoking with cardiac function.

Different physiological mechanisms may influence the results of this study. As a general principle, all echocardiographic measurements will be reduced by increasing afterload

(64, 93). Although myocardial velocity and deformation measurements are less affected than blood flow velocities (64, 93), increased afterload may influence the results. This concerns arterial blood pressure for the LV and the suggested pulmonary arterial resistance for RV function (99).

Both obesity and hypertension are related to a sedentary lifestyle, and previously it has been shown that LV systolic and diastolic function is related to physical activity (94). Table 3 shows that the results for waist circumference, body surface area and BMI were nearly identical, suggesting that these measurements may be used interchangeably as markers for obesity in this population. However, the associations of cardiac function with height were not in line with those above mentioned. This seems to indicate that BSA is not an obesity independent measure of body size, in contrast to what has previously been hypothesized. Thus, height may be a better parameter of obesity independent body size. The associations of strain and strain rate measurements with height were weaker, probably because those measurements already are adjusted for LV size.

Previous studies have suggested that a certain proportion of patients with hypertension and obesity may have increased interstitial fibrosis and LV geometrical changes (41, 42, 100), and it is possible that the observed reduced cardiac function in our study may be attributed to similar characteristics. Thus, the association of lower cardiac function with higher level of the risk factors may be explained in two ways. Firstly, by subclinical dysfunction that may be present in a modest proportion of the participants, and secondly by a gradual but general reduction in cardiac function that may be attributed to unfavourable levels of the measured risk factors. In this cross-sectional study we are not able to differentiate between the possible mechanisms, but we may hypothesize that both are important. Former publications could illustrate this: Firstly, with exercise training a general improvement of physiological factors exemplified by oxygen consumption is achieved (101). On the other hand, ‘the prevention

paradox' describes the paradox of in order to prevent one single cardiovascular event by treating hypercholesterolemia with statin therapy; many individuals must take medications with no apparent benefit (36).

6.4 Cut-off values vs. normal values

Since the variability of most echocardiographic measurements is significant, the relation between cut-off values and normal ranges usually is best illustrated by Figure 14. Thus, there is a need for normal values, and to obtain normal values large population studies are needed to show the distribution of certain measurements according to sex and age.

The paradigm of normality is challenging. First, if the population studied is selected only by exclusion of individuals with overt disease, the result may be inclusion of individuals with subclinical disease and the corresponding normal ranges will be too low. On the other hand, exclusion of everyone with any kind of pathology will result in a supra normal reference range. Thus, cut-off values and normal values are fundamental different, and both approaches have limitations. Cut-off values favour the classification of disease, which may lead to over diagnosing, while normal ranges favour the classification of normality and may lead to under diagnosing. Nevertheless, normal ranges are more transferable to daily clinical practice as it better reflect the variation of normality.

6.5 Limitations

The participants of Study 2-4 were randomly selected among healthy individuals in the general population of mainly northern European Caucasian descent, and therefore, it is uncertain to which degree the results can be generalized to other ethnic populations. In Study 2-4 information on smoking was based on questionnaire data, and no further validation of

smoking was conducted. Blood samples were non-fasting, and in the analyses, we adjusted for time since last meal in an attempt to take this limitation into account. Thus, cholesterol levels were not in steady state and this could limit the analyses. We therefore restricted the analyses to test for associations of cardiac function with HDL- and non HDL-cholesterol, and triglycerides, being the most fasting sensitive, were excluded from the analyses.

According to our general aim of obtaining reference values for different echocardiographic indices, including deformation imaging, the use of customised software limits the generalization of the reference values. However, as discussed above, the customised software were the only available software where full information about segmental borders, and the process used to calculate myocardial deformation could be published. In addition, performing the analyses with the aim to obtain segmental reference ranges resulted in the need for excluding all segments with non-optimal tracking of segment borders. The need for exclusion of segments with non-optimal tracking would have been less critical if only global measurements were aimed, and in that case optimal tracking of the apical and basal ROIs would be sufficient. We included comparison of different methods to take these limitations into account, and to make these normal values useful in a wide clinical setting. However, using commercial speckle tracking software is attractive due to time consumption and the fact that the most useful normal values should be assessed by commercial software.

6.6 Conclusions

6.6.1 General conclusion

We present normal reference ranges for mitral and tricuspid annular tissue Doppler velocities and segmental and global deformation indices, as well as for conventional echocardiographic indices. Reduced left and right ventricular function was associated with higher age and higher level of cardiovascular risk factors in a healthy population. Cardiac function, as assessed by

mitral and tricuspid annular tissue Doppler velocities and LV deformation indices, differed by age and sex. Thus, there is a need for age and sex specific normal reference ranges.

6.6.2 Specific conclusions

In Study 1 we concluded that modern echocardiographic equipment allows reproducible measurements of most global indices of LV performance. Repeated analyses of the same recordings underestimate the clinically relevant inter-observer reproducibility obtained by separate examinations by approximately 40% for most measurements of LV function. Averaging tissue Doppler measurements is recommended in order to optimize reproducibility. Global averages of segmental deformation indices have approximately the same reproducibility as the other global measurements, but segmental measurements have higher variability.

In Study 2 we presented reference values for conventional Doppler indices, pulsed wave and colour tissue Doppler velocities as indices of LV function, and pulsed wave tissue Doppler velocities from the tricuspid annulus according to age and sex. The absolute velocities differed between Doppler methods, but the results were highly correlated. Averaging the values from the inferoseptal and anterolateral myocardial walls give a fair measure of global LV annular velocity. The presented difference in LV and RV function indices by age and sex suggests that recommendations of normal limits should be specified according to age and sex.

In Study 3 we present reference values for global and segmental longitudinal end-systolic strain and peak systolic strain rate according to age and sex. Left ventricular strain and strain rate was consistently higher in women across segments, and there was a highly significant decrease with increasing age in both sexes. The presented reference values corresponded well

with other specified methods, and are widely applicable for strain and SR measurements in clinical settings; except for tissue Doppler derived strain rate measurements, which showed significantly higher mean values and far wider range. We recommend that clinicians use the presented reference values for segmental strain and strain rate measurements in individual clinical decision making with special awareness of methodological and technical limitations of the method used.

In Study 4 we found that unfavourable levels of conventional risk factors were clearly associated with reduced left and right ventricular systolic and diastolic function in a population of individuals without known cardiovascular disease, hypertension or diabetes; suggesting the possibility of subclinical cardiac dysfunction. The findings suggest that these risk factors influence cardiac function many years prior to clinical detection. The J-shaped associations of diastolic blood pressure and body mass with LV function indicate that very low blood pressure and extreme leanness may be indicators of prevalent but subclinical cardiac dysfunction.

6.7 Future studies

As the data from the presented echocardiographic study of almost 1300 individuals without known cardiac disease, hypertension or diabetes are available in digital format subsequent studies are possible. Additional studies on normal reference ranges are planned.
With regard to global function, mitral and tricuspid annulus systolic and diastolic velocities have been measured. Longitudinal systolic deformation of left (systolic mitral annulus excursion – MAE) and right ventricle (tricuspid annular plane systolic excursion – TAPSE) will be measured and normal ranges established. Global strain is another measurement of global function, which is normalized for left ventricular length. In the presented material, it is

available as the average of segmental strain values, as given in paper 3. Global strain can be measured directly by speckle tracking, by the commercially available application 2D strain, as was done here for a limited selection. However, another measurement of global strain is simply MAE divided by LV length, which would be much less dependent of scanners and software. Indexing longitudinal shortening for ventricular length seems attractive with regard to increase both sensitivity and specificity of the data (102). In addition, comparison of these methods may be of interest.

Segmental analyses is so far only done for the left ventricle, the right ventricle remains to be studied. How right ventricular function is associated with airway obstruction is unknown. Our database combined with the HUNT database makes further studies attractive.

Another approach is to study the normal ranges for both myocardial velocities and deformation with different commercial software, and to compare how the use of ultrasound scanners from different companies influences the results.

Almost 300 individuals were randomized to both echocardiographic examination, exercise testing and ultrasound examination of the brachial artery to assess endothelial function. This provides a basis for further investigation of the association of cardiac function with other specific markers of health standard as well as physical performance.

The collaboration with the HUNT organization makes studies on the association of cardiac function with both established and future markers of cardiac risk and function possible. Over time, clinical end-points will be available from local and national registries, to assess correspondence with baseline echocardiographic data. The selection of a healthy population will claim long perspective for such studies, but inclusion of only healthy individuals could make the results applicable in the general population.

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Paper 1

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Paper 2

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Paper 3

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Paper 4

Cardiovascular risk factors and systolic and diastolic cardiac function: a tissue Doppler and speckle tracking echocardiographic study

Brief title: Cardiac function associated with risk factors. The HUNT Study.

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Abstract

Objectives: We aimed to study how common risk factors are associated with left and right ventricular function in a low risk population.

Methods: The association of cardiac function with common risk factors was assessed in a random sample of 1266 individuals, free from hypertension, diabetes or cardiovascular disease, by a combination of speckle tracking and tissue Doppler imaging methods.

Results: Higher age and higher levels of body-mass index, systolic and diastolic blood pressure, and non-high density lipoprotein (non-HDL) cholesterol were associated with lower left ventricular (LV) function, whereas higher high density lipoprotein (HDL) cholesterol was associated with better LV function. In women, smoking was also associated with reduced LV function. LV function was lower also at low levels of diastolic pressure and BMI. Reduced right ventricular function was related to higher age, smoking, higher diastolic blood pressure and non-HDL cholesterol, and lower HDL cholesterol.

Conclusions: These findings suggest that conventional risk factors may predict cardiac function many years prior to clinical disease. The J-shaped associations related to diastolic blood pressure and body mass index may suggest that in some individuals, low levels of these factors may indicate underlying but unknown disease.

Keywords

Blood pressure, cholesterol, obesity, population, strain

Common risk factors influence the risk of cardiovascular morbidity and mortality (1, 2), but little is known about their influence on cardiac function. Previous studies, using ejection fraction (EF) to assess cardiac function, have shown little effect of age (3) and no clear association with clinical symptoms of heart failure (4). The restricted appropriateness of EF for quantification of left ventricular (LV) function (5-7) may be explained by increased radial shortening as longitudinal left ventricular systolic function declines (7, 8). However, studies using tissue Doppler (TD) and speckle tracking (ST) echocardiography have shown reduced LV function in patients with hypertension, diabetes mellitus or ischemic heart disease, and reduced LV function with increasing age in individuals without known cardiovascular disease (9-15). Data on association of cardiac function with risk factors in low risk population are scarce (10, 11). Also, studies using blood flow Doppler have shown reduced LV diastolic function with increasing age, but no age-related effect on systolic function (15-17).

Longitudinal indices may be the best measures of LV function (18). Therefore, we have used tissue Doppler and speckle tracking echocardiography, as well as traditional echocardiographic measures to study the association of established cardiovascular risk factors with cardiac function in a population sample of 1266 individuals without known cardiovascular disease, hypertension or diabetes.

Methods

STUDY POPULATION. The Echocardiography study within the third wave of the HUNT Study (The Nord-Trøndelag Health Study) in Norway, has been described in detail elsewhere (14, 15). Participants in the HUNT Study (19) were not eligible if they answered 'Yes' to questions of whether they had or ever had been diagnosed with cardiovascular disease, hypertension or diabetes. Among eligible people, we randomly selected 1296 men and women, but excluded 30 participants with arrhythmias, myocardial or valvular pathology

disclosed at echocardiography from further analyses, as this could influence the deformation analysis (14). Validation of the inclusion criteria was performed by the physician echocardiographer (HD). The Echocardiography study was approved by the Regional Committee for Medical Research Ethics, and conducted according to the second Helsinki Declaration. Written informed consent was obtained from all participants.

ANTHROPOMETRICS AND LABORATORY TESTS. The HUNT Study included self-administered questionnaires (medical history and smoking habits), clinical measurements (anthropometry and blood pressure) and blood samples, as previously described (19). Renal function was assessed by the Modification of Diet in Renal Disease (MDRD) equation to calculate the estimated glomerular filtration rate (eGFR) (20), where reduced renal function is usually indicated by values lower than 60 ml/min per 1.73m^2 (21). Smoking information was categorized as never, former, occasional or current smoking, where the latter three categories were grouped into a category of 'ever smoking' in the analyses. Blood pressure was measured three times by trained staff using a Dinamap 845XT (Critikon; GE HealthCare). Measurements were made after two minutes rest with the arm on a table, and the average of the second and third measurement was used in the analyses (19). Non-fasting blood samples were collected at study attendance, centrifuged and placed in a refrigerator before transportation to the IEC 17025 accredited laboratory at Levanger Hospital on the same day. Serum analyses were performed in fresh blood samples, on an Architect ci8200 (Abbott Laboratories, IL, USA). All analyses were performed by photometric methods. The coefficients of variation at the laboratory were 1.4-1.7% for glucose, 1.1-1.3% for cholesterol, 1.0-1.7% for high density lipoprotein (HDL) cholesterol and 1.9-2.4% for creatinine.

ECHOCARDIOGRAPHIC ACQUISITION, ANALYSIS AND REPRODUCIBILITY. All examinations were conducted by one experienced physician echocardiographer (HD), and

participants were examined in the left-lateral decubitus position with a Vivid 7 scanner (version BT06, GE Vingmed Ultrasound, Horten, Norway) using a phased-array transducer (M3S and M4S).

Blood flow Doppler recordings were done in four and five chamber views as described in the recommendations by ASE/EAE (22). Mitral flow was measured with sample volume between the mitral leaflets and analyzed for early (E) and late (A) diastolic filling, and the E/A ratio was calculated. LV internal dimensions were analyzed on parasternal M-mode echocardiograms with the ultrasound beam at the tip of the mitral leaflet. Longitudinal end-systolic strain (strain), defined as the percent shortening of myocardial segments during contraction, was analyzed semi automatically by a combination of tissue Doppler and speckle tracking (14) by customized software (GcMat; GE Vingmed Ultrasound, Horten, Norway) that runs on a MATLAB platform (MathWorks, Inc., Natick, MA, USA). Seven kernels (chosen regions of the myocardium) sized 5x5 mm defining segment borders were tracked with tissue Doppler along the ultrasound beam and gray-scale speckles perpendicular to the ultrasound beam. Segmental strain was calculated from the variation of segment length. Global longitudinal end-systolic strain was analyzed as the global average in a 16 segment model of the left ventricle (23). Mitral and tricuspid annular systolic and early diastolic velocities were assessed by pulsed wave tissue Doppler (pwTD) (Vivid 7 scanner, version BT06, GE Vingmed Ultrasound, Horten, Norway) (15). Peak systolic (S') and peak early diastolic (e') velocities were measured in the base of the lateral, septal, anterior and inferior left ventricular wall, and the average of the four myocardial walls is presented as a global measure of LV function. Right ventricular (RV) function was assessed by pwTD by measuring S' and e' in the base of RV free wall at the tricuspid annulus. The localizations used for measurement of S' and e' are shown in Figure 1.

Reproducibility of the echocardiographic analyses has previously been described (14, 15, 24). Briefly, the test retest mean error (the absolute difference between the two sets of observations, divided by the mean of the observations) of the measurements of cardiac function was 4-8% in the left ventricle, and 12-14% in the right ventricle. The intraobserver mean error was 2% and 4%, respectively.

OTHER MEASURES OF LV SYSTOLIC FUNCTION. Association of cardiac risk factors with peak systolic longitudinal strain rate, peak systolic mitral annular velocities by color tissue Doppler and EF are shown in Supplementary data only. However, except for EF these data were in line with those presented in 'Results'.

STATISTICAL ANALYSIS. As all cardiac function indices were correlated (all Pearson's $R \geq 0.2$, all $p<0.001$), associations between cardiovascular risk factors and cardiac function were estimated by multivariate linear regression analyses with the different cardiac function measures as dependent variables. The cardiac function measures were log transformed, and the regression coefficients are presented as the percentage difference in cardiac function per standard deviation higher risk factor level with the corresponding 95% confidence intervals. In the analyses, age was included as a covariate, and in the analyses of lipids and glucose we also included time since last meal as a covariate, since the blood samples were non-fasting. We used fractional polynomial regression analyses to model associations of the risk factors with cardiac function (Figure 2, Figure 3 and Supplemental Figures). In tables and illustrations, we have used the absolute value of the echocardiographic indices of cardiac function. The statistical analyses were performed using SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA) and Stata for Windows (version 10, 1985–2007; StataCorp LP, College Station, Texas).

Results

Table 1 shows basic characteristics of the study participants (663 women and 603 men). Mean age was 47.8 (SD, 13.6) years among women and 50.6 (SD, 13.7) years among men. A total of 1266 echocardiograms were analyzed, and each echocardiographic measurement was obtained in at least 96% of the participants.

ASSOCIATIONS OF RISK FACTORS WITH CONVENTIONAL MEASURES OF CARDIAC FUNCTION. Table 2 shows that mitral inflow E/A ratio was lower with higher age, higher body mass index (BMI), higher systolic and diastolic blood pressure, higher non-HDL cholesterol, lower HDL cholesterol and was also lower among smokers ($p=0.18$ for HDL cholesterol in women, $p=0.13$ for male smokers and all other $p\leq0.07$). Indexed LV mass was higher with higher age, higher blood pressure and higher BMI. Age influenced all measurements, but for LVOT velocity time integral and mitral peak E velocity the associations with other risk factors were weak and not consistent. There were no clear associations of any risk factor with cardiac function, as measured by fractional shortening.

ASSOCIATIONS OF RISK FACTORS WITH NEW MEASURES OF CARDIAC FUNCTION. In both men and women, higher age, higher BMI, higher systolic and diastolic blood pressure and higher non-HDL cholesterol were all associated with reduced indices of LV systolic and diastolic function (Table 3). Ever smoking was associated with reduced indices of LV systolic and diastolic function in women, but not in men, whereas lower eGFR was associated with reduced indices of LV systolic and diastolic function in men, but not in women. In both men and women, higher HDL cholesterol was associated with better LV systolic and diastolic function. Thus, the overall results showed that LV strain was reduced by approximately 5% per 5 kg/m^2 increase in BMI, and reduced by approximately 4% per 10 mmHg increase in diastolic blood pressure. The corresponding reductions in early diastolic LV function were approximately 7% for both BMI and diastolic blood pressure. In

multivariable analyses, we explored whether these associations could be influenced by potentially confounding factors, including heart rate, blood pressure and body surface area, but the results were not substantially altered after multivariable adjustment (results not tabulated).

Especially for BMI, there were indications of an inverted J-shaped association, with reduced LV function also at the lower end of the distribution (Figure 2). LV strain was slightly reduced for men with BMI under 23 kg/m^2 and for women with BMI under 20 kg/m^2. Among men, there was a similar J-shaped association for diastolic blood pressure (Figure 3), with reduced LV strain under diastolic pressure of 50-60 mmHg. For some of the other factors, there was suggestive but not consistent evidence for J-shaped associations with cardiac function.

We also assessed mean arterial blood pressure, waist circumference, body surface area and creatinine related to LV function, as measured by strain and pwTD mitral annular systolic and early diastolic velocity (results not tabulated). The associations for these factors did not substantially differ from those presented above.

Table 3 and Figure 4 show that ever smokers had approximately 4-5% reduced systolic and early diastolic RV function compared to never smokers. The difference between current and never smokers was even larger. In comparison, there was no clear association of smoking with LV function in men (Table 2). Current smoking among women, but not for men, was associated with lower LV strain compared to never smoking (p=0.05). Higher diastolic blood pressure was also associated with reduced RV function, except for systolic function in women. Reduced RV function was observed in men, but not in women with high BMI.

ASSOCIATIONS OF RISK FACTORS WITH OTHER MEASURES OF LV FUNCTION. In Supplemental material the associations of cardiovascular risk factors with

mitral annular velocity by color tissue Doppler, strain rate and EF, can be found. The associations of cardiac risk factors with these methods, except for EF, were in line with those presented. Supplemental Figures show the associations of the presented risk factors with LV end-systolic strain and early diastolic mitral annular velocity.

Discussion

In this population study of 1266 men and women without known cardiovascular disease, hypertension or diabetes, conventional cardiovascular risk factors were clearly associated with left and right ventricular function as assessed by tissue Doppler and speckle tracking echocardiography. Thus, cardiac function was gradually reduced with increasing blood pressure, BMI and non-HDL cholesterol, and with decreasing HDL cholesterol and eGFR. Cardiac function was poorer in ever smokers than never smokers. Except for smoking, the strength of the associations was consistently stronger for left than right ventricular function. For BMI and diastolic blood pressure, there was some evidence that the association with LV function may have a J-shaped form.

The participants of the study were randomly selected among healthy individuals in the general population, and participants with significant echocardiographic pathology were excluded from the analyses. Information on smoking was based on questionnaire data, and no further validation of smoking was conducted. The participants were of northern European Caucasian descent, and therefore, it is uncertain to which degree the results can be generalized to other ethnic populations. However, results from the large Multi-Ethnic Study of Atherosclerosis suggest that race may not be associated with LV function as measured by cardiac tagged magnetic resonance imaging (25). To minimize the effect of noise, only segments with optimal tracking of segment borders by visual assessment were accepted for the strain analyses, and 10.9 (SD, 3.8) segments per person were the average basis for

calculating global systolic deformation indices (14). This ensures optimal quality of the remaining data, influenced as little as possible by measurement bias due to image quality. Due to the large amount of data we have chosen to present a selection of traditional echocardiographic measures, mitral and tricuspid annular velocities by pwTD and global strain in this manuscript, and the other measures are presented in Supplemental material only.

Previously, some echocardiographic studies have suggested that patients with hypertension, metabolic syndrome, diabetes, renal failure or obesity may have subclinical cardiac dysfunction, and that cardiac function decreases with age also in people without cardiovascular disease (9-11, 14, 15, 26-32). However, few studies have addressed whether cardiac function in healthy people, assessed by modern echocardiographic methods, is associated with blood pressure, serum lipids, renal function, or BMI. The results of this study suggest that conventional risk factors are reliable and consistent markers for cardiac function, and not only markers of future morbidity and mortality. Thus, our findings correspond to the evidence from large follow-up studies of unselected populations that have shown strong associations with the risk and mortality of cardiovascular disease related to the same risk factors (1, 2, 33, 34).

Many studies have displayed U- or J-shaped associations of blood pressure and BMI with cardiac morbidity and mortality (34-36). We found evidence for inverted J-shaped associations of diastolic blood pressure and BMI with LV function. Thus, LV function was not only reduced at high levels of diastolic pressure, but also among people with pressure lower than approximately 60 mmHg. A recent meta-analysis and clinical guidelines suggest that people with diastolic blood pressure under 70 mmHg may be at increased risk for coronary heart disease (1, 35, 37), and it has been suggested that low diastolic pressure may reflect underlying pre-clinical disease, or increased pulse pressure due to vascular disease or aggressive antihypertensive treatment (35). However, none of the participants of the present

study were taking hypertensive medication. That overweight or obesity is associated with reduced left ventricular function has also been shown by others (28, 38, 39). However, the inverted J-shaped form of the association, suggesting reduced LV function in very lean or thin people, has not been noted previously. The J-shape was most pronounced when LV function was assessed by longitudinal strain. This may add credibility to the finding, because strain measurements are adjusted for LV size, and LV size is correlated with lean body mass.

The participants of this study were purposely selected to represent healthy people without cardiovascular disease. Nonetheless, the observed J-shaped associations may suggest that low diastolic pressure or very low BMI could be signs of pre-clinically reduced cardiac function, or not yet acknowledged disease, also in apparently healthy individuals (36, 40).

There is a well established association of smoking with increased cardiovascular risk (41, 42), and we found that ever smoking was associated with reduced RV function in both men and women, but associated with reduced LV function only in women. Based on our results, smoking appears to be more strongly related to RV than LV function, and if correct, it seems plausible that increased pulmonary arterial resistance related to smoking may increase RV load and reduce RV function. However, only 65 of the men who participated reported daily smoking, and the low prevalence of daily smoking limited our possibility to detect any association of smoking with cardiac function.

Different physiological mechanisms may influence the results of this study. As a general principle, all echocardiographic measures will be reduced by increasing afterload (43, 44). Although myocardial velocity and deformation measures are less affected than blood flow velocities (43, 44), increased afterload may influence the results. This concerns arterial blood pressure for the LV and the suggested pulmonary arterial resistance for RV function (45). A steeper reduction in cardiac diastolic than systolic function has also been observed by others, and studies using blood flow Doppler have suggested a reduced diastolic function with

increasing age, but with less pronounced effects on systolic indices (15-17). We found no clear association of risk factors with systolic blood flow indices, but by the sensitive speckle tracking and tissue Doppler indices a clear association with cardiac risk factors was shown. The more pronounced associations with diastolic indices may presumably be related to abnormal relaxation without major changes in ejection time. In addition, end-systolic measurements may be more influenced by heart rate than peak systolic measurements which most often occur in early systole. However, adjustment for heart rate did not substantially influence the presented data.

Both obesity and hypertension are related to a sedentary lifestyle, and previously it has been shown that LV systolic and diastolic function is related to physical activity (46). The results for waist circumference, body surface area and BMI were nearly identical, suggesting that these measures may be used interchangeably as markers for obesity in this population.

Previous studies have suggested that a certain proportion of patients with hypertension and obesity may have increased interstitial fibrosis and LV geometrical changes (29, 47, 48), and it is possible that the observed reduced cardiac function in our study may be attributed to similar characteristics. Thus, the lower cardiac function may partly be explained by subclinical dysfunction that may be present in a modest proportion of the participants, and partly by a gradual but general reduction in cardiac function that may be attributed to unfavorable levels of the measured risk factors.

The Supplemental material shows that the ejection fraction measurements may not be useful in the detection of small differences in LV function, and this corresponds to the conclusions of other studies (3, 5-7). The use of a one-dimensional method to calculate ejection fraction is a limitation in this study, but we present the data in Supplementary Table. However, our purpose was not to compare the different echocardiographic methods, but to study the associations of different risk factors with the best indices of LV and RV function.

We also found that lower eGFR was associated with reduced LV function in men, but not in women. It has been suggested that patients with chronic renal failure may have subclinical LV dysfunction (30), but no previous study has shown that renal function in a healthy population, estimated by eGFR, may be associated with cardiac function. The clear association of reduced LV function with reduced renal function in men, but not in women, may indicate that the validity of the MDRD equation could differ by sexes, as indicated in other studies (49).

In this population study of individuals without known cardiovascular disease, hypertension or diabetes, we found that unfavorable levels of conventional risk factors were clearly associated with reduced left and right ventricular function; suggesting the possibility of subclinical cardiac dysfunction. The findings suggest that these risk factors influence cardiac function many years prior to clinical detection. The J-shaped associations of diastolic blood pressure and body mass with LV function indicate that very low blood pressure and extreme leanness may be indicators of prevalent but subclinical cardiac dysfunction.

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Figure 1 - Echocardiographic measurements and study population

A) Mitral annular velocity curve from the septum by pulsed wave tissue Doppler echocardiography in apical four chamber view. Sample volume is positioned close to the septal insertion of the mitral leaflets, and peak systolic velocity (S`), early diastolic velocity (e`) and late diastolic velocity (a`) were measured at the maximum of the solid Doppler spectrum with low gain setting. B) Color tissue Doppler assessed septal and lateral mitral annular velocities in apical four chamber view. S`, e` and a` were measured at the peaks of the Doppler curves. C) Age distribution of the participants. D) Strain curves from one myocardial wall. End-systolic strain (S_{es}) marked by blue arrows.

Figure 2 - Association of body mass index with longitudinal left ventricular end-systolic strain

Age-adjusted fractional polynomial regression plot of global longitudinal left ventricular end-systolic strain by body mass index. Estimated mean (line) and 95% confidence interval (shadow) displayed. Blue lines refer to men and red lines refer to women. Abbreviations: BMI=body mass index.

Figure 3 - Association of diastolic blood pressure with longitudinal left ventricular end-systolic strain

Age adjusted fractional polynomial regression plot of global longitudinal left ventricular end-systolic strain by diastolic blood pressure. Explanations as in figure 2.

Figure 4 - Associations of smoking with peak systolic and early diastolic tricuspid velocities

Mean and 95% confidence interval for tricuspid systolic (A and B) and early diastolic (C and D) velocities by smoking habit in women and men, respectively. Level of significance for

higher velocities in never smokers compared to ever smokers shown. Explanations: Never=never smokers, Ex=former smokers, Occ=occasional smokers and Current=current smokers. Level of significance between never smokers and ever smokers is shown.

Table 1 Characteristics of the study population

	Women	Men	
	Mean (SD)	Mean (SD)	**P-value**
Sex (n)	663	603	
Age (years)	47.8 (13.6)	50.6 (13.7)	<0.001
Height (cm)	166.0 (6.1)	179.1 (6.5)	<0.001
Weight (kg)	71.5 (12.6)	86.0 (12.7)	<0.001
Body mass index (kg/m^2)	25.8 (4.1)	26.5 (3.4)	<0.001
Waist circumference (cm)	88.5 (11.7)	95.9 (9.8)	<0.001
Systolic blood pressure (mmHg)	127 (17)	133 (14)	<0.001
Diastolic blood pressure (mmHg)	71 (10)	77 (10)	<0.001
Heart rate (bpm)	65.9 (10.0)	63.0 (10.0)	<0.001
Ever smokers (%)	54.8	49.6	<0.001
Blood measurements			
Serum glucose (mmol/L)	5.3 (0.8)	5.6 (1.4)	<0.001
Total serum cholesterol (mmol/L)	5.5 (1.1)	5.6 (0.9)	0.74
Serum non-HDL cholesterol (mmol/L)	4.1 (1.1)	4.3 (0.9)	<0.001
Serum HDL-cholesterol (mmol/L)	1.5 (0.3)	1.2 (0.3)	<0.001
Serum creatinine (µmol/L)	79.1 (10.0)	95.0 (11.6)	<0.001
Estimated glomerular filtration rate (MDRD), mL/min/1.73 m^2	69 (11)	75 (12)	<0.001
Time since last meal (hours)	2.7 (2.1)	2.8 (2.0)	<0.001
Conventional echocardiographic measurements			
Interventricular septum diastolic thickness (mm)	8.1 (1.4)	9.5 (1.5)	<0.001
Left ventricular diastolic internal dimension (mm)	49 (4)	53 (6)	<0.001
Left ventricular posterior wall diastolic thickness (mm)	8.2 (1.4)	9.6 (1.4)	<0.001
Fractional shortening (%)	36 (7)	36 (7)	0.08
Ejection fraction, Teichholz formula (%)	65.4 (9.2)	64.2 (9.7)	<0.05
Left ventricular outflow tract velocity time integral (cm)	21.4 (3.5)	20.3 (3.6)	0.28
Mitral peak early (E) velocity (cm/s)	75 (16)	65 (15)	0.11
Mitral inflow E/A ratio	1.4 (0.6)	1.3 (0.5)	0.12
Left ventricular mass index (g/m^2)	77 (18)	95 (22)	<0.001

P-value shows level of significance between sexes. Abbreviations: HDL = high density lipoprotein, non-HDL = non high density lipoprotein, MDRD = Modification of Diet in Renal Disease equation, SD = standard deviation.

Table 2 Percentage difference in conventional echocardiographic indices per standard deviation difference in common cardiac risk factors

Covariate		N	Covariate SD	Percentage difference (95% CI) of different conventional echocardiographic indices per standard deviation difference in covariates		
				Fractional shortening	Mitral peak E velocity	Mitral E/A ratio
Age*	Women	663	13.6 years	-0.8 (-2.6 to 1.1), p=0.41	-7.0 (-8.6 to -5.3), p<0.001	-25 (-27 to -23), p<0.001
	Men	603	13.7 years	0.2 (-1.8 to 2.2), p=0.83	-7.3 (-9.1 to -5.5), p<0.001	-22 (-25 to -20), p<0.001
BMI	Women	647	4.2 kg/m^2	-1.0 (-2.8 to 0.9), p=0.29	-0.2 (-1.9 to 1.4), p=0.76	-5.3 (-7.6 to -3.0), p<0.001
	Men	594	3.5 kg/m^2	-1.6 (-3.6 to 0.5), p=0.13	0.5 (-1.3 to 2.3), p=0.57	-5.6 (-8.0 to -3.1), p<0.001
Systolic blood pressure	Women	610	17.4 mmHg	1.2 (-0.9 to 3.3), p=0.26	1.4 (-0.5 to 3.3), p=0.16	-5.0 (-7.7 to -2.3), p<0.001
	Men	565	13.9 mmHg	1.4 (-0.8 to 3.6), p=0.20	2.5 (0.5 to 4.4), p=0.01	-4.5 (-7.2 to -1.8), p=0.001
Diastolic blood pressure	Women	610	10.4 mmHg	0.1 (-1.9 to 2.0), p=0.95	-1.3 (-3.0 to 0.4), p=0.13	-6.9 (-9.3 to -4.5), p<0.001
	Men	565	10.2 mmHg	-2,2 (-4.4 to -0.1), p=0.04	-3.5 (-5.4 to -1.6), p<0.001	-9.8 (-12.4 to -7.3), p<0.001
Non-HDL cholesterol†	Women	640	1.08 mmol/L	-1.0 (-3.1 to 1.1), p=0.35	-2.5 (-4.4 to -0.6), p=0.01	-2.6 (-5.3 to 0.2), p=0.07
	Men	591	0.95 mmol/L	0.8 (-1.2 to 2.9), p=0.42	-1.5 (-3.3 to 0.4), p=0.13	-4.5 (-7.0 to -1.9), p<0.001
HDL cholesterol†	Women	640	0.34 mmol/L	-0.1 (-2.0 to 1.7), p=0.88	1.8 (0.0 to 3.5), p=0.05	1.7 (-0.8 to 4.2), p=0.18
	Men	591	0.30 mmol/L	-0.4 (-2.4 to 1.6), p=0.70	0.8 (-1.2 to 2.7), p=0.44	4.0 (1.4 to 6.6), p=0.003

	Women	339/280	Ever vs. never	0.0 (-3.6 to 3.7), p=0.99	-3,4 (-6,7 to -0,2), p=0.04	-5,8 (-10,5 to -1,1), p=0.02
Smoking‡	Men	278/283	Ever vs. never	-1.8 (-5.9 to 2.2), p=0.38	0.1 (-2,3 to 4.9), p=0.49	-3.9 (-8,9 to 1.1), p=0.13
	Women	495	11.2 ml/min per 1.73m^2	-2.6 (-5.1 to -0.1), p=0.04	-0.8 (-2.9 to 1.3), p=0.44	-0.4 (-3.5 to 2.6), p=0.79
eGFR	Men	477	11.5 ml/min per 1.73m^2	-0.6 (-3.3 to 2.0), p=0.64	2.2 (-0.1 to 4.4), p=0.06	1.3 (-1.9 to 4.5), p=0.42
	Women	640	0.81 mmol/L	0.3 (-1.6 to 2.2), p=0.75	-1.7 (-3.6 to 0.2), p=0.08	-4.1 (-6.8 to -1.4), p=0.003
Glucose*	Men	591	1.39 mmol/L	-0.5 (-3.0 to 2.0), p=0.69	0.4 (-1.5 to 2.3), p=0.70	-1.3 (-3.9 to 1.3), p=0.33

*Association with age is not adjusted for other factors in this table, †adjusted also for time since last meal, ‡difference in left ventricular function between ever smokers and never smokers. Abbreviations: BMI = body mass index (kg/m^2), CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL = high density lipoprotein, N = number and SD = standard deviation.

Table 3 Percentage difference in left ventricular function per standard deviation difference in common cardiac risk factors

Covariate		N	Covariate SD	Percentage difference (95% CI) in left ventricular function per standard deviation difference in covariates by different echocardiographic indices		
				Systolic annular velocity	Global longitudinal strain	Early diastolic annular velocity
Age*	Women	663	13.6 years	-8.0 (-9.1 to -7.0), p<0.001	-3.9 (-4.9 to -2.9), p<0.001	-22 (-24 to -21), p<0.001
	Men	603	13.7 years	-5.9 (-7.1 to -4.6), p<0.001	-3.1 (-4.3 to -1.9), p<0.001	-21 (-22 to -19), p<0.001
BMI	Women	647	4.2 kg/m^2	-1.3 (-2.4 to -0.2), p=0.02	-3.1 (-4.1 to -2.1), p<0.001	-4.4 (-5.8 to -2.9), p<0.001
	Men	594	3.5 kg/m^2	-2.6 (-3.9 to -1.4), p<0.001	-3.9 (-5.1 to -2.8), p<0.001	-6.7 (-8.4 to -5.0), p<0.001
Systolic blood pressure	Women	610	17.4 mmHg	-1.4 (-2.6 to -0.1), p=0.03	-3.0 (-4.1 to -1.8), p<0.001	-5.9 (-7.6 to -4.3), p<0.001
	Men	565	13.9 mmHg	-1.2 (-2.6 to 0.1), p=0.07	-2.4 (-3.7 to -1.1), p<0.001	-5.4 (-7.2 to -3.5), p<0.001
Diastolic blood pressure	Women	610	10.4 mmHg	-1.6 (-2.7 to -0.4), p=0.007	-2.5 (-3.6 to -1.4), p<0.001	-6.0 (-7.5 to -4.4), p<0.001
	Men	565	10.2 mmHg	-2.9 (-4.2 to -1.6), p<0.001	-5.2 (-6.4 to -4.0), p<0.001	-9.0 (-10.6 to -7.3), p<0.001
Non-HDL cholesterol†	Women	640	1.08 mmol/L	0.0 (-1.3 to 1.3), p=0.99	-2.2 (-3.4 to -1.0), p<0.001	-2.1 (-3.9 to -0.4), p=0.02
	Men	591	0.95 mmol/L	-2.0 (-3.3 to -0.7), p=0.003	-2.3 (-3.6 to -1.0), p<0.001	-4.4 (-6.3 to -2.6), p<0.001
HDL cholesterol†	Women	640	0.34 mmol/L	0.7 (-0.5 to 1.9), p=0.24	2.1 (1.0 to 3.2), p<0.001	1.5 (-0.1 to 3.1), p=0.06
	Men	591	0.30 mmol/L	2.0 (0.7 to 3.4), p=0.003	3.5 (2.2 to 4.7), p<0.001	4.4 (2.6 to 6.3), p<0.001
Smoking‡	Women	339/280	Ever vs. never	-2,5 (-4,7 to -0,3), p=0.03	-0,8 (-2,8 to 1,3), p=0.47	-4,8 (-7,8 to -1,7), p=0.002
	Men	278/283	Ever vs. never	-0.3 (-2,9 to 2.2), p=0.80	-1.0 (-4,5 to 2.6), p=0.43	-1.0 (-4,5 to 2,6), p=0.60

	Women	495	11.2 ml/min per 1.73m^2	-0.6 (-2.0 to 0.7), p=0.35	-0.3 (-1.6 to 1.1), p=0.67	0.5 (-1.4 to 2.4), p=0.60
Egfr	Men	477	11.5 ml/min per 1.73m^2	2.1 (0.5 to 3.7), p=0.01	2.1 (0.6 to 3.7), p=0.006	3.5 (1.3 to 5.7), p=0.002
	Women	640	0.81 mmol/L	0.7 (-0.4 to 1.9), p=0.27	-0.9 (-2.0 to 0.2), p=0.10	-2.6 (-4.2 to -1.0), p=0.001
Glucose[*]	Men	591	1.39 mmol/L	0.6 (-1.0 to 2.2), p=0.45	-1.1 (-2.6 to 0.4), p=0.16	-0.7 (-2.9 to 1.5), p=0.51

Explanations and abbreviations as in Table 2.

Table 4 Percentage difference in right ventricular performance per standard deviation difference in common cardiac risk factors

Covariate		N	Covariate SD	Percentage difference (95% CI) in right ventricular function per standard deviation difference in covariates by different echocardiographic indices	
				Systolic annular velocity	Early diastolic annular velocity
Age*	Women	663	13.6 years	-3.4 (-4.6 to -2.2), p<0.001	-10.3 (-12.0 to -8.7), p<0.001
	Men	603	13.7 years	-1.7 (-3.1 to -0.2), p=0.02	-10.6 (-12.7 to -8.5), p<0.001
BMI	Women	647	4.2 kg/m^2	-0.3 (-1.5 to 0.9), p=0.58	0.0 (-1.4 to 1.5), p=0.98
	Men	594	3.5 kg/m^2	-3.1 (-4.8 to -1.4), p<0.001	-2.1 (-4.2 to 0.0), p=0.05
Systolic blood pressure	Women	610	17.4 mmHg	1.2 (-0.2 to 2.6), p=0.09	-0.8 (-2.7 to 1.2), p=0.43
	Men	565	13.9 mmHg	2.8 (1.2 to 4.4), p<0.001	0.6 (-1.7 to 2.9), p=0.61
Diastolic blood pressure	Women	610	10.4 mmHg	-0.6 (-1.8 to 0.7), p=0.37	-2.5 (-4.2 to -0.7), p=0.006
	Men	565	10.2 mmHg	-2.3 (-3.8 to -0.7), p=0.004	-5.3 (-7.5 to -3.1), p<0.001
Non-HDL cholesterol†	Women	640	1.08 mmol/L	-1.5 (-2.9 to -0.1), p=0.04	-2.4 (-4.4 to -0.4), p=0.02
	Men	591	0.95 mmol/L	-1.3 (-2.9 to 0.2), p=0.09	-1.5 (-3.8 to 0.7), p=0.18
HDL cholesterol†	Women	640	0.34 mmol/L	1.3 (0.1 to 2.6), p=0.04	2.0 (0.2 to 3.8), p=0.03
	Men	591	0.30 mmol/L	1.0 (-0.6 to 2,5), p=0.22	2.1 (-0.1 to 4.4), p=0.06

	Women	339/280	Ever vs. never	-2,8 (-5,2 to -0,3), p=0.03	-5.7 (-9.1 to -2.3), p<0.001
Smoking‡	Men	278/283	Ever vs. never	-3.8 (-6.7 to -0.8), p=0.01	-4.4 (-8.7 to -0.2), p=0.04
	Women	495	11.2 ml/min per 1.73m^2	-1.0 (-2.5 to 0.6), p=0.22	-0.6 (-2.9 to 1.6), p=0.57
eGFR	Men	477	11.5 ml/min per 1.73m^2	0.0 (-1.8 to 1.9), p=0.97	0.7 (-2.1 to 3.5), p=0.62
	Women	640	0.81 mmol/L	0.5 (-0.8 to 1.7), p=0.44	-2.0 (-3.8 to -0.2), p=0.03
Glucose†	Men	591	1.39 mmol/L	-0.1 (-1.9 to 1.7), p=0.93	-2.1 (-4.7 to 0.6), p=0.12

Explanations and abbreviations as in Table 2.

Figure 1

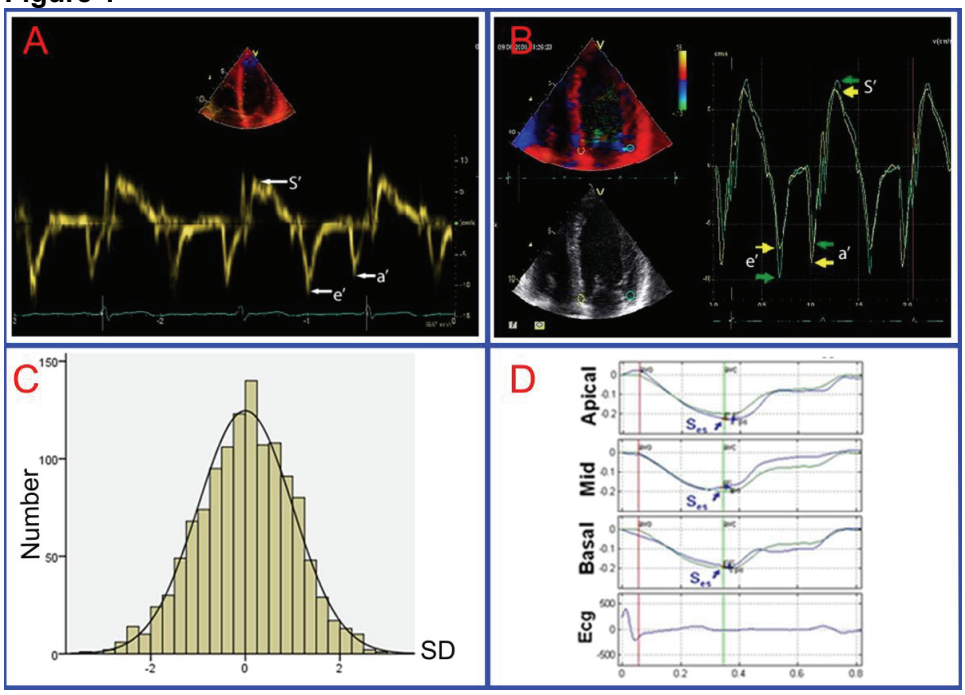


Figure 2

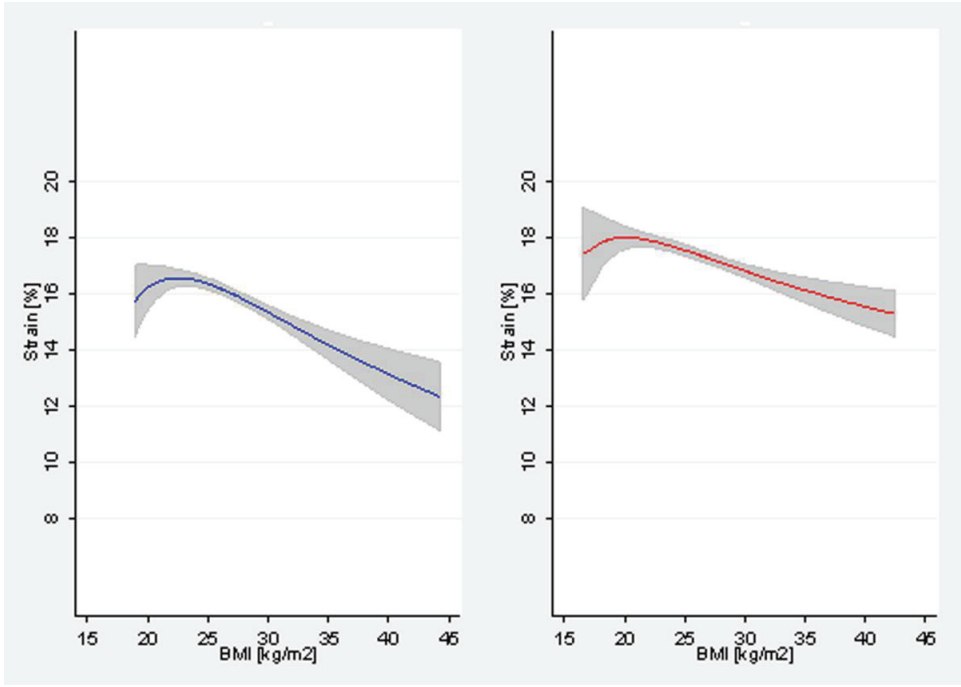


Figure 3

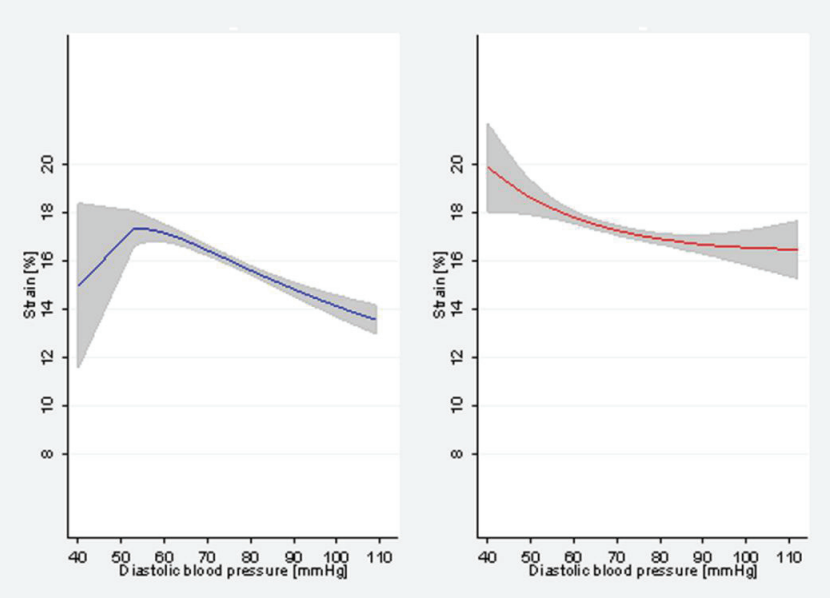
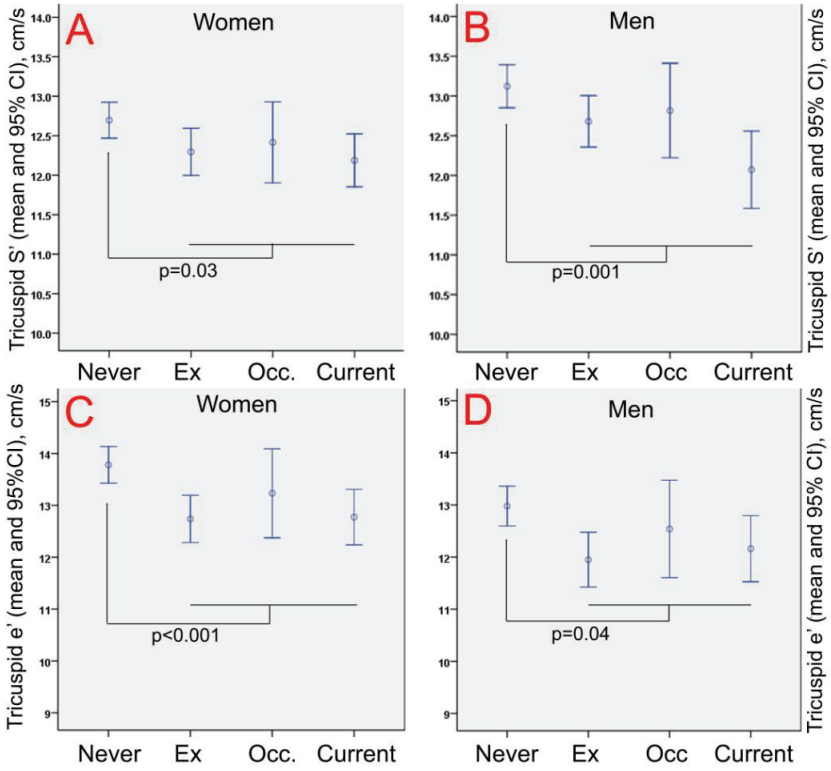

Strain [%]
8
10
12
14
16
18
20
40
50
60
70
80
90
100
110
Diastolic blood pressure [mmHg]
Strain [%]
8
10
12
14
16
18
20
40
50
60
70
80
90
100
110
Diastolic blood pressure [mmHg]

Figure 4


A
Women
Tricuspid S' (mean and 95% CI), cm/s
p=0.03
Never
Ex
Occ.
Current
B
Men
Tricuspid S' (mean and 95% CI), cm/s
p=0.001
Never
Ex
Occ
Current
C
Women
Tricuspid e' (mean and 95%CI), cm/s
p<0.001
Never
Ex
Occ.
Current
D
Men
Tricuspid e' (mean and 95% CI), cm/s
p=0.04
Never
Ex
Occ
Current

SUPPLEMENTAL MATERIAL

Supplemental methods

The ejection fraction was calculated by Teichholz formula from motion mode echocardiograms (1-3). Global peak systolic strain rate was calculated as the temporal derivative of strain, and the method has been recently described in detail (3). Color tissue Doppler (cTD) mitral annular velocities were assessed by customized software (GcMat; GE Vingmed Ultrasound, Horten, Norway) that runs on a MATLAB platform (MathWorks, Inc., Natick, MA, USA) (2). Positioning of regions of interest was performed as described for pwTD. Peak systolic mitral annular velocities reflect the average of septal, anterolateral, inferior and anterior wall.

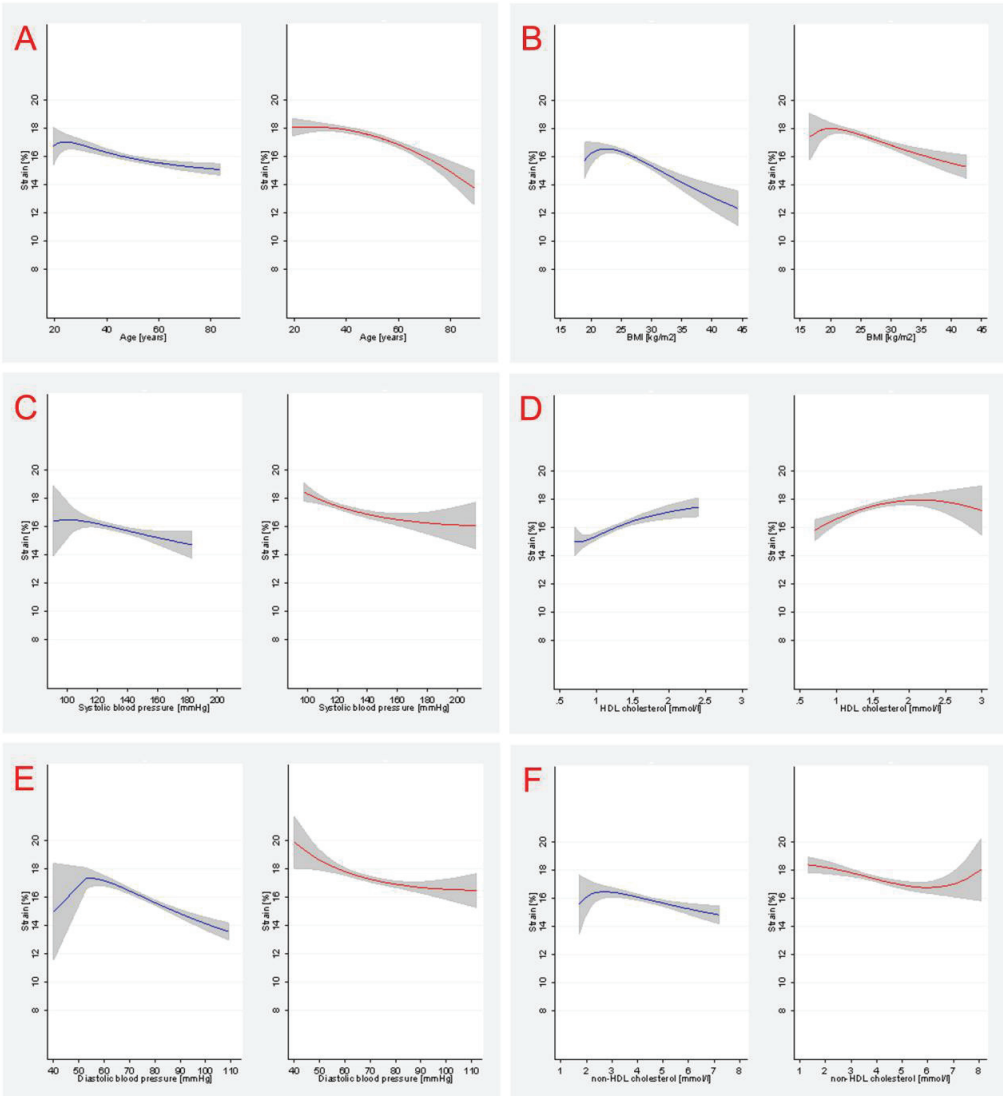
Supplemental Table 1 Percentage difference in left ventricular function per standard deviation difference in common cardiac risk factors

				Percentage difference (95% CI) in left ventricular function per standard deviation difference in covariates by different echocardiographic indices		
Covariate		**N**	**Covariate SD**	**Mitral annulus velocity (cTD)**	**Global systolic strain rate**	**Ejection fraction (Teichholz)**
Age*	***Women***	663	13.6 years	-8.7 (-9.9 to -7.5), p<0.001	-4.2 (-5.2 to -3.1), p<0.001	-0.7 (-2.1 to 0.7), p=0.36
	Men	603	13.7 years	-7.1 (-8.6 to -5.6), p<0.001	-3.3 (-4.4 to -2.3), p<0.001	0.6 (-0.7 to 2.0), p=0.37
BMI	***Women***	647	4.2 kg/m^2	-2.0 (-3.2 to -0.8), p=0.001	-1.9 (-3.0 to -0.9), p<0.001	-0.9 (-2.4 to 0.5), p=0.19
	Men	594	3.5 kg/m^2	-1.9 (-5.2 to -2.2), p<0.001	-2.8 (-3.8 to -1.8), p<0.001	-1.8 (-3.2 to -0.4), p=0.01
Systolic blood pressure	***Women***	610	17.4 mmHg	-1.6 (-2.9 to -0.2), p=0.02	-1.1 (-2.2 to -0.0), p=0.04	0.8 (-0.9 to 2.4), p=0.34
	Men	565	13.9 mmHg	-1.9 (-3.5 to -0.3), p=0.02	-0.9 (-2.0 to 0.1), p=0.09	1.2 (-0.3 to 2.7), p=0.11
Diastolic blood pressure	***Women***	610	10.4 mmHg	-1.5 (-2.8 to -0.3), p=0.02	-1.0 (-1.9 to 0.0), p=0.05	0.2 (-1.3 to 1.7), p=0.80
	Men	565	10.2 mmHg	-2.8 (-4.3 to -1.3), p<0.001	-3.2 (-4.2 to -2.1), p<0.001	-1.0 (-2.4 to 0.4), p=0.19

Non-HDL cholesterol[†]	***Women***	640	1.08 mmol/L	-0.3 (-1.7 to 1.1), p=0.70	-0.9 (-2.2 to 0.3), p=0.15	-1.1 (-2.8 to 0.6), p=0.19
	Men	591	0.95 mmol/L	-2.0 (-3.6 to -0.4), p=0.01	-1.3 (-2.4 to -0.2), p=0.02	0.1 (-1.2 to 1.5), p=0.84
HDL cholesterol[†]	***Women***	640	0.34 mmol/L	0.8 (-0.5 to 2.0), p=0.25	2.1 (0.9 to 3.2), p<0.001	0.4 (-1.2 to 1.9), p=0.65
	Men	591	0.30 mmol/L	2.6 (1.0 to 4.2), p=0.001	1.8 (0.7 to 2.9), p<0.001	0.2 (-1.2 to 1.6), p=0.83
Smoking[‡]	***Women***	339/280	Ever vs. never	-1.4 (-3.8 to 1.0), p=0.26	-1.6 (-3.7 to 0.5), p=0.14	0.2 (-2.7 to 3.0), p=0.89
	Men	278/283	Ever vs. never	1.0 (-2.0 to 4.1), p=0.50	0.2 (-1.9 to 2.3), p=0.85	-1.4 (-4.2 to 1.3), p=0.31
eGFR	***Women***	495	11.2 ml/min per 1.73m^2	-0.4 (-2.0 to 1.1), p=0.59	-0.7 (-1.9 to 0.5), p=0.25	-1.9 (-3.9 to 0.0), p=0.05
	Men	477	11.5 ml/min per 1.73m^2	0.9 (-1.1 to 2.8), p=0.38	1.2 (-0.1 to 2.5), p=0.07	-0.1 (-1.9 to 1.6), p=0.87
Glucose[†]	***Women***	640	0.81 mmol/L	0.9 (-0.5 to 2.3), p=0.54	0.5 (-0.8 to 1.8), p=0.43	0.6 (-1.1 to 2.3), p=0.51
	Men	591	1.39 mmol/L	0.8 (-0.8 to 2.5), p=0.31	-0.2 (-1.3 to 0.9), p=0.78	-0.1 (-1.6 to 1.3), p=0.84

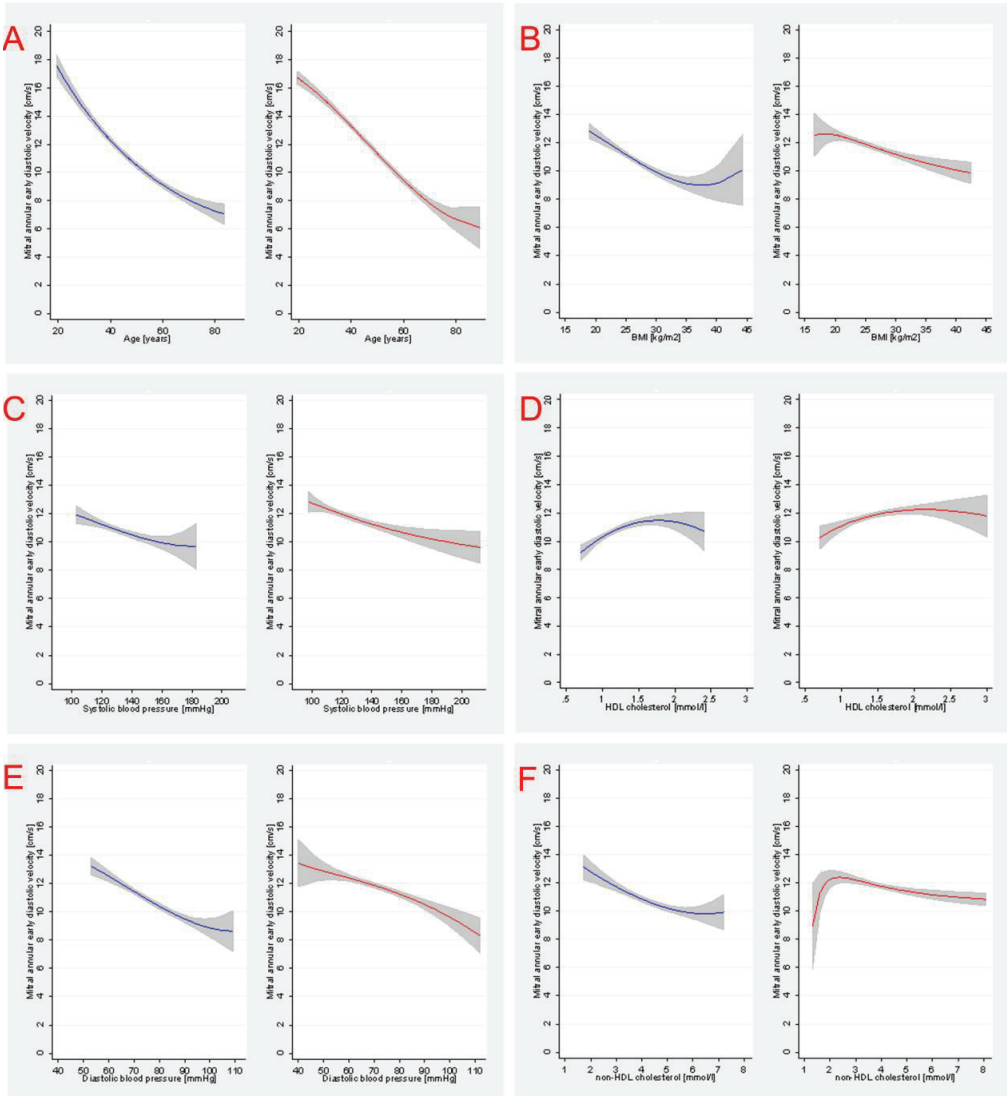
The methods used to assess the data are recently described (2, 3). The table shows age adjusted data. [*]Age is not adjusted for other factors in this table, [†]adjusted also for time since last meal, [‡]values are difference between ever smokers and never smokers and N describes daily smokers/never smokers. Abbreviations: cTD=color tissue Doppler echocardiography, others as described in manuscript.

Supplemental Figure 1 Sex specific associations between cardiac risk factors and LV end-systolic strain



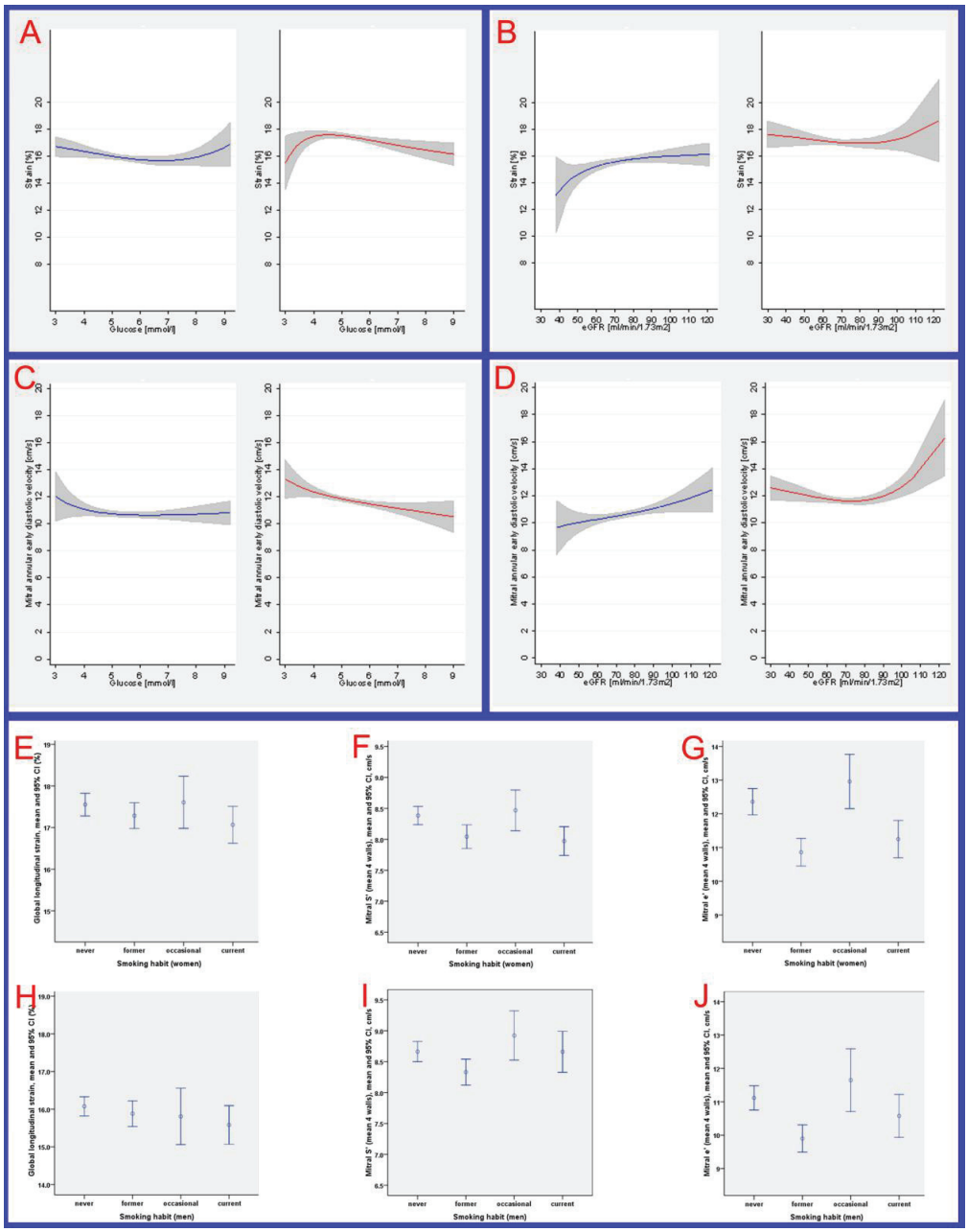
Fractional polynomial regression plots of global longitudinal left ventricular end-systolic strain by age (A), body mass index (B), systolic blood pressure (C), HDL-cholesterol (D), diastolic blood pressure (E) and non-HDL cholesterol (F). Estimated mean (line) and 95% confidence interval (shadow) displayed. Blue lines refer to men and red lines refer to women. Abbreviations: BMI=body mass index, HDL=high density lipoprotein. All plots except for A adjusted for age.

Supplemental Figure 2 Sex specific associations between cardiac risk factors and mitral e'



Fractional polynomial regression plots of early diastolic mitral annular velocity by age (A), body mass index (B), systolic blood pressure (C), HDL-cholesterol (D), diastolic blood pressure (E) and non-HDL cholesterol (F). Explanations and abbreviations as in Supplemental Figure 1.

Supplemental Figure 3 Sex specific associations between cardiac risk factors and different measures of cardiac function



Supplemental Figure 3A-D displays sex-specific and age adjusted; -global longitudinal strain by A) glucose and B) estimated glomerular filtration rate (eGFR), -mitral annular early

diastolic velocity by C) glucose and D) eGFR. Figure 3E-J displays global longitudinal strain, mitral annular systolic and early diastolic velocities by smoking habits in women (E-G), and men (H-J) respectively. There was a significant difference with better LV function in never smokers compared to ever smokers in women (all $p \leq 0.03$, except for strain analyses. No significant difference between never smokers and ever smokers in men.

References

1. Thorstensen A, Dalen H, Amundsen BH, Aase SA, Stoylen A. Reproducibility in echocardiographic assessment of the left ventricular global and regional function, the HUNT study. Eur J Echocardiogr 2010; 11:149-56.

2. Dalen H, Thorstensen A, Vatten L, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and tissue Doppler velocities in a population free from cardiovascular disease.
The HUNT study in Norway. Circ Cardiovasc Imaging 2010; 3:614-22.

3. Dalen H, Thorstensen A, Aase SA, Ingul CB, Torp H, Vatten L, Stoylen A. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the HUNT study in Norway. Eur J Echocardiogr 2010; 11:176-83.

Appendix

Invitasjon til HUNT 3

Viktig
Enkelt
Gratis

Du inviteres herved til å delta i den tredje store Helseundersøkelsen i Nord-Trøndelag (HUNT 3). Ved å delta får du en enkel undersøkelse av din egen helse, og du gir samtidig et viktig bidrag til medisinsk forskning.

Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk, er HUNT-veteran eller møter for første gang. Tilsvarende undersøkelse er tidligere gjennomført i 1984-86 (HUNT 1) og 1995-97 (HUNT 2 og Ung-HUNT). For å kunne studere årsaker til sykdom, er det viktig at også de som tidligere har deltatt møter fram.

Vennligst fyll ut spørreskjemaet, og ta det med når du møter til undersøkelse.

Undersøkelsen tar vanligvis ca 1/2 time. Du vil få brev med resultater fra dine prøver etter noen uker. Dersom noen av resultatene er utenom det normale, vil du bli anbefalt undersøkelse hos fastlegen din.

Du kan lese mer om HUNT 3 i den vedlagte brosjyren eller på www.hunt.ntnu.no. Har du spørsmål, kan du også ringe til HUNT forskningssenter, tlf 74075180.

Vel møtt til undersøkelsen!

Vennlig hilsen

Steinar Krokstad
Førsteamanuensis
Prosjektleder HUNT 3

Jostein Holmen
Professor, daglig leder
HUNT forskningssenter

Stig A. Slørdahl
Professor, dekanus
Det medisinske fakultet, NTNU

Tid og sted for oppmøte

Dersom det foreslåtte tidspunktet ikke passer for deg, behøver du ikke bestille ny time. Du kan møte når det passer deg innenfor åpningstiden, men det kan da bli noe ventetid. Du kan også møte i en annen kommune, hvis det skulle passe bedre. Takk for at du deltar!

Åpningstida:

hunt 3
Helseundersøkelsen i Nord-Trøndelag

NTNU
HUNT forskningssenter

En time for bedre folkehelse

Slik fyller du ut skjemaet

- Skjemaet vil bli lest maskinelt.
- Det er derfor viktig at du krysser av riktig: **Rett** ☒ **Galt** ☐ ☑
- Krysser du feil sted, retter du ved å fylle boksen slik: ■
- Skriv tydelige tall: 0 1 2 3 4 5 6 7 8 9
- Bruk bare svart eller blå penn. Ikke bruk blyant eller tusj.

HELSE OG DAGLIGLIV

1 Hvordan er helsa di nå?

☐ Dårlig ☐ Ikke helt god ☐ God ☐ Svært god

2 Har du noen langvarig (minst 1 år) sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv?

Ja	Nei
☐	☐

Hvis ja:
Hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet	☐	☐	☐
Har nedsatt syn	☐	☐	☐
Har nedsatt hørsel	☐	☐	☐
Hemmet pga. kroppslig sykdom	☐	☐	☐
Hemmet pga. psykisk sykdom	☐	☐	☐

3 Har du kroppslige smerter nå som har vart mer enn 6 måneder?

Ja	Nei
☐	☐

4 Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 uker?

Ingen	Meget svake	Svake	Mode-rate	Sterke	Meget sterke
☐	☐	☐	☐	☐	☐

5 I hvilken grad har din fysiske helse eller følelses-messige problemer begrenset deg i din vanlige sosiale omgang med familie eller venner i løpet av de siste 4 uker?

Ikke i det hele tatt	En del	Litt	Mye	Kunne ikke ha sosial omgang
☐	☐	☐	☐	☐

HELSETJENESTER

6 Har du i løpet av de siste 12 måneder vært hos:

	Ja	Nei
Fastlege/allmennlege	☐	☐
Annen legespesialist utenfor sykehus	☐	☐
Konsultasjon uten innleggelse		
- ved psykiatrisk poliklinikk	☐	☐
- ved annen poliklinikk i sykehus	☐	☐
Kiropraktor	☐	☐
Homøopat, akupunktør, soneterapeut, håndspålegger eller annen alternativ behandler	☐	☐

7 Har du vært innlagt i sykehus i løpet av de siste 12 måneder?

Ja	Nei
☐	☐

SYKDOMMER OG PLAGER

8 Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder?

Ja	Nei
☐	☐

9 Har du noen gang de siste 5 år brukt medisiner for astma, kronisk bronkitt, emfysem eller KOLS?

Ja	Nei
☐	☐

10 Bruker du, eller har du brukt, medisin mot høyt blodtrykk?

Ja	Nei
☐	☐

11 Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:
(Sett ett kryss pr. linje)

Hvis ja, hvor gammel var du **første** gang?
Eksempel: 34 *år gammel*

	Ja	Nei	Hvis ja, hvor gammel var du første gang?
Hjerteinfarkt	☐	☐	*år gammel*
Angina pectoris (hjertekrampe)	☐	☐	*år gammel*
Hjertesvikt	☐	☐	*år gammel*
Annen hjertesykdom	☐	☐	*år gammel*
Hjerneslag/hjerneblødning	☐	☐	*år gammel*
Nyresykdom	☐	☐	*år gammel*
Astma	☐	☐	*år gammel*
Kronisk bronkitt, emfysem, KOLS	☐	☐	*år gammel*
Diabetes (sukkersyke)	☐	☐	*år gammel*
Psoriasis	☐	☐	*år gammel*
Eksem på hendene	☐	☐	*år gammel*
Kreftsykdom	☐	☐	*år gammel*
Epilepsi	☐	☐	*år gammel*
Leddgikt (reumatoid artritt)	☐	☐	*år gammel*
Bechterews sykdom	☐	☐	*år gammel*
Sarkoidose	☐	☐	*år gammel*
Beinskjørhet (osteoporose)	☐	☐	*år gammel*
Fibromyalgi	☐	☐	*år gammel*
Slitasjegikt (artrose)	☐	☐	*år gammel*
Psykiske plager som du har søkt hjelp for	☐	☐	*år gammel*

12 Har du noen gang fått påvist for høyt blodsukker?

Ja	Nei
☐	☐

Hvis ja: I hvilken situasjon første gang?

☐ Ved helseundersøkelse... ☐ Under sykdom ...
☐ Under svangerskap ... ☐ Annet ...

SKADER

13 Har du noen gang hatt:

	Ja	Nei	Hvis ja, hvor gammel var du **første** gang?
Eksempel:			3 4 *år gammel*
Lårhalsbrudd	☐	☐	___ *år gammel*
Brudd i handledd/underarm	☐	☐	___ *år gammel*
Brudd/sammenfall av ryggvirvler	☐	☐	___ *år gammel*
Nakkesleng (whiplash)	☐	☐	___ *år gammel*

14 Har du foreldre, søsken eller barn som har, eller har hatt, følgende sykdommer?
(Sett ett kryss pr. linje)

	Ja	Nei	Vet ikke
Hjerneslag eller hjerneblødning før 60 års alder	☐	☐	☐
Hjerteinfarkt før 60-års alder	☐	☐	☐
Astma	☐	☐	☐
Allergi/høysnue/neseallergi	☐	☐	☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐
Kreftsykdom	☐	☐	☐
Psykiske plager	☐	☐	☐
Beinskjørhet (osteoporose)	☐	☐	☐
Nyresykdom (ikke nyresten, urinveisinfeksjon, urinlekkasje)	☐	☐	☐
Diabetes (sukkersyke)	☐	☐	☐

15 Har noen av dine besteforeldre, dine foreldres søsken eller dine søskenbarn fått diagnosen diabetes (type 1 eller type 2)?

Ja ☐ Nei ☐

HVORDAN FØLER DU DEG?

16 Har du <u>de to siste uker</u> følt deg:
(Sett ett kryss pr. linje)

	Nei	Litt	En god del	Svært mye
Trygg og rolig?	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst?	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom?	☐	☐	☐	☐

17 Har du noen gang i livet opplevd at noen over lengre tid har forsøkt å kue, fornedre eller ydmyke deg?

Ja ☐ Nei ☐

TOBAKK

18 Røykte noen av de voksne <u>innendørs</u> da du vokste opp? Ja ☐ Nei ☐

19 Røykte mora di da du vokste opp? Ja ☐ Nei ☐

20 Røyker du selv?

Nei, jeg har <u>aldri</u> røykt ☐
Hvis du <u>aldri</u> har røykt, hopp til spørsmål 22.
Nei, jeg har sluttet å røyke ☐
Ja, sigaretter <u>av og til</u> (fest/ferie, ikke daglig) ☐
Ja, sigarer/sigarillos/pipe <u>av og til</u> ☐
Ja, sigaretter <u>daglig</u> ☐
Ja, sigarer/sigarillos/pipe <u>daglig</u> ☐

21 A Svar på dette hvis du <u>nå</u> røyker **daglig** eller <u>tidligere</u> har røykt **daglig**:

Hvor mange sigaretter røyker eller røykte du vanligvis <u>daglig</u>? ___ *sigaretter pr. dag*

Hvor gammel var du da du begynte å røyke <u>daglig</u>? ___ *år gammel*

Hvis du tidligere har røykt daglig, hvor gammel var du da du sluttet? ___ *år gammel*

21 B Svar på dette hvis du røyker eller har røykt **av og til**, men <u>ikke daglig</u>:

Hvor mange sigaretter røyker eller røykte du vanligvis <u>i måneden</u>? ___ *sigaretter pr. mnd*

Hvor gammel var du da du begynte å røyke <u>av og til</u>? ___ *år gammel*

Hvis du tidligere har røykt <u>av og til</u>, hvor gammel var du da du sluttet? ___ *år gammel*

22 Bruker du, eller har du brukt, snus?

Nei, aldri ☐ Ja, av og til ☐
Ja, men jeg har sluttet ☐ Ja, daglig ☐
Hvis du <u>aldri</u> har brukt snus, hopp til spørsmål 23.

Hvis ja:
Hvor gammel var du da du begynte med snus? ___ *år gammel*

Hvor mange esker snus bruker/brukte du <u>pr. måned</u>? ___ *esker snus pr. måned*

Hvis du bruker eller har brukt både sigaretter og snus, hva begynte du med først?

Snus ☐ Sigaretter ☐
Omtrent samtidig ☐ Husker ikke ☐
(innenfor 3 måneder)

Da du begynte å bruke snus, var det for å prøve å slutte å røyke eller for å redusere røykinga?

Nei ☐
Ja, for å slutte å røyke ☐
Ja, for å redusere røykinga ☐

MATVARER

23 Hvor ofte spiser du vanligvis disse matvarene? *(Sett ett kryss pr. linje)*

	0-3 ganger pr. mnd	1-3 ganger pr. uke	4-6 ganger pr. uke	1 gang pr. dag	2 ggr el mer pr. dag
Frukt/bær	☐	☐	☐	☐	☐
Grønnsaker	☐	☐	☐	☐	☐
Sjokolade/smågodt	☐	☐	☐	☐	☐
Kokte poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Pølser/hamburgere	☐	☐	☐	☐	☐
Fet fisk (laks, ørret, sild, makrell, uer som pålegg/middag)	☐	☐	☐	☐	☐

24 Bruker du følgende kosttilskudd? *(Sett ett kryss for hvert kosttilskudd)*

	Ja, daglig	Av og til	Nei
Tran	☐	☐	☐
Omega-3-kapsler	☐	☐	☐
Vitamin- og/eller mineraltilskudd	☐	☐	☐

25 Hvor mange glass drikker du vanligvis av følgende?
½ liter = 3 glass *(Sett ett kryss pr. linje)*

	Sjelden eller aldri	1-6 gl. pr uke	1 gl. pr. dag	2-3 gl. pr. dag	4 gl. eller mer pr. dag
Vann, farris o.l	☐	☐	☐	☐	☐
Helmelk (søt/sur)	☐	☐	☐	☐	☐
Annen melk (søt/sur)	☐	☐	☐	☐	☐
Brus/saft med sukker	☐	☐	☐	☐	☐
Brus/saft uten sukker	☐	☐	☐	☐	☐
Juice eller nektar	☐	☐	☐	☐	☐

26 Hvor mange kopper kaffe/te drikker du pr. døgn? *(Sett 0 dersom du ikke drikker kaffe/te daglig)*

	Koke-kaffe	Annen kaffe	Te
Antall kopper			

27 Hvor mange kopper kaffe drikker du om kvelden (etter kl 18)? Antall kopper

ALKOHOLBRUK

28 Omtrent hvor ofte har du i løpet av de siste 12 måneder drukket alkohol? *(Regn ikke med lettøl)*

4-7 ganger pr. uke ☐ Ca 1 gang pr. måned ☐
2-3 ganger pr. uke ☐ Noen få ganger pr. år ☐
ca 1 gang pr. uke ☐ Ingen ganger siste år ☐
2-3 ganger pr. måned ☐ Aldri drukket alkohol ☐

29 Har du drukket alkohol i løpet av de siste 4 uker? Ja ☐ Nei ☐

Hvis ja:
Har du drukket så mye at du har kjent deg sterkt beruset (full)?
Nei ☐
Ja, 1-2 ganger ☐
Ja, 3 ganger eller mer ☐

30 Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av 2 uker? *(Regn ikke med lettøl)* *(Sett 0 hvis du ikke drikker alkohol)*

	Øl	Vin	Brenne-vin
Antall glass			

31 Hvor ofte drikker du 5 glass eller mer av øl, vin eller brennevin ved samme anledning?

Aldri ☐ Ukentlig ☐
Månedlig ☐ Daglig ☐

MOSJON/FYSISK AKTIVITET

Med mosjon mener vi at du f.eks går tur, går på ski, svømmer eller driver trening/idrett.

32 Hvor ofte driver du mosjon? *(Ta et gjennomsnitt)*

Aldri ☐
Sjeldnere enn en gang i uka ☐
En gang i uka ☐
2-3 ganger i uka ☐
Omtrent hver dag ☐

33 Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? *(Ta et gjennomsnitt)*

Tar det rolig uten å bli andpusten eller svett ☐
Tar det så hardt at jeg blir andpusten og svett ☐
Tar meg nesten helt ut ☐

34 Hvor lenge holder du på hver gang? *(Ta et gjennomsnitt)*

Mindre enn 15 minutter ☐ 30 minutter – 1 time ☐
15-29 minutter ☐ Mer enn 1 time ☐

35 Har du vanligvis minst 30 minutter fysisk aktivitet daglig på arbeid og/eller i fritida? Ja ☐ Nei ☐

36 Omtrent hvor mange timer sitter du i ro på en vanlig hverdag? *(Regn med både jobb og fritid)* Antall timer ☐

ARBEID

37 Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt? *(Sett ett kryss)*

For det meste stillesittende arbeid *(f.eks skrivebordsarbeid, montering)* ☐

Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarb., undervisning)* ☐

Arbeid hvor du går og løfter mye *(f.eks postbud, pleier, bygningsarbeid)* ☐

Tungt kroppsarbeid *(f.eks skogsarbeid, tungt jordbruksarbeid, tungt bygningsarbeid)* ☐

HØYDE/VEKT

38 Omtrent hva var din høyde da du var 18 år?

☐ cm Husker ikke ☐

39 Omtrent hva var din kroppsvekt da du var 18 år?

☐ kg Husker ikke ☐

40 Er du fornøyd med vekta di nå?

Ja ☐ Nei, for lett ☐ Nei, for tung ☐

41 Har du forsøkt å slanke deg i løpet av de siste 10 år?

Nei ☐ Ja, noen ganger ☐ Ja, mange ganger ☐

42 Er din kroppsvekt minst 2 kg lavere nå enn for 1 år siden? Ja ☐ Nei ☐

Hvis ja:

Hva er grunnen til dette?

Slanking ☐ Sykdom/stress ☐ Vet ikke ☐

ALVORLIGE LIVSHENDELSER SISTE 12 MÅNEDER

43 Har det vært dødsfall i nær familie? *(barn, ektefelle/samboer, søsken eller foreldre)* Ja ☐ Nei ☐

44 Har du vært i overhengende livsfare pga. alvorlig ulykke, katastrofe, voldssituasjon eller krig? Ja ☐ Nei ☐

45 Har du hatt samlivsbrudd i ekteskap eller i lengre samboerforhold? Ja ☐ Nei ☐

46 Hvis du har svart ja på et eller flere av spm 43, 44 eller 45; i hvilken grad har du hatt reaksjoner på dette de siste 7 dager?

Ikke i det hele tatt ☐ I moderat grad ☐
Litt ☐ I høy grad ☐

OPPVEKST - DA DU VAR 0-18 ÅR

47 Hvem vokste du opp sammen med?

Mor ☐ Andre slektninger ☐
Far ☐ Adoptivforeldre ☐
Stemor/stefar ☐ Foster-/pleieforeldre ☐

48 Ble dine foreldre skilt, eller flyttet de fra hverandre, da du var barn?

Nei ☐
Ja, før jeg var 7 år ☐
Ja, da jeg var 7-18 år ☐

49 Døde noen av dine foreldre da du var barn?

Nei ☐
Ja, før jeg var 7 år ☐
Ja, da jeg var 7-18 år ☐

50 Vokste du opp med kjæledyr?

Nei ☐
Ja, katt ☐ Ja, hund ☐
Ja, hest ☐ Ja, annet levende dyr ☐

51 Hvor mye melk eller yoghurt drakk du vanligvis?

Sjelden/ aldri	1-6 gl. pr. uke	1 glass pr. dag	2-3 gl. pr. dag	Mer enn 3 glass pr. dag
☐	☐	☐	☐	☐

52 Vokste du opp på gård med husdyr? Ja ☐ Nei ☐

53 Når du tenker på barndommen/oppveksten din, vil du beskrive den som:

Svært god ☐ Vanskelig ☐
God ☐ Svært vanskelig ☐
Middels ☐

ALT I ALT

54 Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd? *(Sett ett kryss)*

Svært fornøyd ☐ Nokså misfornøyd ☐
Meget fornøyd ☐ Meget misfornøyd ☐
Ganske fornøyd ☐ Svært misfornøyd ☐
Både/og ☐

Dissertations

Dissertations at the Faculty of Medicine, NTNU

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2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

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1979

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1980

6. Størker Jørstad: URAEMIC TOXINS
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1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

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1984

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78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
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86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
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91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.

102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
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113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
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117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.

161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97

191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
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206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
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211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
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229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY

243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE

271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
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